The role of depression in sexual behaviour linked to STI and HIV transmission: a study of HIV-negative and untested gay, bisexual, and other men who have sex with men in England

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I, Ada Rose Miltz confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

HIV transmission remains ongoing among men who have sex with men (MSM). Depressive symptomatology has been linked to sexual risk-taking among sexually active MSM in the U.S. Data in Europe are lacking. The aim of this thesis was to investigate the role of depressive symptoms in sexual behaviours linked to STI/HIV transmission among gay, bisexual, and other MSM in the UK, using data from two studies. AURAH (Attitudes to, and Understanding of, Risk of Acquisition of HIV) was a cross-sectional study of HIV-negative MSM attending 20 genitourinary medicine (GUM) clinics across England (2013-2014). Men reporting recent sex were included in analysis (N=1340). PROUD was a randomized trial to assess the effectiveness of pre-exposure prophylaxis among MSM reporting condomless sex (CLS), and therefore at high-risk for HIV acquisition, in England (2012-2014, N=540 at baseline). Across studies/time-points, prevalence of depressive symptoms (PHQ-9≥10) ranged from 12.4%-14.4%; associated factors included lower socio-economic status, lower supportive network, concealment of sexuality, bisexual-identity, anti-gay attitudes, recreational drug use, and intimate partner violence. Among sexually active men in AURAH, depressive symptoms were associated with all measures of CLS, including previous sexually transmitted infection and post-exposure prophylaxis (PEP) use, even after adjusting for socio-demographics and recreational drug use (adjusted prevalence ratio for ≥2 CLS partners: 1.28 95% CI: 1.05, 1.56; $p=0.013$). In structural equation modelling, depression was associated with CLS indirectly via low self-efficacy (perceived inability to ensure condom-use when desired) ($p<0.001$). Among the PROUD sample of men reporting CLS, depressive symptoms were associated with PEP use, but not with greater versus lower levels of CLS. Among samples with high levels of sexual risk, factors with disinhibiting effects (i.e. drug use) may better explain differences in behaviour. Among sexually active GUM clinic attendees, management of depression alongside interventions surrounding self-efficacy may play an important role in HIV/STI prevention.

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Chapter 1

1 Introduction

This thesis addresses the relationship between depression and sexual behaviour linked to HIV and STI transmission among individuals at highest risk of sexual acquisition of HIV in high-income countries: men who engage in anal sex with other men. The introduction has nine parts. In part one, the overall thesis aims and objectives are stated. In part two, the mechanisms of sexual transmission of HIV and reasons for increased risk of HIV acquisition among men who have sex with men (MSM) are described. This thesis focuses on data from the United Kingdom (UK) and in part three the current epidemiology of HIV among MSM in the UK is presented. This is followed by the rationale for continued HIV prevention research in part four. In part five, the population of interest in this thesis is further defined by describing associated identities/communities. Key events in the HIV/AIDS epidemic are presented together with changing perceptions of HIV within gay and bisexual communities. Epidemiological trends over time in sexual risk behaviour, STIs, and HIV in high-income countries are presented. In part six, the minority stress theory is described. Depression is defined in part seven and in part eight the prevalence of depression and its association with sexual risk behaviour among sexual minority men is presented. Possible mechanisms by which depression might influence sexual behaviour are described. Part nine concludes the introduction by presenting the rationale for this PhD thesis, the thesis hypothesis, and the sources of data for analysis.

1.1 Thesis aims and objectives

The overall aim of this PhD thesis is to investigate prevalence and correlates of clinically significant depressive symptoms and the relationship of depressive symptoms with HIV/STI sexual transmission risk behaviours among gay, bisexual, and other men who have sex with men (MSM). This is in order to inform clinical care and HIV prevention, and thus provide insight into the extent to which addressing/managing depressive symptoms may play a role in HIV/STI prevention. This thesis uses data from two UK studies: *'The Attitudes to, and Understanding of, Risk of Acquisition of HIV' (AURAH)* cross-sectional observational study and from the PROUD randomized trial.

1.1.1 Objectives

Among HIV-negative gay, bisexual, and other MSM in the UK investigate:

(i) Prevalence of depressive symptoms and treatment for depression
(ii) Association of socio-demographic and lifestyle factors with depressive symptoms
(iii) Association of psychosocial factors with depressive symptoms

(iv) Association of depressive symptoms with sexual risk behaviour
(v) Association of depressive symptoms with self-efficacy for sexual safety
(vi) Association of self-efficacy for sexual safety with sexual risk behaviour
(vii) Indirect association of depressive symptoms with sexual risk behaviour via self-efficacy for sexual safety

As described in detail in the following section, objectives (i) and (ii) are addressed in Chapters 4 and 7. Objective (iii) is addressed in Chapter 7. Objectives (iv), (v), and (vi) are addressed in Chapters 5 and 8. Objective (vii) is addressed in Chapter 6. In each results chapter, findings are discussed in the context of existing literature and the limitations of the findings are discussed. The implications of the thesis findings are discussed in the final conclusion (Chapter 9).

1.1.2 Specific objectives of thesis chapters

Chapter 1: (a) introduce HIV and describe reasons for increased risk of HIV acquisition among MSM; (b) describe the epidemiology of HIV among MSM in the UK; (c) present rationale for continued HIV prevention research; (d) define sexual minority populations; (e) describe key events in the HIV/AIDS epidemic together with changing perceptions of HIV within gay and bisexual communities, and present epidemiological trends in sexual risk behaviour and STIs/HIV in high-income countries; (f) describe the minority stress theory; (g) define depression; (h) describe the existing literature on the prevalence of depression and association with sexual risk behaviour and possible mechanisms for association among MSM; (i) present the thesis rationale and hypothesis.

Chapter 2: conduct two literature reviews.
Literature review (i): review studies that have investigated the relationship between depression and sexual risk behaviours among samples of MSM or HIV-negative MSM in high-income countries (North America, Australia, New Zealand, and countries in Western Europe) in order to: (a) describe instruments used to measure depression and associated prevalence; (b) review the relationships found between depression and sexual behaviour measures, according to study recruitment setting and in the context of key sample characteristics.

Literature review (ii): review all studies that have investigated HIV sexual transmission risk behaviours in samples of MSM or HIV-negative MSM in the UK, in order to: (a) evaluate differences in the prevalence of sexual behaviour across study recruitment settings; (b) assess correlates of sexual behaviour, considering factors other than depression.

Chapter 3: (a) describe the methodology of the AURAH study and the PROUD trial; (b) define the variables used in the thesis; (c) make explicit the hypothesized causal connection between depressive symptoms and sexual behaviour using a directed acyclical graph (DAG), whereby

the hypothesized relationships between psychosocial variables of relevance to both depression and sexual behaviour among sexual minority men are presented; (d) describe the statistical methods used in the thesis; (e) describe the methodological weaknesses of AURAH and PROUD.

Chapter 4: using data from the AURAH study: (a) describe the prevalence of depressive symptom measures, treatment for depression, and psychological co-morbidities; (b) investigate the cross-sectional association of socio-demographic (age, country of birth and ethnicity, sexual identity, markers of socio-economic status, relationship status, and study region) and lifestyle/psychosocial factors (smoking, alcohol consumption, recreational drug use, supportive networks, and disclosure of sexual orientation) with depressive symptoms.

Chapter 5: using data from the AURAH study to investigate: (a) the relationship of depression measures with condomless sex and other sexual behaviour measures, and the potential confounding/moderating effects of recreational drug use; (b) the relationship between depressive symptoms and measures of low self-efficacy for sexual safety; (c) the relationship between measures of low self-efficacy for sexual safety and sexual behaviour measures; (d) the potential mediating effects of low self-efficacy on the relationship between depressive symptoms and sexual behaviour.

Chapter 6: using data from the AURAH study, develop a structural equation model (SEM) based on the DAG presented in Chapter 3, in order to examine the indirect effect of depressive symptoms on sexual behaviour through the mechanism of self-efficacy for sexual safety.

Chapter 7: using data from the PROUD trial to investigate across study time-points: (a) the prevalence of depression measures; (b) the association of socio-demographic (age, country of birth and ethnicity, sexual identity, markers of socio-economic status, relationship status, and study region) and lifestyle/psychosocial factors (alcohol consumption, recreational drug use, intimate partner violence, age at first sexual debut, negative attitudes towards gay sexuality, and disclosure of sexual orientation) with depressive symptoms.

Chapter 8: using data from the PROUD trial to investigate across study time-points: (a) the relationship of depression measures with condomless sex and other sexual behaviour measures, and the potential confounding/moderating effects of psychosocial factors; (b) the relationship between depressive symptoms and measures of low self-efficacy for sexual safety; (c) the relationship between measures of low self-efficacy for sexual safety and sexual behaviour measures; (d) the potential mediating effects of low self-efficacy on the relationship between depressive symptoms and sexual behaviour.

Chapter 9: discuss the implications of the thesis, comparing and bringing together the AURAH and PROUD study findings, and make recommendations for clinical and prevention policy and future research.

I conceptualized the hypothesis investigated in this thesis, conducted both literature reviews, conducted all data-analyses and interpretation, and undertook for AURAH, all data management and for PROUD, variable derivation. I lead the design of a short survey that was distributed to PROUD participants.

Publications and presentations arising from this thesis, to date, are listed in Appendix section 11.1.

1.2 Human immunodeficiency virus

The human immunodeficiency virus (HIV) pandemic was first recognized in the early 1980s. The HIV virus was isolated in 1983 [1, 2] and confirmed to be the causative agent associated with the acquired immunodeficiency syndrome (AIDS) in 1984 [3, 4]. HIV is a retrovirus that belongs to the *Retroviridae* family and genus *Lentivirus*. HIV is transmitted through three main routes: sexual transmission, blood contact, and mother-to-child transmission. HIV attacks the immune system of the infected individual, causing progressive immunosuppression, and increasing risk of opportunistic infections, cancers, and death. Prior to the advent of effective treatment, the median survival time from HIV infection was around ten years [5]. Effective treatment for HIV - triple combination antiretroviral treatment (ART) - was introduced in the mid-1990s. The prognosis of HIV has been transformed since the introduction of ART. HIV-positive individuals with access to treatment now have greatly improved life expectancy, nearing that of the general population [6-12]. The plasma HIV viral load, which is a measure of the level of HIV replication in circulating blood, is one of the primary markers used to monitor the success of treatment. Effective treatment of HIV results in reduction of the plasma viral load, the aim being the reduction of viral load to a level undetectable with standard assays. Suppression of HIV viral load is usually associated with restoration of immune function to a level that is comparable with that seen in individuals not infected with HIV. An undetectable viral load is also associated with a dramatically reduced risk of HIV transmission to a sexual partner [13-17]. Until recently, treatment policy for HIV recommended that initiation of ART be delayed until the level of immunosuppression, of the HIV-infected individual, posed a significant risk to health. This was done in order to balance the treatment benefit with its potential risk of side-effects. However, in 2015, it was demonstrated in a large international randomized controlled trial (START) that starting ART earlier confers a reduction in risk of serious illness [18]. Given the potential public health and individual clinical benefit, new guidelines recommend treating individuals with HIV from the time of their diagnosis [19-21].

1.2.1 Sexual transmission of HIV

Sexual transmission of HIV usually takes place via condomless sex i.e. sexual intercourse without a condom, referred to throughout this thesis as CLS [15]. HIV crosses the epithelial barriers that cover the mucosal surfaces of the genital track and anus/rectum [22]. Genital and rectal tissues are populated with dendritic cells, macrophages, T cells and other cells that participate in immune responses. These cells express chemokine receptors (mainly CD4 and CCR5) that are susceptible to HIV infection [23, 24]. In addition to the vaginal/cervical epithelia, the rectal canal represents the most efficient route for HIV transmission [22]. The rectal canal consists of only a single layer of epithelium covering mucosal tissue, where activated innate immune cells are plentiful [25]. Any destruction to epithelial integrity enables direct access to target cells and establishment of infection in the mucosa [23]. Receptive anal sex (i.e. having a partner insert their penis into one's rectum with ejaculation) is the most efficient sexual practice for transmitting HIV, at an estimated 1.4% (95% CI: 0.2%, 2.5%) per act probability and 40.4% (95% CI: 6.0%, 74.9%) per partner probability (18-fold higher than for vaginal sex) [26]. The depletion of CD4+ lymphocytes, a type of white blood cell that is crucial to fighting infection, plays a critical role in the pathogenesis of HIV [25, 27, 28].

1.2.2 Men who have sex with men and HIV

The first indication of the global HIV/AIDS pandemic was recognized in October of 1981, when the number of cases of Kaposi sarcoma, a rare type of cancer in North America and Europe, was occurring among young gay-identified men in New York and San Francisco with alarming frequency [29]. On the heels of this report, it became clear that a number of gay-identified men were suffering from an unusual number of opportunistic infections and immunodeficiency [30, 31].

The term men who have sex with men has been used since at least 1990, with the abbreviation MSM coined in 1994 by public health researchers [32]. The purpose of the term MSM was to acknowledge that behaviours not identities conferred risk for HIV. The term MSM has since become the status quo in HIV epidemiological research. Essentially, MSM is a broader category, including gay- and bisexual-identified men, heterosexual-identified men who have sex with men, male sex workers, and men who have sex with men in all male settings such as prisons. As a result, it endeavours to encompass diverse identities and terms that may exist across cultures, social class, and ethnicity [33, 34]. Use of this term is discussed further in section 1.5.2.

1.2.3 MSM, risk of HIV, and vulnerability to other STIs

MSM continue to be one of the population groups with the greatest risk of sexual transmission of HIV in many parts of the world [35, 36]. If the transmission probability of receptive condomless anal sex was similar to that of condomless vaginal sex, the five year cumulative incidence of HIV in MSM would be reduced by an estimated 80-90% [37]. MSM are unique sexual beings in

that they can acquire HIV through receptive CLS and then pass it on through insertive CLS. In addition, MSM are vulnerable to rectal sexually transmitted infections (STIs) including *Neisseria gonorrhoea, Chlamydia trachomatis, Treponema pallidum* (syphilis), *lymphogranuloma venereum* (LGV), and *Herpes simplex* virus (HSV). Rectal STIs can present on the perianal skin and anal canal, causing inflammation of the rectal mucosa (clinical proctitis), anal discharge and pain, and sores in and/or on the anus. Rectal STIs and their treatment have important implications in the control of HIV as they are implicit in both transmission and susceptibility [38-40] [41].

1.3 Epidemiology of HIV among MSM in the United Kingdom

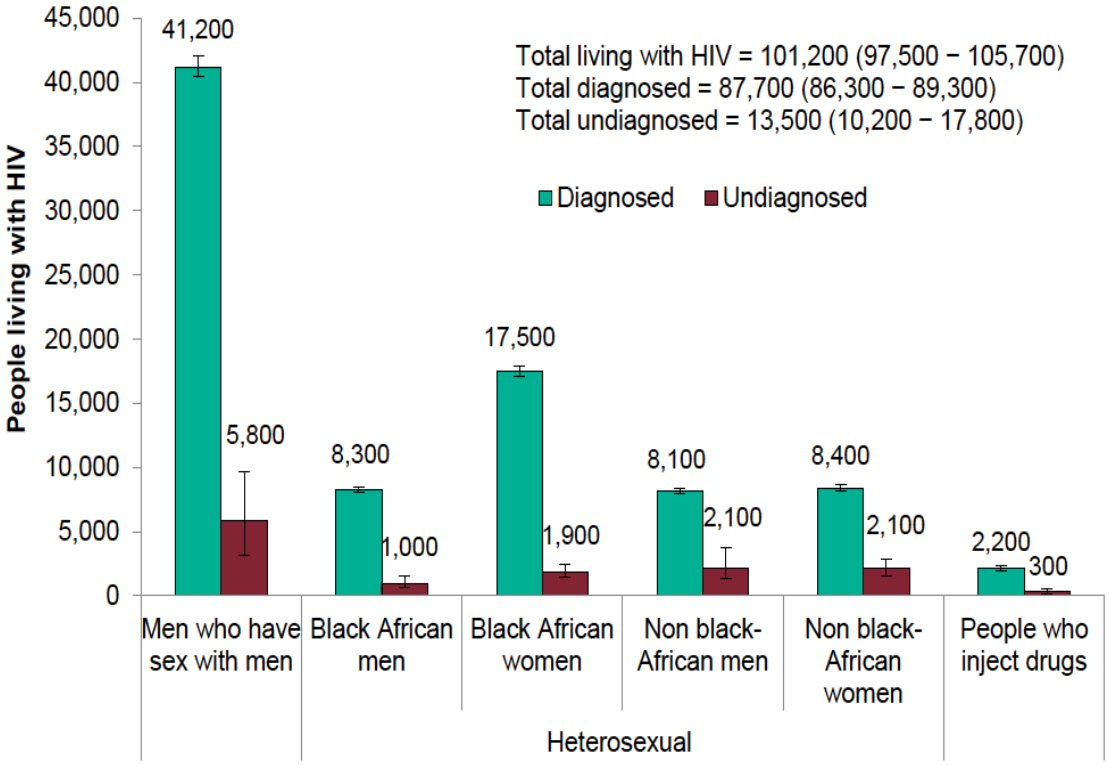
At the time of writing this thesis, national HIV surveillance data was available up to 2015 in the UK.

1.3.1 Prevalence of HIV in the UK

Figure 1 presents the estimated number of individuals living with HIV (diagnosed and undiagnosed) in 2015 across exposure groups (MSM, black African ethnicity, injection drug users), calculated using the multi-parameter evidence synthesis model (MPES), which takes into account multiple data sources [42]. In total, 101200 (95% credible interval: 97500, 105700) individuals were estimated to be living with HIV. Of these individuals, an estimated 47000 (95% credible interval: 44200, 50900) were MSM (Figure 1). Based on the assumption that 3.3% of men in the UK have had sex with a man in the past five years, it was estimated that the prevalence of HIV among MSM was one in 17 (58.7 [95% credible interval: 51.2, 68.0] per 1000). In London, the prevalence was estimated to be higher at one in seven MSM (135 [95% credible interval: 101, 184] per 1000). Of the 47000 MSM estimated to be living with HIV, 12% (95% credible interval[i]: 7-19%) were estimated to have an undiagnosed HIV infection [42].

[i] 95% credible interval presents the statistical uncertainty surrounding estimates from a Bayesian analysis (i.e. from the MPES model) 42. Kirwan PD, Chau C, Brown AE, Gill ON, Delpech VC. HIV in the UK-2016 report. London: Public Health England, 2016.

Figure 1: Estimated number of people living with HIV (both diagnosed and undiagnosed), using MPES, by exposure group (all ages): UK, 2015, from Public Health England 2016 report: Kirwan et al. 2016 [42]



1.3.2 Incidence of HIV in the UK

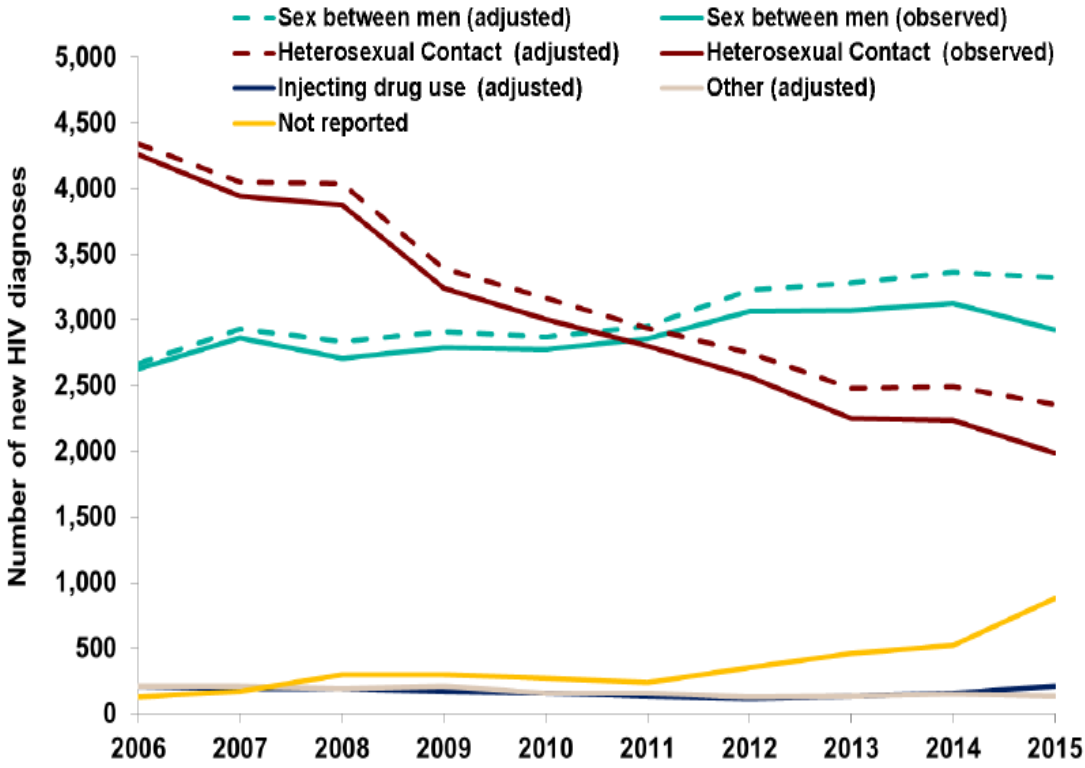
In 2015, 6095 men and women were diagnosed with HIV[ii]. Figure 2 shows the number of new HIV diagnoses over the period of 2006-2015, according to exposure group (sex between men, heterosexual contact, injecting drug use). For MSM, observed estimates and estimates adjusted according to the distribution of exposure groups from data with complete information, are shown in green. In 2015, 3320 new HIV diagnoses were reported among MSM[iii] (1307 new diagnoses among MSM resident in London); constituting 54% of all new HIV diagnoses in the UK [43]. Although the number of new HIV diagnoses was slightly higher in 2014 (N=3360), it appears that numbers remained high in 2015 among MSM, despite initiatives to counter new infections and the ready availability of ART over the past decade. An individual-based stochastic computer simulation model [44-47] has reconstructed the HIV epidemic among MSM in the UK (1980-2012) to model the relative influences of sexual risk behaviour change, rates of HIV testing, and ART-induced virologic suppression on HIV incidence (diagnosed and undiagnosed cases) [15]. This model suggests that it is the counter-effect of concomitant increases in CLS amongst MSM as a whole that has resulted in a net increase in HIV incidence over a period in which ART coverage

[ii] Of note, the decline in number of new diagnoses of HIV via heterosexual contact, as shown in Figure 2 , is attributed to changing migration patterns, as more men and women born in sub-Saharan Africa have an HIV infection diagnosed in their respective countries rather than after having migrated to the UK 43. Chau C, Kirwan P, Brown A, Gill N, Delpech V. HIV diagnoses, late diagnoses and numbers accessing treatment and care. London: Public Health England, 2016.

[iii] The incidence of HIV (i.e. number of new cases/total population at risk) among MSM in the UK is not reported.

and viral suppression has been increasing. Furthermore, studies suggest that the majority of new HIV infections are from people unaware of their HIV status [14, 15, 48-52]. In 2015, 30% of MSM (n=777/2628) were diagnosed at late stage of infection [43].

Figure 2: New HIV diagnoses by exposure group over time; 2006-2015, from Public Health England 2016 report: Chau et al. 2016 [43]



1.3.3 Changes in HIV diagnosis in 2016

Prior to submitting this thesis, a short report was published [53] suggesting that compared to observations made in 2015, a substantial decrease in the number of new HIV diagnoses was seen at five genitourinary medicine (GUM) clinics in London at the end of 2016. The drop was considered to reflect a decrease in incidence given the concomitant increase in median CD4 count at diagnosis. Smaller declines, however, were seen at other GUM clinics in London and elsewhere in England. It was suggested that use of pre-exposure prophylaxis (PrEP) was likely to have contributed to the observed decrease in new diagnoses. PrEP is discussed in section 1.4.2.

1.4 HIV prevention

Although the prognosis of HIV infection has dramatically improved [6-9], living with HIV and taking lifelong treatment can substantially impact on quality of life. For many individuals an HIV diagnosis can be deeply disenfranchising. There is evidence that HIV continues to impact on

mental health and well-being even in the era of successful treatment [15, 54, 55]. Efforts need to remain focused on reducing new HIV infections.

1.4.1 Sexual healthcare provision in the UK

GUM clinics provide open access, confidential, high-quality, and free STI and HIV testing and care on the UK National Health Service (NHS) [53]. The British Association for Sexual Health and HIV (BASHH) sets national guidelines and standards for specialists in genitourinary medicine [56]. Guidelines suggest that all sexually active MSM should test for HIV and other STIs at least annually and those considered to be at high-risk should test every three months [57]. Testing on a three monthly basis is recommended for MSM following CLS with a new partner, diagnosis of a new STI, and recreational drug use, which may be a marker of high-risk behaviour [57].

1.4.2 Prevention interventions

Promotion of condom-use and HIV testing is the backbone of HIV prevention [58-63]. Behavioural interventions to increase condom-use encompass a range of educational, motivational, peer-group, skills-building, and community normative approaches [64]. A recent review shows that although a large number of behavioural interventions have been evaluated, the majority demonstrated modest reductions in self-reported sexual risk behaviour, and often no effects on HIV incidence [64]. Studies have mostly been conducted in the U.S. Of note, treatment of STIs is also a strong public health intervention in its own right but has had mixed results in trials in which the effect on prevention of HIV acquisition was assessed [65].

Novel biomedical interventions include the use of oral ART for post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP) and to reduce infectiousness among HIV-positive individuals (i.e. Treatment as Prevention, TasP) [16, 66-74]. Individuals can take PEP soon after possible exposure to HIV in order to reduce their risk of acquiring HIV. A follow-up HIV test is required. BASHH guidelines for use of PEP were published in 2006 [75-78]. PEP is increasingly being recommended for MSM following CLS [79]. Efficacy of PEP is dependent on accurate perceptions of risk, engagement in sexual health care, and willingness to report sexual risk-taking.

Individuals who test negative for HIV can take PrEP (daily or intermittently) prior to potential HIV exposure, in order to reduce their risk of acquiring HIV. There are several studies showing that Truvada-based PrEP is efficacious at preventing HIV acquisition through sex: iPrEx [67], IPERGAY [74], and PROUD [80] (86% reduction in HIV incidence among MSM). PrEP was approved in the U.S. by the FDA in 2012 [81] and in France in 2015 [82]. In May 2016, BASHH together with the British HIV Association (BHIVA) issued a statement that PrEP should be made available within a comprehensive HIV prevention package to MSM in the UK [83]. PrEP was authorized by the European Medicines Agency in July 2016 [84] and on April 10th 2017, the

decision was made to make PrEP available on the NHS in Scotland [85]. At the time of writing this thesis, PrEP was not available in England on the NHS. The Court of Appeal established that NHS England has the legal power to commission PrEP services in England and Wales [86]. Private clinics are able to prescribe PrEP, but not without significant cost to the user, which has led to many individuals buying generic versions of the drug online from overseas [87].

TasP is the use of immediate/early HIV treatment to be taken by individuals diagnosed with HIV, in order to reduce the risk of transmission to their sero-different partners (i.e. HIV-negative partners) [16, 68, 88, 89]. As described above in section 1.3.2, results from UK modeling work suggests that although novel biomedical interventions such as TasP (which requires high levels of HIV testing) may have an appreciable effect on reducing HIV incidence among populations at risk, concomitant increases in CLS may greatly undermine the positive impact of TaSP [15]. It is possible that these findings may also apply to interventions involving PrEP, especially given that not all potentially at-risk individuals will be willing or able to take PrEP consistently. Therefore, efforts need to remain focused on promotion of condom-use and further investigating potentially effective behavioural interventions, particularly in the UK, is required.

1.5 Sexual minority men, sexual behaviour, and HIV

1.5.1 Biological sex, gender identity, and sexual orientation

The interface between biological sex, gender identity, and sexual orientation can be complex. Sex is a function of biological characteristics of males and females, whereas, gender is a separate construct which refers to socially constructed roles, attributes, and behaviours. Gender identity is based on self-conception and experience as being female, male, another gender, or no gender [90-92]. Gender minorities include individuals who identify as transgender (who experience little or no connection between their biological sex assigned at birth and their gender identify), intersex (biological characteristics at birth do not fit into a binary measure of male or female), and non-binary/gender queer [90-92]. Sexual orientation is defined by sexual attraction, sex of sexual partners, and sexual identity. Sexual minority men include individuals who identify as monosexual (gay/homosexual), plurisexual (bisexual, pansexual [sexual attraction to members of any biological sex or gender identity], fluid, queer), or asexual. Queer is an umbrella term used by individuals in the LGBTQA (lesbian, gay, bisexual, transgender, queer, asexual) community to indicate an identity that is not straight/heterosexual and incorporates complex dynamics of gender identity [90-92].

1.5.2 Defining this population for research purposes

The indiscriminate use of the term MSM has received criticism. Young and Meyer [32] have suggested that use of the term MSM takes an ahistorical view of sexual minority communities, can obscure the complex dynamics of sexual orientation and gender identity, and removes from

the sexual minority man his power to name himself. Furthermore, they suggest that the term MSM disregards the fact that while some men may have sex with men, others may also engage in long-term, committed, emotional relationships with men. These relationships may occur in the context of communities and social networks in which sexual identity is shared.

Although the term MSM is often used for simplicity throughout this thesis when reviewing previous research, I have decided to recognize that the vast majority of 'MSM' participating in HIV research are gay-identified (and to a lesser extent bisexual-identified). Identity related factors are meaningful and powerful forces in people's lives. Treating MSM as a homogenous group (a phenomena known as the out-group homogeneity bias [93]) denies individuals the importance of their unique experiences of growing up, coming out, and finding themselves amongst a community of individuals united by their identity and lifestyles.

The nomenclature of research populations at risk of HIV is clearly complex. In this thesis, I hope to capture the role of sexual identity in behaviours leading to HIV transmission by carefully naming the population under study, which comprises different communities/groups at risk of HIV, as 'gay, bisexual, and other MSM', and as far as numbers allow, assessing differences according to sexual identity within this population. When describing a conceptual model, presented in the Methods chapter and investigated in Chapter 6, the relationships are hypothesized for a population group referred to as sexual minority men. Bisexual men are referred to specifically, but this includes men of other plurisexual identity labels. The section below specifically examines the impact that key events in the HIV/AIDS epidemic have had on the gay community.

This thesis addresses literature from North America, Western Europe, Australia, and New Zealand. Factors that drive trends in HIV epidemiology may be very different between low- and middle-income countries, and high-income countries. When studies are described in the following sections of this introduction, it is important to be cognizant that research among sexual minorities is complicated by the lack of a contact list for all members of the population (the sampling frame). Accordingly, it is not feasible to select a random sample of sexual minority men. Instead, most studies recruit men from community/commercial gay venues, producing samples which may not be fully representative of the sexual minority population in the country of study. This issue is discussed further in Chapter 2.

1.5.3 Gay community and sexual behaviour in the context of HIV

Gay and bisexual communities have had a unique experience with regard to HIV and as a result have had a unique socio-cultural response to the epidemic. Gay and bisexual men have been in the highest HIV/AIDS risk group since the very beginning of the epidemic. At this time virtually nothing was known about the pathology of the virus and its transmission routes. Gay sexuality (and bisexuality) was, and still is in some respects, a stigmatized identity. The appearance of a

deadly virus with no known means of prevention or cure had a profound impact on gay and bisexual men, many of whom lost partners and peers, experiencing a substantial reduction in their social support networks [94, 95]. The impact of the AIDS epidemic on gay (and bisexual) communities cannot be overstated. Perhaps no other group of people is more equipped to deal with the shifting challenges that have occurred over the last decade in the epidemic. With that said, section 1.5.3.1 presents landmark events in the history of the HIV epidemic and their impact on perceptions of HIV transmission within gay (and bisexual) communities.

1.5.3.1 Changing perceptions of risk

This section draws predominantly on findings from a qualitative study of 37 gay men recruited from community/commercial gay venues and GUM clinics across Scotland in the late 90's to explore the role of new HIV-related health technologies on changing HIV risk management for the gay community [96-98]. Prior to the isolation of HIV in 1983 and against the backdrop of unprecedented sexual freedom of the 1970s, the threat of HIV/AIDS swept through the gay (and bisexual) community unhindered. Since any sexual partner could potentially be infected, the necessity to indiscriminately use condoms became paramount [96, 99]. The initial death and destruction wrought by the epidemic stirred a robust community safe sex ethos. Universal condom-use became the prescribed status quo [96, 99].

With the identification of HIV and introduction of HIV antibody testing, however, men could for the first time, discern the HIV status of their sexual partners and determine their risk of transmission from or to a partner. As a result, indiscriminate condom-use was no longer perceived to be of absolute necessity [96]. If arrived upon through a process of mutual HIV testing, disclosure, and selection of practices that matched the HIV serostatus discordancy or concordancy of partnerships, CLS no longer lay outside the realm of what was acceptable sexual behaviour. These behavioural changes are commonly referred to as 'relapse', but controversially so. The natural shift in understanding of and capacity to deal with HIV galvanized the grass roots movement of 'risk reduction', to balance the gains and losses of 'bareback' sex i.e. intentional CLS [96]. Common risk reduction practices include sero-sorting, whereby individuals only have CLS with partners of the same HIV status as themselves. Seropositioning involves active allocation of sexual positioning during anal sex i.e. taking an insertive or receptive position, based on HIV status. A known HIV-positive partner would assume the receptive rather than insertive role to protect their partner from ejaculation. Other practices include withdrawal and the concept of negotiated safety, whereby partners practicing CLS come to an agreement to use condoms with other sexual partners [96, 100-102].

With enduring fear in the background, HIV antibody testing also created distinct categories of men for the first time: those who were negative, those who were positive, and those whose HIV status was unknown. With this came a sense of 'Othering' of those in the community who were known to be HIV-positive, upon whom, all of a sudden, 'risk' and responsibility was attributed. At

this time motivation to test and disclose was tenuous [98]. Against this backdrop of sparse testing, an assumption that sero-negativity accompanied non-disclosure of an HIV status was documented [103-105].

The introduction of ART in 1996 was met with a significant decrease in HIV associated morbidity and mortality [6-12]. It was widely felt that the advent of ART had profoundly changed attitudes to HIV within the gay community [97]. The perception of HIV shifted from it being a death sentence to a chronic, long-term, yet manageable infection. Following the introduction of ART, HIV testing was encouraged within gay communities [106]. Furthermore, in 2008, a group of Swiss HIV clinicians and researchers issued a statement indicating that the risk of transmitting HIV through CLS was extremely low if the HIV diagnosed partner has a suppressed HIV plasma viral load for at least six months and no other STI [107]. It was widely felt that this new HIV-related information had once again changed perceptions of HIV risk within the gay community [108]. Information from The Swiss HIV Cohort Study suggested that sexual behaviour patterns may have changed among HIV diagnosed individuals in Switzerland. There was some evidence to suggest that participants on ART reported higher levels of CLS with sero-different partners following the publication of the 'Swiss Statement' [109]. Yet even before this statement was released, studies from outside Europe suggested that HIV-negative MSM perceived a number of sexual practices with HIV diagnosed MSM on ART as less risky than with men not on ART [110]. More recent data has noted an increased likelihood in HIV-negative MSM to engage in CLS in sero-different relationships (i.e. with an HIV-positive partner) where their partner reports an undetectable viral load [111]. However, it is of note that the number of studies investigating this association among HIV-negative men is limited.

1.5.4 Epidemiological trends in condomless sex and STIs/HIV in high-income countries

This section gives an overview of HIV surveillance data from MSM in high-income countries from the late 1970s onwards. The methodological details of UK studies are described in Chapter 2. There is some evidence from England to suggest that diagnoses of syphilis began to decrease in the late 1970s and continued to fall during the early '80s [112]. However, research carried out in the late 1980s and early 1990s noted an increase in CLS [113], perhaps reflecting the gay community response to HIV antibody testing with risk reduction strategies. Similarly, in the post-ART era, during the late 1990s and into early 2000, studies in the UK, France, Germany, Switzerland [114-129], Australia, Canada, and the U.S. [130-142] found a substantial increase in self-reported sexual risk behaviour, namely CLS with a partner of unknown or sero-different HIV status, regardless of age or HIV status. In San Francisco, the proportion of MSM reporting CLS with one or more partners doubled between 1994 and 1999 and continued to increase into early 2000 [130, 138]. In London, the proportion of MSM reporting CLS with one or more casual partners more than doubled between 1998 and 2001 [126]. Rectal STI incidence (gonorrhoea, syphilis, and LGV) also increased significantly during the late 1990s and into early 2000 across Western European countries and in the U.S. [112, 127, 128, 143-156]. The first syphilis

outbreak among MSM was reported in Hamburg in 1997 [157] and was followed by large outbreaks in London, Paris, and Dublin [158-160]. The first outbreak of LGV among MSM was reported in Rotterdam in 2003 [161] and subsequent large outbreaks were reported in the UK and France [162-173]. Most cases of LGV and syphilis were among older, white, and HIV-positive MSM [162-173].

Mirroring the rise in CLS and STI incidence, an increase in HIV incidence was observed in Amsterdam [52], Vancouver [174], Ontario [175], London [176], and Rome [177] up to mid-2000. In Amsterdam, London, and San Francisco, although STI incidence increased overall among MSM, the increase in HIV incidence was only found among older (34 years or older), but not younger men [52, 148, 176, 178]. In London, the observed increase in HIV incidence from 1997-2004 among older men was not significant [176]. In any case, an increase in the uptake of HIV testing was observed during this period in London. It was suggested that this was most likely as a result of both newfound HIV treatment optimism and introduction of opt-out testing, whereby all patients were offered a test regardless of symptoms or risk factors [179, 180]. The number of HIV tests among MSM attending GUM clinics in London increased from 5114 in 1997 to 9387 in 2002 (84% increase). Elsewhere in England, Wales, and Northern Ireland, the number of tests increased from 5030 to 8864 (76% increase) and in Scotland from 1040 in 1997 to 2513 in 2004. Improvements in HIV reporting systems may have also contributed to the increase in number of diagnoses among MSM in the UK and elsewhere [176]. Furthermore, there is some evidence to suggest that men continued to practice HIV risk reduction strategies after 1996 [119]. Serosorting was widely reported among HIV-positive gay-identified men in New York, San Francisco, Montreal, Sydney, and London [100, 126, 181-184]. More men effectively practicing risk reduction may have explained the stable incidence of HIV among younger men, and at the same time, the rise in other STIs, for which transmission risk remained. Furthermore, surveillance data from the UK and Belgium suggested that a significant proportion of MSM diagnosed with syphilis were reporting recent oral sex without a condom [158, 159, 185, 186]. Although syphilis can be acquired through this sexual practice, it carries a substantially lower risk of HIV transmission than CLS. Together with the disproportionate circulation of syphilis and LGV among diagnosed HIV-positive MSM, these factors might help to further explain the stable incidence of HIV and also the rise in STI incidence observed among younger men between the period 1996 to mid-2000 [187]. The increase in sexual risk behaviour and STI incidence observed during the decade following the introduction of ART, reportedly began to stabilize in London [126], Sydney [188], and San Francisco [189].

Following the 'Swiss Statement' in 2008, there has been a clear and persisting increase in STIs and HIV diagnoses in Western Europe, the U.S., Canada, New Zealand, and Australia [15, 64, 142, 190-195]. Diagnosis of gonorrhea among MSM in England increased 32% from 2013 to 2014 (from 13,629 to 18,029) [193], and this increase is highly concerning given the risk for emergence of resistant strains of gonorrhea [196]. Furthermore, from 2013 to 2014, syphilis, chlamydia, and

genital herpes diagnoses among MSM in England increased by 46%, 26%, and 10% respectively [193]. In the U.S., the estimated number of new diagnoses of HIV infection among MSM rose from 27,001 in 2011 to 27,588 in 2012, 27,642 in 2013, and 29,418 in 2014 [194]. Increased uptake of STI and HIV testing cannot fully explain the rise in incidence [197]. It is of note, the apparent decline in HIV incidence observed among MSM in the UK in 2015 and steeper decline in some GUM clinics in London at the end of 2016, may reflect the use of PrEP (see section 1.3.3). Similarly in the U.S. the number of new diagnoses of HIV among MSM has declined slightly in 2015 to 26376 [198, 199]. In San Francisco, a free[iv] and easy-to-access PrEP programme has been rolled-out since 2014. The number of new HIV diagnoses dropped substantially to 255 in 2015 (17% decrease since 2014) and 223 in 2016 in San Francisco [200].

1.5.4.1 Quantifying the impact of changing community perceptions of HIV risk on condomless sex and HIV/STI transmission

Historically, trends in sexual risk behaviour have been attributed to the changed perception of HIV as a chronic and manageable rather than terminal illness and changed perception of transmission risk with HIV-positive sexual partners on treatment [106]. However, a number of longitudinal studies conducted in the Netherlands and U.S. reported conflicting results as to whether HIV treatment and transmission optimism is associated with sexual risk behaviour [131, 201-205]. Therefore, although it appears that gay communities reacted to the advent of ART and release of the Swiss Statement with changing perceptions of and methods of dealing with HIV, it is now generally accepted that at a population-level, HIV optimism alone is insufficient by itself to explain increases in sexual risk behaviour and STI/HIV incidence [129, 205-208]. It is perhaps possible, that even in the upcoming era of PrEP, trends in sexual risk behaviour may not be fully explained by changing perceptions of HIV transmission.

1.6 Sexual minority men and minority stress theory

The emergence of the HIV epidemic in the 1980s prompted an unprecedented medical and social interest into the sexual behaviour of sexual minority men, and sexual minority lifestyles in general, to assess the profound burden of HIV in these communities. One aspect of the new research agenda was the investigation of the impact of sexual minority status itself on health. The most widely used theoretical framework to culminate from this work is Meyer's minority stress theory [209-211], which describes stress processes in sexual minority populations. Key features of the minority stress theory are described below. The initiation of research into depression, its association with sexual risk behaviour, and possible mechanisms of association among sexual minority men, is presented in section 1.8. Of note, in-depth research into other psychosocial factors, which are recreational drug use and intimate partner violence, was also initiated as a result of the minority stress theory. Evidence for elevated prevalence of these

[iv] Support is provided to access full medical coverage.

psychosocial factors among sexual minority men and a link with sexual minority stress is presented in Appendix section 11.4. These psychosocial factors are defined and their association with sexual risk behaviour is described in the literature review of Chapter 2 (sections 2.5.3, 2.5.4, and 2.6.3.2).

1.6.1 Minority stress and its origins

1.6.1.1 History of violence against sexual minority men in high-income countries

Antigay state-sanctioned violence and discrimination has been perpetrated throughout history; from Nazi extermination of homosexuals to violent and often fatal enforcement of 'sodomy laws' [212]. Textbox 1 presents the timeline of political events concerning sexual minority men in the UK [213, 214]. Of note, until 1973, gay sexuality was characterised as a mental health disorder in the Diagnostic and Statistical Manual (DSM) of mental disorders, devised by the American Psychiatric Association for use in clinical practice. Men with 'homosexual tendencies' were sometimes subjected to shock/aversion therapy. These conditioning-based approaches, so-called 'reparative therapy', were proven unsuccessful and highly harmful in the 1980's [209, 215-217].

Textbox 1: Time-line of political events concerning sexual minority men in the UK up to 2014[v]

1967	England & Wales	Homosexual acts in private between men aged over 21 years were decriminalized
1973	U.S. (relevant to all high income countries)	Declassification of homosexuality as a mental disorder (DSM)
1981	Scotland	Homosexual acts in private between men aged over 21 years were decriminalized
1982	Northern Ireland	Homosexual acts in private between men aged over 21 years were decriminalized
1988	UK	Illegal for a local authority to "intentionally promote homosexuality or promote the teaching in schools of the acceptability of homosexuality as a pretend family relationship" (Section 28 of the Local Government Act)
2003	UK	Section 28 of the Local Government Act repealed
2004	UK	Civil Partnership Act passed
2010	UK	Illegal to discriminate against anyone based on a range of characteristics, including sexual orientation and gender reassignment status (Equalities Act)
2013	England & Wales	Marriage between same-sex partners approved
2014	Scotland	Marriage between same-sex partners approved

1.6.1.2 Conflict and prejudice

From the early days of Durkheim to the works of Pearlin, Merton, and Moss in the 20th century, social theorists have described the profound stress that occurs when an individual's values and experiences in the world are incompatible with social structures, norms and institutions. Minority persons are likely to feel conflicted, as mainstream cultural norms do not usually reflect those of the minority group [219-222]. Social comparison and symbolic interaction theorists describe the adverse consequences of negative social interactions. Perpetual negative feedback from others, such as stereotyping and prejudice, has the potential to lead to deep seeded negativity about the self, which may lead to poor mental health outcomes [223-225]. Prejudice is a noxious environment for minority individuals. In Meyer's minority stress model, homophobic taunts can lead to: (i) internalized homophobia, (ii) pervasive expectations of rejection, and (iii) non-disclosure of one's sexual orientation [209, 226-228]. These three elements will be discussed in more detail in the next section. In essence, to be in continual conflict with a discriminatory social environment is considered the source of minority stress [210, 229]. Minority stress is classified as unique, that is not a feature of stresses common to the general population, such as finances, but an additional, pervasive layer of stress that requires additional coping mechanisms. It is also

[v] On 31st January 2017 an amendment to the Policing and Crime Bill was passed ('Turings Law'), which posthumously pardoned thousands of gay and bisexual men convicted of consensual same-sex relationships. As part of this bill, statutory pardons will also be granted to the living.218. Gyimah S. Thousands officially pardoned under 'Turing's Law'. Ministry of Justice; 2017.

considered to be chronic and socially biased as it stems from social processes rather than individual events, such as losing a business [210, 230-234].

1.6.2 Objective and subjective stressors: the role of personal identification in Meyer's minority stress model

The social and personal meanings that are attached to sexual identities and the stress they entail varies from person to person. Stress may also be independent of self-identification with an assigned minority status. For instance, a man may have a male sexual partner but identity as heterosexual. If this man is perceived to be associated with gay sexuality, he may experience the same prejudices that self-identified gay/bisexual men are subjected to. In the minority stress model these have been termed as objective stressors. They are independent of an individual's perceptions and appraisals, as opposed to subjective stressors which are associated with self-identity as a sexual minority, and are characterised by the three cornerstones of the minority stress model: (i) internalized homophobia, (ii) expectations of rejection, and (iii) concealment [209, 226-228].

Internalized homophobia is a process of self-stigmatization by directing negative antigay social values/attitudes towards the self. It is internal and insidious, often resulting in deep conflict and poor self-regard, with negative consequences such as pervasive expectations of rejection in one's life. Due to the significance of early life socialization experiences, residual internalized homophobia may be a permanent fixture throughout a sexual minority individual's life-course. If individuals integrate a high degree of antigay attitudes into their perception of self, mental health problems may follow [211, 235-239].

Concealment of and secrecy around one's identity is often adopted as a coping strategy out of fear of the perceived negative consequences of disclosing a stigmatized identity. Although a common coping strategy, it is one that has the potential to backfire, as the constant preoccupation and cognitive effort involved in hiding one's identity is a heavy burden to bear, and can become highly stressful [227]. Expressing emotions and disclosing important aspects of oneself is profoundly important in maintaining physical and mental health. Inhibition and repression of one's thoughts and feelings have been shown to impact immune functioning and other health outcomes [240, 241]. Furthermore, concealment adds to mental distress by disallowing individuals to affiliate with others who are of the same sexual identity. Smart and Wegner (2000) describe the experience of concealment as a "Private hell" (page 229 [242]). Although in many regions of the world acceptance of sexual minority individuals has evolved considerably over the last few decades, concealment of sexual identity is not necessarily restricted to adolescence, but may be pervasive throughout adulthood as well. Concealment of sexual orientation is often prevalent in the work place for instance, with adverse consequences for psychological functioning and job-related outcomes [243, 244].

1.6.3 Minority stress and resilience

"Stress and resilience interact in predicting mental disorder" (page 679 [209]). The process of coming out for a sexual minority individual, which among this generation may often occur during adolescence, can be a highly stressful experience. In the minority stress model, there are three main factors which can ameliorate the effects of stress on psychological functioning through self-acceptance: (i) family support, (ii) personal resources including personality characteristics, and (iii) group resources/social structural factors including community solidarity and cohesiveness. Sexual minority communities counteract stress by establishing a social environment with alternative structures and values that validate the experiences and feelings of minority individuals. In social evaluation theory, group affiliation allows members to appraise themselves in comparison to other like-minded members, rather than members of the dominant culture [225, 245-247]. Therefore, identifying with a minority status, in itself, can ameliorate stress through opportunities for affiliation, social support, and coping. For individuals who do not identify as a sexual minority, but do engage in non-heteronormative behaviour, these opportunities for positive coping may not be available. Of note, factors (ii) and (iii) are greatly intertwined, since accessing community facilities greatly depends on personality variables. Similarly, where certain communities are forbidden and community services are hidden, as in many regions of the world, even highly resourceful persons will struggle with coping as a minority.

Stress related to sexual minority status does occur within the broader context of environmental circumstance, including the advantages or disadvantages related to an individual's socio-economic status. Therefore, socio-economic factors may also be a strong determinant of the degree of exposure to stresses and coping resources [248, 249].

1.6.4 Current social climate for sexual minority men in high-income countries

In many countries steps have been taken to abolish state-sanctioned discrimination against sexual minority individuals, including the Equalities Act in 2010 and approval of marriage between same-sex partners in 2013 in England and Wales (see Textbox 1). This legislation has most likely helped in reducing a climate of stigmatization and devaluation. However, 'coming out' may still remain a highly stressful experience for some sexual minority individuals due to rejection or fear of rejection by friends and family- reflecting that mainstream culture remains relatively heterosexist [250, 251]. Therefore, while the social and political environment may have changed dramatically over recent decades, reducing prejudice and conflict, there are certainly indicators that some individuals still experience discrimination and denigration in various contexts based on their sexual orientation (see section 1.8.1).

1.7 Depression: definition, prevalence, and management

1.7.1 Defining depression

This section (1.7.1.1 to 1.7.3.2) deals with a general definition of depression. The measuring of depression for research purposes is discussed in Chapter 2 (section 2.4.2).

1.7.1.1 Cognitive model of depression

Support for Aaron Beck's cognitive model of depression[vi] has gathered over the past 40 years of systematic research [252, 257-264]. The model proposed that the meaning assigned to early life stress such as parental loss or childhood abuse/maltreatment, can transform into durable negative attitudes and biases about the self, regarding personal adequacy, acceptability and worth. For instance, 'If I lose an important person, I am helpless' [262, 265, 266]. Dysfunctional attitudes/beliefs (unlovable, inadequate, worthless, helpless) are thought to become embedded within cognitive structures labelled cognitive schemas[vii] in the meaning assignment system. This results in cognitive vulnerability i.e. sensitization of individuals to later negative events [266]. When cognitive schemas are activated by an event, they distort the information processing system, producing an attentional bias, whereby, attentional resources are directed towards negative stimuli and negatively biased interpretations. The result is a systematic cognitive bias in information processing, leading to the symptoms of depression: sadness, hopelessness, loss of motivation, and regressive behaviours such as social withdrawal and inactivity [257, 262, 267, 268].

The impact of activated schemas depends on the intensity of a negative experience and the threshold for activation. Systematic stressful events can lower the threshold [267]. A full-blown major depression characterized by profound anhedonia (inability to feel pleasure in normally

[vi] Of note, a number of other models of depression have been theorized. Extending the cognitive model of depression, the model of triadic reciprocal causation dictates that individuals with depression tend to create depressing environments by constantly interpreting life events in pessimistic ways. This in turn often elicits negative reactions and evaluations from other individuals with whom they interact, ultimately validating the depressed individuals negative outlook on life. In the diathesis-stress model of depression, individuals are carriers of inherent vulnerabilities that under taxing stressors give rise to depression. Other models of depression include the biased causal explanations theory. Essentially, this theory is similar to the cognitive model of depression and observes that depression is a function of ascribing failures to personal deficiencies. Treatments based on these theories have not been widely developed, but instead rely on cognitive behavioural therapy 252. Young J, Rygh JL, Weinberger AD, Beck AT. Cognitive Therapy for Depression. In: Barlow DH, editor. Clinical Handbook of Psychological Disorders A step-by-step treatment manual. 4th ed. New York: Guilford Press; 2008, 253. Coyne JC. Essential papers on depression. New York: New York University Press; 1985, 254. Joiner TE, Jr. Contagious depression: existence, specificity to depressed symptoms, and the role of reassurance seeking. Journal of personality and social psychology. 1994;67(2):287-96, 255. Peterson C, Seligman ME. Causal explanations as a risk factor for depression: theory and evidence. Psychol Rev. 1984;91(3):347-74, 256. Bandura A. Self-efficacy. The exercise of control. New York: W.H. Freeman and Company; 1997..

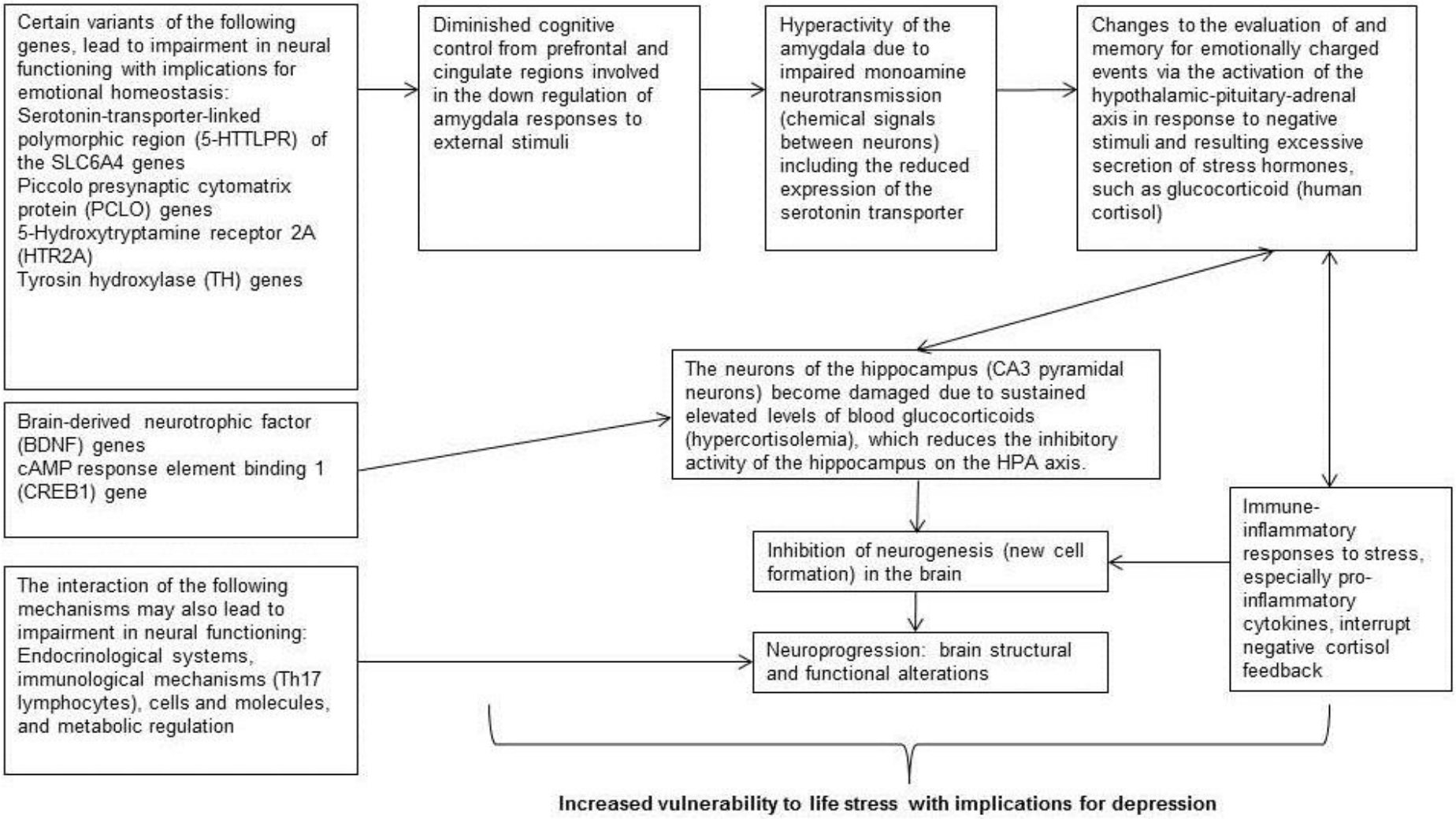
[vii] Cognitive schemas are mental concepts in cognitive psychology that represent constructions of reality (which are profoundly entrenched emotion-based beliefs) through early life experiences with significant others. Schemas remain dormant in the subconscious memory until activated by a life event. Stimulated schemas inform an individual about what to expect from a variety of experiences and situations 252. Young J, Rygh JL, Weinberger AD, Beck AT. Cognitive Therapy for Depression. In: Barlow DH, editor. Clinical Handbook of Psychological Disorders A step-by-step treatment manual. 4th ed. New York: Guilford Press; 2008.

pleasurable activities) and sleep and appetite disturbance, is different from that of depressive symptom episodes. Dysfunctional attitudes/beliefs may become integrated into affective (relating to mood and feelings), motivational, behavioural, and physiological, as well as, cognitive schemas. As a result of systematic activation, these schemas may become organized into a depressive *mode*, a network of negative schemas [257, 269]. A severe adverse event or accumulation of negative events may trigger the cognitive schemas that activate the other schemas. The activated mode takes complete control of the information processing system, which is evidenced by increased negative appraisals and rumination. At this time, resources are taken away from adaptive schemas such as coping and problem solving. When fully activated, the mode becomes relatively autonomous and is no longer sensitive to external events i.e. positive events do not attenuate negative thinking. The result is total immersion of the personality in a full-blown major depression. It has been suggested that adaptive schemas can be reactivated in cognitive behavioural therapy (CBT), as discussed below [262].

1.7.1.2 Parallels between biological and psychological concepts: genetic vulnerability and data from neurophysiological studies

Not all individuals subjected to traumatic experiences become depressed. There is some evidence to suggest that the presence of certain gene variations and their impact on neural functioning greatly influences the degree of cognitive vulnerability to depression. Figure 3 presents biological mechanisms which may predispose individuals to depression. In summary, biological predisposition may operate through the presence of genetic variants [270-282], suboptimal serotonergic neurotransmission, hyperactivity of the amygdala [283, 284] as well as changes to many other brain regions [256, 283, 285-294], sustained high blood concentrations of stress hormones [295-300], and inhibition of new brain cell formation together with metabolic/ endocrinological mechanisms [297, 301, 302] leading to a reorganizing of neural structures. For instance, studies have shown that the presence of the short variant of the 5-HTTLPR gene and subsequent neural functioning may sensitize individuals to life experiences and result in the formation of negative attitudes [265, 303-306]. In the cognitive model of depression, frequent activation of dysfunctional attitudes can lead to the symptoms of depression. A number of studies have found that individuals with the short variant of the 5-HTTLPR gene experience higher levels of clinically significant depression and suicidality [297, 307-312]. Questions have been raised however, about the generalizability of these findings [313]. Regardless, findings from genetic, neuroimaging, and neuroendocrine studies, do appear to complement the cognitive model of depression dictated by Aaron Beck decades previously. That is, the relationships between external stimuli, biological predisposition, neural dysfunction and depression established in the neuroscience literature appear to run parallel to the cognitive model of external stimuli, cognitive factors and depression established in the cognitive psychology literature.

Figure 3: Possible elements involved in biological predisposition to depression*



* References of studies from which this information was derived are presented in section 1.7.1.2 above.

1.7.1.3 Categories of depression

The most common form of depression is called unipolar depression. It is characterised by the presence of a number of typical symptoms for at least two weeks: feeling down, having difficulty enjoying things, feeling like one has to push oneself to get anything done, difficulty sleeping, exhaustion, loss of appetite, trouble concentrating, and feeling pessimistic about the future [252, 314]. The severity of the depression is determined based on how many symptoms are present and how severely an individual experiences them. Accordingly, depression can then be classified as mild, moderate, or severe [252, 314, 315].

There are chronic and non-chronic forms of depression [252, 314]. The latter may include a single episode or recurrent episodes with full recovery between episodes. Dysthymia is a chronic depressive disorder characterised as a milder change in mood, which is similar to depression, and lasts at least two years. Symptoms often include feelings of being unsettled, unhappy or down, but unlike depression, dysthymia does not affect everyday life- the symptoms may change from day to day and week to week [252, 314]. Clinical opinion suggests that the onset of dysthymia around mid-adolescence often determines the chronic nature of the depression [316, 317]. Furthermore, evidence from the U.S. National Comorbidity Survey (N=5877) suggests that chronic depression is more evident in individuals who experience a traumatic event in childhood/adolescence [318]. In a U.S. study of individuals with early-onset dysthymia (N=97), which incorporated annual semistructured interviews over a period of eight years, those who experienced early-onset dysthymia and early life trauma were more likely to present with an increase in depression severity over time compared to individuals with dysthymia and no early life trauma [317].

Some individuals may be particularly affected by depression during the darker winter months, known as seasonal affective disorder. Some mothers may experience depression after giving birth to a child (postnatal depression). Depression may also be a consequence of bipolar disorder. Bipolar disorder is characterised by alternating phases of extreme mood, with typical symptoms of depression in one phase and manic euphoria[viii] in another [252, 314].

1.7.2 Prevalence of depression in the UK

Depression is widespread and deeply debilitating. In the Adult Psychiatric Morbidity Survey (2014), 3.3% of 7500 adults (16 years and older) residing in private households in England were classified as having clinically significant symptoms of depression in the week prior to an interviewer administered structured interview using the Clinical Interview Schedule-Revised (CIS-R). Of the 15.7% of adults who were classified as having a common mental health disorder of clinical significance by CIS-R (including depression, generalized anxiety disorder, phobias,

[viii] Characterized by extreme activity with little sleep, self-confidence to the point of delusion, and irritability.

obsessive compulsive disorder, or panic disorder), 67.2% self-reported that they had experienced depression at some point in their lives [319, 320].

1.7.3 Managing depression

Professional help is most often needed to overcome the symptoms of depression and to assess possible suicide risk, safeguarding concerns, and adherence and response to treatment [315, 321].

1.7.3.1 Psychopharmacological interventions

The pharmacotherapist intervenes at the neurochemical level. In the UK, antidepressants are prescribed for individuals with moderate to severe depression, often in combination with psychosocial treatment. Textbox 2 presents common antidepressants prescribed in the UK [315, 321].

Textbox 2: Common antidepressants prescribed in the UK

First line treatments:	Generic selective serotonin reuptake inhibitors (SSRI) *citalopram, sertraline, fluoxetine, or paroxetine*	Block the reabsorption of serotonin by nerve cells in the brain in order to increase levels of serotonin
Second line treatments:	Tricyclic antidepressants and non-reversible monoamine oxidase inhibitors *lofepramine and phenelzine*	Block the reabsorption of serotonin and norepinephrine
Other treatment strategies:	Combination therapy or augmentation with lithium	Help increase serotonergic neurotransmission

Although antidepressant treatment is widespread, there are some significant concerns. Many antidepressants are cardiotoxic and weaken the heart [322, 323]. It is also estimated that even among individuals who initially respond to an antidepressant, about one in three patients will experience a worsening of their symptoms over the subsequent six months [324]. In a recent meta-analysis of four trials, in which all participants were initially treated with SSRIs and were then randomized to placebo or continued SSRI treatment, SSRIs were found to have a modest (13% higher) protective effect against relapse compared to placebo [324].

1.7.3.2 Psychosocial interventions

The psychotherapist intervenes at the cognitive, affective, and behavioural levels [256, 325]. In general, psychotherapy seeks to restore a sense of personal capability to do the things that

provide satisfaction and purpose to one's life [326, 327]. Beck's development of CBT, based on the cognitive model of depression described in section 1.7.1.1, is the most studied, validated and clinically applied work on depression psychotherapy [252, 263, 264]. CBT includes two major components: (i) analysis of erroneous assumptions, inferences, and conclusions in the routinized faulty habits of thinking and (ii) graded behavioural assignments to disconfirm misbeliefs, provide mastery experiences that affirm personal capabilities, and restore positive self-evaluations. In a U.S. controlled trial, where outpatient individuals aged 18 to 70 years with major depressive disorder (N=240) were randomized to receive an SSRI, CBT, or placebo (double blinding in the treatment arm), therapy was found to be as effective as medication in terms of depression severity and rates of remission. It was noted that the degree of effectiveness of therapy depended on the level of therapist experience/expertise [328]. CBT is not however without its controversies [252]. In a meta-analysis, CBT was not found to be superior to non-cognitive psychotherapy treatments on child and adolescent depression [329]. Nevertheless, the risk of depression relapse has been found to be highest for individuals who respond to antidepressants without the support of any form of psychotherapy [330, 331].

1.8 Sexual minority men and depression

In this section (1.8.1 to 1.8.2), evidence regarding the prevalence of depression among sexual minority men and its association with sexual risk behaviour is described. In sections 1.8.3 to 1.8.4, the possible mechanisms by which depression might lead to sexual risk behaviour are presented.

1.8.1 Studies comparing the prevalence of depression between sexual minorities and their heterosexual counterparts in high-income countries

There appears to be consistent evidence that depression prevalence is elevated among sexual minority men compared to their heterosexual counterparts in high-income countries. One meta-analysis has investigated studies conducted from 1996-2005. Among 160 gay, bisexual, and other MSM, the lifetime prevalence of depression was found to be higher compared to that in 6010 other men (pooled prevalence ratio [PR] 2.58 95% CI: 1.92, 3.47), and the prevalence of depression in the past year was similarly elevated (pooled PR 2.41 95% CI: 1.80, 3.23). Studies included three population-based surveys from the U.S. and one population-based survey from Western Europe: the third National Health and Nutrition Examination Survey, National Comorbidity Survey, McArthur Foundation National Survey of Midlife Development in the United States, and the Netherlands Mental Health Survey and Incidence Study [332].

A recent systematic review has synthesised findings from 199 studies (using a range of measures of depression), the vast majority of which were from the U.S. Studies of adults residing in private households in the U.S. included the Behavioral Risk Factor Surveillance

Study [333], California Quality of Life Survey[334], National Health Interview [335], National Epidemiologic Survey on Alcohol and Related Conditions [336], and National Health and Nutrition Examination Survey [337]. The review reported elevated levels of depression (as well as generalized anxiety disorder) among lesbian, gay- and bisexual-identified individuals in the vast majority of their reviewed studies. Elevated prevalence was observed across these different orientations compared to heterosexual [338].

A number of recent studies of adults residing in private households in Western European countries have also investigated the prevalence of depressive symptoms among sexual minority individuals: the 2007-2009 Netherlands Mental Health Survey and Incidence Study (NMHSIS, N=6646) [339], the 2006 Context of Sexuality in France study (CSF, N=9622) [340], the 2007 Adult Psychiatric Morbidity Survey (APMS, N=7403) [341], and the 2010-2012 British National Survey of Sexual Attitudes and Lifestyles (Natsal-3, N=6293 men) [342]. The sample size of the sexual minority sub-group ranged from 60 in NMHSIS [339] to 190 individuals in Natsal-3 [342]. Depression was measured using the Composite International Diagnostic Interview (symptoms in the past year) in NMHSIS [339], self-report of feeling depressed in the past year in CSF [340], the CIS-R (symptoms in the past week) in APMS [341], and a shortened version of the Patient Health Questionnaire (PHQ-2, symptoms in the past two weeks) in Natsal-3 [342]. The prevalence of depression was found to be significantly higher among sexual minority individuals, including after adjustment for socio-demographic factors in APMS [341]. For instance, the prevalence was 39.0% among gay-identified men and 28.1% among bisexual-identified men for self-reported depression in CSF [340], and 4.1% among gay- and bisexual-identified men and women on the CIS-R in APMS [341]. The comparable prevalence of depression among heterosexual identified individuals was 17.0% [340] and 2.7% [341] in CSF and APMS respectively. Furthermore, the prevalence of major depression on the Composite International Diagnostic Interview was elevated among men who reported sex with men in the past year (at 9.0%) in NMHSIS [339] and the prevalence of depression on the CIS-R was elevated among individuals who reported any same-sex partners (at 4.0%) in APMS [341]. In Natsal-3, although the prevalence of depressive symptoms on the PHQ-2 was similar among men who reported sex with a man in the past five years compared to men who did not, the MSM group was more likely to self-report having received treatment for depression in the past year, including after adjusting for age (14.0% vs. 5.8%, OR 2.75 95% CI: 1.69, 4.47; $p<0.001$) [342].

1.8.1.1 Minority stress and depression

Although certain factors described above in section 1.6.3 can ameliorate the effects of stress on psychological functioning, the minority stress theory may explain why the prevalence of depression is elevated among sexual minority men [339, 340] [338, 343-345]. In the 2007 APMS, 4.9% of sexual minority individuals reported discrimination on the grounds of sexuality, compared to 1.6% of heterosexual identified individuals ($p<0.001$). Among sexual minorities, unfair treatment perceived to be due to sexual orientation was associated with depression (OR 6.95 95% CI:

2.74, 17.67). The same was true among individuals reporting any same-sex partners (OR 7.91 95% CI: 2.90, 21.58) [341]. Studies of U.S. MSM have also found associations between perceived discrimination on the basis of sexual orientation and depressive symptoms [346, 347].

Although MSM may be at increased risk for mental health disorders, it is possible that the gap will close over time as the legal and social landscape of sexual minority communities progress and stigma diminishes. It may then be that the major factors associated with depressive symptoms mirror those found for heterosexuals, namely, socio-economic hardship [348-351].

1.8.2 Association between depression and sexual risk behaviour

One meta-analysis of studies published up to 1999, has examined the association between depression and CLS among MSM [352]. Findings across studies were inconsistent and in combined estimates there was no significant relationship of depression with measures of CLS. The vast majority of included studies were conducted in the U.S. In studies conducted up to 2014, there was evidence that depressive symptoms were associated with higher prevalence of CLS (including with multiple partners and partners of an unknown or sero-different status) [353-368] and with HIV seroconversion [369] among samples of MSM. A number of studies failed to find an association [346, 347, 370-373]. Two studies were conducted in Europe; one in the UK (1999) [355] and the other in Belgium (2008) [358], both studies finding an association between depressive symptoms and measures of CLS. These studies were identified via a comprehensive literature search of all high-income country studies (in the regions investigated in this thesis) on sexual behaviour among MSM samples including HIV-negative MSM. The purpose and findings of the thesis literature review are presented and discussed in detail in Chapter 2.

1.8.3 Mechanisms by which depression leads to sexual risk behaviour

There may be a number of explanations for how depression may lead to sexual risk. The main explanations involve elements of feeling unable to maintain or 'not caring' about sexual safety. The behavioural consequences of depression have been described in two theories: social cognitive theory and cognitive escape theory, described below.

1.8.3.1 Depression and behaviour: social cognitive theory

Albert Bandura began to publish work on his social cognitive theory in the 1980s. Social cognitive theory aimed to describe how cognitive activities can be used to explain and encourage behavioural adaptation and change[ix]. Personal agency is the capacity to create

[ix] Of note, in addition to social cognitive theory there are two other models commonly used to theorize pathways leading to behavioural change. These are the health belief model and the theory of reasoned action/planned behaviour. The health belief model explains behavioural choice as a function of the perceived gains and losses, whereby attitudes to and perceptions of the outcome of this behaviour are emphasised. In the theory of reasoned action/planned behaviour, behaviour is a function of intentions, which are governed by behavioural and social norms and attitudes 374. Fisher WA, Fisher JD, Rye BJ. Understanding and promoting AIDS-preventive behavior: insights from the theory of reasoned action.

action. Social cognitive theory rejects the dualistic notion of the self, whereby one is considered an agent only when acting or managing one's environment. This theory dictates that individuals are also agents when they are "reflecting on their experiences and exerting self-influence" (page 5 [256]). The latter is termed 'beliefs of personal efficacy' or simply, 'self-efficacy', and it is said to constitute the key factor of agency. Essentially, if an individual does not perceive that they have the capacity to produce a certain outcome, then they will not attempt to make it happen[x]. How one judges one's personal efficacy is thought to come about through a complex interaction of "microsensory, perceptual, and information processing activities" (page 4 [256]).

Feeling hopeless about the future is one of the key features of depression. Hopelessness runs in parallel to perceived inefficacy in gaining highly valued outcomes. In line with the cognitive model of depression, in social cognitive theory, depression is thought to stem from a perceived inefficacy to change adverse/traumatic life circumstances [256, 262]. Depression may also perpetuate a feeling of being incapable of influencing events and social conditions that significantly impact on one's life. Bandura suggests that repeated self-devaluation and demoralizing/disparaging thoughts breed depression, which in turn further diminishes an appreciation of one's better qualities and enhances self-critical reactions and reduces self-rewarding ones, leading to a lower sense of self-efficacy [256].

1.8.3.2 Self-efficacy for sexual safety

When navigating sexual risk reduction, individuals have to exercise control over themselves as well as their partners. Although sexual knowledge and favourable attitudes towards condom-use are important, following a social cognitive perspective on behavioural management, the main requirement for effective sexual risk reduction is perceived self-efficacy to exercise control in interpersonal relationships [379, 380]. There are a number of psychosocial factors that may lower one's sense of efficacy to exercise self-protective control in sexual situations; drug and alcohol use, experiences of sexual coercion/abuse, and perhaps most commonly, depression [256, 381-387].

Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 1995;14(3):255-64.
375. Carmel S. The Health Belief Model in the research of AIDS-related preventive behavior. Public health reviews. 1990;18(1):73-85, 376. Aggleton P, O'Reilly K, Slutkin G, Davies P. Risking everything? Risk behavior, behavior change, and AIDS. Science (New York, NY). 1994;265(5170):341-5.
377. Mustanski BS, Newcomb ME, Du Bois SN, Garcia SC, Grov C. HIV in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions. J Sex Res. 2011;48(2-3):218-53, 378. Wulfert E, Wan CK. Safer sex intentions and condom use viewed from a health belief, reasoned action, and social cognitive perspective. Ibid. 1995;4:293-305.

[x] Of note, Bandura states that the concept of self-efficacy is not the same as the concept of self-esteem, as feelings of self-worth and value do not always equate to positive beliefs of personal efficacy, and similarly, perceived inefficacy to produce a certain outcome is not always associated with a low self-esteem. Therefore, these concepts although similar are not the same. 256. Bandura A. Self-efficacy. The exercise of control. New York: W.H. Freeman and Company; 1997.

1.8.3.3 Interventions to improve self-efficacy for sexual safety

There is some evidence to suggest that learning self-regulative skills greatly improves one's sense of efficacy to resist peer pressures and exert control in interpersonal relationships i.e. negotiate condom-use. Self-regulation is a function of internal standards and evaluative reactions to behaviour. Self-regulation may include motivation through self-incentives or other such forms of cognitive self-guidance. Obtaining self-regulative skills may involve learning how to cope with/successfully manage potentially adverse situations. Bandura suggests this is best achieved by being guided through experiences and equipped with the knowledge and skills needed to effectively exercise control over risky situations, thereby fostering a sense of mastery [(256)]. Research by Kelly (1995) [(388)] produced formative work on the effectiveness of self-regulatory programmes for self-protective sexuality through improvement of perceived efficacy to exercise personal control over sexual practices.

1.8.3.4 Depression and behaviour: cognitive escape theory

In cognitive escape theory, individuals turn their attention away from threatening cues, completely or partially escaping from personal self-awareness. The cognitive escape model suggests that for behaviours that are desirable, such as sex (for reasons of physical pleasure as well as seeking connectedness and acceptance), the rational process by which perceived risk of HIV/STIs might result in subsequent behavioural response such as condom-use, may be reversed.

Sensation-seeking and HIV-related worry may represent two pathways leading to sexual risk-taking via cognitive escape coping. Sensation-seeking (and sexual compulsivity) is a personality characteristic that is associated with impulsive behaviour [(389, 390)], as described in Appendix section 11.4.1.1, and has been established as a theoretical precursor to cognitive escape [(391)]. Men with this personality trait may be 'determined' to perceive themselves to be at low risk irrespective of the circumstances, and as such may avoid or be unable to adequately respond to information to the contrary, in order to escape from restrictive sexual norms [(392, 393)]. This first pathway takes the form of suppression of and/or distraction from any thoughts that extend too far into the future.

Many gay and bisexual men enter and conduct their sexual life-course against the backdrop of HIV. HIV related worry is facilitated by pervasive prevention messages. The lack of a cure or vaccine means that there is no imminent end to demands for sexual safety. It has been posited that fear may make some men 'determined' to perceive the threat of HIV infection to be uncontrollable, in order to escape from worry and conduct their sex lives unhindered by stress [(394-396)]. This second pathway takes the form of fatalistic beliefs about HIV- the notion that acquiring HIV is inevitable.

Cognitively escaping from awareness of HIV risk and sexual norms may make men particularly vulnerable to STI/HIV transmission [397]. Cognitive escape has been linked, theoretically, to CLS [396, 398]. Cognitive escape may be facilitated by highly stimulating sexual contexts and drug use. The relationship between drug use and cognitive disengagement (including both thought suppression/short-term thinking and fatalistic beliefs) is most likely bi-directional [397, 399].

1.8.3.5 Depression, lowered self-efficacy for sexual safety, and engagement in cognitive escape: implications for sexual risk-taking

Conceptually, cognitive escape and self-efficacy are linked. Low self-efficacy for coping is thought to make escape tendencies more likely. The perceived lack of control in interpersonal relationships (low self-efficacy for sexual safety) may translate into the belief that failure to protect oneself is inevitable. The threat of sexual transmission of HIV, which is viewed as personally uncontrollable is then tuned out (cognitive escape) [400]. In the self-regulation and coping literature on sexual minority men, an established hypothesis is that those who experience depressive symptoms may be more likely to engage in escapism as a coping strategy, characterised by fatalistic beliefs such as helplessness or powerlessness in the face of the HIV threat [397, 401-404]. The thesis hypothesis is presented in detail in section 1.9.1.

1.8.4 Investigating mechanisms of association between depression and CLS in epidemiological studies

Project Mix (2004-2006) is the only high-income country study (U.S.) of MSM (N=1540) [362] to have investigated mechanisms of effect for the relationship between depression and CLS. There was support from this study for lowered self-efficacy and cognitive escape as such mechanisms. Findings from Project Mix are discussed in detail in Chapter 2 section 2.4.8 and Chapter 6 section 6.4.2.

1.8.5 Anxiety and thoughts of suicide/self-harm

This thesis focuses on depression, and as such, the literature review presented in Chapter 2 examines studies of depression. However, findings on the association between generalized anxiety disorder (GAD) and sexual risk behaviour, and suicidal ideation (thoughts/planning of suicide)/thoughts of self-harm and sexual risk behaviour are also presented in this thesis. These findings will be discussed in the context of the findings on depression.

Historically, GAD has received very little clinical and research attention compared to other common anxiety disorders (including panic disorder and post-traumatic stress disorder) and depression. GAD was first described in the third edition of the DSM in 1980. Since this time, the definition of GAD has undergone frequent revision. GAD was originally associated with fairly minimal impairment in psychological functioning. It is now understood that some individuals have a temperamental predisposition to worry, which may be exacerbated by stressful life

events resulting in excessive, uncontrollable, and chronic worry [252, 405]. Based on data from the World Mental Health (WMH) surveys in the U.S., Australia, and New Zealand (N=30532), the lifetime prevalence of GAD was estimated to be around 8% [405]. Based on data collected from WMH surveys in 26 countries between 2001-2012 (N=147261), the majority of individuals with lifetime (81.9%) and 12-month (70.8%) GAD had at least one comorbid mental health disorder. Major depression was the most common comorbidity, found in 52.6% of lifetime GAD cases and 40.9% of 12-month GAD cases [405].

Literature on self-harm and suicide is vast. Briefly, self-harm tends to first occur during adolescence. In a systematic review of studies of adolescent samples, published between 2005 to 2011, the mean life-time prevalence of self-inflicted injury was 18.0% across studies [406]. Based on data collected from WMH surveys in 17 countries (N=84850), the prevalence of suicidal ideation was estimated to be around 9.2% [407]. Recurrent thoughts of death are a common symptom in a major depressive episode [408]. Depression is the psychiatric diagnosis most commonly associated with suicidal ideation and suicide [409].

1.9 Thesis rationale

The literature review conducted in Chapter 2 demonstrates some evidence of a relationship between depressive symptoms and sexual behaviour among MSM. The association and magnitude of effect may vary according to the setting and specific sample of MSM under study. It remains unclear in which samples of MSM the relationship is present and there is no general consensus on the magnitude of the effect. Furthermore, the vast majority of studies have been conducted in the U.S. There is a lack of data in Europe, including the UK. Psychological symptom distress has been found to be associated with CLS among HIV outpatients in the UK [410-414]. Although HIV prevention has been a public health priority among MSM in the UK/Europe, mental health has not generally been a focus of European studies of HIV/STI risk and prevention among sexual minority men. The health care infrastructure is different in the U.S. and UK and mental health facilities and services may also differ, with implications for the treatment and prevalence of depression. The potential role of depression in sexual health and transmission of HIV is not well understood in the UK.

Additionally, there is a lack of research in the U.S. and no UK/European studies into the mechanisms by which the relationship between depressive symptoms and sexual behaviour operates. Therefore, implications for intervention remain uncertain. Current research into the mechanisms through which the association between depression and CLS operates is needed.

Only recently a small number of UK studies have begun to examine the prevalence of depressive symptoms among sexual minority men: Natsal-3 (2010-2012; N=190) [342], The Stonewall Gay & Bisexual Men's Health Survey (2011; N=5416) [415], survey of MSM recruited

online (2016; N=179) [416], and survey of MSM recruited from a GUM clinic (1999; N=122) [355]. In most of these studies, the sample size was too small to allow for meaningful analysis of associated factors. Until 1973, gay sexuality was cited in the DSM as constituting a mental health disorder. Research into psychological distress among sexual minority men has been a politically charged area, so as not to perpetuate the pathologizing of gay men. This may account for the lack of research into the prevalence of mental health conditions and associated factors among sexual minority men in the UK. However, in recent years there has been a visible shift in the UK research agenda to address mental health & wellbeing among the general population and sexual minorities in particular, for whom it is being increasingly recognized that the burden of psychological distress may be higher. The prevalence of depressive symptoms and association with socio-demographic, lifestyle, and psychosocial factors needs to be further investigated among sexual minority men in the UK. The specific objectives for each of the remaining chapters included in this thesis are presented in section 1.1.2.

1.9.1 Thesis hypothesis

Given the self-regulation and coping literature on depressive symptoms, it is hypothesized that among a group of gay, bisexual, and other MSM, depressive symptoms would be associated with increased sexual risk behaviour, in other words increased levels of CLS. This relationship is hypothesized to be partially but not fully confounded by recreational drug use, childhood sexual abuse, and intimate partner violence (as discussed in section 3.5 of Chapter 3). Low self-efficacy for sexual safety is hypothesized to be on the casual pathway between depression and sexual risk behaviour. More specifically, a depressive syndrome (be it chronic or episodic) is often associated with feelings of personal inadequacy, worthlessness, and hopelessness/loss of motivation. In terms of one's sex life, it is hypothesized here that depressive symptoms lower one's perceived ability to exercise self-protective control in sexual situations where this is desired. Furthermore, it is thought that this perception may for some individuals translate into the notion that acquiring HIV is inevitable- a fatalism towards one's sexual health. This form of 'escape coping' and resultant lack of self-regulation, may increase the chances of potentially risky sexual situations.

1.9.2 The AURAH and PROUD studies

This thesis investigates two studies, firstly, the Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH) study and secondly, the PROUD trial. AURAH is a cross-sectional study of HIV-negative or unknown status individuals attending 20 GUM clinics across England from 2013 to 2014 [417]. It is the largest study of HIV-negative MSM attending GUM clinics in the UK (N=1484). Findings will be useful in informing intervention and prevention programmes that aim to reach these target populations. Participants were asked to self-complete a confidential questionnaire that collected detailed information on socio-demographic, lifestyle, health, and sexual behaviour measures. Included as part of this questionnaire, was the PHQ-9, a common

instrument used to measure self-reported depressive symptoms in clinical and research settings.

The Pre-exposure Option for reducing HIV in the UK, the PROUD trial, assessed the effectiveness of PrEP [80]. PROUD was an open-label, randomized controlled trial at 13 GUM clinics across England. To be enrolled, men had to be HIV-negative and report a specific behavioural profile: CLS in the previous three months and be of the opinion that they would have CLS in the next three months. From 2012-2014, men were randomly assigned (1:1) to receive PrEP (245mg of tenofovir disoproxil and 200mg of emtricitabine) at enrolment (n=275) or after a period of one year (n=269). Follow-up continued for at least two years, until 2016. At baseline, socio-demographic, lifestyle, and sexual behaviour data was collected. The PROUD trial also incorporated the PHQ-9 at baseline and as part of the subsequent annual questionnaires. At follow-up, psychosocial data, including that on internalized homophobia, age at anal sex debut (sex at a very young age may include experiences of childhood sexual abuse [CSA]), and intimate partner violence (IPV), was collected. As described in detail in Chapters 2 (section 2.6.3.2) and 3 (section 3.5), the latter two of these factors together with recreational drug use are hypothesized in this thesis to confound the relationship between depressive symptoms and sexual risk behaviour.

Measurement of depressive symptoms in two large MSM samples of differing behavioural profiles in England over a recent time period, in AURAH and PROUD, offers the fortuitous opportunity to investigate prevalence and correlates of depression, and the relationship with sexual risk behaviour in both studies, and to compare findings. PROUD also adds to findings from AURAH by allowing an investigation into the association between markers of internalized homophobia and depression, and the relationship between depressive symptoms and sexual behaviour adjusted for recreational drug use, a young age at anal sex debut, and IPV. In addition, as a longitudinal study, PROUD also provides the opportunity to investigate changes in depression prevalence over time. The weaknesses of AURAH and PROUD in addressing the thesis hypothesis are discussed in Chapter 3.

Chapter 2

2 Literature review

2.1 Aims

This chapter presents a review of quantitative studies, for which the aim was two-fold. Firstly, to investigate the relationship between depression measures and sexual behaviour among samples of MSM including HIV-negative MSM in North America, Western Europe, Australia, and New Zealand. Secondly, to investigate the prevalence of CLS measures and their association with other factors among MSM in UK studies including HIV-negative MSM.

2.2 Introduction

2.2.1 Rationale for literature review

As stated in section 1.9, the relationship between depression and sexual behaviour remains unclear. In particular, there is a need for systematic documentation of relevant studies, to investigate in which samples of MSM the relationship between depressive symptoms and sexual behaviour is present and to assess the magnitude of the effect, and to gain insights into mechanisms of effect. All studies that have investigated the link between depression and sexual behaviour among MSM in high-income countries will be reviewed in the first section of this chapter (review i). Studies will be reviewed according to recruitment site and in the context of key sample characteristics, including the prevalence of sexual behaviour, in order to better understand in which contexts the relationship is present.

For the second section of this chapter (review ii), all UK studies that have investigated sexual behaviour among HIV-negative MSM will be further reviewed. The aim of this section is to: (i) describe differences in the prevalence of CLS measures across recruitment sites, in order to suggest, based on information from review (i), in which UK samples depressive symptoms may be associated with increased sexual risk behaviour, and (ii) describe factors that have been investigated and found to be associated with sexual behaviour among MSM in the UK. This is useful in identifying potential confounding or mediating factors when assessing the relationship between depression and sexual behaviour.

In the proceeding sections, study designs, sampling strategies, and methods of data collection that have been commonly used in survey studies of MSM are presented, as this is crucial to understanding the terminology used throughout reviews (i) and (ii).

2.2.2 Rationale for quantitative studies of MSM

MSM remain the group at greatest risk of sexual acquisition of HIV in high-income countries **[15, 43, 64, 142, 190-197]**. There is a need for systematic quantitative research on large groups of MSM in order to gather information on self-reported sexual risk behaviour that is relatively precisely estimated. This is required to guide public health planning, programming, and funding for HIV prevention efforts. It is of note however, that quantitative research is limited in its capacity to elicit deeper insights into behaviour, perceptions, feelings, and understanding. For this, qualitative approaches to research may be required, whereby texts and images, alongside numbers and statistics, are analysed in order to decode, translate, and come to terms with the meaning of social phenomena [418].

2.2.3 Study design

Different study designs can be chosen in order to satisfy the research question. Broadly speaking, if the research question concerns the prevalence of a behavioural/biological factor, then a cross-sectional design is satisfactory. In a cross-sectional study, all factors are measured at one time. Such a study gives a 'snapshot' of a population and involves no follow-up. If the research question concerns incidence, a longitudinal study (cohort or interventional) is required. In a longitudinal study participants are followed over time. In the simplest design, two cohorts of participants without the outcome of interest, one with the exposure of interest and one without, are followed over time with repeated or continuous monitoring of the outcome. The incidence rate of the outcome is then compared between the exposed and unexposed cohorts. Confounding can be accounted for by matching the unexposed cohort to the exposed cohort on key socio-demographic factors or by measuring known confounders and adjusting for measures in statistical analysis. In interventional longitudinal studies, confounding can be controlled for via the randomization of participants to the intervention or control group. The occurrence of confounding factors would theoretically be equally distributed between groups [419]. Cross-sectional designs usually require fewer resources and are less time constraining than longitudinal study designs. Cross-sectional studies have been most commonly used to assess sexual behaviour among MSM [419].

When interpreting findings from different study designs, it is important to consider temporality. If a study aims to assess the relationship between an exposure and an outcome, ideally it should be known that the exposure was present before the outcome occurred. A cross-sectional survey cannot usually evaluate the temporality of an association as it is often not possible to conclude with confidence that the exposure preceded the outcome, since both the exposure and outcome were measured at the same time. The exception being, for exposures that are fixed from birth or those that are likely to be fixed from a relatively early age, including ethnicity, sexual identity, and level of education.

2.2.4 Sampling strategies for studies of sexual behaviour among MSM

In the context of survey research, MSM constitute a 'hard-to-reach' population. A 'hard-to-reach' population is often made up of relatively few individuals and sampling is complicated by the lack of a contact list or register of some kind for all members (the sampling frame). Population-based research requires a sampling frame and provides the most unbiased estimates at a population level. Sampling strategies that involve recruiting a representative sample of MSM from the general population cannot be done since no such contact lists are available. It is possible to use a large population-based research study in order to obtain a subset of MSM. However, this approach may not be feasible, as a very large sample needs to be recruited to obtain a sufficient number of individuals with relatively uncommon characteristics [420, 421]. Researchers can also use a general population sample but actively boost the number of participants with certain characteristics.

2.2.4.1 Study setting

The most common approach to sampling a 'hard-to-reach' population is for the researcher to identify a location in which individuals of interest are conveniently available. A convenience sample is one that is easily accessible i.e. attendees at an event or venue or a self-selection of individuals volunteering to participate. Volunteer samples are ones in which individuals respond to study advertisements such as on posters, in newspapers, or on the Internet [422-424].

In research related to MSM, a common approach is the recruitment of men who have contact with sexual health services. Another approach is to recruit men from gay cafes, bars, clubs, saunas, and other venues on the gay scene, or from community events/venues associated with sexual minority communities [120]. These approaches to recruitment only reach men who attend the particular recruitment site and are more likely to recruit those who are regular attenders. The emergence of the Internet provides another common way of recruiting MSM for behavioural research. Large numbers of men can be recruited in this way. However, the major disadvantage to Internet studies is that the number of men who came into contact with the online advertisement but chose not to self-select for participation, and as such the characteristics of these individuals, is unknown.

2.2.4.2 Sampling method

There are a number of methods that can be used to select a sample, not all of which are equal in their ability to select samples that are representative of the target population. They fall into one of two categories: probability or non-probability sampling methods. Probability sampling methods require a sampling frame. There are a number of ways in which a probability sample can be selected from a sampling frame, including simple random sampling in which every individual has the same probability of being selected for the sample. Simple random sampling is the gold-standard but may be impractical or too expensive. In some instances researchers may

want to include individuals with relatively rare characteristics in the sampling frame, for which the research question is of particular interest. In this case, a random selection method called stratified random sampling is employed. Researchers assign a greater than simple random probability of selecting units with particular characteristics i.e. different sampling probabilities are employed across strata. Another method, called systematic random sampling is similar to simple random sampling but does not involve separate random selection of each unit. A sampling interval is first calculated. For instance, if the sampling frame consisted of households, the number of households in the population divided by the number of households required for the sample would be calculated to generate the sampling interval. A random household number would then be selected between one and the sampling interval as the starting point. The sampling interval number is repeatedly added to select subsequent households [422]. Stratified and systematic random sampling methods can be combined in a two stage process i.e. a sampling frame can be separated into strata and units then systematically sampled from the strata. This is called multistage sampling and can include various other random sampling methods, through two or more stages [422]. Since probability samples can assign probability values of being selected for the study, the strength of the study sample with regards to generalizability i.e. the external validity, can be assessed [422].

Non-probability sampling does not require a sampling frame. Selecting a convenience sample involves non-probability sampling methods, with the exception being that two techniques are able to approximate probability-based sampling methods. These two techniques are discussed after the non-probability forms of sampling. In a convenience sample, one common method of selection is consecutive selection of participants. Another form of non-probability sampling, which allows for a number of different techniques, is purposive sampling. This method selects members of a convenience sample who have particular characteristics of interest to the research question. Selected participants can be asked to recommend people they know with the desired study criteria, called 'snow-ball sampling'. Purposive sampling can also be used to include an array of subject characteristics in predefined proportions, called quota sampling. Taking measures to over (or under) represent particular individuals may reflect a need to simulate the actual proportion in the target population (proportional) or, more commonly, may be used for analytic reasons (disproportionate).

There are two techniques which are sometimes used in research on MSM that can approximate probability-based sampling methods. These are time-location sampling (TLS) and respondent-driven sampling (RDS) [425, 426]. In TLS and RDS, the probability of selection is not known *a priori*, however weightings are calculated after data collection in order to determine, *a posteriori*, the probability of selection [424, 427]. For instance, in TLS, a complete list of venues visited by the target population and the times at which they are visited is drawn up [424]. These are called venue-day-time units (VDTs). [421] These units make up a sampling frame. A simple random sample (or stratified sample) of the VDTs is selected. Individuals at these VDTs are

consecutively sampled. In order to approximate a probability-based sample, weightings that correct for differences between individuals in terms of the frequency with which they attend venues are then calculated.[425] The RDS method begins with a small number of peers, recruited purposively from the target population, called 'seeds'. The 'seeds' recruit the first wave of participants who in turn recruits the second wave.[428] The survey ends when the desired size of the sample is reached. To establish weightings it is necessary to collect information on the size of each individuals network [424, 429].

Regardless of whether probability or non-probability methods of sample selection are utilized, a convenience sample is biased since the members of it have self-selected and are all similar in at least one way. Therefore, any results will only be truly generalizable to those individuals reachable in a convenience sample [422].

2.2.5 Method of data collection

The only feasible method of collecting data on sexual behaviour in quantitative research is by questionnaire, which may be administered or self-completed. Capturing sexual behaviours on a questionnaire is subject to social desirability bias i.e. participants may respond in a way that is deemed favourable by others, which may result in an underestimation of behaviours. Self-completion of questionnaires is often used in studies of sexual behaviour to ensure greater privacy of responses and encourage more accurate reporting of stigmatized behaviours. A number of computerized survey instruments are now commonly used in studies of MSM. These include audio computer-assisted self-interviewing (ACASI), computer-assisted self-interviewing (CASI), and computer-assisted telephone interviewing (CATI). The advantages of these methods include the ability to automate the branching of questions, directly check for missing responses and consistency, and provide tailored feedback based on responses, as well as cost advantages [430].

2.3 Methodology for literature review (i) and (ii)

2.3.1 Location of literature

The following electronic databases were searched: Pubmed, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials. The search strategy is presented in Appendix section 11.5 Table 45. A single initial search strategy was used for both reviews. Sexual and HIV testing behaviour terms were searched for including PrEP and PEP. The reference lists of eligible studies were also searched. The literature was reviewed up to 15/11/2017. Studies conducted after 2014 were not reviewed in this chapter, but are included in the discussion of AURAH and PROUD results chapters.

2.3.2 Inclusion and exclusion criteria

For review (i), studies were included if they were conducted from 1996 to 2014[xi] and investigated the link between any measure of depression and any measure of sexual behaviour or HIV incidence among HIV-negative MSM in North America, Western Europe, Australia, or New Zealand. Studies were also eligible if they investigated a composite measure of depression and anxiety, although studies which just investigated anxiety were not eligible for this review. A search of reference lists of eligible studies was also undertaken. Studies that recruited only individuals known to be HIV-positive were excluded. For review (ii), studies were included if they were conducted from 1996 to 2014 and investigated HIV sexual transmission risk behaviours among HIV-negative MSM in the UK. Studies that recruited only individuals known to be HIV-positive were excluded. In both reviews, for studies that investigated online samples of men, only those that included men resident in the appropriate countries under review (i.e. only UK for review ii) were eligible for inclusion. Both observational and interventional studies were eligible for inclusion. Longitudinal studies which began prior to 1996 were still eligible for inclusion if follow-up data collection took place after 1996 and findings were presented for the post 1996 period. Only studies that included a quantitative component were eligible for inclusion.

2.3.3 Data extraction

Results from all studies identified as eligible were reviewed. All eligible studies were organized and summarized according to their recruitment setting. If a mixed method approach to recruitment was utilized, for instance if men were recruited from sexual health clinics, gay venues, and online, then studies were described under the site at which the largest proportion of the sample was recruited. For studies that used mixed approaches to recruitment and did not report the proportion recruited from each site, the following rules were considered to be appropriate: (i) if online sampling was reported, this method of recruitment was assumed to have generated the largest number of men for study participation and (ii) if a number of community/commercial gay venues were sited together with clinics as sites of recruitment, the former was assumed to have generated the largest number of men for study participation. Studies that recruited only from sexual health clinics were described in the clinic section. Of note, GUM clinics and LGBT health care facilities are referred to collectively as sexual health clinics in review (i). When individuals who were previously diagnosed as HIV-positive were included, data for the remainder of the sample was extracted where possible.

[xi] These dates were chosen as a result of the introduction of ART in 1996 and since AURAH and PROUD recruited men up to 2014.

2.4 Results review (i): studies that have investigated depression and sexual behaviour among HIV-negative MSM in high-income countries

2.4.1 Relevant studies

In total, 22 studies (26 publications) and one meta-analysis were identified that recruited a sample of MSM or HIV-negative MSM from North America or Western Europe between 1996 and 2014, and investigated the relationship between depressive symptoms and a measure of CLS or HIV incidence. No studies that fit these criteria were identified from Canada, Australia, or New Zealand. Two of the 22 studies were conducted in Europe; one in the UK [355] and the other in Belgium [358]. The remaining studies were conducted in the U.S. [41, 346, 347, 353, 354, 356, 357, 359-373, 431]. In terms of recruitment site, two studies recruited men from the general U.S. population. One UK study recruited men from a GUM clinic. Two U.S. studies recruited men from an LGBT health and research facility specializing in HIV care (including HIV/STI testing). Nine studies recruited men from community or commercial gay venues, and eight studies recruited men online. One meta-analysis of studies conducted up to 1999 was identified. The findings from this meta-analysis are discussed in section 2.4.4.1. Of note, at the time of submitting this thesis (December 2017), no studies were identified that would have been eligible for this review but recruited men from 2015 onwards.

In section 2.4.1.1 to 2.4.1.4 below, each study is described in terms of sampling strategy, inclusion criteria, method of data collection, and sample size, according to recruitment setting.

2.4.1.1 General population

The Urban Men's Health Study (UMHS) [41, 354] recruited MSM in Chicago, Los Angeles, New York, and San Francisco (1996-1998) via household probability telephone sampling (referred to as a random digit-dial sample) of areas identified to be of moderate to high MSM residential density. Men were eligible for study inclusion if they self-identified as gay or bisexual, or reported sexual contact with other men since age 14. CATI was utilized for data collection. The sample size was 2674 MSM. It is of note that obtaining a population-based sample of MSM of this size is unusual for reasons stated in section 2.2.4 above. However, the sample size was achieved by including in the sampling frame, neighborhoods known to be of high sexual minority residential density.

The Chicago Male Drug Use and Health Survey (CMDUHS) [359] was a supplement to a general population study that used a probability sampling method to select men and women resident in households in Chicago (2002-2003). The CMDUHS sampled areas identified to be of high MSM residential density. In a face-to-face screening of individuals from randomly selected households, in predetermined neighborhoods, men were deemed eligible for study inclusion if

they self-identified as gay or bisexual, or reported a history of consensual sex with other men. ACASI was utilized for data collection. The sample size was 216 MSM.

2.4.1.2 Sexual health clinics

Beck et al. 2003 [355] recruited a convenience sample of MSM in east London (1999), who were attending a weekly gay men's GUM clinic. All men were asked to self-complete a questionnaire. The sample size was 122 MSM.

Reisner et al. 2009 [366] recruited a convenience sample of MSM in Boston (2006-2009), who were attending the Fenway Community Health center, a health and research facility specializing in HIV care among the LGBT community. The study was advertised in the Fenway center, and MSM who self-completed a questionnaire volunteered for study participation. The sample size was 189 MSM.

The iPrEx clinical trial [67, 360] was conducted in six countries (U.S., South Africa, Thailand, Peru, Ecuador, and Brazil) and randomized MSM (and transgender women) to daily oral PrEP or placebo, plus a comprehensive package of prevention services. In the U.S., men were recruited from the Fenway center (2007-2009). To be included in the trial men had to report one of the following behaviours in the six months prior to the initial study screening visit: (i) anal sex with three or more male partners, (ii) diagnosis of STI, (iii) transactional sexual activity, or (iv) CLS with an unknown or HIV-positive status partner. Enrolled men were asked to fill out a behavioural survey using CASI. The majority of U.S participants identified as Hispanic/Latino ethnicity. Of note, from July 2009 onwards, men were asked to provide regular data on symptoms of depression. It has been investigated based on U.S. data from 2009 onwards (N=2131), whether depressive symptoms were associated with sexual risk-taking.

2.4.1.3 Community and commercial gay venues

The Young Men's Survey (YMS) [347] recruited a probability sample of MSM in Seattle (1998), who were attending bars, clubs, businesses, parks, and social organizations (time-location sampling). Men were eligible for study inclusion if they were aged between 23-29 years and reported having sex with men. An interviewer administered the survey to participants. The sample size was 429 MSM.

The EXPLORE study [368, 369] was conducted in Boston, Chicago, Denver, New York, San Francisco, and Seattle, and randomized HIV-negative MSM to receive a behavioural intervention or standard risk reduction counseling. EXPLORE had mixed methods of recruitment: venue-based, clinic-based, and Internet-based. Men recruited from community/commercial gay venues represented the largest proportion of the sample (data not shown). Specifically, a consecutive sample of MSM who were attending clubs, bars,

bathhouses, sex clubs, health clubs, and video arcades, were recruited (1999-2001). EXPLORE also recruited MSM through referrals from other cohort studies, community agencies and clinics (purposive sampling), and current study participants were asked to refer other men (snowball sampling). EXPLORE also recruited MSM online. Men were eligible for study inclusion if they reported having had anal sex with a man in the past year and had not been involved in a mutually monogamous relationship in the past two years with an HIV-negative male partner. ACASI was utilized for data collection. The sample size was 4295 MSM.

Dudley et al. 2004 [370] promoted a study on sexual decision making among MSM to LGBT youth groups and advertised the study on posters and fliers distributed to gay venues, in five cities in Midwestern U.S. (exact recruitment period not published, assumed to take place around 2002-2003). Men were eligible for study inclusion if they were aged between 13-21 years and self-identified as gay or reported having had sex with a man. Men who volunteered for study participation were asked to self-complete a pen-and-paper questionnaire. The sample size was 154 MSM.

The Multicenter AIDS Cohort Study (MACS) [431] was conducted in Baltimore, Pittsburgh, Chicago, and Los Angeles, and consisted of a prospective (20 years of follow-up) study among initially HIV-negative MSM. MACS was advertised in gay magazines and in gay medical practices. Initial assessments took place from 1984 to 1991. MSM who completed a questionnaire volunteered for study participation. MACS also recruited a smaller convenience sample of MSM attending gay bars and baths and through referrals from gay activists (purposive sampling). Current study participants were also asked to refer other men (snowball sampling). ACASI was utilized for data collection. The sample size was 4003 MSM.

The Sex and Love Study (version 2.0) [371], recruited a convenience sample of MSM in New York (2003-2004), who were attending a series of LGBT community events. All men who walked past the research booth at each community event were asked to self-complete a pen-and-paper questionnaire. Men were eligible for study inclusion if they self-identified as gay or bisexual. The sample size was 669 MSM.

Project MIX [362] was conducted in New York, Chicago, San Francisco, and Los Angeles, and consisted of a behavioural intervention for MSM. Project MIX had mixed methods of recruitment: venue-based and Internet-based. Men recruited from community/commercial gay venues represented the largest proportion of the sample (data not shown). Specifically, a consecutive sample of MSM who were attending bars, clubs, and gay businesses and agencies, were recruited (2004-2006). Project MIX also recruited MSM through referrals from local agencies/organizations and community advisory board members (purposive sampling). Current study participants were also asked to refer other men (snowball sampling). Since the study was also advertised on flyers and information cards distributed to community and commercial gay

venues, some men who were included in the study volunteered to participate. Project MIX also recruited MSM online. Men were eligible for study inclusion if they reported two or more occasions of alcohol use or one or more occasions of non-injection drug use during or immediately before sex, and reported CLS with an unknown or HIV sero-different status male partner in the past six months. ACASI was utilized for data collection. The sample size was 1540 MSM.

The HONOR project [372] recruited a convenience sample of MSM in Seattle, San Francisco, Los Angeles, Denver, Minneapolis, and New York, who were attending gay venues at which individuals of American Indian, Alaska Native or First Nation heritage/identity reside, work, or socialize (2005-2007). Since the HONOR project was also advertised in newsletters, brochures, and posters distributed to community and commercial gay venues, some men who were included in the study volunteered to participate. Finally, HONOR also used partial network sampling[xii] and respondent-driven sampling techniques to recruit an additional small sample of men. Men were eligible for study inclusion if they identified as American Indian or Alaska Native/First Nations ethnicity, and self-identified as gay, bisexual, or transgender, or reported having engaged in same-sex sexual behaviour in the past year. CASI was utilized for data collection. The sample size was 173 MSM.

De Santis et al. 2008 [356] recruited a convenience sample of MSM in South Florida (exact recruitment period not published, assumed to take place around 2006-2007). This study had mixed methods of recruitment: venue-based and clinic-based. Men recruited from community/commercial gay venues represented the largest proportion of the sample (data not shown). Specifically, MSM who were attending bars, clubs, parties/social events, and places of worship, were recruited. This study also recruited men who were attending sexual health clinics. A consecutive sample of men was asked to self-complete a pen-and-paper questionnaire. The majority of participants identified as Hispanic/Latino ethnicity. The sample size was 205 MSM.

San Francisco's fourth implementation of the National HIV Behavioral Surveillance System (NHBS) [363] recruited a probability sample of MSM in San Francisco (2014), who were attending a range of community and commercial gay venues (time-location sampling). All men were asked to participate in the study. Men were eligible for study inclusion if they reported having had sex with a man in the past year. An interviewer administered the survey to participants. The sample size was 322 MSM. Analyses were conducted separately for HIV-negative (N=240) and HIV-positive men (N=82).

[xii] Network sampling in household surveys involves individuals being linked to households of relatives and others with whom they have well-defined relationships, and who could serve as good proxy respondents 432. Shimizu I, Sirken M. Network Sampling for Rare Trait Inference ASA Section on Survey Research Methods: National Center for Health Statistics; [8th July 2016]. Available from: www.amstat.org/sections/srms/proceedings/y2006/files/jsm2006-000397.pdf.

2.4.1.4 Online

Frontiers in Prevention (FIP) [353] recruited an online sample of MSM residing in New York (2005-2006). Men were eligible for study inclusion if they reported using the Internet to meet men at least twice per month, self-identified as a barebacker or as someone who practices barebacking, had intentional anal CLS during the previous two months with a man met over the Internet, and used at least one of six identified popular Internet sites for barebacking. CASI was utilized for data collection. The sample size was 120 MSM. Analyses were conducted separately for HIV-negative (N=89) and HIV-positive men (N=31).

Men of Asia Prevention Study (MAPS) [357] recruited a sample of MSM residing in Washington and Philadelphia (2004-2007). MAPS had mixed methods of recruitment: Internet-based and venue-based. Men recruited online represented the largest proportion of the sample (data not shown). A smaller sample of MSM was recruited through referral from community-based organizations and by actively approaching potentially eligible men attending bars, public sex areas, Pride events, and ethnic specific gay events (purposive sampling). Men were eligible for study inclusion if they self-identified as Asian/Pacific ethnicity and reported sex with a man in the past year. CASI was utilized for data collection. The sample size was 319 MSM.

Vanden Berghe et al. 2014 [358] recruited a sample of MSM residing in Belgium (2008). This study had mixed methods of recruitment: Internet-based and venue-based. Men recruited online represented the largest proportion of the sample (data not shown). A smaller, volunteer sample of MSM was recruited via advertisement on posters distributed to gay venues. Men were eligible for study inclusion if they reported anal sex with a casual partner in the past six months and a negative HIV status. Participants were given a link to the survey online. The sample size was 591 MSM.

The Bareback Project [346] recruited a probability sample of MSM across the U.S. (2008-2009), who were using one of 16 websites (around half of men were recruited from bareback sex websites). Men were consecutively asked to participate in a telephone interview if the first letter of their username and ethnicity matched a randomly selected profile utilized by different recruiters on different days. Recruitment took place during all hours of the day and night. The sample size was 332 MSM.

P18 Cohort Study [365] recruited a sample of MSM residing in New York (2009-2011). The P18 Cohort had mixed methods of recruitment: Internet-based and venue-based. Men recruited online represented the largest proportion of the sample (data not shown). A smaller sample of MSM who were attending gay venues and community centres, or were present at parks, and college campuses and dormitories, was recruited. Men were eligible for study inclusion if they were aged 18 or 19 years old, reported having been sexually active with a man in the past six months, and reported a negative or unknown HIV status. Multiracial men and men of black,

Latino, and Asian-Pacific Islander ethnicity were over-sampled. ACASI was utilized for data collection. Of note, sexual behaviour was measured using the interviewer-administered 'Time Line Follow Back (TLFB) calendar method', in which participants were asked to provide a retrospective account of their sexual behaviour over the past four weeks on a calendar. At baseline, the sample size was 598 MSM and at the six months follow-up the sample size was 509 MSM.

Maksut et al. 2016 [373] recruited a sample of MSM residing in Atlanta (2012-2014). This study had mixed methods of recruitment: Internet-based and venue-based. Men recruited online represented the largest proportion of the sample (data not shown). A smaller sample of MSM who were attending bars, clubs, and bathhouses, and were present in parks and street locations, was also recruited. Men were eligible for study inclusion if they identified as black or African American ethnicity, reported CLS with a man in the past year, and a negative HIV status. ACASI was utilized for data collection. The sample size was 450 MSM.

The One Thousand Strong panel [364] recruited an online sample of MSM across the U.S. The exact recruitment period was not published, given that the first report was published in 2015, the study is assumed to have taken place around 2013-2014. Men who were recruited were existing members of the Community Marketing and Insight panel, which consisted of over 22000 gay and bisexual men from across the U.S. Men were recruited online, as well as, to a lesser degree, from LGBT organizations and events, and via advertisements in LGBT media. Panelists were invited to complete a short screening questionnaire online. Men were eligible for study inclusion if they self-identified as male and as gay or bisexual, and reported a negative HIV status. Participants were given a link to the full survey online. The sample size was 1071 MSM. Of note, the association between depressive symptoms and sexual risk behaviour was investigated among 1033 men who did not report PrEP use.

Martinez et al. 2016 [433] recruited a sample of Latino MSM residing in New York (2014). This study had mixed methods of recruitment: Internet-based and venue-based. Men recruited online represented the largest proportion of the sample (data not shown). A smaller sample of MSM who were attending community-based organizations was also recruited. Current study participants were also asked to refer other men (snowball sampling). Men were eligible for study inclusion if they were aged 18 years or older and identified as Latino ethnicity. An interviewer administered the survey. The sample size was 176 MSM.

2.4.2 Measures of depression

Table 1 presents the measures of depression used among the 22 studies that recruited a sample of MSM or HIV-negative MSM from North America or Western Europe between 1996 and 2014. In all studies, symptom questionnaires were utilized for measuring depression. These were the Center for Epidemiological Studies-Depressed Mood Scale (CES-D), the Beck

Depression Inventory-II (BDI-II), the Patient Health Questionnaire (PHQ-9), the Hospital Anxiety and Depression Scale (HADS), and the SF-36 Health survey. In Textbox 3 a description of these symptom questionnaires is presented. Internal consistency reflects the coherence of the components of a questionnaire scale [434]. Coefficient alpha is the most common measure of internal consistency and is routinely reported in psychological research on personality and mood assessment [435]. Alphas below .70 are considered to be indicative of poor reliability and predictive validity[xiii] [437]. The alpha coefficient for each of the five depression symptom questionnaires utilized in studies identified in this review, is presented in Textbox 3. References for the studies in which these alpha coefficients were derived, are as follows: CES-D [438-440], BDI-II [353, 441], PHQ-9 [442-445], HADS [446], and the SF-36 Health Survey [370].

Seventeen studies (20 publications) measured depressive symptoms using the CES-D (see Table 1). The cut-off for depression was considered to be a score of >22 in two studies, >21 in one study, ≥16 in eight studies, >16 in one study, and >10 in another study. Two studies investigated categories of depressive symptom severity ('low, middle, high' or 'none, mild, major'), two studies split the CES-D score into quartiles, and two studies treated the score as continuous. Furthermore, three studies investigated a shortened version of the CES-D; one study used a 9-item questionnaire and the other two studies used a 10-item questionnaire. Even though the CES-D was the most commonly used depressive symptom questionnaire in studies identified in this review, the definitions and classifications of depression varied widely across studies. Of the remaining five studies, depressive symptoms were measured using the BDI-II in two studies [353, 365], the PHQ-9 in one study [363], HADS in one study [355], and the SF-36 Health survey in the final study [370].

2.4.3 Prevalence of depression

Table 1 shows the prevalence of depression among the 22 identified studies. Five studies across recruitment settings presented the prevalence of depression according to CES-D≥16 and estimates ranged from 22.8% to 54.9% (both of these estimates were from men recruited from community/commercial gay venues). In the one publication that presented the prevalence of depression according to CES-D>22, the estimate was 47.4%. The mean depression score was 10.7 [353] and 9.8 [365] in the two studies which used the BDI-II, and 3.0 [370] in the one study that used the SF-36 Health survey. The prevalence of major and other depressive syndromes was 13.0% in the one study that used the PHQ-9 [363]. Finally, the prevalence of 'case level' depression was 6.9% in the one study that used HADS [355]. It appears there was no clear pattern in prevalence of depressive symptoms according to recruitment setting or study selection criteria. Of note, the prevalence of clinically significant depressive symptoms on the

[xiii] It is of note that there are some limitations to the coefficient alpha. For instance, it has been suggested that a higher alpha may be obtained via use of almost identical content in the scale. In this instance, although the alpha coefficient suggests higher consistency, in reality, with item redundancy, this scale may not be very useful 436. Loevinger J. The attenuation paradox in test theory. Psychological bulletin. 1954;51(5):493-504.

PHQ-9 (score of ≥10) has been investigated in the general UK population and this is presented and discussed in section 4.4.3 of Chapter 4.

Textbox 3: Symptom questionnaires for measuring depression

CES-D: a 20-item questionnaire based on a Likert-type scale of symptoms in the past week, with scores ranging from 0 (rarely/none of the time) to 3 (most/all of the time), and total scores ranging from 0 to 60. A score of 16 and above is often used to indicate depression. However, there is some evidence to suggest that a higher cut-off is preferable in order to reduce the number of false positive classifications of depression. The CES-D has high internal consistency (correlation between items on the questionnaire), with an alpha coefficient of 0.85.

PHQ-9: a 9-item questionnaire based on a Likert-type scale of symptoms in the past two weeks, with scores ranging from 0 (not at all) to 3 (nearly every day), and total scores ranging from 0 to 27. A score of 10 or above is considered to indicate a clinically significant depressive condition. A major depressive syndrome can also be defined by report of at least five symptoms more than half the days or nearly every day, including either question 1 (concerning anhedonia) or question 2 (concerning depressed mood/hopelessness). A major or other depressive syndrome (including dysthymia, seasonal affective disorder, and bipolar disorder) can also be defined by report of at least two symptoms more than half the days or nearly every day, including either question 1 or question 2. The internal consistency of the PHQ-9 has been found to be high, with an alpha coefficient ranging from 0.89 to 0.86.

SF-36 Health Survey: includes a five item subscale measuring symptoms of anxious or depressed mood during the past four weeks. The questionnaire is based on a Likert-type scale with scores ranging from 1 (none of the time) to 6 (all of the time), with total scores ranging from 0 to 30. Higher scores indicate higher levels of anxiety and depression. The internal reliability of the SF-36 Health Survey has been found to be high, with an alpha coefficient of 0.85.

BDI-II: a 21-item questionnaire whereby each item is scored on a four-point scale, ranging from 0 (absence of the symptom) to 3 (severe symptom). Scores of 0-13 are indicative of minimal depression, 14-19 of mild depression, 20-28 of moderate depression, and scores of ≥29 of severe symptoms. The BDI contains two subscales: the cognitive-affective subscale and the somatic subscale. The internal consistency of the BDI-II has been found to be high, with an alpha coefficient of 0.84.

HADS: comprises of fourteen questions; seven questions for anxiety and seven for depression. A separate score is generated for anxiety and depression. The questionnaire is based on Likert-type scales of symptoms in the past week, with scores ranging from 0 to 3, and total scores ranging from 0 to 21. The separate depression and anxiety scores are classified into the following categories: Normal (0-7), borderline abnormal (8-10), abnormal (11-21). The internal consistency of HADS has been found to be high, with an alpha coefficient ranging from 0.67 to 0.90 (mean 0.82).

2.4.4 Relationship between depressive symptoms and sexual behaviour measures

2.4.4.1 Meta-analysis

Crepaz and Marks conducted a meta-analysis of studies assessing the association between depressive symptoms and sexual risk behaviour up to 1999 [352]. The review did not restrict to MSM populations. The vast majority of included studies were conducted in the U.S. Findings across studies were inconsistent (and statistically heterogeneous). In combined estimates, there was no significant relationship of depression (or anxiety) with measures of CLS (including condomless penetrative or oral sex, frequency of condom-use, numbers of sex partners, or their composite indices). Stratifying by sample population (MSM, substance users, or other) or HIV status did not significantly moderate the association (estimates not published). Of the studies included in this meta-analysis, five investigated the relationship between depression and sexual risk behaviour among HIV-negative MSM: Coping in Health and Illness Project, N=53 MSM recruited from community/commercial gay venues, unadjusted association found [447]; Dilley et al. 1998, N=55 MSM recruited from community/commercial gay venues, no unadjusted association found [448]; Strathdee et al. 1998, N=371 MSM recruited from sexual health clinics, unadjusted association found (disappeared after adjusting for education, substance use, and social support) [449]; Amsterdam cohort study, N=118 MSM recruited from community/commercial gay venues, no unadjusted association found [450]; University of California, San Francisco (UCSF) Coping Project, N=66 MSM recruited from community/commercial gay venues, no unadjusted association found [451]. In addition, two studies investigated a sample of MSM which included both HIV-positive and HIV-negative men; one study finding the reverse association (i.e. depression was associated with less sexual risk-taking) in unadjusted and adjusted analysis (N=384) [452] and the other finding no association in unadjusted analysis (N=381) [453]. All of these studies recruited MSM before or up to 1996. The sample size was small in each study.

Crepaz and Marks suggested that there may be two opposing associations of depressive symptoms. In some individuals, depression may lead to increased sexual risk behaviour and in others to no sexual activity as a result of lowered libido and interest in sex. If the association operates in both directions, assessment of this relationship is problematic since opposing trends can result in an observed overall lack of association. For instance, if a study population includes participants who report recent sex and those who do not, and if the prevalence of depressive symptoms is highest among men who report no sex and among men who report sexual risk-taking, then investigating the relationship of depression with CLS versus no CLS in this sample may result in no association being found. Any difference in prevalence of depressive symptoms that exists between men who report CLS and men who report condom-protected sex would be obscured due to the fact that the ‘no sex’ and ‘condom-protected sex’ groups had been

combined as the comparator group. This hypothesis has informed the presentation of results in this review, as described in section 2.4.4.2 below.

2.4.4.2 Classification of studies conducted from 1996 to 2014 in high-income countries and study findings

Table 1 presents findings from the 22 studies (1996 to 2014) identified in the review, relating to the association between depression and sexual risk behaviour. The classification of study findings is somewhat complicated by the investigation of a number of different sexual behaviour measures in most studies and a significant and independent relationship observed for some measures but not others. In order to summarize the findings, presented first in the table are studies for which an unadjusted and/or adjusted association between depression and at least one measure of sexual behaviour (or HIV incidence) was found. Presented after this, are the studies that found no unadjusted or adjusted association with any measure of sexual behaviour considered. If unadjusted and adjusted results were reported, an association was considered to be present if the adjusted results were statistically significant. Accordingly, studies which found a significant unadjusted association that disappeared after adjustment were not considered to present an association, with the exception of one study (see section 2.4.7). The limitations of this approach are discussed in section 2.4.9.

In Table 1, the studies are documented according to recruitment setting. In addition, in view of the hypothesis discussed above, results are shown in the context of the prevalence of sexual behaviour reported by the sample. In the section below, the unadjusted and adjusted study results presented in Table 1 are discussed in relation to: (i) recruitment setting, (ii) measure of sexual behaviour, (iii) socio-demographic characteristics, and (iv) prevalence of recent sex. When reporting recent sex this refers to anal sex with a man within the recall period used in each study, which could be up to 12 months. In section 2.4.5.5 the sexual behaviour profile of samples is discussed in the context of the study recruitment setting. Identifying whether certain behavioural profiles occur more frequently in certain study settings and thus, whether any patterns exist in terms of the study setting and association found, may be useful in understanding in which populations targeted interventions addressing depression and sexual risk may be most effective/beneficial. Describing patterns, if they do exist, may also be useful in order to extrapolate to other similar yet understudied regions such as Europe.

2.4.5 Overall study findings

Of the 22 identified studies, 20 had a cross-sectional design and two were longitudinal. The implications of study design are discussed in section 2.4.6. Overall, 15 studies (68%) found at least one significant association between depression and sexual risk behaviour. In each of the 15 studies, the association was in the same direction; participants who had depressive symptoms were more likely to report sexual risk behaviour than those without depressive

symptoms. The impact of adjusting for variables on the magnitude of the association found is discussed in section 2.4.7 below.

Seven studies did not find evidence for an association between depressive symptoms and sexual behaviour. Two studies observed an association before adjustment which disappeared after adjusting for socio-demographic factors [372], poly-drug use, childhood sexual abuse (CSA), intimate partner violence (IPV), and sexual compulsivity [371]. One study did not find an association in unadjusted or adjusted analysis [347], two studies investigated the association in unadjusted analysis only [373, 433], and two studies investigated the association in adjusted analysis only [346, 370]. Across these seven studies, the sample size was small, ranging from 154 men [370] to 669 men [371]. The possible lack of statistical power may explain the lack of association observed. However, a number of very small studies were still able to detect a difference between men with depressive symptoms and men without in terms of sexual risk-taking: MAPS (N=62) [357], FIP (N=89) [353], Beck et al 2003 (N=122) [355], De Santis et al 2008 (N=205) [356], including in adjusted analysis: CMDUHS (N=177) [359], Reisner et al 2009 (N=189) [366], and NHBS (N=240) [363].

2.4.5.1 Findings according to recruitment setting

Of 22 studies identified in this review, two recruited men from the general population, three from sexual health clinics, nine from community and/or commercial gay venues, and eight from online. Of the two general population-based studies, both found an association between depressive symptoms and a measure of sexual risk behaviour. Similarly, all three studies of sexual health clinic attendees found an association between depression and a measure of sexual risk behaviour. Of the nine gay venue-based studies, five found an association with a measure of sexual risk behaviour and four did not. Of the eight studies which recruited men online, five found an association with a measure of sexual risk behaviour and three did not. It is difficult to conclude from these findings whether the association between depression and sexual behaviour is more consistently demonstrated in samples recruited from certain settings. The implications of recruitment site are discussed in the context of sexual behaviour profiles of samples in section 2.4.5.5 below.

2.4.5.2 Findings according to measures of sexual behaviour

In the 22 studies identified in this review, the most common measure of sexual behaviour collected was CLS with one or more partners (recall periods included the past month [n=2], past two months [n=1], past three months [n=5], past six months [n=1], and past year [n=2]), followed by CLS with an unknown or HIV sero-different status partner (recall periods included the four most recent sex partners [n=1], past month [n=1], past three months [n=1], past six months [n=2], and past year [n=1]). Other studies investigated CLS with one or more casual/non-monogamous/non-primary partners (N=4), receptive CLS with one or more partners (N=2),

receptive CLS with an unknown or HIV sero-different status partner (N=2), receptive CLS with one or more casual/non-monogamous/non-primary partners (N=3), insertive CLS with one or more casual/non-monogamous/non-primary partners (N=2), and HIV seroconversion (N=2). Investigated in one study only, were the following measures: insertive CLS with one or more partners, CLS with a non-primary partner or two or more partners, insertive and/or receptive CLS with multiple, casual, or unknown/HIV sero-different status partners, number of acts of CLS (including with an HIV-positive partner), the Safer Sex Behaviour Questionnaire (SSBQ), and composite measures of risk/risk reduction.

Of the six studies that investigated the association between depressive symptoms and CLS with one or more partners, one found an association with depressive symptoms and five did not. Of the six studies that investigated the association with CLS with an unknown/sero-different status partner, four found an association and two did not. There does appear to be a pattern whereby the relationship with depression was more consistently found for CLS with an unknown/sero-different status partner compared to CLS with one or more partners. However, it is difficult to make any firm conclusions given the range of different recall periods investigated and the fact that although a number of studies investigated report of 'any CLS', half of these studies did not investigate the association with depressive symptoms.

2.4.5.3 Findings according to participant socio-demographic characteristics

Of the 22 studies identified in this review, 18 reported the proportion of participants who had previously received an HIV diagnosis. In Project MIX [362], separate analyses were conducted among samples including (47%) and excluding men who self-reported an HIV-positive status. Of the ten studies that included only HIV-negative or unknown status men, nine found evidence of an association between depressive symptoms and a measure of sexual risk behaviour (including Project MIX). Of the nine studies that included HIV-positive men, five found evidence of an association between depressive symptoms and a measure of sexual risk behaviour (including Project MIX). This could be taken to indicate evidence to suggest that the relationship between depressive symptoms and sexual risk behaviour is more consistent among samples of HIV-negative/unknown status MSM. However, this comparison is unfortunately complicated by the very wide range in prevalence of HIV sero-positivity reported by participants: 9.8% to 59.0%. The prevalence of self-reported HIV sero-positivity ranged from 10-51% among studies that found an association between depressive symptoms and a measure of sexual risk behaviour and from 11-59% among studies that did not find an association. It is difficult to conclude from these findings whether the association between depression and sexual behaviour differs by HIV status.

Of the 22 studies, seven (predominantly) recruited men of BAME (black, Asian, or other minority ethnicity). De Santis et al 2008 [356] recruited mainly Hispanic and Latino men, MAPS[357] recruited only Asian men, the P18 Cohort [365] recruited mainly ethnic minority men, HONOR [372]

recruited only men who identified as American Indian/Alaskan Native, Maksut et al 2016 [373] recruited only men of black ethnicity, Martinez et al 2016 [433] recruited only men of Latino ethnicity, and the majority of U.S. participants in the iPrEx trial [67, 360] identified as Hispanic/Latino ethnicity. Of these seven studies, four found an association between depressive symptoms and a measure of sexual risk behaviour. Of the 15 studies that did not predominantly recruit men of BAME, 11 found an association between depressive symptoms and a measure of sexual risk behaviour. There does not appear to be any obvious pattern whereby the relationship with depression was more consistent in certain ethnic groups.

Of the 22 studies, three recruited young MSM. The P18 Cohort [365] recruited only men aged 18-19 years, Dudley et al 2004 [370] recruited only men aged 13-21 years, and YMS [347] recruited only men aged 23-29 years. Of these three studies, one (P18 Cohort) found an association between depressive symptoms and a measure of sexual risk behaviour. Of the 19 studies that did not predominantly recruit younger MSM, 14 found an association between depressive symptoms and a measure of sexual risk behaviour. Although it appears that the association was more consistent in samples including older MSM, it is difficult to conclude the presence of such a pattern given the small number of studies which investigated young MSM.

2.4.5.4 Findings according to prevalence of recent sex

In line with Crepaz and Marks' theory of opposing associations, there is some evidence to suggest that the relationship between depressive symptoms and sexual behaviour is affected by the prevalence of recent sex in the sample. Of the 22 studies identified in this review, eleven reported the proportion of men reporting recent anal sex with a man (either in the results or implicit as part of the inclusion criteria). In nine out of these eleven studies, all or almost all participants (98-100%) reported recent sex [353, 357-359, 362, 363, 365, 367-369, 373]. In the remaining two studies, <98% of participants reported recent sex- the prevalence was 59.9% (past three months) [370] and 72.0% (past year) [372]. Of the nine studies in which all or almost all participants reported recent sex, eight studies (88.9%) found evidence of an association between depressive symptoms and a measure of sexual risk behaviour. Of the two studies in which the prevalence of recent sex was lower, neither found evidence of an association between depressive symptoms and a measure of sexual risk behaviour. Interpreting these findings may however, be complicated by the relatively small number of studies presenting the prevalence of anal sex and the different recall periods among studies that did.

2.4.5.5 Sexual behaviour profile of samples and recruitment site

Of all 22 studies identified in this review, six reported both the prevalence of recent sex and CLS with one or more partners (either in the results or implicit as part of the inclusion criteria). Of the four studies which reported the prevalence of recent sex to be ≥98%, the prevalence of CLS with one or more partners was 21.0% (past month) [365], 96.0% (past two months) [353],

69.1% (past six months) [367-369], and 100% (past year). Of the two studies which reported a lower prevalence of recent sex, the prevalence of CLS with one or more partners was 22.1% (past three months) [370] and 48.6% (past year) [372]. The prevalence of CLS appears to be higher in studies with a higher prevalence of recent anal sex[xiv].

When considering the recruitment setting of the ten studies that reported the prevalence of CLS with one or more partners, three recruited men from sexual health clinics, three from community/commercial gay venues, and four from online. The prevalence of CLS with one or more partners was 56.0% (past month) [355], 60.0% (past three months) [360], and 79.9% (past year) [366] in studies of sexual health clinic attendees. In studies of community/commercial gay venue attendees the prevalence was 22.1% (past three months) [370], 69.1% (past six months) [367-369], and 48.6% (past year) [372]. Finally, in studies of men recruited online the prevalence was 21.0% (past month) [365], 96.0% (past two months) [353], 50.6% (past three months) [433], and 100% (past year) [373]. It appears that the prevalence of CLS with one or more partners is higher in studies which recruited men from sexual health clinics and online compared to studies which recruited men from community/commercial gay venues. However, as a result of the differing recall periods investigated, it is difficult to directly compare the prevalence of sexual behaviour between studies. Furthermore, it is of note, two of the online recruited samples [353, 373], that reported the prevalence of CLS with one or more partners, incorporated inclusion criteria requiring men to report recent CLS. These inclusion criteria explain the CLS prevalence of 96-100%.

2.4.6 Temporality of association

The vast majority of studies identified in this review incorporated a cross-sectional design. As a result, it is not possible to conclude the direction of causality. It is possible that the associations observed between depressive symptoms and increased sexual risk behaviour may operate in the opposite direction; it could be that in some men sexual risk-taking leads to symptoms of depression. It is also possible that the association operates in both directions. There is a large body of theoretical work, however, suggesting that depression can lead to CLS (see section 1.8.3). Two studies were identified in this review that incorporated a longitudinal design and investigated the association between depressive symptoms and HIV incidence (EXPLORE [367-369] and MACS [361, 431]). Although an association with HIV incidence was only observed in EXPLORE, men with depressive symptoms at baseline of MACS were more likely to be placed in the high sexual risk trajectory group than the low sexual risk trajectory group after eleven years of observation, including after adjustment for socio-demographic factors and substance use. These findings provide some evidence in favour of concluding that depression leads to CLS.

[xiv] Although this is as expected, it was also possible that samples of sexually active men may not report (high levels of) CLS.

It is of note, of the 22 studies identified in this review, none investigated whether the prevalence of sexual risk behaviour was lower among men who were receiving treatment for depression and did not report depressive symptoms. It is therefore, not possible to comment based on findings from this review, as to whether the effect of depression on sexual behaviour was reversed with the removal of symptoms with treatment. Such an investigation would be helpful in providing further evidence of causality. Criteria for concluding evidence of causality is discussed in section 3.4.4 of Chapter 3 and further explored in the final conclusion chapter of this thesis.

2.4.7 Magnitude of effect

Unfortunately, it is very difficult to compare the magnitude of associations found given that multiple measures of depression and sexual behaviour were investigated, using various statistical methodologies. Depression measures on CES-D were most commonly investigated with sexual behaviour measures in logistic regression models, producing odds ratios, ORs (N=12) [41, 347, 358-362, 364, 366, 367, 371, 372]. Of these 12 studies, eight found an association with a measure of sexual risk behaviour [358-362, 364, 366, 367]. The magnitude of these ORs ranged from 1.3 for the association between CES-D≥16 and CLS with an unknown/HIV-positive status partner at last episode of sex (EXPLORE, men recruited from community/ commercial gay venues)[367], to 5.72 for the association between high scores on CES-D versus low scores and report of both insertive and receptive CLS with multiple, casual, or unknown/HIV sero-different status partners in the past six months (CMDUHS, general population study)[359]. In both studies these ORs were adjusted for socio-demographic factors and alcohol and drug use.

Of the 15 studies that found an association with a measure of sexual risk behaviour, three reported the association in unadjusted and adjusted analysis [353, 366, 367] (Table 1). In two out of these three studies, the association was somewhat attenuated after adjusting for a set of variables. In FIP (N=89) [353], a depressive symptom score was investigated as the dependent variable and the association with CLS with an HIV-positive partner in the past two months was attenuated after adjustment for socio-demographic factors (ethnicity, income, and educational attainment) [353]. In EXPLORE (N=4295) [367], the association between depressive symptoms and CLS with an unknown/HIV-positive status partner at last episode of sex was attenuated after adjustment for socio-demographic and lifestyle factors (age, ethnicity, educational attainment, income, and substance use). In the remaining study (Reisner et al 2009, N=189 [366]) the association between depressive symptoms and a composite measure of risk increased after adjustment for socio-demographic and lifestyle factors (age, ethnicity, educational attainment, income, disclosure of sexual orientation, HIV status, STI history, drug and alcohol use, and sexual partner meeting venues). It is of note, that one other study (Vanden Berghe et al 2014, N=591 [358]) reported the association in unadjusted and adjusted analysis. The following factors were included in adjusted analysis: age, education, alcohol use, drug use, markers of sensation seeking, risk perception regarding insertive CLS, risk perception regarding receptive CLS,

perceived social norm for condom-use, and markers of unsupportive social interactions. The significant unadjusted association disappeared after adjusting for these factors. However, levels of social support are thought to be highly correlated with depression [358, 454, 455]. As a result, this study was classified as having found an association between depression and sexual risk behaviour. It is possible that the association between depressive symptoms and sexual risk behaviour is not independent of socio-demographic and lifestyle factors. With so few studies in this review presenting unadjusted and adjusted model estimates, it is difficult to examine this further.

In most epidemiological studies, it is a matter of debate which factors should be adjusted for in analysis. Some socio-demographic factors are fixed from birth or from a relatively early age (e.g. ethnicity, sexual identity, level of education), whereas recreational drug use may be a consequence or prederminant of depresssion. One study in this review was considered not to show a relationship since the association disappeared after adjusting for socio-demographic factors, poly-drug use, CSA, IPV, and sexual compulsivity. Since it is possible that one or more of these factors is on the causal pathway, it is difficult to judge the extent to which this study provides evidence for depression being a risk factor for sexual risk behaviour.

2.4.8 Mechanisms of effect

Of the 22 studies identified in this review, one (Project MIX [362]) investigated potential factors on the causal pathway between depression and sexual risk behaviour using mediational analysis. Mediational analysis investigates whether the association between an exposure and outcome operates fully or partially via an intermediate factor(s) within a hypothesized causal chain [456]. Mediational analysis is revisited in further detail in Chapter 3 section 3.4.2. In Project MIX, it was hypothesized that the relationship between depression and sexual risk behaviour would be partially mediated by self-efficacy for sexual safety, cognitive escape, and avoidant coping (avoidance of situations/thoughts that trigger anxiety) [362]. Adjusting for age, income, education level, ethnicity, HIV status, and research site, depressive symptoms were found to be associated with higher numbers of CLS partners of unknown or HIV sero-different status in the past three months indirectly via low self-efficacy for sexual safety or cognitive escape tendencies. As a result, it was reported in this study that psychological vulnerabilities and dysfunctional coping processes may be possible mechanisms of effect for the relationship of depression with sexual risk behaviour. Further details of the mediational analysis in Project MIX are presented in Chapter 6 in the context of findings in this thesis.

2.4.9 Summary

There was considerable evidence based on this review of 22 high-income country studies of MSM (1996-2014) for an association between depression and increased sexual risk behaviour, but with varying estimates of magnitude of effect. There was little evidence to suggest that the

presence of an effect varied according to study recruitment setting, socio-demographic characteristics of the sample, or the measure of sexual behaviour investigated. However, the number of studies with certain socio-demographic characteristics (i.e. a younger age group) was too small to allow for more meaningful comparisons. There was some evidence to suggest that the presence of an effect was dependent on the proportion of the study population that was sexually active. There are, however, a number of limitations to interpreting findings from this review. Whether an association between depressive symptoms and sexual risk behaviour remained statistically significant after adjustment was subject to which set of variables was adjusted for. Where sets of adjusted variables differed, studies may be estimating a different effect/answering a different question. Furthermore, examining whether associations are statistically significant is subject to the study sample size and whether adjustment takes place at all is subject to the sample size. Finally, there is the issue of publication bias, whereby studies that report an association between depression and sexual behaviour may be more likely to be submitted or accepted for publication compared to studies that report weaker or no associations. Therefore, it is possible that the interpretation of study findings for review in this thesis was subject to bias. It is perhaps reassuring however, that the pattern of overall study findings appeared to be in line with that hypothesized by Crepaz and Marks decades previously. Findings from review (i) and potential implications will be discussed in detail together with the findings from review (ii), at the end of this chapter.

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs. no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
UMHS [41, 354], U.S. (N=2881), general population	17% [ll]	CES-D<16 **CES-D≥16**	/	/	CLS 2+/ any CLS (no primary partner)	12 months	/	19.0% 25.6% χ^2 test *p<0.001*	/	/	/
					Receptive CLS with unknown/ sero-different partner	12 months	/	3.2% 3.6% χ^2 test *p>0.100*	/	/	/
		CES-D≤22 **CES-D>22**	/	/	CLS with unknown/ sero-different partner	4 most recent sex partners	/	/	OR	1 1.1 [0.8, 1.5]	Age, education, ethnicity, income, HIV status
CMDUHS [359], U.S. (N=177), general population	15%	CES-D: Low≤2 Middle≤7 **High≥8 (23.2%)**	6 months	100%	Only insertive[xxviii] CLS & risky partner[n]	6 months	14.7%	/	OR[o]	1 0.94 [0.41, 2.19] 0.41 [0.11, 1.44]	Drug use, drinking, HIV status, race
					Only receptive[xxix] CLS & risky partner[n]	6 months	15.8%	/	OR[o]	1 0.69 [0.22, 2.21] 0.50 [0.13, 1.97]	Drug use, drinking, HIV status, race
					Insertive & receptive CLS & risky partner[n]	6 months	9.6%	/	OR[o]	1 2.99 [0.65, 1.37] 5.72 [1.76, 18.9]	Drug use, drinking, HIV status, race

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
Beck et al 2003[355], UK (N=122), sexual health clinics	9.8%	HADS<11 **HADS≥11 (6.9%[k])**	/	/	CLS 1+ partners	1 month	56.0%[l]	/	/	/	/
					CLS with unknown/sero-different partner: Yes No	1 month	43.6%[m]	% reporting: HADS≥11[p] 13.6% 2.7% χ^2 test *p=0.010*	/	/	/
Reisner et al 2009[366], U.S. (N=189), sexual health clinc	51%	CES-D<16 **CES-D≥16 (43.4%)**	/	/	CLS with 1+ partners	12 months	79.9%	/	/	/	/
					Composite measure of sexual risk-taking[z]	12 months	20.1%	1 2.08 [0.99, 4.55] *p<0.050*	OR	1 3.13 [1.09, 9.09] *p<0.050*	Socio-demographic and lifestyle factors[xii]
iPrEx[360], 6 countries (N=2131[xxiii]), sexual health clinics	0%	/	/	/	Baseline: CLS with 1+ partners	3 months	60.0%	/	/	/	/
		CES-D quartiles: ≤7 8-12 13-19 >19 Median=12 Mean=14			Receptive CLS with 1+ partners[xxiii]	3 months	61.0%	/	OR[xxii]	1 1.17 [0.88, 1.57] 1.21 [0.90, 1.61] 1.46 [1.09, 1.94] *p=0.012*	Age, study site, anti-depressants, number of sexual partners

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
EXPLORE [367-369], U.S. (N=4295), community/ commercial gay venues	0% [t]	CES-D quartiles: 7-12 13-17 **18-22** **>23** **(14.2% for score 18+)**	6 months	98%	CLS 1+ partners [t]	6 months	69.1%	/	/	/	/
					Receptive CLS 1+ partner	6 months	48.0%	/	/	/	/
					Insertive CLS 1+ partner	6 months	54.9%	/	/	/	/
					HIV seroconversion	4 year follow-up	2.1 per 100 person years [va] n=258	1 1.94 [1.45, 2.56] 1.96 [1.33, 2.89] 2.44 [1.47, 4.03]	HR [x]	1 1.48 [1.12, 1.96] [w] [w]	Socio-demographic, lifestyle, and sexual behaviour measures [xi]
					CLS with unknown/HIV+ partner	6 months	/	/	RR (GEE [y])	Higher CLS with higher depression score (estimate not shown) *p<0.001*	Age, education, ethnicity, randomization arm, study site
		CES-D<16 **CES-D≥16 (47.0%)**			CLS with unknown/HIV+ partner	Most recent episode of sex	16%	1 1.5 [1.3, 1.7] p<0.001	OR (GEE)	1 1.3 [1.2, 1.5] p<0.001	Age, ethnicity, education, income, substance use

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
MACS [361, 431], U.S. (N=4003 from 1984-2004; N=419 from 2003-2004), community/ commercial gay venues	0%[t]	1984-2004: CES-D<16 **CES-D≥16**	/	/	HIV seroconversion	30 year follow-up	n=436	1 0.83 [0.64, 1.08]	HR[xa]	1 0.83 [0.63, 1.09]	Socio-demographics, lifestyle factors, sexual behaviour[iii]
	0%	2003-2004: CES-D<16 **CES-D≥16 (54.9%)**	/	/	Risk group [xviii]: Moderate (vs. low)	Sexual risk trajecto-ries (2003-2011)	22.9%	/	OR[xix]	1 1.37 [0.73, 2.55]	Study site, age, ethnicity, education, income, substance use
					Risk group [xviii]: High (vs. low)	Sexual risk trajecto-ries (2003-2011)	14.1%	/	OR[xix]	1 2.36 [1.14, 4.92]	Study site, age, ethnicity, education, income, substance use

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
Project MIX[362], U.S. (N=1540 full sample[xb]; N=599 HIV-negative sample), community/ commercial gay venues	47%	CES-D9: mean severity score[b] **Moderate (39.0%) High (22.0%)**	6 months	100%	CLS with unknown/sero-different partner[c]	3 months	72.5%	*F*(1, 1.523)=10.45 β=0.084 R^2=0.007 *p<0.010*	RR[d]	F(2, 1522)=26.22[e] β=0.060 R^2=0.032 *p<0.001*	Self-efficacy for sexual safety
	0%[h]	CES-D9 symptoms: ≤at times **>at times (score>2: 39.0%)**			CLS with 1+ non-primary partners	3 months	60%	/	OR	1 1.27 [0.90, 1.80]	Age, education, ethnicity, city
					Receptive CLS with 1+ non-primary partners	3 months	27%	/	OR	1 1.58 [1.07, 2.33]	
					Insertive CLS with 1+ non-primary partners	3 months	39%	/	OR	1 0.86 [0.59, 1.23]	
De Santis et al 2008[356], U.S. (N=205), community/ commercial gay venues	**/**	CES-D≤16 **CES-D>16 (33.7%)**	/	/	SSBQ[a] score<78 (indication of lower levels of safer sex behaviour)	/	52.2%	*F*(1, 203)= 4.312 R^2=0.144 *p=0.039*	RR[d]	/	/

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
NHBS [(363)], U.S. (N=240) community/ commercial gay venues	0%[h]	PHQ-9 major & other depressive syndromes: No[xxvii] **Yes (13.0%)**	12 months	100%	CLS with unknown/HIV+ partner	6 months	/	/	Marginal risk difference [xiv]	Reference -16.5 [-22.7, -10.2]	Age, ethnicity, poverty, social support, discrimination, alcohol
					Receptive CLS with unknown/ sero-different partner	6 months	/	/	Marginal risk difference [xiv]	Reference -6.4 [-10.8, -2.1]	Age, ethnicity, poverty, social support, discrimination, alcohol
FIP [(353)] U.S. (N=89 HIV-men; N=120 overall, 26% HIV+), online	0%	BDI-II mean score (10.7; SD=1)	2 months	100%[s]	CLS 1+ occasions	2 months	96%[q]	/	/	/	/
					Frequency of CLS with HIV+ partner	2 months	Media n=1,IQ R=3	0.23 Spearman's rho *p<0.05*	/	/	/
					Any CLS with HIV+ partner: Yes No	2 months	49.4%	% reporting high BDI-II scores[p]; 13.5% 7.9% Mann-Whitney U test *p=0.016*	RR[r]	BDI-II as dependent variable: Wald (1, n= 83)=4.49; *p=0.034*	Ethnicity, income, education

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
MAPS[(357)], U.S. (N=62[xxvi]), online	/	CES-D: None (≤15) Mild Major (27+)	12 months	100%	CLS with 1+ partners	3 months	/	15.8% 25.0% 62.5% χ^2 test *p=0.04*	/	/	/
Vanden Berghe et al 2014[(358)], Belgium (N=591), online	0%[h]	CES-D≤21 **CES-D>21[f]** **(29.3%)**	6 months	100%[g]	CLS with casual partner	6 months	34.0%	1 1.66 [1.16, 2.37] *p=0.006*	OR	1 0.94 [0.58, 1.54] *p=0.806*[i]	Socio-demographic and lifestyle factors[j]
P18 Cohort [(365)], U.S. (N=509), online	0%[xv]	BDI-II score: Minimal 0-9 Mild 10-18 **Moderate** 19-29 **Severe** 30-36	12 months	100%[xvi]	Acts of CLS: 0 1 >1	4 weeks	4.6 mean acts SD=7	0.09 Spearman's rho *p<0.05*	/	/	/
		BDI-II mean score (9.8; SD=8.7)			CLS with 1+ partners	4 weeks	21.0%	/	IRR[xvii]	0.99 [0.97, 1.01] *p=0.228*	Drugs, alcohol, relationship, education, SES, compulsive sexual behaviour

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association found (for each study significant associations are shown in red)											
One Thousand Strong [364], U.S. (N=1033), online	0%[h]	CES-D[xx] mean score (16.3; SD=11.5)	/	/	CLS with a casual partner	3 months	32.0%	/	OR	1.21 [0.96, 1.54] *p=0.11*	Age, ethnicity, education, relationship
					Receptive CLS with a casual partner		/	/	OR	1.43 [1.08, 1.90] *p<0.01*	
					Insertive CLS with a casual partner		/	/	OR	1.17 [0.90, 1.51] *p=0.24*	
					CLS events with casual partners		/	/	RR[xxi]	1.40 [1.23, 1.60] *p<0.001*	
					Receptive CLS events with casual partners		/	/	RR[xxi]	1.97 [1.67, 2.32] *p<0.001*	
					Insertive CLS events with casual partners		/	/	RR[xxi]	1.19 [1.02, 1.38] *p=0.02*	
		CES-D: Quadratic term			CLS events with casual partners		/	/	RR[xxi]	1.32 [1.08, 1.63] *p<0.01*	
					Receptive CLS events with casual partners		/	/	RR[xxi]	1.63 [1.25, 2.12] *p<0.001*	
					Insertive CLS events with casual partners		/	/	RR[xxi]	1.09 [0.87, 1.36] *p=0.44*	

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association not found											
YMS [(347)], U.S. (N=429), community/ commercial gay venues	/	CES-D<16 **CES-D≥16 (22.8%)**	/	/	CLS with non-monogamous partner	6 months	8.9%	1 1.57 [0.80, 3.10]	OR	1 1.08 [0.51, 2.30]	Education, 50+ lifetime sex partners, age at first anal sex<18
					Receptive CLS with non-monogamous partner	6 months	6.1%	1 1.23 [0.66, 2.27]	OR	1 0.86 [0.43, 1.71]	Education, 50+ sex partners, age at first anal sex<18, age at first oral sex<18, forced sex
Dudley et al 2004[(370)], U.S. (N=154), community/ commercial gay venues	/	SF-36 Health Survey [iv] mean score (3.0, SD=1.1)	3 months	59.9%	CLS with 1+ partners	3 months	22.1% [vb] 39.2% [vi]	/	RR[vii]	β=0.04 *p>0.05*	Age, relationship, personality traits, risk behaviour[vii]
Sex and Love [(371)], U.S. (N=669), community/ commercial gay venues	11%	CES-D≤22 **CES-D>22 (47.4%)**	/	/	CLS with non-primary partner of unknown/ sero-different status	3 months	11.5%	1 2.04 [1.23, 3.37]	OR	1 1.62 [0.89, 2.96]	Age, education, ethnicity, income, HIV status, poly-drug use, CSA, IPV, sexual compulsivity

Table 1: Studies conducted from 1996 that have investigated the association between depression and sexual risk behaviour among samples of MSM, including HIV-negative MSM, in North America and Western Europe, according to whether an association was found and recruitment setting (continued)

	HIV+ (self-report)	Prevalence of depression	Prevalence of sexual intercourse (with a man)		Prevalence of CLS (with a man)			Association of depression with sexual risk behaviour			
Study, country, sample size of MSM, recruitment setting [xiii]:	%	Measure **%depressed**	Recall period	%	Measure	Recall period	%	Prevalence of sexual behaviour in those without and with depression and unadjusted association	Measure of effect size	Adjusted association for depression vs no depression	Variables adjusted for
Association not found											
HONOR [(372)], U.S. (N=173)[ix], community/ commercial gay venues	34%	CES-D<10 **CES-D≥10 (54.1%)**	12 months	72%	CLS with 1+ partners	12 months	48.6%	1 1.5 [0.8, 2.8]	OR	1 1.0 [0.5, 2.1]	Age, housing status
					CLS with unknown/sero-different partner	12 months	20.0%	1 2.3 [1.0, 5.0]	OR	1 1.8 [0.7, 4.3]	Age, housing status
Bareback Project [(346)], U.S. (N=332)[viii], online	59%	CES-D<16 **CES-D≥16 (26.7%)**	/	/	Proportion of anal sex acts that involve condoms	3 months	/	/	Beta values from SEM	*p=0.370*	Demographic and psychosocial factors[xxx]
Maksut et al 2016[(373)], U.S. (N=230 YBMSM; N=220 OBMSM [xxiv]), online	0%[h]	YBMSM: CES-D10<10 **CES-D10≥10 (45.0%)**	12 months	100% [xxv]	CLS with 1+ partners	3 months	/ (100% past year)	1 1.02 [0.99, 1.04]	RR[xxi]	/	/
		OBMSM: CES-D10<10 **CES-D10≥10 (50.8%)**			CLS with 1+ partners	3 months	/ (100% past year)	1 1.01 [0.99, 1.03]	RR[xxi]	/	/
Martinez et al 2016[(433)], U.S. (N=176), online	34%	CES-D10<10 **CES-D10≥10 (69.4%)**	/	/	CLS with 1+ partners	3 months	50.6%	χ^2= 3.48, *p>0.05* (proportions not shown)	/	/	/

OR= Odds Ratio using logistic regression; RR= Risk Ratio using linear regression (or negative binomial regression); HR= Hazard Ratio using cox regression; GEE= generalized estimating equations; SD= standard deviation; IQR= Interquartile range.

[a] The SSBQ is a 27-item measure of sexual behaviour that collects information on barrier methods used during sex, participation in high-risk sexual behaviour, exchange of body fluids during sex and communication skills to negotiate safe sex practices.

[b] The mean severity score was not reported, only the prevalence of depressive symptom severity categories was presented, however continuous scores were investigated in analyses presented.

[c] Investigated as a continuous variable in linear regression. The mean number of CLS partners of unknown/sero-different status in the past three months was 3 (standard deviation=5).

[d] Effect estimates from standard linear regression models. Reporting (higher levels of) depressive symptoms on CES-D was associated with increased reporting of sexual risk behaviour.

[e] As the CES-D depression severity score increased so did reporting of the number of CLS partners of unknown/sero-different status. It is of note that two variables (self-efficacy and cognitive escape) were considered to be on the causal pathway between depressive symptoms and sexual risk behaviour, and were therefore, investigated in mediational analysis. The estimate shown in the table is from the model adjusted for self-efficacy; the estimate from the model adjusted for cognitive escape is very similar ($F(2, 1522)=8.59$; $\beta=0.062$; $R^2=0.011$; $p<0.001$). These findings are discussed in detail in Chapter 6.

[f] Indicates symptoms of acute depression.

[g] To be included in the study, all men had to have reported at least one episode of anal sex with a casual partner in the past six months.

[h] Men who self-reported an HIV positive status were excluded from this study.

[i] Although this association was no longer significant after adjustment for factors, the unadjusted analysis is focused upon when reporting findings from this study, since a measure of supportive networks was included in the adjusted model, and levels of social support are thought to be highly correlated with depression (see section 1.6.3).

[j] Age, education, markers of sensation seeking, alcohol use, drug use, risk perception regarding insertive CLS, risk perception regarding receptive CLS, markers of unsupportive social interactions, and perceived social norm for condom-use.

[k] 21 men had missing data on CLS with an unknown/sero-different partner. Since the prevalence of depression was presented according to men who reported this sexual risk behaviour and men who did not, the denominator reported for the overall prevalence of depression was 101 instead of 122 (the full sample size reported).

[l] Based on denominator of 117 men.

[m] Based on denominator of 101 men.

[n] Multiple, casual, or HIV sero-different or unknown partners in the past six months.

[o] Based on a multinomial logistic regression model, whereby each sexual risk behaviour measure is compared to men who reported no CLS or no risk partner.

[p] Depression was investigated as the dependent variable in unadjusted analysis.

[q] Based on sample of 120 HIV+ and HIV- men.

[r] Reporting CLS with an HIV positive partner in the past two months was associated with elevated depressive symptoms on BDI-II in standard linear regression.

[s] It is assumed that almost all men would have reported sexual intercourse in the past two months given that 96% of the whole study sample (N=120) reported at least one occasion of CLS in the past two months, and that at enrollment, men were required to have reported intentional CLS with a man met over the Internet, during the past two months, to be included in the study.

[t] Antibody testing was performed at baseline, and men who received a positive test result were not included in the study.
[u] Men were excluded from the study if they reported a mutually monogamous relationship for two or more years with a man known to be HIV negative.
[va] Overall HIV incidence over the course of the four year study.
[w] Not reported since not found to be significant.
[xa] Using Cox regression analysis.
[y] Effect estimate not presented since it was investigated whether depression mediates the association between CSA and CLS measures. It was reported that depression was associated with CLS with an unknown/HIV positive partners, even after adjustment for CSA, but data were not presented.
[z] This measure has been inverted for the sake of uniformity in this table. This measure was in fact investigated as a composite measure of risk reduction. Participants were asked whether they engaged in (i) rimming, (ii) mutual masturbation, (iii) digital penetration, (iv) use of sex toys, or (v) 100% condom-use, in the past year to specifically reduce their risk of acquiring/transmitting HIV. Men who answered 'yes' to at least one of these five options were considered to be risk reducers. Men who reported condom-use 100% of the time in the past year were also considered to be risk reducers and men who reported CLS with one or more partners in the past year were not considered to be risk reducers. Men with depressive symptoms were less likely to be considered risk reducers (OR 0.48 95% CI: 0.22, 1.01; adjusted OR 0.32 95% CI: 0.11, 0.92) and thereby, more likely to report sexual risk taking as shown in the derived estimates in the table.
[ii] Based on denominator of 2667 men who responded to the question regarding HIV status.
[iii] Age at baseline, ethnicity, cohort, study center, education level, number of sexual partners, number of insertive CLS sexual partners, number of receptive CLS partners, insertive rimming, cocaine use, methamphetamine use, needle use, ecstasy use, popper use, and alcohol consumption.
[iv] Measures symptoms of anxious or depressed mood within the past month, with six response options ranging from 'all of the time' to 'none of the time'. Higher scores indicate higher levels of anxiety and depression.
[vb] Of all 154 men included in the analysis.
[vi] Of the 88 men who reported anal sex in the past three months.
[vii] Risk ratio by hierarchical linear regression, which determines whether variables of interest explain a statistically significant amount of variance in the dependent variable. In this study, hierarchical linear regression was used to determine whether higher levels of depression contributed significantly to the prediction of frequency of CLS beyond the variance accounted for by age, relationship status, personality variables (impulsive decision making, high sensation seeking, and internalized homophobia), and other risk behaviour (number of anal sex partners in the past three months, alcohol use and marijuana use).
[viii] The inclusion criteria for this study required that all men reported using the Internet specifically to find other men with whom they could engage in CLS.
[ix] All of whom identified as American Indian/Alaskan Native.
[xb] Study inclusion criteria required that men reported two or more occasions of alcohol use/one or more occasions of non-injection drug use during or immediately before sex, and reported CLS with an unknown or HIV sero-different male partner in the past six months.
[xi] Ethnicity, number of male sex partners (past 6 months), receptive CLS, insertive CLS, use of amphetamine, alcohol use, and self-reported STI diagnosis.
[xii] Age, ethnicity, education, income, 'outness', HIV status, STI history, drug and alcohol use, and sexual partner meeting venues.
[xiii] In some cases, the setting at which the largest proportion of the sample was recruited was not reported, in the context of mixed approaches to recruitment. In such cases, if online sampling was reported, this method of recruitment was assumed to have generated the largest number of men for study participation, and if a range of community/commercial gay venues was sited together with clinics (referred to as sexual health clinics rather than GUM clinics, given that GUM is a UK specific term) as sites of recruitment, the former was again assumed to have generated the largest number of men for study participation.

[xiv] Marginal risk differences (using marginal structural models with inverse-probability-of-exposure weighting, binomial distributions, and identity links) were used to show the difference in risk of the outcome between the exposure groups of interest, averaged over the population of interest.
[xv] At baseline (2009-2010) men were required to self-report a seronegative or unknown HIV status in order to be eligible for study enrolment. The association between depression and sexual risk behaviour is investigated at the six month follow-up. Although it is not reported whether some men were diagnosed with HIV from baseline to the time of the six month follow-up, it seems likely that the vast majority of participants were not known to be HIV positive (especially given the age group of the study: 18-19 year olds).
[xvi] To be eligible for study enrolment men had to have reported being 'sexually active with another man during the 6 months prior to interview' (page 1433) at baseline. At the six month follow-up it was therefore assumed that all men would have been sexually active in the past year (this data was not given). It is of note however, that the requirement of being sexually active does not necessarily mean anal sex with man.
[xvii] Based on negative binomial regression.
[xviii] Each individuals sexual risk trajectory was modelled, based on a sexual risk behaviour score for every six month interval between study visits. For instance, the sexual risk behaviour score was generated as follows, not engaging in any anal sex since the last visit was given a score of 0 and engaging in anal sex but no CLS since the last visit was given a score of 1, higher scores were given for engaging in insertive CLS and higher still for engaging in receptive CLS since the last visit. Men who scored <4 at a particular six month interval were considered to indicate a 'low risk interval', and those who score ≥4 at a particular six month interval were considered to indicate a 'high-risk interval'. Sexual risk trajectories were modelled and individuals were placed in one of three groups: low risk, moderate risk, or high-risk, depending on the amount of low and high-risk intervals reported- with a greater number of high-risk intervals, men were placed in the high-risk group and vice versa.
[xix] Group-based (Nagin's) trajectory modelling using Proc Traj.
[xx] Adapted to ask participants about symptoms within the past three months rather than past week.
[xxi] Based on negative binomial regression models.
[xxii] Using mixed level logistic regression. Random effects for study site were included.
[xxiii] Based on the sample of 2131 men who had completed at least one CES-D. The mean number of months prior to CES-D completion was 15 (the CES-D depression symptom questionnaire was only incorporated after July 2009, at which time it became apparent that the prevalence of depression related adverse events was very high, 296 events recorded during follow-up.
[xxiv] YBMSM= young (≤29 years of age) black MSM; OBMSM= old (≥30 years of age) black MSM. Men who identified as black or African American were included.
[xxv] Men were only eligible for study inclusion if they reported CLS in the past year with a man, therefore it follows that 100% of men would have reported anal sex with a man in the past year.
[xxvi] Self-identified Asian MSM, only 62 of whom had data on depressive symptoms and CLS.
[xxvii] Men who were categorized as having a major depressive syndrome or other depressive syndrome on PHQ-9 (including dysthymia, seasonal affective disorder, bipolar disorder) were compared to men who did not.
[xxviii] No receptive CLS reported.
[xxix] No insertive CLS reported.
[xxx] Demographic factors (not defined), substance use, attitudes to condom-use, childhood maltreatment, and sex-related preferences.

2.5 Results review (ii): UK studies that have investigated sexual behaviour among HIV-negative MSM

2.5.1 Relevant UK studies

In total, 27 UK studies conducted from 1996-2014, comprising of 68 separate surveys, that recruited a sample of MSM or HIV-negative MSM and investigated measures of HIV sexual transmission risk behaviour, were identified. Most of these studies consisted of a serial cross-sectional design, whereby the recruitment of men for survey completion was repeated over a number of years. A brief summary of all studies identified is given below according to recruitment setting. Table 2 presents each study with the year of recruitment and sample size, according to recruitment setting. Table 2 also shows in which surveys sexual behaviour measures considered to be most frequently collected in behavioural surveillance studies of HIV transmission among MSM, were measured. The most common measures of CLS were considered to be: (i) CLS with one or more partners, (ii) CLS with two or more partners, and (iii) CLS with a partner of unknown or sero-different HIV status. For measure (iii), a sero-different partner includes both HIV-negative and HIV-positive men, depending on the HIV status of the man reporting the CLS. It is of note however, that determining whether a partner is of a sero-different HIV status is complicated by the fact that, depending on the timing of the last HIV test, an individual who may consider himself to be HIV-negative may in fact be HIV-positive. Where studies collected information on measures (i), (ii), or (iii), a tick is shown in Table 2. The CLS measures presented in Table 2 do not cover all sexual behaviour measures that each study collected. The prevalence of CLS measures (i)-(iii) are presented and discussed in section 2.5.2.

In addition, Table 2 shows in which surveys socio-demographic and psychosocial factors defined *a priori* to be of greatest relevance to sexual behaviour, as well as mental health, among MSM, were measured. Key socio-demographic factors were considered to be: age, ethnicity, sexual identity, education, and relationship status. These variables were considered to constitute the major demographic factors and the most common socio-economic measures. Key psychosocial factors were considered to be: depression, recreational drug and alcohol use, childhood sexual abuse (CSA), and intimate partner violence (IPV). Where information on a factor was collected, a tick is shown in Table 2. The measures presented in Table 2 do not cover all socio-demographic and psychosocial variables that each study collected. Of note, one of the studies in Table 2 that measured depression [(355)], was also included in review (i). The other studies in Table 2 that measured depression were not included in review (i) since they did not investigate the association between depression and sexual behaviour. A review of socio-demographic and psychosocial factors investigated and found to be associated with sexual behaviour measures, is presented in section 2.5.4.

2.5.1.1 General population

Only the British National Survey of Sexual Attitudes and Lifestyles (Natsal) recruited MSM from the British general population. Natsal uses a multistage probability sampling method to select men and women resident in private households in Britain and consists of a cross-sectional survey, which has been conducted three times to date [457, 458].

2.5.1.2 Sexual health clinics

Ten studies recruited convenience samples of men from GUM clinics, mostly for one-off surveys. Seven studies recruited MSM from GUM clinics in London [102, 355, 459-466] or Brighton [467], including one randomized controlled trial (RCT) of a cognitive behavioural intervention to reduce STIs among gay-identified men in London [461]. Three studies recruited MSM from GUM clinics in several cities across the UK [35, 468, 469]. These included two annual behavioural surveillance surveys: the *Lymphogranuloma venereum* (LGV) Enhanced Surveillance system [468] and the GUM clinic activity dataset (GUMCADv2) [469]. GUMCADv2 is an anonymized, patient-level, electronic dataset which collects information on STI diagnoses from all patients attending GUM clinics and other sexual health services in England [470]. The socio-demographic characteristics of each patient is collected for GUMCAD at the first clinic attendance. Information on sexual orientation is ascertained as part of sexual history taking in clinic and is incorporated into the GUMCAD dataset.

2.5.1.3 Community and commercial gay venues

Eight studies recruited a convenience sample of men from community or commercial gay venues. Of these studies, five used time-location sampling (TLS) to recruit men visiting gay bars, clubs, and saunas: The Gay Men's Sexual Health Survey (GMSHS) in England (conducted 14 times to date) [117, 120, 144, 471-473], the GMSHS in Glasgow and Edinburgh (conducted six times to date)[180, 474-476], Testing Barriers project in Glasgow and Edinburgh (conducted three times to date) [96-98, 103-105, 477], and two one-off cross-sectional surveys in Edinburgh [478] and Glasgow (Make Your Position Clear, MYPC) [479, 480]. One study, the Gay Men's Survey, recruited a consecutive sample of men visiting gay bars, clubs, and saunas in London (one-off survey) [481], and another study, the 4 gym project, recruited a consecutive sample of MSM attending gyms in central London (conducted seven times to date) [116, 129, 482-487]. The final study recruited a volunteer sample of MSM reading gay magazines for an HIV risk reduction intervention addressing sadomasochistic sex (the 'SM' sex study) in London. An RCT was set up to establish its efficacy [488].

2.5.1.4 Online

Finally, eight studies recruited a volunteer sample of men online, predominantly from gay dating websites: The Gay Men's Sex Survey (GMSS) across the UK (conducted 13 times to date) [489-497], The Sigma Panel in England (monthly programme of focused questions) [414], The Internet

and HIV Study in London (conducted twice to date) [464-466], The Men and Sexual Health (MESH) Project of BAME and migrant MSM across the UK (one-off survey) [498, 499], the Sexual Attitudes and Lifestyles of London's Eastern Europeans (SALLEE) Project in London (one-off survey) [500], the Social Media, MSM and Sexual Health (SMMASH) Survey in Scotland, Wales, Northern Ireland, and the Republic of Ireland (one-off survey) [481, 501, 502], the Dean Street at Home (DS@H) study across the UK (one-off survey) [503], and a one-off survey of young MSM (aged 18-25 years) across the UK [504].

The majority of studies in this review included men known to be HIV-positive. Across studies, the proportion of men reporting a positive HIV status ranged from 6.4% (SMMASH) [501] to 22% (4 gym project) [116]. The vast majority of studies incorporated self-completion questionnaires. With the exception of two studies (the 'SM' sex study [488] and an RCT of GUM clinic attendees [461]), all consisted of a cross-sectional design and most carried out serial (repeated) surveys, which did not include the linking of participants between surveys. At the time of submitting this thesis (December 2017), one study was identified that would have been eligible for this review but recruited men from 2015 onwards [416]. In this cross-sectional survey study, users of a popular geosocial-networking smartphone app for gay, bisexual, and other MSM were recruited in January 2016 (N=179). Advertisements were limited to users in London. Information was collected on a range of socio-demographic, health, and lifestyle factors, as well as sexual behaviours including HIV testing and PEP use. Of note, depressive symptoms were measured on the PHQ-2 and the prevalence observed is described in Chapter 4. The association between depressive symptoms and sexual behaviour measures was not investigated, only factors associated with PEP awareness and use has been assessed. The key measures of CLS investigated in this review were not collected [416].

Table 2: UK studies of sexual behaviour among MSM and collection of key socio-demographic, psychosocial, and sexual behaviour measures

	Age	Ethnicity	Sexual identity	Education	Relation-ship status	Depression	Drug use	Drinking	CSA[J]	IPV[K]	CLS with 1+ partner Recal period in months:			CLS with 2+ partners Recal period in months:			CLS with unknown/ sero-different partner Recal period in months:		
Study											3	6	12	3	6	12	3	6	12
General population:																			
Natsal-1 1990 (N=90[f])[(115)]	✓	✓		✓	✓		✓	✓											
Natsal-2 2000 (N=133[f])[(115)]	✓	✓		✓	✓		✓	✓					✓						
Natsal-3 2010-2012 (N=190[f])[(342)]	✓	✓	✓	✓	✓	✓[i]	✓	✓					✓			✓			
GUM clinics:																			
Clinic survey 1995-1996 (N=285)[(462)]			✓												✓				
Clinic survey 1997-1998 (N=470)[(102)]	✓	✓									✓								
Clinic-based RCT 1995-1997 (Baseline N=361)[(461)]	✓	✓		✓									✓						
Clinic-based intervention 1999 (N=65 HIV testing) 2000 (N=292 HIV testing)[(460)]	✓	✓																	
Clinic-based survey 1999 (N=122)[(355)]	✓	✓	✓	✓	✓	✓[h]	✓		✓				✓						
The Internet and HIV Study (HIV testing clinics) 2002-2003 (N=404)[(465)]	✓	✓	✓	✓	✓		✓				✓						✓		
LGV Enhanced Surveillance System 2004-2010 (N=1281)[(468)]	✓	✓	✓																
Clinic survey 2005 (N=2162)[(35)]	✓	✓									✓								
Clinic survey 2005-2007 (N=301)[(467)]	✓	✓	✓	✓															

Table 2: UK studies of sexual behaviour among MSM and collection of key socio-demographic, psychosocial, and sexual behaviour measures (continued)

	Age	Ethnicity	Sexual identity	Education	Relation-ship status	Depression	Drug use	Drinking	CSA[J]	IPV[k]	CLS with 1+ partner Recal period in months:			CLS with 2+ partners Recal period in months:			CLS with unknown/ sero-different partner Recal period in months:		
Study											3	6	12	3	6	12	3	6	12
GUM clinics:																			
Clinic surveillance data 2011-2014 (N=16422)[(469)]	✓	✓	✓																
Community/commercial gay venues:																			
GMSHS England 1996[b] (N=2482)[(144)]	✓	✓														✓			
GMSHS England 1997[b] (N=2121)[(144)]	✓	✓														✓			
GMSHS England 1998[b] (N=2068)[(144)]	✓	✓														✓			
GMSHS England 1999[c] (N=2030)[(117)]													✓						✓
GMSHS England 2000[c] (N=1058[d])[(117, 473)]	✓	✓		✓									✓			✓			✓
GMSHS England 2001 (N=1138[d])[(473)]	✓	✓		✓									✓						✓
GMSHS England 2002 (N=907[d])[(473)]	✓	✓		✓									✓						✓
GMSHS England 2003 (N=1235[d])[(473)]	✓	✓		✓									✓						✓
GMSHS England 2004 (N=1173[d])[(473)]	✓	✓		✓									✓						✓
GMSHS England 2005 (N=1291[d])[(473)]	✓	✓		✓									✓						✓

Table 2: UK studies of sexual behaviour among MSM and collection of key socio-demographic, psychosocial, and sexual behaviour measures (continued)

	Age	Ethnicity	Sexual identity	Education	Relation-ship status	Depression	Drug use	Drinking	CSA[J]	IPV[K]	CLS with 1+ partner Recal period in months:			CLS with 2+ partners Recal period in months:			CLS with unknown/ sero-different partner Recal period in months:		
Study											3	6	12	3	6	12	3	6	12
Community/commercial gay venues:																			
GMSHS England 2006 (N=927[d])[(473)]	✓	✓		✓									✓						✓
GMSHS England 2008 (N=920[d])[(473)]	✓	✓		✓									✓						✓
GMSHS England 2011 (N=842[d])[(472, 505)]	✓	✓		✓									✓			✓			✓
GMSHS England 2013 (N=647[d])[(473)]	✓	✓		✓									✓						✓
GMSHS Scotland 1996 (N=2276)[(475)]	✓			✓	✓								✓			✓			✓
GMSHS Scotland 1999 (N=2498)[(475)]	✓			✓	✓								✓			✓			✓
GMSHS Scotland 2002 (N=1734)[(118)]	✓			✓									✓			✓			✓
GMSHS Scotland 2005 (N=1744)[(506)]	✓			✓												✓			✓
GMSHS Scotland 2008 (N=1330)[(477, 507, 508)]	✓															✓			
GMSHS Scotland 2011[e] (N=1515)[(509)]	✓		✓	✓			✓	✓					✓			✓			✓
Testing Barriers 1999-2000 (N=713)[(104, 477)]	✓			✓									✓			✓			

Table 2: UK studies of sexual behaviour among MSM and collection of key socio-demographic, psychosocial, and sexual behaviour measures (continued)

	Age	Ethnicity	Sexual identity	Education	Relation-ship status	Depression	Drug use	Drinking	CSA[J]	IPV[K]	CLS with 1+ partner Recal period in months:			CLS with 2+ partners Recal period in months:			CLS with unknown/ sero-different partner Recal period in months:		
Study											3	6	12	3	6	12	3	6	12
Community/commercial gay venues:																			
Testing Barriers 2002 (N=283)[104, 477]	✓			✓									✓			✓			
Testing Barriers 2003 (N=275)[105, 477]	✓			✓									✓			✓			
Community-based survey 1998 (N=506)[478]	✓						✓	✓			✓								
MYPC intervention 2010 (10-month follow-up N=784) [479, 480]	✓			✓									✓			✓			✓
Gay Men's Survey 2011 (N=1216) [481]	✓		✓	✓									✓						
Gym-based intervention 1997 (Baseline N=1004)[482-484]	✓	✓	✓	✓	✓		✓				✓								
4 gym project 1998 (N=834)[116]	✓	✓	✓	✓	✓												✓		
4 gym project 1999 (N=630)[116]	✓	✓	✓	✓	✓												✓		
4 gym project 2000 (N=739)[487]	✓	✓	✓	✓	✓	✓[g]	✓	✓									✓		
4 gym project 2001 (N=735)[116]	✓	✓	✓	✓	✓												✓		
4 gym project 2002 (N=828)[116]	✓	✓	✓	✓	✓												✓		
4 gym project 2003 (N=498)[116]	✓	✓	✓	✓	✓												✓		
Community-based RCT ('SM sex' Study) 2003 (N=50)[488]	✓	✓		✓							✓		✓				✓		✓
Online:																			
GMSS[a] 1998 (N=6315)[510]	✓	✓	✓	✓	✓				✓				✓			✓			✓

Table 2: UK studies of sexual behaviour among MSM and collection of key socio-demographic, psychosocial, and sexual behaviour measures (continued)

	Age	Ethnicity	Sexual identity	Education	Relation-ship status	Depression	Drug use	Drinking	CSA[J]	IPV[K]	CLS with 1+ partner Recal period in months:			CLS with 2+ partners Recal period in months:			CLS with unknown/ sero-different partner Recal period in months:		
Study											3	6	12	3	6	12	3	6	12
Online:																			
GMSS[a] 1999 (N=9322)[511]	✓	✓	✓	✓			✓						✓			✓			✓
GMSS[a] 2000 (N=9789)[489]	✓	✓	✓	✓	✓								✓						
GMSS[a] 2001 (N=14616)[490]	✓	✓		✓															
GMSS[a] 2002 (N=16871)[492]	✓	✓	✓	✓	✓								✓						
GMSS[a] 2003 (N=14551)[493]	✓	✓		✓	✓														
GMSS[a] 2004 (N=16002)[494]	✓	✓		✓	✓		✓	✓											
GMSS[a] 2005 (N=16426)[495]	✓	✓		✓									✓						
GMSS[a] 2006 (N=12155)[496]	✓	✓	✓	✓	✓		✓	✓					✓						
GMSS[a] 2007 (N=8716)[497]	✓	✓	✓		✓														✓
GMSS[a] 2008 (N=7461)[512]	✓	✓	✓	✓	✓								✓			✓			
GMSS[a] 2010 (EMIS) (N=15456)[505, 513]	✓		✓				✓	✓								✓			
GMSS 2014 (N=15360)[514]	✓	✓	✓	✓	✓		✓	✓				✓	✓						
The Internet and HIV Study (online) 2002 (N=4974)[464, 466]	✓	✓	✓	✓	✓		✓				✓						✓		
The Internet and HIV Study (online) 2003 (N=2539)[465]	✓	✓	✓	✓	✓		✓				✓						✓		
MESH 2007-2008 (N=13278)[498, 499]	✓	✓	✓	✓			✓				✓						✓		
SALLEE 2009 (N=691)[500, 515]	✓	✓		✓			✓												✓
The Sigma Panel 2011- 2012 (9 'Blasts' N=224-1823)[414, 516-523]	✓	✓		✓	✓		✓												

Table 2: UK studies of sexual behaviour among MSM and collection of key socio-demographic, psychosocial, and sexual behaviour measures (continued)

	Age	Ethnicity	Sexual identity	Education	Relation-ship status	Depression	Drug use	Drinking	CSA[j]	IPV[k]	CLS with 1+ partner Recal period in months:			CLS with 2+ partners Recal period in months:			CLS with unknown/ sero-different partner Recal period in months:		
Study											3	6	12	3	6	12	3	6	12
Online:																			
SMMASH 2012-2013 (N=2668)[481, 501]	✓	✓	✓	✓	✓								✓			✓			
Online survey 2012-2013 (N=702)[504]	✓	✓	✓	✓	✓								✓						
DS@H[l] 2012-2014 (N=17361)[503]	✓																		

[a] Annual GMSS reports are available from 1998 onwards. No survey was undertaken in 2009. In 2010, the survey was conducted as part of the European MSM Internet Sex survey (EMIS).
[b] Changes in sexual behaviour over time from the 1996 to 1998 survey was investigated.
[c] Changes in sexual behaviour over time from the 1996 to 2000 survey was investigated. Of note, the denominator (number of participants who returned a questionnaire) was not reported for the 1999 survey. Since it was stated; 'Similar numbers of questionnaires were returned each year' (page 237)[118], an average of the survey samples from 1996, 1997, 1998, and 2000 is presented as an approximation of the survey sample in 1999 (N=2030).
[d] Participants who had an HIV-negative Orasure test result.
[e] Although the final GMSHS Scotland was undertaken in 2014, no papers had been published on this data at the time of this thesis completion.
[f] Men reporting at least one male partner with whom they had genital contact in the five years prior to interview.
[g] One question: 'generally in the past 6 months I have felt depressed' (response options: strongly agree; agree; strongly disagree; disagree).
[h] Depressive symptoms and anxiety on HADS and self-esteem on the Rosenberg self-esteem scale.
[i] Depressive symptoms on PHQ-2 and reporting having received treatment for depression from a health professional over the past year.
[j] Childhood sexual abuse.
[k] Intimate partner violence.
[l] Information was collected on report of CLS with an unknown/HIV-positive status partner since the last negative HIV test.

2.5.2 Prevalence of CLS across UK recruitment settings

Of all 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 58 presented a prevalence estimate for: (i) CLS with one or more partners, (ii) CLS with two or more partners, or (iii) CLS with a partner of unknown or sero-different HIV status. Of these 58 studies, 41 presented the prevalence of CLS measures in the past year, two presented the prevalence in the past six months, and 15 presented the prevalence in the past three months (see Table 2). Of the remaining ten studies, two asked questions about insertive and receptive CLS separately [490, 493], one asked whether participants considered their past sexual practices to be risky and if so to describe why they considered this to be the case [494], and three focused entirely on HIV testing rates [460, 503] and acceptability of home sampling kits for STI/HIV [467]. Furthermore, two studies investigated episodes of LGV [468] and PEP prescription[469], another focused entirely on attitudes to, experiences of and access to condom-use[414, 516-523], and finally, Natsal-1 did not ask about condom-use during sex [115].

Given the amount of data collected on this recall period, the prevalence of CLS measures (i), (ii), and (iii) in the past year is presented in Figure 4 below, Figure 29 (in Appendix section 11.6), and Figure 30 (in Appendix section 11.6) respectively. The prevalence of CLS measures (i) and (iii) in the past three months is also presented in Figure 31 and Figure 32 (in Appendix section 11.6) respectively. Repeated surveys were treated as separate studies. All relevant estimates found for each study were included. Figures are colour coded according to recruitment setting. The dashed reference lines provided demarcate whether the prevalence estimates are below or above 25% or 50% depending on whether the scale went up to 50% (Figure 29, Figure 30, and Figure 32) or 100% (Figure 4 and Figure 31) respectively. No test of significance is implied by these reference lines, they are used only as a visual aid to compare estimates.

The differences observed between studies in prevalence estimates of CLS measures may reflect differences in study recruitment, bearing in mind that some studies used mixed approaches to recruitment (GMSS and GMSHS England). Differences may, however, also reflect variation in study population characteristics, inherent differences in different cities, method of ascertainment of information (i.e. self-report versus interviewer administered; CASI versus paper), and trends in behaviour over calendar time. It is not possible to disentangle these effects. That being said, there does appear to be a pattern in the differences observed between prevalence estimates according to study recruitment site for each measure of CLS and across both recall periods presented. This is briefly discussed for the measure of CLS with one or more partners in the past year (Figure 4).

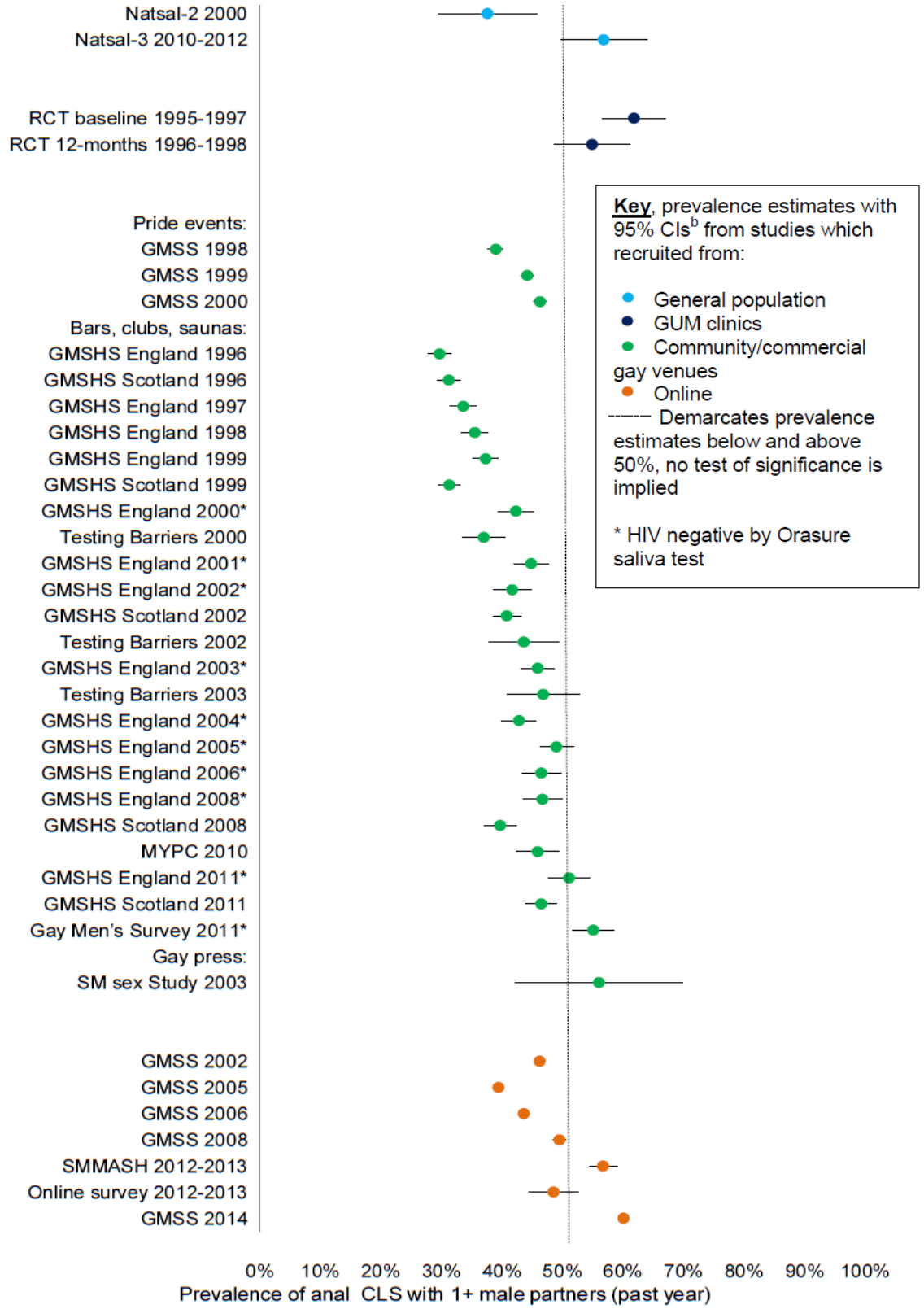
Natsal represents a gold standard as it is a representative sample of the general population. The prevalence estimates in Figure 4 were 37.6% and 56.8% in Natsal-2 and Natsal-3.

Unfortunately, estimates derived from the Natsal MSM sub-sample are relatively imprecise given the small sample size (Natsal-2 N=133; Natsal-3 N=190). The estimates derived from clinic samples come from one RCT of the same men surveyed at baseline (1995-1997) and 12-months later. Since some men were randomized to a cognitive behavioural intervention to reduce STIs, the baseline prevalence estimate of 61.8% may be more relevant when comparing with other studies. This baseline prevalence of CLS among men attending GUM clinics appears to be the highest estimate found. The confidence interval is however somewhat wide given the relatively small sample size of 361 men. Men recruited online also appear to report a slightly higher prevalence of CLS in the past year (range from: 39.4%-60.1%) compared to men recruited from community and commercial gay venues (range from: 29.7%-56.0%). Of note, similar patterns were observed when investigating CLS with one or more partners in the past three months (see Appendix section 11.6 Figure 31).

In Figure 4, within the recruitment category of community and commercial gay venues, men recruited from Pride events appear to report a somewhat higher prevalence of CLS (range from: 39.0%-46.3%) compared to men recruited from bars, clubs, and saunas (range from: 29.7%-55.1%). Due to the transitory nature of Pride events and elevated celebratory tone, it is perhaps possible that these events elicit greater opportunity for risk-taking. Furthermore, bars, clubs, and saunas may serve as intervention sites, and men who regularly attend these venues may be more likely to be exposed to health promotion messages. Although men who attend Pride events are most likely to be community attached gay or bisexual-identified men, Pride events may also attract men who are not particularly active on the scene. Online sampling may also recruit a broader cross-section of men, some of whom may have fewer connections to the gay community, with fewer opportunities to be exposed to health interventions and lower levels of community affiliation and social support. Lower levels of social support may have negative consequences for health and wellbeing, as discussed in detail in section 1.6.3. Finally, the high prevalence observed in the SM sex Study (56.0%) which consisted of a volunteer sample of men reading gay magazines, may not be surprising given that men volunteered for an intervention addressing sadomasochistic sex, which may as a sexual practice involve greater risk-taking. As seen in the very wide confidence interval (95% CI: 42.2%, 69.8%), the number of men participating in this study was very small (N=50), making it difficult to accurately compare this particular prevalence estimate.

Finally, it is notable in Figure 4, that the prevalence of CLS appears to increase over time (1996-2011) within the repeated GMSHS England surveys. Trends in sexual behaviour may to some extent reflect changed perceptions of HIV following the introduction of ART in the late 1990s and dissemination of new HIV related information, namely the release of the Swiss Statement in 2008, as discussed in sections 1.5.3.1-1.5.4 of the thesis introduction. The apparent increase over time may reflect increased engagement in CLS or increased reporting of CLS on behavioural surveys.

Figure 4: Proportion of MSM reporting anal CLS with one or more male partners in the past year, from UK studies[a] which include HIV-negative men (1996-2014) and according to study recruitment site



[a] In GMSHS England 2000-2013, the prevalence estimate pertains to men resident in London only.
[b] Binomial 95% confidence intervals using Wald test.

2.5.3 Defining other key factors in the context of sexual behaviour among MSM

2.5.3.1 Defining recreational drug use

Recreational drug use refers to the use of chemical substances for leisure, to intentionally get 'high', rather than medical purposes. Most drugs used for recreational purposes are illicit and fall into one of three categories: hallucinogens (affecting what one sees, feels, and hears, including acid/LSD), 'downers' (affecting thought processes, heart rate, and breathing, including cannabis/marijuana), and 'uppers' (affecting speed of speech, reactions, and heart rate, including methamphetamine/crystal meth, amphetamine/speed, ecstasy/E, cocaine/crack) [(524)].

2.5.3.2 Defining childhood sexual abuse and intimate partner violence

CSA is defined as sexual victimization perpetrated during childhood and adolescence, whether perpetrated by caregivers, adults or peers [(525)]. IPV is defined as violent behaviour, which is not restricted to physical force but may also encompass emotional/psychological and/or sexual harm, carried out by or directed towards a spouse or other intimate partner [(526)]. One may be either a victim or perpetrator of IPV, or both receive and carry out abuse with a partner[xv].

Many theories have postulated the mechanisms leading to IPV, both as a victim and perpetrator, for which there are four main schools of thought: (i) psychoanalytic theories [(530-545)], (ii) social theories [(545-547)], (iii) cognitive behavioural theories [(545, 548-560)], and (iv) family and systems theories [(545, 561, 562)]. Textbox 4 provides a brief description of these theories. In summary, although the theories are rooted in disciplines of varying perspective on social phenomena, dysfunctional relationships formed with primary caregivers in early childhood and the ameliorating effects of socio-economic advantage and social support are clearly pivotal themes.

[xv] In Johnson's categorization of IPV dynamics, violence between partners often occurs in the form of: (i) intimate terrorism, whereby one partner carries out abuse via a range of control tactics that are likely to escalate over time in a cyclical pattern of abuse, remorse, pursuit, tension build-up and abuse (cycle of violence theory), (ii) mutual violent control, whereby both partners are abusive and controlling, (iii) violent resistance, whereby one partner is violent and the other responds in violent self-defence, or (iv) situational couple violence, whereby one or both partners are abusive but the abuse is not attached to a pattern of escalating control 527. Johnson MP. A typology of domestic violence. Intimate terrorism, violent resistance, and situational couple violence. United States of America: Northeastern University Press; 2008, 528. Melander LA, Noel H, Tyler KA. Bidirectional, unidirectional, and nonviolence: a comparison of the predictors among partnered young adults. Violence and victims. 2010;25(5):617-30, 529. Cycle of Violence: Women's Center. Youth & Family Services; 2017 [May 3rd 2017]. Available from: http://www.womenscenteryfs.org/index.php/get-info/prevention/education/14-cycle-of-violence.

Textbox 4: Theories predicting the onset and maintenance of IPV

Psychoanalytic theories	Social theories	Cognitive behavioural theories	Family and systems theories
Object relations theory: Abuse and neglect in childhood can manifest in adulthood as persistent feelings of unworthiness, an inability to regulate emotional responses, and a deep sense of rage as an accompaniment to the enduring search to fulfil unmet dependency needs. Some individuals develop complex psychological defences necessary for survival, which become highly integrated into one's personality structure, and may prevent individuals from recognizing and avoiding abuse in adult intimate partnerships.	**Control theory:** some individuals may have a need to obtain and maintain control and power within a relationship. Various forms of abuse may be utilized in order to achieve control, including physical force and/or psychological/emotional abuse. Individuals who seek control/power, often do not have strong attachments to significant others and accordingly do not fear negative reactions from others.	**Social learning theory:** social behaviours are learnt via the observation and imitation of others, predominantly those individuals seen as 'role models' in one's life. In the context of IPV victimization and perpetration, individuals may have learnt to carry out or receive abusive behaviours.	**Family systems theory:** combines elements from psychoanalytic theories (the relationship dynamic formed with caregivers in early life), social learning theory (the observation and imitation of role model behaviour), and social isolation theory (the role of community and social networks).
Attachment theory: abuse from a primary caregiver results in insecure and anxious emotional ties (attachments) between an infant and caregiver and dysfunctional patterns of relating to the self and others in future relationships.	**Resource theory:** suggests an association between wealth and perpetration of physical violence. Individuals with limited resources may be more likely to resort to physical force to exert control over partners, in the absence of other means with which to exert control.	**Behaviour genetics theory:** among individuals exposed to abuse in childhood, the presence of certain genes encoding aggressive behaviour, may determine violent expression towards an intimate partner.	**Family life cycle theory:** life cycle transitions (i.e. divorce and death) may stress the family unit, leading to familial dysfunction and increased risk of IPV, depending on the context of each partner's family history.
Violence as trauma theory: if the brain's limbic system is subject to an onslaught of violence induced trauma, a survival technique called 'psychological numbing' may be activated. Due to the inability to integrate memories of abuse into the larger memory structure in this state, violence is often repeated via re-enactment/alignment with individuals who carry out abuse.	**Exosystem factor theory:** in the context of having grown up with an abusive caregiver, stressful life events (i.e. job loss) and substance use, may trigger violent episodes towards an intimate partner.	**Reactive aggression:** some individuals are more prone to react to negative life events with rage and aggression, with an urge to hurt others.	**Microsystem factor theories:** stress placed on the time and resources of a family (i.e. having a disabled child) and economic dependency on a partner may increase the risk of IPV.
	Social isolation theory: among child abuse victims, the increased risk of adult IPV perpetration associated with economic disadvantage and life stressors is thought to be ameliorated by social support systems and community cohesion, and thereby exacerbated by social isolation.	**Learned helplessness:** individuals exposed to repeated abuse may lose motivation to extricate themselves from a violent situation, as they develop a durable attitude that no form of action on their behalf will possibly produce a positive outcome.	

2.5.4 Factors associated with CLS measures among MSM in the UK

Of the 68 UK studies identified in review (ii), data was collected in 66 studies for age, 52 for ethnicity, 30 for sexual identity, 53 for educational attainment, 28 for relationship status, 19 for recreational drug use, and in ten studies for alcohol use (Table 2). A small sub-set of these studies, some of which combined a number of repeated surveys (across different studies), have investigated the association of these factors with common measures of CLS: nine studies for age [118, 477, 482, 489, 509-512, 563], seven for ethnicity [482, 489, 496, 498, 499, 510-512], two for sexual identity [509, 510], eight for educational attainment [118, 482, 489, 496, 509, 510, 512, 563], four for relationship status [482, 496, 510, 512], five for recreational drug use [478, 484, 487, 509, 511], and two studies for alcohol use [478, 509]. Table 46- Table 52 in Appendix section 11.7 presents all unadjusted and/or adjusted associations of key socio-demographic and psychosocial factors with CLS measures (i) to (iii). Findings are summarized below.

Report of CLS with one or more partners was found to be associated with younger age [482, 489], lower levels of education [510], being in an ongoing relationship [482, 496, 510], substance use [511], and anabolic steriod use [484] in unadjusted and/or adjusted analysis. However, other studies failed to find an association with age [510, 511], education [482, 489], and anabolic steriod use [487] in unadjusted analysis, or with education [496] after adjusting for other socio-demographic factors.

Report of CLS with two or more partners was found to be associated with younger age [118, 477, 512, 563], lower levels of education [512] and any recreational drug use [509] in unadjusted and/or adjusted analysis. However, other studies failed to find an association with age [509] and education [509], as well as relationship status [512] in unadjusted analysis, or with education [118, 563], use of poppers (inhaled drug consisting of nitrites with euphoria-inducing effects) [509], or use of viagra [509] after adjusting for socio-demographic factors [118, 563] and substance use [509].

Report of CLS with a partner of unknown/sero-different HIV status was found to be associated with younger age [563], use of marijuana before or during sex [478], use of poppers before or during sex [478], and use of party drugs (ecstasy, LSD, amphetamine, and cocaine) before or during sex [478] in unadjusted and/or adjusted analysis. Other studies failed to find an association with education [509, 563] as well as use of any recreational drugs [509] in unadjusted analysis, or with age [509], use of poppers [509], or use of viagra [509] after adjusting for socio-demographic factors and recreational drug use.

Of note, for each factor and across CLS measures, there was no pattern whereby studies that failed to find an association had a smaller sample size (Table 46- Table 52 in Appendix section 11.7). A lack of statistical power does not appear to account for the lack of associations found in some studies.

Ethnicity [482, 489, 496, 498, 510-512], sexual identity [509, 510], and alcohol use (including 'always/sometimes drunk on alcohol' and 'drinking before/during sex') [478, 509] was not found to be associated with measures of CLS in unadjusted and/or adjusted analysis. In one study [509], an unadjusted association was observed between bisexual identity and CLS with two or more partners in the past year, but this relationship disappeared after adjusting for socio-demographic factors, frequency of gay scene use, and alcohol and drug use. Only two studies investigated associations with sexual identity and alcohol use.

Of the 68 UK studies of sexual behaviour among MSM (if repeated surveys are considered as separate studies), three collected data on depression (Table 2) [342, 355, 564]. Of these three studies, one, a GUM clinic sample in 1999 (N=122), investigated the association between depressive symptoms and sexual risk behaviour. The results of this study were discussed in review (i). A higher prevalence of depressive symptoms (HADS score ≥11) was observed among men who reported CLS with an unknown/HIV-positive status partner than men who did not, in unadjusted analysis (see Table 1) [355]. Similarly, the association between CSA and common measures of CLS has not been investigated, as measures of CSA have not been explicitly collected. It was investigated whether sexual assualt and non-consensual sex in childhood and adulthood was associated with CLS with one or more partners in the past year in two studies (see Appendix section 11.7 Table 53) [355, 510]. Both studies investigated unadjusted associations only, one study finding that men who reported sexual assualt in childhood and/or adulthood were more likely to report CLS [510], and the other finding no association with non-consensual sex [355]. No UK studies of sexual behaviour among MSM have collected data on IPV (Table 2).

2.6 Discussion

2.6.1 Relationship between depressive symptoms and sexual behaviour measures

Of the 22 eligible studies identified in review (i), the majority (68%) found an association between a measure of depressive symptoms and increased sexual risk behaviour [353-368] (or HIV seroconversion [369]), including after adjustment for socio-demographic factors and recreational drug use [366, 367, 369]. Unfortunately, it is difficult to draw conclusions on the magnitude of the association given the various measures of depressive symptoms and sexual behaviours investigated across different statistical methodologies. There does appear to be some evidence to suggest that the association between depressive symptoms and sexual risk behaviour is attenuated after adjusting for socio-demographic factors and substance use. However, the number of studies which presented unadjusted and adjusted estimates was small (N=3 [353, 366, 367]). Small sample sizes and a lack of statistical power may explain why an association was not found between depressive symptoms and any measure of sexual behaviour investigated in seven studies [346, 347, 370-373, 433]. Two of these studies observed an unadjusted

association which disappeared after adjusting for socio-demographic factors [372], poly-drug use, CSA, IPV, and sexual compulsivity [371].

2.6.2 Theory of opposing associations between depression and sexual behaviour: implications of prevalence of recent sex

The association between depressive symptoms and sexual behaviour did not appear to be more consistently demonstrated in samples investigating certain measures of sexual risk-taking or in samples with certain socio-demographic profiles (including HIV status, age, and ethnicity). However, there was some evidence that the association was more consistently demonstrated in samples where almost all men reported (recent) sexual intercourse compared to samples which included a higher proportion of men who did not report (recent) sex.

Crepaz and Marks' theory of opposing associations of depressive symptoms suggests that depression may result in increased sexual risk behaviour in some individuals and in others in sexual inactivity due to lowered libido and interest in sex. Opposing trends may result in an observed overall lack of association. In line with this theory, findings from review (i) suggest that studies that did not separate MSM who were not sexually active from those having condom-protected sex may have underestimated the effect of depression on condom-use. It is of note, however, that only half of identified studies presented the prevalence of recent anal sex (n=11/22) and different recall periods were utilized among studies that did.

2.6.2.1 Reasons for opposing associations between depression and sexual behaviour

Crepaz and Marks hypothesized that although the presence of moderate/chronic low-level depressive symptoms may be associated with sexual risk-taking, acute or chronic symptoms may have the opposite effect by reducing sexual interest and libido [352]. They also made a case for investigating an inverted U-shape relationship whereby the likelihood of engaging in sexual activity decreases as depressive symptoms become more severe. In the cognitive model of depression (see section 1.7.1.1), a total immersion of the personality in a full-blown major depression is characterized by profound anhedonia (inability to feel pleasure in normally pleasurable activities) and sleep and appetite disturbance [257, 269]. However, in the five studies identified in review (i) that investigated categories of depressive symptom severity, the highest level of depression was associated with increased reporting of CLS measures compared to lower but still clinically significant levels of depression [357, 359, 360, 365, 367-369].

It has also been suggested by Alvy et al 2011 [362], in Project Mix, that the type of coping mechanism employed by individuals with depression may determine the direction of association. Some individuals with depression may be more likely to engage in escape coping processes characterised by externalizing responses such as sexual risk-taking and substance use. Other individuals with depression may be more likely to engage in alternative coping

mechanisms characterised by internalizing responses, such as social withdrawal and sexual inactivity. Collecting samples of men with certain behavioural profiles such as high levels of sexual activity and drug use may therefore include only men who are more likely to react to depression with externalising responses. This explanation of opposing associations was described in the framework of the cognitive escape model. For a description of the theory of cognitive escape, see section 1.8.3.4.

Further evidence for the different responses to depression theory described above, may come from the internalizing-externalizing model. The internalizing-externalizing model is often used as a theoretical framework for understanding the co-occurrence of psychosocial phenomena [565, 566]. In this model, internalization is defined as the expression of distress inwards. Internalizing disorders include those of depression and anxiety. Externalization is defined as the expression of distress outwards and disorders include attention deficit/hyperactivity disorder (ADHD), antisocial personality disorder, and substance use disorders. Following this theoretical framework, it has been suggested in genetic studies that: (i) the presence of certain genes encoding impulse regulation and behavioural disinhibition may explain the co-occurrence of sensation seeking, substance use, and ADHD [567], and (ii) the presence of certain genes[xvi] may confer risk for the co-occurrence of internalizing (in particular major depression) and externalizing disorders such as substance use [307, 566, 568-573]. It has also been suggested that environmental factors may confer risk for the co-occurrence of depression and externalizing disorders [566]. Therefore, depending on genetic/environmental predisposition, it is possible that some individuals may cope with depression with more externalising responses, whereas, others may cope with more internalizing responses.

2.6.2.2 Recruitment setting

Based on findings in review (i), there appears to be some evidence to suggest that recruitment of men from certain settings, including sexual health clinics and possibly online, may elicit samples with unique behavioural profiles. Among sexually active samples of men reporting a high prevalence of CLS, the association between depressive symptoms and sexual risk behaviour may be more likely to be observed. This does not necessarily mean that a sexual

[xvi] This includes the serotonin transporter gene, serotonin 2A receptor gene, and dopamine D4 receptor gene. 307. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science (New York, NY). 2003;301(5631):386-9, 568. Sakai JT, Young SE, Stallings MC, Timberlake D, Smolen A, Stetler GL, et al. Case-control and within-family tests for an association between conduct disorder and 5HTTLPR. American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics. 2006;141B(8):825-32, 569. Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, McGuffin P, et al. Gene-environment interaction analysis of serotonin system markers with adolescent depression. Molecular psychiatry. 2004;9(10):908-15, 570. Mik HM, Ehtesham S, Baldassarra L, De Luca V, Davidge K, Bender D, et al. Serotonin system genes and childhood-onset aggression. Psychiatric genetics. 2007;17(1):11, 571. Lopez Leon S, Croes EA, Sayed-Tabatabaei FA, Claes S, Van Broeckhoven C, van Duijn CM. The dopamine D4 receptor gene 48-base-pair-repeat polymorphism and mood disorders: a meta-analysis. Biological psychiatry. 2005;57(9):999-1003, 572. Rowe DC, Stever C, Chase D, Sherman S, Abramowitz A, Waldman ID. Two dopamine genes related to reports of childhood retrospective inattention and conduct disorder symptoms. Molecular psychiatry. 2001;6(4):429-33.

health clinic or online sample has to be recruited in order to find an association. The recruitment or analysis of men from the general population or from community/commercial gay venues may be restricted so as to obtain a sexually active sample. For instance, among studies that recruited men from community/commercial gay venues in review (i), compared to YMS [347], Dudley et al 2004[370], Sex and Love [371], and HONOR [372], a number of studies including EXPLORE [367-369], Project MIX[362], and NHBS [363], restricted the recruitment of men to those reporting recent anal sex. The latter studies found an association between depressive symptoms and sexual risk behaviour. Furthermore, an association between depressive symptoms and sexual risk behaviour was also found in a general population sample which restricted the analysis to men reporting recent anal sex [359]. However, there may be implications for intervention in understanding which sites may be more likely to consist of men of certain behavioural profiles.

When investigating the 68 UK studies of sexual behaviour among MSM identified in review (ii), the prevalence of CLS measures appeared to be higher in studies which recruited men from sexual health clinics and online, compared to the general population and community/ commercial gay venues. These findings appear to reiterate those found in review (i). Given that the primary purpose of attending sexual health clinics is to screen for HIV and other STIs, it follows that the vast majority of attendees will be sexually active and have engaged in CLS. Recruitment of MSM online compared to in gay venues, may produce samples of men who are less likely to be affiliated to sexual minority communities and less likely to have been exposed to health interventions. This may have implications for psychological functioning and sexual risk-taking respectively. Findings from mostly U.S. studies in review (i), suggest that the association between depressive symptoms and sexual behaviour may be more consistently demonstrated in sexually active samples reporting a high prevalence of CLS. It is possible that this relationship may also be observed among MSM recruited from GUM clinics and online in the UK. The only UK study to investigate the association between depressive symptoms and sexual behaviour was conducted among a GUM clinic sample of 122 MSM in 1999 [355]. This study found an association between depressive symptoms and increased sexual risk-taking in unadjusted analysis. Therefore, based on findings from review (i) and (ii), it may be that targeted interventions in the UK addressing depression and sexual risk may be most effective in a GUM clinic setting and possibly online. However, the UK, and European region as a whole, still remains understudied. As stated in section 1.9, findings from the U.S. may not be generalizable to a UK/European setting given the potential impact of the differing health care infrastructure on treatment and prevalence of depression. Further studies investigating the association between depressive symptoms and sexual behaviour are needed in the UK.

2.6.3 Other factors associated with CLS measures among MSM in the UK: a comparison with studies in other high-income countries

2.6.3.1 Socio-demographic factors

There appears to be some evidence to suggest that among MSM in the UK, younger age, lower levels of educational attainment, and being in an ongoing relationship (for any CLS) is associated with CLS measures including with multiple partners and partners of an unknown/sero-different HIV status. However, associations with age and educational attainment were not consistently demonstrated. Studies from other high-income countries, mainly the U.S., do appear to support evidence for an association of younger age and socio-economic disadvantage with sexual risk behaviour [491, 574-577].

2.6.3.2 Psychosocial factors

Measures of recreational drug use were consistently associated with CLS measures across UK studies. Associations with some individual drugs including poppers and Viagra, disappeared after adjusting for use of other recreational drugs. It is of note that, 'chemsex' is a recently described phenomenon in the UK [578-584]. Chemsex is the intentional use of novel psychoactive substances (usually one or more of mephedrone, gamma-hydroxybutrate/gamma-butyrolactone [GHB/GBL] and methamphetamine) during or immediately before sex. Chemsex appears to occur among self-identified gay men to stimulate sexual arousal and prolonged sexual episodes. It typically occurs in private homes or commercial sex-on-premises venues such as saunas or sex clubs and as a group sexual activity. Qualitative work (2013-2014) among a volunteer sample of MSM suggests that serosorting practices are common among HIV-positive men who engage in chemsex. At the same time, it suggests that a number of men whose last HIV test was negative had unintentional CLS as a direct result of 'chem' use.

The relationship between recreational drug use and sexual risk behaviour has also been consistently and strongly demonstrated in studies of MSM from other high-income countries [397, 585-600], mainly the U.S. These include two separate literature reviews of drugs used in dance clubs/rave parties ('club-drugs') published up to 2005 [598, 599] and a recent meta-analysis of amphetamine-type stimulants (including methamphetamine and ecstasy) and HIV seropositivity [600]. The association may be due to direct autonomic or central nervous system mechanisms that increase arousal, decrease anxiety, and disinhibit sexual activity [397, 601-603]. Men may also use substances strategically to induce a state of cognitive release and escape from rational self-awareness, which then results in risk [397, 597]. Sexually-oriented settings on the gay scene may present opportunities for drug-induced cognitive disengagement and sexual risk [397]. Drug use may become associated with sexuality through social learning of gay bars, clubs, and saunas as settings where gay sexuality is sanctioned and celebrated [120].

Although this data has not been collected in UK studies of sexual behaviour among MSM, two meta-analyses of mainly U.S. studies, up to 2014, have investigated the association of CSA [604] and IPV [605] with CLS and HIV seropositivity, both finding strong overall associations.

It is noteworthy, that among MSM (most studies conducted in U.S.) recreational drug use [41, 346, 358, 454, 564, 606-609], CSA [368, 610], and IPV [605] has also been found to be independently associated with depressive symptoms, including in a meta-analysis of studies up to 2013 [605]. CSA has also been linked to IPV [611] and substance use [604], and IPV to substance use in a meta-analysis of studies up to 2013 [605]. It has been suggested in syndemic theory that it is the synergistic interactions of two or more co-occurring psychosocial health problems that compound the risk of HIV infection among MSM [371, 612-614]. The hypothesized relationships in this thesis are presented in a conceptual model in the next chapter (Figure 8). Of note, recreational drug use, CSA, and IPV are considered to be possible confounders of the association between depressive symptoms and sexual risk behaviour, and self-efficacy for sexual safety is considered to be a possible mediator of this relationship.

2.6.4 AURAH and PROUD studies: implications for intervention in a UK setting

Data from the AURAH study and PROUD trial is investigated in this thesis. The methodologies of these studies are described in detail in the next chapter. The AURAH study provides an opportunity to examine the relationship between depressive symptoms on PHQ-9 and measures of sexual behaviour among MSM attendees of GUM clinics across England from 2013-2014. The PROUD trial provides an opportunity to investigate this relationship among a volunteer sample of MSM who were required to have reported CLS in the previous three months and be of the opinion that they would have CLS in the next three months. Therefore, it will be possible to conclude in this thesis, whether depressive symptoms are associated with increased reporting of sexual behaviours linked to HIV and STI transmission, among current samples of sexually active MSM in the UK. The thesis hypothesis is presented in section 1.9.1.

In Chapters 4 and 7 of this thesis, the prevalence of depression measures on PHQ-9 and associated factors are investigated using data from AURAH and PROUD respectively. Findings from AURAH and PROUD relating to the association of depressive symptoms with sexual behaviour are presented in Chapters 5 and 8 respectively and are discussed in the context of findings from this literature review. The potential mechanisms through which depression might lead to CLS, for which there is a dearth of research in high-income countries, is examined in Chapter 6. The potential implications of these findings for targeted interventions are discussed in the final conclusion chapter of this thesis.

Chapter 3

3 Thesis methods

This chapter presents an overview of the data management tasks undertaken as part of this thesis and the AURAH and PROUD study methods and selection of participants for analysis. In addition, the definition of variables used in analysis and epidemiological concepts and the statistical methodology employed in this thesis, are described. To conclude this chapter, the methodological limitations of the AURAH and PROUD studies are discussed. Full details of the AURAH study methods are presented in Appendix section 11.8 and of the PROUD trial methods in Appendix section 11.9. These appendix sections contain detailed information on the identification of the sample population, method of sample selection, sample power calculation, questionnaire, statement of ethical approval, and data processing [80, 417, 615].

3.1 Data management

At the time of starting this PhD (07/2014), data collection procedures for AURAH were complete and baseline data collection was complete for PROUD. This section gives an overview of my involvement in the data management of AURAH and PROUD.

Data cleaning and derivation of variables for the AURAH study was solely my responsibility. The raw AURAH dataset was received in eight batches over a period of one year (July 2014-July 2015). During this year, I checked the data for errors and inconsistencies, including use of automated data checking terms in Stata: *'assert'* [616]. Any errors were corrected and attempts were made to resolve inconsistencies by investigating the original individual scanned questionnaires and defining rules for multiple responses and implausible combinations of variables. A set of derived variables was created for analysis. Appendix section 11.8.5 (Table 58-Table 62) includes a detailed description of these processes.

The PROUD baseline and 12-month questionnaire datasets were received in Stata on September 6th 2016. Following discussion with the MRC CTU team on November 2nd 2016, where I presented preliminary findings at the CTU team meeting, it was decided that data from the 24-month questionnaire (n=333) should also be incorporated. This data was received on December 16th 2016. The PROUD trial data has been managed by Dr Ellen White and Dr David Dunn based at the MRC CTU. All data management procedures that I have carried out and are relevant to this thesis are described in detail in Appendix section 11.9.5. These predominantly involved dealing with inconsistent responses to sexual behaviour and variable derivation.

3.2 Study methods/participants

3.2.1 The AURAH study methods

The AURAH (Attitudes to, and Understanding of, Risk of Acquisition of HIV) study is a cross-sectional questionnaire study that recruited men and women from 20 GUM clinics in England. Men and women were eligible for inclusion in the study if they met the following criteria: aged 18 years or over without diagnosed HIV. The questionnaire was only provided in the English language. Clinic attendees were consecutively sampled. After five months of consecutive sampling, it became clear that the proportion of the populations of interest (MSM and black African men and women) was not reaching the targets set for analytic purposes. Accordingly, sampling switched to disproportionate quota purposive methods, in order to 'over represent' and recruit until the required proportion of the populations of interest were enrolled. Over the 17 month study period (June 2013 and November 2014) a total of 4380 eligible patients were approached and asked to participate in this study. Of those approached, 3340 (76%) gave consent to take part in the study by self-completing a confidential questionnaire that sought detailed information on socio-demographic factors, health and well-being, lifestyle factors, HIV-related information, and sexual risk behaviour. A description of all questions asked is presented in Appendix section 11.8.4. The number of completed questionnaires finally collected was 2630 and thus, the response rate was 60% (2630/4380) of eligible patients approached and 79% (2630/3340) of those who gave consent. Information on gender and clinic site was noted for all GUM clinic attendees approached as part of the AURAH study. Information on HIV/STI testing and results of HIV testing was collected from clinic records for all consenting study participants. The possibility of response bias among all men and women who were approached and all those consenting to participate was investigated in Appendix section 11.8.6.1 Table 63 and Table 64. Findings appear to suggest minimal response bias. However, it was only possible to investigate whether consent to participate and survey completion differed according to a very limited number of factors collected (gender, clinic site, HIV/STI testing, and results of HIV testing).

3.2.2 AURAH study participants

3.2.2.1 Selection of MSM sample

This thesis focuses solely on MSM recruited for study participation, the remainder of the AURAH study sample will not be investigated here. Men were included in the analyses presented in this thesis if they met at least one of the following criteria: (i) reported being gay or bisexual including other plurisexual identity labels: pansexual, omnisexual, open, queer, and other identities that are not explicitly based on attractions to one sex/gender [617], or (ii) reported anal sex with a man in the past three months, or (iii) reported having disclosed to their family,

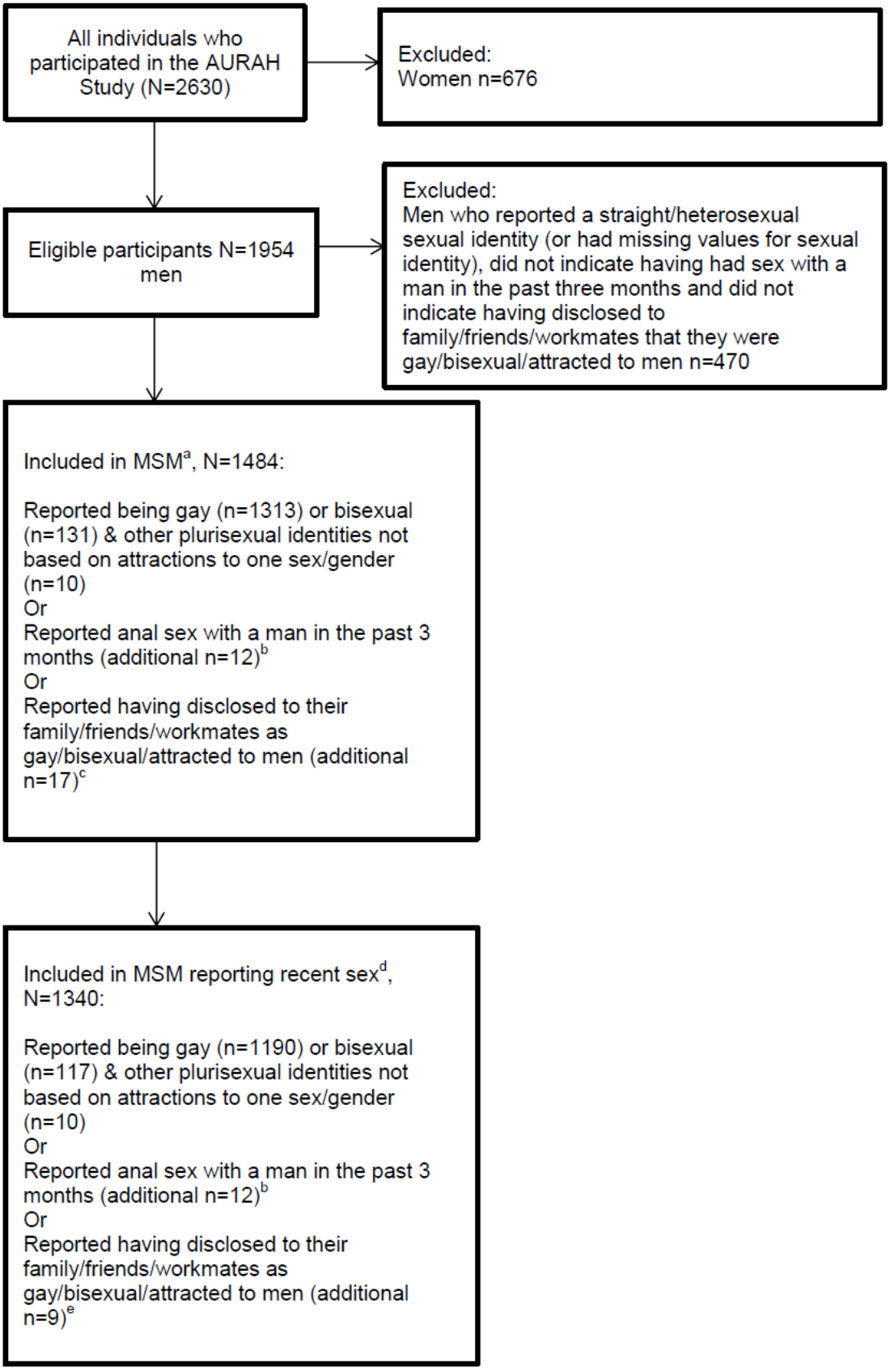
friends, or workmates as being gay, bisexual, and/or attracted to men. In total, 1484 men were defined as MSM, see Figure 5.

3.2.2.2 Restricting to men who reported recent sex

Crepaz and Marks authored the only meta-analysis which has included samples of MSM in an assessment of the association between depressive symptoms and sexual risk behaviour [352]. As a result of this work, Crepaz and Marks suggested that there may be two opposing associations of depressive symptoms. In some individuals, depression may result in increased sexual risk behaviour and in others in lowered libido/interest in sex and sexual inactivity (see section 2.4.4.1). Accordingly, assessment of this relationship may be problematic since opposing trends can result in an observed overall lack of association. Findings from review (i) of this thesis provide some support in favour of this theory of opposing trends (see section 2.4.5.4). Informed by these findings and as a result of the overall aim being to inform HIV prevention in the UK, this thesis focused on the distinction between men who reported sexual risk behaviour and men who were sexually active but did not report risk behaviour. Therefore, only MSM who reported recent sex were included in the main AURAH analyses. However, levels of depression among MSM who were not sexually active were also investigated, in order to better understand the potentially complex relationship of depressive symptoms with sexual behaviour. In line with findings from review (i) and (ii) of this thesis, the proportion of AURAH GUM clinic attendees who did not report recent sex was small (N=144; 9.7%).

In order to acknowledge the inclusion of plurisexual identified men in our definition of MSM, men were eligible for inclusion regardless of whether they reported recent anal sex with a man or recent vaginal or anal sex with a woman. In total, 1340 MSM reported anal and/or vaginal sex in the past three months, see Figure 5. Of note, Figure 6 presents the overlap between the three inclusion criteria for MSM categorization (based on sexual identity, sexual behaviour, and disclosure of sexual orientation) among a) all 1484 MSM and b) 1340 MSM reporting recent sex. The vast majority of MSM investigated in this thesis, identified as gay or bisexual (including other plurisexual identities), reported anal sex with a man in the past three months, and reported having disclosed their sexual orientation to family, friends, and/or work colleagues.

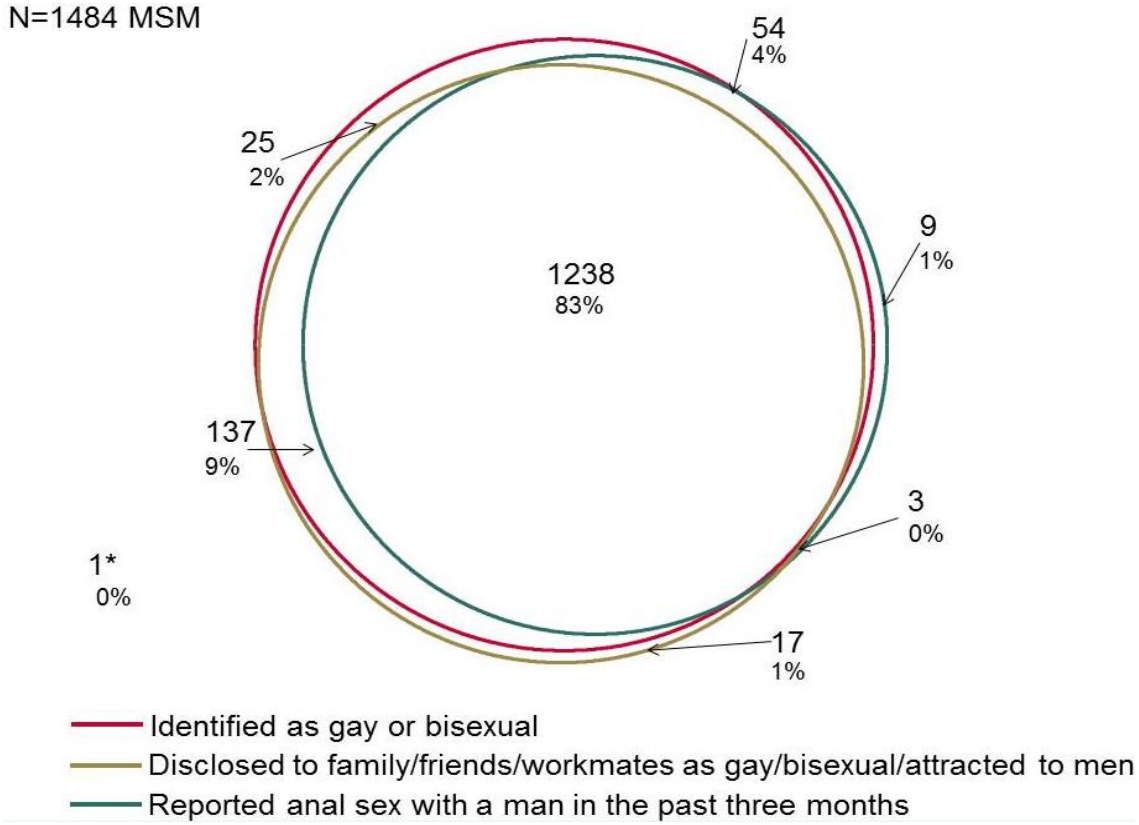
Figure 5: Inclusion criteria for MSM in the AURAH study



[a] Of note, one man ticked the 'other' sexual identity box and stated "Straight but occasionally play with men". This man reported no to having had sex with a man in the past three months and did not respond to the question concerning having disclosed being gay/bisexual/attracted to men, to family/friends/workmates. This man was coded as 'straight' in the analysis; however, given his statement he was included in the MSM category. This was deemed the most appropriate decision; which does not affect the main analysis among MSM who reported recent sex, since this man did not report recent sex with a man or woman.
[b] The majority of these men reported their sexual identity to be straight/heterosexual (n=8). The remaining men did not respond to the sexual identity question (n=4).
[c] Almost all of these men reported their sexual identity to be straight/heterosexual (n=16). One of these men did not respond to the sexual identity question.
[d] Of note, two additional men were included who identified as heterosexual and wrote a note specifying having/had sex with men. These men reported vaginal sex with a woman in the past three months.
[e] All of these men reported their sexual identity to be straight/heterosexual.

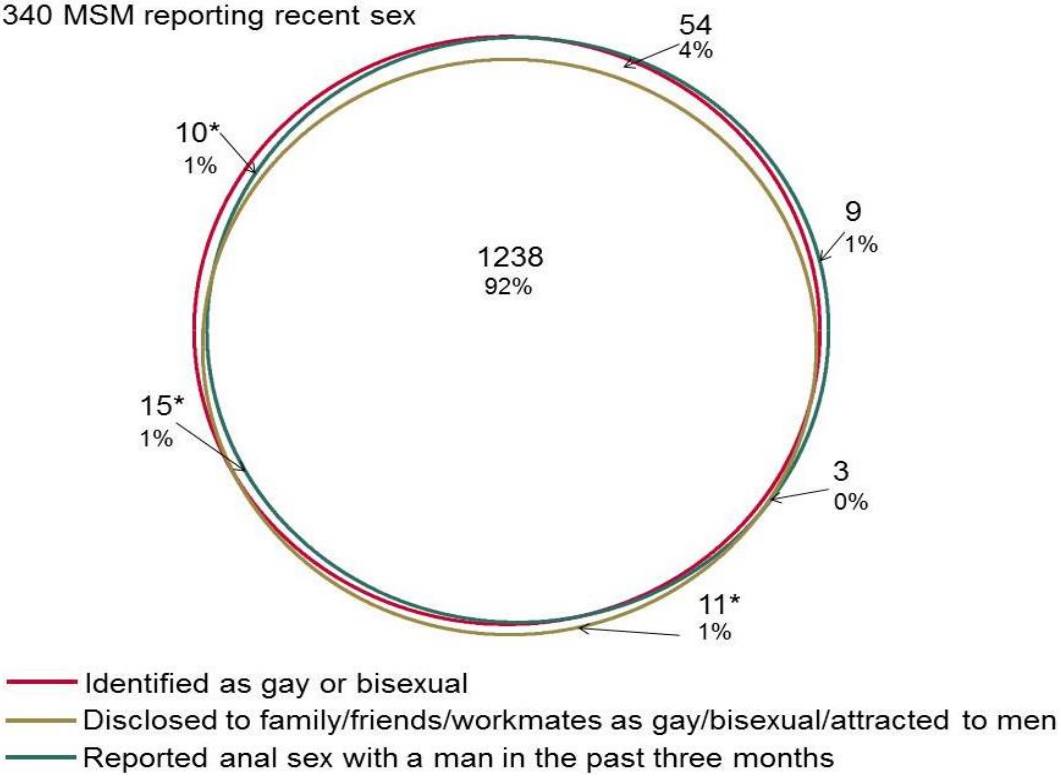
Figure 6: Intersection of inclusion criteria for MSM in the AURAH study

a) N=1484 MSM



* One man specified "Straight but occasionally play with men", see footnote [a] under Figure 5.

b) N=1340 MSM reporting recent sex



* Reported sex with a woman in the past three months.

3.2.2.3 Diagnosis of HIV, socio-demographic characteristics, clinic site, and reasons for attendance

Overall, 1112 of 1484 MSM (83.1%) had an HIV test on the day of the AURAH questionnaire. Four men tested HIV-positive (0.3% overall), all of whom were included in the 1340 MSM who reported recent sex. These HIV-positive men were retained in the sample for analyses, as they were not diagnosed with HIV at the time of questionnaire completion. The socio-demographic factors investigated in this thesis are defined below in section 3.3.5. The prevalence of these socio-demographic factors is presented in Chapter 4 (Table 5). Briefly, of the 1340 MSM, 89% identified as gay, 10% as bisexual or another plurisexual identity label, and 1% as straight. Eighty-two percent of men were of white ethnicity; median age was 31 years. Overall, 57% were born in the UK, 67% had a university degree, and 76% were attending a clinic in London. In London, a large proportion of men were recruited from 56 Dean Street clinic (n=478) and the Mortimer Market Centre (n=240). Outside of London, a large proportion of men were recruited from a clinic in Brighton (Claude Nicol Centre, n=173) (see Appendix section 11.8.1 Table 54). The majority of men (68.1%) reported attending the clinic for a routine screening test. A small number of men (N=154) specified reasons other than routine screening, getting a symptom checked or treated, and getting contraception or contraceptive advice. These other reasons included: clinical trial (n=50), Hepatitis B vaccination (n=41), PEP (get/follow-up) (n=32), collecting results/treatment (n=17), and counselling/information (n=3).

3.2.3 The PROUD trial methods

The PROUD trial (Pre-exposure Option for reducing HIV in the UK) was a multi-centre, open label RCT, at 13 GUM clinics across England [80], evaluating the benefit of PrEP as part of a package of HIV risk reduction interventions for HIV-negative gay men. Recruitment took place between November 2012 and April 2014, and participants had the opportunity to remain in follow-up for at least two years. Men, and transgender women[xvii], aged 18 years or older who were attending one of the recruiting clinics for a routine visit and reported CLS on more than one occasion with a man in the past three months, were asked if they were interested in PrEP, and if so were provided with information sheets on the PROUD trial. Posters and electronic screens in participating GUM clinics, advertisements on social media, and distribution of business cards and leaflets by community organizations during outreach activities were also used to promote the study. Individuals who were interested in the study could download the information sheet from the study website. Individuals from clinic and non-clinic recruitment were eligible for inclusion if at the enrolment visit, they had an HIV-negative test result, reported anal CLS with a man on more than one occasion within the past three months, and reported that they were likely to have anal CLS with a man in the next three months. A total of 544 men underwent randomization; 275 to the immediate arm and 269 to the deferred arm. Given the nature of the non-clinic recruitment, it was difficult to determine the response rate of all eligible men. Of note, deferral of PrEP was initially set until the 12 month point, however, an unexpectedly high incidence of HIV observed during the deferral period (9.0 per 100 person-years, 90 CI: 6.1, 12.8), led to a recommendation from the Trial Steering Committee in October 2014 that all participants should be offered PrEP [80].

The PROUD trial collected information on socio-demographic factors, lifestyles, health and well-being, and sexual behaviour at baseline. A similar version of the questionnaire, excluding socio-demographics and including psychosocial factors, was given to participants on an approximately annual basis thereafter; the 12-month questionnaire was completed between November 2013 and June 2015 and the 24-month questionnaire was completed between November 2014 and June 2016. A description of all questions asked is presented in Appendix section 11.9.4.

[xvii] Of note, transgender women were included in PROUD eligibility. In total, three transgender women enrolled in PROUD. Of these three women, none identified as transgender on the baseline questionnaire. Questions on gender identity were not asked about on the follow-up questionnaires (anecdotal information from Dr Mitzy Gafos, social science lead on the PROUD team). For simplicity sake, PROUD participants are referred to as ‘men’ throughout this thesis.

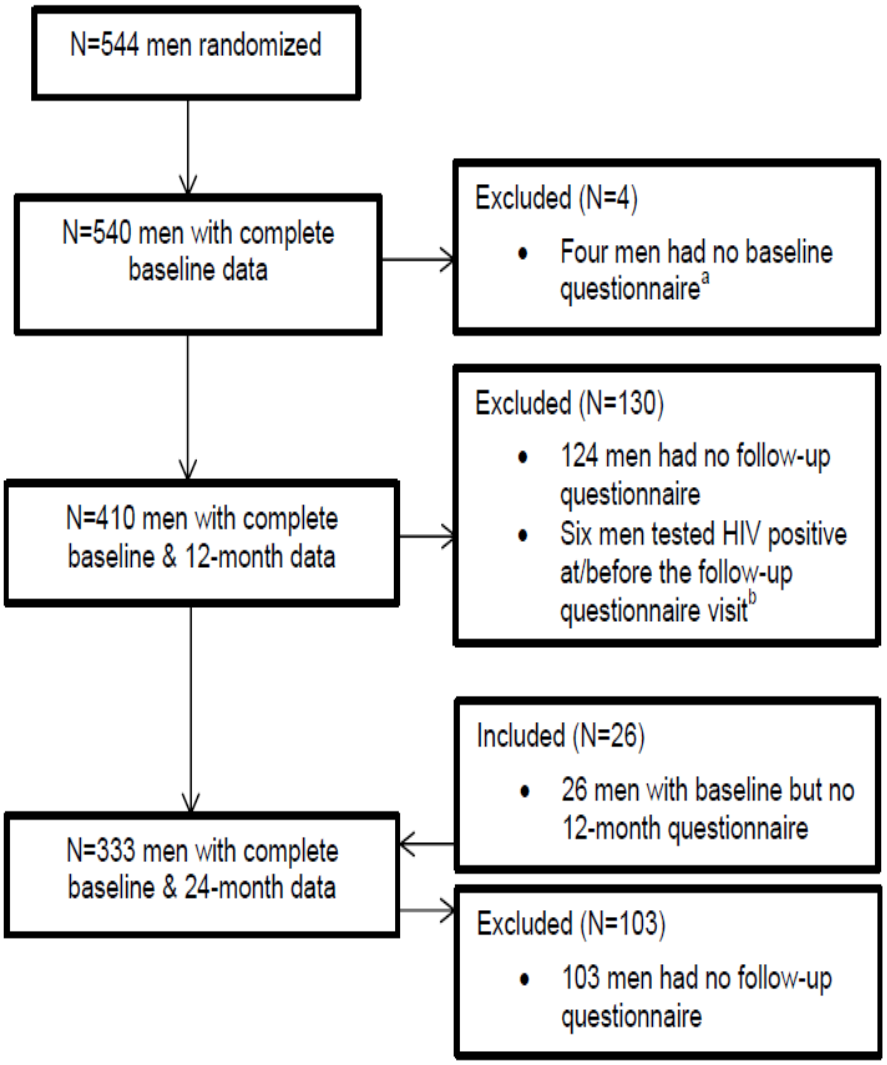
3.2.4 PROUD trial participants

Figure 7 shows the inclusion of men in analyses presented in this thesis. Overall, 540 men completed a questionnaire at baseline. Only data from men who remained HIV-negative at the time of filling out the follow-up questionnaire was analysed at the 12- and 24-month time-points, since this thesis focused on men at risk of HIV acquisition. This included 410 HIV-negative men who completed a 12-month questionnaire and 333 HIV-negative men who completed a 24-month questionnaire. Of the 130 men who did not contribute data for analysis at month-12, 124 did not complete the follow-up questionnaire, of whom 20 had received an HIV-positive diagnosis since baseline. The remaining six men completed a 12-month questionnaire but were diagnosed with HIV at or before the follow-up visit and were excluded from analysis[xviii]. An additional 103 men did not complete the 24-month questionnaire. Of these men, two had received an HIV-positive diagnosis since the 12-month questionnaire.

Due to the loss of individuals completing behavioural questionnaires at follow-up, see Figure 7, it was deemed important to investigate whether depression, as well as socio-demographic factors, was associated with loss-to-follow-up. This was in order to determine the possibility of response bias. There was no difference between men with depressive symptoms and men without symptoms at baseline in terms of completing the 12-month questionnaire (22.5% vs. 24.2%; χ^2 test p=0.780) and at the 12-month questionnaire in terms of completing the 24-month questionnaire (27.1% vs. 24.8%; χ^2 test p=0.702). Findings were similar when stratifying by trial arm, for 12-month questionnaire completion (immediate arm [24.1 vs. 20.5%; χ^2 test p=0.648]; deferred arm [20.0% vs. 27.9%; χ^2 test p=0.444]) and 24-month questionnaire completion (immediate arm [27.8% vs. 22.8%; χ^2 test p=0.519]; deferred arm [26.1% vs. 26.9%; χ^2 test p=0.934]). At baseline, younger men ([<25 years] χ^2 test p=0.002), men who were born in the UK and BAME (χ^2 test p=0.015), and men who reported a non-university degree level of education (χ^2 test p=0.008) were less likely to complete a 12-month questionnaire. The association with age and UK born/ethnicity was only present among men randomized to the immediate PrEP arm. The association with education was only present among men randomized to the deferred arm.

[xviii] In total 26 study participants received an HIV-positive diagnosis after baseline questionnaire completion, 21 men in the deferred arm and five men in the immediate group. Three men, one in the deferred and two in the immediate arm, had a reactive HIV antigen-antibody test result but non-reactive point-of-care test result at baseline, and were not aware of their status at this time.

Figure 7: Inclusion of PROUD participants for data analysis at each time-point



[a] Four men were identified who had been randomized but had not completed a baseline questionnaire.
[b] Six men were identified who acquired HIV before or at the time of the 12-month questionnaire completion. Whether these latter men were aware of their HIV test result at the time of completing the survey is not possible to deduce, and as such all of these six men were excluded from further analyses.

3.2.4.1 Socio-demographic characteristics

Information on socio-demographic factors was collected at baseline of the PROUD trial. The socio-demographic factors investigated in this thesis are defined below in section 3.3.10. The prevalence of these socio-demographic factors is presented in Chapter 7 (Table 22). Briefly, 96% of men identified as gay, 3% as bisexual or another plurisexual identity label (one man identified as queer), and 1% as straight. Eighty-two percent of men were of white ethnicity;

median age was 35 years. Overall, 60% were born in the UK, 61% had a university degree, and 69% participated at a site in London at baseline.

3.3 Definition of variables

3.3.1 Variable definitions in the AURAH study

3.3.2 Symptoms of depression and other mental health disorders

This thesis focuses on clinically significant depressive symptoms assessed using a symptom questionnaire and categorised using a cut-off point, but it also investigates depressive symptom severity, two criteria-based depressive syndromes, and self-report of receiving treatment for depression, as well as briefly examining GAD, and suicidal ideation/self-harm. The definition of these measures is described in detail below.

3.3.2.1 Measures of depression on PHQ-9 based on standard algorithms

The PHQ-9 is a nine-item screening tool based on the Diagnostic and Statistical Manual of Mental Disorders version four. The internal consistency of items on the PHQ-9 has been described in detail in Textbox 3. The PHQ-9 was used to measure the prevalence of clinically significant depressive symptoms in AURAH and PROUD. In the PHQ-9, participants are asked to rate how often over the past two weeks they have been bothered by nine specific problems (Textbox 5).[443] A depressive symptom score is generated by summing responses for each question coded as follows: 'not at all' (0), 'several days' (1), 'more than half the days' (2), and 'nearly every day' (3), resulting in a total score with a possible range from 0 to 27. Of note, in this thesis, a missing response was included in the 'not at all' category with a score of 0. The handling of missing data is discussed in section 3.3.11 below. The depressive symptom score is categorized as follows: No symptoms of depression/minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27). A cut-off point of 10 or greater is considered a 'yellow flag' on the PHQ-9, to indicate a possible clinically significant depressive condition. This is the most commonly used measure of depression based on the PHQ-9, and was the main measure of depressive symptoms investigated in this thesis. Questionnaire-based measures of depression may be limited in that they do not encompass a full evaluation of symptoms by a mental health professional. However, in a validation study when the distribution of PHQ-9 scores were investigated according to depression diagnostic status in U.S. primary care and obstetrics/gynaecology patients interviewed by a (blinded) mental health professional, the vast majority of patients (93%) with no depressive disorder had a PHQ-9 score less than 10, while 88% with major depression had scores of 10 or greater [443]. Additional validation studies have been conducted, all of which have reported similar findings, across geographical locations [444, 618-627].

A diagnostic algorithm for a major depressive syndrome was defined as a total score of at least five 'positive' responses, including either question 1 or question 2. With the exception of question 9, a 'positive' response was defined as having the symptom 'more than half the days' or 'nearly every day'. For question 9, a 'positive' response was defined as having the symptom 'several days' or more frequently [442]. A diagnostic algorithm for major and other depressive syndromes (dysthymia, seasonal affective disorder, bipolar disorder) was defined as a total score of at least two 'positive' responses, including either question 1 or question 2 [442].

Of note, following the nine problems presented on the PHQ-9, AURAH participants were asked 'If you were bothered by any of these problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?'

Textbox 5: PHQ-9 and GAD-7 scales

Depression and anxiety measures	
PHQ-9 scale	1. Little interest or pleasure in doing things 2. Feeling down, depressed, or hopeless 3. Trouble falling or staying asleep, or sleeping too much 4. Feeling tired or having little energy 5. Poor appetite or overeating 6. Feeling bad about yourself-or that you are a failure or have let yourself or your family down 7. Trouble concentrating on things, such as reading the newspaper or watching television 8. Moving or speaking so slowly that other people could have noticed/being so restless that it is hard to sit still 9. Thoughts that you would be better off dead, or of hurting yourself in some way
GAD-7 scale	1. Feeling nervous, anxious or on edge 2. Not being able to stop or control worrying 3. Worrying too much about different things 4. Becoming easily annoyed or irritable 5. Trouble relaxing 6. Being so restless that it is hard to sit still 7. Feeling afraid as if something awful might happen

3.3.2.2 Receiving treatment for depression

Participants were asked whether they were receiving medical treatment or therapy for depression, and/or for any other mental health condition. Participants were also asked whether they had ever been told by a doctor that they have a mental health condition and, if so, to specify their condition. Finally, participants were asked 'which statements best describe your own state of health today' on EuroQoL 5D (questionnaire on health-related quality of life [628]); one of the five domains is anxiety/depression with the following response options: 'I am not

anxious or depressed', 'I am moderately anxious or depressed', and 'I am extremely anxious or depressed'. For the measure of treatment for depression and anxiety/depression on EuroQoL 5D, a missing response was included in the no treatment and no anxiety/depression categories.

3.3.2.3 Generalized anxiety disorder

The GAD-7 scale is a standard seven item questionnaire used to measure symptoms of anxiety, with response options for each symptom: not at all (0), several days (1), more than half the days (2), and nearly every day (3) (Textbox 5) [629]. In this thesis, a missing response was included in the 'not at all' category with a score of 0. Although the GAD-7 was originally developed to diagnose GAD, it also has good sensitivity and specificity as a screening tool of panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD) [630]. An anxiety symptom score was generated by summing responses for each of the seven questions. The standard definition of a total score of ≥10 (from potential range 0 to 21) was used to define GAD. As for the PHQ-9, a cut-off point of 10 or greater is considered a 'yellow flag' on GAD-7.

3.3.2.4 Suicidal ideation/self-harm

Suicidal ideation/self-harm, referred to as suicidal ideation for simplicity throughout this thesis, was defined as a positive response to the final PHQ-9 question: 'Thoughts that you would be better off dead, or of hurting yourself in some way'. Participants were considered to screen positive if they answered 'several days', 'more than half the days', or 'nearly every day' to this question. A missing response was included in the 'not at all' category.

3.3.3 Sexual behaviour measures

Eight sexual behaviour measures were considered for analysis: six were related to CLS (regardless of the sex of the partner) and two were related to partner numbers. Participants were asked questions about anal and vaginal sex in the past three months. Four measures of CLS (anal or vaginal) in the past three months were defined:

i) CLS with one or more partners
ii) CLS with two or more partners
iii) CLS with at least one unknown and/or HIV-positive status partner (excludes men who reported no partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART')
iv) Receptive CLS with an unknown HIV status partner

Measure (iv) included men who reported always being the receptive partner and those who reported being sometimes the receptive and sometimes the insertive partner. Only men who reported that they did not know the HIV status of any of their partners could be included, as for

those who reported knowing some or all of their partners' HIV status, it was not possible to distinguish whether this was the HIV-positive partner with whom the participant had insertive or receptive CLS. Furthermore, it is of note that although measure (i) CLS with one or more partners was investigated in this thesis, it is acknowledged that CLS should not in itself be pathologized since the act of CLS will often occur within the context of loving and mutually supportive relationships, and that strategies may also be used to try and reduce any perceived risk of HIV transmission. The limitations of investigating measure (i) in the context of STI/HIV transmission, are discussed in Chapter 5.

Participants were asked whether they had been diagnosed with an STI in the past year. Although the site of infection was not specified, a rectal STI diagnosis was defined as report of one of four bacterial infections: (i) gonorrhoea, (ii) chlamydia, (iii) syphilis, or (iv) LGV. As described in section 1.2.3, rectal STIs and their treatment have important implications in the control of HIV and are often taken as a proxy measure for CLS. Participants were asked about the diagnosis of genital herpes and as such HSV was not included as part of the definition of rectal STIs.

Finally, PEP use in the past year, having eleven or more new sexual partners in the past year, and group sex (sex with more than one person on the same occasion) in the past three months, was also ascertained. For each of the measures described above, a missing response was included in the no CLS or no high partner number category.

3.3.4 Self-efficacy for sexual safety and reasons for non-condom-use

The following statement was used to measure self-efficacy: 'I feel confident that, if I want to, I can make sure a condom is used during sex with any partner, in any situation.' If a participant strongly agreed with this statement this was considered to indicate high self-efficacy for sexual safety; all other responses (tend to agree, tend to disagree, strongly disagree, undecided/no opinion/not relevant to me, and missing) were not considered to indicate high self-efficacy. This categorisation was chosen for high self-efficacy for sexual safety due to the very high proportion of participants who agreed with this statement, therefore, it was believed appropriate to separate participants who specified 'tend to agree' from those who specified 'strongly agree'.

Participants were also asked the degree to which they agreed with the following statement: 'I find it difficult to discuss condom use with any new sexual partner'. If a participant agreed (tend to or strongly) with this statement, this was considered to indicate difficulty in negotiating condom-use. All other responses (tend to disagree, strongly disagree, undecided/no opinion/not relevant to me, and missing) were not considered to indicate difficulty in negotiating condom-use.

Men were also asked reasons for non-condom-use, for which the following options were given (one or more could be chosen): ‘Didn’t think about using a condom or did not have a condom’, ‘Don’t like using condoms or it’s more enjoyable/close without a condom’, ‘My partner didn’t want to use a condom’, ‘Felt unable to discuss condom use’, ‘Got carried away or was under the influence of alcohol or drugs’, and ‘Difficult for me/partner to keep erection or ejaculate when using a condom’.

3.3.5 Other covariates

The other (self-reported) variables investigated in Chapters 4 and 5 include:

- *Age group* in six categories: <25, 25-29, 30-34, 35-39, 40-44, or ≥45 years

- *Country of birth and ethnicity*: UK born & white ethnicity, UK born & BAME (black, Asian, and minority ethnicity), non-UK born & white ethnicity, or non-UK born & BAME

- *Study region*: London, South, or Midlands/Yorkshire and the Humber (the study clinics within each region are presented in Appendix section 11.8.1 Table 54)

- *Education*: educated to university degree level or not (including a missing response)

- *Employment status*: employed full- or part-time or other (unemployed, student, permanently/temporarily sick, looking after home, retired, other, or a missing response)

- *Financial hardship*: having enough money to cover basic needs (e.g. for food and heating) all of the time, most of the time, or none/some of the time

- *Housing status*: home-owner, renting (private or council), or unstable/other (homeless, temporary accommodation, staying with partner, friends, family, or other)

- *Sexual identity*: gay, bisexual (including other plurisexual identities that are not explicitly based on attractions to one sex/gender [617]), or straight/heterosexual

Men, who did not select the ‘straight/heterosexual’ option when asked about their sexuality, were asked ‘what proportion of the following groups know that you are gay, bisexual and/or attracted men?’ The groups included: (i) close family, (ii) friends, and (iii) workmates. Response options for each group included: all/almost all, >half, half, <half, and few/none. Five variables regarding disclosure of sexual orientation were derived.

- *Disclosure of sexual orientation to close family*: all/almost all, some (<half, half, or >half), or few/none

- *Disclosure of sexual orientation to friends*: all/almost all, some (<half, half, or >half), or few/none
- *Disclosure of sexual orientation to workmates*: all/almost all, some (<half, half, or >half), or few/none
- *'Out' to all/almost all friends, work colleagues, and close family*: all/almost all or less (including a missing response)
- *'Out' to few/no friends, work colleagues, and close family*: few/none or more (including a missing response)

- *Relationship status*: ongoing relationship with a partner (wife or civil partner or girlfriend/boyfriend) or not (including a missing response)

Based on a modified version of the Duke-UNC Functional Social Support Questionnaire [631], participants were asked the level (as much as I would like; almost as much as I would like; some, but would like more; less than I would like; much less than I would like) at which they received the following help/support from other people: 'I have people who care what happens to me', 'I get love and affection', 'I get chances to talk to someone I trust about my personal problems', 'I get invitations to go out and do things with other people', and 'I get help when I am sick in bed'. The response options were coded as 1 to 5, starting with as much as I would like (coded as 1). The total score across the five questions for each participant was generated. A total score of 5-10 was coded as 5 (low levels of a supportive network), 10-15 as 4, 15-20 as 3, 20-24 as 2 and 25 as 1 (high levels of a supportive network).

- *Supportive network*: social support score based on a modified version of the Duke-UNC Functional Social Support Questionnaire; 1 (highest), 2, 3, 4, or 5 (lowest) [631]

- *Regular smoking*: current cigarette smoker or otherwise (including a missing response)

Participants were asked the first two questions of the WHO AUDIT-C questionnaire: (i) 'How often do you have a drink that contains alcohol?' and (ii) 'How many units of alcohol do you drink on a typical day when you are drinking?' An alcohol use score was generated by summing responses for each question. Question (i) was coded as follows: 'never' (0), 'monthly or less' (1), '2-4 times per month' (2), '2-3 times per week' (3), and '4+ times per week' (4). Question (ii) was coded as follows: '1-2' (0), '3-4' (1), '5-6' (2), '7-9' (3), and '10+' (4). The total score had a possible range from 0 to 8 [632]. Given that the AUDIT-C questionnaire incorporated a third question (how often have you had 8 or more units if male on a single occasion in the last year), which was not included in AURAH, a total score of less than six (instead of less than five) was considered to indicate lower risk drinking and a score of six or more (instead of five or more) was considered to indicate higher-risk drinking in this thesis.

- *Higher-risk alcohol consumption*: higher-risk score of ≥6 or lower risk/no alcohol consumption score of <6 (including a missing response to both questions (i) and (ii))

All participants were asked to report whether they had used recreational drugs in the past three months and, if so, to select which drug or drugs from the following list of 18 options; acid, lysergic acid diethylamide (LSD), or magic mushrooms (all grouped as psychedelics); anabolic steroids; cannabis (marijuana, grass); cocaine (coke); crack; codeine; crystal meth (methamphetamine); ecstasy (MDMA or E); GHB (GBL or liquid ecstasy); heroin, ketamine (k); khat (chat); mephedrone; morphine; opium; poppers (amyl nitrites); speed (amphetamine); erectile dysfunction drugs (Viagra); and other (whereby participants were asked to specify the drug). Other drugs specified were coded to the above categories where appropriate (in most cases participants specified one of the drug options under a different or street name).

- *Number of recreational drugs used in the past three months*: none (including a missing response), 1, 2-4, or ≥5.
- *Poly-drug use*: use of three or more recreational drugs or not (including a missing response)
- *Chemsex-associated drug use*[xix]: use of at least one psychoactive substance that is commonly used before/during sex (crystal methamphetamine, mephedrone or GHB/GBL[(578-580)]) or not (including a missing response)
- *Club-drug use*[xx]: use of at least one club-drug (mephedrone, GHB/GBL, ketamine, cocaine or ecstasy/MDMA) or not (including a missing response)

The specification of variables in Chapter 6 differs slightly. These variables are described in Chapter 6 section 6.2.3.1.

3.3.6 Variable definitions in the PROUD trial

3.3.7 Symptoms of depression

The definition of PHQ-9 depression measures, including suicidal ideation/self-harm, is described in detail in section 3.3.2. Information on symptoms of anxiety was not collected as part of PROUD questionnaires.

[xix] There may be other drugs that are used for chemsex, including Viagra, ketamine, ecstasy, cocaine, poppers, and alcohol, but these drugs do not cause the same degree of sexual disinhibition nor the same amount of harm that is possible with crystal methamphetamine, mephedrone and GHB/GBL (based on anecdotal report from David Stuart, the substance use lead at 56 Dean Street, 18/09/2015).

[xx] This measure was developed in consultation with David Stuart, the substance use lead at 56 Dean Street (18/09/2015). At this time, these drugs were thought to be most commonly used by gay men on the clubbing scene, based on interviews conducted by David Stuart with over 1500 MSM seeking support from ChemSex clinics at 56 Dean Street, and anecdotal reports from the LGBT drug/alcohol service 'Antidote' at the charity London Friend, as relayed by David Stuart. Although it was thought to be of interest to investigate 'club-drug use', it is acknowledged, that there is a great deal of cross-over between club-drugs and chemsex-drugs. Therefore, these measures are not compared in any way throughout this thesis, but rather examined together as measures of drug use which may be relevant to MSM in the context of HIV prevention research. Furthermore, it is also acknowledged that trends in club-drug use may have changed since the conception of the club-drug variable in 2015.

3.3.7.1 Receiving treatment for depression

At the baseline visit men were asked by study staff to note down any medication they were taking. I identified all men who specified that they were taking a medication that has been licensed for treatment of depression. Two members of the PROUD trial team (Professor McCormack and Dr White) independently reviewed participants' responses, in order to ensure that all appropriate treatments specified had been identified. Responses included; amitriptyline, bupropion, sertraline, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, sertraline, venlafaxine, as well as 'antidepressant' and 'serotonin'.

3.3.8 Sexual behaviour measures

Ten sexual behaviour measures were considered for analysis: seven were related to CLS and three were related to partner numbers. PROUD trial participants were asked about the number of partners (any and new) with whom the participant had anal sex in the past three months, with how many of these partners a condom was used and whether the participant was the insertive or receptive partner, as well as information about the most recent episode of anal sex and knowledge of partner HIV status. Five measures of CLS in the past three months were defined:

(i) CLS with at least two receptive and/or insertive CLS partners (of note, this measure is phrased in such a way to acknowledge the difficulty in distinguishing whether men who reported one receptive CLS partner and one insertive CLS partner [n=61 at baseline, n=37 at month-12, and n=29 at month-24] were referring to the same partner or two different partners)

(ii) CLS with at least five receptive and/or insertive CLS partners (derived due to the very high proportion of men reporting at least two CLS partners)

(iii) CLS with at least one partner with whom they knew were HIV-positive but did not know whether treatment was being taken

(iv) Receptive CLS with an HIV-positive partner not known to be on treatment

(v) Last CLS with an unknown/HIV-positive partner not known to be on treatment

At baseline, participants were asked whether they had been diagnosed with an STI in the past year. A rectal STI diagnosis was defined as report of one of four (rectal) bacterial infections: (i) rectal gonorrhoea, (ii) rectal chlamydia, (iii) syphilis, and (iv) LGV. Furthermore, at baseline self-reported PEP use in the past year was also ascertained.

The three measures of partner numbers included:

(i) Ten or more new anal sex partners in the past three months

(ii) Receptive anal sex with ten or more partners in the past three months

(iii) Group sex in the past three months (collected as part of the 12- and 24-month questionnaires only)

Of note, for each of the measures described above, a missing response was included in the no CLS or no high partner number category. Although it was originally planned to investigate HIV and STI incidence, and PrEP adherence, it become clear that collection of this data was not sufficient/the sample size was too limited to allow for meaningful analysis.

3.3.9 Self-efficacy for sexual safety and reasons for non-condom-use

At the 12- and 24-month follow-up, men were asked the extent to which they agreed or disagreed with a series of statements on condom-use and sexual satisfaction. The following statement was used to measure self-efficacy: 'The sex I have is always as safe as I want it to be'. If a participant strongly agreed with this statement this was considered to indicate high self-efficacy for sexual safety, all other responses (agree, disagree, strongly disagree, neural/uncertain, and missing) were not considered to indicate high self-efficacy. Participants were also asked the degree to which they agreed with the following statement: 'I find it easy to say 'no' to sex I don't want'. If a participant disagreed (disagree or strongly disagree) with this statement they were considered to indicate difficulty in saying no to unwanted sex, again all other responses (agree, strongly agree, neutral/uncertain, and missing) were not considered to indicate difficulty in saying no to unwanted sex. Of note, although one's ability to say no to unwanted sex is a component of self-efficacy for sexual safety, one may theoretically have high self-efficacy for sexual safety (i.e. always have sex that is as safe as one wants it to be) but difficulty in saying no to unwanted sex. Finally, participants were asked the degree to which they agreed with the following statement: 'I am happy with my sex life'. If a participant disagreed (disagree or strongly disagree) with this statement they were considered to indicate being unhappy with their sex life. All other responses (agree, strongly agree, neutral/uncertain, and missing) were not considered to indicate unhappiness with one's sex life.

Men were also asked reasons for non-condom-use, for which the following options were given (and one or more could be chosen): 'I don't like using condoms', 'He doesn't like using condoms', 'Condoms weren't discussed', 'We don't use condoms with each other but do with other partners', 'Neither of us had any condoms', 'I didn't consider myself at risk of HIV', 'I was under the influence of alcohol', 'I was under the influence of drugs', 'I am faithful to him', 'He is faithful to me', 'It is more enjoyable without a condom', 'I was only dipping', 'I lose erections with condoms' (only asked in the annual follow-up questionnaires) and 'Other'.

3.3.10 Other covariates

The other (self-reported) variables investigated in Chapters 7 and 8 include:

- *Age group* in six categories: <25, 25-29, 30-34, 35-39, 40-44, or ≥45 years

Baseline only;

- *Country of birth and ethnicity*: UK born & white ethnicity, UK born & BAME (black, Asian, and minority ethnicity), non-UK born & white ethnicity, or non-UK born & BAME

- *Study region*: London or outside London

- *Education*: educated to university degree level or not (including a missing response)

- *Employment status*: employed full- or part-time or other (unemployed, student, retired, other, or a missing response)

- *Sexual identity*: gay, bisexual (including other plurisexual identities that are not explicitly based on attractions to one sex/gender [617]), or straight/heterosexual

- *Relationship status*: ongoing relationship with a partner (wife/husband or civil partner or girlfriend/boyfriend) or not (including a missing response)

- *Higher-risk alcohol consumption* based on the first two questions of the WHO AUDIT-C questionnaire [632] (questions and scoring are described above in section 3.3.5): higher-risk score of ≥6 or lower risk/no alcohol consumption score of <6 (including a missing response to both questions). Of note, the response options included in PROUD for the first WHO AUDIT-C question ('How often have you had a drink containing alcohol in the last 90 days?') were 1 frequency lower than that specified in the WHO questionnaire, for instance, '2 or 3 times a month' instead of '2 to 4 times a month', and 'once or twice a week' instead of '2 to 3 times a week'. It is therefore possible, that the higher-risk alcohol consumption variable examined in PROUD constitutes a different measure to that investigated in AURAH, whereby the prevalence may be slightly overestimated in PROUD. The potential difference in measures is discussed in the limitations section of PROUD results chapters.

All participants were asked to report whether they had used recreational drugs in the past three months and, if so, to select which drug or drugs from a list of 19 options including 'other' (see section 3.3.5).

- *Number of recreational drugs used in the past three months*: none (including a missing response), 1, 2-4, or ≥5
- *Poly-drug use*: use of three or more recreational drugs or not (including a missing response)

- *Chemsex-associated drug use*: use of at least one psychoactive substance that is commonly used before/during sex (crystal methamphetamine, mephedrone or GHB/GBL[578-580]) or not (including a missing response)
- *Club-drug use*: use of at least one club-drug (mephedrone, GHB/GBL, ketamine, cocaine or ecstasy/MDMA) or not (including a missing response)

12- and 24-month questionnaires only;

Participants were given a set of circumstances in which individuals might have sex and were asked when last they had had sex under these circumstances (if ever) even if it is not typical. One of these circumstances included 'sex after using recreational drugs'. Response options included: never, >six months ago, within the last six months, within the last three months, and within the last four weeks. Sex after using recreational drugs is referred to throughout this thesis as sexualized drug use.

- *Recently had sex after using recreational drugs (sexualized drug use)*: yes (within the last four weeks/last three months) or no (within last six months, >six months ago, never, or a missing response)

Participants were asked 'How old were you the very first time you had any sexual contact with a male, or a male had any sexual contact with you?' and 'How old were you the very first time you had anal intercourse (top or bottom) with a male?' The UK Sexual Offences Act 2003 stipulates the legal age of sexual consent to be 16 and that children under age 13 have no legal capacity to consent to any form of sexual activity since they cannot fully comprehend nor are they developmentally prepared for it [633]. Two measures of age at anal sex debut were investigated, including cut-offs of age <13 and age ≤15. Reports of sexual intercourse before age 13 may include experiences of CSA, however, since information was not collected on the age of the sexual partner and whether they felt forced, it is possible that some participants may not have experienced forced/coerced sex. Furthermore, experiences of CSA may occur at ages older than 13 years. Therefore, although it was of interest in this thesis to investigate a very young age at sexual debut as this measure may include many cases of CSA, it may not reflect or pick up all sexual abuse experienced. The limitation of considering this measure to be indicative of CSA is discussed in Chapters 7 and 8. Of note, a third measure was derived in order to investigate the time delay between first sexual contact and anal sex.

- *Age <13 at first anal sex*: yes or no (age ≥13 at first anal sex)

- *Age ≤15 at first anal sex*: yes or no (age >15)

- *Time between any sexual contact and anal sex with a male*: same time, 1-2 years, 3-4 years, or 5+ years

Participants were asked five questions about IPV victimization and five questions about IPV perpetration. Each question had the following four response options: never, yes- more than 1 year ago, yes within the last year with former partner, and yes within the last year with current partner. The five IPV victimization questions included the following: 'Have you ever felt frightened of the behaviour of a partner', 'Have you ever needed to ask a partner's permission to work, go shopping, visit relatives, or visit friends (i.e. beyond the usual of being considerate to and checking with a partner)', 'Have you ever been hit, slapped, kicked or otherwise physically hurt by a partner', 'Have you ever been forced to have sex or made to engage in some sexual activity when you did not want to', and 'Have you ever been forced to have sex without a condom when you did not want to'. Similarly, the five IPV perpetration questions included the following: 'Have you ever behaved in a manner that has made a partner feel frightened', 'Has a partner ever needed to ask your permission to work, go shopping, visit relatives, or visit friends (i.e. beyond the usual of being considerate to and checking with a partner)', 'Have you ever hit, slapped, kicked or otherwise physically hurt a partner', 'Have you ever forced a partner to have sex or engage in some sexual activity when he did not want to', and 'Have you ever forced a partner to have sex without a condom when he did not want to'. Responding with 'yes' (more than 1 year ago, within the last year with former partner, or within the last year with current partner) to at least one of the five IPV victimization questions was considered to indicate any IPV victimization and responding with 'yes' to at least one of the five IPV perpetration questions was considered to indicate any IPV perpetration. Of note, following the ten IPV questions, participants were asked 'If you answered yes in the last year to any question above, do you think joining PROUD has influenced these behaviours?', with response options; no, yes in a positive way, or yes in a negative way.

- *Any IPV victimization*: reported any form of IPV victimization or not (including a missing response)
- *IPV victimization in the past year*: reported any form of IPV victimization in the past year or not (including a missing response)
- *Any IPV perpetration*: reported any form of IPV perpetration or not (including a missing response)
- *IPV perpetration in the past year*: reported any form of IPV perpetration in the past year or not (including a missing response)

Participants were asked eight questions surrounding attitudes towards gay sexuality based on the 26-item Internalized Homophobia Scale (IHS) [634]. Each question had the following five response options: strongly agree, agree, neutral or uncertain, disagree, and strongly disagree. The eight questions included the following: (i) 'I feel comfortable in gay bars', (ii) 'I feel comfortable being seen in public with an obviously transgender/gay person', (iii) 'I feel comfortable discussing homosexuality in a public situation', (iv)'I feel comfortable being a transgender/gay man', (v) 'Homosexuality is morally acceptable to me', (vi) 'Even if I could change my sexual orientation I wouldn't', (vii) 'Obviously effeminate homosexual men make me

feel uncomfortable' and (viii) 'Social situations with transgender/gay men make me feel uncomfortable'. Responding with 'strongly agree' or 'agree' to questions (vii) or (viii), or with 'strongly disagree' or 'disagree' to questions (i), (ii), (iii), (iv), (v), or (vi) was considered to indicate having negative attitudes towards gay sexuality.

- Internalized homophobia: negative attitudes towards gay sexuality or not (including a missing response)

Participants were asked how many of their (i) work colleagues, (ii) friends, and (iii) close family, know that they are gay/transgender/have sex with men. Response options for groups (i)-(iii) included: all/almost all, >half, <half, few, and none. Five variables regarding disclosure of sexual orientation were derived.

- Disclosure of sexual orientation to work colleagues: all/almost all, some (<half or >half), few, or none
- Disclosure of sexual orientation to friends: all/almost all, some (<half or >half), few, or none
- Disclosure of sexual orientation to close family: all/almost all, some (<half or >half), few, or none
- 'Out' to all/almost all work colleagues, friends, and close family: all/almost or less (including a missing response)
- 'Out' to few/no work colleagues, friends, and close family: few/none or more (including a missing response)

3.3.11 Handling of missing data

Where non-response to a question was considered to indicate non-occurrence of a measure, this is included in the definition of variables above. For instance, a missing response for education was considered to indicate non-university education and a missing response for recreational drug use was considered to indicate that zero drugs had been taken. Similarly, for the PHQ-9 and GAD-7, non-response to an item on the inventory was considered as absence of that specific symptom. This was done as there appeared to be a common response pattern in which only those symptoms that had been experienced were ticked. Where missing responses were included in the definition of variables, the proportion of missing values is provided when reporting the prevalence of measures in results chapters. The proportion of missing values was ≤5% for all variables used in analyses. Initial analyses that were undertaken to investigate whether excluding missing values (when defining each variable) had an impact on findings, demonstrated that this was not the case.

3.4 Epidemiological concepts: hypothesized causal effects

3.4.1 Directed acyclical graphs

In epidemiological studies, it is important to define the hypothesized causal effects of exposures on the outcome of interest. Directed acyclical graphs (DAG) provide a framework in which a set of hypothesized causal effects can be generated, producing a conceptual model. In a DAG, arrows are drawn between variables of interest in order to make explicit the hypothesis made about the causal connection [635-637]. Only one causal direction can be specified. For instance, either factor A is causing factor B or factor B is causing factor A, or neither of these is true. Hypothesized relationships can be either positive or negative.

Defining a set of hypothesized causal effects is useful in order to clarify which variables may be potential confounders, effect modifiers, and mediators of the relationship between the exposure of interest and outcome. This will inform the analysis. In addition, it is possible to generate analyses to assess how consistent or otherwise the data are with the conceptual model. These concepts are discussed below. Of note, in most studies it is not possible to prove that observed relationships are in fact causal. Investigating evidence for causality is discussed in section 3.4.4.

3.4.2 Investigating confounding, effect modification, and mediation

A confounding factor is associated with both the exposure variable and the outcome variable and is not considered to be an intermediary step in the hypothesized causal pathway. Confounding can be adjusted for in the analysis if information on the potential confounding factor is available. If a potential confounding factor is distributed unequally among the exposure variable categories, it may completely or partially reduce, or increase, the observed association between the exposure and outcome when added to a regression model [638].

Effect modification occurs when the association between the exposure variable and the outcome variable differs depending on the level of a third variable. Dealing with effect modification involves examining the association between the exposure and the outcome separately for each level of the effect modifying variable in a regression model. Effect modification is sometimes referred to as interaction and an effect modifier as an interactor [638].

Mediation occurs when the association between the exposure and outcome operates fully or partially through an intermediate factor(s) within a hypothesized causal chain [456]. If a factor is found to be a mediating variable this would mean that in order for the exposure to lead to the outcome, it must first cause the mediating variable(s), which then in turn leads to the outcome. The most common approach to mediated analysis stems from the work of Kenny and

colleagues and is referred to as the 'causal steps' approach [639, 640]. A series of four steps, using regression modelling, are required to reasonably conclude potential mediation:

1. The exposure must be significantly associated with the outcome
2. The exposure must be significantly associated with the mediating variable
3. The mediating variable must be significantly associated with the outcome
4. The association between the exposure and outcome should be reduced (or completely blocked) when the mediating variable is added to the model

It has been suggested that this approach is insufficient on its own to allow conclusions to be made regarding potential mediation, as it does not provide estimates of the mediated effect and standard errors. It is therefore, not possible to assess the significance of the mediated effect and any conclusions drawn may be subject to type I or II errors [456]. There are two other common approaches to mediational analysis, which extend the causal steps approach: the difference of coefficients method and the product of coefficients method. In both methods, the difference between the effect of the exposure on the outcome with and without the mediating variable in the model is measured [456]. Under most circumstances, these approaches will produce identical estimates of the mediated effect.

3.4.2.1 Investigating mediation using structural equation modelling

The product of coefficients method is often used in a structural equation model (SEM) framework. SEM produces estimates of the direct effect of the exposure on the outcome, the indirect effect of the exposure on the outcome via the mediating variable (or multiple variables in complex mediational chains), and the total effects in a single model [456]. A significant indirect effect suggests that the hypothesized intermediate factor may be on the causal pathway. The Sobel formula is used to test the significance of the indirect effect by dividing the estimate of the mediated effect by one of several standard error estimates [641].

3.4.3 Investigating the conceptual model

SEM is also a means by which to assess whether the data are consistent with a given set of causal relationships, since it allows for more flexible specification of relationships. Nearly any variable can be allowed to be correlated, or constrained to be uncorrelated, with another variable. It is helpful to examine more than one conceptual model in SEM in order to investigate which hypothesis the data are more consistent with. In this way, SEM is also a means by which to generate further hypotheses.

3.4.4 Evidence for causality

In 1965, Sir Austin Bradford Hill proposed nine 'aspects of association' that should be considered when evaluating epidemiological data and concluding causation [642]. These nine aspects of association were integrated into the so called Bradford Hill Criteria, which is to this

day commonly used as a guide to causal inference. The strongest evidence for causality comes from longitudinal study designs in which temporality can be inferred. In particular, evidence is more robust for randomized trials as they also control for confounding. Other criteria for determining whether a relationship is causal include strength of association, consistency, specificity, biological gradient, biological plausibility, coherence, experiment, and analogy. These criteria are defined in Textbox 6.

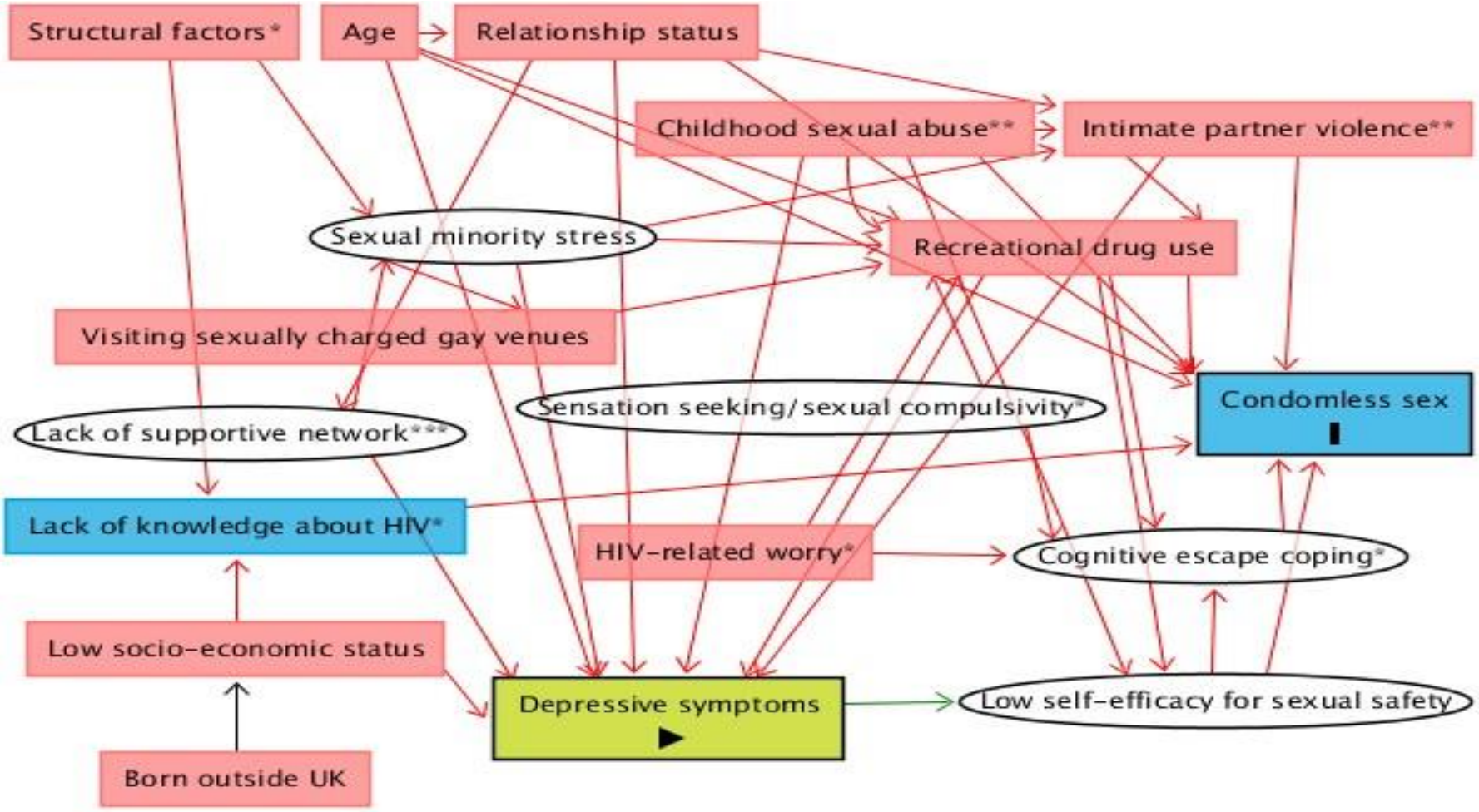
Textbox 6: Bradford Hill Criteria; adapted from research by Fedak et al 2015 [642]

Criterion:		Description
1	Strength of the association	An association cannot be considered causal unless statistically significant. Statistical significance is dependent, however, on the sample size. Therefore, the magnitude of an association is important regardless of statistical significance. The stronger the association, i.e. the greater the magnitude, the more likely it is to be causal.
2	Consistency	The association is consistently demonstrated across epidemiological studies of varying geographical locations, populations, and methods.
3	Specificity	Specific associations are more likely to be causal. A specific association requires that the exposure only causes one outcome.
4	Temporality	Epidemiologic study designs, in which temporality can be inferred, are more persuasive in causal inference.
5	Biological gradient	The presence of a dose-response relationship, whereby the outcome increases with increased exposure, supports inference of a causal association.
6	Biological plausibility	Existing biological and social models should explain the mechanism by which the exposure may lead to the outcome under investigation.
7	Coherence	Similar to biological plausibility, there should be a 'coherent story', based on all knowledge available, which explains the direction of association.
8	Experiment	Epidemiologic studies that encompass experimental manipulation, i.e. introduction of an intervention targeting the exposure, most likely leads to the strongest support for causal inference.
9	Analogy	Causal inference of an observed association may be enhanced if a similar exposure is found to be associated with a similar outcome.

3.5 Causal pathways hypothesized in this thesis

In order to make explicit the hypotheses made about the causal connections between socio-demographics, psychosocial factors and depressive symptoms, and between depressive symptoms and CLS in this thesis, a DAG [635-637] was drawn using DAGitty software [643]. The DAG is presented in Figure 8 below. All arrows shown leading to depression and CLS were derived from observed relationships based on previous literature presented in Chapters 1 and 2 (and in Appendix sections 11.4.1- 11.4.2.1), although such relationships have not been proved to be causal. It is of note that implicit within this conceptual model, is that CLS is often a desirable behaviour for reasons of intimacy and pleasure. Where the sex is desired, perceived risk of STIs/HIV may result in behavioural adaptation via condom-use for some individuals but not others, reflected in the factors shown leading to CLS in the DAG. All arrows shown leading to psychosocial factors (CSA, IPV, recreational drug use, and sexual minority stress) and psychological constructs (self-efficacy and cognitive escape) were informed by previous literature. The arrows shown between the following factors were hypothesized causal relationships which were not informed by findings from previous studies: age and relationship status, structural factors (socio-cultural norms regarding sexuality, as described in section 1.6.1.2 of Chapter 1, which may be supported by religious doctrines) and lack of knowledge about HIV, having been born outside the UK and low socio-economic status, low socio-economic status and lack of knowledge about HIV, and relationship status and lack of supportive network.

Figure 8: Directed acyclical graph of hypothesized causal connections between socio-demographics, psychosocial factors and depressive symptoms**, and between depression and CLS, among sexual minority men**



Key:

Primary exposure of interest
Outcome
Ancestor (a direct or indirect cause) of outcome
Ancestor (a direct or indirect cause) of exposure *and* outcome
Unobserved (hypothetical variable that attempts to measure real phenomena)
Causal pathway
Possible alternative pathway: in this instance, these are potential pathways through which depression might lead to CLS. For instance, depression might lead to lower levels of a supportive network, which in turn might lead to stress related to a sexual minority status, frequently visiting sexually charged gay venues, recreational drug use, and finally CLS. If the arrow was shown going from depression to supportive network, as opposed to the other way around, this pathway would be shown as green instead of pink. Each pink square represents the variables that are direct/indirect ancestors of depressive symptoms and CLS but this does not necessarily mean that the pink square variable is on a pathway between depression and CLS. For instance, this is not the case for UK born even though it is an indirect ancestor of both depressive symptoms and CLS.

Arrows represent assumed causal links. Bi-directional arrows between:

1. Depression and drug use
2. Gay venues and drug use
3. Drug use and cognitive escape
4. Drug use and self-efficacy
5. Supportive network and minority stress
6. Intimate partner violence and drug use
7. Intimate partner violence and depression
8. Depression and supportive network

* Not collected in the AURAH or PROUD study.

** Not collected in the AURAH study.

*** Not collected in the PROUD study.

**** It was decided that although collected as part of the AURAH study, markers of HIV optimism and use of dating apps would not be included in the hypothesized model of the relationship between depression and CLS among sexual minority men. HIV optimism would have been included in the hypothesized model under the assumption that it was a direct cause of CLS. Dating app use (which refers in general to use of the Internet to find a sexual partner and specifically to geosocial networking apps) would have been included in the hypothesized model under the assumption that it was a direct cause of recreational drug use, and an indirect cause of depression and CLS. In order to keep the model succinct, these factors were not included. Furthermore, it is of note, CSA may be an earlier marker of IPV in adulthood. Since CSA specifically concerns sexual abuse/sexual coercion, an arrow is only shown going from CSA to self-efficacy for sexual safety, and not from IPV to self-efficacy for sexual safety, however, it is possible that IPV in adulthood (especially forms of sexual IPV) may also lower one's self-efficacy for sexual safety. Finally, younger age was hypothesized to be linked to depressive symptoms, recreational drug use, and CLS. Older age was hypothesized to be linked to having an ongoing relationship with a partner. Being in an ongoing relationship with a partner was hypothesized to be linked to higher levels of a supportive network, lower levels of depressive symptoms, intimate partner violence and CLS.

All the factors represented by pink squares in Figure 8, including sexual minority stress, lower supportive network, and sensation seeking/sexual compulsivity, are hypothesized to be ancestors of the primary exposure of interest and of the outcome i.e.to indirectly cause both depression and CLS, or directly cause one and indirectly cause the other. There are five factors in Figure 8 that are hypothesized to directly cause both depression and CLS. These are recreational drug use, CSA, IPV, younger age, and being in an ongoing relationship. Since these factors are not hypothesized to be on the causal pathway between depressive symptoms and CLS, they are potential confounders of this relationship. The inclusion of these factors in adjusted models is described in the next section. Of note, recreational drug use, a very young age at anal sex debut, which may include experiences of CSA, and IPV were also investigated as potential effect modifiers of the relationship between depressive symptoms and CLS.

Low self-efficacy for sexual safety is hypothesized to be the main mechanism mediating the association between depressive symptoms and CLS in Figure 8. Lack of self-efficacy is hypothesized to lead directly to CLS and indirectly via a process of cognitive escape. Since only one causal pathway can be presented in the DAG, the green arrow is only shown from depression to self-efficacy and not self-efficacy to CLS. It is of note that AURAH did not ask questions surrounding CSA or IPV, and neither AURAH nor PROUD collected information on knowledge of HIV[xxi], markers of cognitive escape coping, personality traits associated with sensation seeking/sexual compulsivity, or fear of HIV due to pervasive prevention messages (HIV-related worry). The PROUD trial collected information on age at anal sex debut but as discussed above in section 3.3.10, although reports of sexual intercourse before age 13 may include experiences of CSA, this measure may not reflect or pick up all sexual abuse experienced. Furthermore, structural factors cannot be extrapolated from the AURAH or PROUD questionnaire, and a comprehensive measure of minority stress was not investigated in either study. Modelling of the DAG is described in the next section. This includes depicting the hypothesized relationships between factors collected, in a SEM, in order to investigate the indirect effect of self-efficacy for sexual safety and examine consistency of the conceptual model with the data.

3.6 Statistical methodology

This section describes the main statistical methods used in analysis in this thesis, further details are given in individual chapters.

[xxi] Knowledge of HIV refers to awareness and understanding of HIV transmission routes, susceptibility (i.e. with a concurrent STI), and prevention and risk reduction strategies (biomedical interventions and community approaches to risk reduction such as sero-sorting and sero-positioning). This includes an understanding of the implications of an HIV viral load in terms of infectiousness.

3.6.1 Analyses based on cross-sectional data from the AURAH study

3.6.2 Modified Poisson regression

Logistic regression is often used when the outcome is binary, in order to produce odds ratios (ORs) to describe the association between an exposure and the binary outcome variable. However, ORs can be somewhat difficult to interpret, as they are not intuitive, do not relate directly to percentages, and may be misinterpreted as risk ratios or prevalence ratios. Modified Poisson regression, so termed by Zou (2004), can be used in order to produce risk ratios or prevalence ratios when the outcome (dependent variable) is binary. Poison regression is a generalized linear model with a log link and a Poisson distribution [(644)]. Ordinary Poisson regression is usually used for analysis of count outcomes, the counts being non-negative integer values, usually describing the occurrence of certain events[xxii]. Use of Poisson regression with a binary outcome will result in underdispersed data, since the data exhibits less variation than expected by a model based on a Poisson distribution. Underdispersion will result in standard errors[xxiii], p-values, and confidence intervals that are too large, since the error term is miss-specified when the underlying data are binomially distributed [(644)]. Zou (2004) found that this issue can be solved via the use of a robust error variance procedure, called a sandwich estimator. The sandwich error term can correct the variance overestimation by relaxing the assumption that the data are from a Poisson distribution [(645)]. Accordingly, modified Poisson regression, was used for unadjusted and adjusted analysis of binary outcomes for cross-sectional analyses in Chapters 4 and 5 of this thesis, in order to produce prevalence ratios (PRs). Of note, overall p-values for heterogeneity based on the Wald test in modified Poisson regression and p-values for tests for linear trend, whereby categorical variables are treated as continuous in the model, are presented. Effect modification via use of interaction terms and the causal steps approach to mediation was investigated in modified Poisson models in Chapter 5. Analyses were performed using STATA statistical software [(646)]. One disadvantage of the use of PRs rather than ORs is that, when investigating the association between depressive symptoms and sexual risk behaviour, the magnitude of the PRs cannot be directly compared across sexual behaviours of different prevalence. For a common outcome measure, whereby the underlying prevalence may be high, the PR is likely to be of smaller magnitude compared to that for rare outcomes. For instance, a prevalence of 10% may be doubled resulting in a PR of 2, but a prevalence of 60% cannot be doubled and therefore cannot result in a PR of 2. Accordingly, PRs should be considered together with the prevalence of the outcome.

[xxii] The dependent variable has the probability of being 0, 1, 2, 3, 4, 5 etc.

[xxiii] The standard error is the accuracy with which a sample represents a population. The calculation for the standard error is based on the sample size and standard deviation. The standard deviation is how much the members of a group differ/deviate from the mean value for the group. The calculation for the standard deviation is based on the value for each member of the group, the mean value, and the sample size. 644. Cummings P. Methods for estimating adjusted risk ratios. The Stata Journal. 2009;9(2):175-96.

3.6.3 Structural equation modelling

SEM has been introduced in sections 3.4.2 and 3.4.2.1 above. Of further note, SEM allows unobserved (latent) variables to be treated as if they were observed. Latent variables are defined as constructs that are not real, but come from the 'imagination of the researcher', as opposed to traits, which exist in people. For latent variables, a hypothetical variable attempts to measure real phenomena. For instance, the construct of self-efficacy is not real, but there are real phenomena or personality traits to which researchers apply this term [647-650].
Acknowledging variables as latent rather than observed can have clear advantages. Latent variables account for unreliability of measurement but in regression analysis/SEM, the regression coefficients/path coefficients will be biased for unreliable observed variables [456, 651]. In addition, SEM can be used to correct for non-normality in the data and for missing data problems. Finally, as Bryan et al (2007) put it, "it is more satisfying to simultaneously test the validity of the entire theory as hypothesized in the context of a structural model" [456] (page 366).

The same DAG as that presented above in Figure 8 but depicting the hypothesized relationships between factors collected in the AURAH questionnaire, is presented in Chapter 6 Figure 16. SEM was used to explore the conceptual model (DAG) in Chapter 6 in order to investigate mediation and examine consistency of the model with the data. Mplus is the main SEM software capable of handling categorical data and as such, all analyses were performed using MPlus statistical software [652, 653].

3.6.4 Dealing with hierarchical data

In Chapter 5, when investigating the association between depressive symptoms and sexual behaviour, a variable describing the region of GUM clinic site recruitment, referred to as the study region, was investigated as a random-effect (with random intercepts) in a multilevel mixed-effects Poisson regression model. This was in order to take into account the hierarchical structure of the data. When comparing this model[xxiv] to a model that incorporated study clinic site as a fixed-effect in a Poisson regression, the pseudo R^2 was identical. This was the case at each stage of the model building procedure described below, and for each outcome. As a result, and since it was not of interest in this thesis to compare the within-group variance with the between group variance, it was decided that the study region would be investigated as a fixed-effect in a Poisson model with a robust variance estimator.

3.6.5 Adjustment for confounders

When investigating the association between depressive symptoms and sexual risk behaviour, depressive symptoms and self-efficacy for sexual safety, and self-efficacy for sexual safety and sexual risk behaviour, in Chapter 5, factors were adjusted for in two stages. In the first stage,

[xxiv] As well as a Poisson model incorporating a clustered sandwich estimator, which relaxes the assumption that observations are independent and allows for intragroup correlation.

socio-demographic factors assumed not to be on the causal pathway were adjusted for. These included hypothesized confounders in the DAG in Figure 8 with a direct causal link to sexual behaviour (age and relationship status) as well as factors that may be proxy measures for knowledge about HIV (UK born and educational attainment). In the second stage, these same socio-demographic factors were adjusted for plus lifestyle factors hypothesized to be confounders, in order to assess the extent to which the association was attenuated. The two models are shown below. Of note, when investigating socio-demographic and lifestyle factors associated with depressive symptoms in Chapter 4, adjustment for factors in Model 1 was investigated only.

1. Model 1 with socio-demographic variables: age group in four categories *(<25, 25-34, 35-39, or 40+)*, university education *(yes or no/missing)*, born in the UK *(yes or no),* self-reported sexual identity *(gay or bisexual/straight)*, ongoing relationship *(yes or no/missing)*, and study region *(London, South, or Midlands/Yorkshire & the Humber)*.

2. Model 2 with the same socio-demographic variables shown above plus lifestyle variables: number of recreational drugs used *(0/missing, 1, 2-4, or 5+)*, higher-risk alcohol consumption (modified *WHO AUDIT-C higher-risk score of ≥6 or lower risk/no alcohol consumption score of <6/missing)*, and regular smoking *(yes or no/missing)*.

Initial analyses undertaken to investigate whether adjusting for age grouped into six categories (<25; 25-29; 30-34; 35-39; 40-44; ≥45 years) or adjusting for age as a continuous variable had an impact on findings, demonstrated that this was not the case.

3.6.6 Longitudinal data from the PROUD trial

For reasons described above in section 3.3.8, although originally planned it was not possible to investigate HIV/STI incidence in this thesis using longitudinal data from the PROUD trial. As a result, cross-sectional associations with depressive symptoms and sexual risk behaviour measures were investigated in this thesis, at each PROUD time-point and by pooling data from each time-point. The statistical methods used to do this, are described below.

3.6.7 Generalised estimating equations

Standard regression modelling assumes that all observations are independent of each other. Longitudinal data contains repeated measures from the same individual over time. In general, observations from the same individual are more similar to each other than observations from different individuals. Use of standard regression models to analyse data with correlated observations tends to produce standard errors that will underestimate the true sample-to-

sample variation and hypothesis test probabilities[xxv] that will be too low. Confidence intervals will also be unrealistically narrow [644, 645]. Generalized estimating equations (GEEs) treat the data as if it were cross-sectional, while dealing with variance underestimation for correlated observations in longitudinal studies. This is achieved via the use of a robust estimation of standard error procedure. In GEEs, the estimated coefficients are based on variations within and between individuals, and it is possible to investigate the effects of time-invariant and time-variant independent variables on the dependent variable. GEEs were chosen for analysis of longitudinal data from the PROUD trial, since the prevalence rather than incidence of outcomes was investigated in this thesis. Compound symmetry was used for the correlational structure via use of the 'exchangeable' option in STATA, since it was assumed that the observations on a given participant were more correlated than those between different participants. A Poisson model with a log link was fitted in GEEs in order to produce PRs in Chapters 7 and 8 [655, 656]. As described in section 3.6.2 for modified Poisson regression, estimates are presented with overall p-values for heterogeneity (based on the Wald test) and p-values for tests for linear trend. Effect modification via use of interaction terms was investigated in GEEs in Chapter 8. Although originally planned, based on initial findings it was deemed unnecessary to investigate mediation via the causal steps approach or SEM. All analyses were performed using STATA statistical software [646]. It is of note that cross-sectional data from PROUD at each time-point (baseline, 12-month, and 24-month questionnaire) was also investigated using modified Poisson regression, as described in section 3.6.2.

3.6.8 Adjustment for confounders

The PROUD trial collected longitudinal data. With the exception of age, information on socio-demographic and lifestyle factors was only collected at the baseline questionnaire. When investigating associations at month-12 and month-24 in modified Poisson models, and when combining data from each study time-point using GEEs, it was necessary to decide which of these socio-demographic and lifestyle factors were likely to remain the same over the course of the two year study and which factors were likely to change. It was considered appropriate to assume that information on country of birth, study region, education, employment status, and sexual identity would most likely not change over the course of the study, and as such, the baseline value of these variables was included in modified Poisson models at follow-up and in GEE models. It was however, considered inappropriate to assume that relationship status, higher-risk drinking, and recreational drug use in the past three months would not change over the two year period of the study, and as such, these variables were not included in modified Poisson models at follow-up or in GEE models.

[xxv] Hypothesis tests consist of testing the probability that the null hypothesis, that there is no difference between two population proportions for instance, is true.654. Kohler U, Kreuter F. Data Analysis Using Stata. 3rd ed. Texas: StataCorp LP; 2009.

In Chapter 8, investigating the association between depressive symptoms and sexual risk behaviour, at baseline, month-12, and month-24 in modified Poisson models, and when combining data from each study time-point using GEEs, different factors were adjusted for in two stages given the collection of data at different time-points. In the first stage, socio-demographic factors assumed not to be on the causal pathway were adjusted for. These included hypothesized confounders in the DAG in Figure 8 with a direct causal link to sexual behaviour (age and relationship status) as well as factors that may be proxy measures for knowledge about HIV (UK born and educational attainment). In the second stage, these same socio-demographic factors were adjusted for plus psychosoical factors hypothesized to be confounders, in order to assess the extent to which the association was attenuated. The two stages of adjustment at each study time-point are presented below. Of note, when investigating socio-demographic and psychosocial factors associated with depressive symptoms in Chapter 7, adjustment for factors in Model 1 was investigated only. Furthermore, in Chapter 8, when examining associations at month-12 and month-24 in modified Poisson models, adjustment for factors in Model 1 was investigated only. Adjustment for psychosocial factors in Model 2 was investigated in GEEs given the increased statistical power associated with combining observations from baseline, month-12, and month-24.

1. Model 1 with socio-demographic variables:
    - Baseline; age group in four categories *(<25, 25-34, 35-39, or 40+)*, university education *(yes or no/missing)*, born in the UK *(yes or no),* self-reported sexual identity *(gay or bisexual/straight)*, ongoing relationship *(yes or no/missing),* and study region *(London or outside London)*.
    - 12- and 24-month questionnaire; same as above excluding ongoing relationship.
    - GEEs; same as above excluding ongoing relationship.

2. Model 2 with the same socio-demographic variables shown above plus psychosocial variables:
    - Baseline; number of recreational drugs used *(0/missing, 1, 2-4, or 5+)*, and higher-risk alcohol consumption (*WHO AUDIT-C higher-risk score of ≥6 or lower risk/no alcohol consumption score of <6/missing)*.
    - GEEs; any IPV victimization (yes or no/missing) and age <13 years at anal sex debut (yes or no).

Of note, when investigating the association between depressive symptoms and self-efficacy for sexual safety, and self-efficacy for sexual safety and sexual risk behaviour at the 12- and/or 24-month questionnaire, in Chapter 8, the same two-stage adjustment procedure as that described above was investigated, with the exception of any IPV victimization, which was excluded from

Model 2. In Figure 8, only recreational drug use and CSA were hypothesized to be confounders of these associations.

Initial analyses undertaken to investigate whether adjusting for age grouped into six categories (<25; 25-29; 30-34; 35-39; 40-44; ≥45 years) or adjusting for age as a continuous variable had an impact on findings, demonstrated that this was not the case.

3.6.9 Patient and Public Involvement in PROUD findings

Given findings in this thesis from the PROUD trial, and the usual practice of Patient and Public Involvement (PPI) in the interpretation of PROUD findings, in conjunction with PROUD investigators, I designed a short PPI survey that was distributed to PROUD participants. This was interpreted using a qualitative analytic approach. The methodology and findings are presented in Chapters 7 and 8.

3.6.10 Evidence for causality in this thesis

In the final conclusion chapter, the Bradford Hill criteria are evaluated based on findings from this thesis, in order to provide a framework to consider whether the observed association between depressive symptoms and sexual behaviour measures is likely to be causal.

3.7 Methodological limitations

3.7.1 General weaknesses of the AURAH study

The AURAH study is important in the context of GUM services but it does not necessarily allow us to generalize to all MSM in the UK. The use of non-probability sampling methods may also call into question the external validity of the sample i.e. the men recruited for AURAH may not be representative of all men attending GUM clinics in England. Some attempts were made to try and improve external validity; at study start, all sites were asked to identify different clinic days/times each week for recruitment.

The cross-sectional design of the study is another potential weakness. As mentioned in section 3.4.4, although it is often not possible to definitively conclude causality, longitudinal study designs provide the strongest evidence in favour of concluding an observed relationship to be causal. Whereas, making inferences as to whether observed relationships in cross-sectional study designs are causal, is particularly difficult as it is not possible to be assured of the direction of association. For example, unemployment and substance use may be causal factors in the development of depression. On the other hand, those with depressive symptoms may be more likely to be unable to work, or to use substances to cope with negative life stresses. Similarly, it may be the case that CLS leads to symptoms of depression, rather than occurring

as a result of such symptoms, or that the association operates in both directions. Finally, a number of important additional factors that may have a bearing on the link between depressive symptoms and sexual behaviour were not collected in the AURAH study. These include CSA and IPV in adulthood.

3.7.1.1 Potential sources of bias

In the AURAH study, behaviours that are thought to be socially unacceptable may have been under-reported, resulting in reporting bias/social desirability bias. Bias may have been reduced via the use of self-completion questionnaires, attempts to create a private space for survey completion, provision of an envelope to create a sense of anonymity, and by not allowing clinic staff to see the questionnaire. Additionally there were a number of inconsistent responses to the sexual lifestyle section in the AURAH questionnaire (see Appendix section 11.8.5.3). Therefore, it is important to be mindful throughout this thesis that self-reported sexual behaviour may be subject to errors and biases.

Furthermore, the AURAH study nurse coordinator identified 15 clinical centres for study participation based on previously successful research collaborations and on the understanding that the centre could facilitate access to large numbers of HIV-negative MSM and black African men and women. It is therefore possible, that selection bias may have affected the choice of venues for the survey. Bias may have been reduced by incorporating into the study a large number of GUM clinic sites (N=20) across England.

3.7.2 General weaknesses of the PROUD trial

In the context of consistent PrEP use, CLS may no longer place an individual at higher-risk for HIV acquisition. Therefore, in the immediate PrEP arm of the PROUD trial, it is PrEP adherence that is the risk behaviour of interest. Some men may use PrEP intermittently, and in such circumstances, CLS during a non-PrEP use period, may place an individual at risk. As such measuring ‘unprotected sex’ whereby an individual is not on PrEP and reports CLS, may be the most appropriate measure of sexual risk. However, due to the lack of data on PrEP adherence, it was not possible to investigate how participants matched PrEP adherence to sexual risk behaviour. Furthermore, PROUD was initially designed as a pilot study to investigate feasibility, and therefore, the sample size is limited. This may affect the precision of the estimates and increase the chances of a type II error (a false negative finding). Findings must therefore, be interpreted with caution. Finally, the PROUD study population did not include bisexual men reporting recent sex with women only. Excluding these men may not provide a full picture of the role of depression in sexual behaviour among sexual minority men.

3.7.2.1 Potential sources of bias

Social desirability bias may also be relevant to the PROUD trial, since information on sexual behaviour, age at anal sex debut, and intimate partner violence was requested. Ways in which this form of bias may have been overcome in PROUD are similar to that for AURAH (section 3.7.1.1). Three additional types of bias may have been operating during the PROUD trial and require consideration: (i) performance bias, (ii) attrition bias, and (iii) contamination bias. Firstly, performance bias occurs when one study arm receives more attention from investigators of the trial than the other study arm. In PROUD, individuals in the immediate arm received a greater number of screening tests for STIs as a result of more regular study clinic attendance than men in the deferred arm (mean 4.2 versus 3.6), biasing the randomized comparison between the two arms with regards to STI incidence. However, this potential source of bias does not affect the findings presented in this thesis given that STI incidence was not investigated and STI diagnosis in the past year was only investigated at baseline.

Secondly, attrition bias occurs when there are systematic differences between groups in terms of loss-to-follow-up from a study. In PROUD, 130 men who completed a baseline questionnaire did not complete a 12-month questionnaire and 103 men who completed a 12-month questionnaire did not complete a 24-month questionnaire. Upon investigation (see section 3.2.4), it appears that men without a 12-month questionnaire may have differed significantly in baseline socio-demographic factors (age, country born/ethnicity, education) to men with a 12-month questionnaire. Perhaps combining data from each time-point in GEEs, as described above (section 3.6.7), may have, to some extent, addressed this source of bias.

Thirdly, contamination bias occurs when members of the control arm of a trial are exposed to the intervention. In PROUD, it is possible that men in the deferred arm were taking PrEP from study start. Two men enrolled twice in the PROUD trial in order to access PrEP, after first being randomized to the deferred group. It has been suggested that other men in the deferred arm may have co-enrolled without being detected. It is also possible that men accessed PrEP through the Internet or used someone else's PrEP or HIV antiretroviral medication as PrEP, for instance if obtained as PEP. In the context of this thesis, this emphasises the need to address the PROUD sample in the context of biomedical intervention (both PEP and PrEP).

3.7.3 Considering type I error

A maximum probability of making a type I error (a false positive finding), was set at 0.05, indicating that there was no greater than a 5% chance of making a type I error. The AURAH study consisted of a large sample of men (N=1340), in which multiple exposures and multiple outcomes were addressed. It is possible that this may have increased the likelihood of finding an effect due to chance. However, the analyses in this thesis investigated a clear, pre-defined hypothesis about depression and sexual risk. Furthermore, emphasis is placed on the pattern of results rather than solely on significance testing. Several different sexual behaviour measures

were assessed in order to examine whether the pattern of results was consistent across measures of CLS and higher partner numbers.

Multiple testing also took place when investigating the relationship between depression measures and sexual behaviour measures at each time-point of the PROUD trial. It is inevitable that some significant findings will appear just by chance, resulting in type I error. However, merging data from each time-point in GEE models should have reduced the occurrence of any possible type I errors.

Chapter 4

4 Prevalence of depressive symptoms and associated factors among gay, bisexual, and other men who have sex with men in the AURAH study

4.1 Introduction

As described in the thesis introduction (section 1.8.1), the prevalence of depression appears to be elevated among sexual minority men compared to their heterosexual counterparts in high-income countries [332, 338-342]. Stress associated with a sexual minority status, as described in Meyer's minority stress model, may account for the elevated prevalence of depression [211, 223-225, 235-239, 245-247]. Among sexual minority men, socio-economic status [248, 249] and social support [225, 245-247], as well as other psychosocial factors, such as recreational drug use, CSA, and IPV [41, 368, 454, 605, 610, 657, 658] [604, 605, 611, 658-666], may be associated with depressive symptoms.

In the first three results chapters of this thesis, data from the AURAH study is investigated. The AURAH study questionnaire incorporated the PHQ-9, a standard instrument that is commonly used to measure self-reported depressive symptoms in clinical and research settings, as described in section 3.3.2.1 of Chapter 3. The AURAH questionnaire also incorporated the GAD-7 (assessing anxiety symptoms) and asked participants about mental health diagnoses and treatments, including specifically treatment for depression, see sections 3.3.2.2-3.3.2.3. The aim of this chapter was to investigate among HIV-negative (or unknown status) gay, bisexual, and other MSM, who reported recent anal or vaginal sex, the prevalence of depressive symptoms on PHQ-9 and the association with socio-demographic and lifestyle factors. The second aim of this chapter was to present the prevalence of anxiety on GAD-7, mental health diagnoses, and treatment for mental health conditions.

4.2 Statistical methods

A detailed description of the variables investigated in analyses presented in this Chapter, is included in Chapter 3 section 3.3.1.

The prevalence of each of the nine individual PHQ-9 depressive symptoms is presented. The prevalence of depressive symptoms according to PHQ-9 criteria is presented using three definitions: (score of ≥10, major depressive syndrome, major and other depressive syndromes). The prevalence of suicidal ideation and medical treatment/therapy for depression is also presented. Of note, in order to more accurately present the prevalence of men with depression who were receiving treatment, men with either depressive symptoms (PHQ-9≥10) or who

reported receiving treatment for depression were considered to account for all men with any evidence of current depression, since treatment in the absence of symptoms may indicate successfully treated depression. The prevalence of GAD on GAD-7, as well as the diagnosis and treatment of any mental health disorder, was also assessed.

Associations of socio-demographic and lifestyle factors (see section 3.3.5) with depressive symptoms (PHQ-9≥10) were assessed using χ^2 tests, χ^2 tests for trend, and Fisher's exact test (when expected numbers were small) for univariable analysis. Associations are presented unadjusted and adjusted for key socio-demographic factors (see section 3.6.5) using modified Poisson regression with a robust variance estimator, see section 3.6.2 [645]. An additional analysis was undertaken to assess the relationship of socio-demographic and lifestyle factors with depressive symptoms when including the 144 men who did not report recent sex (N=1484 MSM). A sensitivity analysis was undertaken using different PHQ-9-based definitions of depressive symptoms (major depressive syndrome and major and other depressive syndromes).

4.3 Results

4.3.1 Prevalence of depressive symptom measures on PHQ-9

Table 3 presents the prevalence of the nine depressive symptoms on PHQ-9. The proportion of individuals who had missing responses to symptoms is presented as a footnote under Table 3. As described in section 3.3.11 of Chapter 3, missing responses were considered to indicate that the symptom was not present. Overall, the most commonly experienced symptom, for at least several days over the past two weeks, was 'feeling tired or having little energy', followed by 'trouble falling or staying asleep, or sleeping too much', and 'feeling down, depressed, or hopeless'.

Following the PHQ-9 depressive symptoms, participants were asked 'If you were bothered by any of these problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?' Of the 1099 participants who had responded 'several days' or more to at least one symptom, 53.5% said 'not at all' difficult to the question posed above, 35.6% said somewhat difficult, 4.4% said very difficult, and 1.6% said extremely difficult (4.9% did not respond).

Table 3: Prevalence of PHQ-9 depressive symptoms in AURAH N=1340

	Not at all[a] %	Several days %	>half the days %	Nearly every day %
PHQ-9 1) Little interest or pleasure in doing things	70.1%	23.7%	3.9%	2.4%
PHQ-9 2) Feeling down, depressed, or hopeless	61.0%	30.0%	5.9%	3.1%
PHQ-9 3) Trouble falling or staying asleep, or sleeping too much	52.8%	30.5%	10.1%	6.6%
PHQ-9 4) Feeling tired or having little energy	46.6%	38.0%	10.1%	5.4%
PHQ-9 5) Poor appetite or overeating	75.2%	16.0%	5.8%	3.0%
PHQ-9 6) Feeling bad about yourself-or that you are a failure or have let yourself or your family down	61.2%	26.2%	7.8%	4.8%
PHQ-9 7) Trouble concentrating on things, such as reading the newspaper or watching television	75.7%	15.8%	5.7%	2.8%
PHQ-9 8) Moving or speaking so slowly that other people could have noticed/being so restless that it is hard to sit still	76.2%	17.2%	4.8%	1.8%
PHQ-9 9) Thoughts that you would be better off dead, or of hurting yourself in some way	88.3%	8.1%	2.5%	1.2%

[a] Includes missing responses, which were considered to indicate no such problem experienced. The proportion missing out of total N=1340 was: 1.5%, 1.3%, 1.3%, 1.3%, 1.3%, 1.0%, 1.2%, 1.0%, and 1.2% for the nine items on PHQ-9 respectively.

Table 4 presents the prevalence of depressive symptom measures on PHQ-9. The prevalence of clinically significant depressive symptoms (PHQ-9≥10) was 12.4% (166/1340). Of these 166 men, 54.8% had moderate depressive symptom severity, 30.1% of men had moderately severe symptoms, and 15.1% had severe symptoms of depression. When considering the full distribution of the PHQ-9 score among all 1340 men, 66.7% had no/minimal symptoms of depression and 20.9% had mild symptoms, and were not considered to indicate clinically significant depressive symptoms. Furthermore, 6.8% had moderate symptoms, 3.7% had moderately severe symptoms, and 1.9% had severe symptoms of depression, and were considered to indicate clinically significant depressive symptoms.

In total, 6.3% of men met the diagnostic algorithm for major depression (n=85), and 10.2% of men met the diagnostic algorithm for major and other depressive syndromes (n=136). As expected, all 85 men who were classified as having a major depressive disorder screened positive for clinically significant depressive symptoms. An additional 81 men screened positive for the measure of clinically significant depressive symptoms. Of these 81 men, the vast majority (85.2%) was classified as having moderate depressive symptoms, 13.6% as having moderately severe symptoms, and one man as having severe symptoms. Of 136 men who were

classified as having a major or other depressive syndrome, 105 (77.2%) screened positive for clinically significant depressive symptoms and 31 (22.8%) did not.

The prevalence of suicidal ideation on PHQ-9 was 11.7% (n=157). Of men who scored positive for depressive symptoms (≥10) more than half, 57.2% (n=95/166) screened positive for suicidal ideation.

Table 4: Prevalence of depressive symptom measures[a] on PHQ-9 in AURAH

	MSM reporting anal or vaginal sex in the past three months [N=1340]
	n (%) 95% CI
Clinically significant depressive symptoms (score of ≥10)	166 (12.4%) 10.7%, 14.3%
Depression severity: None/minimal Mild Moderate Moderately severe Severe	 894 (66.7% 95% CI: 64.1%, 69.2%) 280 (20.9% 95% CI: 18.8%, 23.2%) 91 (6.8% 95% CI: 5.6%, 8.3%) 50 (3.7% 95% CI: 2.8%, 4.9%) 25 (1.9% 95% CI: 1.3%, 2.7%)
Major depressive syndrome	85 (6.3%) 5.2%, 7.8%
Major and other depressive syndromes	136 (10.2%) 8.6%, 11.9%
Suicidal ideation	157 (11.7%) 10.1%, 13.6%

[a] For a definition of each measure see section 3.3.2.1 in Chapter 3.

4.3.2 Receiving medical treatment or therapy for depression

Overall, the proportion of men who reported receiving treatment for depression (medical or other) was 9.2% (123/1340). Of the 166 men with depressive symptoms (PHQ-9≥10), treatment for depression was reported by 28.9% (n=48). Of the 1174 men without depressive symptoms (PHQ-9<10), 6.4% (n=75) reported treatment for depression. Among the 241 men with any evidence of current depression (PHQ-9≥10 and/or receiving treatment for depression), 51.0% (n=123) reported receiving treatment for depression.

4.3.3 Anxiety, depression, and other mental health disorders

4.3.3.1 Generalized anxiety disorder on GAD-7

The prevalence of generalized anxiety disorder on GAD-7 (score of ≥10) was 10.2% (n=137). Of men who scored positive for depressive symptoms (PHQ-9≥10), 60.8% (n=101/166) also scored positive for GAD on GAD-7 (≥10). Similarly, men who scored positive for GAD were

much more likely than men who did not to score positive for depressive symptoms on PHQ-9 (73.7% vs. 5.4%; χ^2 p-value<0.001).

4.3.3.2 Anxiety and depression on EuroQoL 5D

The prevalence of moderate/extreme anxiety or depression on EuroQoL 5D, which asks about one's state of health today, was 34.8% (n=466), much higher than the proportion positive for depressive symptoms on PHQ-9. Of these 466 men, 30.9% (n=144) screened positive for depressive symptoms on PHQ-9 (≥10). Of the 166 men who screened positive for depressive symptoms, the vast majority (86.8%) reported being anxious or depressed on EuroQoL 5D.

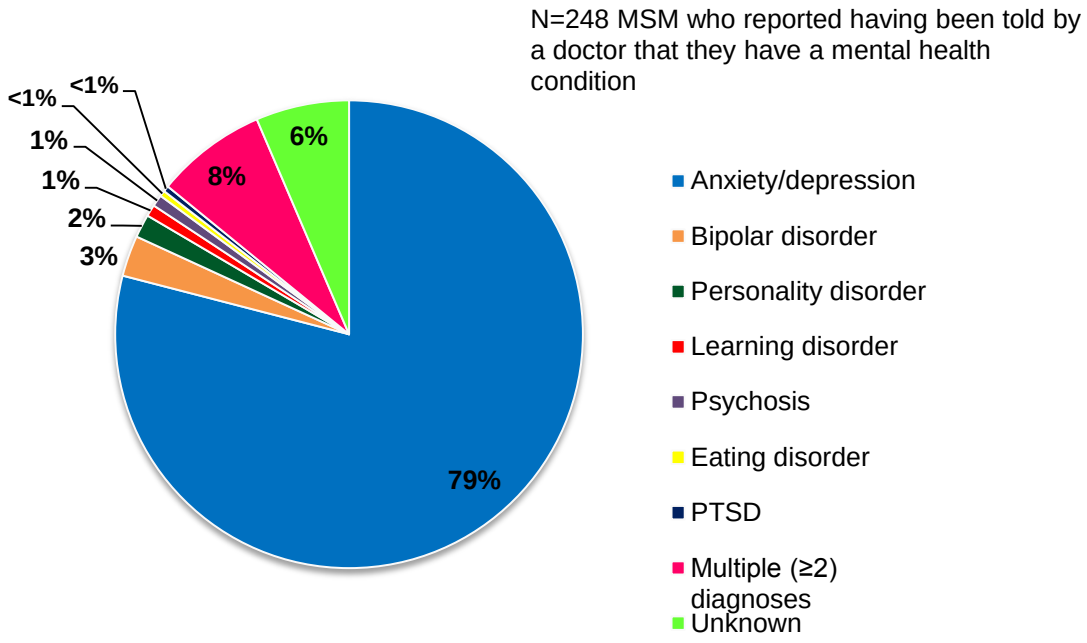
4.3.3.3 Anxiety/depression diagnosis and other mental health disorders

When participants were asked whether a doctor had ever told them that they have a mental health condition, 18.5% (n=248/1340) of men responded that a doctor had. The prevalence of conditions specified is presented in Figure 9. The prevalence of anxiety and depression is presented together given that a number of men specified both conditions. Of the 248 men who reported having ever been told by a doctor that they have a mental health condition, 196 men (79.0%) specified anxiety and/or depression. A smaller proportion of men specified the following conditions: bipolar disorder (n=7; 2.8%), personality disorder[xxvi] (n=4; 1.6%), psychosis[xxvii] (n=2; 0.8%), and learning disorder[xxviii] (n=2; 0.8%) [667-669]. One man specified an eating disorder and one man specified PTSD. Although bipolar disorder and PTSD may fall under the categories of depression and anxiety respectively, given that these conditions were specifically cited, they are presented separately here. Nineteen men (7.7%) specified multiple conditions.

Of note, of the 166 men who screened positive for depressive symptoms (PHQ-9≥10), 75 men (45.2%) reported ever having been told by a doctor that they have a mental health condition. Of these 75 men, 59 (78.7%) specified depression and/or anxiety, ten (13.3%) specified multiple diagnoses, one man had a missing response, and the five remaining men specified bipolar, personality disorder, psychosis, learning disorder, or PTSD.

[xxvi] All men specified borderline personality disorder.
[xxvii] This includes one man who specified schizophrenia.
[xxviii] This includes men who specified ADHD and Asperger syndrome.

Figure 9: Prevalence of mental health conditions among those ever diagnosed by a doctor in AURAH

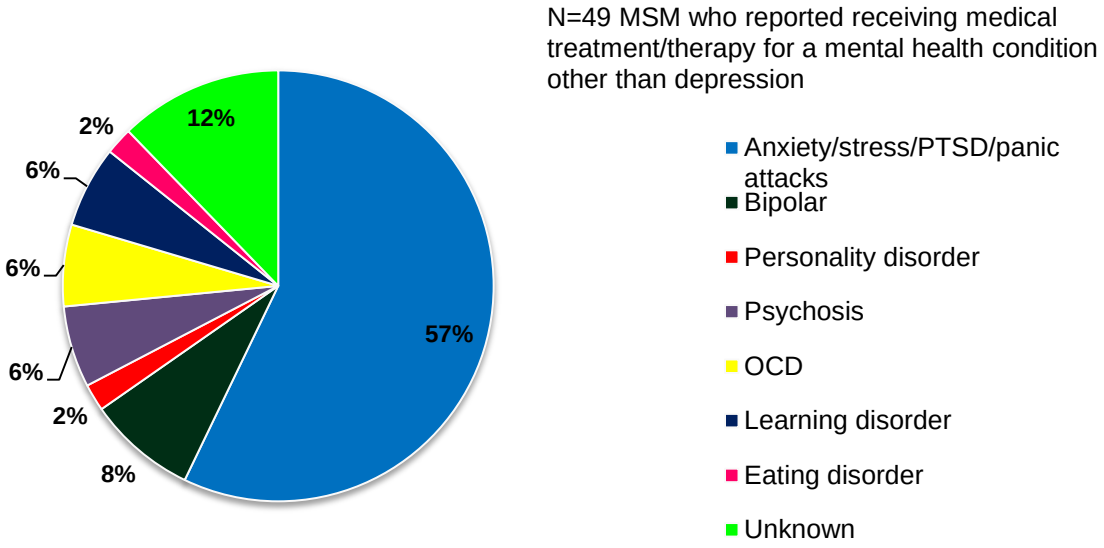


4.3.3.4 Treatment of anxiety and other mental health disorders

Overall, 3.7% (n=49) of men reported receiving medical treatment or therapy for a mental health condition other than depression at the time of the questionnaire. In Figure 10, the mental health conditions for which participants reported receiving treatment are presented. Of the 49 men who reported receiving treatment for a mental health condition other than depression, 28 men (57.1%) specified anxiety; 24 men specified anxiety/GAD, two men specified PTSD, one man specified panic attacks, and one man specified stress. Furthermore, 6 men (12.2%) had a missing response, 4 men (8.2%) specified bipolar, and three men (6.1%) specified OCD, psychosis (schizophrenia), and a learning disorder (ADHD). One man specified a borderline personality disorder and one man specified an eating disorder.

Of note, of the 166 men who screened positive for depressive symptoms (PHQ-9≥10), 20 men (12.0%) reported receiving treatment for a mental health condition other than depression. Of these 20 men, treatment was reported by ten men (50.0%) specifying anxiety/stress/PTSD/ panic attacks, three men (15.0%) specifying OCD, two men (10.0%) specifying a learning disorder, bipolar, and a missing response, and one man specifying psychosis.

Figure 10: Prevalence of currently receiving treatment/therapy for a mental health condition other than depression in AURAH



4.3.4 Prevalence of other psychosocial factors

The prevalence of socio-demographic factors is described in Chapter 3 section 3.2.2.3, and is presented below in Table 5, together with the prevalence of lifestyle/psychosocial factors. Of the 1340 men, the prevalence of reporting using 0, 1, 2-4, and 5 or more recreational drugs in the past three months was 43.2%, 20.1%, 22.5%, and 14.2% respectively; 56.8% reported recent recreational drug use. The prevalence of chemsex-associated drug use was 23.4%. Higher-risk alcohol consumption was reported by 19.3% of men. Overall, 48.7% of men reported having disclosed their sexual orientation to all or almost all of their close family, friends, and work colleagues, whereas, 4.2% reported having disclosed to few or none of these individuals. Thirty percent of men reported very high levels of a supportive network.

4.3.5 Socio-demographic and lifestyle factors associated with depressive symptoms (PHQ-9≥10)

Table 5 shows the association of socio-demographic and lifestyle factors with depressive symptoms (PHQ-9 ≥10) among the 1340 men. There were very strong associations between depressive symptoms and indicators of lower socio-economic status (financial hardship, non-employment, non-home-ownership, and non-university education), with prevalence of depressive symptoms increasing from 7% to 50% with increasing level of financial hardship. Depression was also very strongly associated with lower levels of a supportive network: prevalence increased from 4% to 49% from high to low categories of social support. Depressive symptoms were also associated with younger age, identifying as bisexual, Midlands/ Yorkshire/Humber region of recruitment, lower levels of disclosure of sexual orientation to work

colleagues, smoking, higher-risk drinking, and greater number of recreational drugs used. A significant trend was observed between lower levels of disclosure of sexual orientation to friends and higher prevalence of depressive symptoms, and the overall association was of borderline significance. The following factors were not associated with depressive symptoms: having been born in the UK and ethnicity, disclosure of sexual orientation to close family, being 'out' to all/almost all or few/no friends, work colleagues, and close family, and ongoing relationship status. After adjusting for key socio-demographic factors (see footnote under Table 5), the factors listed above remained significantly associated with depression, with some attenuation in the magnitude of effect, with the exception of study region, disclosure of sexual orientation to friends, and smoking, which were no longer significant. The strongest associations remained with socio-economic factors and supportive network, for instance the adjusted relative difference in prevalence across categories of financial hardship and levels of a supportive network was five-fold and ten-fold respectively.

When investigating the relationship of socio-demographic and lifestyle factors with depressive symptoms (PHQ-9≥10) among all 1484 MSM in AURAH (prevalence: 12.5%, n=185/1484), an identical pattern of associations was observed (Appendix section 11.10, Table 65), the only exception being that smoking remained associated with depressive symptoms after adjustment for key socio-demographic factors. Of note, the prevalence of depressive symptoms (PHQ-9≥10) among the 144 MSM in AURAH who did not report recent anal or vaginal sex was 13.2%. This is addressed in Chapter 8 in the context of further exploring the depression profile of men reporting different sexual behaviours.

In the sensitivity analyses, results were broadly similar when investigating associations with the other measures of depressive symptoms on PHQ-9 (major depressive syndrome and major and other depressive syndromes), see Appendix section 11.11 Table 66. There were some differences in terms of which adjusted associations were statistically significant, but the pattern of associations was very similar.

Table 5: Unadjusted and adjusted associations of socio-demographic and lifestyle factors[f] with depressive symptoms on PHQ-9 (score≥10) among 1340 MSM who reported anal or vaginal sex in the past three months in AURAH

N=1340 MSM reporting sex in the past 3 months			PHQ-9 ≥10 (n=166; 12.4%)					
		N (%)	%	*p-value*[b]	Unadjusted PR[95% CI]	Overall *p-value*	Adjusted PR[95% CI]	Overall *p-value*
Age (years)	<25 25-29 30-34 35-39 40-44 45+	235 (17.8%) 344 (26.0%) 255 (19.3%) 175 (13.2%) 125 (9.5%) 188 (14.2%)	19.6% 14.2% 7.8% 9.1% 8.8% 9.6%	*0.001* *<0.001*[c]	2.04 [1.23, 3.41] 1.49 [0.89, 2.48] 0.82 [0.45, 1.51] 0.95 [0.50, 1.81] 0.92 [0.45, 1.88] 1	*0.001* *0.001*[c]	1.79 [1.06, 3.01] 1.57 [0.93, 2.63] 0.91 [0.50, 1.67] 1.02 [0.54, 1.95] 1.02 [0.50, 2.07] 1	*0.032* *0.006*[c]
Born in the UK and ethnicity	Yes, white Yes, BAME No, white No, BAME	676 (51.2%) 86 (6.5%) 408 (30.9%) 151 (11.4%)	12.4% 17.4% 10.5% 11.9%	*0.346*	1 1.40 [0.85, 2.32] 0.85 [0.60, 1.20] 0.96 [0.59, 1.55]	*0.336*	1 1.03 [0.60, 1.74] 0.98 [0.69, 1.39] 1.08 [0.65, 1.77]	*0.989*
Study region	London South Other	1017 (75.9%) 241 (18.0%) 82 (6.1%)	11.4% 13.7% 20.7%	*0.038*	1 1.20 [0.84, 1.72] 1.82 [1.15, 2.87]	*0.032*	1 1.16 [0.80, 1.67] 1.37 [0.84, 2.25]	*0.401*
University Education	Yes No/missing[a]	891 (66.5%) 449 (33.5%)	9.3% 18.5%	*<0.001*	1 1.98 [1.50, 2.63]	*<0.001*	1 1.86 [1.37, 2.51]	*<0.001*
Employment status	Employed Not employed/ missing[a]	1069 (79.8%) 271 (20.2%)	10.1% 21.4%	*<0.001*	1 2.12 [1.59, 2.83]	*<0.001*	1 1.49 [1.06, 2.09]	*0.020*
Money to cover basic needs (financial hardship)	Always Mostly At times/no	958 (71.7%) 281 (21.0%) 97 (7.3%)	7.2% 16.7% 49.5%	*<0.001* *<0.001*[c]	1 2.32 [1.64, 3.28] 6.87 [5.07, 9.31]	*<0.001* *<0.001*[c]	1 1.95 [1.36, 2.80] 5.16 [3.64, 7.30]	*<0.001* *<0.001*[c]
Housing status	Home owner Renting Unstable/other	369 (27.9%) 764 (57.8%) 188 (14.2%)	3.8% 13.9% 21.3%	*<0.001* *<0.001*[c]	1 3.66 [2.12, 6.30] 5.61 [3.13, 10.04]	*<0.001* *<0.001*[c]	1 3.66 [2.07, 6.48] 4.48 [2.40, 8.36]	*<0.001* *<0.001*[c]
Self-reported sexual identity[e]	Gay Bisexual Straight	1190 (89.1%) 127 (9.5%) 19 (1.4%)	11.4% 22.1% 5.3%	*0.004*[d]	1 1.74 [1.21, 2.50][e]	*0.003*	1 1.61 [1.11, 2.31][e]	*0.011*

Table 5: Unadjusted and adjusted associations of socio-demographic and lifestyle factors[f] with depressive symptoms on PHQ-9 (score≥10) among 1340 MSM who reported anal or vaginal sex in the past three months in AURAH (continued)

N=1340 MSM reporting sex in the past 3 months			PHQ-9 ≥10 (n=166; 12.4%)					
		N (%)	%	*p-value*[b]	Unadjusted PR[95% CI]	Overall *p-value*	Adjusted PR[95% CI]	Overall *p-value*
How many friends know you are gay/bisexual/attracted to men	All/almost all Some Few/none	1006 (76.1%) 250 (18.9%) 66 (5.0%)	11.1% 15.6% 18.2%	*0.052* *0.016*[c]	1 1.40 [1.00, 1.96] 1.63 [0.95, 2.81]	*0.050* *0.013*[c]	1 1.28 [0.88, 1.88] 1.16 [0.62, 2.17]	*0.440* *0.317*[c]
How many work colleagues know you are gay/bisexual/attracted to men	All/almost all Some Few/none	794 (60.8%) 277 (21.2%) 236 (18.1%)	11.7% 7.6% 18.6%	*0.001* *0.044*[c]	1 0.65 [0.41, 1.02] 1.59 [1.15, 2.21]	*0.001* *0.055*[c]	1 0.68 [0.43, 1.09] 1.47 [0.99, 2.17]	*0.012* *0.192*[c]
How many close family know you are gay/bisexual/attracted to men	All/almost all Some Few/none	869 (66.0%) 205 (15.6%) 242 (18.4%)	12.1% 12.2% 13.6%	*0.807* *0.547*[c]	1 1.01 [0.67, 1.52] 1.13 [0.78, 1.62]	*0.805* *0.547*[c]	1 0.97 [0.64, 1.47] 0.87 [0.57, 1.33]	*0.810* *0.535*[c]
'Out' to all/almost all friends, work colleagues and close family	Yes No	652 (48.7%) 688 (51.3%)	11.5% 13.2%	*0.338*	1 1.15 [0.86, 1.53]	*0.339*	1 1.15 [0.84, 1.58]	*0.387*
'Out' to few/no friends, work colleagues and close family	Yes No	56 (4.2%) 1284 (95.8%)	19.6% 12.1%	*0.092*	1.63 [0.94, 2.82] 1	*0.083*	1.10 [0.60, 2.03] 1	*0.765*
Ongoing relationship	Yes No/missing[a]	579 (43.2%) 761 (56.8%)	10.5% 13.8%	*0.073*	1 1.31 [0.97, 1.76]	*0.075*	1 1.27 [0.94, 1.72]	*0.118*
Supportive network	1: High levels 2 3 4 5: Low levels	400 (30.1%) 464 (34.9%) 284 (21.3%) 130 (9.8%) 53 (4.0%)	4.3% 6.7% 17.3% 33.1% 49.1%	*<0.001* *<0.001*[c]	1 1.57 [0.88, 2.80] 4.06 [2.39, 6.90] 7.78 [4.60, 13.17] 11.54 [6.72, 19.81]	*<0.001* *<0.001*[c]	1 1.40 [0.78, 2.51] 3.84 [2.24, 6.59] 6.83 [3.96, 11.77] 10.19 [5.82, 17.83]	*<0.001* *<0.001*[c]
Current smoker	Yes No/missing[a]	334 (24.9%) 1006 (75.1%)	17.7% 10.6%	*0.001*	1.66 [1.24, 2.23] 1	*0.001*	1.33 [0.98, 1.81] 1	*0.071*
Higher-risk alcohol consumption	Yes No/missing[a]	259 (19.3%) 1081 (80.7%)	17.8% 11.1%	*0.003*	1.60 [1.17, 2.19] 1	*0.003*	1.53 [1.11, 2.12] 1	*0.009*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	579 (43.2%) 269 (20.1%) 302 (22.5%) 190 (14.2%)	8.8% 13.8% 12.9% 20.5%	*<0.001* *<0.001*[c]	1 1.56 [1.05, 2.32] 1.47 [0.99, 2.17] 2.33 [1.59, 3.42]	*<0.001* *<0.001*[c]	1 1.52 [1.02, 2.28] 1.53 [1.02, 2.29] 2.41 [1.63, 3.57]	*<0.001* *<0.001*[c]
Chemsex-associated drug use	No/missing Yes	1027 (76.6%) 313 (23.4%)	11.2% 16.3%	*0.017*	1 1.46 [1.07, 1.97]	*0.016*	1 1.60 [1.17, 2.19]	*0.003*

Adjusted models: Each factor included in a separate model and adjusted for: age (included as four categories: <25, 25-29, 30-39, 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.

[a] University Education: 0.3% (n=4) missing. Employed: 1.4% (n=19) missing. Ongoing relationship: 0.2% (n=3) missing. Smoke regularly: 0.4% (n=5) missing. Heavy drinking: 1.2% (n=16) missing. Recreational drug use: 0.8% (n=11) missing.

[b] Pearson χ^2 test

[c] Test for trend.

[d] Fisher's exact test.

[e] A Fisher's exact test p-value is presented for univariable comparison of the three groups presented, however, in unadjusted and adjusted Poisson analyses; self-reported sexual identity is categorised into two groups: gay or bisexual/straight.

[f] For a definition of each measure see section 3.3.5 in Chapter 3.

4.4 Discussion

4.4.1 Summary of results

Among MSM reporting recent sex, the prevalence of depressive symptoms (PHQ-9≥10) was 12.4%. Half of men with any evidence of current depression reported receiving medical treatment or therapy for depression. There was a very strong association between symptoms of depression and anxiety: 61% of men who scored positive for depressive symptoms (≥10) also scored positive for GAD (≥10). Younger age, markers of lower socio-economic status, and lower levels of a supportive network were consistently and strongly associated with depressive symptoms (PHQ-9≥10). Reporting depressive symptoms was also associated with identifying as bisexual or straight, low levels of disclosure of sexual orientation to work colleagues, higher-risk drinking, and greater number of recreational drugs used.

4.4.2 Prevalence of depressive symptoms in studies of MSM

In AURAH, the prevalence of clinically significant depressive symptoms on the PHQ-9 i.e. a score of ≥10, was 12.4% (166/1340) among men who reported recent anal or vaginal sex. Five UK studies have investigated depression among MSM. In Natsal-3, the prevalence of depressive symptoms on the interviewer-administered PHQ-2 (PHQ-2 score of ≥3), a 'first step' screen for depression rather than a diagnostic tool, was 8.9% (95% CI: 5.5%, 14.3%, n/N= 17/190) among all MSM and 6.4% (95% CI: 3.5%, 11.7%, n/N= 7/107) among gay-identified MSM [(342)]. Using the same definition (PHQ-2≥3), the prevalence of depression among MSM who reported recent sex in AURAH was 9.3% (95% CI: 7.8%, 10.9%, n/N=124/1340); among all MSM in AURAH the comparable prevalence was 9.5% (95% CI: 8.1%, 11.1%, n/N=141/1484). Therefore, the prevalence of depressive symptoms found among the large sample of MSM attending GUM clinics in AURAH appears comparable to that found in the smaller general population sample of MSM from Natsal-3.

In a study of 179 users of a popular geosocial-networking smartphone app for gay, bisexual, and other MSM in London (2016), the prevalence of depressive symptoms using the same definition (PHQ-2≥3) was twice as high at 22.3% (n=40) [(416)]. The very high prevalence noted in this study may be explained by inclusion of participants living with HIV, among whom the prevalence of depression is known to be higher [(670)]. In total, 11.4% of participants self-reported an HIV-positive status. A high proportion of younger participants may also explain the high prevalence of depressive symptoms observed since the prevalence of depression is known to be higher among younger individuals (see section 4.4.5 below). Seventy percent of participants were aged less than 41 years. Furthermore, given the nature of a volunteer sample, it is possible that men who elected to partake in this survey were more likely to report symptoms of depression. This may be particularly true as the study was advertised as a health and wellbeing

survey. It was reported that 1410 app users clicked the advertisement and were taken to the survey page, and 202 users completed the survey (14.3%) [671]. On the other hand, it may be that men who use dating apps have a higher burden of depressive symptoms. It may be that these men are more likely to use recreational drugs or alternatively, are less likely to be affiliated to the gay community and have lowers levels of a supportive network.

A similarly high prevalence of depressive symptoms was reported in the Stonewall Gay & Bisexual Men's Health Survey (2011), which was conducted among 5416 gay, bisexual and other MSM living in England, Wales, and Scotland. This study collected information on depressive symptoms using the PHQ-9 as part of an online survey, using a snowball sampling method for study recruitment. The prevalence of depressive symptoms (PHQ-9≥10) was 21.3% (1155/5416). As suggested above, the very high prevalence noted may be as a result of inclusion of participants living with HIV and/or who are younger in age. Information was not collected on HIV status in this study, however, it was reported that 78% of participants were less than 45 years of age. Furthermore, there may be problems associated with snowball sampling, as it does not always capture a sample that is representative of the target population - gay and bisexual communities in the UK.

In the 4 gym project in 2000 (N=739) [564], 40% (309/772) of men said that they strongly agreed or agreed with the statement: 'generally in the past 6 months I have felt depressed'. Similarly, in the AURAH study, 35% of men reported being moderately or extremely anxious or depressed when asked about one's 'state of health today'. Therefore, the prevalence of self-reported depression may be higher than that found via use of symptom questionnaires. Although in AURAH, participants were attending a GUM clinic at the time of survey completion and may have been awaiting HIV/STI screening and getting symptoms checked. As a result, it is reasonable to assume that one may have been feeling anxious or depressed on that particular day. In addition, although individuals may perceive themselves to be experiencing depression, this may not be of a severity or duration sufficient enough to warrant fulfillment of a clinical definition of depression on a symptom questionnaire. Finally, in 1999 a consecutive sample of 122 MSM attending a GUM clinic in East London was recruited. In total, 13.9% (n=14) of MSM were considered to indicate borderline depressive symptoms on HADS and 6.9% (n=8) definite symptoms [355].

When considering alternative definitions based on PHQ-9, the prevalence of a major depressive syndrome in AURAH was 6.3% among men who reported recent sex. The prevalence of major and other depressive syndromes was 10.2%. Similarly, in the one study identified in review (i) of this thesis (Table 1) to investigate depression using PHQ-9 (NHBS [363]), the prevalence of major and other depressive syndromes was 13.0% among U.S MSM attending community/commercial gay venues in 2014 (N=240).

4.4.3 Comparing the prevalence of depressive symptoms between the AURAH study of MSM and the general UK population

There is limited data on the prevalence of depressive symptoms in the general UK population, using PHQ-9-based definitions. In the summer of 2007, severe flooding in England prompted the Health Protection Agency to investigate the impact of flooding on mental health (2007/2008). Survey participants were selected, using probability-based methods, from flooded and non-flooded populations. In non-flooded populations, the prevalence of depressive symptoms (PHQ-9≥10) was 7.0% and this figure included women, among whom rates of depression are most often higher [672]. Comparing this estimate to the AURAH study suggests that the prevalence of depressive symptoms may be somewhat higher among MSM compared to the general population, but other socio-demographic factors (such as age, socioeconomic status, region, and calendar period) may confound this comparison. In Natsal-3, of all 5533 men who reported ever having had sex, 8.5% screened positive for depression on PHQ-2 (score of ≥3) [673]. The equivalent prevalence (PHQ-2 ≥3) for AURAH was 9.3% among MSM who reported recent sex and 9.5% among all MSM, suggesting that the prevalence of depressive symptoms may be similar or slightly higher among MSM compared to the general population. There are a number of other probability-based and general population-based survey studies that have collected information on depression among individuals in the UK, none however, have incorporated the PHQ-9 [350, 674-678]. In AMPS (2007), less than 2% of male participants were classified as having a depressive episode (including mild, moderate, and severe) on CIS-R and an additional 7% were classified as having a mixed anxiety and depressive disorder [350].

4.4.4 Comparing the prevalence of depressive symptoms between MSM and their heterosexual counterparts, in high-income countries

There does appear to be consistent evidence that depression prevalence is elevated among MSM compared to their heterosexual counterparts in a number of studies in high-income countries, mainly the U.S. Evidence comes from a meta-analysis of studies conducted up to 2005 [332], a recent systematic review of U.S. studies [338], two recent population-based studies in the Netherlands [339] and France [340], and from Natsal-3 [342] and AMPS [341] in the UK. These studies are described in detail in section 1.8.1 of Chapter 1.

4.4.5 Association of socio-demographic and lifestyle factors with depressive symptoms

A number of quantitative studies from high-income countries have investigated factors associated with depressive symptoms among samples of MSM including HIV-negative MSM: in the UK [341, 415, 564] (although one study investigated male and female sexual minorities[341]), Belgium [358], U.S. [41, 346, 347, 354, 356, 364, 365, 368, 370, 371, 606-609, 679-681], Australia [454], and in the iPrEX trial spanning multiple countries [360]. Symptoms of depression on symptom questionnaires (and self-reported feelings of depression [564]) have been found to be strongly associated with markers of lower socio-economic status (unemployment, lower education, and lower income)

[346, 347, 354, 356, 364, 371, 415, 454, 606, 681], lower levels of a supportive network [358, 415, 454], and perceived discrimination on the basis of sexual orientation [341, 346, 347]. Extensive theoretical research has also linked sexual minority stress to poor mental health outcomes [209, 210, 226, 227, 229, 235-238, 240, 241, 245-247, 682]. Of note, economic hardship has also been established as strongly associated with poor mental health in UK general population-based research (the British Household Panel Survey (BHPS) 1992-1998, the Whitehall II study 1988, UK Census 2001, and AMPS 2007) [348-351].

Furthermore, younger age [346, 358, 360, 364, 415, 454, 606-609], recreational drug use [41, 346, 358, 454, 564, 606-609], describing one's sexuality as bisexual [354, 415, 679, 680], and not living with a male partner/not being in an ongoing relationship with a partner [415, 564], have been found to be associated with depressive symptoms in previous studies. The association between ethnicity and depressive symptoms has been inconsistent [347, 356, 415, 564]. The association of other psychosocial factors, including CSA and IPV, with depression is described in section 2.6.3.2 of Chapter 2, and will be discussed in detail in Chapter 7 in the context of findings from the PROUD trial.

In line with previous studies, in the AURAH study, markers of socio-economic hardship were strongly associated with depressive symptoms as well as other measures of depression on PHQ-9, providing further evidence for a critical role of poverty and socio-economic hardship in poor mental health among UK MSM. Reporting lower levels of a supportive network was also strongly associated with depression measures on PHQ-9 in AURAH. Furthermore, the prevalence of depressive symptoms was twice as high in men reporting a bisexual or other identity that is not based on attraction to one sex/gender compared to those reporting a gay sexual identity in AURAH. In Natsal-3, the prevalence of depressive symptoms (PHQ-2) was also higher among all 190 MSM (34 of whom identified as bisexual) than the 107 men who identified as gay (8.9% vs. 6.4% respectively) [342]. In addition to an overall mental health inequality between the sexual minority and sexual majority, as described in detail in section 1.8.1, inequalities may also exist within sexual minorities. The same has been found among sexual minority women [683]. Perhaps this may reflect higher levels of social support available in a more established and potentially cohesive community, such as the gay community. Bisexual men may be even more vulnerable to isolation as a sexual minority.

Finally, similar to findings from previous studies in high-income countries, younger age, greater number of recreational drugs used, and low levels of disclosure of sexual orientation to work colleagues, was associated with depressive symptoms in AURAH. Chemsex-associated drug use in the past three months was also found to be associated with depression measures. There is emerging evidence from qualitative work suggesting that for some individuals, engagement in chemsex is associated with psychological distress including depression [579], reasons for this are explored in detail in section 7.3.8 of Chapter 7. In AURAH, depressive symptoms were also

associated with smoking regularly and higher-risk drinking. Having been born in the UK and ethnicity was not associated with depressive symptoms in AURAH.

4.4.6 Treatment for depression

In AURAH, half of those with evidence of current depression reported receiving medical treatment/therapy for depression. Although this may suggest some under treatment of depression, it is not possible to discern the number of men who had been offered treatment, whether treatment had been interrupted, and whether relapse of symptoms had occurred following treatment. It is also unclear how this estimate of treatment coverage compares to the general UK population, especially given this sample consists of men who are actively engaging in health care.

4.4.7 Prevalence of generalized anxiety disorder and suicidal ideation

In AURAH, the prevalence of GAD on GAD-7 was 10.2% among men who reported recent anal or vaginal sex. This may be higher than the estimated 8% lifetime prevalence of GAD among men and women in the U.S., Australia, and New Zealand [405]. The majority (74%) of men in the AURAH study who scored positive for GAD also scored positive for depressive symptoms on PHQ-9 (score of ≥10). This is in line with previous work, which suggests that mental health comorbidity is very common among individuals with GAD, and depression is the most common comorbidity [405]. Previous studies have also found similar socio-economic associations with GAD as those with depression; younger age, lower levels of education, unemployment, and lower levels of family income [405].

In AURAH, the prevalence of suicidal ideation on PHQ-9 was 11.7% among men who reported recent anal or vaginal sex. The 'suicidal ideation' question on PHQ-9 asks about both suicidal ideation ('Thoughts that you would be better off dead') and self-harm ('or of hurting yourself in some way'). The life-time prevalence of self-harm is estimated to be around 18.0% in adolescence (the time at which it tends to first occur) [406]and the life-time prevalence of suicidal ideation is estimated to be around 9.2% among adults [407]. In the AURAH study, the majority (57%) of men who scored positive for depressive symptoms (≥10) were considered to indicate suicidal ideation and this is in line with findings from previous studies of men and women [408, 409].

4.4.8 Limitations

The general methodological limitations of the AURAH study are discussed in section 3.7.1 of Chapter 3. In this specific analysis, it is important to note that the prevalence of depression and other mental health measures may have been underestimated if individuals with depressive symptoms/other mental health conditions were more likely to be in the 40% of clinic attendees approached who did not complete the AURAH questionnaire. Furthermore, it was not possible

to investigate the relationship of internalised homophobia or expectations of rejection, CSA and IPV, with depression measures in the AURAH study. Finally, men were asked about the use of three recreational drugs commonly used in the context of chemsex, however, men were not asked in AURAH whether these drugs had been taken before or during sex.

4.4.9 Summary of discussion

The prevalence of depressive symptoms among MSM in the setting of UK GUM clinics appears to be similar to that found among MSM selected from the British general population, based on the small Natsal sample. Consistent evidence suggests that the prevalence of depressive symptoms is higher among sexual minority individuals compared to their heterosexual counterparts. The majority of these studies were conducted in the U.S. Based on consistent findings in the literature and the strong associations found in AURAH, socio-economic status and supportive networks appear to be crucial factors linked to depression. Findings from the AURAH study also appear to support extensive theoretical, as well as epidemiological, research into the link between stress related to sexual minority status and depression. Findings from the AURAH study also support evidence that depressive symptoms among MSM are more common among younger men, men who use a higher number of recreational drugs, and report higher-risk alcohol consumption. In line with emerging evidence, the prevalence of depressive symptoms among men who reported a bisexual or other plurisexual identity label in the AURAH study was twice as high compared to men who identified as gay. Finally, there does appear to be some evidence of potential under treatment of possible clinically significant depressive conditions. The implications of these findings are discussed in Chapter 9.

Chapter 5

5 Investigating the relationship between depressive symptoms and sexual behaviour among gay, bisexual, and other men who have sex with men in the AURAH study

5.1 Introduction

Symptoms of depression have been found to be associated with increased sexual risk behaviour (and HIV seroconversion [369]) in studies of MSM [353-368], mainly in the U.S. Although HIV prevention has been a priority among MSM in the UK/Europe, mental health has traditionally not been a focus of European studies of risk and prevention, and the role of depression in sexual behaviour linked to STI and HIV transmission is not well understood. To date, two European cross-sectional studies have investigated the relationship between symptoms of depression and sexual behaviour. In a UK GUM clinic sample of 122 MSM in 1999, a higher prevalence of depressive symptoms (HADS score ≥11) was observed among men who reported CLS with an HIV-positive/unknown status partner (Table 1) [355]. In a Belgian volunteer and online sample of 591 HIV-negative MSM who reported anal sex with a casual partner (2008), depressive symptoms (CES-D >21) were associated with CLS in unadjusted analysis (Table 1) [358].

Given the self-regulation and coping literature on depressive symptoms, it is hypothesized in this thesis that among sexual minority men, depressive symptoms would lower self-efficacy for sexual safety and increase the chances of sexual risk behaviour, and that this association would be partially but not fully confounded by recreational drug use, CSA, and IPV. The aim of this chapter was to address this hypothesis and thereby the lack of data on mental health and sexual behaviour among MSM at risk of HIV acquisition in the European context. This chapter uses data from the AURAH study to investigate among gay, bisexual, and other MSM reporting recent sex: (i) the relationship between depressive symptoms and sexual behaviour measures, and the potential confounding/moderating effects of recreational drug use, and (ii) a causal steps approach to the question of whether low self-efficacy for sexual safety mediates the association between depressive symptoms and sexual behaviour measures. Also presented, is the association of GAD on GAD-7, and suicidal ideation on PHQ-9, with sexual behaviour measures.

5.2 Statistical methods

A detailed description of the variables investigated in analyses presented in this Chapter is included in Chapter 3 section 3.3.1.

Analyses are conducted among MSM who reported anal or vaginal sex in the past three months. The prevalence of each of the eight sexual behaviour measures defined in section 3.3.3 of Chapter 3 is presented. The relationship between depressive symptoms (PHQ-9≥10) and sexual behaviour measures was assessed using χ^2 tests, χ^2 tests for trend, and Fisher's exact test (when expected numbers were small) for univariable analysis, and modified Poisson regression with a robust variance estimator in order to produce adjusted PRs [645]. Associations are presented unadjusted, adjusted for key socio-demographic factors, and finally adjusted for the same key socio-demographic factors plus lifestyle factors (see section 3.6.5), in order to assess the extent to which the associations were attenuated when accounting for recreational drug use, alcohol use, and smoking. Of note, the relationship between level of PHQ-9 depressive symptom severity (none/minimal, mild, moderate, moderately severe, or severe) and sexual behaviour measures was also investigated adjusted for key socio-demographic factors. Findings from this analysis are mentioned in the text for the measure of CLS with one or more partners and are summarized for the other sexual behaviour measures. A sensitivity analysis was undertaken using different PHQ-9-based definitions of depressive symptoms (major depressive syndrome and major and other depressive syndromes [including major depression and dysthymia]). The relationship between depressive symptoms (PHQ-9≥10) and sexual behaviour measures was also assessed using logistic regression in order to produce adjusted ORs. This was in order to compare the magnitude of associations across sexual behaviour measures (see section 3.6.2).

Further analyses were performed in order to investigate the potential moderating effects of recreational drug use on the relationship between depressive symptoms (PHQ-9≥10) and sexual behaviour measures. For the purpose of this analysis, three measures of recreational drug use in the past three months were investigated: (i) poly-drug use, (ii) club-drug use, and (iii) chemsex-associated drug use [578-580]. Three separate modified Poisson regression models, including drug use measures (i), (ii), or (iii) and an interaction term between depressive symptoms and the measure of drug use, were investigated, adjusted for key socio-demographic and lifestyle factors. The presence of an interaction would indicate the need to present the PR's separately for men who reported the measure of drug use and men who did not.

A causal steps approach to mediational analysis [639, 640] was investigated in this chapter, see section 3.4.2. Based on this approach, in addition to investigating the relationship between depressive symptoms and sexual behaviour, the following associations were investigated:

1. The association between depressive symptoms and low self-efficacy measures
2. The association between low self-efficacy measures and sexual behaviour measures
3. The association between depressive symptoms and sexual behaviour measures adjusted for low self-efficacy measures

It is of note that three additional analyses were undertaken in order to explore whether the relationship between depressive symptoms (PHQ≥10) and sexual behaviour is different in samples of differing sexual risk behaviour profiles: (i) among men who reported anal sex with a man in the past three months (N=1304), (ii) among men who reported anal or vaginal CLS in the past three months (N=853), and (iii) among men who reported anal CLS in the past three months (N=815). Findings are briefly compared to those observed in the main analysis, among the 1340 men who reported anal/vaginal sex in the past three months.

The association between depressive symptoms and reasons for non-condom-use among men reporting anal or vaginal CLS (N=853) was also investigated. Models are presented unadjusted and adjusted for key socio-demographic factors. A number of further investigations were then conducted among the 1340 men who reported recent sex. The association of a four category variable describing the current presence/absence of depressive symptoms (PHQ-9≥10) and medical treatment/therapy for depression (symptoms plus treatment, symptoms no treatment, no symptoms with treatment, or no symptoms no treatment) with sexual behaviour measures was assessed. Models are presented unadjusted and adjusted for key socio-demographic factors. The relationship of suicidal ideation on PHQ-9 and GAD on GAD-7 with sexual behaviour measures was also investigated. Models are presented unadjusted, adjusted for key socio-demographic factors, and adjusted for the same key socio-demographic factors plus lifestyle factors. Finally, the unadjusted association of socio-demographic and lifestyle factors with sexual behaviours was assessed.

5.3 Results

5.3.1 Prevalence of sexual behaviour measures

The prevalence of CLS and other sexual behaviour measures is presented in Table 6. Overall, 63.7% (n=853) of men reported CLS in the past three months. Of these men, 91.7% (n=782) had CLS with men only, 3.9% (n=33) had CLS with both men and women, and 4.5% (n=38) had CLS with women only. Of note, of the 782 men who reported CLS with men only in the past three months, 27.2% (n=213) reported CLS having occurred with one long-term partner only. Of the 38 men who reported CLS with women only in the past three months, 36.8% (n=14) reported CLS having occurred with one long-term partner only. Overall, 32.1% of men reported CLS with two or more partners and 35.4% had CLS with at least one unknown and/or HIV-positive status partner (excluding men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART'). Fourteen percent of men had receptive CLS with an unknown status partner. Thirty-six percent of men reported eleven or more new sexual partners in the past year and 37.0% reported group sex in the past three months. Thirty-two percent of men reported having been diagnosed with a

bacterial STI in the past year and 15.5% of men reported PEP use in the past year. The proportion of missing values for each sexual behaviour question was ≤5%, see footnote [a] under Table 6.

Table 6: Prevalence of sexual behaviour measures[a] in AURAH

N=1340 MSM who reported anal/vaginal sex (past three months)	n (%; 95% CI)
CLS with one or more partners	853 (63.7%; 61.0%, 66.2%)
CLS with two or more partners (past 3 months)	430 (32.1%; 29.6%, 34.6%)
CLS with unknown/HIV-positive status partner(s)[b] (past 3 months)	474 (35.4%; 32.9%, 38.0%)
Receptive CLS with an unknown status partner (past 3 months)	187 (14.0%; 12.2%, 15.9%)
Self-reported bacterial STI diagnosis (past year)	423 (31.6%; 29.1%, 34.1%)
PEP use (past year)	207 (15.5%; 13.6%, 17.5%)
Eleven or more new sexual partners (past year)	483 (36.0%; 33.5%, 38.7%)
Group sex (past 3 months)	496 (37.0%; 34.5%, 39.6%)

[a] For the questions that were asked separately for male and female sexual partners, the proportion of missing values incorporated into the 'no' sexual behaviour category comprised of men who did not answer either the male or female partner questions, or who answered one but did not provide a positive response i.e. reported no CLS or no HIV-positive partner. CLS: 0.3% (n=4) missing. Number of CLS partners: 0.4% (n=6). Knowledge of the HIV status of your partner(s) (No, all, or some): 1.6% (n=22). CLS with an HIV-positive partner: 3.0% (n=40). Position during anal sex (insertive, receptive, or both): 0.9% (n=12). The following questions were not asked separately for male and female sexual partners: bacterial STI diagnosis: 1.3% (n=17) missing, PEP use: 1.0% (n=14), 11+ new sexual partners: 1.0% (n=14), and group sex: 0.6% (n=8).
[b] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

5.3.2 Relationship between depressive symptoms and sexual behaviour measures

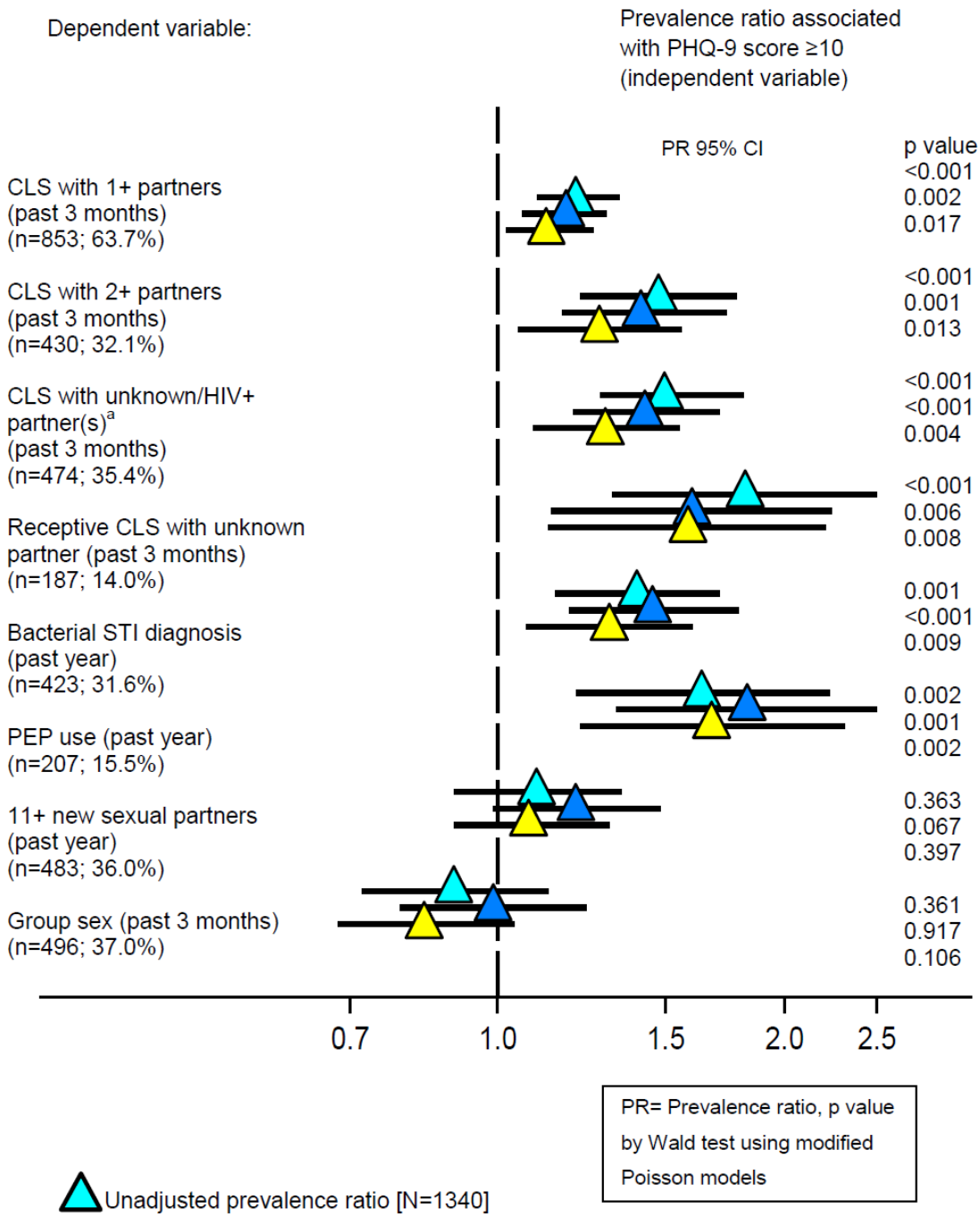
The prevalence of depressive symptoms on PHQ-9 (≥10) was 12.4% (166/1340), see section 4.3.1 of Chapter 4. Depressive symptoms were associated with all measures of CLS. Men with depressive symptoms were more likely than those without symptoms to report CLS with one or more partners (74.7% vs. 62.1%), CLS with two or more partners (44.6% vs. 30.3%), CLS with unknown/HIV-positive status partners (50.6% vs. 33.2%), receptive CLS with an unknown status partner (22.9% vs. 12.7%), bacterial STI diagnosis (42.2% vs. 30.1%), and PEP use (23.5% vs. 14.3%); $p<0.01$ for all, χ^2 tests. Among men with depressive symptoms, the prevalence of CLS with one or more partners was 70.3% among men with moderate depressive symptom severity, 78.0% among men with moderately severe symptoms, and 84.0% among men with severe symptoms of depression. Depressive symptoms were not associated with the remaining two sexual behaviour measures: the prevalence of depressive symptoms was similar among men with and without eleven or more new partners in the past year (39.2% vs. 35.6%; $p=0.372$) and among men reporting and not reporting group sex in the past three months (37.5% vs. 33.7%; $p=0.350$).

Figure 11 shows unadjusted and adjusted PRs. After adjusting for key socio-demographic factors, depressive symptoms were associated with all measures of CLS partners (≥1 [PR 1.18 95% CI: 1.06, 1.30; *p=0.002*], ≥2 [PR 1.42 95% CI: 1.17, 1.74; *p=0.001*], unknown/HIV-positive status [PR 1.43 95% CI: 1.20, 1.71; *p<0.001*], receptive unknown status [PR 1.60 95% CI: 1.14, 2.24; *p=0.006*]), and with bacterial STI diagnosis [PR 1.46 95% CI: 1.19, 1.79; *p<0.001*] and PEP use [PR 1.83 95% CI: 1.33, 2.50; *p<0.001*]. Adjustment for key socio-demographic factors resulted in some attenuation of the associations with CLS measures. This attenuation appears to be predominantly driven by the inclusion of university education in the model for each measure of CLS. Adjustment for key socio-demographic factors resulted in slightly accentuated associations with STI and PEP use, which appeared to be predominantly driven by inclusion of age in each model. After adjusting additionally for smoking, alcohol, and recreational drug use, all of these associations were attenuated to some extent, but they remained significant (CLS ≥1 [PR 1.13 95% CI: 1.02, 1.26; *p=0.017*], CLS ≥2 [PR 1.28 95% CI: 1.05, 1.56; *p=0.013*], CLS unknown/HIV-positive status [PR 1.30 95% CI: 1.09, 1.55; *p=0.004*], receptive CLS unknown status [PR 1.58 95% CI: 1.13, 2.21; *p=0.008*], bacterial STI diagnosis [PR 1.31 95% CI: 1.07, 1.60; *p=0.009*], and PEP use [PR 1.68 95% CI: 1.22, 2.31; *p=0.001*]). Attenuation appears to be predominantly driven by the inclusion of number of recreational drugs used in each model. Depressive symptoms were not associated with having eleven or more new sexual partners in the past year or with group sex in the past three months, in unadjusted or adjusted analyses.

Figure 11 is repeated with ORs from logistic regression models and presented in Appendix section 11.12 (Figure 33). When using ORs as the measure of association, the magnitude of associations was very similar across the different measures of CLS (including STI diagnosis and PEP use).

Of note, a significant trend was observed when investigating the relationship between level of depressive symptom severity and all measures of CLS partners, including bacterial STI diagnosis and PEP use, after adjusting for key socio-demographic factors. The relationship was in the same direction for all measures of CLS, whereby increasing depressive symptom severity was associated with increased CLS, STI, and PEP prevalence. For instance, for the measure of CLS with one or more partners, the following estimates were observed: mild depression PR 1.10 95% CI: 1.00, 1.21; moderate depression PR 1.14 95% CI: 0.98, 1.32; moderately severe depression PR 1.28 95% CI: 1.09, 1.49; severe depression PR 1.35 95% CI: 1.10, 1.65; versus no/minimal depression, trend test p-value<0.001. Estimates were similar for the other measures of CLS, whereby the trend test p-value was ≤0.004 for all measures. Level of depressive symptom severity was not associated with report of eleven or more new sexual partners or group sex.

Figure 11: Unadjusted and adjusted associations of depressive symptoms (PHQ-9≥10) with sexual behaviours among 1340 MSM who reported anal or vaginal sex in the past three months in AURAH



[a] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

Table 67 (Appendix section 11.12) presents findings from three additional analyses. The pattern of associations was identical among the 1304 MSM reporting recent anal sex. When considering measures other than CLS with one or more partners, a similar pattern of associations was found among the 853 MSM reporting recent anal/vaginal CLS. Although associations between depressive symptoms and CLS with two or more partners and CLS with an unknown/HIV-positive status partner were considerably attenuated after adjustment for smoking, drinking, and recreational drug use. Among the 815 MSM reporting recent anal CLS, associations with CLS measures, including bacterial STI diagnosis, were considerably attenuated after adjustment for smoking, drinking, and recreational drug use. These findings are explored further and their implications are discussed in Chapter 8 in the context of findings from the PROUD trial of MSM reporting recent anal CLS.

In the sensitivity analyses, results were broadly similar, although somewhat weaker, when investigating associations with the other measures of depressive symptoms on PHQ-9 (a major depressive syndrome and major and other depressive syndromes), see Appendix section 11.13 Table 68 and Table 69.

5.3.2.1 Moderating effects of recreational drug use

When investigating interactions between depressive symptoms and measures of recreational drug use, the association between depressive symptoms and CLS measures, including PEP use, appeared somewhat stronger among men who reported the measure of drug use compared to men who did not (Table 7). However, most tests of interaction were not significant (Table 7), the exception being for the measure of eleven or more new sexual partners in the past year. There was some evidence that depressive symptoms were associated with this measure among men who reported club-drug use in the past three months, whereas the relationship was non-existent among men who did not. A borderline significant interaction was also observed for the relationship between depressive symptoms and bacterial STI diagnosis, according to club-drug use. The direction of this association was the same in both groups, but the association was somewhat stronger among non-club-drug users.

Table 7: Association between depressive symptoms (PHQ-9≥10) and sexual behaviour measures according to recreational drug use in the past three months, in AURAH

N=1340	PR [95%CI] for association of depressive symptoms (PHQ-9≥10) with sexual behaviour measures								
Dependent variables:	Poly-drug use (n=341) Adjusted[a] PR[95% CI]	No poly-drug use (n=999) Adjusted[a] PR[95% CI]	Interaction term *p-value*	Chemsex-drug use (n=313) Adjusted[a] PR[95% CI]	No chemsex-drug use (n=1027) Adjusted[a] PR[95% CI]	Interaction term *p-value*	Club-drug use (n=459) Adjusted[a] PR[95% CI]	No club-drug use (n=881) Adjusted[a] PR[95% CI]	Interact-ion term *p-value*
CLS with 1+ partners	1.25 [1.11, 1.41]	1.07 [0.93, 1.24]	*0.323*	1.27 [1.11, 1.46]	1.08 [0.94, 1.24]	*0.239*	1.19 [1.06, 1.34]	1.08 [0.92, 1.26]	*0.718*
CLS with 2+ partners	1.43 [1.13, 1.80]	1.18 [0.88, 1.60]	*0.741*	1.46 [1.15, 1.87]	1.19 [0.88, 1.60]	*0.518*	1.44 [1.14, 1.83]	1.14 [0.82, 1.59]	*0.508*
CLS with an unknown/ HIV-positive status partner	1.51 [1.22, 1.87]	1.19 [0.91, 1.54]	*0.558*	1.47 [1.17, 1.84]	1.22 [0.95, 1.57]	*0.695*	1.39 [1.11, 1.74]	1.24 [0.95, 1.63]	*0.862*
Receptive CLS with an unknown status partner	1.58 [0.91, 2.75]	1.51 [1.00, 2.26]	*0.977*	1.75 [1.01, 3.03]	1.46 [0.97, 2.20]	*0.888*	1.47 [0.88, 2.46]	1.63 [1.06, 2.51]	*0.537*
STI diagnosis (past year)	1.26 [0.98, 1.63]	1.43 [1.07, 1.92]	*0.320*	1.16 [0.90, 1.51]	1.49 [1.11, 1.99]	*0.153*	1.22 [0.94, 1.57]	1.60 [1.17, 2.18]	*0.057*
PEP use (past year)	1.79 [1.18, 2.74]	1.54 [0.95, 2.50]	*0.807*	1.64 [1.10, 2.43]	1.61 [0.97, 2.67]	*0.899*	1.82 [1.22, 2.70]	1.53 [0.90, 2.61]	*0.595*
11+ new sexual partners (past year)	1.24 [0.99, 1.55]	0.97 [0.70, 1.34]	*0.156*	1.31 [1.06, 1.63]	0.97 [0.70, 1.36]	*0.076*	1.38 [1.10, 1.73]	0.86 [0.59, 1.25]	*0.023*
Group sex	0.86 [0.67, 1.10]	0.89 [0.62, 1.29]	*0.821*	0.96 [0.77, 1.18]	0.76 [0.51, 1.13]	*0.289*	0.94 [0.74, 1.20]	0.76 [0.49, 1.19]	*0.396*

[a] All models are adjusted for age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, and higher-risk drinking.

5.3.3 Relationship between depressive symptoms and measures of self-efficacy for sexual safety

The prevalence of high self-efficacy for sexual safety was 67.2% (n=900) and 10.6% (n=142) for difficulty negotiating condom-use. The prevalence of each individual response option given for these measures is presented in Table 8. Of note, of the 900 men who indicated high self-efficacy for sexual safety, the vast majority (92.2%) did not report difficulty negotiating condom-use.

Table 8: Prevalence of self-efficacy for sexual safety and difficulty negotiating condom-use in AURAH

N=1340 MSM who reported recent anal/vaginal sex		n (%)
'I feel confident that, if I want to, I can make sure a condom is used during sex with any partner, in any situation'	Strongly agree Tend to agree Undecided/no opinion/not applicable Tend to disagree Strongly disagree	900 (67.9%) 342 (25.8%) 36 (2.7%) 38 (2.9%) 9 (0.7%)
'I find it difficult to discuss condom-use with any new sexual partner'	Strongly disagree Tend to disagree Undecided/no opinion/not applicable Tend to agree Strongly agree	754 (57.0%) 346 (26.2%) 81 (6.1%) 90 (6.8%) 52 (3.9%)
High self-efficacy for sexual safety	Yes No[a]	900 (67.2%) 440 (32.8%)
Difficulty negotiating condom-use	Yes No[b]	142 (10.6%) 1198 (89.4%)

[a] Includes all other responses, including missing responses (1.1%).
[b] Includes all other responses, including missing responses (1.3%).

Table 9 presents the unadjusted and adjusted associations between depressive symptoms and high self-efficacy for sexual safety and difficulty negotiating condom-use. Men with depressive symptoms (PHQ-9≥10) were less likely to report high self-efficacy for sexual safety and more likely to report difficulty negotiating condom-use than men without depressive symptoms. Adjusted for key socio-demographic factors, depressive symptoms were inversely associated with high self-efficacy and were associated with difficulty negotiating condom-use. These associations remained with some attenuation, after additional adjustment for smoking, drinking, and recreational drug use.

The other depression measures on PHQ-9 were also associated with high self-efficacy for sexual safety and again this association remained after adjustment for key socio-demographic factors, and additional adjustment for smoking, drinking, and recreational drug use. The other depression measures were not however, associated with difficulty negotiating condom-use, in unadjusted or adjusted analysis (see Appendix section 11.14 Table 70 and Table 71).

Table 9: Unadjusted and adjusted associations of depressive symptoms (PHQ-9≥10) with high self-efficacy for sexual safety and difficulty negotiating condom-use in AURAH

N=1340 MSM reporting anal/vaginal sex in the past 3 months			High self-efficacy for sexual safety (n=900; 67.2%)				Difficulty negotiating condom-use (n=142; 10.6%)			
		N (%)	% *p-value*[a]	Unadjusted PR[95% CI] Overall *p-value*[b]	Adjusted[c] PR[95% CI] Overall *p-value*[b]	Adjusted[d] PR[95% CI] Overall *p-value*[b]	% *p-value*[a]	Unadjusted PR[95% CI] Overall *p-value*[b]	Adjusted[c] PR[95% CI] Overall *p-value*[b]	Adjusted[d] PR[95% CI] Overall *p-value*[b]
Depressive symptoms (score≥10)	Yes No	166 (12.4%) 1174 (87.6%)	56.6% 68.7% *0.002*	0.82 [0.72, 0.95] 1 *0.006*	0.82 [0.71, 0.94] 1 *0.006*	0.83 [0.73, 0.96] 1 *0.011*	18.7% 9.5% *<0.001*	1.98 [1.37, 2.84] 1 *<0.001*	1.77 [1.18, 2.63] 1 *0.005*	1.76 [1.18, 2.61] 1 *0.005*

[a] Pearson χ^2 test
[b] p-value by Wald test using modified Poisson models.
[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.
[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.

5.3.4 Relationship between measures of self-efficacy for sexual safety and sexual behaviour

Men with high self-efficacy for sexual safety were less likely than those without to report CLS with one or more partners, CLS with two or more partners, CLS with an unknown/HIV-positive status partner, receptive CLS with an unknown status, bacterial STI diagnosis, and PEP use, see Table 10. Similarly, men who reported difficulty negotiating condom-use were more likely than those who did not to report CLS measures (Table 10).

Table 10: Unadjusted associations of high self-efficacy for sexual safety and difficulty negotiating condom-use with sexual behaviour measures in AURAH

N=1340 MSM reporting recent anal/vaginal sex			CLS with 1+ partners	CLS with 2+ partners	CLS with unknown/ HIV-positive partner	Receptive CLS with unknown status partner	Bacterial STI diagnosis (past year)	PEP use (past year)	11+ new sexual partners (past year)	Group sex
		N (%)	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]
High self-efficacy for sexual safety	Yes No	900 (67.2%) 440 (32.8%)	55.7% 80.0% *<0.001*	24.3% 48.0% *<0.001*	26.9% 52.7% *<0.001*	10.3% 21.4% *<0.001*	29.2% 36.4% *0.008*	13.6% 19.3% *0.006*	35.4% 37.3% *0.513*	35.4% 40.2% *0.089*
Difficulty negotiating condom-use	Yes No	142 (10.6%) 1198 (89.4%)	80.3% 61.7% *<0.001*	45.8% 30.5% *<0.001*	55.6% 33.0% *<0.001*	23.2% 12.9% *0.001*	36.6% 31.0% *0.171*	19.7% 14.9% *0.136*	35.2% 36.1% *0.827*	33.1% 37.5% *0.307*

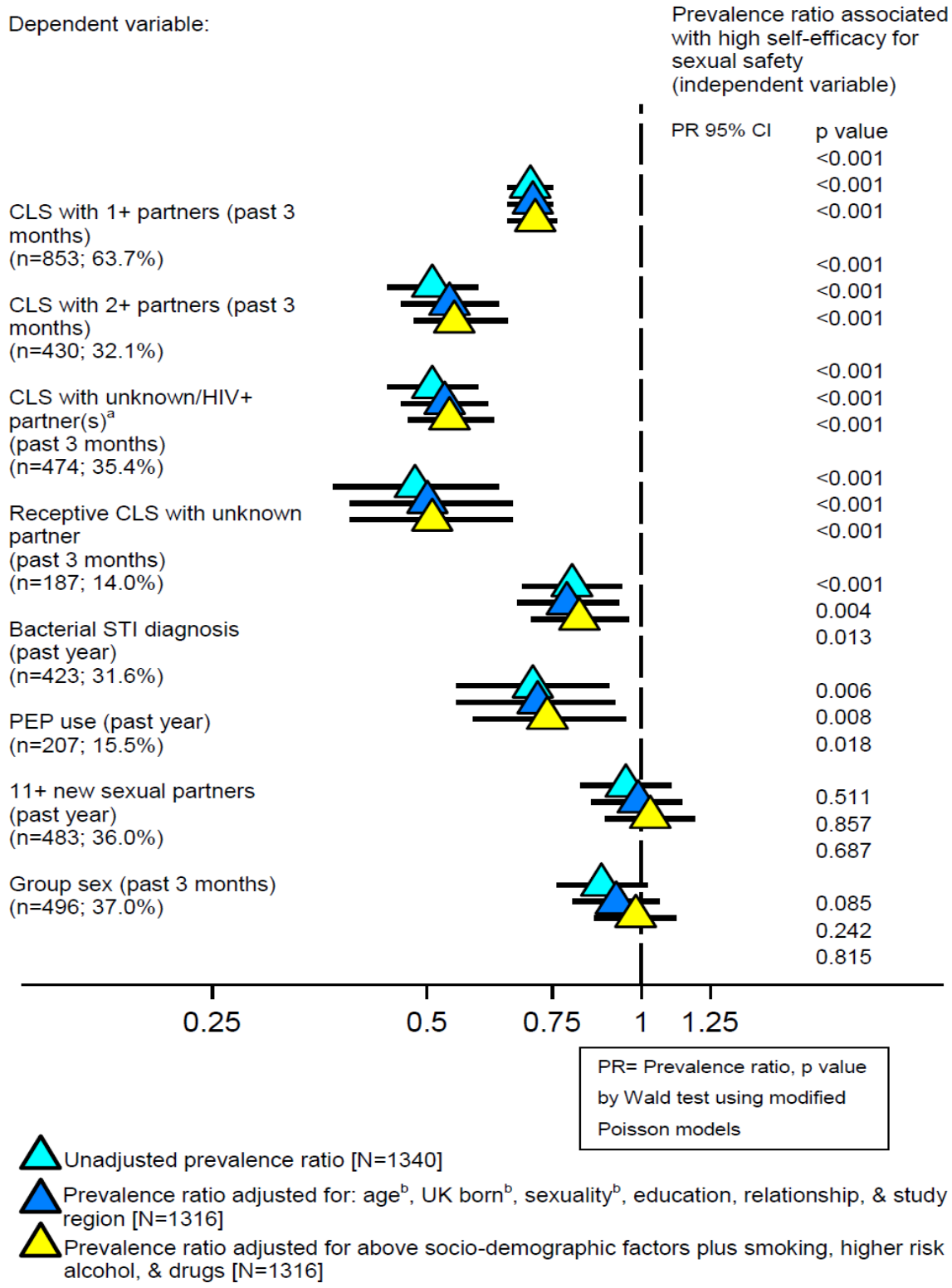
[a] Pearson χ^2 test.

Figure 12 and Figure 13 show unadjusted and adjusted PRs. Adjusted for key socio-demographic factors and additionally adjusted for smoking, drinking, and recreational drug use, high self-efficacy remained associated with lower prevalence of CLS partners, STI diagnosis, and PEP use. High self-efficacy was not associated with report of eleven or more new sexual partners or group sex, in unadjusted or adjusted analysis. Adjusted for key socio-demographic factors and additionally adjusted for smoking, drinking, and recreational drug use, difficulty negotiating condom-use remained associated with lower prevalence of CLS partners. Difficulty negotiating condom-use was not associated with bacterial STI diagnosis, PEP use, report of eleven or more new sexual partners, or group sex, in unadjusted or adjusted analysis.

In terms of the magnitude of the associations, among men reporting high self-efficacy for sexual safety, the prevalence of CLS with two or more partners, CLS with an unknown/HIV-positive status partner, and receptive CLS with an unknown status partner, was half of that observed among men who did not report high self-efficacy. For these measures of CLS, the PR of approximately 0.50 remained the same after adjusting for socio-demographic factors and additionally adjusting for smoking, drinking, and recreational drug use. For the measures of bacterial STI diagnosis and PEP use in the past year, for which the overall prevalence was similar to other CLS measures, the difference in prevalence observed between men who reported high self-efficacy and men who did not, was not as striking. This resulted in weaker PRs of 0.80 for STI diagnosis and 0.70 for PEP use. These estimates remained unchanged after adjustment. The largest difference in prevalence was observed for the measure of CLS with one or more partners, however, given the high prevalence of this measure overall, the resulting PR was 0.70. Again, this estimate remained unchanged after adjustment.

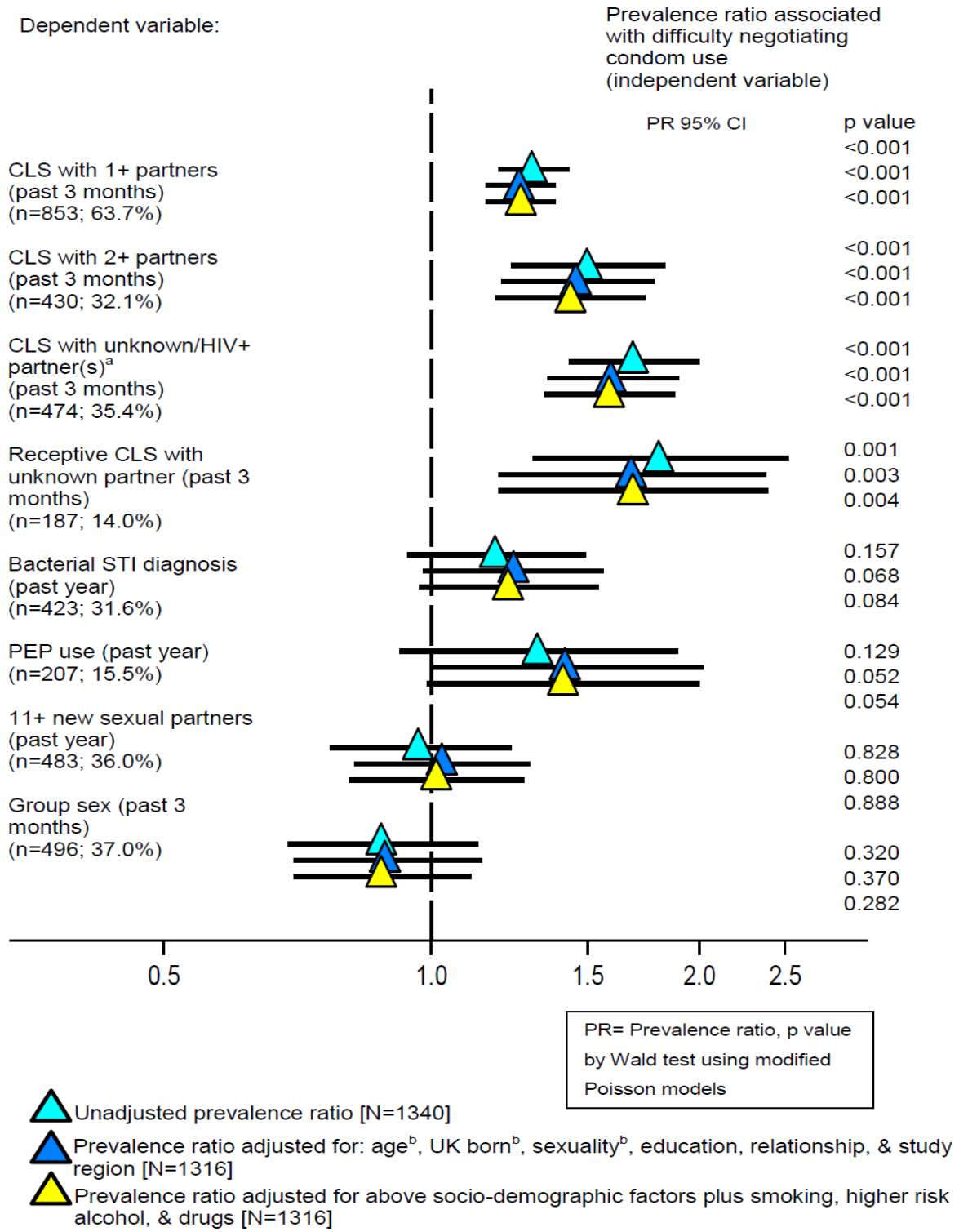
When investigating associations with difficulty negotiating condom-use, for each measure of CLS, the PR was weaker than that observed for high self-efficacy for sexual safety. The exception being, that the prevalence of receptive CLS with an unknown status partner was still twice as high among men who reported difficulty negotiating condom-use. Accordingly, the large PR of 2.0 was only observed for the most infrequently reported measure of CLS overall. For all measures of CLS, PRs remained unchanged after adjustment.

Figure 12: Unadjusted and adjusted associations of high self-efficacy for sexual safety with sexual behaviours among 1340 MSM who reported anal or vaginal sex in the past three months in AURAH



[a] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.
[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

Figure 13: Unadjusted and adjusted associations of finding it difficult to negotiate condom-use with sexual behaviours among 1340 MSM who reported anal or vaginal sex in the past three months in AURAH



[a] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.
[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

5.3.5 Relationship between depressive symptoms and sexual behaviour measures adjusted for measures of low self-efficacy for sexual safety

Adjusting additionally for high self-efficacy attenuated the association between depressive symptoms and all sexual behaviours investigated in Table 11. The relationship with CLS with one or more partners and CLS with two or more partners disappeared, and the relationship with CLS with an unknown/HIV-positive status partner was attenuated to borderline significance. Adjusting additionally for difficulty negotiating condom-use (instead of self-efficacy) also attenuated the associations found between depressive symptoms and sexual behaviour measures, but the degree of attenuation tended to be less than that observed for self-efficacy.

Table 11: Impact of adjusting for high self-efficacy and difficulty negotiating condom-use on the relationship between depressive symptoms and CLS measures, STI diagnosis, and PEP use, in AURAH

	PHQ-9 ≥10 (n=166; 12.4%)		
Dependent variables:	Adjusted for socio-demographics[b] + lifestyle factors[c]	Adjusted for socio-demographics[b] + lifestyle factors[c] + high self-efficacy	Adjusted for socio-demographics[b] + lifestyle factors[c] + difficulty negotiating condom-use
	PR[95% CI] *p-value*[a]	PR[95% CI] *p-value*[a]	PR[95% CI] *p-value*[a]
CLS with 1+ partners (past 3 months)	1.13 [1.02, 1.26] 1 *0.017*	1.08 [0.98, 1.20] 1 *0.137*	1.11 [1.00, 1.23] 1 *0.048*
CLS with 2+ partners (past 3 months)	1.28 [1.05, 1.56] 1 *0.013*	1.18 [0.98, 1.44] 1 *0.087*	1.23 [1.01, 1.50] 1 *0.039*
CLS with an unknown/HIV-positive status partner (past 3 months)	1.30 [1.09, 1.55] 1 *0.004*	1.19 [1.00, 1.42] 1 *0.050*	1.23 [1.03, 1.48] 1 *0.023*
Receptive CLS with an unknown status partner (past 3 months)	1.58 [1.13, 2.21] 1 *0.008*	1.46 [1.04, 2.05] 1 *0.030*	1.51 [1.07, 2.13] 1 *0.019*
STI diagnosis (past year)	1.31 [1.07, 1.60] 1 *0.009*	1.27 [1.04, 1.56] 1 *0.019*	1.28 [1.05, 1.57] 1 *0.016*
PEP use (past year)	1.68 [1.22, 2.31] 1 *0.001*	1.61 [1.78, 2.21] 1 *0.003*	1.62 [1.16, 2.25] 1 *0.004*

[a] p-value by Wald test using modified Poisson models.
[b] Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.
[c] Smoking, higher-risk drinking, and recreational drug use.

5.3.6 Relationship between depressive symptoms and reasons for non-condom-use among men reporting recent CLS

The prevalence of reasons for non-condom-use among the 853 men, who reported anal/vaginal CLS in the past three months, is presented in Table 12. More than one reason could be selected. The most common reasons were: got carried away/under the influence (n=369; 43.3%), don't like/more enjoyable without (n=353; 41.4%), and their/partner's difficulty in keeping an erection/ejaculating (n=205; 24.0%).

Table 12: Prevalence of reasons for non-condom-use among 853 men reporting recent CLS in AURAH

N=853 MSM reporting recent anal/vaginal CLS	
Reasons for non-condom-use[a]:	n (%)
'Didn't think about using a condom or did not have a condom'	131 (15.4%)
'Don't like using condoms or it's more enjoyable/close without a condom'	353 (41.4%)
'My partner didn't want to use a condom'	147 (17.2%)
'Felt unable to discuss condom-use'	37 (4.3%)
'Got carried away or was under the influence of alcohol or drugs'	369 (43.3%)
'Difficult for me/partner to keep erection or ejaculate when using a condom'	205 (24.0%)

[a] In total, 65 (7.6%) MSM reporting recent anal/vaginal CLS did not tick any of the six reasons provided for CLS with a man or a woman.

Table 13 presents the unadjusted associations between depressive symptoms (PHQ-9≥10) and reasons for non-condom-use among men reporting recent CLS. Men with depressive symptoms were more likely than those without to report having gotten carried away/been under the influence, their/their partner's difficulty in keeping an erection/ejaculating with a condom, and also tended to be more likely to report their partner not wanting to use a condom.

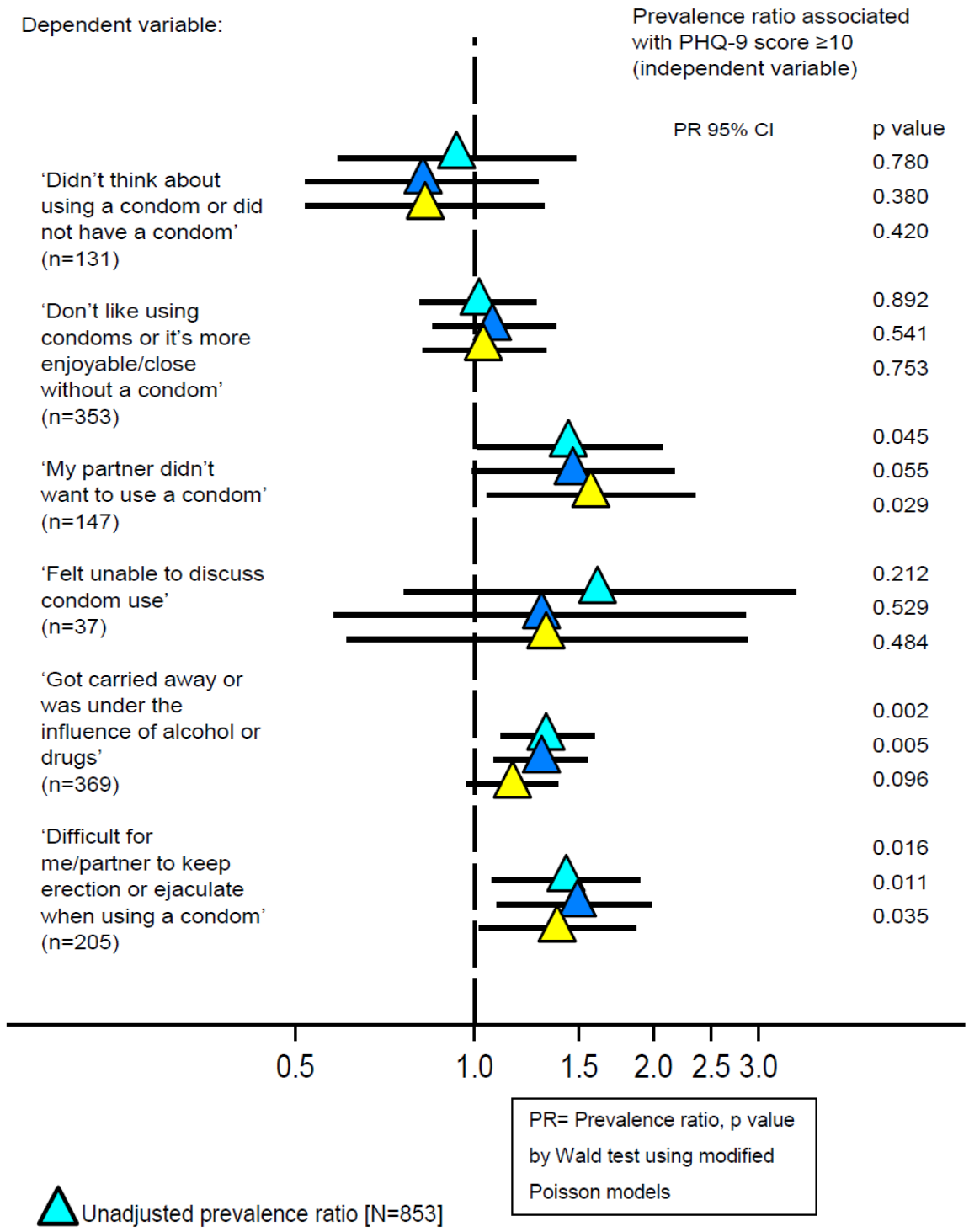
Table 13: Unadjusted associations of depressive symptoms with reasons reported for non-condom-use in the past three months in AURAH

N=853 MSM reporting recent anal/vaginal CLS			'Didn't think about using a condom or did not have a condom'	'Don't like using condoms or it's more enjoyable/close without a condom'	'My partner didn't want to use a condom'	'Felt unable to discuss condom-use'	'Got carried away or was under the influence of alcohol or drugs'	'Difficult for me/partner to keep erection or ejaculate when using a condom'
		N (%)	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]
Depressive symptoms (score≥10)	Yes No	124 (14.5%) 729 (85.5%)	14.5% 15.5% *0.779*	41.9% 41.3% *0.893*	23.4% 16.2% *0.050*	6.5% 4.0% *0.211*	54.8% 41.3% *0.005*	32.3% 22.6% *0.020*

[a] Pearson χ^2 test.

Figure 14 shows unadjusted and adjusted PRs. After adjusting for key socio-demographic factors, associations with CLS reasons were similar or slightly attenuated. After adjusting additionally for smoking, drinking, and recreational drug use, depressive symptoms remained associated with the following reasons for non-condom-use: my partner didn't want to use a condom and difficult for me/partner to keep an erection or ejaculate when using a condom. Not surprisingly, the association with reporting 'got carried away/was under influence of alcohol or drugs' disappeared after additional adjustment for smoking, drinking, and recreational drug use. Depressive symptoms were not associated with the following reasons for non-condom-use, in unadjusted or adjusted analysis: didn't think about using a condom or did not have a condom, don't like using condoms or it's more enjoyable/close without a condom, and felt unable to discuss condom-use. Of note, the pattern of associations was very similar when investigating the other measures of depression on PHQ-9 (data not shown).

Figure 14: Unadjusted and adjusted associations of depressive symptoms on PHQ-9 (≥10) with reasons for non-condom-use among 853 men who reported recent anal/vaginal CLS in AURAH



[a] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

5.3.7 Receiving medical treatment or therapy for depression

The prevalence of treatment for depression was 51.0% (123/241) among men with any evidence of current depression (see section 4.3.2). The prevalence of CLS measures, STI diagnosis, and PEP use according to evidence of depression (symptoms and/or treatment), is presented in Table 14. Men with any evidence of current depression tended to be more likely to report measures of sexual risk than those without evidence of depression. Adjusted PRs for associations with CLS with one or more partners, STI diagnosis, and PEP use, were higher for men who reported depressive symptoms (with or without treatment) than for those who reported treatment but no current symptoms. For the other measures of CLS, prevalence was elevated for all depression categories, compared to no depression.

Table 14: Unadjusted and adjusted associations of symptoms/treatment for depression with CLS measures, STI diagnosis, and PEP use, in AURAH

N=1340 MSM reporting recent anal/vaginal sex			**CLS with one or more partners**		
Depressive symptoms (PHQ-9≥10):	Receiving treatment for depression:	N (%)	% *p-value*[a]	Unadjusted PR[95% CI] *p-value*[b]	Adjusted[c] PR[95% CI] *p-value*[b]
Yes	Yes	48 (3.6%)	81.3%	1.32 [1.14, 1.52]	1.26 [1.08, 1.46]
Yes	No	118 (8.8%)	72.0%	1.17 [1.03, 1.32]	1.30 [1.02, 1.30]
No	Yes	75 (5.6%)	68.0%	1.10 [0.94, 1.30]	1.06 [0.90, 1.24]
No	No	1099 (82.0%)	61.7%	1	1
			0.006	*<0.001*	*0.006*
			CLS with two or more partners		
Depressive symptoms (PHQ-9≥10):	Receiving treatment for depression:	N (%)	% *p-value*[a]	Unadjusted PR[95% CI] *p-value*[b]	Adjusted[c] PR[95% CI] *p-value*[b]
Yes	Yes	48 (3.6%)	54.2%	1.83 [1.39, 2.41]	1.65 [1.23, 2.21]
Yes	No	118 (8.8%)	40.7%	1.37 [1.08, 1.74]	1.37 [1.08, 1.75]
No	Yes	75 (5.6%)	40.0%	1.35 [1.01, 1.81]	1.35 [1.01, 1.80]
No	No	1099 (82.0%)	29.7%	1	1
			<0.001	*<0.001*	*0.001*
			CLS with unknown/HIV-positive status partner(s)[c]		
Depressive symptoms (PHQ-9≥10):	Receiving treatment for depression:	N (%)	% *p-value*[a]	Unadjusted PR[95% CI] *p-value*[b]	Adjusted[c] PR[95% CI] *p-value*[b]
Yes	Yes	48 (3.6%)	54.2%	1.69 [1.29, 2.22]	1.50 [1.11, 2.02]
Yes	No	118 (8.8%)	49.2%	1.53 [1.25, 1.88]	1.48 [1.20, 1.82]
No	Yes	75 (5.6%)	50.7%	1.58 [1.25, 2.01]	1.57 [1.23, 2.00]
No	No	1099 (82.0%)	32.0%	1	1
			<0.001	*<0.001*	*<0.001*
			Receptive CLS with an unknown status partner		
Depressive symptoms (PHQ-9≥10):	Receiving treatment for depression:	N (%)	% *p-value*[a]	Unadjusted PR[95%CI] *p-value*[b]	Adjusted[c] PR[95% CI] *p-value*[b]
Yes	Yes	48 (3.6%)	25.0%	2.10 [1.25, 3.51]	1.68 [0.94, 2.99]
Yes	No	118 (8.8%)	22.0%	1.85 [1.27, 2.69]	1.71 [1.16, 2.52]
No	Yes	75 (5.6%)	24.0%	2.01 [1.30, 3.11]	2.08 [1.34, 3.21]
No	No	1099 (82.0%)	11.9%	1	1
			<0.001	*<0.001*	*0.001*
			Self-reported bacterial STI diagnosis (past year)		
Depressive symptoms (PHQ-9≥10):	Receiving treatment for depression:	N (%)	% *p-value*[a]	Unadjusted PR[95% CI] *p-value*[b]	Adjusted[c] PR[95% CI] *p-value*[b]
Yes	Yes	48 (3.6%)	35.4%	1.19 [0.80, 1.76]	1.34 [0.91, 1.96]
Yes	No	118 (8.8%)	44.9%	1.50 [1.21, 1.87]	1.52 [1.21, 1.92]
No	Yes	75 (5.6%)	33.3%	1.12 [0.80, 1.56]	1.12 [0.81, 1.55]
No	No	1099 (82.0%)	29.9%	1	1
			0.009	*0.004*	*0.003*
			PEP use (past year)		
Depressive symptoms (PHQ-9≥10):	Receiving treatment for depression:	N (%)	% *p-value*[a]	Unadjusted PR[95% CI] *p-value*[b]	Adjusted[c] PR[95% CI] *p-value*[b]
Yes	Yes	48 (3.6%)	25.0%	1.77 [1.06, 2.96]	2.05 [1.21, 3.47]
Yes	No	118 (8.8%)	22.9%	1.62 [1.13, 2.33]	1.78 [1.22, 2.58]
No	Yes	75 (5.6%)	17.3%	1.23 [0.73, 2.06]	1.28 [0.77, 2.12]
No	No	1099 (82.0%)	14.1%	1	1
			0.018	*0.014*	*0.002*

[a] Pearson χ^2 test.
[b] p-value by Wald test using modified Poisson models.
[c] Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.

5.3.8 Generalized anxiety disorder and suicidal ideation

Compared to depressive symptoms on PHQ-9 (≥10), a similar pattern of associations was found for GAD on GAD-7 with sexual behaviour measures, high self-efficacy for sexual safety, and difficulty negotiating condom-use (see Appendix section 11.15 Table 72- Table 75). Likewise, compared to depressive symptoms on PHQ-9 (≥10), a very similar pattern of associations was found for suicidal ideation on PHQ-9 with sexual behaviour measures. However, suicidal ideation was not associated with measures of self-efficacy (see Appendix section 11.15 Table 72- Table 75). In terms of the magnitude of the associations, for each measure of CLS, including bacterial STI diagnosis and PEP use, the PRs observed for GAD, were very similar, although in each case slightly weaker, than that observed for depressive symptoms (PHQ-9≥10). The same was true when comparing PRs observed for suicidal ideation and depressive symptoms.

5.3.9 Relationship of socio-demographic and lifestyle factors with sexual behaviour measures

Table 76 in Appendix section 11.16 presents the unadjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures. Reporting CLS with multiple partners and partners of an unknown or HIV-positive status was associated with older age (albeit of borderline significance with the latter CLS measure), attending a study recruitment clinic outside of London, a non-university degree level education, financial hardship, not being in an ongoing relationship, lower levels of a supportive network, smoking regularly, higher-risk drinking, greater number of recreational drugs used, and chemsex-associated drug use. Reporting CLS with two or more partners also appeared to be associated with having been born in the UK and being BAME, and had a borderline significant association with a self-reported straight sexual identity. Reporting CLS with multiple partners and partners of an unknown or HIV-positive status was not associated with employment status or housing situation in unadjusted analysis. A similar pattern of associations was found with report of CLS with one or more partners, with some exceptions. This measure was not associated with age, levels of a supportive network, or higher-risk drinking, and was more common among men reporting an ongoing relationship with a partner. Reporting receptive CLS with an unknown status partner was associated with attending a study recruitment clinic outside of London, a non-university degree level education, not being in an ongoing relationship, lower levels of a supportive network, and chemsex-associated drug use. A borderline significant trend was observed with increasing financial hardship.

Bacterial STI diagnosis was associated with age 30-34 years (from which point onwards the prevalence of STI diagnosis appeared to decrease), non-university degree level education, being employed, a self-reported gay sexual identity, greater number of recreational drugs used, and chemsex-associated drug use. A borderline significant association was also observed with higher-risk drinking. PEP use was associated with lower levels of a supportive network, greater number of recreational drugs used, and chemsex-associated drug use. Borderline significant associations were also found with not being in an ongoing relationship and attending a study recruitment clinic in the South of England.

Reporting eleven or more new sexual partners and group sex was associated with older age, higher-risk drinking, greater number of recreational drugs used, and chemsex-associated drug use. Reporting eleven or more new partners was also associated with white ethnicity, a more stable housing situation, reporting a gay sexual identity, not being in an ongoing relationship, and lower levels of a supportive network. Group sex was also associated with being employed, in unadjusted analysis.

5.4 Discussion

5.4.1 Summary of results

As hypothesized in this thesis (see section 1.9.1), depressive symptoms (PHQ-9≥10) were associated with all measures of CLS, bacterial STI diagnosis, and PEP use, independently of socio-demographic factors and smoking, alcohol, and drug use. Associations were also observed among men who did not report (i) poly-drug use, (ii) chemsex-drug use, and (iii) club-drug use. However, depressive symptoms were not associated with having eleven or more new sexual partners or group sex. Depressive symptoms were independently associated with lower self-efficacy for sexual safety. High self-efficacy for sexual safety was independently associated with all measures of CLS, bacterial STI diagnosis, and PEP use. Adjusting for self-efficacy for sexual safety attenuated the association between depressive symptoms and CLS measures. Reporting difficulty negotiating condom-use was also independently associated with depression and with all CLS measures; adjustment for this measure resulted in some attenuation of the association between depression and CLS measures. For some measures of CLS, the adjusted prevalence was higher among men who reported depressive symptoms (with or without treatment) than men who reported treatment but no current symptoms. The pattern of associations described above was very similar when investigating other measures of depression on PHQ-9, including suicidal ideation. Associations were also similar when investigating GAD on GAD-7 and the implications of these findings are discussed in Chapter 9 in the context of exploring evidence for a causal association between depressive symptoms and sexual risk behaviour.

5.4.2 Prevalence of sexual behaviour measures

AURAH estimates of CLS prevalence appear to be somewhat higher or similar to those observed in review (ii) of this thesis (section 2.5.2) for GUM clinic samples and online samples. The prevalence of CLS with one or more partners was 63.7% and 35.4% for CLS partners of an unknown/HIV-positive status in the past three months among AURAH men who reported recent sex. Among all 1484 MSM the prevalence was 57.5% and 31.9% respectively. The prevalence of CLS with one or more partners in the past three months was 38.9% and 41.8% in the two GUM clinic samples [35, 102] of review (ii). The prevalence of CLS with unknown/sero-different HIV status partners in the past three months was 27.0% and 31.0% in the two online samples (no data available from GUM clinics for this CLS measure [464, 466, 498, 499]. Prevalence estimates from AURAH appear to reiterate the conclusions of review (i) and (ii), that MSM attending GUM clinics may be more likely to report a high prevalence of CLS compared to MSM attending gay venues or those selected from the general population, see section 2.5.2. This might be expected, since the primary reason for attending a GUM clinic is for screening and/or treatment of STIs acquired through CLS. These findings may have implications for HIV prevention interventions addressing depression, as described below and discussed in the final conclusion chapter of this thesis.

5.4.3 Comparing AURAH findings to other studies investigating depression and CLS among MSM in review (i)

As described in review (i) of this thesis (section 2.4.5.4), in U.S (and Western European) studies of MSM the association between depressive symptoms and increased sexual risk behaviour may be more consistently demonstrated among samples where all or almost all men reported (recent) sexual intercourse (CMDUHS [359], EXPLORE [367-369], Project MIX [362], NHBS [363], FIP [353], MAPS [357], P18 Cohort [365], Vanden Berghe et al 2014 [358]), compared to samples which included a higher proportion of men who did not report recent sex (Dudley et al 2004 [370], HONOR [372], Maksut et al 2016 [373]), see Table 1. In line with findings from review (i), a strong relationship was observed between depressive symptoms and measures of CLS in the AURAH study of sexually active GUM clinic attendees. In a sexually active study sample men may be more likely to have an externalised response to depressive symptoms such as cognitive escape, with implications for sexual risk-taking and substance use, rather than internalised response, such as withdrawal [362]. The pairing of depression and externalizing behaviours may be a function of genetic predisposition and/or environmental influences (see section 2.6.2.1) [307, 566, 568-573].

5.4.4 Comparing AURAH findings to UK studies investigating depression and CLS among the general population of men

Natsal-3 (2010-2012) is the only UK study to have investigated the relationship between depressive symptoms (PHQ-2≥3) and sexual risk behaviour among the British general

population (N=13507 individuals who reported ever having had sex, N=5533 men). Among men who did not report receiving treatment for depression in the past year, and after adjusting for age, screening positive for depression (PHQ-2≥3) was associated with greater odds of two or more female sexual partners in the past year (AOR 1.45 95% CI: 1.06, 1.97), concurrent partnerships in the past five years (AOR 1.39 95% CI: 1.03, 1.89), knowing/perceiving their most recent partner to have had sex with somebody else in the past five years (AOR 1.37 95% CI: 1.04, 1.82), and 'quite a lot' or greater self-perceived risk of STI (AOR 2.09 95% CI: 1.41, 3.09). Depressive symptoms were not however, associated with report of two or more CLS partners in the past year after adjustment for age (AOR 1.29 95% CI: 0.92, 1.81) [(673)]. Of the 5533 men in this sample, 91.3% reported at least one sexual partner in the past year (5054/5533). Following on from the previous section, the fact that not all men reported sex in the past year may explain the apparent lack of association between depressive symptoms and CLS among the general UK population. However, comparing these findings to the AURAH study may be complicated by the exclusion of men who reported receiving treatment for depression in the past year in the Natsal-3 analysis. The relationship may also be unique to MSM. Of note, in a recent study of Natsal-3 participants who reported at least one sexual partner in the past year (N=4839 men), there was some evidence for an association between screening positive for depression (PHQ-2≥3) and lacking interest in sex for a period of three or more months in the past year, after adjusting for age (AOR 2.95 95% CI: 2.26, 3.85). Lack of interest in sex was strongly related to a lack of recent sexual activity [(684)].

5.4.5 Depression, recreational drug use, and sexual behaviour

Findings from the AURAH study suggest that recreational drug use is strongly associated with CLS. Higher levels of drug use among those with depressive symptoms may in part confound the link between depression and CLS, but drug use is unlikely to solely explain this relationship. Although the association between depression and sexual risk generally appeared weaker in the non-drug use groups, there was no statistical evidence to suggest this was the case. Depressive symptoms were significantly associated with some sexual behaviour measures among men who did not report significant levels of drug use, again suggesting that a relationship operates independently of drug use. Furthermore, although reporting symptoms of depression was not associated with reporting eleven or more new sexual partners in the past year, this relationship was apparent among men who reported club-drug use. With regards to partner numbers, and perhaps in the context of sexually orientated settings on the gay scene, it may be that it is the combination of depressive symptoms and drug use that is most strongly associated with escape tendencies (see section 1.8.3.4), and hence engagement in sex with a high number of partners, in line with that described in syndemic theory (see section 2.6.3.2).

Of note, the relationship between recreational drug use and depression is in practice most likely bidirectional. For instance, men with depressive symptoms may engage in recreational drug use as a form of self-medication and/or in order to induce a state of cognitive release [(397)]. The

complex relationship between depressive symptoms and recreational drug use, and sexual risk behaviour, is further addressed in Chapter 6.

5.4.6 Depression, self-efficacy for sexual safety, and sexual behaviour

Findings from the AURAH study suggest that low self-efficacy for sexual safety and difficulty negotiating condom-use may be potential mechanisms through which depression leads to CLS, which may explain why a relationship was observed with CLS measures but not higher partner numbers. Self-efficacy for sexual safety is a psychological construct that describes one's confidence in one's ability to produce a certain desired outcome (see section 1.8.3.1), which in the context of this thesis, is keeping oneself safe of STI/HIV acquisition. If an individual does not perceive that they have the capacity to keep themselves sexually safe, then they may not attempt to make it happen. In the AURAH study, condom-use was considered to be the behaviour that produces the desired outcome of sexual safety. Condom-use requires exertion of control in an interpersonal situation, most likely in the form of discussion and negotiation. It therefore follows, that a low self-efficacy for sexual safety via condom-use may be associated with increased reporting of CLS, but not necessarily partner numbers.

Among men reporting CLS, depressive symptoms were also independently associated with a reason for CLS being that a sexual partner did not want to use a condom, or difficulty/a partners' difficulty in keeping an erection/ejaculating. This may reflect the notion that depression can impact on self-assertion in interpersonal relationships and self-protective behaviours. The fact that men who reported depressive symptoms were more likely to report PEP use, suggests that although depression may impair discussion/negotiation of safe sex practices, there is still an overarching desire to be safe and protect oneself after this interaction is over.

5.4.7 Symptoms and treatment for depression in relation to sexual risk

In the AURAH study, there was no consistent evidence to imply that treatment of depression may reduce sexual risk-taking. The extent to which this question can be addressed given the cross-sectional design of the study is limited. Inference may be complicated by a number of factors including severity of symptoms prior to treatment, type, duration, and frequency of treatment, timing of treatment in relation to symptoms, the presence of other psychological conditions, and sensitivity of the PHQ-9 in capturing all cases of depressive symptoms.

5.4.8 Socio-demographic and lifestyle factors associated with sexual behaviour

Unlike in AURAH, in other UK studies of sexual behaviour among MSM (identified in review (ii) of this thesis, section 2.5.4) there is some evidence to suggest that younger men are more likely to engage in CLS (including with multiple partners and partners of an unknown/sero-different HIV status) [118, 477, 482, 489, 512, 563] [563]. There is also some evidence from studies in other high-income countries, mainly the U.S., for an association between younger age and sexual risk

behaviour [491, 574-577]. It is possible that in AURAH the age association with sexual risk may be affected by the demographics of people attending GUM clinics.

Furthermore, although a relationship was observed in the AURAH study, alcohol use has not been found to be associated with CLS measures in the two other UK studies that have investigated this association among MSM [478, 509]. In terms of other factors, findings from the AURAH study are similar to other UK studies of sexual behaviour among MSM, in which there is some evidence to suggest that being in an ongoing relationship is associated with CLS with one or more partners [482, 496, 510], lower levels of educational attainment are associated with CLS (including with multiple partners) [510, 512], and in which ethnicity and sexual identity have not been found to be associated with multiple CLS partners and CLS partners of an unknown/sero-different HIV status [482, 489, 496, 498, 509-512]. These relationships may not be surprising given that the act of CLS will often occur within the context of stable, loving relationships, which foster greater assurance of the HIV status of a partner. The possible mechanisms by which lower levels of educational attainment are associated with sexual risk behaviour are most likely complex. Educational attainment may be a proxy measure for knowledge of HIV (see section 3.5) and may be associated with socio-economic disadvantage with implications for increased levels of depression, recreational drug use, and IPV [248, 249]. It is possible that educational attainment may also affect socio-cultural norms and expectations regarding condom-use.

Finally, as in AURAH, in other UK studies of sexual behaviour among MSM, recreational drug use has been consistently linked to CLS measures [511] [478, 484, 509]. As described in detail in section 2.6.3.2, recreational drug has also been linked to sexual risk behaviour in studies of MSM in other high-income countries (one study conducted in the Netherlands, one study in Australia, and the remainder in the U.S.) [397, 585-600]. Possible mechanisms of effect are also discussed in section 2.6.3.2.

5.4.9 Limitations

The general methodological limitations of the AURAH study are discussed in section 3.7.1 of Chapter 3. In this specific analysis, it is important to note that the prevalence of depression and associations with sexual behaviour may have differed among the 40% of individuals approached who did not complete a questionnaire. Although it is acknowledged in this thesis that CLS should not in itself be pathologized, in the AURAH study of GUM clinic attendees, the majority of recent CLS reported did not occur with one long-term partner only, therefore, most CLS was CLS with a non-regular partner. It is of note though, that for a small proportion of men reporting CLS in AURAH, the act of CLS may occur in the context of loving and mutually supportive relationships and carry no risk of HIV/STI transmission. This issue is further discussed in the final conclusions chapter (section 9.2.2). Furthermore, as discussed in section 3.7.1, the cross-sectional methodology used in the AURAH study prohibits us from making inferences about causality. In particular, the PHQ-9 enquires about symptoms during the

previous two weeks whereas the recall periods for sexual behaviour were longer (past three months/past year). However, since depression questionnaires aim to provide a diagnostic measure of a chronic mental health condition it is not unreasonable to assume that in many cases depression may have preceded the recent sexual behaviour reported. Nevertheless, the association between depression and sexual behaviour may operate in both directions (as discussed in Chapter 9).

It is important to note that multiple testing took place when investigating whether the relationship between depressive symptoms and sexual behaviour measures varied according to poly-, chem-, and club-drug use. Since multiple drug measures and multiple sexual behaviour measures were investigated, it is inevitable that some significant results will appear just by chance. Furthermore, 166 men were classified as having depressive symptoms. Accordingly, the numbers investigated become quite small when stratifying by drug use measures, and power for interaction tests was limited.

Assessing the extent to which factors such as alcohol use, recreational drug use, or self-efficacy measures 'explain' the association between depressive symptoms and CLS measures is limited by measurement error in those factors. The observed variables may not fully capture all the relevant variation in these measures. Therefore, it is important to assess the extent to which associations are attenuated, rather than whether they are fully 'explained'.

Finally, it was hypothesized in this thesis that CSA and IPV may confound the relationship between depressive symptoms and sexual behaviour. Unfortunately, AURAH did not collect information on CSA or IPV. It was also not possible to investigate certain personality characteristics associated with sensation seeking and sexual compulsivity, nor markers of cognitive escape, which may also be useful in understanding why some men engage in CLS.

Finally, the infrastructure required to re-contact all sexually active MSM participants to ask them for their interpretation of why depressive symptoms may have been linked to measures of CLS in the AURAH study, was not set up. Involving patients in the interpretation of findings, via a qualitative analysis of verbal or written responses, would have been helpful in better understanding the possible mechanisms of effect.

5.4.10 Summary of discussion

The AURAH study provides further evidence that depressive symptoms are associated with CLS measures among samples of MSM reporting recent sex and provides further insight into this relationship among MSM in the European context. Furthermore, in line with the hypothesis set forth in this thesis, recreational drug use appears to partially but not fully confound the association between depressive symptoms and CLS measures in the AURAH study. Reporting a greater number of recreational drugs used and chemsex-associated drug use was

consistently and strongly associated with measures of sexual risk-taking, in line with previous literature, suggesting a critical role of drug use in sexual risk behaviour. Findings also suggest that self-efficacy for sexual safety may be on the causal pathway between depression and CLS, supporting the hypothesis in this thesis. A more thorough approach to mediational analysis (SEM) is described and investigated in the next chapter, in order to determine the statistical significance of the indirect effect of self-efficacy. Reporting medical treatment or therapy for depression did not appear to consistently reduce the prevalence of sexual risk behaviour measures among men with depressive symptoms. However, as noted above, there are a number of factors which may distort this investigation, and these findings should be interpreted with caution.

Chapter 6

6 Investigating a conceptual model for the relationship between depression and condomless sex among gay, bisexual, and other men who have sex with men in the AURAH study

6.1 Introduction

Using data from MSM recruited in four U.S. cities for Project MIX between 2004 to 2006, Alvy et al (2011) [362] presented evidence that both lowered self-efficacy for sexual safety and cognitive escape tendencies, as well as a composite measure of the two, significantly mediated the association between depression and CLS partners of unknown or HIV sero-different status in the past three months. These findings were based on an analysis using the distribution of the product method, which is similar to approaches described in section 3.4.2 of Chapter 3 that test the significance of the mediated effect. There is a lack of recent research into the potential mechanisms by which depression might lead to sexual risk-taking, and no UK/European studies. The aim of this chapter was to investigate whether data from the AURAH study are consistent with the hypothesis that depression is associated with CLS indirectly through lowered self-efficacy for sexual safety. This analysis uses the same sample of men as that investigated in the previous chapters; gay, bisexual, and other MSM from the AURAH study who reported recent anal or vaginal sex (N=1340). Structural equation modelling (SEM) was used to address this question. SEM does not circumvent the issue that causal effects cannot be established in observational cross-sectional studies. However, it does allow for specification of relationships between any variables (including latent variables) and specification of more complex relationships in the model, distinguishing between direct and indirect effects [652, 653].

6.2 Methods

6.2.1 Hypothesized relationship between depression and sexual risk behaviour among sexual minority men in the AURAH study

The DAG shown in Figure 15 presents the hypothesized causal connection between depressive symptoms and CLS, whereby self-efficacy for sexual safety was hypothesized to be on the casual pathway. In Figure 16, the DAG presents the hypotheses made about causal connections of socio-demographic and lifestyle factors collected in the AURAH study with depressive symptoms and CLS. All arrows depicted in the DAG were derived from observed relationships based either on findings from Chapters 4 and 5 or other previous literature presented in Chapters 1 and 2, although such relationships have not been proved to be causal. Of note, for each variable shown on the DAG in Figure 16, the category labelled is the non-

reference category for binary variables and the group furthest from the reference category for ordered categorical variables. For instance, the factor 'financial hardship' includes categories: (i) always enough money (reference category), (ii) mostly enough money, or (iii) at times/never enough money, and as a result, is termed financial insecurity in the DAG. This was in order to capture the way in which the conceptual model was fitted into the framework of SEM. Therefore, the description of factors in Figure 16 does not reflect the direction in which the relationship is hypothesized; rather the hypothesized relationships depicted can be either positive or negative. For instance, higher educational attainment, a supportive network, and older age are hypothesized to lead to lower levels of depressive symptoms, and thus a negative estimate in SEM. The remaining postulated relationships are discussed in the context of the results of the model.

Figure 15: Directed acyclical graph of causal connection between depressive symptoms and CLS among sexual minority men, based on data from AURAH

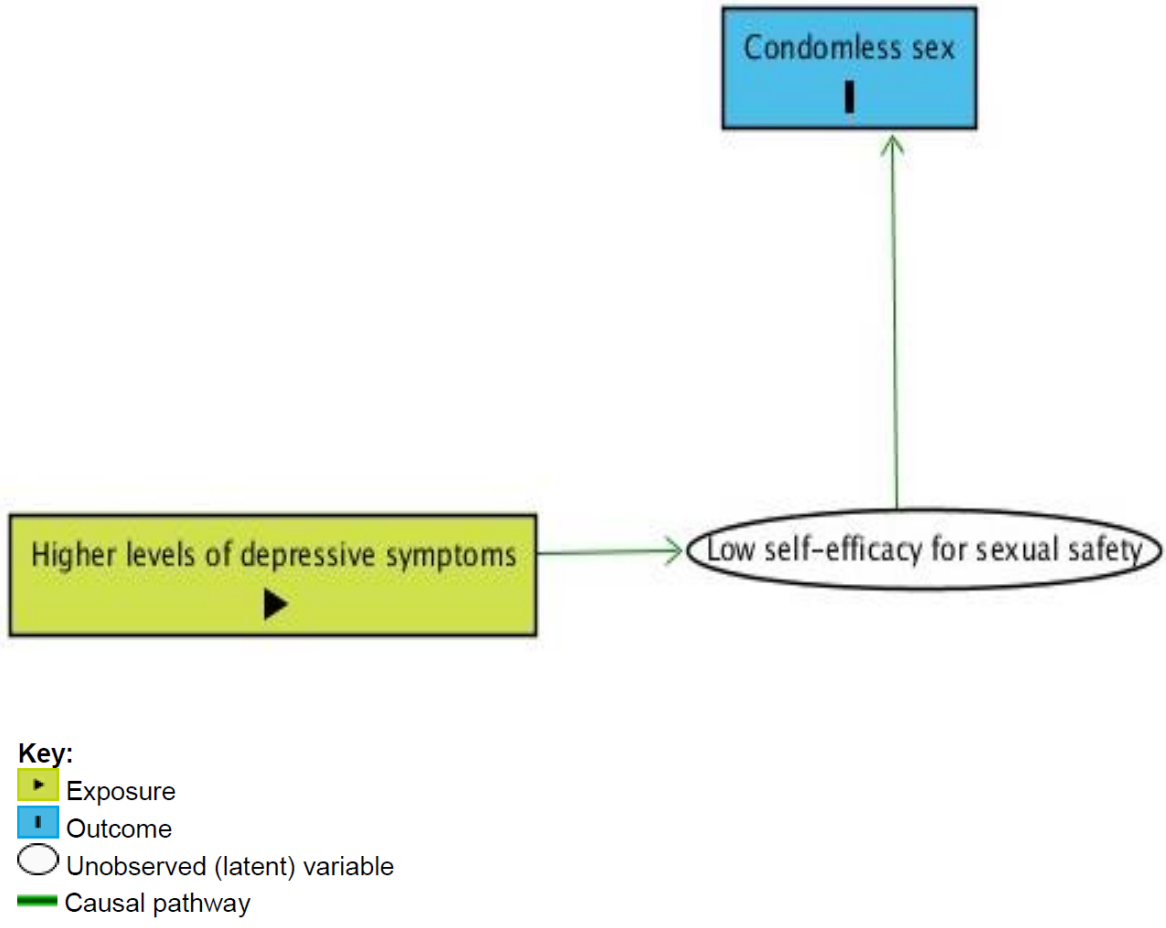
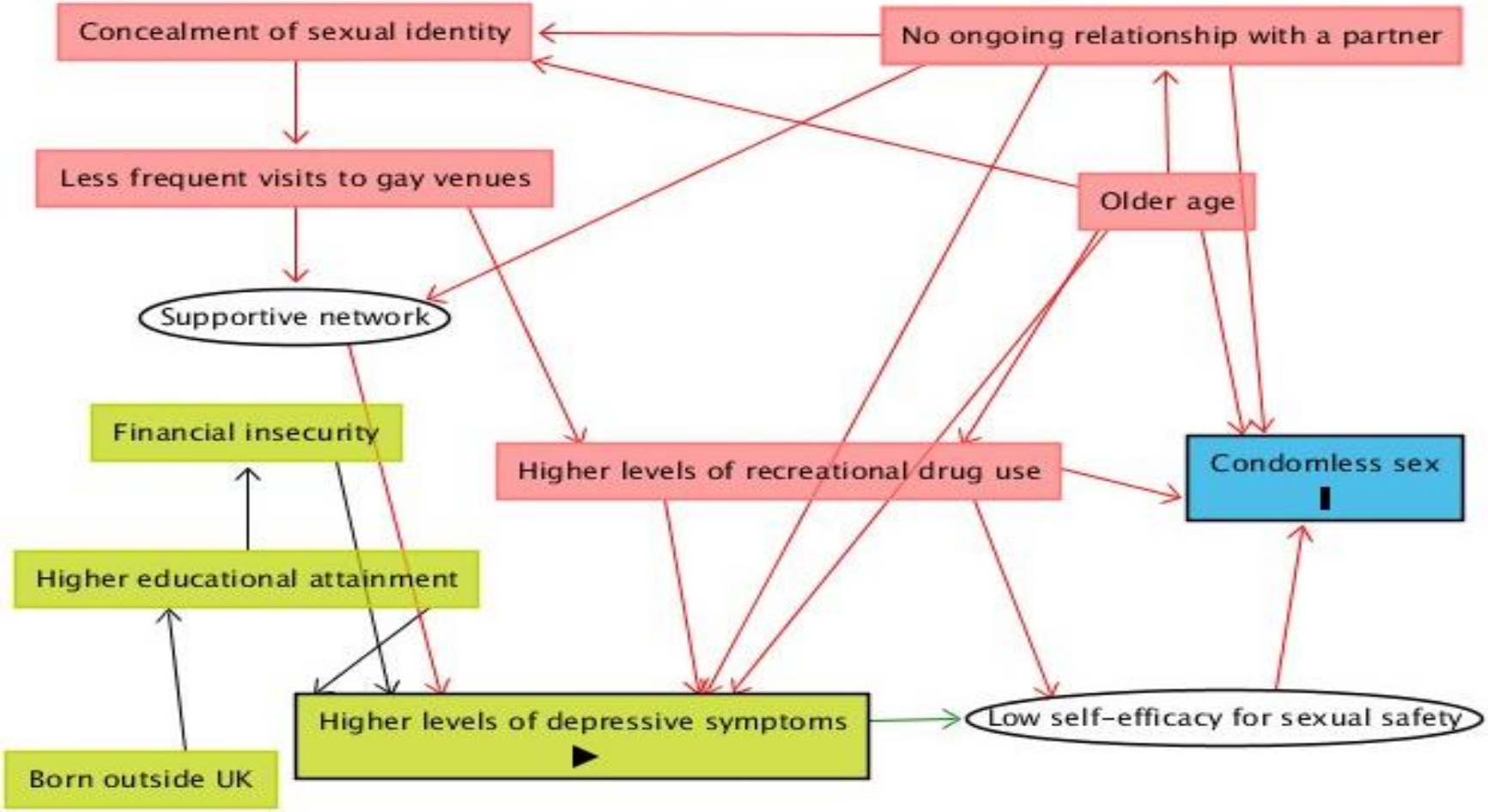


Figure 16: Directed acyclical graph of causal connections* between socio-demographic and lifestyle factors and depressive symptoms, and between depression and CLS, among sexual minority men, based on data from AURAH



Key (detailed description in Chapter 3):


Exposure


Outcome


Ancestor of exposure


Ancestor of exposure *and* outcome


Unobserved (latent) variable


Causal pathway


Possible alternative pathways

* The pathways indicated could represent either positive or negative associations

6.2.2 Variables investigated in this chapter

The same measures of CLS as those defined in Chapter 3 section 3.3.3 and investigated in the previous chapter, were examined in this chapter. CLS with one or more partners was the main measure focused upon when reporting the results. Findings are compared to those observed when investigating the other measures of CLS: CLS with two or more partners, CLS with an unknown/HIV-positive[xxix] status partner, and receptive CLS with an unknown status partner. However, the definition of other variables investigated differed. Below is a description of the variables specific to this chapter that were selected before the analysis since they are related to both depressive symptomatology and CLS.

6.2.2.1 Unobserved (latent) variables

Depressive symptoms, self-efficacy for sexual safety, and supportive networks were considered to be unobserved (latent) variables (see section 3.6.3), for which a factor analysis (as described below) was incorporated into the SEM model. For depressive symptoms, the nine observable items on the PHQ-9 questionnaire (coded 0 to 3) were thought to 'potentially shadow' (i.e. represent) the construct of depression. For the statements indicating self-efficacy for sexual safety and difficulty negotiating condom-use, described in section 3.3.4, the response options were coded as 1 to 5, starting with 'strongly agree' (coded as 1) for the first statement and 'strongly disagree' (coded as 1) for the second statement, so that a high score amounts to lower self-efficacy for both items. These two observable items were thought to potentially shadow the construct of self-efficacy for sexual safety. It is of note, that a latent construct with only two 'shadowing' indicators may be acceptable if the latent construct is specified to be correlated with at least one of the other factors in a measurement model [(653)], which was the case here.

The five observable items on the Duke-UNC Functional Social Support Questionnaire, described in section 3.3.5, were thought to potentially shadow the construct of a supportive network. The response options were coded as 1 to 5, starting with 'much less than I would like' (coded as 1). Of note, having a supportive network may be, to a large extent, a function of community affiliation. For plurisexual identified sexual minority men, affiliating one's self to one cohesive community may be more difficult. Therefore, these men may be more likely to experience low levels of a supportive network, and thus depressive symptoms. However, sexual identity was not included in this model. Due to small numbers, it was not possible to stratify the sample and investigate the conceptual model separately for different identities under the umbrella of sexual minority status. Furthermore, although it was of interest in this thesis to investigate whether sexual minority identities affected the prevalence of depressive symptoms reported, it was not the focus of this thesis to examine whether other factors relevant to sexual

[xxix] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

minority men's sexual and mental health differed between gay- and bisexual-identified men. It was deemed inappropriate to include the variable of sexual identity when not fully understanding its exact role in the model. Therefore, the model was examined among sexual minority men in general, but there may be limitations in assuming all sexual minority identities are similar.

6.2.2.2 Observed variables

Age and number of recreational drugs used were investigated as continuous variables in order to increase the degrees of freedom in the SEM and improve power. In the case of recreational drug use specifically, it was hypothesized that vulnerability to depression and the chances of engaging in CLS would increase with increasing number of drugs used. Given that the weighted least squares estimator employed, as described below, does not make distributional assumptions about observed variables, the non-normal distribution of age and recreational drug use was not considered a major problem [685, 686]. Of note, other measures of age and recreational drug use were also investigated in additional analyses in order to determine the effect of differing measurements on associations found. Age was investigated in six categories (18-24; 25-29; 30-34; 35-39; 40-44; 45+) and as a dichotomous variable (<45; ≥45). Based on a previous AURAH analysis [687], there appears to be a difference in prevalence of recreational drug use between men aged less than 45 years and men aged 45 years and older, hence the cut-off of age chosen for the dichotomous variable. Four different measures of recreational drug use were examined: number of recreational drugs used (0; 1; 2-4; 5+), poly-drug use, chemsex-drug use, and club-drug use.

The following additional observed variables were investigated: financial security (all of the time, most of the time, some of the time, or never), level of educational attainment (no qualifications, O levels/GCSEs, A levels, vocational qualifications, or university degree or higher), and frequency of attending gay cafes, pubs, bars, nightclubs/discos, or saunas (two or more times a month or less than twice a month). Other variables investigated have been defined in section 3.3.5: born in the UK, ongoing relationship with a partner, poly-drug use, chemsex-drug use, club-drug use, and 'out' to few/no friends, work colleagues, and close family. Of note, some categorical variables (financial security and educational attainment) were not dichotomized in this chapter since estimates derived from SEM are more intuitive for associations with ordered categorical variables (see section 6.2.3.2). Using categorical instead of derived binary variables also allows more information to be incorporated into the model. However, for the other ordered categorical variables, frequency of gay scene use and concealment of sexual identity, binary measures were derived. These factors were considered to play an important role in the conceptual model, as evidenced by most hypothesized indirect pathways operating through these two variables (see section 6.2.3.3). As a result, it was deemed necessary to define a cut-off indicating frequent gay scene use and concealment of sexual identity.

A comprehensive measure of sexual minority stress was not investigated in the AURAH study. Only one component of the stress, characteristic of sexual minority men, was captured; concealment of sexual identity. In this context, it was deemed more appropriate to investigate the association of concealment with supportive networks rather than investigating the association in the other direction as was shown in the DAG in Chapter 3 (Figure 8), due to the importance of disclosure in fostering supportive networks for sexual minority men [209, 225, 245-247]. Of note, an arrow is not drawn from concealment to depression in Figure 16 since it was investigated whether concealment was associated with depression indirectly via lower levels of a supportive network in this chapter. Furthermore, although higher levels of recreational drug use were hypothesized to be associated with sexual minority stress (Figure 8), this was not thought to be the case when investigating concealment as the only component of minority stress. Unlike the phenomenon and sequelae of internalised homophobia and fear of rejection, concealment of one's sexual identity and the stress associated was not thought to lead to greater drug use. Men who conceal their sexual identities are thought to be less likely to be active on the gay scene where opportunities to 'cognitively escape' using drugs are more available.

6.2.3 Statistical methods

6.2.3.1 Investigating latent variables via questionnaire items in the AURAH study- Measurement model

A factor analysis was used to obtain estimates of the constructs that cannot be measured directly (depression, self-efficacy for sexual safety, and supportive network), by relating them to variables that were directly measured. The latent construct should explain differences between individuals in their answers to the observable questions asked in the questionnaire. For instance, depression itself should explain why some individuals answer 'yes' to a lack of interest in things and some individuals do not. Although not a primary objective in this chapter, factor analysis also allowed the investigation of which observable question item was the most important i.e. contributed more weight. The item with the largest factor loading (the link between the observed variable and the latent variable) is considered the most important in explaining the specific latent variable.

6.2.3.2 Investigating hypothesized causal pathways in the conceptual model- Structural model

An SEM was undertaken in order to investigate the conceptual model depicted in Figure 16. All relationships (i.e. regression pathways) hypothesized were specified in MPlus. Since this SEM consists of binary, ordered categorical, and continuous outcome measures, a generalized weighted least square based robust estimator (the mean and variance-adjusted WLS, WLSMV) was used in order to control for heteroscedasticity of the error term. The link function for

weighted least square estimators is Probit link [653], which is the function that has been the most commonly used and studied in the estimation of models with categorical outcome measures [688-692]. The key feature of SEM is to calculate a model fit test. The model estimated variance-covariance matrix is the proportion of variance accounted for in all dependent measures by the set of independent measures specified. The model fit test determines the extent to which the variance-covariance matrix differs from the observed sample variance-covariance matrix. If the difference is not statistically significant then this provides no evidence against the null hypothesis that the model supports the plausibility of postulated relationships among the variables [653].

In order to evaluate the model fit, the following test results were examined in this chapter: The χ^2 p-value, the comparative fit index (CFI), the tucker-lewis index (TLI), and the root mean square error of approximation (RMSEA) test. If the χ^2 p-value is >0.05 then there is considered to be no evidence to contradict the model structure, however, the χ^2 is highly sensitive to sample size. If the sample is large then a significant p-value will almost always arise regardless of the magnitude of difference between the observed variance-covariance matrix and model estimated variance-covariance matrix . The χ^2 is also sensitive to the number of variables specified in the model (it increases when variable number increases). Given the limitations of the χ^2 test, the other model fit indices, described below, were used to guide the conclusion as to the model fit [653].

The CFI and TLI are comparative fit index tests that examine the specified model against the null model where nothing is significantly related (i.e. assumes zero covariances between observed variables). If values are ≥0.90 then the model is considered to have a satisfactory fit, and if the values are ≥0.95 then the model fit is considered to be good. Although the TLI tends to produce lower model fit indices to the CFI, the same cut-off values are utilized [653]. The RMSEA is a more recently proposed test. It is an absolute index of fit test that examines whether the specified model fits the data 'well-enough' instead of comparing it to a null model. The RMSEA measures the average lack of fit per model degree of freedom by adjusting for the degrees of freedom; the error of approximation reflects the lack of fit of the specified model to the population. Simulation studies have demonstrated that the model fit indices produced by the RMSEA perform better than the other model fit indices described above, and are now the most commonly used in applications of SEM [693-697]. If the value of RMSEA is ≤0.08 then the model is considered to have an adequate fit and if the value is ≤0.06 then the model fit is considered to be good. Additionally, the value of RMSEA is reported with a 90% confidence interval (CI). In a well-fitting model, the higher confidence limit should be ≤0.08 [698]. Finally, a close-fit test for the null hypothesis is reported for the RMSEA, if the p-value is >0.05, the null hypothesis cannot be rejected, and as such it can be suggested that the specified model has a 'close fit'.

The coefficients produced by SEM are standardized coefficients i.e. Beta values. The standardization of estimates for continuous independent variables was calculated using the function 'STDYX' and for binary/categorical independent variables using 'STDY' in MPlus. The Beta coefficients represent the amount of change (in standard deviation units) in a dependent variable per one standard deviation change of an independent variable. For a binary independent variable the coefficient is interpreted as the change in the dependent variable in standard deviation units when the independent variable changes from 0 to 1. Binary dependent variables are treated as continuous. In SEM, the interpretive value of the Beta coefficients extends only to that of comparing effect sizes in order to determine which factor is of 'greater importance' to the model; the greater the coefficient the greater the importance. A positive coefficient indicates a positive relationship with the dependent variable and a negative coefficient indicates the opposite, an inverse relationship with the dependent variable. The p-values correspond to the estimates adjusted for their standard errors (equivalent to the z score). Of note, in MPlus the 'full information maximum likelihood' (FIML) approach is used in model estimation to deal with missing data. FIML assumes 'missingness' to be Missing Completely at Random or Missing at Random [653]. Since missingness was <5% in the study for any variable/for >1 variable, any bias due to missing data was expected to be low.

6.2.3.3 Investigating whether depression is associated with CLS indirectly via self-efficacy for sexual safety- Mediational analysis

In the Poisson model presented in Chapter 5 (Table 11), whereby the association between depressive symptoms (PHQ-9≥10) and CLS was investigated adjusted for measures of self-efficacy (high self-efficacy for sexual safety and difficulty negotiating condom-use), it is assumed that all effects are direct- the coefficient for depression includes both the direct and the indirect effects. In SEM however, it is possible to derive two estimates; one for the direct effect of depressive symptoms on CLS and one for the indirect effect of depressive symptoms on CLS via self-efficacy for sexual safety. In order to demonstrate this and compare findings from the Poisson model to those from SEM, factor scores from the depression factor analysis and self-efficacy factor analysis were imported into Stata to be examined in a modified Poisson regression model. A mediator pathway was then specified in MPlus in order to investigate the hypothesis that depression causes CLS indirectly through lowered self-efficacy for sexual safety.

Additionally, further mediator pathways were specified in order to investigate the hypotheses that: (i) concealment of sexual identity causes depression indirectly via less frequent gay venue attendance and lower levels of a supportive network, (ii) concealment of sexual identity leads to lower levels of recreational drug use via less frequent gay venue attendance, (iii) less frequent gay venue attendance leads to less depression via lower levels of recreational drug use, and (iv) higher levels of educational attainment lead to less depression via financial security.

6.2.3.4 *Investigating whether the indirect effect of depression on CLS is similar among men who took recreational drugs and men who did not- Testing for moderating effects*

The potential moderating effects of recreational drug use were investigated in this chapter in two stages. In the first stage, measurement invariance was investigated for the latent construct of depression. Determining measurement invariance is as a result of examining whether individual items measuring a latent construct in a factor analysis function equivalently. It was investigated whether the measure of depression was well specified and captured equivalent constructs among: (i) men who reported poly-drug use and men who did not, (ii) men who reported chemsex-drug use and men who did not, and (iii) men who reported club-drug use and men who did not.

In the second stage, structural invariance was investigated by examining whether the indirect association of depression with CLS through lowered self-efficacy for sexual safety was different among: (i) men who reported poly-drug use and men who did not, (ii) men who reported chemsex-drug use and men who did not, and (iii) men who reported club-drug use and men who did not. Of note, this analysis followed on from the finding that the indirect effect of depressive symptoms on CLS through self-efficacy for sexual safety was consistent with the data.

6.2.3.5 *Investigating alternative causal pathways between depressive symptoms and CLS with one or more partners- Exploratory analysis*

The main hypothesis upon which this work is based is that symptoms of depression lead to CLS. Given the use of DAG to present this hypothesis, which requires strong prior assumptions about direction of associations to be made, the possibility that the association may operate in the opposite direction (CLS leads to depression) was not investigated, but is discussed when considering evidence for causality in Chapter 9 (section 9.2.3).

The main analysis in this chapter assesses support for the hypothesis that depressive symptoms lead to CLS via lower self-efficacy, as depicted in Figure 15. However, four alternative causal pathways between depressive symptoms and CLS with one or more partners were also examined in order to determine whether the overall model fit improved i.e. whether alternative pathways appeared to be more consistent with the data. This entailed changing the direction of the arrows in the DAG for the link between recreational drug use and depressive symptoms and recreational drug use and self-efficacy for sexual safety. Although it is acknowledged that this is not the common practice associated with DAG use, it was deemed to be of interest in this thesis to examine the extent to which the association between depressive symptoms and CLS may also be operating via recreational drug use. The relationship between recreational use and depression (and recreational use and self-efficacy for sexual safety) is in practice most likely bidirectional. The four alternative pathways investigated included:

(i) model without self-efficacy for sexual safety
(ii) model where symptoms of depression cause CLS indirectly through higher levels of recreational drug use (no direct cause between depressive symptoms and CLS)
(iii) model where symptoms of depression cause CLS indirectly through lowered self-efficacy for safety and where symptoms of depression cause CLS indirectly through higher levels of recreational drug use
(iv) model where symptoms of depression cause CLS indirectly via lowered self-efficacy for sexual safety and higher levels of recreational drug use.

6.3 Results

6.3.1 Descriptive statistics

For those variables which were redefined or investigated for the first time in this chapter, the prevalence is given here; the prevalence of other factors is presented in Chapters 4 and 5. Of the 1340 men who reported recent sex, the median age was 31 (interquartile range [IQR] =13) and the mean number of recreational drugs used in the past three months was 1 (IQR=3). Being educated to O levels/GCSEs, A levels, vocational qualifications, or university degree level was reported by 9.1%, 18.1%, 3.1%, and 67.2% of men respectively, and 2.6% of men reported no educational qualifications. Financial security all of the time, most of the time, some of the time, or never was reported by 71.7%, 21.0%, 5.2%, and 2.0% of men respectively. Fifty-two percent of men reported visiting gay venues two or more times a month. Finally, the proportion of men who reported receiving care, love and affection, chances to talk to someone, invitations to go out, and help when sick, as much as they would like (indicating higher levels of a supportive network), was 66%, 48%, 57%, 57%, and 55% respectively.

6.3.2 Measurement model

The model (which included depressive symptoms, self-efficacy for sexual safety, and support network) terminated normally, with p-values <0.001 for all factor items. Table 15 presents findings from the factor analysis of the nine items on the PHQ-9. In the factor analysis, the following item on the PHQ-9 appeared to be the most important for depression: ‘feeling down, depressed, or hopeless’, this was followed by ‘little interest or pleasure in doing things’, ‘feeling bad about yourself-or that you are a failure or have let yourself or your family down’, and ‘thoughts that you would be better off dead, or of hurting yourself in some way’.

When investigating poly-drug use and club-drug use as potential moderators in the measurement model, the mean depression factor analysis score was not significantly different between men who reported poly-drug use and men who did not (p=0.075). The depression mean was however, found to be different between men who reported club-drug use and men

who did not (p=<0.001). Regardless, when investigating measurement invariance of the depression factor analysis, scalar invariance/strong factorial invariance was achieved. In other words, the responses to the observable factor items were not significantly different between men who reported poly-drug use and men who did not (p=0.093) and men who reported club-drug use and men who did not (p=0.114). However, the depression mean was significantly different between men who reported chemsex-drug use and men who did not (p<0.001) and scalar invariance/strong factorial invariance was not achieved (p=0.031). Men who reported chemsex-drug use and men who did not may have answered the PHQ-9 depression questionnaire in a significantly different way, perhaps giving greater weight to different problem items on the scale. On further investigation, although the highest depression factor loading among both men who reported chemsex-drug use and men who did not, was for 'feeling down, depressed, or hopeless' (0.853 and 0.876 respectively), the pattern of factor loading importance differed from then onwards. For example, for men who reported chemsex-drug use, the second highest factor loading was for 'little interest or pleasure in doing things'(0.822) and the third for 'poor appetite or overeating' (0.822), whereas, for men who did not report chemsex-drug use, the second was for 'feeling bad about yourself-or that you are a failure or have let yourself or your family down' (0.820), and the third for 'thoughts that you would be better off dead, or of hurting yourself in some way' (0.814). Of note, findings (i.e. factor loadings, FL) from the factor analysis of the items shadowing self-efficacy for sexual safety and supportive network are presented in Figure 17.

Table 15: Factor loadings for nine items on the PHQ-9 scale of depression in AURAH

Individual question items on the PHQ-9 scale	Factor loadings
1. Little interest or pleasure in doing things	0.821
2. Feeling down, depressed, or hopeless	0.881
3. Trouble falling or staying asleep, or sleeping too much	0.718
4. Feeling tired or having little energy	0.772
5. Poor appetite or overeating	0.753
6. Feeling bad about yourself-or that you are a failure or have let yourself or your family down	0.819
7. Trouble concentrating on things, such as reading the newspaper or watching television	0.757
8. Moving or speaking so slowly that other people could have noticed/being so restless that it is hard to sit still	0.746
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0.817

6.3.3 Structural model

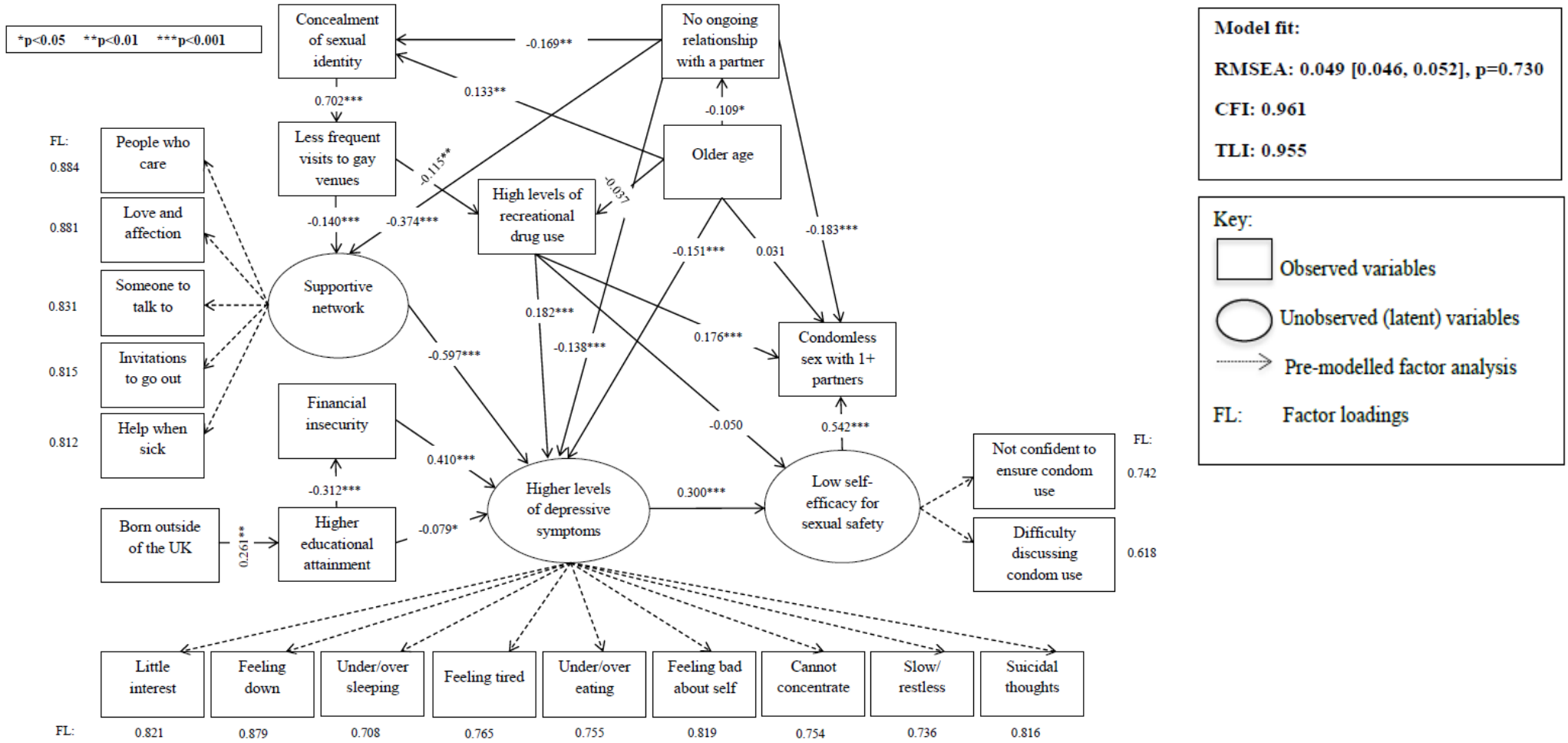
The χ^2 test for the model fit was 1084.478, df. 261, p-value <0.001; given the large size of the sample investigated, this significant finding is not unusual and is difficult to interpret. However, the RMSEA value was 0.049 (0.046, 0.052; p=0.730), the CFI was 0.961, and the TLI was 0.955. These model fit indices fall within the category of 'good' fit for all tests, as well as 'close fit' for the RMSEA close-fit test (based on the p-value). Although the conceptual model did not fit the data perfectly (as no model usually does), given that the model fit estimates were found to be good, it was considered that the model was not substantially inconsistent with the data.

Figure 17 presents the results of the SEM. Below is a description of the adjusted associations found in this model, see Figure 17 for sets of adjusted variables. Financial insecurity (Beta= 0.410; p<0.001) and greater number of recreational drugs used (Beta= 0.182; p<0.001) was associated with higher levels of depressive symptoms. Older age (Beta= -0.151; p<0.001), higher educational attainment (Beta= -0.079; p=0.039), no ongoing relationship with a partner (Beta= -0.138; p<0.001), and higher levels of a supportive network (Beta= -0.597; p<0.001) was associated with lower levels of depressive symptoms. Higher levels of depressive symptoms were associated with low self-efficacy for sexual safety (Beta= 0.300; p<0.001) and low self-efficacy for sexual safety (Beta= 0.524; p<0.001) was associated with CLS. Furthermore, greater number of recreational drugs used (Beta= 0.176; p<0.001) was associated with CLS. Report of no ongoing relationship with a partner was inversely associated with CLS (Beta= -0.183; p<0.001) i.e. being in an ongoing relationship was associated with CLS. Of note, in line with the hypothesis set forth in this thesis, the Beta value for the association between self-efficacy and CLS was larger than that for the other factors (number of recreational drugs used and ongoing relationship status), indicating its greater relevance to CLS in the conceptual model.

In terms of the other relationships, older age was associated with concealment of sexual identity (Beta= 0.133; p=0.001), and report of no ongoing relationship with a partner was inversely associated with concealment of sexual identity (Beta= -0.169; p=0.002) i.e. being in an ongoing relationship was associated with concealment. Concealment of sexual identity was associated with less frequent visits to gay venues (Beta= 0.702; p<0.001), and this relationship produced the largest Beta value in the model. Reporting no ongoing relationship with a partner (Beta= -0.374; p<0.001) and less frequent visits to gay venues (Beta= -0.140; p<0.001) was associated with lower levels of a supportive network. Less frequent visits to gay venues was associated with lower levels of recreational drugs used (Beta= -0.115; p=0.001). Finally, older age was inversely associated with report of no ongoing relationship with a partner (Beta= -0.109; p=0.008) i.e. younger age was associated with not being in an ongoing relationship, having been born outside of the UK was associated with higher educational attainment (Beta= 0.261; p=0.003), and higher educational attainment was associated with less financial insecurity (Beta= -0.312; p<0.001).

Age was not associated with CLS or number of recreational drugs used. Number of recreational drugs used was not associated with self-efficacy for sexual safety. These non-significant pathways were not removed from the model since these relationships were hypothesized *a priori*, and the model fit for this conceptual model was good. However, these non-significant pathways were further explored in two ways. First, other categorizations of age and recreational drug use were investigated. Neither a categorical nor dichotomous version of age groups was associated with CLS with one or more partners (0.017; p=0.423, and 0.057; p=0.571 respectively) or levels of recreational drugs use (-0.006; p=0.713, and -0.084; p=0.316 respectively). All other model estimates remained the same and the model fit was unchanged. The association with self-efficacy for sexual safety remained non-significant when investigating the number of recreational drugs used in four categories, poly-drug use, chemsex-drug use, and club-drug use. The model estimates for the association with depressive symptoms and CLS with one or more partners in Figure 17 did not appear particularly sensitive to changes in recreational drug use measures. All other model estimates remained the same, although older age was inversely associated with club-drug use (-0.137; p<0.001), and the model fit was unchanged. Second, two additional indirect pathways that were hypothesized prior to model refitting were investigated. Findings are described in the mediational analysis section below.

Figure 17: Structural equation model of the link between depression and CLS with one or more partners in AURAH



6.3.4 Mediational analysis

When investigating factor scores from the depression factor analysis and self-efficacy factor analysis in a modified Poisson regression model in Stata, in an unadjusted model, the PR for the association between depression scores and CLS with one or more partners was 1.03 (95% CI: 1.01, 1.06) with a p-value of 0.002. In an unadjusted SEM with only the depression factor analysis and a link specified between depression and CLS with one or more partners, the p-value was <0.001 (Beta= 0.141). After adjusting for self-efficacy scores in the Poisson model, the association between depression scores and CLS with one or more partners was 1.00 (95% CI: 0.98, 1.02) with a p-value of 0.916. Similarly, including self-efficacy for sexual safety in the SEM with a link specified between depression and self-efficacy and self-efficacy and CLS, the p-value for the direct effect of depression on CLS with one or more partners was 0.496 (Beta= 0.028). Therefore, both the Poisson model and SEM indicate that after adjusting for self-efficacy for sexual safety there is no direct association between depression and CLS with one or more partners, suggesting that self-efficacy confounds this association. This causal steps approach to mediation, as investigated in the previous chapter, can go no further. SEM however, provides us with an additional piece of information, which gives evidence as to whether self-efficacy is on the causal pathway i.e. whether self-efficacy mediates this association (see Chapter 3 section 3.4.2). The p-value for the indirect effect of depression on CLS with one or more partners was <0.001 (Beta= 0.113).

When investigating the hypothesis-driven model depicted in Figure 16, depression was associated with CLS indirectly through lowered self-efficacy for sexual safety (Beta= 0.163 95% CI: 0.113, 0.213, S.E. 0.025, z-score=Est/S.E. 6.387, p<0.001). It is of note, that when including an additional direct link between depression and CLS in the model, the p-value for the indirect effect remained the same (Beta= 0.162) and the p-value for the direct effect was 0.970 (Beta= 0.002).

In addition, concealment of sexual identity was associated with depression indirectly through less frequent visits to gay venues and lower levels of a supportive network (0.059 95% CI: 0.022, 0.096, S.E. 0.019, Est/S.E. 3.107, p=0.002). Less frequent visits to gay venues was also associated with less depression indirectly through lower levels of recreational drug use (-0.021 95% CI: -0.035, -0.007, S.E. 0.007, Est/S.E. -2.959, p=0.003). Higher educational attainment was associated with less depression indirectly through greater financial security (-0.128 95% CI: -0.167, -0.089, S.E. 0.020, Est/S.E. -6.451, p<0.001). Of note, in an additional analysis, older age (continuous variable) was associated with lower levels of recreational use via concealment of sexual identity and less frequent visits to gay venues (-0.011 95% CI: -0.021, -0.002, S.E. 0.005, Est/S.E. -2.337, p=0.019) and to be inversely associated with CLS with one or more partners via concealment of sexual identity, less frequent visits to gay venues, and lower levels of recreational drug use (-0.002 95% CI: -0.004, <0.001, S.E. 0.001, Est/S.E. -2.074, p=0.038). The model fit was unchanged in this additional analysis.

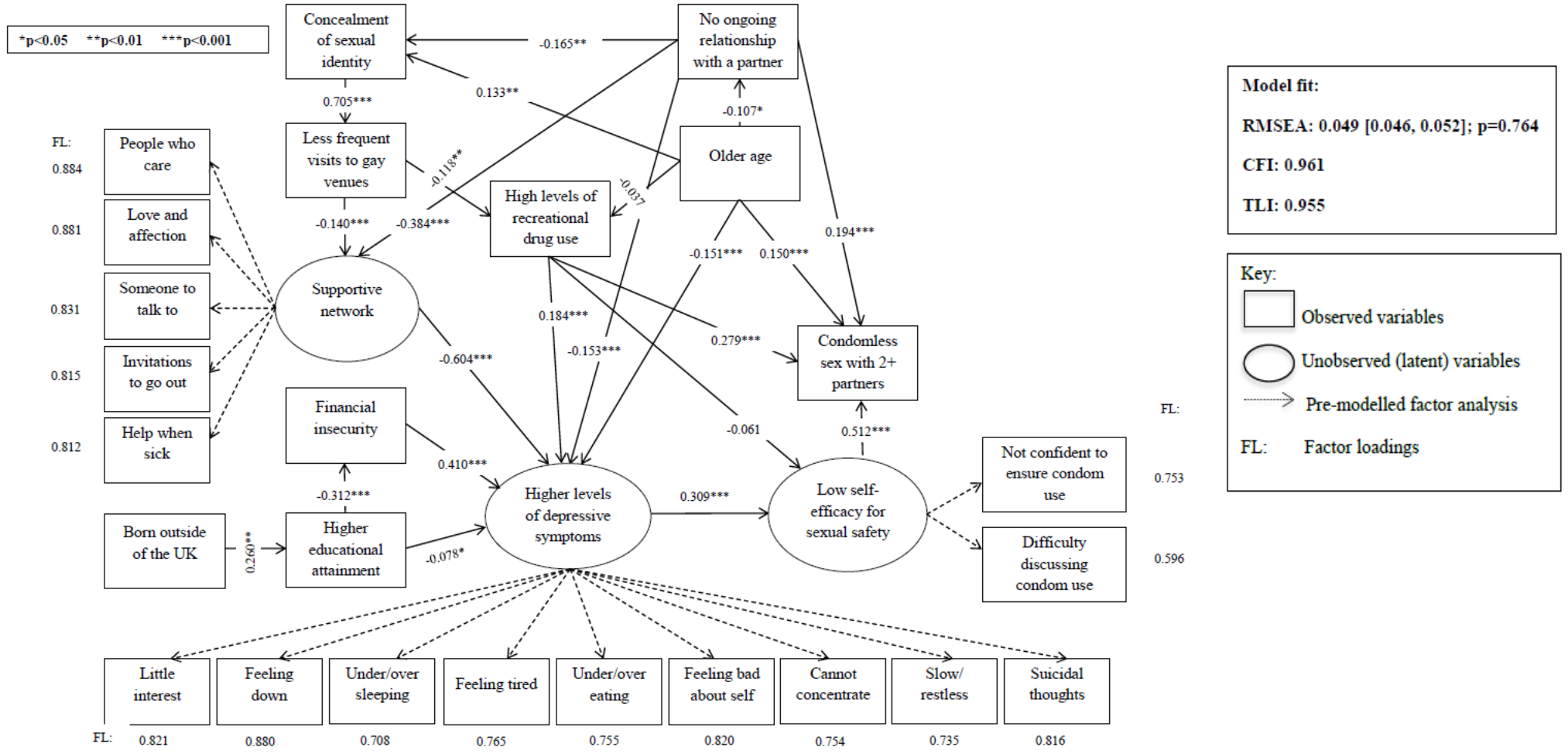
As shown in Table 16, for each CLS measure, the conceptual model fit the data well and low self-efficacy for sexual safety was found to significantly mediate the association with depression. For each CLS measure, the pattern of associations was similar and each meditational analysis was significant. The differences observed were as follows: older age and not being in an ongoing relationship was associated with all three CLS measures and greater number of recreational drugs used had a borderline association with report of receptive CLS with an unknown status partner. Figure 18 presents findings for CLS with two or more partners.

Table 16: Goodness of fit and mediational analysis findings when including other CLS measures in the conceptual model, in AURAH

CLS-related activity in the past three months	RMSEA	CFI	TLI	Estimate 95% CI; S.E.; Est./S.E.; p-value for indirect effect of depression on CLS, mediated by low self-efficacy for sexual safety
CLS with two or more partners	0.049 [0.046, 0.052]; p=0.764	0.961	0.955	0.158 95% CI 0.106, 0.211; 0.027; 5.893; <0.001
CLS with an unknown/HIV+ status partner[a]	0.049 [0.046, 0.052]; p=0.713	0.960	0.955	0.190 95% CI: 0.134, 0.247; 0.029; 6.639; <0.001
Receptive CLS with an unknown status partner	0.049 [0.046, 0.052]; p=0.712	0.960	0.954	0.168 95% CI 0.105, 0.231; 0.032; 5.260; <0.001

[a] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

Figure 18: Structural equation model of the link between depression and CLS with two or more partners in AURAH



6.3.5 Testing for moderating effects

When investigating CLS with one or more partners, CLS with two or more partners, and CLS with an unknown/HIV-positive status partner, there was a significant indirect effect for men who did not report poly-drug use and for men who did report poly-drug use, and the difference in strength for the indirect effect was not significant between groups (Table 17). The same pattern was found when stratifying by men who reported chemsex-drug use and men who did not, and by men who reported club-drug use and men who did not. When investigating receptive CLS with an unknown status partner, there was a significant indirect effect for men who did not report poly-drug use, but not for men who did report poly-drug use, although the difference in strength for the indirect effect was not significant between groups. The same pattern was found when stratifying by chemsex-drug use, and a significant indirect effect was found for men who did report club-drug use. The indirect effect of depressive symptoms on CLS through self-efficacy for sexual safety did not appear to be different among men who took recreational drugs and men who did not.

Table 17: Indirect effect of depression on CLS among men who reported recreational drug use and men who did not, in AURAH

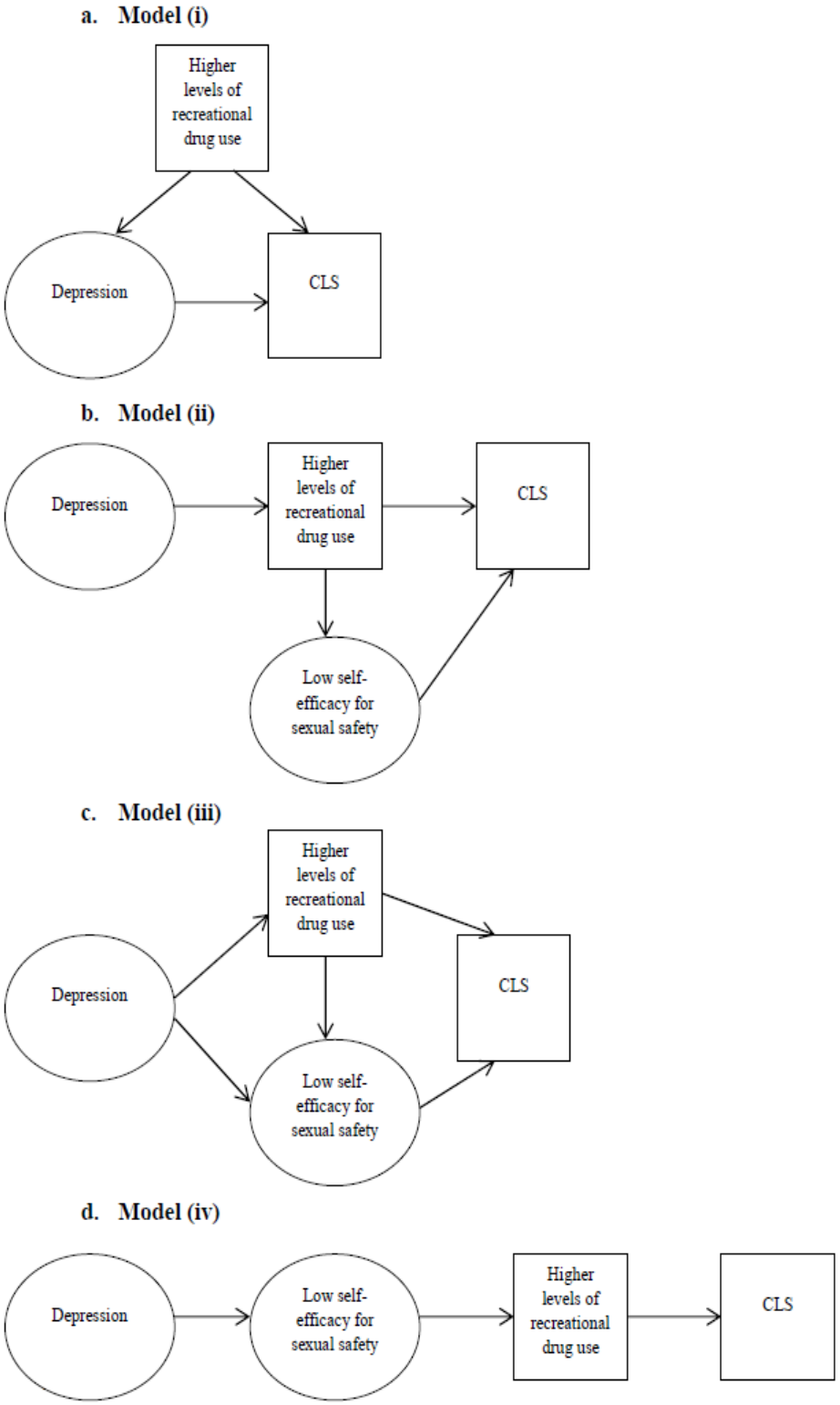
CLS-related activity in the past three months	No poly-drug use Parameter p-value	Poly-drug use Parameter p-value	Difference in strength for indirect effect p-value	No chemsex-drug use Parameter p-value	Chemsex-drug use Parameter p-value	Difference in strength for indirect effect p-value	No club-drug use Parameter p-value	Club-drug use Parameter p-value	Difference in strength for indirect effect p-value
CLS with one or more partners	0.115 <0.001	0.195 0.005	-0.080 0.272	0.125 <0.001	0.192 0.004	-0.067 0.347	0.121 <0.001	0.207 0.001	-0.085 0.217
CLS with two or more partners	0.119 <0.001	0.142 0.008	-0.022 0.711	0.128 <0.001	0.183 0.003	-0.055 0.417	0.112 <0.001	0.196 0.002	-0.084 0.224
CLS with an unknown/HIV+ status partner[a]	0.162 <0.001	0.168 0.008	-0.005 0.939	0.162 <0.001	0.226 0.003	-0.064 0.448	0.159 <0.001	0.224 0.001	-0.065 0.406
Receptive CLS with an unknown status partner	0.169 <0.001	0.069 0.089	0.100 0.098	0.159 <0.001	0.091 0.070	0.068 0.309	0.167 0.001	0.114 0.024	0.053 0.446

[a] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

6.3.6 Exploratory analysis

Figure 19 presents the four alternative causal pathways between depressive symptoms and CLS with one or more partners investigated. In exploratory model (i), higher levels of depressive symptoms were associated with CLS directly (0.164; p<0.001). In exploratory model (ii), higher levels of recreational drug use were associated with low self-efficacy for sexual safety (0.379; p<0.001), and higher levels of depressive symptoms were associated with CLS indirectly via higher levels of recreational drug use (0.047 95% CI: 0.011, 0.083, S.E. 0.018, Est/S.E. 2.543, p=0.011). In exploratory model (iii), higher levels of depressive symptoms were associated with CLS indirectly via low self-efficacy for sexual safety (0.156 95% CI: 0.107, 0.205, S.E. 0.025, Est/S.E. 6.229, p<0.001) and at the same time, indirectly via higher levels of recreational drug use (0.032 95% CI: 0.014, 0.051, S.E. 0.009, Est/S.E. 3.476, p=0.001). In exploratory model (iv), low self-efficacy for sexual safety was associated with higher levels of recreational drug use (0.453; p<0.001), and higher levels of depressive symptoms were associated with CLS indirectly via low self-efficacy for sexual safety and higher levels of recreational drug use (0.072 95% CI: 0.046, 0.099, S.E. 0.013, Est/S.E. 5.391, p<0.001).

Figure 19: Exploratory models with altered causal pathways between depressive symptoms and CLS with one or more partners[a], based on data from AURAH



[a] It is of note, that these exploratory models also include all of the other pathways specified in Figure 15 i.e. including the other factors hypothesized to be associated with depressive symptoms, recreational drug use, and CLS.

Table 18 presents a comparison of the model fit indices between the hypothesis-driven conceptual model, depicted in Figure 16, and exploratory models (i) to (iv), whereby model (iii) (Figure 19c) appeared to be marginally more consistent with the data.

Table 18: Comparing model fit indices of models with differing causal pathways between depressive symptoms and CLS with one or more partners, in AURAH

Models (in order of better model fit)[a]	RMSEA	CFI	TLI
Exploratory model (iii) (Figure 19c)	0.048 [0.045, 0.051]; p=0.875	0.962	0.957
Hypothesis-driven model (Figure 16)	0.049 [0.046, 0.052]; p=0.730	0.961	0.955
Exploratory model (i) (Figure 19a)	0.051 [0.048, 0.054]; p=0.341	0.963	0.958
Exploratory model (ii) (Figure 19b)	0.054 [0.051, 0.057]; p=0.011	0.951	0.945
Exploratory model (iv) (Figure 19d)	0.054 [0.051, 0.057]; p=0.007	0.951	0.944

[a] Ranked according to the RMSEA first. Although relative model fit statistics (information criterion statistics; AIC, BIC, and ABIC) do exist and are commonly used for model comparison, these indices cannot be estimated for models with categorical variables, which use a weighted least squares estimator.

It is of note, based on findings from this exploratory analysis, higher levels of recreational drug use were associated with low self-efficacy for sexual safety only in models not adjusted for depression (exploratory models (ii) and (iv)). It appears that depression may confound this association. Accordingly, it was investigated, in the hypothesis-driven model (Figure 16), whether higher levels of recreational drug use were associated with low self-efficacy for sexual safety indirectly via depression. The indirect effect was significant (0.052 95% CI: 0.030, 0.074, S.E. 0.011, Est/S.E. 4.621, p<0.001; the model fit was the same as that in Figure 17.

6.4 Discussion

6.4.1 Summary of results

The conceptual model investigated in this chapter, using SEM, was found to be consistent with AURAH data. Findings provide support for the thesis hypothesis that depression is associated with CLS (including CLS with multiple partners and partners of an unknown/HIV-positive status, and receptive CLS with unknown status partners) indirectly via lowered self-efficacy for sexual safety. When exploring the effects of altering the causal pathway, the model fit was marginally improved when depression was considered to lead to CLS indirectly via higher levels of recreational drug use as well as indirectly via low self-efficacy for sexual safety. Removing the indirect effect via low self-efficacy for sexual safety reduced the model fit. The indirect association was also apparent among men who did not report poly-, chemsex-, and club-drug use. These findings suggest that the indirect effect is not primarily due to higher levels of recreational drug use. Although low self-efficacy and recreational drug use may both play a role in the causal pathway between depression and CLS, specifying an indirect effect via low self-

efficacy and then higher levels of recreational drug use, reduced the model fit (although the indirect effect remained significant). These findings suggest that there are in fact two distinct indirect effects whereby depression is associated with CLS either by lowering one's self-efficacy for sexual safety or by leading to higher levels of recreational drug use. These results add to the analysis described in Chapter 5, as indirect effects could not be directly tested using Poisson regression analysis.

6.4.2 Comparing AURAH findings to other studies investigating the indirect effect of depression on CLS through self-efficacy for sexual safety

As described in Chapter 2 section 2.4.8, one high-income country study has investigated whether the relationship between depression and CLS is mediated by other psychological vulnerabilities and dysfunctional coping processes, using baseline data from Project MIX (see section 2.4.1.3) [(362)]. In all analyses, age, income, education level, ethnicity, HIV status and research site were adjusted for. The investigators found that higher levels of depression were associated with higher cognitive escape tendencies[xxx] (*F*=152.96, *p<0.001*), higher levels of avoidant coping[xxxi] (*F*=396.42, *p<0.001*), and lower levels of self-efficacy for sexual safety[xxxii] (*F*=32.12, *p<0.001*). Furthermore, low self-efficacy for sexual safety (*F*=41.71, *p<0.001*) and cognitive escape tendencies (*F*=6.69, *p<0.05*) were associated with higher numbers of CLS partners of unknown or HIV sero-different status in the past three months, when adjusting additionally for depression. In order to investigate the significance of mediation, the authors used the PRODCLIN program, which computes tables of critical values to create asymmetrical confidence intervals based on the distribution of the product of two factors [(652)], a method similar to the difference of coefficients method and the product of coefficients method described in section 3.4.2 of Chapter 3. This mediational analysis did not take place in the framework of SEM. Consistent with findings in this chapter however, low self-efficacy for sexual safety and cognitive escape tendencies were found to mediate the association between depression and sexual risk behaviour- the confidence intervals produced in PRODCLIN did not include the value 0.

In Project MIX, a composite measure of low self-efficacy for sexual safety and/or cognitive escape tendencies was also investigated and found to significantly mediate the association. When controlling for this composite measure in the model, depression was no longer associated with CLS [(362)]. Similarly, in this chapter, the total effect of depressive symptoms on CLS with one or more partners was equal to the indirect effect since the direct effect was equal to 0. Although it was not possible as part of the AURAH study to investigate markers of cognitive escape tendencies, recreational drug use was also found to mediate the association between

[xxx] On a 7-item scale previously developed by the authors to specifically assess the use of drugs and sex to cognitively escape i.e. 'When I am high or drunk I am more likely to want to have anal sex with a man'.
[xxxi] Mean score on the Behavioural Disengagement subscale of COPE.
[xxxii] On a 7-item scale designed to investigate participants' confidence in their ability to practice safer sex i.e. 'I am confident that I can have safer sex even if my partner doesn't want to; disagreeing that they could be 'sexually safe' on four or more items was considered to indicate low self-efficacy for sexual safety.

depression and CLS. As described in section 2.6.3.2, recreational drug use may directly lead to sexual risk-taking via autonomic or central nervous system mechanisms that increase sexual arousal and disinhibition, or indirectly by inducing a state of cognitive release and escape from rational self-awareness [397, 597].

It is of note, in another study, self-efficacy[xxxiii] has also been found to partially mediate the association between depressive symptoms (CES-D>16) and CLS in the past six months among MSM residing in one of seven Cape Town townships in South Africa (N=316). A Sobel test (see section 3.4.2) was used and was controlled for age, income and education. The sample reported high levels of alcohol and drug use and a high number of sexual partners [699]. The fact that results are consistent in different geographical settings is re-assuring in terms of trying to establish a causal link.

6.4.3 Comparing AURAH findings to other studies investigating depression among MSM using SEM

One U.S. and one UK study have previously employed SEM to study depression among sexual minority individuals. In a SEM using data from the Bareback Project (see section 2.4.1.4), it was hypothesized that depression was directly and indirectly associated with sexual risk behaviour via attitudes toward condom-use (based on a modified version of Brown's 1984 scale). The model was said to fit the data well. The direct effect of depression on sexual risk behaviour was not significant (coefficient not reported; *p=0.246*). However, depression was significantly associated with more negative attitudes towards condom-use (-0.15; *p=0.005*) and more positive attitudes towards condom-use were significantly associated with a greater proportion of sexual acts that were protected by a condom in the past month (0.29; *p<0.001*). Results from the meditational analysis were not reported perhaps due to the small sample size (N=332). The authors stated that they used applicable items from Brown's (1984) scale [700], which may include for example, the following statements: 'I would be comfortable suggesting that my partner and I use a condom', 'Condoms are unreliable', and 'Condoms are pleasant to use'. Lower scores across items used indicated lower interest in using condoms to keep one's self sexually safe. Since higher levels of depression were associated with lower condom attitude scores, which was in turn associated with more sexual risk behaviour, these findings appear to be similar to those found in the AURAH study.

The Avon Longitudinal Study of Parents and Children recruited a consecutive sample of pregnant women attending care in Avon (N=3710) and collected data from their children up to age 18. In a SEM, it was hypothesized that sexual minority status was associated with problem alcohol use indirectly via depressive symptoms (on the Short Mood and Feelings

[xxxiii] Based on scores from the following statements: 'Someone can talk me out of using condoms by telling me they love me', 'I find it difficult to tell a male sex partner that I want to use condoms', 'Someone can talk me out of using condoms by telling me they are HIV-negative', and 'I find it difficult to insist that condoms are used if I have very strong feelings for the man I am going to have sex with'.

Questionnaire). This indirect mechanism was significant (*Z*=3.2, *p=0.001*). Although sexual minority status may be associated with depression (see section 1.8.1), evidence from AURAH suggests that, among MSM specifically, concealment of sexual identity is also associated with depression indirectly through less frequent visits to gay venues and lower levels of a supportive network. Depressive symptoms were also associated with recreational drug use in the AURAH study.

6.4.4 Other socio-demographic and psychosocial factors associated with sexual behaviour

Based on findings from review (ii) of this thesis (section 2.5.4) [118, 477, 482, 489, 512, 563] [563] and other studies in high-income countries [491, 574-577], it was hypothesized that younger age would be associated with CLS measures among sexual minority men in the AURAH study. Similar to findings from univariable analysis in the previous chapter, age (continuous, categorical, and dichotomous measures) was not associated with CLS with one or more partners in a SEM adjusted for relationship status, recreational drug use, and self-efficacy. However, upon further investigation younger age was found to be associated with CLS indirectly via a greater tendency to be 'out' with one's sexual orientation, be active on the gay scene and be using higher levels of recreational drugs. Again, similar to the previous chapter, older age was found to be directly associated with CLS with two or more partners, CLS with partners of an unknown/HIV-positive status, and receptive CLS with unknown status partners in SEM. Differences between studies may reflect different recruitment sites, inter-city differences, and different measures of sexual behaviour.

Furthermore, as in the previous chapter, in the SEM, not being in an ongoing relationship with a partner was associated with less CLS, and this is in line with that previously observed in the UK [482, 496, 510]. In the SEM, not being in an ongoing relationship was associated with CLS with multiple partners. This association has been investigated in one other UK study of MSM [512], which failed to find a link in unadjusted analysis.

Finally, as has been previously observed in the UK [511] [478, 484, 509] and other high-income countries [397, 585-600], higher levels of recreational drug use were associated with CLS measures in the SEM (as in Poisson models in the previous chapter). Based on the Beta standardized estimates, however, low self-efficacy for sexual safety was a more 'important' factor for CLS than drug use.

6.4.5 Socio-demographic and pscyhosocial factors associated with depressive symptoms

The same associations with depression as that observed in the previous Poisson analysis presented in Chapter 4 and in previous studies (including theoretical studies of sexual minority stress) of MSM in high-income countries (see sections 1.6 and 2.6.3.1- 2.6.3.2) were also found in the SEM in this chapter. The exception to this was the association observed with ongoing

relationship with a partner in SEM. Although not being in an ongoing relationship with a partner was associated with lower levels of a supportive network, which was in turn associated with more depression, there also appeared to be a direct association between no ongoing relationship with a partner and less depression. Unfortunately, it was not possible to investigate whether the association between ongoing relationship with a partner and depressive symptoms was different among men with a supportive network and men without, since supportive network was an unobserved variable and testing for moderation in SEM requires the effect-modifier to be an observed categorical variable. Using data from the same sample of men, by use of standard interaction χ^2 tests, it was investigated whether the association between ongoing relationship with a partner and depressive symptoms (PHQ-9≥10) was different among men who reported higher levels of a supportive network (total score across the five questions was 20-25) and men who did not (total score<20). Although the p-values were not significant, among men with higher levels of a supportive network, men with no ongoing relationship with a partner appeared to report more depressive symptoms than men with an ongoing partner (6.3% vs. 4.8%; p=0.330). Among men with lower levels of a supportive network, men with no ongoing relationship with a partner appeared to report less depressive symptoms than men with an ongoing partner (23.6% vs. 29.2%; p=0.208). These findings suggest that men with low levels of social support despite having an ongoing stable partner may suffer worse depressive symptomatology than men with low levels of social support and no stable partner, due to the profound burden associated with an unhappy partnership. Another possibility is that IPV may be occurring within the context of an ongoing relationship, which may in turn lead to depression (as suggested in the literature [41, 605]).

Findings from the SEM also extended those observed in Chapter 4, whereby concealment of sexual identity was associated with depression indirectly through less frequent visits to gay venues and lower levels of a supportive network. Less frequent visits to gay venues was also associated with less depression indirectly through lower levels of recreational drug use, and finally, higher educational attainment was associated with less depression indirectly through greater financial security. Furthermore, it appeared that in men who reported chemsex-drug use, anhedonia (decrease in pleasure in everyday life) and poor appetite/overeating were some of the most important factors explaining the presence of depression, perhaps reflecting the direct psychological and physical effects of drug use itself.

Of note, of factors investigated to be directly associated with depressive symptoms, the largest Beta coefficient was observed for the inverse association with higher levels of a supportive network, in line with that observed in Chapter 4, and the second largest was for financial insecurity. These two factors had a considerably greater estimate of effect compared to each of the other factors included in the model (including recreational drug use). The largest Beta coefficient in the model for direct effects was that observed for the association between concealment of sexual identity and less frequent visits to gay venues.

6.4.5.1 Other hypothesized relationships

Higher levels of recreational drug use were hypothesized to lead to low self-efficacy for sexual safety, however, no such association was found in the SEM. In the AURAH study, men were asked about their current attitudes towards condom-use and use of recreational drugs in the past three months. Unlike depression, which may be chronic and affect every aspect of one's life, the psychoactive effects of drug use may be immediate and short-lived. It may be that although at the time of taking drugs one's (perceived) ability to maintain sexual safety was diminished, it was not possible to capture this phenomenon based on the measure of current attitudes towards condom-use in AURAH. However, findings from the exploratory analysis also shed light on the lack of association observed; higher levels of recreational drug use may be associated with low self-efficacy for sexual safety indirectly via depression. This finding reflects the importance of the role that depression most likely plays in self-efficacy for sexual safety.

Younger age was hypothesized to lead to higher levels of recreational drug use, but no such association was found in the SEM. However, based on findings from an additional analysis, younger age was associated with higher levels of recreational drug use via less concealment of sexual identity and more frequent visits to gay venues. Findings from the model where club-drug use was investigated as the measure of recreational drug use reiterate these findings, as younger age was directly associated with club-drug use. Of note, this is in line with that found in a study of U.S. MSM of black ethnicity (recruited online 2012-2014), whereby younger MSM (≤29 years of age) were more likely than older MSM (≥30 years of age) to identify as gay, homosexual, same gender loving, or bisexual [(373)].

Furthermore, although not hypothesized, reporting no ongoing relationship with a partner was associated with less concealment of sexual identity, even after adjusting for age. This is a surprising finding, which may reflect the fact that the gender of the partner was not specified. Perhaps men who reported a female partnership were less likely to disclose being gay, bisexual and/or attracted to men. However, there may certainly be other interpretations, for instance, being in an ongoing partnership with a man may for some individuals create an additional psychological barrier to coming out as it entails not only disclosure of one's sexual orientation but also one's life choices.

Finally, contrary to what was hypothesized, having been born outside of the UK was associated with higher educational attainment. This may not be surprising however, given that the majority of men were residing in London (75.9%) and may represent a select group of migrants of higher socio-economic status who were seeking job opportunities in London.

6.4.6 Limitations

The general methodological limitations of the AURAH study are discussed in section 3.7.1 of Chapter 3. In this specific analysis, it is important to note that depression was treated as an unobserved variable, however, there is evidence to suggest that the PHQ-9 measures depression quite accurately (see section 3.3.2.1). Nevertheless, there are many different scales to measure symptoms of depression (see section 2.4.2). Therefore, despite the possible limitations, depressive symptoms were considered to be latent.

Issues surrounding temporality in cross-sectional study designs are discussed in section 5.4.9. DAGs represent so-called 'recursive models', which use unidirectional arrows to show the direction of causation. Bidirectional relationships (including feedback loops) are not conventionally depicted, and if they were, this model would then be considered 'non-recursive'. Although non-recursive models may be theoretically plausible, they most often produce estimation problems in the framework of SEM, and in many cases are simply inestimable. Interest in using DAGs in epidemiology began to rise in the early 21St Century due to their use in formalizing certain types of biases and ease in representing recursive models for SEM. However, there are limitations that come hand-in-hand with the rule-bound nature of DAGs [(701)]. It is often only the use of scientific theories which are used to conceptualise the causal relationships hypothesized. DAGs cannot themselves provide insight into whether a phenomenon is conceptualized appropriately. Therefore, it is possible, especially in the social and behavioural sciences, that the hypothesized causal sequence may operate in the other direction, with implications for intervention [(701)]. The DAGs presented in this Chapter assume one direction but see Chapter 3 section 3.5 for a description of which associations are assumed to be bidirectional.

AURAH did not collect information on markers of cognitive escape coping and as such it was not possible to assess the role of this psychological construct in the causal pathways leading to CLS. Finally, there will inevitably be measurement error when attempting to capture psychosocial phenomenon on the AURAH questionnaire. Measurement error may have affected the estimated strength of the associations and as a result, the relative magnitude of one association versus another. However, it is reassuring that similar associations were found in other studies which investigated measures of self-efficacy for sexual safety.

6.4.7 Summary of discussion

Presented in this chapter is the first SEM to investigate a conceptual model of hypothesized causal links between socio-demographic, psychosocial, and sexual behaviour measures among sexual minority men. It is also the first analysis in the UK to investigate possible mechanisms of effect for the relationship between depressive symptoms and sexual risk behaviour. Findings support evidence from three studies (Project MIX [(362)], study of Cape Town MSM [(699)], the Bareback Project [(346)]) that depressive symptoms are associated with CLS indirectly via low self-

efficacy for sexual safety. Findings from AURAH also suggest that depressive symptoms may additionally be associated with CLS indirectly via higher levels of recreational drug use- albeit to a lesser extent, since low self-efficacy for sexual safety appears to be a more 'important' factor leading to CLS.

Using Poisson regression models in the previous chapter, recreational drug use was consistently associated with CLS measures, in line with that found in other high-income country studies of MSM. In addition, using SEM in this chapter, younger age was associated with CLS indirectly via a greater tendency to be 'out' with one's sexual orientation, be active on the gay scene and be using higher levels of recreational drugs.

Using Poisson regression models in the previous chapter, younger age, non-university degree education, financial insecurity, lower levels of a supportive network, and greater number of recreational drugs used were strongly associated with depressive symptoms, in line with that found in other high-income country studies of MSM. In addition, using SEM in this chapter, the type of depressive symptoms reported by men who engaged in chemsex-drug use and men who did not was found to differ. Furthermore, although a sexual minority status may be stressful, findings from the SEM suggest that higher levels of disclosure of one's sexual orientation may be protective against mental health problems. Concealment of sexual identity was found to be associated with depression indirectly through less frequent visits to gay venues and lower levels of a supportive network. At the same time, however, less frequent visits to gay venues was also found to be associated with less depression indirectly through lower levels of recreational drug use. Younger age was found to be associated with higher levels of recreational drug use via less concealment of sexual identity and more frequent visits to gay venues. Finally, findings also suggest that being in an ongoing relationship with a partner may lead to higher or lower levels of depressive symptoms, depending on the reported level of support from other individuals in one's life. A supportive network may be the most 'important' factor for depression, alongside socio-economic disadvantage.

The implications of these complex pathways for possible intervention are discussed in the final conclusion chapter of this thesis.

Chapter 7

7 Prevalence of depressive symptoms and associated factors among gay, bisexual, and other men who have sex with men in the PROUD trial

7.1 Introduction

The PROUD trial enrolled HIV-negative men who reported CLS in the previous three months and were of the opinion that they would have CLS in the next three months. In order to measure depressive symptoms, the PHQ-9 scale was incorporated into the baseline and annual questionnaires. It was of interest in this thesis to see whether an investigation of depressive symptoms on PHQ-9 among men in the PROUD trial would elicit similar findings to the AURAH study, given the somewhat differing behavioural profiles of these studies. As a longitudinal study, PROUD also provides the opportunity to investigate changes in depression prevalence over time. Furthermore, unlike in AURAH, as part of the annual PROUD questionnaire, psychosocial data, including that on internalized homophobia, age at anal sex debut (sex at a very young age may include experiences of childhood sexual abuse [CSA]), and intimate partner violence (IPV), was collected. Therefore, PROUD additionally allows an investigation into the association between a marker of internalized homophobia, a very young age at anal sex debut, and IPV with depressive symptoms, factors which are considered to be of importance with regards to mental health among sexual minority men. The aim of this chapter was to investigate the prevalence of depressive symptom measures on PHQ-9 and socio-demographic, lifestyle, and psychosocial factors associated with depressive symptoms across study time-points in the PROUD trial.

7.2 Statistical methods

A detailed description of the variables investigated for analyses presented in this Chapter is included in Chapter 3 section 3.3.6.

The prevalence of each individual PHQ-9 symptom is presented for PROUD participants at baseline, month-12 and month-24. The prevalence of depressive symptoms according to PHQ-9 criteria (≥10, major depressive syndrome, major and other depressive syndromes [including major depression and dysthymia] and suicidal ideation) was investigated in each PROUD trial arm and time-point. Prevalence was compared across trial arms at each time-point using χ^2 tests and across time-points using McNemar's χ^2 test to account for correlated responses. The prevalence of antidepressant use at baseline was also assessed (see section 3.3.7.1). In order to more accurately present the prevalence of men with depression who were receiving antidepressant medication, men with either depressive symptoms (PHQ-9≥10) or who reported

antidepressant use at baseline were considered to account for all men with any evidence of current depression at baseline, since treatment in the absence of symptoms may indicate successfully treated depression.

The cross-sectional association of socio-demographic and lifestyle factors (see section 3.3.10) with depressive symptoms (PHQ-9≥10) at baseline was assessed using χ^2 tests, χ^2 tests for trend, and Fisher's exact test (when expected numbers were small) for univariable analysis, and modified Poisson regression with a robust variance estimator in order to produce adjusted prevalence ratios [645]. Associations were adjusted for key socio-demographic factors (see section 3.6.8). The cross-sectional association of psychosocial factors with depressive symptoms (PHQ-9≥10) at the 12- and 24-month questionnaires was assessed using χ^2 tests, χ^2 tests for trend, and Fisher's exact test. Adjusted associations were not investigated since many psychosocial measures had very small cell counts.

Poisson GEEs were also used in this Chapter (see section 3.6.7) to assess the cross-sectional association of factors with depressive symptoms, including all data points from the baseline, 12- and 24-month questionnaire, allowing for correlation between responses across time-points for each individual. The main advantage of this approach is that power is increased, as all data points are utilised in a single model. In GEE models, depressive symptoms (PHQ-9≥10) were investigated as the main time-varying dependent variable. For a description of the way in which values at each time-point were used for independent variables in GEE models, see section 3.6.8. Associations are presented unadjusted and adjusted for key socio-demographic factors (see section 3.6.8); including study time-point due to the observed change in depressive symptom prevalence over time in PROUD. A sensitivity analysis was undertaken using different PHQ-9-based definitions of depressive symptoms (major depressive syndrome and major and other depressive syndromes) as time-varying dependent variables in GEE models.

The final section of this chapter was dedicated to assessing the association of factors with the change in prevalence of depressive symptoms from baseline to the 12-month questionnaire. Four analyses were performed. In the first analysis, unadjusted associations between socio-demographic, lifestyle, and psychosocial factors with change in depression scores from baseline to the 12-month questionnaire were investigated. The distribution of change in depression scores was approximately normal, it was therefore decided that comparing mean change scores between groups was appropriate and had more interpretative value than medians. A two-sample t-test, specifying unequal variances where necessary, was performed. In the second analysis, unadjusted associations between socio-demographic, lifestyle, and psychosocial factors with incidence of depressive symptoms (PHQ-9≥10) at the 12-month questionnaire among men who scored <10 on the PHQ-9 at baseline, were investigated. Associations were assessed using χ^2 tests, χ^2 tests for trend, and Fisher's exact test. During the process of discussing findings with the PROUD study team, it became apparent that after the

enrolment date of April 2013, participants were asked to disclose their response to the suicidal ideation question on the PHQ-9 ('Thoughts that you would be better off dead, or of hurting yourself in some way') to their enrolling clinician. This was as a result of one man taking his life during the course of study. Due to this change in reporting policy, in the third analysis, it was examined whether the prevalence of suicidal ideation and depressive symptoms (PHQ-9≥10) changed significantly after April 1st 2013.

Finally, given the findings of this chapter and the common practice of Patient and Public Involvement (PPI) in aiding the interpretation of PROUD findings, a short PPI survey was designed and distributed to PROUD participants. The survey presented key findings and asked participants to help us interpret the data through the lens of their experience. The advantage of being able to ask participants to give their views on study results is that they are able to comment having had direct experience of being enrolled in the study and using PrEP. The link to the PPI survey (via survey monkey) was incorporated into an email, which explained the findings and the purpose of the survey, see Appendix section 11.19 Textbox 7, and was sent to all PROUD participants who voluntarily signed up to the mailing list (N=157; 28.9%). The survey asked for comments on different sets of findings, see Appendix 11.19 Textbox 8; the first concerned the change in prevalence of depressive symptoms over the first year of the study, and the final two concerned the relationship found between depressive symptoms and measures of sexual behaviour. The latter two questions will be presented and described in detail in Chapter 8. A thematic analysis approach was used to analyse and summarize PPI responses. A thematic analysis method involves sorting each response into different groups (numerically coded) that more succinctly describe the data. The different codes are then analysed and themes/patterns are searched for, whereby a theme should reflect some level of meaning and (preferably) pattern within the data in relation to the research question [(702)]. Eventually, the different codes are sorted into overarching themes and sub-themes. In this analysis, the themes were identified within the explicit meaning of the data, without looking beyond what the participant had written, often referred to as a semantic approach. The social science lead of the PROUD trial, Dr Gafos, independently reviewed the participants' responses and checked whether the codes, themes, and sub-themes suggested appeared appropriate. Any discrepancies were discussed and resolved by Dr Gafos and myself. After the responses had been organised to show themes and sub-themes in the semantic content of the data, these themes were summarized and an attempt was made to theorise the significance and implications of the themes. The purpose of PPI is not to ascertain responses that are representative of all men who participated in PROUD, but to add to the researcher's perspective when interpreting findings.

7.3 Results

7.3.1 Prevalence of depressive symptom measures across trial arms and time-points

Table 19 presents the prevalence of the nine depressive symptoms on PHQ-9 for each time-point. The proportion of individuals who did not respond to each question is presented as a footnote under Table 19. As described in section 3.3.11 of Chapter 3, missing responses were considered to indicate that the symptom was not present. Identical to that reported in the AURAH study (Table 3), the most commonly experienced symptom, for at least several days over the past two weeks, was ‘feeling tired or having little energy’, followed by ‘trouble falling or staying asleep, or sleeping too much’, and ‘feeling down, depressed, or hopeless’, for all time-points.

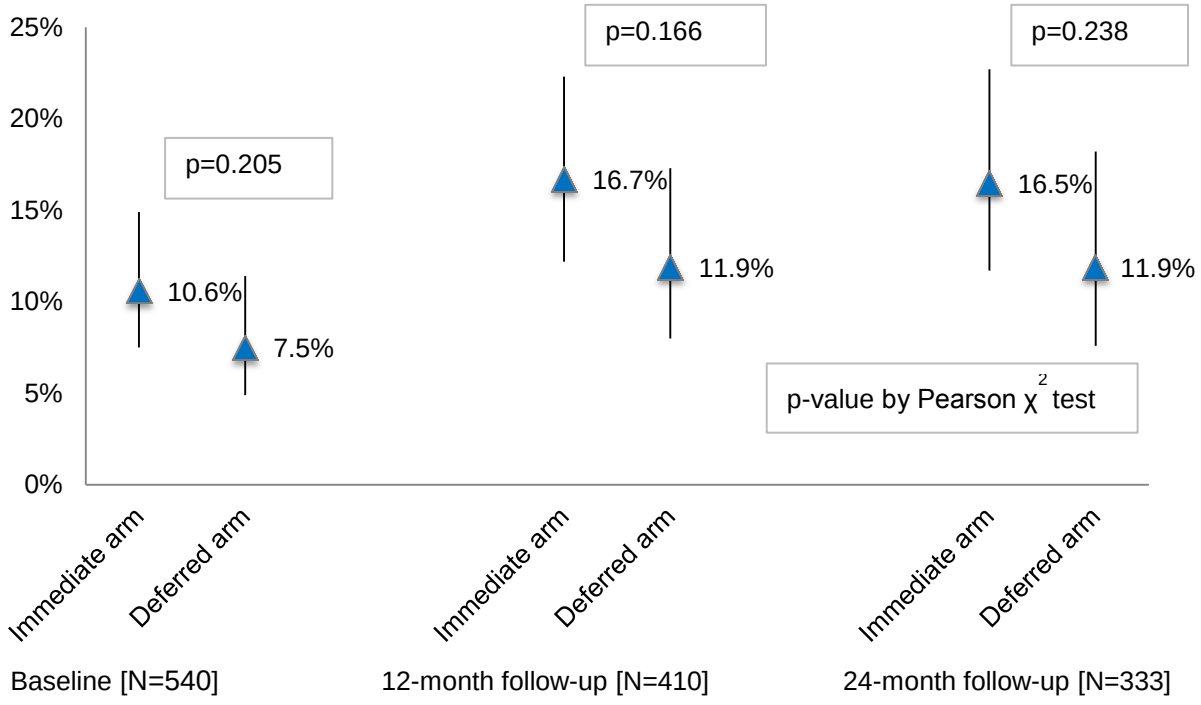
Table 19: Prevalence of PHQ-9 depressive symptoms in PROUD

	Baseline [N=540]				Month-12 [N=410]				Month-24 [N=333]			
	Not at all[a] %	Several days %	> half the days %	Nearly every day %	Not at all[a] %	Several days %	> half the days %	Nearly every day %	Not at all[a] %	Several days %	> half the days %	Nearly every day %
PHQ-9 1) Little interest or pleasure in doing things	70.2%	23.7%	3.9%	2.2%	66.1%	23.2%	7.3%	3.4%	66.4%	23.7%	5.4%	4.5%
PHQ-9 2) Feeling down, depressed, or hopeless	66.7%	25.7%	5.4%	2.2%	60.7%	28.8%	6.6%	3.9%	61.3%	27.9%	6.0%	4.8%
PHQ-9 3) Trouble falling or staying asleep, or sleeping too much	54.8%	31.1%	9.1%	5.0%	47.8%	35.4%	10.5%	6.3%	49.3%	31.8%	11.7%	7.2%
PHQ-9 4) Feeling tired or having little energy	51.5%	39.3%	5.7%	3.5%	47.3%	38.5%	10.2%	3.9%	42.6%	41.1%	8.4%	7.8%
PHQ-9 5) Poor appetite or overeating	73.2%	20.4%	3.7%	2.8%	66.3%	20.5%	9.0%	4.2%	69.1%	18.6%	7.8%	4.5%
PHQ-9 6) Feeling bad about yourself-or that you are a failure or have let yourself or your family down	70.6%	19.4%	7.6%	2.4%	67.3%	22.7%	4.6%	5.4%	68.2%	20.7%	6.0%	5.1%
PHQ-9 7) Trouble concentrating on things, such as reading the newspaper or watching television	78.3%	14.3%	4.3%	3.2%	68.8%	21.0%	5.9%	4.4%	70.0%	19.8%	5.7%	4.5%
PHQ-9 8) Moving or speaking so slowly that other people could have noticed/being so restless that it is hard to sit still	89.1%	8.0%	1.9%	1.1%	84.6%	9.8%	3.4%	2.2%	87.4%	8.4%	2.1%	2.1%
PHQ-9 9) Thoughts that you would be better off dead, or of hurting yourself in some way	89.1%	8.5%	1.7%	0.7%	88.8%	6.8%	2.9%	1.5%	84.4%	11.7%	1.8%	2.1%

[a] Includes missing responses, which were considered to indicate no such problem experienced. The proportion missing at baseline was: 4.1%, 3.9%, 3.9%, 3.9%, 4.3%, 3.9%, 4.3%, 4.1%, and 4.1% for the nine PHQ-9 questions respectively. The proportion missing at the 12-month questionnaire was: 1.2%, 1.2%, 1.7%, 2.0%, 1.7%, 2.0%, 1.2%, 1.2%, and 1.5% respectively. The proportion missing at the 24-month questionnaire was: 0.9%, 0.9%, 1.5%, 0.9%, 0.9%, 1.2%, 0.6%, 0.6%, and 0.6% respectively.

In PROUD, among the 540 men at baseline, the prevalence of depressive symptoms (PHQ-9≥10) was 9.1% (49/540). Among the 410 men at the 12-month questionnaire, the prevalence was 14.4% (59/410), and among the 333 men at the 24-month questionnaire, the prevalence was also 14.4% (48/333). The prevalence of depressive symptoms did not differ significantly between men who were randomized to immediate PrEP and men who were randomized to deferred PrEP, at any time-point, see Figure 20. There was also no difference in the prevalence of depressive symptoms at the 12-month questionnaire between men who were prescribed PrEP before the 12-month questionnaire visit (includes all men in the immediate arm and 25 men in the deferred arm) and men who were not (15.8% vs. 12.4%; Pearson χ^2 test p=0.343).

Figure 20: Prevalence of depressive symptoms (PHQ-9≥10) by trial arm and timepoint, among all men with data at each time-point in PROUD

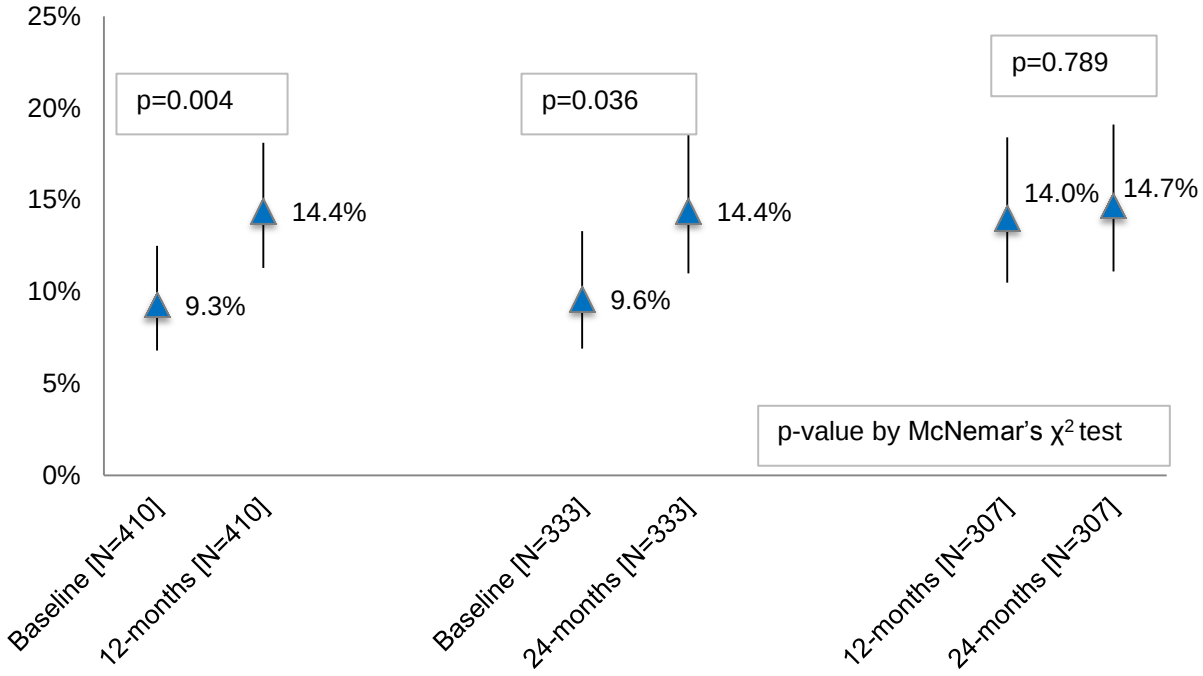


Among the 410 men who completed the 12-month questionnaire, the prevalence of depressive symptoms increased significantly from baseline to month-12, see Figure 21. Of the 38 men (9.3%) who reported depressive symptoms at baseline, 57.9% (n=22) also reported depressive symptoms at the 12-month questionnaire (i.e. persistent depressive symptoms). Of the 372 men who did not report depressive symptoms at baseline, 37 (10.0%) reported depressive symptoms at the 12-month questionnaire.

Among the 333 men who completed the 24-month questionnaire, the prevalence increased significantly from baseline to month-24. Among the 307 men who completed the 12- and 24-

month questionnaire, the prevalence of depressive symptoms was not significantly different between month-12 and 24, see Figure 21.

Figure 21: Changes in prevalence of depressive symptoms (PHQ-9≥10) over time among men with data at both time-points (randomized groups are combined) in PROUD



The prevalence of a major depressive syndrome on PHQ-9 was 5.0% at baseline, 9.0% at the 12-month questionnaire, and 8.7% at the 24-month questionnaire. The prevalence of major depression was not significantly different across trial arms at any time-point, see Table 20. The pattern of increase over time in depressive symptoms, was also observed for the measure of major depressive syndrome on PHQ-9, see Table 21. The prevalence of major and other depressive syndromes on PHQ-9 was 8.9% at baseline, 12.4% at the 12-month questionnaire, and 8.7% at the 24-month questionnaire. The prevalence of major and other depressive syndromes on PHQ-9 did not differ significantly across trial arms at any time-point, see Table 20. Although prevalence for this measure tended to be higher at month-12- and 24 compared to baseline, the changes were not statistically significant, see Table 21.

The prevalence of suicidal ideation on PHQ-9 was 10.9% at baseline, 11.2% at the 12-month questionnaire, and 15.6% at the 24-month questionnaire. The prevalence of suicidal ideation was significantly higher among men in the immediate PrEP arm than men in the deferred PrEP arm at the 12-month questionnaire, but this was not the case at the 24-month questionnaire, see Table 20. Among the 307 men who completed the 12- and 24-month questionnaires, the prevalence of suicidal ideation increased significantly from month-12 to 24, see Table 21. When investigating whether the prevalence of suicidal ideation increased significantly from the 12-

month questionnaire to the 24-month questionnaire among men in the immediate PrEP arm and men in the deferred PrEP arm separately, suicidal ideation increased significantly at month-24 in the deferred arm (McNemar's χ^2 test p=0.012) but not in the immediate arm (McNemar's χ^2 test p=0.297). The prevalence of depressive symptoms according to categories of severity is presented in Table 20 and Table 21.

Table 20: Prevalence of other PHQ-9 depression measures across trial arms among all men with data at each time-point in PROUD

	Baseline [N=540]			12-month [N=410]			24-month [N=333]		
	Immediate [N=273] n (%)	Deferral [N=267] n (%)	*p-value*[a]	Immediate [N=216] n (%)	Deferral [N=194] n (%)	*p-value*[a]	Immediate [N=182] n (%)	Deferral [N=151] n (%)	*p-value*[a]
Depression severity: None/minimal Mild Moderate Moderately severe Severe	 198 (72.5%) 46 (16.9%) 14 (5.1%) 11 (4.0%) 4 (1.5%)	 203 (76.0%) 44 (16.5%) 13 (4.9%) 5 (1.9%) 2 (0.8%)	*0.559*[b]	 148 (68.5%) 32 (14.8%) 16 (7.4%) 14 (6.5%) 6 (2.8%)	 134 (69.1%) 37 (19.1%) 11 (5.7%) 6 (3.1%) 6 (3.1%)	*0.404*	 121 (66.5%) 31 (17.0%) 16 (8.8%) 8 (4.4%) 6 (3.3%)	 103 (68.2%) 30 (19.9%) 10 (6.6%) 5 (3.3%) 3 (2.0%)	*0.796*[b]
Major depressive syndrome	17 (6.2%)	10 (3.8%)	*0.186*	23 (10.7%)	14 (7.2%)	*0.226*	20 (11.0%)	9 (6.0%)	*0.105*
Major and other depressive syndromes	28 (10.3%)	20 (7.5%)	*0.259*	31 (14.4%)	20 (10.3%)	*0.216*	27 (14.8%)	14 (9.3%)	*0.124*
Suicidal ideation	33 (12.1%)	26 (9.7%)	*0.381*	34 (15.7%)	12 (6.2%)	*0.002*	31 (17.0%)	21 (13.9%)	*0.434*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

Table 21: Changes in prevalence of other PHQ-9 depression measures over time among men with data at both time-points (randomized groups are combined) in PROUD

	Baseline N=410]	12-month [N=410]	Proportion difference between baseline and 12-month [N=410]	Baseline [N=333]	24-month [N=333]	Proportion difference between baseline and 24-month [N=333]	12-month [N=307]	24-month [N=307]	Proportion difference between 12- and 24-month [N=307]
	n (%)	n (%)	p-value[a]	n (%)	n (%)	p-value[a]	n (%)	n (%)	p-value[a]
Depression severity: None/minimal Mild Moderate Moderately severe Severe	 301 (73.4%) 71 (17.3%) 22 (5.4%) 12 (2.9%) 4 (1.0%)	 282 (68.8%) 69 (16.8%) 27 (6.6%) 20 (4.9%) 12 (2.9%)	/	 241 (72.3%) 60 (18.0%) 18 (5.4%) 10 (3.0%) 4 (1.2%)	 224 (67.2%) 61 (18.3%) 26 (7.8%) 13 (3.9%) 9 (2.7%)	/	 210 (68.4%) 54 (17.6%) 22 (7.2%) 13 (4.2%) 8 (2.6%)	 206 (67.1%) 56 (18.2%) 23 (7.5%) 13 (4.2%) 9 (2.9%)	/
Major depressive syndrome	20 (4.9%)	37 (9.0%)	*0.004*	16 (4.8%)	29 (8.7%)	*0.024*	27 (8.8%)	29 (9.5%)	*0.739*
Major and other depressive syndromes	38 (9.3%)	51 (12.4%)	*0.085*	34 (10.2%)	41 (12.3%)	*0.336*	40 (13.0%)	39 (12.7%)	*0.886*
Suicidal ideation	44 (10.7%)	46 (11.2%)	*0.777*	39 (11.7%)	52 (15.6%)	*0.102*	33 (10.8%)	49 (16.0%)	*0.014*

[a] McNemar's χ^2 test

7.3.2 Receiving antidepressant medication at baseline

Overall, the proportion of men who reported antidepressant use at baseline was 8.5% (46/540). Antidepressant use was reported by 20.4% (n=10) of the 49 men with depressive symptoms (PHQ-9≥10) and 7.3% (n=36) of the 491 men without. Among the 85 men with any evidence of current depression (PHQ-9≥10 and/or receiving antidepressant medication), 54.1% (n=46) were receiving antidepressant medication.

7.3.3 Prevalence of other psychosocial factors

The prevalence of socio-demographic factors at baseline is described in Chapter 3 section 3.2.4.1 and is presented below in Table 22. The prevalence of lifestyle/psychosocial factors is presented in Table 23 and Table 24. Of the 540 men at baseline (Table 23), 72.5% reported recent recreational drug use; the prevalence of reporting 0, 1, 2-4, or 5 or more recreational drugs in the past three months was 27.4%, 16.1%, 29.4%, and 27.0% respectively. The prevalence of chemsex-associated drug use was 42.8%. Higher-risk alcohol consumption was reported by 32.0% of men. Of the 410 men who completed the 12-month questionnaire (Table 24), the prevalence of sexualized drug use (see section 3.3.10) was 54.6%. The prevalence of anal sex debut with a male before the age of 13 years was 5.6%. In total, the prevalence of any IPV victimization and perpetration was 44.9% and 19.5% respectively. Overall, the prevalence of reporting negative views about gay sexuality, taken as a marker of internalized homophobia, was 41.7%. Finally, 48.4% of men reported having disclosed their sexual orientation to all or almost all of their close family, friends, and work colleagues, whereas, 2.3% reported having disclosed to few or none of these individuals. Similar proportions were observed among the 333 men who completed the 24-month questionnaire (Table 24).

7.3.4 Association of socio-demographic and lifestyle factors with depressive symptoms (PHQ-9≥10) at baseline

Table 22 presents the unadjusted and adjusted associations of socio-demographic factors with depressive symptoms at baseline. In unadjusted analysis, younger men (particularly those aged <25) and those who did not report being employed were more likely to report depressive symptoms. There was also some evidence that the prevalence of depressive symptoms was higher among men who reported not being in an ongoing relationship compared to men who did. Adjusting for key socio-demographic factors, younger age and not being employed remained associated with depressive symptoms. In adjusted analysis, the association between on-going relationship status and depressive symptoms was attenuated.

Table 22: Unadjusted and adjusted associations of socio-demographic factors[h] with depressive symptoms at baseline in PROUD

N=540 men at baseline			Depressive symptoms (PHQ-9≥10)			
		N (%)	%	*p-value*[b]	Unadjusted PR [95% CI] *p-value*[e]	Adjusted[f] PR [95% CI] *p-value*[e]
Age	<25 25-29 30-34 35-39 40-44 45+	54 (10.0%) 96 (17.8%) 114 (21.1%) 97 (18.0%) 81 (15.0%) 98 (18.2%)	22.2% 8.3% 12.3% 6.2% 3.7% 6.1%	*0.003* *0.002*[c]	3.63 [1.44, 9.13] 1.36 [0.49, 3.78] 2.01 [0.80, 5.02] 1.01 [0.34, 3.03] 0.60 [0.16, 2.35] 1 *0.006* *0.003*[c]	3.49 [1.38, 8.84] 1.25 [0.44, 3.54] 1.95 [0.76, 5.01] 1.01 [0.33, 3.09] 0.60 [0.15, 2.40] 1 *0.007* *0.006*[c]
Born in the UK and white ethnicity	Yes, white Yes, BAME No, white No, BAME	287 (53.4%) 35 (6.5%) 152 (28.3%) 64 (11.9%)	9.1% 14.3% 6.6% 12.5%	*0.315*[d]	1 1.58 [0.65, 3.84] 0.73 [0.36, 1.47] 1.38 [0.65, 2.91] *0.368*	1 1.05 [0.48, 2.32] 0.75 [0.35, 1.60] 1.38 [0.61, 3.10] *0.635*
Self-reported sexual identity[g]	Gay Bisexual Straight	513 (95.7%) 17 (3.2%) 6 (1.1%)	9.0% 13.0%	*0.457*[d]	1 1.45 [0.49, 4.33] *0.501*	1 1.35 [0.53, 3.44] *0.524*
University Education	Yes No/missing[a]	327 (60.6%) 213 (39.4%)	8.9% 9.4%	*0.837*	1 1.06 [0.61, 1.82] *0.837*	1 0.93 [0.53, 1.64] *0.799*
Employed	Yes No/missing[a]	439 (81.3%) 101 (18.7%)	6.8% 18.8%	*<0.001*	1 2.75 [1.62, 4.69] *<0.001*	1 2.44 [1.36, 4.37] *0.003*
Ongoing relationship	Yes No/missing[a]	246 (45.6%) 294 (54.4%)	6.5% 11.2%	*0.057*	1 1.73 [0.97, 3.06] *0.062*	1 1.56 [0.89, 2.75] *0.121*
Study region	London Outside London	375 (69.4%) 165 (30.6%)	9.3% 8.5%	*0.752*	1 0.91 [0.50, 1.64] *0.753*	1 0.81 [0.41, 1.60] *0.541*

[a] University Education: 0.2% missing. Employment: 0.4% missing. Ongoing relationship: 0.2% missing.
[b] Pearson χ^2 test
[c] Test for trend.
[d] Fisher's exact test.
[e] p value by Wald test using Poisson regression.
[f] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/other), university education, relationship status, and London study clinic site.
[g] A dichotomized version of self-reported sexual identity is investigated in univariable analysis due to very small numbers: gay or bisexual/other.
[h] For a definition of each measure see section 3.3.10 in Chapter 3.

Table 23 presents the unadjusted and adjusted associations of lifestyle factors with depressive symptoms at baseline. Depressive symptoms were not associated with higher-risk drinking, number of recreational drugs used in the past three months, or chemsex-associated drug use. There does, however, appear to be a pattern in terms of report of the number of recreational drugs used, whereby men who reported no drug use and men who reported five or more drugs used, had a higher prevalence of depressive symptoms compared to men reporting 1and 2-4 drugs. When investigating whether the individual recreational drugs asked about in PROUD were associated with depressive symptoms (see section 3.3.10), men who reported crystal methamphetamine use in the past three months were more likely to report depressive symptoms than men who did not (15.3% versus 7.7%; p=0.018). This was the only drug found to be associated with depressive symptoms. This association remained after adjustment for key socio-demographic factors (PR 2.02 95% CI: 1.11, 3.66; p=0.021).

Table 23: Unadjusted and adjusted associations of lifestyle factors[g] with depressive symptoms at baseline in PROUD

N=540 men at baseline			Depressive symptoms (PHQ-9≥10)			
		N (%)	%	*p-value*[b]	Unadjusted PR [95% CI] *p-value*[e]	Adjusted[f] PR [95% CI] *p-value*[e]
Higher-risk drinking	Yes No/missing[a]	173 (32.0%) 367 (68.0%)	10.4% 8.5%	*0.460*	1.23 [0.71, 2.14] 1 *0.460*	1.18 [0.65, 2.13] 1 *0.591*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	148 (27.4%) 87 (16.1%) 159 (29.4%) 146 (27.0%)	10.1% 4.6% 6.9% 13.0%	*0.114* *0.399*[c]	1 0.45 [0.16, 1.32] 0.68 [0.32, 1.44] 1.28 [0.68, 2.43] 0.133 *0.445*[c]	1 0.48 [0.17, 1.32] 0.76 [0.34, 1.69] 1.33 [0.70, 2.50] 0.151 *0.362*[c]
Chemsex-associated drug use	No Yes	309 (57.2%) 231 (42.8%)	8.1% 10.4%	*0.357*	1 1.28 [0.75, 2.19] *0.359*	1 1.33 [0.77, 2.27] *0.304*

[a] Higher-risk drinking: 3.3% missing. Recreational drug use: 3.0% missing.
[b] Pearson χ^2 test
[c] Test for trend.
[d] Fisher's exact test.
[e] p-value by Wald test using Poisson regression.
[f] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/other), university education, relationship status, and London study clinic site.
[g] For a definition of each measure see section 3.3.10 in Chapter 3.

7.3.5 Association of psychosocial factors with depressive symptoms at the 12- and 24-month questionnaire

Table 24 presents the unadjusted associations of psychosocial factors with depressive symptoms (PHQ-9≥10) at the 12- and 24-month questionnaires. Men who reported having experienced fear of, emotional abuse or control from, physical violence, and sexual abuse from an intimate partner, and perhaps specifically from a former partner within the past year, were more likely to report depressive symptoms at both month-12 and 24, compared to those who had not had such experiences. Although the numbers are extremely small, some of these proportions are quite striking. For instance, at both months 12 and 24, of the men who said they had been 'hit, slapped, kicked or otherwise physically hurt' by a former partner within the past year, about 40% reported depressive symptoms. When investigating the composite measure of any IPV victimization, at both months 12 and 24, men who reported ever having been a victim of partner abuse were twice as likely to report clinically significant depressive symptoms. The difference in prevalence of depressive symptoms was even greater when comparing men who reported any IPV victimization in the past year to those who did not.

The proportion of men reporting depressive symptoms is again striking among those who indicated having behaved in a way that has made a former partner within the past year feel frightened, at 61.5% at month-12 and 40.0% at month-24. The remaining IPV perpetration questions were not associated with depressive symptoms, although a borderline association was observed between 'asking a partners' permission' and depressive symptoms at month-12. It was not possible to investigate questions concerning sexual IPV perpetration, given that only one man across both time-points gave a response other than never. When investigating the composite measure of any IPV perpetration (emotional/psychological and/or physical) at both months 12 and 24, men who reported ever having been a perpetrator of partner abuse were almost three times as likely to report depressive symptoms. The difference in prevalence of depressive symptoms was again greater when considering any IPV perpetration in the past year.

When examining the series of statements about attitudes towards one's sexuality, the proportion of men reporting depressive symptoms was higher among men who indicated a more negative attitude towards gay sexuality than those who did not at the 12-month questionnaire. For instance, almost half of men who disagreed with the statement that they feel comfortable being a transgender/gay man reported depressive symptoms. When investigating a composite measure of these statements, depressive symptom prevalence was twice as high among men who indicated internalised homophobia compared to men who did not at the 12-month questionnaire (21.6% vs. 9.2%). A similar pattern was observed at the 24-month questionnaire, though differences tended to be somewhat smaller and not statistically significant.

Measures of sexual orientation disclosure to family, friends, and work colleagues were not associated with depressive symptoms at the 12-month questionnaire. However, a lower level of disclosure to work colleagues was associated with depressive symptoms at month-24, and a significant trend was also observed for lower levels of disclosure to friends. At the 24-month questionnaire, men who reported that they were not 'out' to all or almost of their friends, work colleagues, and close family, reported a depressive symptom prevalence twice that of men who did report being 'out' to all or almost all of these individuals.

Sexualized drug use was not associated with depressive symptoms at the 12- or 24-month questionnaire. Anal sex debut with a male, before age 15 years and 13 years, as well as the time from any sexual contact to intercourse with a male, was not associated with depressive symptoms at month-12 or 24. Age at first anal intercourse as a continuous variable was also investigated in a Poisson model with depressive symptoms- there was no association at the 12-month (PR 0.99 95% CI: 0.94, 1.04) or 24-month questionnaire (PR 1.01 95% CI: 0.97, 1.05).

Table 24: Unadjusted associations of psychosocial factors[g] with depressive symptoms at the 12- and 24-month questionnaire in PROUD

		12-month [N=410]		24-month [N=333]	
		N (%)	% PHQ-9≥10 *p-value* [a]	N (%)	% PHQ-9≥10 *p-value* [a]
Sexualized drug use (past 3 months)	Yes No	224 (54.6%) 186 (45.4%)	15.2% 13.4% *0.618*	159 (47.8%) 174 (52.3%)	17.6% 11.5% *0.112*
Age≤15 years at anal sex debut	Yes No	88 (22.3%) 307 (77.7%)	19.3% 13.4% *0.164*	70 (21.8%) 251 (78.2%)	15.7% 14.3% *0.774*
Age<13 years at anal sex debut	Yes No	22 (5.6%) 373 (94.4%)	9.1% 15.0% *0.755*[c]	19 (5.9%) 302 (94.1%)	10.5% 14.9% *0.601*[c]
Time between any sexual contact and intercourse with a male	Same time 1-2 years 3-4 years 5+ years	163 (41.3%) 90 (22.8%) 47 (11.9%) 95 (24.1%)	15.3% 11.1% 19.2% 14.7% *0.632* *0.894*[b]	146 (45.5%) 67 (20.9%) 33 (10.3%) 75 (23.4%)	13.0% 10.5% 18.2% 20.0% *0.347* *0.133*[b]
Frightened of the behaviour of a partner	Never >1 yr ago Last yr, former partner Last yr, current partner	237 (60.6%) 104 (26.6%) 29 (7.4%) 21 (5.4%)	11.0% 14.4% 37.9% 28.6% *0.001*[c]	209 (65.1%) 71 (22.1%) 20 (6.2%) 21 (6.5%)	9.6% 16.9% 25.0% 47.6% *<0.001*[c]
Needed to ask a partner's permission (for work, shopping, visit relatives/ friends)	Never >1 yr ago Last yr, former partner Last yr, current partner	347 (88.1%) 30 (7.6%) 9 (2.3%) 8 (2.0%)	13.3% 26.7% 33.3% 25.0% *0.041*[c]	286 (89.1%) 26 (8.1%) 3 (0.9%) 6 (1.9%)	14.0% 11.5% 66.7% 33.3% *0.057*[c]
Been physically hurt by a partner	Never >1 yr ago Last yr, former partner Last yr, current partner	297 (75.6%) 72 (18.3%) 10 (2.5%) 14 (3.6%)	12.1% 20.8% 40.0% 28.6% *0.010*[c]	244 (76.3%) 54 (16.9%) 13 (4.1%) 9 (2.8%)	11.1% 16.7% 38.5% 55.6% *<0.001*[c]
Forced to have sex/ engage in some sexual activity	Never >1 yr ago Last yr, former partner Last yr, current partner	329 (83.9%) 52 (13.3%) 8 (2.0%) 3 (0.8%)	12.2% 28.9% 25.0% 0.0% *0.013*[c]	270 (84.6%) 35 (11.0%) 8 (2.5%) 6 (1.9%)	12.6% 22.9% 37.5% 33.3% *0.030*[c]
Forced to have sex without a condom	Never >1 yr ago Last yr, former partner Last yr, current partner	356 (90.4%) 32 (8.1%) 6 (1.5%) 0 (0.0%)	12.6% 37.5% 33.3% / *0.001*[c]	295 (92.1%) 22 (6.9%) 3 (0.9%) 0 (0.0%)	13.6% 22.7% 66.7% / *0.019*[c]
Any IPV victimization	No/missing[d] Yes	226 (55.1%) 184 (44.9%)	8.4% 21.7% *<0.001*	199 (59.8%) 134 (40.2%)	9.6% 21.6% *0.002*
Any IPV victimization in the past year	No/missing[d] Yes	346 (84.4%) 64 (15.6%)	11.6% 29.7% *<0.001*	284 (85.3%) 49 (14.7%)	10.6% 36.7% *<0.001*

Table 24: Unadjusted associations of psychosocial factors[g] with depressive symptoms at the 12- and 24-month questionnaire in PROUD (continued)

		12-month [N=410]		24-month [N=333]	
		N (%)	% PHQ-9≥10 *p-value* [a]	N (%)	% PHQ-9≥10 *p-value* [a]
Behaved in a manner that made a partner feel frightened	Never >1 yr ago Last yr, former partner Last yr, current partner	333 (85.0%) 32 (8.2%) 13 (3.3%) 14 (3.6%)	11.7% 12.5% 61.5% 50.0% *<0.001*[c]	274 (85.6%) 28 (8.8%) 5 (1.6%) 13 (4.1%)	11.3% 28.6% 40.0% 46.2% *<0.001*[c]
Partner needed to ask your permission to work, go shopping, visit relatives, or visit friends	Never >1 yr ago Last yr, former partner Last yr, current partner	387 (98.5%) 2 (0.5%) 0 (0.0%) 4 (1.0%)	14.5% 50.0% / 50.0% *0.058*[c]	317 (98.8%) 2 (0.6%) 1 (0.3%) 1 (0.3%)	14.5% 50.0% 0.0% 0.0% *0.471*[c]
Hit, slapped, kicked or otherwise physically hurt a partner	Never >1 yr ago Last yr, former partner Last yr, current partner	346 (87.8%) 36 (9.1%) 2 (0.5%) 10 (2.5%)	13.6% 22.2% 50.0% 30.0% *0.078*[c]	280 (87.2%) 32 (10.0%) 4 (1.3%) 5 (1.6%)	13.9% 18.8% 0.0% 40.0% *0.276*[c]
Any IPV perpetration[e]	No/missing[d] Yes	330 (80.5%) 80 (19.5%)	10.3% 31.3% *<0.001*	273 (82.0%) 60 (18.0%)	11.4% 28.3% *0.001*
Any IPV perpetration in the past year	No/missing[d] Yes	378 (92.2%) 32 (7.8%)	11.4% 50.0% *<0.001*	310 (93.1%) 23 (6.9%)	12.9% 34.8% *0.009*[c]
'Obviously effeminate homosexual men make me feel uncomfortable'	No[f] Yes	326 (79.5%) 84 (20.5%)	12.9% 20.2% *0.087*	262 (78.7%) 71 (21.3%)	13.4% 18.3% *0.292*
'I feel comfortable in gay bars'	Yes[f] No	370 (90.2%) 40 (9.8%)	13.2% 25.0% *0.044*	301 (90.4%) 32 (9.6%)	12.6% 31.3% *0.004*
'Social situations with transgender/gay men make me feel uncomfortable'	No[f] Yes	383 (93.4%) 27 (6.6%)	12.5% 40.7% *<0.001*[c]	308 (92.5%) 25 (7.5%)	14.3% 16.0% *0.500*[c]
'I feel comfortable being seen in public with an obviously transgender/gay person'	Yes[f] No	358 (87.3%) 52 (12.7%)	14.0% 17.3% *0.521*	287 (86.2%) 46 (13.8%)	15.0% 10.9% *0.461*
'I feel comfortable discussing homosexuality in a public situation'	Yes[f] No	385 (93.9%) 25 (6.1%)	12.5% 44.0% *<0.001*[c]	307 (92.2%) 26 (7.8%)	13.7% 23.1% *0.153*[c]
'I feel comfortable being a transgender/gay man'	Yes[f] No	387 (94.4%) 23 (5.6%)	12.4% 47.8% *<0.001*[c]	322 (96.7%) 11 (3.3%)	14.0% 27.3% *0.201*[c]

Table 24: Unadjusted associations of psychosocial factors[g] with depressive symptoms at the 12- and 24-month questionnaire in PROUD (continued)

		12-month [N=410]		24-month [N=333]	
		N (%)	% PHQ-9≥10 *p-value* [a]	N (%)	% PHQ-9≥10 *p-value* [a]
'Homosexuality is morally acceptable to me'	Yes[f] No	404 (98.5%) 6 (1.5%)	14.1% 33.3% *0.208* [c]	325 (97.6%) 8 (2.4%)	14.2% 25.0% *0.324*[c]
'Even if I could change my sexual orientation I wouldn't'	Yes[f] No	380 (92.7%) 30 (7.3%)	12.6% 36.7% *0.001* [c]	312 (93.7%) 21 (6.3%)	13.8% 23.8% *0.169*[c]
Any negative views about gay sexuality (marker of internalised homophobia)	No/missing Yes	239 (58.3%) 171 (41.7%)	9.2% 21.6% *<0.001*	195 (58.6%) 138 (41.4%)	11.8% 18.1% *0.106*
How many friends know you are gay/ transgender/ have sex with men	All/almost all Some Few None	331 (83.0%) 51 (12.8%) 14 (3.5%) 3 (0.8%)	14.5% 15.7% 14.3% 33.3% *0.650*[c] 0.601[b]	265 (80.8%) 42 (12.8%) 18 (5.5%) 3 (0.9%)	13.2% 16.7% 22.2% 66.7% *0.063*[c] 0.032[b]
How many work colleagues know you are gay/ transgender/ have sex with men	All/almost all Some Few None	241 (62.3%) 89 (23.0%) 35 (9.0%) 22 (5.7%)	12.9% 19.1% 17.1% 18.2% *0.439*[c] 0.237[b]	205 (64.5%) 69 (21.7%) 23 (7.2%) 21 (6.6%)	10.2% 20.3% 26.1% 28.6% *0.010*[c] 0.002[b]
How many close family know you are gay/ transgender/ have sex with men	All/almost all Some Few None	292 (73.4%) 56 (14.1%) 34 (8.5%) 16 (4.0%)	12.7% 19.6% 23.5% 18.8% *0.174*[c] 0.068[b]	229 (70.0%) 58 (17.7%) 26 (8.0%) 14 (4.3%)	12.2% 17.2% 23.1% 28.6% *0.124*[c] 0.025[b]
'Out' to all/almost all friends, work colleagues and close family	Yes No	206 (51.6%) 193 (48.4%)	12.6% 17.1% *0.208*	166 (50.6%) 162 (49.4%)	8.4% 21.0% *0.001*
'Out' to few/no friends, work colleagues and close family	Yes No	9 (2.3%) 390 (97.7%)	22.2% 14.6% *0.627*[c]	9 (2.7%) 319 (97.3%)	14.7% 11.1% *0.611*[c]

[a] Pearson χ^2 test

[b] Test for trend.

[c] Fisher's exact test.

[d] A missing response was considered to indicate no IPV. At month-12, the percentage of missing data was 4.4% (n=18) and 4.4% (n=18) for any IPV victimization and any IPV perpetration respectively. At month-24, the percentage of missing data was 3.6% (n=12) and 3.9% (n=13) respectively.

[e] Includes any response other than 'never' or missing to at least one of the three questions presented above (frightened, permission, and physical force).

[f] A missing response to at least one of the eight questions regarding attitudes towards gay sexuality was reported by 5.6% (23/410) of men at month-12 and 5.7% (19/333) of men at month-24. A missing response on all eight questions was reported by 3.7% (15/410) of men at month-12 and 3.6% (12/333) of men at month-24.

[g] For a definition of each measure see section 3.3.10 in Chapter 3.

7.3.6 Association of socio-demographic, lifestyle, and psychosocial factors with depression measures on PHQ-9 at baseline and the 12- and 24-month questionnaire

When investigating the association between socio-demographic factors (assessed at baseline) and depressive symptoms (PHQ-9≥10) (using data from baseline, month-12, and month-24), 540 individuals (at most) and 1283 questionnaire responses were included in GEE models, see Table 25. The following factors were found to be associated with depressive symptoms in unadjusted analyses and analyses adjusted for socio-demographic factors (including study time-point): study time-point (with 50-60% higher prevalence of symptoms at follow-up compared to baseline) and not being employed (prevalence of symptoms was twice as high in men not employed compared to employed men). Although in unadjusted and adjusted analysis, the overall association and test of trend of age with depressive symptoms was not significant, there was some evidence of variation according to age. The prevalence of symptoms was lower in the 35 to 44 age group compared to all other age groups. There was also some suggestion of higher prevalence of symptoms in the small group of men with bisexual/straight identity, though not statistically significant in unadjusted or adjusted analysis. When investigating the association between psychosocial factors (assessed at month-12 and 24) and depressive symptoms, 436 individuals[xxxiv] and 743 questionnaire responses were included in GEE models, see Table 25. The following factors were strongly associated with depressive symptoms in unadjusted and adjusted analyses, whereby the prevalence of symptoms was two to three fold higher: report of any IPV victimization (including in the past year), report of any IPV perpetration (including in the past year), internalised homophobia, and not being 'out' to all/almost all friends, work colleagues, and family.

In the sensitivity analyses, results were similar when investigating associations with the other measures of depressive symptoms on PHQ-9 (a major depressive syndrome and major and other depressive syndromes), see Appendix section 11.17 Table 77 and Table 78. In addition, younger age was associated with both measures and non-university education was associated with major and other depressive syndromes on PHQ-9, in unadjusted and adjusted analysis.

[xxxiv] Twenty-six men completed a 24-month questionnaire but did not complete a 12-month questionnaire.

Table 25: Unadjusted and adjusted associations of socio-demographic and psychosocial factors with depressive symptoms using baseline, 12-, and 24-month PROUD questionnaire data in GEE models

					Depressive symptoms (PHQ-9≥10)			
N=540 men (using data from baseline and follow-ups in GEE models)		Baseline [N=540] n(%)	12-month [N=410] n(%)	24-month [N=333] n(%)	Unadjusted PR [95% CI]	Overall p-value[a]	Adjusted[b] PR [95% CI]	Overall p-value[a]
Study time-point N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Baseline 12-month 24-month	/	/	/	1 1.57 [1.14, 2.18] 1.58 [1.12, 2.23]	*0.009* *0.006* [c]	1 1.60 [1.15, 2.23] 1.63 [1.14, 2.32]	*0.007* *0.004*[c]
Randomized to study trial arm N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	Immediate arm Deferred arm	/	216 (52.7%) 194 (47.3%)	182 (54.7%) 151 (45.4%)	1.40 [0.92, 2.15] 1	*0.121*	1.44 [0.94, 2.21] 1	*0.095*
Age N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	<25 25-29 30-34 35-39 40-44 45+	54 (10.0%) 96 (17.8%) 114 (21.1%) 97 (18.0%) 81 (15.0%) 98 (18.2%)	27 (6.6%) 56 (13.7%) 87 (21.2%) 78 (19.0%) 70 (17.1%) 92 (22.4%)	11 (3.3%) 35 (10.5%) 73 (21.9%) 66 (19.8%) 55 (16.5%) 93 (27.9%)	1.11 [0.57, 2.15] 0.87 [0.49, 1.53] 1.02 [0.62, 1.68] 0.60 [0.33, 1.09] 0.39 [0.19, 0.80] 1	*0.061* *0.374*[c]	1.16 [0.58, 2.31] 0.94 [0.53, 1.66] 1.08 [0.66, 1.77] 0.65 [0.36, 1.18] 0.40 [0.20, 0.83] 1	*0.082* *0.318*[c]
Born in the UK and white ethnicity N=538[d], Obs=1279 [e] ; N=534[f], Obs=1269[g]	Yes, white Yes, BAME No, white No, BAME	287 (53.4%) 35 (6.5%) 152 (28.3%) 64 (11.9%)	223 (54.7%) 22 (5.4%) 114 (27.9%) 49 (12.0%)	184 (55.3%) 17 (5.1%) 88 (26.4%) 44 (13.2%)	1 1.57 [0.80, 3.09] 0.83 [0.52, 1.34] 1.26 [0.72, 2.20]	*0.317*	1 1.41 [0.70, 2.83] 0.83 [0.50, 1.35] 1.18 [0.66, 2.12]	*0.506*
Self-reported sexual identity N=536[d], Obs=1273[e] ; N=536[f], Obs=1273[g]	Gay Bisexual/straight	513 (95.7%) 23 (4.3%)	388 (95.6%) 18 (4.4%)	315 (95.2%) 16 (4.8%)	1 1.75 [0.85, 3.59]	*0.130*	1 1.73 [0.84, 3.59]	*0.140*
University Education N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Yes No/missing	327 (60.6%) 213 (39.4%)	256 (62.4%) 154 (37.6%)	204 (61.3%) 129 (38.7%)	0.85 [0.58, 1.25] 1	*0.414*	0.86 [0.58, 1.28] 1	*0.451*
Employed N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Yes No/missing	439 (81.3%) 101 (18.7%)	332 (81.0%) 78 (19.0%)	276 (82.3%) 57 (17.1%)	1 1.89 [1.26, 2.86]	*0.002*	1 1.80 [1.18, 2.77]	*0.007*
Study region N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	London Outside London	375 (69.4%) 165 (30.6%)	289 (70.5%) 121 (29.5%)	228 (68.5%) 105 (31.5%)	1 0.90 [0.59, 1.37]	*0.610*	1 0.81 [0.52, 1.27]	*0.356*

Table 25: Unadjusted and adjusted associations of socio-demographic and psychosocial factors with depressive symptoms using baseline, 12-, and 24-month PROUD questionnaire data in GEE models (continued)

					Depressive symptoms (PHQ-9≥10)			
N=540 men		Baseline [N=540] n(%)	12-month [N=410] n(%)	24-month [N=333] n(%)	Unadjusted PR [95% CI]	Overall p-value[a]	Adjusted[b] PR [95% CI]	Overall p-value[a]
Sexualized drug use (past 3 months) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	Yes No	/	224 (54.6%) 186 (45.4%)	159 (47.8%) 174 (52.3%)	1.38 [0.93, 2.06] 1	*0.108*	1.34 [0.89, 2.00] 1	*0.157*
Age≤15 years at anal sex debut N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Yes No	/	88 (22.3%) 307 (77.7%)	70 (21.8%) 251 (78.2%)	1.27 [0.80, 2.02] 1	*0.306*	1.20 [0.75, 1.93] 1	*0.451*
Age<13 years at anal sex debut N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Yes No	/	22 (5.6%) 373 (94.4%)	19 (5.9%) 302 (94.1%)	0.71 [0.26, 1.94] 1	0.507	0.71 [0.26, 1.94] 1	*0.499*
Time between sexual contact and intercourse with a male N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Same time 1-2 years 3-4 years 5+ years	/	163 (41.3%) 90 (22.8%) 47 (11.9%) 95 (24.1%)	146 (45.5%) 67 (20.9%) 33 (10.3%) 75 (23.4%)	1 0.74 [0.42, 1.30] 1.26 [0.69, 2.30] 1.23 [0.75, 2.00]	*0.373* *0.310*[c]	1 0.74 [0.42, 1.31] 1.24 [0.68, 2.27] 1.27 [0.77, 2.10]	*0.350* *0.268*[c]
Any IPV victimization N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	226 (55.1%) 184 (44.9%)	199 (59.8%) 134 (40.2%)	1 2.45 [1.63, 3.67]	*<0.001*	1 2.57 [1.71, 3.86]	*<0.001*
Any IPV victimization in the past year N=436[d], Obs=743[e] ; N=432[f], Obs=737 [g]	No Yes	/	346 (84.4%) 64 (15.6%)	284 (85.3%) 49 (14.7%)	1 2.82 [1.88, 4.22]	*<0.001*	1 2.93 [1.96, 4.40]	*<0.001*
Any IPV perpetration N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	330 (80.5%) 80 (19.5%)	273 (82.0%) 60 (18.0%)	1 2.83 [1.89, 4.22]	*<0.001*	1 2.87 [1.91, 4.32]	*<0.001*
Any IPV perpetration in the past year N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	378 (92.2%) 32 (7.8%)	310 (93.1%) 23 (6.9%)	1 3.40 [2.13, 5.41]	*<0.001*	1 3.47 [2.13, 5.64]	*<0.001*
Any negative views about gay sexuality (marker of internalised homophobia) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No/missing Yes	/	239 (58.3%) 171 (41.7%)	195 (58.6%) 138 (41.4%)	1 1.92 [1.30, 2.83]	*0.001*	1 1.91 [1.29, 2.83]	*0.001*
'Out' to all/almost all friends, work colleagues and close family N=434[d], Obs=727[e] ; N=431[f], Obs=722[g]	Yes No	/	206 (51.6%) 193 (48.4%)	166 (50.6%) 162 (49.4%)	1 1.75 [1.17, 2.62]	*0.007*	1 1.75 [1.16, 2.65]	*0.008*

[a] p-value by Wald test using GEE models.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, London study clinic site, and study time-point.
[c] Test for trend.
[d] Number of men contributing observations to the unadjusted model.
[e] Number of observations examined in the unadjusted model.
[f] Number of men contributing observations to the adjusted model.
[g] Number of observations examined in the adjusted model.

7.3.7 Factors associated with changes over time in screening positive for clinically significant depressive symptoms by PHQ-9:

7.3.7.1 Factors associated with change in depression scores from baseline to the 12-month questionnaire

The distribution of change in PHQ-9 depression score from baseline to the 12-month questionnaire is presented in Appendix section 11.18 Figure 34. Change scores were generated by subtracting the PHQ-9 depression score at baseline from the score at month-12; a positive change score signifies an increase in depressive symptoms over time. Overall, the mean change in depression scores was 1 (SD=4.9). The mean change in scores was higher among men aged ≥25 years compared to men aged <25 years (1 vs. -2), and among men who reported any IPV victimization in the past year (3 vs. 1), any IPV perpetration (2 vs. 0), any IPV perpetration in the past year (4 vs. 1), and internalized homophobia (1 vs. 0), compared to men who did not, see Appendix section 11.18 Table 79.

7.3.7.2 Factors associated with incidence of clinically significant depressive symptoms at the 12-month questionnaire among men with no symptoms at baseline

In total, 372 men did not meet the criteria for moderate, moderately severe, or severe depressive symptoms (i.e. scored <10 on the PHQ-9) at baseline. Of these men, 10.0% scored 10 or more on the PHQ-9 at the 12-month questionnaire. The proportion of men reporting new depressive symptoms at month-12 appeared to be significantly higher among men aged 45 years or older and men who reported anal sex debut with a male at age 15 years or younger, although the associations were of borderline significance. Furthermore, men who reported any IPV victimization (15.6% vs. 5.7%), any IPV victimization in the past year (25.5% vs. 7.3%), any IPV perpetration (22.4% vs. 7.2%), any IPV perpetration in the past year (7.8% vs. 41.7%), and internalised homophobia (14.4% vs. 7.1%), appeared to be more likely to report new depressive symptoms compared to men who did not, at month-12 in unadjusted analysis, see Appendix section 11.18 Table 80.

7.3.7.3 PHQ-9 responses after April 1st 2013

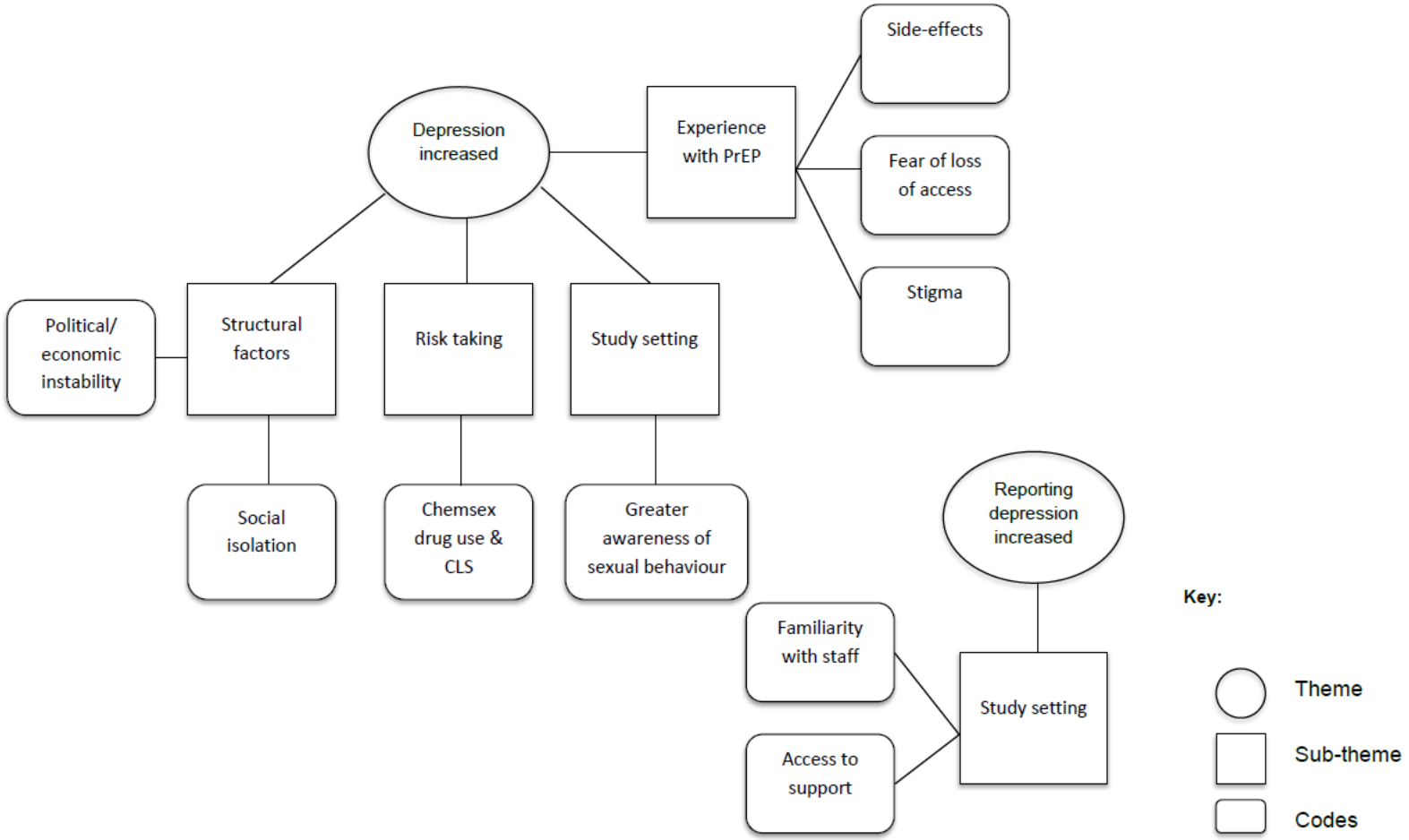
The prevalence of suicidal ideation on PHQ-9 was significantly higher among men who completed their baseline questionnaire before April 1st 2013 (n=71) compared to men who completed their baseline questionnaire on or after April 1st 2013 (n=469) (19.7% vs. 9.6%; Pearson χ^2 test p=0.011). Similarly, the prevalence of depressive symptoms (PHQ-9≥10) was significantly higher among men who completed their baseline questionnaire before April 1st 2013 (21.1% vs. 7.3%; Pearson χ^2 test p<0.001). When further investigating whether the prevalence of depressive symptoms (PHQ-9≥10) increased significantly from baseline to the 12-

month questionnaire among (i) the 57 men who completed their baseline questionnaire before April 1st 2013 and had 12-month data, and (ii) the 353 men who completed their baseline questionnaire after April 1st 2013 and had 12-month data, there was evidence of an increase only for those with baseline completion in the later time period (McNemar's χ^2 test p-values 0.366 and <0.001 respectively).

7.3.8 Participant involvement in the interpretation of findings: summary of PPI responses

In total, 13 men commented on the finding that depression prevalence increased over the first year of the study. The way in which the responses were organised into themes in the semantic content of the data is shown in Figure 22.

Figure 22: Organization of PROUD PPI responses into codes, themes, and sub-themes



Two overarching themes were apparent, the first was that the prevalence of depression was found to increase since the amount of men experiencing depression did indeed increase over the study and the second was that the increase was found since the amount of men reporting rather than experiencing symptoms of depression increased. These views were not necessarily exclusive, as some individuals cited the possibility that both factors may explain the findings. Within the first theme that depression increased, four sub-themes were identified; structural factors, risk-taking, study setting, and experience with PrEP. The second theme that reporting depression increased, consisted of one main concept, that of the study setting.

Within the first theme, the sub-theme of structural factors (reported by three participants) was defined by the recurrent expression that concurrent political/economic instability in the UK may have resulted in an increase in depressive symptoms. Similarly, it was cited that social isolation, presumably as a sexual minority individual, within the context of the socio-political climate at the time of the study, might have resulted in an increase in depressive symptoms.

> *"With the downturn in the economy additional stress could have been a subliminal factor and that the trial had little to do with the depression numbers."*
>
> *"Just look at the economy and it's obvious why! The poor are not only getting poorer but they're being actively persecuted."*
>
> *"The PrEP study was taking place at a politically very difficult and socially very isolating time."*
>
> PROUD PPI responses

Describing structural factors as the reason underlying the increase in depressive symptoms observed, is an interesting concept as socio-economic hardship has consistently and strongly been found to be associated with depressive symptoms in samples of MSM [346, 347, 354, 356, 364, 371, 415, 454, 606, 681] including in AURAH and PROUD, and in general UK population samples [348-350]. It seems possible therefore, that a downturn in the economy may have increased the prevalence of depression in general in the UK. Given the lack of data on PHQ-9 responses among the UK population between 2013-2015 it is very difficult to investigate these suggestions further.

Within the sub-theme of risk-taking (reported by four participants), the discussion of CLS was predominantly linked to chemsex-drug use. It was never explicitly stated that occurrence of CLS or use of chems may have increased after study enrolment. It was, however, acknowledged that taking PrEP was used as a means to reduce the risk of HIV during episodes of sexual risk, especially chemsex, and a link was consistently drawn between chem use and CLS, and chem use and depression.

"Having condomless sex is the 'norm' with chem-sex, and the chems certainly lead to changes in behaviour and perceptions."

"For myself, I did PrEP to avoid hiv risk when having unprotected cheesecake [taken to mean condomless sex]. *To a great extend, I believe it is the drug causing depression instead of the PrEP itself."*

"From personal experience there is a great association between recreational substance abuse - that is "Chem Sex" and "bare back" (condomless) sex. The whole area is pretty awful. Obviously, "chems" can of course lead to depression ("comedowns"). And/or addiction."

"I had my first ever panic attack this year in a group social situation [taken to mean group sexual situation]. *Went to another one - same thing. Sitting in a corner with a panic attack on full for at least an hour. Repeated exposure and finding friends has reduced this in this one particular group meet."*

PROUD PPI responses

Again, such discourse is not surprising given that mephedrone and crystal methamphetamine use is known to cause acute symptoms of anxiety and paranoia in some individuals [524, 579]. Based on recent data from in-depth interviews of 30 men resident in London, it was suggested that chemsex-drug use may cause longer-term mental health problems, including depression, anxiety, and psychosis, in some individuals [579]. Chemsex-associated drug use (past three months) was associated with depressive symptoms among men in the AURAH study (Chapter 4 Table 5), and the type of depressive symptoms reported by men who engaged in chemsex-drug use and men who did not was found to differ somehwat (Chapter 6 section 6.3.2). Although chemsex-associated drug use (past three months) was not associated with depressive symptoms among men in the PROUD trial at baseline, use of crystal methamphetamine was found to be associated. Sexualized drug use (report of sex after recreational drug use in the past three months) was not associated with depressive symptoms at the 12- or 24-month questionnaire in unadjusted analysis. Unfortunately, it was not possible to investigate methamphetamine use (or the measure of chemsex-associated drug use), at the 12- or 24-month questionnaire. It is possible that one or more chemsex-associated drugs may have been linked to depression at the follow-up time-points in PROUD, as the measure of sex after drug use may capture a wide-range of practices/experiences that do not necessarily embody the documented phenomenon of chemsex, which includes specific drugs and often occurs in group sex settings [578-582].

Reflected in the participants' comments presented above, it is not only the immediate and long-term effects of the drugs themselves which may lead to depression, but also the engagement in sexual risk-taking, with potentially multiple partners, that often goes hand-in-hand with chem

use, and may affect one's psychological wellbeing. Although previous studies have predominantly investigated the association between depression and sexual behaviour (Table 1), it is theoretically plausible that sexual risk-taking leads to or exacerbates depression. Reasons for this may include feelings of shame as well as a sense of loss of intimacy with a sexual partner whilst using chemsex-associated drugs [578-584]. The PROUD sample of men reported high levels of CLS partners, perhaps an association was not found between the measure of chemsex-associated drug use and depression since most participants were engaging in CLS with multiple partners and therefore, the prevalence of depression was similar among non-chemsex-drug users.

The sub-theme of study setting appears under both of the main themes (depression increased, n=2 and reporting depression increased, n=4). As a result of the clinical trial set-up and infrastructure, two men suggested that depressive symptoms might have increased due to greater awareness of risk-taking during regular survey completion and STI screening.

> *"Being on the study, due to the 3 month STI screening, means you are more aware of how much sex you are having or not having."*
>
> *"I was shocked when I looked at my monthly record - seeing in black and white the number of times I had had condomless sex. Possibly looking at past performances could cause a participant to become stresses resulting in depression."*
>
> PROUD PPI responses

As described above, it is possible that sexual risk-taking leads to/exacerbates depression. Greater confrontation with one's sexual practices on a regular basis may impact on well-being.

Four men suggested that the burden of depression might have remained the same, but that reporting of depressive symptoms may have increased due to greater familiarity with the questionnaire and/or staff, and as a result of being a part of a clinical trial. Partaking in a trial may be one of the processes that helps individuals recognize/acknowledge their own depression in an environment where access to support is provided.

"Going on the Proud study and dealing with depression happened at the sane time for me. I had stopped taking care of myself and was engaging in high risk behaviour - cruelly going on Proud was one of the steps in starting to deal with my depression."

"Every 12 weeks we were doing other forms, and in that time you got to know the forms. You made a report with the clinical nurse and you are seeing that person over that same period, you make a relationship. Because you are going there regularly and get used to the wording of the questionnaire you create a relationship with the staff and people are getting more trust. Half way through the study I was even signposted to a charity with six counselling sessions."

"Over the course of the study people developed greater trust in the people managing the trial and felt they could be more honest."

"I could well believe that as the participants felt more 'at home' with the study they responded more freely - reflecting an increase in numbers."

PROUD PPI responses

Given the somewhat lower prevalence of depressive symptoms among men in PROUD at baseline compared to the AURAH study (9.1% compared to 12.4%), and similar prevalence observed at month-12 and 24, it seems plausible that the reporting of depressive symptoms may have increased over the first year of the study, as suggested by the participants, due to familiarity with staff and access to support. Although not cited by participants in this survey, another interpretation that was put forth from a researchers point of view was that participants may have been reluctant to divulge information on mental health at baseline due to fear of study exclusion. Since the PROUD trial adhered to an inclusion criteria, it may be that fear of exclusion prevented some men from reporting (greater frequency of) symptoms. Alternatively, men who enrol in a trial such as PROUD are most likely at a point in their lives when they are not experiencing clinically significant depression, as the symptoms of depression may prevent/deter some individuals from active participation. The increase in depression prevalence observed may then reflect a regression to the mean effect.

Finally, the sub-theme of experience with PrEP (reported by four participants), was defined by three concepts; side effects, fear of loss of access, and stigma. Although it was stated that depression was not different among men in the immediate compared to deferred PrEP arm, in the initial email and the PPI survey, it is not surprising given the increase in depressive symptoms in the context of a PrEP trial that participants brought up concepts surrounding experiences with PrEP. One participant suggested that side effects of the drug itself might cause depression.

"I have experienced depression for the first time since I started the trial. I haven't made any significant changes to my lifestyle in this period. I cannot explain the increase in depression unless its a side effect of the drug."

PROUD PPI responses

Efavirenz in antiretroviral treatment of HIV-positive individuals has been linked to neuropsychiatric morbidity, suicidal ideation, and mental health diagnoses [(703)]. Oral FTC/TDF PrEP use has not however, been found to produce such sequelae [(360)].

The concept of fear of loss of access to PrEP is not surprising given that PrEP remained unavailable on the NHS in England over the course of the PROUD trial[xxxv]. This is despite the introduction of a subsidized programme in France in 2015, authorization by the European Medicines Agency in 2016, and availability on the NHS in Scotland in 2017.

"As the trial ran it course, I did become worried about the 'What if' I couldn't continue with the drug. It was a MASSIVE relief to know that I am able to, for a limited period at least, get truvada through clinic -."

PROUD PPI responses

The extent to which a delayed PrEP programme in England may have resulted in increased symptoms of depression is difficult to say. Cheaper generic versions of the drug online from overseas was not available until October 2015 [(87)].

Although the concept of stigma attached to PrEP use was only brought up by two individuals in this PPI survey, it is one that has received a lot of attention in research on PrEP acceptance and adherence.

"It would be easy to write about there being more condom free sex, and that there's stigma attached to doing that, and guilt and self loathing follow - but I don't think I have any personal evidence to back that hypothesis up, to be honest."

"You were negative but not part of the positive community, you were also not fully part of the negative community - difficult place to be! I just said I was HIV positive as it was too difficult to try to explain anything other!"

PROUD PPI responses

In section 1.5.3 of Chapter 1, the safe sex ethos that took hold of gay communities in the early 1980s is described. Against the backdrop of HIV, condom-protected sex took on greater social symbolic meaning beyond that of a barrier method to prevent STIs [(704)]. Individuals to whom this

[xxxv] PrEP remained unavailable on the NHS in England at the time of submitting this thesis in December 2017.

social practice was associated, were considered to be 'sexual citizens' of the gay community, 'good' and responsible men [705]. These notions remain somewhat entrenched in the community [704]. Accordingly, it has been suggested that disassociating PrEP use from the stigma attached to CLS has been challenging, given symbolic community virtues attached to condom-use [704]. In fact, three recent studies of PrEP acceptability and adherence in San Francisco [706], Thailand [707], and Kenya [708], found that PrEP-related stigma was the most commonly reported social harm to arise from PrEP research participation, and was negatively associated with acceptance and adherence. Although it is certainly plausible that PrEP-related stigma may be associated with psychological distress, as described above, being randomized to PrEP prescription in a clinical trial, has not been found to be associated with depressive symptoms on validated questionnaire instruments, neither in the PROUD trial itself, nor the iPrEX trial [360]. It may be that those individuals who experience PrEP-related stigma do not adhere to the medication and associated psychological distress may dissipate as a result. Investigating the relationship between PrEP-related stigma and depression may be complex.

7.4 Discussion

7.4.1 Summary of results

Among PROUD participants, depressive symptoms (PHQ-9≥10) were found to increase significantly from baseline (9.3%) to the 12-month questionnaire (14.4%). Younger men, those who were not employed, and those who reported crystal methamphetamine use in the past three months, were more likely to report depressive symptoms. There was some suggestion of association with report of no ongoing relationship, bisexual/straight-identity, higher-risk drinking, greater number of recreational drugs used, and chemsex-drug use, although findings were not statistically significant. Furthermore, no association was found with UK born/ethnicity, university education, or study region. Measures of IPV, internalised homophobia, and concealment of sexual identity, were strongly associated with depressive symptoms.

7.4.2 Prevalence of depressive symptoms

In PROUD, the prevalence of depressive symptoms (PHQ-9≥10) was 9.1% (49/540) at baseline, 14.4% (59/410) at the 12-month questionnaire, and 14.4% (48/333) at the 24-month questionnaire. Although depression prevalence tended to be higher in the immediate PrEP arm at baseline and throughout the study, prevalence did not differ significantly between trial arms at any time-point, which was in line with that reported in the iPrEX trial [360].

The prevalence of depressive symptoms on PHQ-9 at the 12- and 24-month questionnaire in PROUD was very similar to that among men who reported recent CLS with a man in the AURAH study (15.0%; n=122/815), and twice that observed in the general UK population in 2007/2008 (7% reported PHQ-9≥10) [672]. Natsal-3 (2010-2012) investigated the PHQ-2 and

found the prevalence to be 8.9% (95% CI: 5.5%, 14.3%, n/N= 17/190) among all MSM and 6.4% (95% CI: 3.5%, 11.7%, n/N= 7/107) among gay-identified MSM [342]. Using the same definition (PHQ-2≥3), the prevalence of depression in PROUD was 9.1% at baseline, 12.9% at the 12-month questionnaire, and 12.3% at the 24-month questionnaire. The prevalence of depression (PHQ-2≥3) in AURAH was 10.9% among MSM who reported recent anal CLS with a man. The prevalence of depressive symptoms may be: (i) elevated among MSM compared to the general population, and (ii) elevated among MSM engaging in recent CLS compared to the general MSM population. It is possible however, that other socio-demographic factors may confound this comparison and the number of MSM participating in Natsal-3 was small (n=190).

The prevalence of other depression measures on PHQ-9 at the 12- and 24-month questionnaire in PROUD appears to be similar to that among men who reported recent CLS in the AURAH study. For instance, the prevalence of a major depressive syndrome on PHQ-9 was 9.0% at the 12-month questionnaire in PROUD and 7.7% among men who reported recent CLS with a man in AURAH. The prevalence of suicidal ideation was 11.2% at the 12-month questionnaire in PROUD and 14.1% among men who reported recent CLS with a man in AURAH.

7.4.3 Receiving antidepressant medication at baseline

In the PROUD trial, the prevalence of men with depression who were receiving antidepressant medication at baseline was 54.1%[xxxvi]. In the AURAH study, the prevalence of men with depression who were receiving medical treatment or therapy for depression was 51.0%. In both studies there appears to be some evidence of potential under treatment of possible clinically significant depressive conditions, see section 4.4.6 for a discussion of possible under treatment.

7.4.4 Socio-demographic and lifestyle factors associated with depressive symptoms

In the PROUD trial, younger men, those who did not report being employed, and those who reported methamphetamine use in the past three months were significantly more likely to report depressive symptoms at baseline. Markers of socio-economic hardship (not being employed and non-university education) were associated with measures of depressive symptoms on PHQ-9 in GEE models combining data from all three time-points.

Younger age [346, 358, 360, 364, 415, 454, 606-609], markers of lower socio-economic status [346, 347, 354, 356, 364, 371, 415, 454, 606, 681], lower levels of a supportive network [358, 415, 454], reporting a bisexual identity [354, 415, 679, 680], and recreational drug use [41, 346, 358, 454, 564, 606-609] appear to be important factors for depression in the MSM literature, and this is also what was found to be the case in the AURAH study (Table 5 and Figure 17). Findings from the general UK population also suggest a

[xxxvi] However, it should be noted that the prevalence of depressive symptoms at baseline may have been underreported. This may have resulted in an overestimation of receipt of treatment, but since the measure of treatment did not include therapies other than pharmacological ones, the true prevalence of treatment is likely to be higher.

critical role of socio-economic hardship in poor mental health [348-350]. Although the pattern of associations was very similar in the PROUD trial, some of the differences observed (i.e. between sexual identities and number of recreational drugs used) were not significant. Of note, the non-significant associations observed with chemsex-associated drug use at baseline and report of sexualized drug use at follow-up in PROUD, is discussed in detail in section 7.3.8 above, in the context of participant interpretations of the increase in depression. It may be that due to the limited sample size of the PROUD trial, differences that may exist were not detected. It is also important to note that PROUD consisted of a unique sample of men who all reported high levels of CLS and agreed to participate in an RCT.

Findings from the SEM in Chapter 6 also suggest that being in an ongoing relationship with a partner may lead to lower levels of depressive symptoms via higher levels of a supportive network. At the same time, however, there is some evidence to suggest that being in an ongoing relationship may also lead to higher levels of depressive symptoms among men who do not feel supported by their partner.

7.4.5 Psychosocial factors associated with depressive symptoms

In section 2.5.3.2 of Chapter 2, psychological theories are described, which posit that exposure to abuse as a child and re-victimization/re-enactment in adulthood may distort one's perception of self, particularly one's sense of worthiness, and ability to influence important outcomes in one's life. In two systematic reviews of studies, mainly in the U.S., conducted from 1985-1997 [709] and 1966-2008 [710], markers of CSA were consistently linked to depression measures among the general male population [709]. There is some evidence to suggest, as described in section 2.6.3.2, that CSA is associated with depression [41, 368, 610] and suicidality [610] among MSM. In the PROUD trial, reporting anal intercourse at age 12 or younger was investigated since this measure may include experiences of CSA. A young age at anal sex debut was not associated with measures of depression on PHQ-9. This may be as a result of lack of power and/or this measure may not reflect or pick up all sexual abuse experienced, as some participants may not have experienced forced/coerced sex and some CSA may occur at an older age.

However, strong associations were found between IPV victimization and perpetration and depression measures in the PROUD trial. As described in section 2.6.3.2, evidence from a recent meta-analysis suggests that IPV is associated with depression among MSM [605]. One UK study has investigated the link between IPV and depressive symptoms among MSM [711]. In this cross-sectional survey (2010-2011) of men attending a GUM clinic in London, the same IPV questions as those included in PROUD were asked about (with the exclusion of 'forced to have sex without a condom'). In the London study, among self-identified gay or bisexual men, 33.9% (176/519) reported any IPV victimization and 16.3% (83/510) reported any IPV perpetration [711]. Current depression was measured using HADS (≥8), the prevalence was 12%. Men who

reported IPV perpetration in the past year were twice as likely to report current depression compared to men who did not (20.7% vs. 11.5%). After adjusting for age, income, education, and ethnicity, the association was attenuated to borderline significance (OR 3.7 95% CI: 1.0, 14.6; *p=0.060*). Associations with other measures of IPV were not significant in unadjusted or adjusted analysis. Compared to this clinic sample of MSM in London, men in the PROUD trial reported a higher prevalence of IPV and there were more consistent associations with depressive symptoms.

In terms of IPV in the general population, in the APMS (see section 1.8.1), which collected a multistage random sample of adults living in private households in England in 2007 (n=7047), 23.4% (18.7% of men and 27.8% of women) reported any IPV victimization (physical and/or emotional/psychological), and 5.9% reported any IPV victimization in the past year. After adjusting for socio-demographic factors, any IPV victimization (overall OR 2.8 95% CI: 2.4, 3.3; men OR 2.8 95% CI: 2.2, 3.6; women OR 2.8 95% CI: 2.4, 3.5) and IPV victimization in the past year (overall OR 3.3 95% CI: 2.5, 4.3; men OR 2.7 95% CI: 2.5, 4.3; women OR 3.8 95% CI: 2.7, 5.2) was associated with a composite measure of common mental health disorders[xxxvii] on the CIS-R [712]. Given these findings and that of PROUD, it is surprising that an association with IPV victimization was not found in the London GUM clinic sample of MSM described above. However it is of note, that in the clinic sample the pattern of associations with each individual IPV question, although not statistically significant, was equivalent to that found in PROUD. Perhaps IPV is not as strongly associated with a mild depressive mood as captured on HADS≥8. However, all measures of IPV were associated with major and other depressive syndromes on PHQ-9 in the PROUD trial. Perhaps the small sample size of the clinic study (N=519) prevented the detection of an association. In addition, in the clinic sample, models were adjusted for socio-demographic factors including income. In a recent qualitative study, dyadic inequalities (including education and income differentials) increased the risk of experiencing control and abuse from a partner [713], therefore adjustment for income may have obscured the association between IPV and depressive symptoms. Unfortunately, it was not possible in the PROUD trial to investigate the confounding effect of income/financial security.

Results from PROUD (at month-12 and in GEE models), showed that negative attitudes towards gay sexuality (potentially indicative of internalised homophobia), were associated with all measures of depression on PHQ-9. Furthermore, there was some evidence from month-24 and GEE analyses that lower levels of disclosure of sexual orientation were associated with depressive symptom measures. As described in detail in Chapter 1, extensive theoretical [209, 210, 226, 227, 229, 235-238, 240, 241, 245-247] and epidemiological research [341, 346, 347] has linked stress related to sexual minority status to poor mental health outcomes.

[xxxvii] This includes depressive episodes, mixed anxiety/depression, GAD, panic disorder, phobia, and/or OCD.

Although it was not possible to investigate measures of internalised homophobia in the AURAH study, disclosure of sexual orientation to few/no work colleagues was also associated with depressive symptoms (Table 5 in Chapter 4). In addition, findings from the SEM in Chapter 6 extend AURAH and PROUD findings and suggest that concealment of sexual identity may be associated with depression indirectly through less frequent visits to gay venues and lower levels of a supportive network.

7.4.6 Change in depression over the PROUD trial

Although strong associations were found of psychosocial factors (including IPV and internalised homophobia) with an increase in depression score and incidence of depressive symptoms (from baseline to month-12), there was no evidence to suggest that the increase in depressive symptoms was explained by an increasing prevalence of adverse psychosocial factors over the first year of study. Further evidence for this comes from responses to a question asked after enquiry about IPV; 'If you answered yes in the last year to any question above, do you think joining PROUD has influenced these behaviours?' Of the 70 men who reported IPV in the past year at the 12-month questionnaire, 72.9% said joining PROUD had not influenced these behaviours and 21.4% said 'yes in a positive way' (5.7% had a missing response and no men responded 'yes in a negative way'). Proportions were similar at the 24-month questionnaire. This also implies that IPV did not increase over the time of the study.

Based on findings, it is possible that social-desirability bias and fear of study ineligibility may have accounted for the lower prevalence of suicidal ideation and depressive symptoms observed among the 353 men who completed enrolment after April 2013 and were asked to disclose to study personnel whether they had suicidal thoughts. The assurance of study participation at month-12 and greater familiarity with study staff may explain the observed increase. This interpretation of findings may also be useful in understanding the lower prevalence of suicidal ideation observed among men in the deferred PrEP arm compared to men in the immediate PrEP arm at the 12-month questionnaire. Perhaps men in the deferred arm were hesitant to disclose suicidal thoughts prior to being prescribed PrEP, again for fear of further deferral or study exclusion. This may be reflected in the fact that the prevalence of suicidal ideation increased significantly from the 12- to 24-month questionnaire among men in the deferred arm.

Possible reasons for the increase in reporting of depressive symptoms at the 12-month questionnaire were also given by a small group of participants themselves as part of a PPI survey on PROUD findings. These reasons have been discussed in results section 7.3.8. Briefly, participants identified four main reasons why depression might have increased. The first was that economic instability in the UK may have accounted for the increase in depressive symptoms observed. The second was that risk-taking may be an important determinant of depression in general. Emphasis was often placed on the role that chemsex and associated

CLS may play in mental health, including anxiety and depression. None of the participants specifically theorized that engagement in chemsex increased over the study, thereby explaining the increase in depressive symptoms, however, chemsex was a clear feature in discourse on depression. The third reason was that depressive symptoms may have increased from the time of enrolment since participants were regularly confronted with their recent sexual activity and possible risk-taking due to frequent STI screening and questionnaire taking. Despite reporting that depressive symptoms increased overall among study participants and that no difference was observed between the immediate and deferred PrEP groups, the fourth main reason given concerned experiences with PrEP. This included possible side-effects, stigma attached to using PrEP, and fear of loss of access to PrEP after study completion. Of the PrEP related issues brought up in the context of depression, the concept of stigma was predominantly cited. Finally, participants also suggested that reporting depressive symptoms may have been easier as the study progressed due to greater familiarity with the questionnaire and study staff, and as a result of being a part of the clinical trial process, where access to support was available.

7.4.7 Limitations

The general methodological limitations of the PROUD trial are discussed in section 3.7.2 of Chapter 3. In this specific analysis, it is important to note that the measure of higher-risk drinking was based on the first two questions of the WHO AUDIT-C questionnaire, however, the prevalence may be slightly overestimated since the categories included in the PROUD questionnaire for the first WHO AUDIT-C question are 1 frequency lower (see section 3.3.10). Men were asked about the use of three recreational drugs commonly used in the context of chemsex, however, men were not asked in PROUD whether these drugs had been taken before or during sex. In addition, reporting anal intercourse at a very young age was investigated since this measure may include experiences of CSA. However, since it was not known whether the male sexual debut partner with whom the participant referred was an adult/significantly older and if they felt forced, there was most likely measurement error when attempting to capture experiences of CSA among PROUD participants.

In addition, socio-demographic and lifestyle factors, including the number and type of recreational drugs used in the past three months and report of higher-risk drinking, were only collected at the baseline questionnaire, even though these factors may change over time. It was deemed inappropriate to investigate relationship status and lifestyle factors in GEE models, which would have necessitated carrying forward the baseline value to month-12/24 (see section 3.6.8). It was also only possible to investigate the association between psychosocial factors and depressive symptoms in GEE models among the 436 men with data at the 12- and/or 24-month questionnaire. Furthermore, information on financial security and levels of a supportive network was not collected in the PROUD trial. These factors have been found to be important in the context of depression among MSM. Based on the SEM in Chapter 6, a supportive network was found to be the most ‘important’ factor for depression in the model. It is also of note, that cross-

sectional associations were investigated in this chapter, prohibiting us from making inferences about causality. Finally, when interpreting findings presented in Appendix section 11.18 Table 79, based on the change in depression score from baseline to month-12, it is important to note that the differences between some scores on the PHQ-9 may not be clinically meaningful. Therefore, although a significant difference in means may be detected, this does not necessarily translate into changes of clinical importance.

7.4.8 Summary of discussion

The prevalence of depressive symptoms at month-12 and 24 in the PROUD trial of men, who were required to report CLS in the past three months at enrolment, was similar to that reported by men in the AURAH study who reported recent CLS with a man. Although strong associations were found between psychosocial factors and depressive symptoms, there was no evidence (based on data available) to suggest that these measures increased over the course of the first year of study, thereby explaining an increase in depressive symptoms from baseline. The finding that report of suicidal ideation at enrolment decreased after April 2013 lends support to the notion that some men may have underreported depressive symptoms at baseline. Greater familiarity with the study over time may explain the increase in prevalence of symptoms at month-12, as reiterated by some PROUD participants when asked for their interpretation. Other participant interpretations included socio-economic hardship, chemsex and CLS, and PrEP-related stigma.

Chapter 8

8 Investigating the relationship between depressive symptoms and sexual behaviour among gay, bisexual, and other men who have sex with men in the PROUD trial

8.1 Introduction

Symptoms of depression have been found to be associated with increased sexual risk behaviour (and HIV seroconversion [369]) in a number of studies of MSM [353-368], mainly in the U.S. Three European studies have investigated this relationship. The first was conducted in 1999 among a UK GUM clinic sample of 122 MSM [355] and the second in 2008 among a Belgian volunteer and online sample of 591 HIV-negative MSM [358]. Depressive symptoms were associated with CLS measures in both studies. The third is the AURAH study, under investigation in this thesis, and for which the findings are presented in detail in Chapters 4, 5, and 6. Depressive symptoms were found to have moderate to strong associations with measures of CLS in the past three months and with bacterial STI diagnosis and PEP use in the past year, including after adjustment for socio-demographic factors and additional adjustment for smoking, higher-risk drinking and recreational drug use. Low self-efficacy for sexual safety was found to mediate this association. Further analyses using SEM (chapter 6) supported this, and found evidence that higher levels of recent recreational drug use also mediate this association in a separate pathway, albeit to a lesser extent. The extent to which the relationship between depression and sexual risk is present in different samples of UK/European MSM still remains unclear. The aim of this chapter was to investigate the relationship between depressive symptoms and levels of CLS, and other aspects of sexual behaviour, among men in the PROUD trial. The analyses presented here are similar to those conducted among MSM in the AURAH study, in Chapter 5. However, there is an important difference due to the sample under study. The AURAH analyses compared men having condom-protected sex to men having CLS. The PROUD sample consists solely of men who reported anal CLS with a man in the past three months at enrolment and that it was likely in their opinion that they would have CLS in the next three months. The PROUD analysis therefore addresses a different question in that it compares men having higher levels of CLS to men having lower levels of CLS, in other words, assesses the role of depressive symptoms among a group of men with a higher sexual risk profile.

8.2 Statistical methods

A detailed description of the variables investigated for analyses presented in this Chapter is included in Chapter 3 section 3.3.6.

The prevalence of each derived sexual behaviour measure is presented for PROUD participants at baseline, month-12, and month-24 (see section 3.3.8). The proportion of missing responses to each sexual behaviour measure is also presented.

The cross-sectional association of depressive symptoms (PHQ≥10) with sexual behaviours at baseline and at the 12- and 24-month questionnaire, was assessed using χ^2 tests, χ^2 tests for trend, and Fisher's exact test (when expected numbers were small) for univariable analysis, and modified Poisson regression with a robust variance estimator in order to produce adjusted prevalence ratios [645]. At baseline, associations were adjusted for key socio-demographic factors and then additionally adjusted for lifestyle factors (see section 3.6.8). At the 12- and 24-month questionnaires, key socio-demographic factors, with the exception of ongoing relationship, were adjusted for. Lifestyle factors were not adjusted for at the 12- or 24-month questionnaire (see section 3.6.8). At each time-point, adjusted estimates of those associations that were found to be significant in univariable analysis ($p \leq 0.05$) are presented in tables. Sensitivity analyses were undertaken using different PHQ-9-based definitions of depressive symptoms (major depressive syndrome and major and other depressive syndromes), including suicidal ideation. The association between antidepressant use at baseline and sexual behaviour measures was also described. Of note, although baseline associations are presented in this chapter, findings from Chapter 7, as discussed in section 7.4.6, do suggest that symptoms of depression on PHQ-9 were underreported at the baseline questionnaire. It may, therefore, be necessary to interpret the baseline findings with caution.

Poisson GEE models (see section 3.6.7) were also used to assess the association of depressive symptoms with sexual behaviour measures pooled across time-points. Each sexual behaviour measure was investigated as a time-varying dependent variable in separate GEE models. Information on PEP use and rectal STI diagnosis in the past year was only collected at baseline, therefore these variables were not investigated in the GEE analysis. Associations are presented unadjusted, adjusted for key socio-demographic factors, and adjusted for key socio-demographic factors and psychosocial factors (see section 3.6.8). Of note, given the observed increase in depressive symptoms over the first year of PROUD (see section 7.3.1), it was investigated whether adjusting additionally for study time-point affected the socio-demographic adjusted associations between depressive symptoms and sexual behaviour measures in GEEs. A sensitivity analysis was undertaken using different PHQ-9-based definitions of depressive symptoms, including suicidal ideation, as time-varying independent variables in GEE models. Associations are presented unadjusted and adjusted for key socio-demographic factors.

It was considered whether, in the immediate PrEP arm, CLS may no longer be the sexual risk activity, and that instead, 'risk' would shift to PrEP adherence. It was therefore, thought to be possible that a relationship between depression and CLS may not be observed in the immediate PrEP arm, but may be observed in the deferred PrEP arm. Accordingly, it was investigated whether the study trial arm (immediate versus deferred PrEP) significantly moderated the association between depressive symptoms (PHQ-9≥10) and sexual behaviour measures at month-12 and 24 using modified Poisson regression, and in GEE models combining data from

month-12 and 24. At the 12-month questionnaire, it was also investigated whether PrEP prescription (includes all men randomized to the immediate PrEP arm and 25 men in the deferred PrEP arm) moderated the association. The potential moderating effects of recreational drug use (poly-drug use, chemsex-associated drug use, and club-drug use) at baseline (using modified Poisson models) and reporting any IPV victimization and age <13 years at anal sex debut, at month-12 and 24 (using GEEs) was also investigated. The presence of an interaction would indicate the need to present separate findings.

In order to put the PROUD findings into context, a number of additional analyses from AURAH are included in this chapter. Unadjusted and adjusted associations of depressive symptoms with sexual behaviour measures in AURAH are presented specifically among the group of men who reported anal CLS with a man in the past three months (N=815), as well as the whole sample of 1340 men reporting recent anal or vaginal sex. For these analyses, logistic regression was used in order to produce ORs. Although PRs offer greater ease of interpretation, ORs have the advantage that the magnitude can more easily be compared across the different AURAH subgroups (see section 3.6.2). In addition, the prevalence of depressive symptoms (PHQ-9≥10) in AURAH was examined according to the amount of sex/CLS men reported. Presenting these findings in a scatter plot provides a visual representation of the relationship between depression and increasing sexual risk behaviour.

The association of depression symptoms (PHQ-9≥10) with high self-efficacy for sexual safety, difficulty saying no to unwanted sex, and happiness with one's sex life, and the association of these self-efficacy measures with sexual behaviours was investigated at month-12 and/or 24 in the PROUD sample. Findings from modified Poisson regression are presented unadjusted and adjusted for key socio-demographic factors at each time-point. Findings from GEE models are presented unadjusted, adjusted for key socio-demographic factors, and adjusted for key socio-demographic factors and psychosocial factors (see section 3.6.8), using measures pooled across each time-point. Sensitivity analyses were undertaken using different PHQ-9-based definitions of depressive symptoms, including suicidal ideation, at month-12 and 24. Of note, based on the results of this chapter, the causal steps approach to mediational analysis was not investigated further and an SEM was not carried out.

The association of depressive symptoms (PHQ-9≥10) with reasons reported for non-condom-use at last CLS was investigated at baseline, month-12, and month-24 in unadjusted analysis, and in GEE models combining data from all three time-points. GEE models are presented unadjusted and adjusted for key socio-demographic factors (see section 3.6.8).

The cross-sectional association of socio-demographic and lifestyle factors with sexual behaviours at baseline was assessed in unadjusted analysis. The associations of IPV measures and age at anal sex debut with sexual behaviours, were investigated at month-12 and 24 using

modified Poisson regression, and in GEE models combining data from month-12 and 24. GEE models are presented unadjusted and adjusted for key socio-demographic factors.

Finally, as part of the PPI survey described in detail in Chapter 7 section 7.2, participants were asked to help us interpret PROUD findings on the relationship between depressive symptoms and measures of sexual behaviour. When reviewing participant responses to this survey, a thematic analysis approach was taken. A summary of responses is given in this chapter.

8.3 Results

8.3.1 Prevalence of sexual behaviour measures

The prevalence of each sexual behaviour measure according to questionnaire time-point is presented in Table 26. Among the 540 men at baseline, based on a recall period of three months; 75.9% reported CLS with two or more partners, 40.9% reported CLS with five or more partners, 12.0% reported CLS with an HIV-positive partner not known to be on HIV treatment, 6.5% reported receptive CLS with an HIV-positive partner not known to be on treatment, 27.0% reported an unknown or HIV-positive partner not known to be on treatment at last CLS, 37.0% reported ten or more new sex partners, and 32.4% of men reported receptive anal sex with ten or more partners. Furthermore, 34.1% of men reported PEP use and 37.0% reported rectal STI diagnosis in the past year. Prevalence of CLS measures and partner numbers were broadly similar at the 12- and 24-month time-points compared to baseline. At the 12- (N=410) and 24-month (N=33) follow-ups, 34.6% and 49.0% of men reported group sex in the past three months respectively.

With the exception of the rectal STI diagnosis questions, the proportion of missing values for each sexual behaviour question across all time-points, was ≤5% (the proportion of missing values for PEP use at baseline was very slightly higher at 5.6%), see Appendix section 11.20 Table 81. Overall 9.3% of men had a missing response to rectal chlamydia, rectal gonorrhoea, syphilis, and LGV. The high proportion of missing values for the rectal STI diagnosis questions may not be surprising given the layout of the main STI question: ‘In the past 12 months have you been diagnosed with any of the following?’, a list of STIs with yes/no boxes was then provided. It may have been a common pattern, as was considered to be the case with depressive symptoms on PHQ-9, for participants to only identify and tick those STIs that they recognized or had been diagnosed with. It was therefore, deemed appropriate to consider a non-response to indicate no STI diagnosis.

Table 26: Prevalence of sexual behaviour measures[b] at baseline and the 12- and 24-month questionnaires in PROUD

	Baseline [N=540]	12-month [N=410]	24-month [N=333]
	n (%)	n (%)	n (%)
CLS with 2+ partners (past three months)	410 (75.9%)	303 (73.9%)	249 (74.8%)
CLS with 5+ partners (past three months)	221 (40.9%)	189 (46.1%)	172 (51.7%)
CLS with HIV+ partner[a] (past three months)	65 (12.0%)	44 (10.7%)	42 (12.6%)
Receptive CLS with HIV+ partner[a] (past three months)	35 (6.5%)	26 (6.3%)	29 (8.7%)
Unknown/HIV+ partner[a] at last CLS (past three months)	146 (27.0%)	100 (24.4%)	67 (20.1%)
10+ new sex partners (past three months)	200 (37.0%)	119 (29.0%)	95 (28.5%)
Receptive anal sex with 10+ partners (past three months)	175 (32.4%)	118 (28.8%)	98 (29.4%)
Group sex (past three months)	/	224 (34.6%)	163 (49.0%)
PEP use (past year)	184 (34.1%)	/	/
Rectal STI diagnosis (past year)	200 (37.0%)	/	/

[a] Not known to be on HIV treatment.
[b] For a definition of each measure see section 3.3.8 in Chapter 3.

8.3.2 Relationship between depressive symptoms and sexual behaviour measures

Table 27 presents the unadjusted associations between depressive symptom measures on PHQ-9 and sexual behaviour measures at baseline. Depressive symptoms (PHQ-9≥10) were not significantly associated with any of the CLS measures in unadjusted analysis, although there was some suggestion that men with depressive symptoms were more likely to report an unknown status or HIV-positive untreated partner at last CLS and receptive anal sex with ten or more partners in the past three months. Depressive symptoms were however, associated with PEP use in the past year, whereby men with depressive symptoms were more likely to report PEP use in the past year compared to men without depressive symptoms. This association remained, with some attenuation, after adjustment for key socio-demographic factors and additional adjustment for higher-risk drinking and number of recreational drugs used, Table 28. Of note, men who reported CLS with an HIV-positive partner not known to be on treatment, receptive CLS with an HIV-positive partner not known to be on treatment, ten or more new anal sex partners, and receptive anal sex with ten or more partners, were more likely to report PEP use than men who did not (50.8% vs. 31.8%; 57.1% vs. 32.5%; 48.5% vs. 25.6%; 50.9% vs. 26.0%; all χ^2 p-values ≤0.003, respectively).

The relationship between depressive symptoms and sexual behaviour measures was not significantly different among: (i) men who reported poly-drug use and men who did not, (ii) men who reported chemsex-associated drug use and men who did not, and (iii) men who reported club-drug use and men who did not, in unadjusted or adjusted analysis. The interaction p-values were not significant for any of the sexual behaviour measures (p>0.05).

In the sensitivity analyses, the measure of major and other depressive syndromes on PHQ-9 was also associated with PEP use in the past year in unadjusted (Table 27) and adjusted analysis (Table 28). Major depressive syndrome and suicidal ideation on PHQ-9 had a borderline significant association with PEP use in unadjusted (Table 27) and adjusted analysis (Table 28). In addition, major depressive syndrome and suicidal ideation was associated with report of an unknown or HIV-positive status partner (not known to be on treatment) at last CLS in unadjusted (Table 27) and adjusted analysis (Table 29). Finally, antidepressant use at baseline was not associated with sexual behaviour measures in unadjusted analysis (e.g. 37.0% of men reporting antidepressant use and 41.3% of men not reporting antidepressant use, reported ≥5CLS partners; Pearson χ^2 test p=0.567).

Table 27: Unadjusted associations of depressive symptom measures on PHQ-9 with sexual behaviour measures in the past three months at baseline in PROUD

N=540		CLS with 2+ partners [n=410;75.9%]	CLS with 5+ partners [n=221;40.9%]	CLS with HIV+ partner not treated [n=65;12.0%]	Receptive CLS with HIV+ partner not treated [n=35;6.5%]	Unknown/HIV+ partner not treated at last CLS [n=146;27.0%]	10+ new sex partners [n=200;37.0%]	Receptive anal sex with 10+ partners [n=175;32.4%]	PEP use (past year) [n=184;34.1%]	Rectal STI diagnosis (past year) [n=200;37.0%]
		% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]
Depressive symptoms (PHQ9≥10)	Yes	73.5%	44.9%	10.2%	8.2%	34.7%	38.8%	42.9%	51.0%	38.8%
	No	76.2%	40.5%	12.2%	6.3%	26.3%	36.9%	31.4%	32.4%	36.9%
		0.673	*0.553*	*0.679*	*0.546*[b]	*0.206*	*0.792*	*0.101*	*0.009*	*0.792*
Major depressive syndrome	Yes	77.8%	51.9%	7.4%	7.4%	44.4%	44.4%	40.7%	51.9%	44.4%
	No	75.8%	40.4%	12.3%	6.4%	26.1%	36.7%	32.0%	33.1%	36.7%
		0.817	*0.236*	*0.760*[b]	*0.692*[b]	*0.037*	*0.413*	*0.343*	*0.046*	*0.413*
Major & other depressive syndromes	Yes	77.1%	52.1%	10.4%	10.4%	35.4%	43.8%	37.5%	47.9%	47.9%
	No	75.8%	39.8%	12.2%	6.1%	26.2%	36.4%	31.9%	32.7%	36.0%
		0.844	*0.100*	*0.718*	*0.225*[b]	*0.171*	*0.313*	*0.430*	*0.034*	*0.102*
Suicidal ideation	Yes	83.1%	45.8%	13.6%	8.5%	39.0%	35.6%	33.9%	45.8%	39.0%
	No	75.1%	40.3%	11.9%	6.2%	25.6%	37.2%	32.2%	32.6%	36.8%
		0.175	*0.423*	*0.703*	*0.571*[b]	*0.029*	*0.808*	*0.795*	*0.045*	*0.743*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

Table 28: Unadjusted and adjusted associations of depressive symptom measures on PHQ-9 with PEP use at baseline of PROUD

N=540 men	PEP use in the past year [n=184; 34.1%]		
	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Adjusted[c] PR [95% CI] *p-value*[a]
Depressive symptoms (PHQ-9≥10)	1.58 [1.16, 2.13] *0.003*	1.50 [1.10, 2.03] *0.010*	1.47 [1.08, 1.98] *0.013*
Major depressive syndrome	1.56 [1.07, 2.30] *0.022*	1.47 [0.99, 2.18] *0.055*	1.47 [0.98, 2.20] *0.062*
Major & other depressive syndromes	1.46 [1.06, 2.02] *0.020*	1.40 [1.01, 1.93] *0.043*	1.41 [1.02, 1.94] *0.038*
Suicidal ideation	1.40 [1.03, 1.90] *0.031*	1.35 [0.98, 1.87] *0.062*	1.35 [0.99, 1.84] *0.055*

[a] p-value by Wald test using Poisson regression.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, relationship status, and London study clinic site.
[c] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, relationship status, London study clinic site, higher-risk drinking, and number of recreational drugs used.

Table 29: Unadjusted and adjusted associations of depressive symptom measures on PHQ-9 with last CLS with an unknown/HIV-positive status partner (not believed to be on treatment) at baseline of PROUD

N=540 men	Unknown/HIV+ partner not treated at last CLS [n=146; 27.0%]		
	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Adjusted[c] PR [95% CI] *p-value*[a]
Major depressive syndrome	1.70 [1.09, 2.66] *0.020*	1.84 [1.17, 2.89] *0.008*	1.89 [1.19, 2.98] *0.007*
Suicidal ideation	1.52 [1.07, 2.17] *0.020*	1.52 [1.06, 2.18] *0.023*	1.51 [1.05, 2.17] *0.026*

[a] p-value by Wald test using Poisson regression.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, relationship status, and London study clinic site.
[c] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, relationship status, London study clinic site, higher-risk drinking, and number of recreational drugs used.

The relationship between depressive symptoms (PHQ-9≥10) and sexual behaviour measures was similar at the 12-month questionnaire, see Table 30. There were fewer numbers of men at follow-up, but still no evidence of an association with measures of CLS and partner numbers in unadjusted analysis. In the sensitivity analyses, patterns of association were similar for the other depressive symptom measures on PHQ-9, including suicidal ideation.

The relationship between depressive symptoms (PHQ-9≥10) and sexual behaviour measures was again, similar at the 24-month questionnaire, Table 31. In the sensitivity analyses, similar to

the baseline investigation, a major depressive syndrome on PHQ-9 was associated with report of an unknown or HIV-positive status partner (not known to be on treatment) at last CLS at the 24-month questionnaire, in unadjusted (Table 31) and adjusted analysis (Table 32).

Table 30: Unadjusted associations of depressive symptom measures on PHQ-9 with sexual behaviour measures in the past three months at the 12-month questionnaire in PROUD

N=410		CLS with 2+ partners [n=303;73.9%]	CLS with 5+ partners [n=189;46.1%]	CLS with HIV+ partner not treated [n=44;10.7%]	Receptive CLS with HIV+ partner not treated [n=26; 6.3%]	Unknown/HIV+ partner not treated at last CLS [n=100; 24.4%]	10+ new sex partners [n=119;29.0%]	Receptive anal sex with 10+ partners [n=118;28.8%]	Group sex [n=224; 54.6%]
		% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]
Depressive symptoms (PHQ-9≥10)	Yes	71.2%	42.4%	6.8%	1.7%	23.7%	28.8%	30.5%	50.9%
	No	74.4%	46.7%	11.4%	7.1%	24.5%	29.1%	28.5%	55.3%
		0.608	*0.535*	*0.289*	*0.150*	*0.898*	*0.969*	*0.751*	*0.528*
Major depressive syndrome	Yes	75.7%	46.0%	2.7%	0.0%	21.6%	29.7%	32.4%	51.4%
	No	73.7%	46.1%	11.5%	7.0%	24.7%	29.0%	28.4%	55.0%
		0.797	*0.985*	*0.158*[b]	*0.152*[b]	*0.681*	*0.921*	*0.607*	*0.674*
Major & other depressive syndromes	Yes	78.4%	54.9%	5.9%	2.0%	31.4%	29.4%	37.3%	56.9%
	No	73.3%	44.9%	11.4%	7.0%	23.4%	29.0%	27.6%	54.3%
		0.431	*0.178*	*0.232*	*0.228*	*0.215*	*0.948*	*0.153*	*0.733*
Suicidal ideation	Yes	71.7%	52.2%	4.4%	0.0%	26.1%	32.6%	32.6%	54.4%
	No	74.2%	45.3%	11.5%	7.1%	24.2%	28.6%	28.3%	54.7%
		0.723	*0.380*	*0.204*	*0.098*[b]	*0.776*	*0.570*	*0.543*	*0.967*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

Table 31: Unadjusted associations of depressive symptom measures on PHQ-9 with sexual behaviour measures in the past three months at the 24-month questionnaire in PROUD

N=333		CLS with 2+ partners [n=249; 74.8%]	CLS with 5+ partners [n=172; 51.7%]	CLS with HIV+ partner not treated [n=42;12.6%]	Receptive CLS with HIV+ partner not treated [n=29; 8.7%]	Unknown/HIV+ partner not treated at last CLS [n=67; 20.1%]	10+ new sex partners [n=95; 28.5%]	Receptive anal sex with 10+ partners [n=98; 29.4%]	Group sex [n=163; 49.0%]
		% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]
Depressive symptoms (PHQ-9≥10)	Yes	68.8%	39.6%	12.5%	8.3%	27.1%	29.2%	27.1%	52.1%
	No	75.8%	53.7%	12.6%	8.8%	19.0%	28.4%	29.8%	48.4%
		0.299	*0.071*	*0.980*	*0.591*[b]	*0.193*	*0.916*	*0.700*	*0.639*
Major depressive syndrome	Yes	69.0%	41.4%	10.3%	6.9%	41.4%	27.6%	24.1%	51.7%
	No	75.3%	52.6%	12.8%	8.9%	18.1%	28.6%	29.9%	48.7%
		0.451	*0.247*	*0.488*[b]	*0.526*[b]	*0.003*	*0.906*	*0.513*	*0.754*
Major & other depressive syndromes	Yes	68.3%	39.0%	9.8%	7.3%	29.3%	24.4%	29.3%	56.1%
	No	75.7%	53.4%	13.0%	8.9%	18.8%	29.1%	29.5%	48.0%
		0.307	*0.084*	*0.556*	0.509[b]	*0.119*	*0.531*	*0.981*	*0.328*
Suicidal ideation	Yes	75.0%	48.1%	11.5%	9.6%	25.0%	38.5%	34.6%	51.9%
	No	74.7%	52.3%	12.8%	8.5%	19.2%	26.7%	28.5%	48.4%
		0.968	*0.574*	*0.800*	*0.801*	*0.339*	*0.084*	*0.372*	*0.640*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

Table 32: Unadjusted and adjusted associations of a major depressive syndrome on PHQ-9 with last CLS with an unknown/HIV-positive status partner (not believed to be on treatment) at the 24-month questionnaire in PROUD

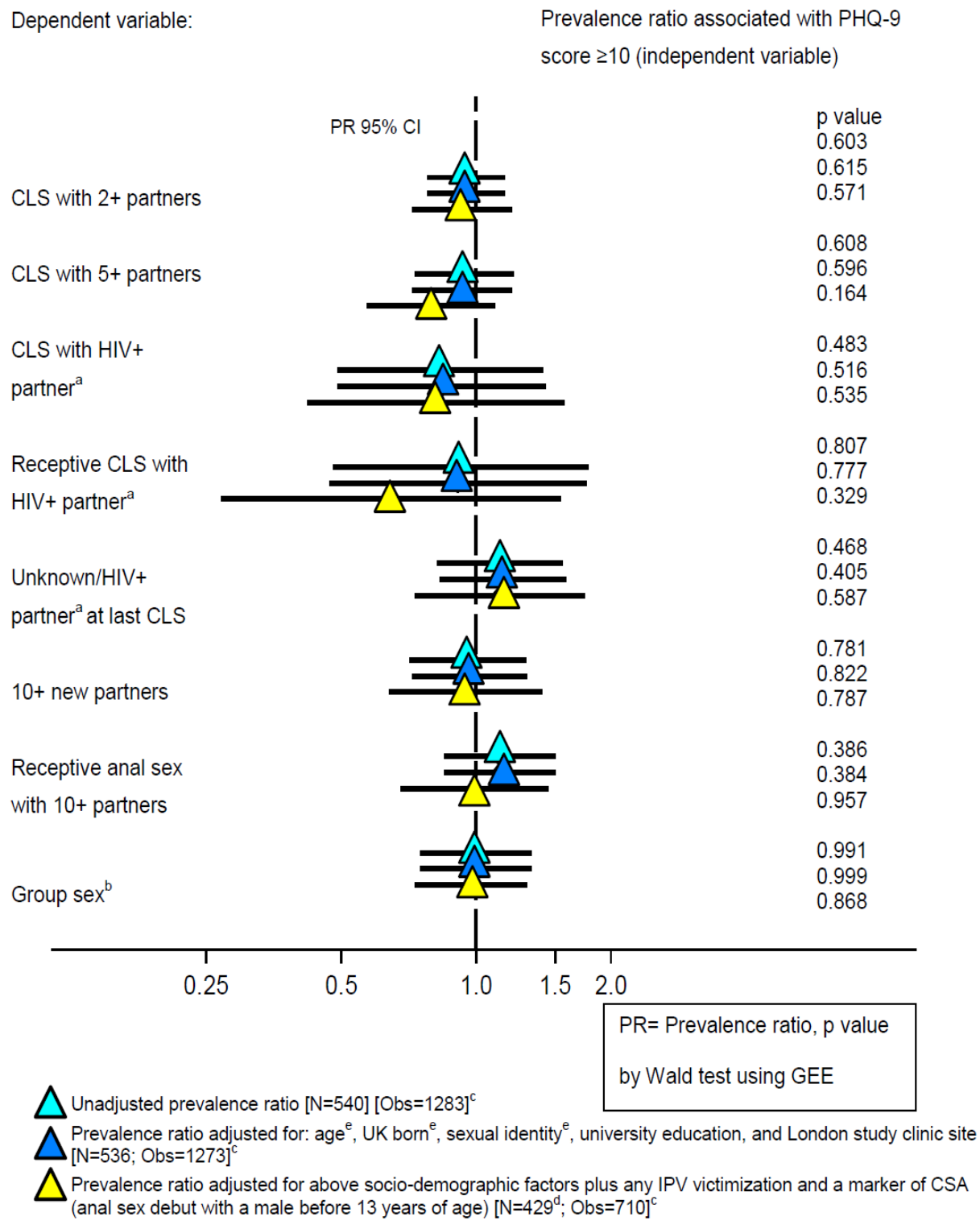
N=333	Unknown/HIV+ partner not treated at last CLS [n=67; 20.1%]	
	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]
Major depressive syndrome	2.29 [1.39, 3.75] *0.001*	2.24 [1.32, 3.81] 0.003

[a] p-value by Wald test using Poisson regression.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, and London study clinic site.

These associations were also investigated when combining data from baseline and the 12- and 24-month questionnaire in GEE models, see Figure 23. Depressive symptoms (PHQ-9≥10) were not associated with any of the sexual behaviour measures investigated at each time-point, in unadjusted[xxxviii] or adjusted analysis[xxxix]. There did appear to be a slight attenuation in the PR after adjusting for any IPV victimization and age <13 years at anal sex debut in addition to socio-demographics, for a number of sexual behaviours. Of note, adjusting additionally for study time-point in the socio-demographic adjusted models had no impact on associations observed in Figure 23. In the sensitivity analyses, when investigating the other depressive symptom measures on PHQ-9, including suicidal ideation, in GEE models, the pattern of associations was identical, Appendix section 11.21 Table 82.

[xxxviii] 540 individuals contributing 1283 questionnaire responses to the model.
[xxxix] 536 and 429 individuals contributing 1273 and 710 questionnaire responses to adjusted models (i) and (ii) respectively.

Figure 23: Unadjusted and adjusted associations of depressive symptoms (PHQ-9≥10) with sexual behaviours in the past three months using baseline, 12-, and 24-month PROUD questionnaire data in GEE models



[a] Not known to be on HIV treatment.
[b] Men were asked whether they had engaged in group sex at the 12-month and 24-month questionnaires only. There were 104 men who did not fill out a questionnaire at either of these follow-up time-points, and therefore, 104 men for whom the question group sex had a missing value (since group sex was coded as yes; no or missing, everyone who filled out a questionnaire had a value). It is therefore of note, that 432, 432, and 427 men contributed data to the first, second, and third adjusted models respectively, with 737, 737, and 710 observations respectively.
[c] Number of observations examined in the model.
[d] Information on psychosocial factors adjusted for in this model was only collected at month 12 and 24, explaining the reduced sample size under analysis.
[e] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

Of note, the relationship between depressive symptoms (PHQ-9≥10) and sexual behaviour measures was not different in the two study trial arms at month-12 or 24, nor was the relationship found to be different between trial arms in GEE models combining data from both follow-up time-points (see Table 33). When investigating whether the relationship between depressive symptoms and sexual behaviours was different at the 12-month time-point, between men who were prescribed PrEP before the 12-month questionnaire and men who were not, the interaction p-values were not significant for any of the sexual behaviours. The relationship between depressive symptoms and sexual behaviour measures was also not different among: (i) men who reported any IPV victimization and men who did not, and (ii) men who reported their anal sex debut with a man before 13 years of age and men who did not, in GEE models.

Table 33: Unadjusted associations of depressive symptoms with sexual behaviour measures in the past three months separately among men randomized to the immediate PrEP arm and men randomized to the deferred PrEP arm at the 12- and/or 24-month questionnaires in PROUD

	PR 95% CI for depressive symptoms (PHQ-9≥10)								
	12- month questionnaire [N=410]			24-month questionnaire [N=333]			12- and 24-month questionnaires in GEE models [N=436 men; Obs=743[c]]		
Dependent variables:	Immediate PrEP arm [N=216] PR [95% CI] *p-value*[a]	Deferred PrEP arm [N=194] PR [95% CI] *p-value*[a]	Interaction term p-value	Immediate PrEP arm [N=182] PR [95% CI] *p-value*[a]	Deferred PrEP arm [N=151] PR [95% CI] *p-value*[a]	Interaction term p-value	Immediate PrEP arm [N=233; Obs=398] PR [95% CI] *p-value*[b]	Deferred PrEP arm [N=203; Obs=345] PR [95% CI] *p-value*[b]	Interaction term p-value
CLS with 2+ partners	1.04 [0.85, 1.26]	0.83 [0.59, 1.16]	*0.255*	0.98 [0.77, 1.24]	0.80 [0.54, 1.17]	*0.370*	1.02 [0.76, 1.38]	0.81 [0.54, 1.23]	*0.402*
CLS with 5+ partners	0.92 [0.64, 1.34]	0.83 [0.46, 1.49]	*0.753*	0.71 [0.45, 1.12]	0.77 [0.42, 1.41]	*0.820*	0.82 [0.55, 1.21]	0.78 [0.46, 1.32]	*0.899*
CLS with HIV+ partner not treated	0.63 [0.20, 1.97]	0.46 [0.06, 3.36]	*0.799*	0.80 [0.25, 2.54]	1.30 [0.42, 4.03]	*0.553*	0.75 [0.33, 1.72]	0.97 [0.35, 2.66]	*0.574*
Receptive CLS with HIV+ partner not treated[e]	/	/	/	0.46 [0.06, 3.45]	1.58 [0.50, 5.00]	*0.296*	0.59 [0.18, 2.01]	1.01 [0.33, 3.15]	*0.455*
Unknown/HIV+ partner not treated at last CLS	0.80 [0.41, 1.54]	1.24 [0.59, 2.62]	*0.388*	1.75 [0.95, 3.20]	0.89 [0.30, 2.65]	*0.287*	1.16 [0.70, 1.94]	1.05 [0.52, 2.14]	*0.829*
10+ new sex partners	1.09 [0.65, 1.82]	0.79 [0.35, 1.79]	0.512	0.97 [0.50, 1.85]	1.14 [0.56, 2.31]	0.738	0.99 [0.62, 1.60]	0.91 [0.49, 1.68]	*0.829*
Receptive anal sex with 10+ partners	1.18 [0.73, 1.93]	0.83 [0.36, 1.87]	*0.460*	0.84 [0.45, 1.60]	1.00 [0.45, 2.21]	*0.747*	1.08 [0.69, 1.69]	0.90 [0.47, 1.72]	*0.661*
Group sex [N=436][c]	0.94 [0.67, 1.32]	0.88 [0.56, 1.38]	*0.814*	1.07 [0.72, 1.59]	1.10 [0.70, 1.73]	*0.922*	1.00 [0.69, 1.45]	0.99 [0.64, 1.55]	*0.969*

[a] p-value by Wald test using Poisson regression.
[b] p-value by Wald test using GEE models.
[c] 104 men had a missing value for group sex at baseline, and the 12- and 24-month questionnaires. Of note, 233 men contributed data for group sex in the immediate arm and 203 men contributed data for group sex in the deferred arm.
[d] Number of observations examined in the model.
[e] Of the 23 men in the deferred PrEP arm who had depressive symptoms at month 12, no one reported receptive CLS with an HIV-positive partner who was not known to be on treatment. It was therefore, not possible to investigate an interaction effect. Of note, of the 26 men in the immediate PrEP arm who had depressive symptoms at month 12, one man reported receptive CLS with an HIV-positive partner who was not known to be on treatment.

8.3.3 Comparing findings from the AURAH study

8.3.3.1 Restricted AURAH sample of men who reported anal CLS

Table 34 presents the original AURAH findings from the 1340 men who reported anal or vaginal sex in the past three months, and the findings from the restricted analysis of 815 men reporting CLS with a man in the past 3 months (the group more comparable to the PROUD sample). Associations are presented as ORs, unadjusted and adjusted for key socio-demographic factors. Among MSM in AURAH who reported CLS, there remained evidence of an association between depressive symptoms (PHQ-9≥10) and CLS with two or more partners, CLS with an unknown or HIV-positive status partner, and bacterial STI diagnosis, but the association was weaker compared to the original analysis of all MSM reporting sex. Similar to the PROUD trial, there remained a strong association between depressive symptoms and PEP use in the restricted analysis, with only slight attenuation compared to the original AURAH analysis.

Table 34: Unadjusted and adjusted associations of depressive symptoms with sexual behaviour measures among AURAH men who reported recent sex and AURAH men who reported recent CLS with a man

Association of depressive symptoms (PHQ-9 ≥10) with sexual behaviour measures		Original AURAH analysis: men reporting recent anal/vaginal sex [N=1340]	Restricted AURAH analysis: men reporting recent anal CLS [N=815]
Dependent variables (past three months):		Odds Ratio [95% CI] *p-value*[c]	Odds Ratio [95% CI] *p-value*[c]
CLS with two or more (male) partners	Unadjusted	1.85 [1.33, 2.57] *p<0.001*	1.54 [1.04, 2.27] *p=0.031*
	Adjusted[b]	1.80 [1.27, 2.56] *p=0.001*	1.60 [1.04, 2.45] *p=0.032*
CLS with an unknown/HIV+ (male) partner[a]	Unadjusted	2.06 [1.48, 2.86] *p<0.001*	1.72 [1.14, 2.58] *p=0.009*
	Adjusted[b]	1.92 [1.35, 2.71] *p<0.001*	1.62 [1.04, 2.52] *p=0.034*
Receptive CLS with an unknown status (male) partner	Unadjusted	2.04 [1.37, 3.05] *p*<0.001	1.65 [1.08, 2.52] *p*=0.020
	Adjusted[b]	1.80 [1.18, 2.75] *p*=0.007	1.45 [0.92, 2.28] *p*=0.111
Bacterial STI diagnosis (past year)	Unadjusted	1.70 [1.22, 2.36] *p*=0.002	1.56 [1.06, 2.30] *p*=0.024
	Adjusted[b]	1.85 [1.30, 2.62] *p*=0.001	1.75 [1.16, 2.65] *p*=0.008
PEP use (past year)	Unadjusted	1.84 [1.24, 2.73] *p=0.002*	1.78 [1.15, 2.75] *p=0.010*
	Adjusted[b]	2.13 [1.40, 3.22] *p<0.001*	2.06 [1.29, 3.27] *p=0.002*

[a] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.
[b] Adjusted for: age (included as four categories: <25, 25-29, 30-39, 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education (yes or no/missing), ongoing relationship with a partner (yes or no/missing), and study region (London, South, or Midland/Yorkshire and the Humber).
[c] p-value using logistic regression.

8.3.3.2 Prevalence of depressive symptoms according to sexual behaviour among all 1484 MSM in the AURAH study

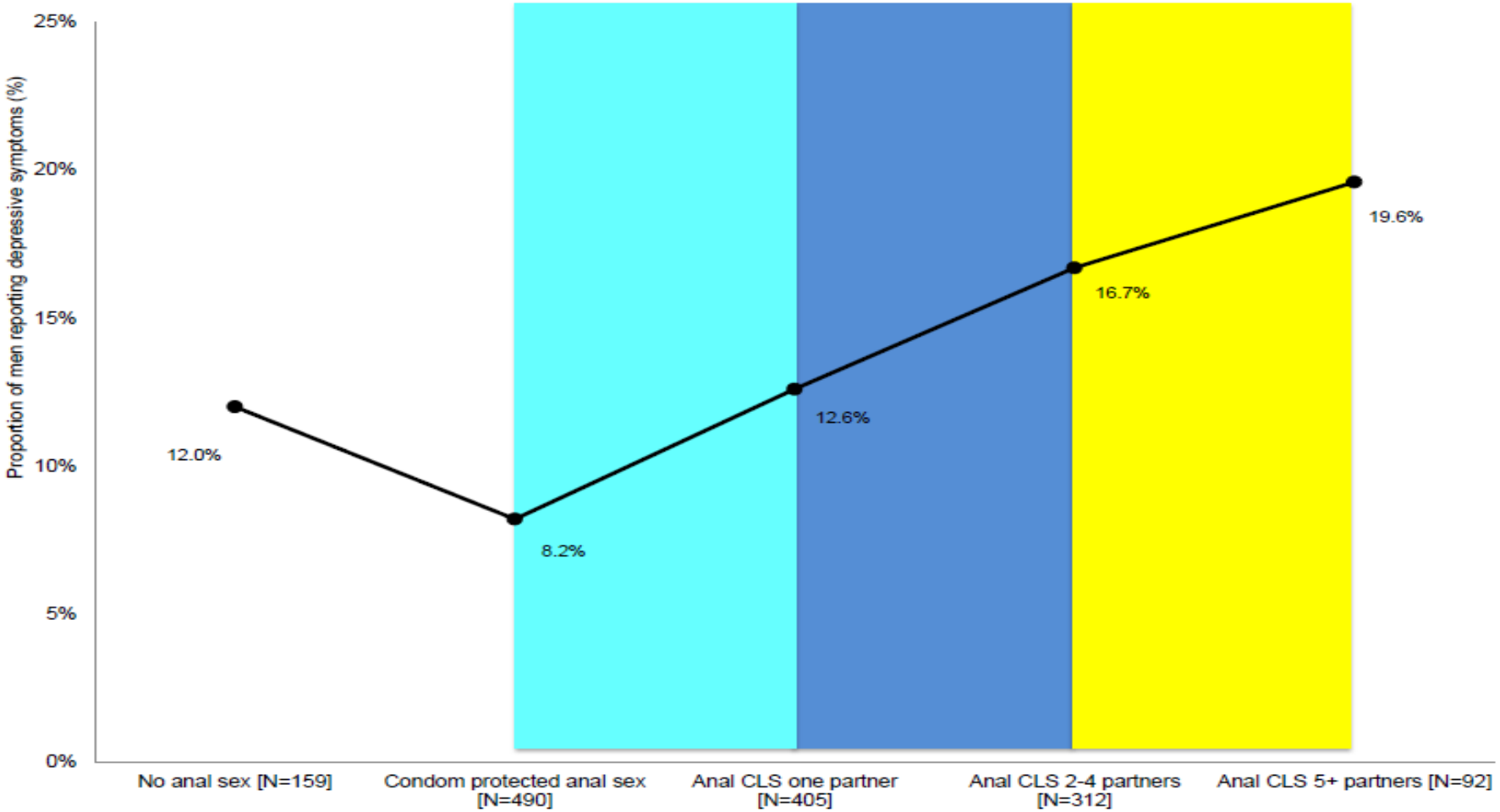
Figure 24 presents the relationship from the opposite perspective, examining the prevalence of depressive symptoms (PHQ-9≥10) according to anal CLS category and level. There appears to be a U-shaped relationship, whereby the prevalence of depressive symptoms is higher among men who reported no anal sex and men who reported an anal CLS partner, and lower among men who reported condom-protected anal sex[xl]. The prevalence of depressive symptoms

[xl] This same U-shaped relationship has also been observed in a previous study of HIV-positive MSM 714. Lampe F, Speakman A, Sherr L, Phillips A, Collins S, Gilson R, et al. Psychological and physical

increases with greater number of anal CLS partners. In the original AURAH analysis, among the sample of men who reported recent anal or vaginal sex, the vast majority of men fall within the section highlighted in light blue (i.e. most men reported either condom-protected sex or one CLS partner). The vast majority of men in the AURAH analysis restricted to men reporting recent anal CLS are falling within the section highlighted in dark blue. Since the vast majority of men in the PROUD trial reported anal CLS with two or more partners, the PROUD sample mainly falls within the section highlighted in yellow. When comparing anal CLS with five or more partners to anal CLS with two to four partners, the relative increase in prevalence of depressive symptoms (17.4%; 19.57%/16.67%) is not so pronounced as when comparing two to four anal CLS partners with one anal CLS partner (32.4%; 16.67%/12.59%), or comparing one anal CLS partner with condom-protected sex (54.3%; 12.59%/8.16%). As such, there is some suggestion that the association between level of anal CLS and depression is less pronounced at higher levels of CLS.

symptoms and sexual behaviour among HIV-diagnosed MSM in the UK. 19th Annual Conference of the British HIV Association; 16-19 April; Manchester, UK2013.

Figure 24: Proportion of 1458[a] MSM reporting depressive symptoms (PHQ-9≥10) according to sexual activity (with a man) in the past three months in the AURAH study



[a] Twenty-six men did not respond to the question *'how many men did you have anal sex with, without a condom?'*; of the 815 men who reported anal CLS with a man in the past three months, six did not respond to this question.

8.3.4 Relationship between depressive symptoms and measures of self-efficacy for sexual safety at the 12- and 24-month questionnaires

High self-efficacy for sexual safety was reported by 21.5% of men at the 12-month questionnaire and 27.6% of men at the 24-month questionnaire. Difficulty saying no to unwanted sex was reported by 11.5% of men at the 12-month questionnaire and 8.1% of men at the 24-month questionnaire. Of note, of the 88 men at month-12 and 92 men at month-24 who indicated high self-efficacy for sexual safety, the vast majority (96.6% and 96.7% respectively) did not report difficulty saying no to unwanted sex. At the 12- and 24-month questionnaires, 18.8% and 20.7% of men reported being unhappy with their sex lives respectively. The prevalence of each individual response option given for these measures is presented in Table 35.

Table 35: Prevalence of self-efficacy for sexual safety, difficulty saying no to unwanted sex, and happiness with one's sex life[d] in the PROUD trial

		12-month questionnaire [N=410]	24-month questionnaire [N=333]
		n (%)	n (%)
'The sex I have is always as safe as I want it to be'	Strongly agree Agree Neutral/uncertain Disagree Strongly disagree	88 (22.3%) 125 (31.7%) 89 (22.5%) 79 (20.0%) 14 (3.5%)	92 (28.5%) 132 (40.9%) 59 (18.3%) 36 (11.2%) 4 (1.2%)
'I find it easy to say 'no' to sex I don't want'	Strongly agree Agree Neutral/uncertain Disagree Strongly disagree	135 (34.2%) 165 (41.8%) 48 (12.2%) 40 (10.1%) 7 (1.8%)	130 (40.5%) 129 (40.2%) 35 (10.9%) 24 (7.5%) 3 (0.9%)
'I am happy with my sex life'	Strongly agree Agree Neutral/uncertain Disagree Strongly disagree	109 (27.5%) 148 (37.3%) 64 (16.1%) 62 (15.6%) 14 (3.5%)	91 (28.2%) 117 (36.2%) 46 (14.2%) 54 (16.7%) 15 (4.6%)
High self-efficacy for sexual safety	Yes No[a]	88 (21.5%) 322 (78.5%)	92 (27.6%) 241 (72.4%)
Difficulty saying no to unwanted sex	Yes No[b]	47 (11.5%) 363 (88.5%)	27 (8.1%) 306 (91.9%)
Unhappy with one's sex life	Yes No[c]	77 (18.8%) 333 (81.2%)	69 (20.7%) 264 (79.3%)

[a] Includes all other responses, including missing responses (3.7% at month 12 and 3.0% at month 24).
[b] Includes all other responses, including missing responses (3.7% at month 12 and 3.6% at month 24).
[c] Includes all other responses, including missing responses (3.2% at month 12 and 3.0% at month 24).
[d] For a definition of each measure see section 3.3.9 in Chapter 3.

Table 36 presents the unadjusted associations between depressive symptom measures on PHQ-9 and high self-efficacy for sexual safety, difficulty saying no to unwanted sex and happiness with one's sex life, at the 12- and 24-month questionnaires. At the 12-month questionnaire, men with depressive symptoms (PHQ-9≥10) were much less likely to report high self-efficacy for sexual safety, compared to men without depressive symptoms. This association remained after adjustment for key socio-demographic factors (PR 0.43 95% CI: 0.20, 0.92; p=0.029). At the 24-month questionnaire however, depressive symptoms were not associated with self-efficacy for sexual safety, and this association did not change after adjustment. In the sensitivity analyses, the other depressive symptom measures on PHQ-9, including suicidal ideation, were also not associated with self-efficacy for sexual safety, at the 12- or 24-month questionnaire, and again this association did not change after adjustment for key socio-demographic factors.

Men with depressive symptoms tended to be more likely to report difficulty in saying no to unwanted sex (Table 36), this association was of borderline statistical significance at the 24-month questionnaire only (PR adjusted for socio-demographic factors: 2.42 95% CI: 1.04, 5.63; p=0.040), see Table 37. In the sensitivity analyses, similar patterns were apparent for the other measures of depressive symptoms, although the associations tended to be stronger (Table 36 and Table 37). Suicidal ideation was also associated with difficulty saying no to unwanted sex at month-24 (Table 36 and Table 37).

Table 36: Unadjusted associations of depressive symptom measures on PHQ-9 with measures of self-efficacy for safety at the 12- and 24-month questionnaires in PROUD

		12-month questionnaire [N=410]			24-month questionnaire [N=333]		
N=410 men		High self-efficacy for sexual safety [n=88; 21.5%] % p-value[a]	Difficulty saying no to unwanted sex [n=47; 11.5%] % p-value[a]	Unhappy with sex life [n=77; 18.8%] % p-value[a]	High self-efficacy for sexual safety [n=92; 27.6%] % p-value[a]	Difficulty saying no to unwanted sex [n=27; 8.1%] % p-value[a]	Unhappy with sex life [n=69; 20.7%] % p-value[a]
Depressive symptoms (PHQ-9≥10)	Yes No	10.2% 23.4% *0.022*	15.3% 10.8% *0.323*	52.5% 13.1% *<0.001*	20.8% 28.8% *0.255*	14.6% 7.0% *0.075*[b]	52.1% 15.4% *<0.001*
Major depressive syndrome	Yes No	13.5% 22.3% *0.217*	21.6% 10.5% *0.055*[b]	62.2% 14.5% *<0.001*	27.6% 27.6% *0.996*	20.7% 6.9% *0.021*[b]	65.5% 16.5% *<0.001*
Major & other depressive syndromes	Yes No	13.7% 22.6% *0.150*	19.6% 10.3% *0.051*	56.9% 13.4% *<0.001*	31.7% 27.1% *0.533*	14.6% 7.2% *0.097*[b]	56.1% 15.8% *<0.001*
Suicidal ideation	Yes No	15.2% 22.3% *0.273*	13.0% 11.3% *0.721*	52.2% 14.6% *<0.001*	19.2% 29.2% *0.140*	17.3% 6.4% *0.014*[b]	46.2% 16.0% *<0.001*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

Table 37: Unadjusted and adjusted associations of depressive symptom measures on PHQ-9 with difficulty saying no to unwanted sex at the 12 and 24-month questionnaires in PROUD

	12-month questionnaire [N=410]		24-month questionnaire [N=333]	
	Difficulty saying no to unwanted sex [n=47; 11.5%]		Difficulty saying no to unwanted sex [n=27; 8.1%]	
	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]
Depressive symptoms (PHQ-9≥10)	1.41 [0.72, 2.76] *0.318*	1.37 [0.72, 2.61] *0.330*	2.08 [0.93, 4.65] *0.075*	2.42 [1.04, 5.63] *0.040*
Major depressive syndrome	2.07 [1.05, 4.09] *0.037*	1.87 [0.96, 3.63] *0.067*	3.00 [1.31, 6.83] *0.009*	3.16 [1.27, 7.85] *0.013*
Major & other depressive syndromes	1.90 [1.01, 3.59] *0.047*	1.75 [0.94, 3.24] *0.077*	2.03 [0.87, 4.75] *0.100*	2.25 [0.90, 5.62] *0.082*
Suicidal ideation	1.16 [0.52, 2.58] *0.720*	1.22 [0.55, 2.75] *0.624*	2.70 [1.28, 5.69] *0.009*	2.95 [1.31, 6.63] *0.009*

[a] p-value by Wald test using Poisson regression.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, and London study clinic site.

Men reporting measures of depression on PHQ-9 were approximately four times more likely to report being unhappy with their sex lives, in fact half or just over half of men with depression measures reported being unhappy with their sex lives (Table 36). These strong associations remained, with little or no attenuation, after adjustment for key socio-demographic factors, Table 38.

Table 38: Unadjusted and adjusted associations of depressive symptom measures on PHQ-9 with happiness with one's sex life at the 12 and 24-month questionnaires in PROUD

	12-month questionnaire [N=410]		24-month questionnaire [N=333]	
	Unhappy with sex life [n=77; 18.8%]		Unhappy with sex life [n=69; 20.7%]	
	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]
Depressive symptoms (PHQ-9≥10)	4.01 [2.79, 5.76] *<0.001*	4.03 [2.81, 5.79] *<0.001*	3.37 [2.30, 4.96] *<0.001*	3.37 [2.28, 4.99] *<0.001*
Major depressive syndrome	4.29 [3.02, 6.11] <0.001	4.25 [2.98, 6.05] <0.001	3.98 [2.76, 5.75] <0.001	3.98 [2.68, 5.89] *<0.001*
Major & other depressive syndromes	4.25 [2.98, 6.07] *<0.001*	4.20 [2.93, 6.02] *<0.001*	3.56 [2.44, 5.21] *<0.001*	3.60 [2.43, 5.33] *<0.001*
Suicidal ideation	3.58 [2.47, 5.20] *<0.001*	3.73 [2.55, 5.44] *<0.001*	2.88 [1.94, 4.29] *<0.001*	2.83 [1.88, 4.26] *<0.001*

[a] p-value by Wald test using Poisson regression.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, and London study clinic site.

In GEE models, depressive symptoms were associated with difficulty saying no to unwanted sex, including after adjustment for key socio-demographic factors and additional adjustment for age <13 years at anal sex debut. Likewise, depressive symptoms were associated with being unhappy with one's sex life, in all adjusted models. Although not statistically significant, there was also evidence of an association of depressive symptoms with lower self-efficacy for sexual safety, see Table 39.

Table 39: Unadjusted and adjusted associations of depressive symptoms with measures of self-efficacy for sexual safety using 12- and 24-month PROUD questionnaire data in GEE models

	Depressive symptoms (PHQ-9≥10)		
N=436 men (using data from month-12 and 24 in GEE models) Dependent variables:	Unadjusted PR [95% CI][d] *p-value*[a]	Adjusted[b] PR [95% CI][d] *p-value*[a]	Adjusted[c] PR [95% CI][d] *p-value*[a]
High self-efficacy for sexual safety	0.65 [0.40, 106] *0.084*	0.64 [0.40, 1.04] *0.073*	0.63 [0.39, 1.02] *0.062*
Difficulty saying no to unwanted sex	1.80 [1.05, 3.08] *0.032*	1.82 [1.05, 3.17] *0.033*	1.80 [1.03, 3.15] *0.038*
Unhappy with sex life	3.37 [2.39, 4.75] *<0.001*	3.30 [2.33, 4.66] *<0.001*	3.25 [2.29, 4.61] *<0.001*

[a] p-value by Wald test.
[b] Age (included as four categories: <25, 25-29, 30-39, 40), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education (yes or no/missing), and London study clinic site (London or outside London).
[c] Age (included as four categories: <25, 25-29, 30-39, 40), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education (yes or no/missing), London study clinic site (London or outside London), and a marker of CSA (anal sex debut with a male before 13 years of age).
[d] The number of men contributing observations to the unadjusted model was 436; the number of observations examined in the unadjusted model was 743. The number of men contributing observations to adjusted model (i) was 432; the number of observations examined in adjusted model (i) was 737. The number of men contributing observations to adjusted model (ii) was 432; the number of observations examined in adjusted model (ii) was 737. The number of men contributing observations to adjusted model (iii) was 429; the number of observations examined in adjusted model (iii) was 710.

8.3.5 Relationship between measures of self-efficacy for sexual safety and sexual behaviour at the 12- and 24-month questionnaires

Reporting high self-efficacy for sexual safety, difficulty saying no to unwanted sex, and being unhappy with one's sex life was not significantly associated with any of the sexual behaviour measures investigated at the 12-month questionnaire, although there was a borderline association between high self-efficacy for sexual safety and group sex, see Table 40. After adjusting for key socio-demographic factors, this latter relationship was significant, see Table 42.

At the 24-month questionnaire, lower self-efficacy for sexual safety and difficulty saying no to unwanted sex was associated with report of an unknown or HIV-positive status partner (not known to be on treatment) at last CLS, and there appeared to be a borderline association between difficulty saying no to unwanted sex and group sex, see Table 41. After adjusting for key socio-demographic factors, the former associations remained but difficulty saying no to unwanted sex was no longer associated with group sex, see Table 42.

Table 40: Unadjusted associations of measures of self-efficacy for sexual safety with sexual behaviour measures in the past three months at the 12-month questionnaire in PROUD

N=410		CLS with 2+ partners [n=303; 73.9%]	CLS with 5+ partners [n=189; 46.1%]	CLS with HIV+ partner not treated [n=44; 10.7%]	Receptive CLS with HIV+ partner not treated [n=26; 6.3%]	Unknown/HIV+ partner not treated at last CLS [n=100; 24.4%]	10+ new sex partners [n=119; 29.0%]	Receptive anal sex with 10+ partners [n=118; 28.8%]	Group sex [n=224; 54.6%]
		% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]
High self-efficacy for sexual safety	Yes	69.3%	45.5%	11.4%	8.0%	17.1%	26.1%	21.6%	63.6%
	No	75.2%	46.3%	10.6%	5.9%	26.4%	29.8%	30.8%	52.2%
		0.269	*0.891*	*0.829*	*0.484*	*0.070*	*0.501*	*0.093*	*0.056*
Difficulty saying no to unwanted sex	Yes	80.9%	46.8%	6.4%	2.1%	27.7%	25.5%	25.5%	59.6%
	No	73.0%	46.0%	11.3%	6.9%	24.0%	29.5%	29.2%	54.0%
		0.249	*0.917*	*0.306*	*0.339*[b]	*0.579*	*0.575*	*0.601*	*0.470*
Unhappy with sex life	Yes	74.0%	42.9%	5.2%	3.9%	24.7%	28.6%	29.9%	59.7%
	No	73.9%	46.9%	12.0%	6.9%	24.3%	29.1%	28.5%	53.5%
		0.978	*0.527*	*0.082*	*0.441*[b]	*0.948*	*0.923*	*0.815*	*0.318*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

Table 41: Unadjusted associations of measures of self-efficacy for sexual safety with sexual behaviour measures in the past three months at the 24-month questionnaire in PROUD

N=333		CLS with 2+ partners [n=249; 74.8%] % p-value[a]	CLS with 5+ partners [n=172; 51.7%] % p-value[a]	CLS with HIV+ partner not treated [n=42; 12.6%] % p-value[a]	Receptive CLS with HIV+ partner not treated [n=29; 8.7%] % p-value[a]	Unknown/HIV+ partner not treated at last CLS [n=67; 20.1%] % p-value[a]	10+ new sex partners [n=95; 28.5%] % p-value[a]	Receptive anal sex with 10+ partners [n=98; 29.4%] % p-value[a]	Group sex [n=163; 49.0%] % p-value[a]
High self-efficacy for sexual safety	Yes No	69.6% 76.8% *0.176*	48.9% 52.7% *0.537*	8.7% 14.1% *0.183*	6.5% 9.5% *0.382*	13.0% 22.8% *0.047*	29.4% 28.2% *0.838*	28.3% 29.9% *0.773*	51.1% 48.1% *0.630*
Difficulty saying no to unwanted sex	Yes No	74.1% 74.8% *0.930*	40.7% 52.6% *0.237*	14.8% 12.4% *0.451*[b]	11.1% 8.5% *0.425*[b]	40.7% 18.3% *0.005*	33.3% 28.1% *0.564*	33.3% 29.1% *0.642*	66.7% 47.4% *0.055*
Unhappy with sex life	Yes No	72.5% 75.4% *0.620*	42.0% 54.2% *0.072*	15.9% 11.7% *0.349*	10.1% 8.3% *0.635*	23.2% 19.3% *0.475*	30.4% 28.0% *0.694*	27.5% 29.9% *0.698*	53.6% 47.7% *0.383*

[a] Pearson χ^2 test.
[b] Fisher's exact test.

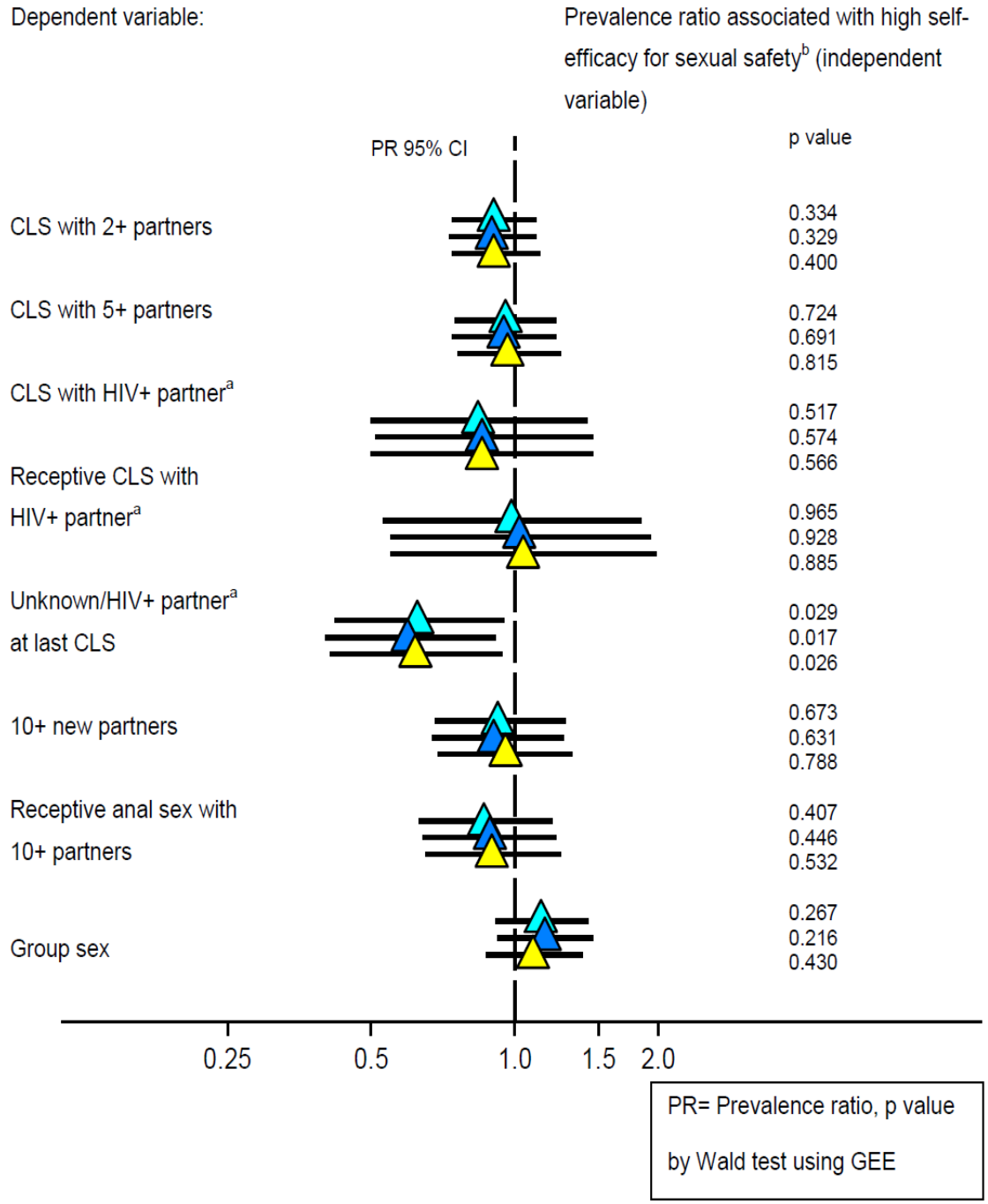
Table 42: Unadjusted and adjusted associations of high self-efficacy for sexual safety and difficulty saying no to unwanted sex with sexual behaviour measures at the 12 and 24-month questionnaires in PROUD

	12-month questionnaire [N=410]		24-month questionnaire [N=333]		12-month questionnaire [N=410]		24-month questionnaire [N=333]	
	Unknown/HIV+ partner not treated at last CLS [n=100; 24.4%]		Unknown/HIV+ partner not treated at last CLS [n=67; 20.1%]		Group sex (past 3 months) [n=224; 54.6%]		Group sex (past 3 months) [n=163; 49.0%]	
	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]	Unadjusted PR [95% CI] *p-value*[a]	Adjusted[b] PR [95% CI] *p-value*[a]
High self-efficacy for sexual safety	0.65 [0.39, 1.06] *0.084*	0.62 [0.37, 1.04] *0.067*	0.57 [0.32, 1.02] *0.058*	0.53 [0.31, 0.92] *0.024*	1.22 [1.01, 1.47] *0.040*	1.25 [1.03, 1.53] *0.027*	1.06 [0.84, 1.35] *0.626*	1.08 [0.85, 1.37 *0.532*
Difficulty saying no to unwanted sex	1.15 [0.70, 1.90] *0.573*	1.16 [0.71, 1.91] *0.554*	2.23 [1.33, 3.72] *0.002*	1.99 [1.14, 3.47] *0.015*	1.10 [0.86, 1.42] *0.448*	1.14 [0.89, 1.45] *0.309*	1.41 [1.05, 1.88] *0.022*	1.29 [0.96, 1.72] *0.087*

[a] p-value by Wald test using Poisson regression.
[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, and London study clinic site.

In GEE models combining data from the 12- and 24-month questionnaires, high self-efficacy for sexual safety was inversely associated with report of an unknown or HIV-positive status partner (not known to be on treatment) at last CLS (PR 0.63 95% CI: 0.42, 0.95), including after adjustment for socio-demographic factors (PR 0.60 95% CI: 0.40, 0.91) and additional adjustment for age <13 years at anal sex debut (PR 0.62 95% CI: 0.41, 0.94), Figure 25. Neither high self-efficacy for sexual safety nor difficulty saying no to unwanted sex was associated with any of the (other) sexual behaviour measures investigated in unadjusted or adjusted analysis, see Figure 25 and Figure 26.

Figure 25: Unadjusted and adjusted associations of high self-efficacy for sexual safety with sexual behaviour measures in the past three months using 12- and 24-month PROUD questionnaire data in GEE models



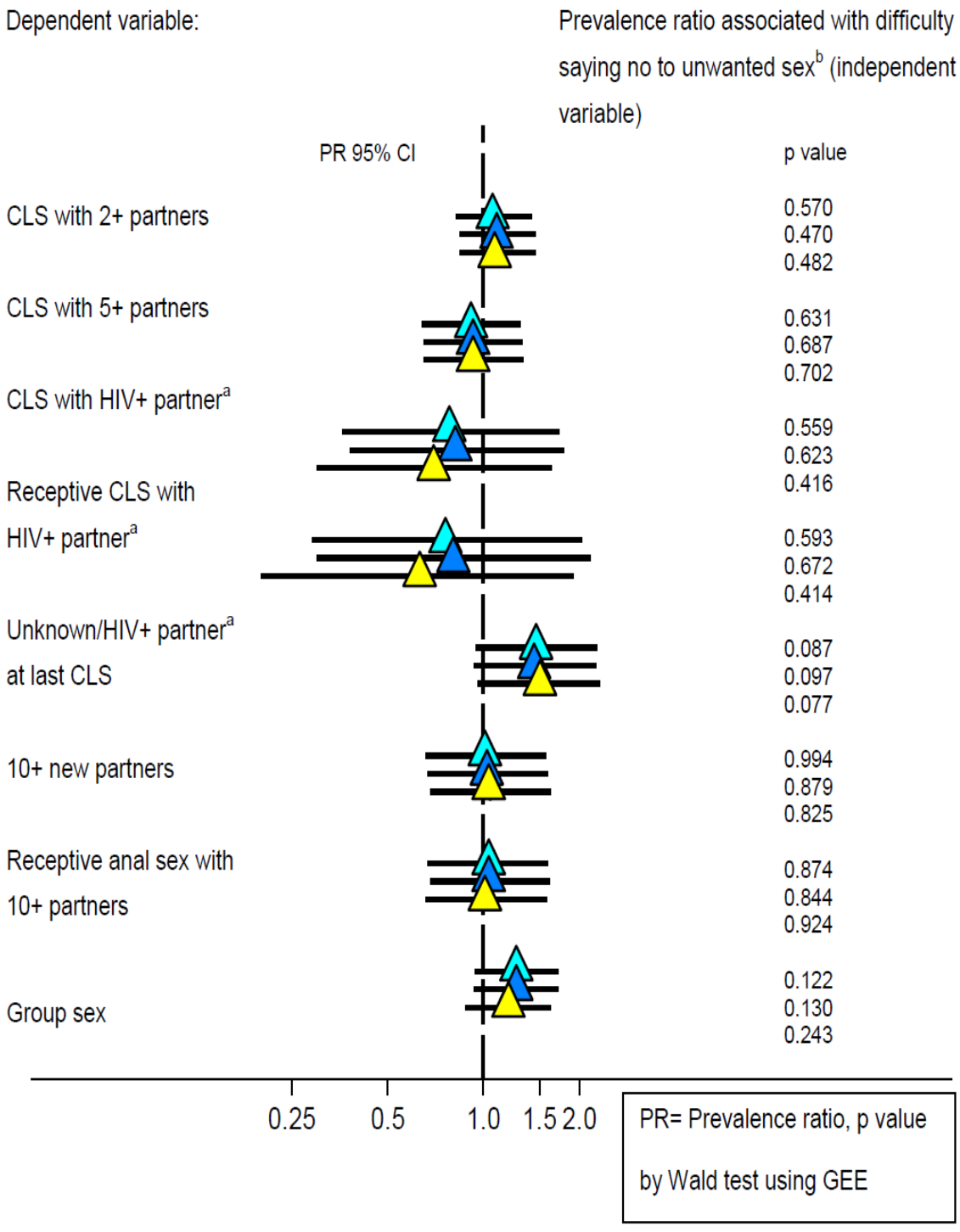
Unadjusted prevalence ratio [N=436] [Obs=743][c]

Prevalence ratio adjusted for: age[d], UK born[d], sexual identity[d], university education, and London study clinic site [N=432; Obs=737][c]

Prevalence ratio adjusted for above socio-demographic factors plus a marker of CSA (anal sex debut with a male before 13 years of age) [N=429; Obs=710][c]

[a] Not known to be on HIV treatment.
[b] Strong agreement with the statement: *'The sex I have is always as safe as I want it to be'*.
[c] Number of observations examined in the model.
[d] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

Figure 26: Unadjusted and adjusted associations of difficulty saying no to unwanted sex with sexual behaviour measures in the past three months using 12- and 24-month PROUD questionnaire data in GEE models



Unadjusted prevalence ratio [N=436] [Obs=743][c]

Prevalence ratio adjusted for: age[d], UK born[d], sexual identity[d], university education, and London study clinic site [N=432; Obs=737][c]

Prevalence ratio adjusted for above socio-demographic factors plus a marker of CSA (anal sex debut with a male before 13 years of age) [N=429; Obs=710][c]

[a] Not known to be on HIV treatment.
[b] Disagreed (disagree or strongly disagree) with the statement:
'I find it easy to say 'no' to sex I don't want'.
[c] Number of observations examined in the model.
[d] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

8.3.6 Relationship between depressive symptoms and reasons reported for last CLS

The prevalence of reasons for non-condom-use at last CLS by time-point is presented in Table 43. The most commonly reported reason was; 'It is more enjoyable without a condom', followed by 'I don't like using condoms', and 'He doesn't like using condoms' (at baseline), and 'I lose erections with condoms' (at the 12- and 24-month questionnaires).

Table 43: Prevalence of reasons for non-condom-use at last CLS, at baseline and the 12- and 24-month questionnaires in PROUD

	Baseline [N=540][a]	12-month questionnaire [N=410][b]	24-month questionnaire [N=333][c]
Reasons for non-condom-use at last CLS:	n (%)	n (%)	n (%)
'I don't like using condoms'	268 (49.6%)	240 (58.5%)	212 (63.7%)
'He doesn't like using condoms'	178 (33.0%)	145 (35.4%)	124 (37.2%)
'Condoms weren't discussed'	140 (25.9%)	122 (29.8%)	93 (27.9%)
'We don't use condoms with each other but do with other partners'	86 (15.9%)	64 (15.6%)	31 (9.3%)
'Neither of us had any condoms'	36 (6.7%)	16 (3.9%)	11 (3.3%)
'I didn't consider myself at risk of HIV'	115 (21.3%)	91 (22.2%)	115 (34.5%)
'I was under the influence of alcohol'	113 (20.9%)	54 (13.2%)	36 (10.8%)
'I was under the influence of drugs'	128 (23.7%)	86 (21.0%)	61 (18.3%)
'I am faithful to him'	39 (7.2%)	32 (7.8%)	27 (8.1%)
'He is faithful to me'	32 (5.9%)	36 (8.8%)	26 (7.8%)
'It is more enjoyable without a condom'	349 (64.6%)	255 (62.2%)	212 (63.7%)
'I was only dipping'	97 (18.0%)	31 (7.6%)	11 (3.3%)
'I lose erections with condoms'[d]	/	146 (35.6%)	137 (41.1%)
'Other' reason	57 (10.6%)	36 (8.8%)	21 (6.3%)

[a] 10 (1.9%) men did not tick any of these reasons for non-condom-use, including the 'other' option.
[b] 3 (0.7%) men did not tick any of these reasons for non-condom-use, including the 'other' option.
[c] All men ticked at least one of these reasons for non-condom-use, including the 'other' option.
[d] Responses to this reason for non-condom-use at last CLS were only collected at the 12- and 24-month questionnaires.

Table 44 presents the unadjusted associations between depressive symptoms (PHQ-9≥10) and reasons for non-condom-use at last CLS at baseline and the 12- and 24-month questionnaires. At baseline, men with depressive symptoms compared to men without were more likely to report a reason for last CLS being 'under the influence of drugs' and 'other' (than the options provided). When investigating the association between depressive symptoms and being under the influence of drugs as a reason for last CLS, the relationship remained after adjusting for key socio-demographic factors (PR 1.53 95% CI: 1.02, 2.30; p=0.041). However, not surprisingly, this relationship disappeared after additionally adjusting for higher-risk drinking and number of recreational drugs used in the past three months (PR 1.29 95% CI: 0.90, 1.84; p=0.168).

At the 12-month questionnaire, the pattern was somewhat different. Men with depressive symptoms compared to men without were more likely to report a reason for last CLS being 'neither of us had any condoms' and 'under the influence of alcohol'. Both associations remained after adjusting for key socio-demographic factors (excluding ongoing relationship with a partner): PRs were 4.68 (95% CI: 1.83, 11.95; p=0.001) and 2.23 (95% CI: 1.30, 3.79; p=0.003) respectively. At the 24-month questionnaire, depressive symptoms were not associated with any of the reasons for last CLS in unadjusted analysis.

The pattern of associations was very similar when investigating the other measures of depressive symptoms on PHQ-9 (data not shown).

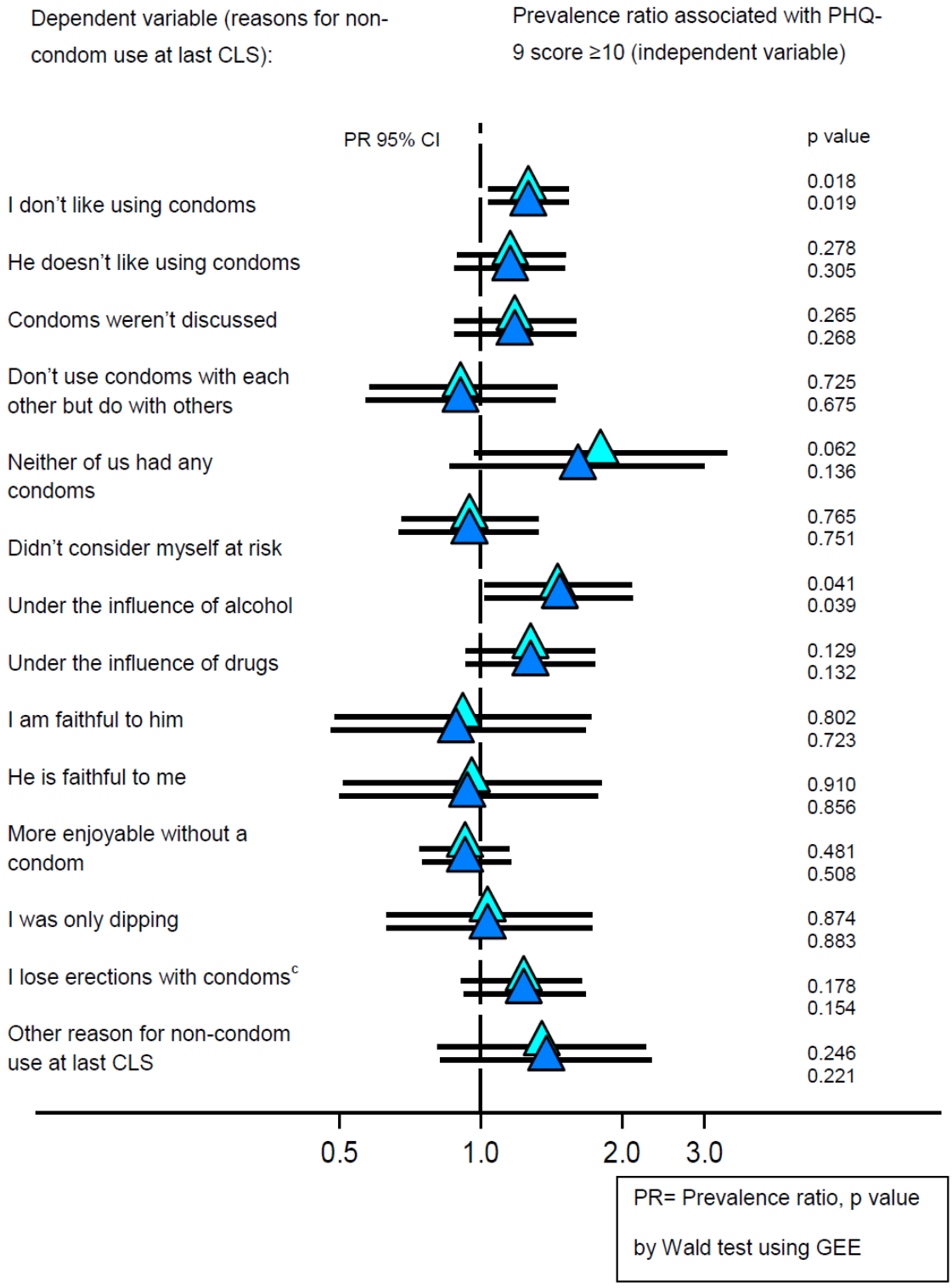
In GEE models, combining data across all three time-points, depressive symptoms (PHQ-9≥10) were associated with report of not liking condoms (PR 1.27 95% CI: 1.04, 1.54) and being under the influence of alcohol (PR 1.46 95% CI: 1.02, 2.10) as reasons for non-condom-use at last CLS, including after adjustment for key socio-demographic factors (PR 1.27 95% CI: 1.04, 1.54 and PR 1.47 95% CI: 1.02, 2.11, respectively), see Figure 27.

Table 44: Unadjusted associations between depressive symptoms and reasons for non-condom-use at last CLS at baseline and the 12- and 24-month questionnaires in PROUD

	Depressive symptoms (PHQ-9≥10)								
	Baseline [N=540]			12-month questionnaire [N=410]			24-month questionnaire [N=333]		
Dependent variables (reasons for non-condom-use at last CLS):	Yes [N=49]	No [N=491]	*p-value*[a]	Yes [N=59]	No [N=351]	*p-value*[a]	Yes [N=48]	No [N=285]	*p-value*[a]
% 'I don't like using condoms'	57.1%	48.9%	*0.270*	61.0%	58.1%	*0.676*	68.8%	62.8%	*0.428*
% 'He doesn't like using condoms'	28.6%	33.4%	*0.493*	45.8%	33.6%	*0.071*	37.5%	37.2%	*0.968*
% 'Condoms weren't discussed'	36.7%	24.9%	*0.070*	33.9%	29.1%	*0.451*	31.3%	27.4%	*0.579*
% 'We don't use condoms with each other but do with other partners'	12.2%	16.3%	*0.460*	17.0%	15.4%	*0.759*	8.3%	9.5%	*0.801*
% 'Neither of us had any condoms'	10.2%	6.3%	*0.219*[b]	11.9%	2.6%	*0.004*[b]	2.1%	3.5%	*0.512*[b]
% 'I didn't consider myself at risk of HIV'	22.5%	21.2%	*0.479*[b]	18.6%	22.8%	*0.478*	31.3%	35.1%	*0.605*
% 'I was under the influence of alcohol'	28.6%	20.2%	*0.168*	23.7%	11.4%	*0.010*	14.6%	10.2%	*0.363*
% 'I was under the influence of drugs'	36.7%	22.4%	*0.024*	28.8%	19.7%	*0.110*	20.8%	17.9%	*0.626*
% 'I am faithful to him'	8.2%	7.1%	*0.481*[b]	5.1%	8.3%	*0.400*	8.3%	8.1%	*0.566*[b]
% 'He is faithful to me'	4.1%	6.1%	*0.429*[b]	10.2%	8.6%	*0.684*	6.3%	8.1%	*0.467*[b]
% 'It is more enjoyable without a condom'	59.2%	65.2%	*0.246*[b]	61.0%	62.4%	*0.840*	56.3%	64.9%	*0.248*
% 'I was only dipping'	22.5%	17.5%	*0.391*	11.9%	6.8%	*0.177*	0.0%	3.9%	*0.175*[b]
% 'I lose erections with condoms'[c]	/	/	/	40.7%	34.8%	*0.380*	50.0%	39.7%	*0.178*
% 'Other' reason	20.4%	9.6%	*0.019*	6.8%	9.1%	*0.557*	10.4%	5.6%	*0.169*

[a] Pearson χ^2 test.
[b] Fisher's exact test.
[c] Responses to this reason for non-condom-use at last CLS were only collected at the 12- and 24-month questionnaires.

Figure 27: Unadjusted and adjusted associations of depressive symptoms with reasons for non-condom-use at last CLS using baseline, 12-month, and 24-month PROUD questionnaire data in GEE models



Unadjusted prevalence ratio [N=540] Obs=1283][a]

Prevalence ratio adjusted for: age[b], UK born[b], sexual identity[b], university education, and London study clinic site [N=536; Obs=1273][a]

[a] Number of observations examined in the model.
[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.
[c] Responses to this reason for non-condom-use at last CLS were only collected at the 12- and 24-month questionnaires. Therefore, the number of men contributing observations to this unadjusted model was 436; the number of observations examined in the unadjusted model was 743. The number of men contributing observations to adjusted model was 432; the number of observations examined in the adjusted model was 737.

8.3.7 Relationship of socio-demographic and lifestyle factors with sexual behaviour measures at baseline

Table 83 and Table 84 in Appendix section 11.22 present the unadjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures at baseline. Men who did not report an ongoing relationship with a partner were more likely to report CLS with two or more partners, CLS with five or more partners, and anal sex with ten or more new sexual partners in the past three months (Table 83), and slightly more likely to report a rectal STI diagnosis in the past year (Table 84). Men who reported using a greater number of recreational drugs and chemsex-associated drug use in the past three months were more likely to report CLS with two or more partners, CLS with five or more partners, anal sex with ten or more new sexual partners, and receptive CLS with ten or more partners in the past three months (Table 83), as well as PEP use and rectal STI diagnosis in the past year (Table 84). Compared to men who identified as gay, the prevalence of anal sex with ten or more new sexual partners was twice as high among men who reported a bisexual or straight sexual identity, Table 83. Men whose study clinic site was in London appeared to report a higher prevalence of PEP use in the past year (Table 84), but lower prevalence of having an unknown or HIV-positive status partner not known to be on treatment the last time they had CLS (Table 83). Finally, there appeared to be a borderline significant trend between younger age and rectal STI diagnosis in the past year, Table 84. All of the associations described above remained after adjustment for key socio-demographic factors, with the exception of relationship status with rectal STI diagnosis, and study clinic region with PEP use. The following factors were not associated with any of the sexual behaviour measures at baseline: born in the UK and ethnicity, university education, employment, and higher-risk drinking (Table 83 and Table 84).

8.3.8 Relationship between measures of IPV and age at sexual debut with sexual behaviour measures at the 12- and/or 24-month questionnaires

When investigating the association of IPV measures with each sexual behaviour measure in modified Poisson regression models at each time-point, no associations were found at the 24-month questionnaire in unadjusted analysis or analysis adjusted for key socio-demographic factors. However, at the 12-month questionnaire, any IPV victimization was associated with receptive CLS with an HIV-positive partner not known to be on treatment (adjusted PR 2.84 95% CI: 1.27, 6.36; p=0.011) and any IPV victimization in the past year and any IPV perpetration was associated with group sex (adjusted PR 1.32 95% CI: 1.09, 1.60; p=0.004 and

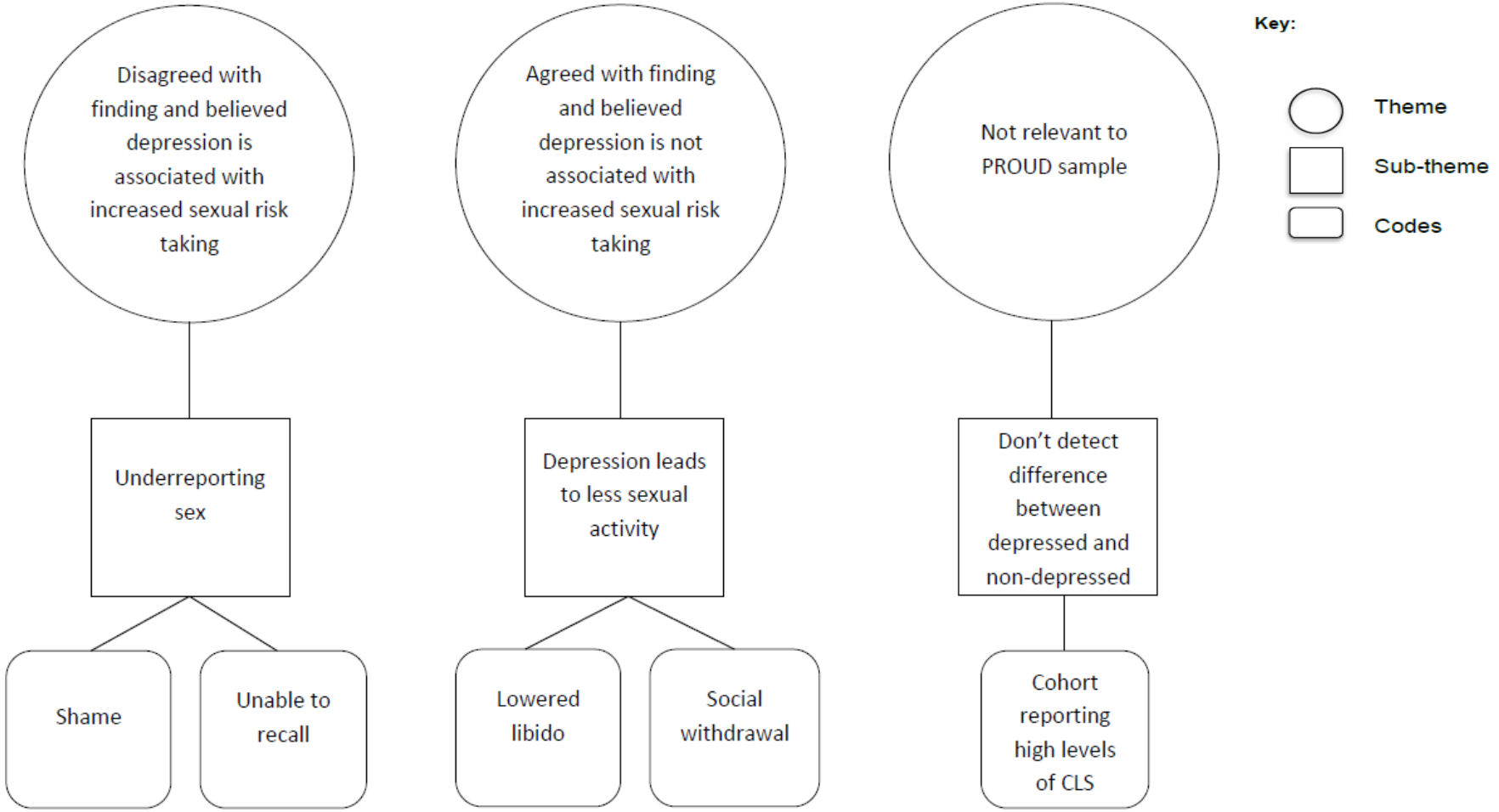
adjusted PR 1.40 95% CI: 1.16, 1.69; p<0.001, respectively). In GEEs, measures of lifetime IPV victimization and perpetration were not associated with any of the sexual behaviour measures investigated, in unadjusted or adjusted analyses (see Appendix section 11.23 Figure 35 and Figure 36). However, any IPV victimization within the past year was associated with group sex (adjusted PR 1.37 95% CI: 1.06, 1.76; p=0.015). Measures of IPV within the past year were not associated with the other sexual behaviour measures.

At the 12-month questionnaire, no associations were found of anal sex debut before age 13 and at age 15 years or younger with sexual behaviour measures, in unadjusted analysis or analysis adjusted for key socio-demographic factors. At the 24-month questionnaire, both measures of sexual debut were associated with report of CLS with five or more partners (adjusted PR 1.68 95% CI: 1.28, 2.22; p<0.001 and adjusted PR 1.34 95% CI: 1.06, 1.69; p=0.015, respectively). In GEEs, no associations were observed, in unadjusted or adjusted analyses.

8.3.9 Participant involvement in the interpretation of findings: summary of PPI responses

In total, 12 men commented on the finding that men who were depressed did not report a higher number of sexual partners, or more sex without a condom, than men who were not depressed. The way in which the responses were organized into themes in the semantic content of the data is shown in Figure 28.

Figure 28: Organization of PROUD PPI responses into codes, themes, and sub-themes



Based on a thematic analysis approach, three overarching themes were identified. The first was that men disagreed with the finding and suggested that depression was indeed associated with increased sexual risk-taking. The second was that men agreed with the finding that depression was not associated with increased sexual risk-taking and the third was that the association under investigation was not relevant to the PROUD sample of men. The views expressed by each individual were exclusive to one of the three themes. Within the first, second, and third theme described above, the following sub-themes are described: underreporting of sex, depression leads to less sexual activity, and do not detect a difference between depressed and non-depressed men, respectively.

Within the sub-theme of underreporting of sex (n=1), one man suggested that shame and an inability to recall past sexual practices, may prevent individuals from accurately reporting their recent sexual behaviour history on questionnaires. This man cited an inability to recall sexual risk-taking specifically in the context of chemsex and group sex.

> *"Aside from Embarrassment, and without claiming that all condomless casual sex involves solvent abuse, guys under the influence may not actually remember how many partners they have had in a group sex encounter."*
>
> PROUD PPI responses

Although it was not explicitly stated, given the question for which this response was provided, it may be possible that this man was referring in particular to those who may experience depression. For instance, men with depressive symptoms may be less likely to remember, perhaps as a result of the link between depressive symptoms and recreational drug use, or allow themselves to be cognitively aware of past sexual practices. Poly-drug use and chemsex-drug use have been found to be associated with depressive symptoms in the AURAH study (Table 5 in Chapter 4 and sections 6.3.2- 6.3.3 in Chapter 6), and use of methamphetamine has been found to be associated with depressive symptoms at baseline of the PROUD trial (section 7.3.4). The link between recreational drugs and depressive symptoms has also been observed in other studies of MSM [41, 346, 358, 454, 564, 606-609]. Furthermore, findings from the SEM in Chapter 6 suggest that in some men with depression, CLS may occur as a result of recreational drug use (section 6.3.6). In the self-regulation and coping literature, there is consistent evidence that those who experience depressive symptoms are more likely to engage in avoidant coping [362, 403, 715] and cognitive escape [401-404], coping strategies which both involve escaping self-awareness. If men with depressive symptoms were less likely to be able to recall past sexual behaviour and underreported any sexual risk-taking, this could provide some insight into why an association was not found between depression and increased sexual behaviour.

The sub-theme of depression leading to less sexual activity (n=4), was defined by responses that depressive symptoms (or treatment for depression) lead to lowered libido and social withdrawal.

"Depression decreases sex drive."

"I've definitely gone out and sought sex when feeling slightly depressed. When feeling /very/ depressed, however - enough that I might honestly report it, there are other factors at play. I end up sleeping a lot more. You're not clubbing when asleep in bed. I don't think people might /want/ me at that stage either, and when you're hating on self in that mode, why would you expect anyone else to be interested? You just don't show your face. I don't think there's a direct correlation between risky behaviour and depression - it isn't the more depressed, the worse it gets. Introversion and avoidance of other people kicks in at a point, which literally prevents such risk taking."

"Depression certainly reduce the willingness for sex. When I am depressed I am more involved with friends or on my own rather than going for sex."

"Once I was medicated citalopram - my libido decreased unless I was taking recreational drugs."

PROUD PPI responses

Although depressive symptoms were not associated with increased sexual risk-taking in the PROUD trial, the opposite, that depression leads to reduced sexual behaviour, was also not found to be the case. These notions, however, do reflect the suggestion by Crepaz and Marks [352] that in some individuals, current depressive symptoms may result in lowered libido/interest in sex and no sexual activity. In the AURAH study there was some suggestion that men with depressive symptoms were more likely to report no recent sex compared to condom-protected sex (as well as being more likely to report recent CLS) (see section 8.3.3).

The sub-theme of not detecting a difference between depressed and non-depressed men (n=4), was defined by the suggestion that the PROUD study cohort consisted of men who were all taking risks (engaging in CLS). This sentiment was expressed by four men in various ways, including that all men in PROUD were simply having sex and that gay men are greater risk takers in general, that all men included in PROUD had to have disclosed recent CLS, and that all men in PROUD were aware of and already had insight into the reasons for engagement in CLS.

"That sounds to me like simply "men had sex"."

"Gay men as a whole are greater risk takers. I don't think depressed gay men are more likely to have risky sex but grey area is recreational drug use, this is where depression can affect sexual behaviour (I think there is a link there, looking for escapism)."

"I think it is still due to having admitted having condomless sex and be HIV negative."

"It's because they most likely already had insight into the reasons why they were taking risks."

PROUD PPI responses

In the context of the question asked, these statements may indicate that an association was not observed between depressive symptoms and levels of CLS, since all men in PROUD were engaging in CLS, and were aware that they would likely continue to do so. Therefore, a difference was not detected between depressed and non-depressed men.

Finally, 11 men commented on the finding that depressive symptoms were associated with report of PEP use in the past year at baseline. Six men responded to this question; two men gave responses 'n/a' and 'Don't know', two men commented on PEP use whilst taking PrEP (since the finding was based on baseline data, these responses were not reviewed), and one man did not comment on the link between depression and PEP. All six men who responded to the question stated that PEP use is linked to sexual risk-taking, and two men brought up chemsex-drug use in the context of taking PEP.

"Again, I used PEP after Chem sex."

"Sniffed a substance when offered…On PEP the following morning."

PROUD PPI responses

Chemsex-associated drug use was associated with all sexual behaviour measures investigated in the AURAH study (see Appendix section 11.16 and section 6.3.3 in Chapter 6). In PROUD, chemsex-drug use was associated with CLS with multiple partners (two or more and five or more), reporting ten or more new sexual partners, receptive anal sex with ten or more partners, PEP use, and rectal STI diagnosis, at baseline. Furthermore, qualitative work (2013-2014) among a volunteer sample of MSM suggests that a number of men whose last HIV test was negative had unintentional CLS as a direct result of 'chem' use [579, 580, 583].

With regards to the link found between depressive symptoms and PEP use, two main themes were identified. Four men suggested that depression may lead to sexual risk-taking, in

particular, three men indicated that it may be a lack of self-care that results in risk-taking, and one man cited 'emotional issues' as a predictor.

> *"I started taking risks because I wasn't taking self care . I was on PEP twice , didn't do it other times , didn't think it mattered for me - nobody cared, I didn't care enough about myself."*
>
> *"Depressed people are less likely to 'look after' themselves, as the literature shows."*
>
> *"So, in my case I stopped caring. I went to a sauna as had no friends in the area and nothing to do that way."*
>
> *"I'd say risk taking behaviours (drug taking, condomless sex) seem more likely in people who are managing emotional issues."*
>
> PROUD PPI responses

These suggestions appear to be in line with that hypothesized in this thesis, see section 1.9.1, that feeling unable (low self-efficacy) leads to lack of self-care and regulation (escape tendencies characterised by fatalistic beliefs), increasing the chances of sexual risk behaviour. Alternatively, two men suggested that sexual risk-taking, which is associated with PEP use, may lead to depression. One of these men suggested that chemsex may lead to depression, and that it is the effect of the 'chems' themselves that specifically result in depression.

> *"I used PEP after Chem sex, I believe depression is related to drug use."*
>
> PROUD PPI responses

As discussed in detail in section 7.3.8, chemsex has been linked to depression [524, 579], including in the AURAH study (Table 5 in Chapter 4 and sections 6.3.2- 6.3.3 in Chapter 6). Although chemsex-associated drug use (past three months) was not associated with depressive symptoms among men in the PROUD trial at baseline, methamphetamine use was found to be associated. The other man highlighted the role that 'self-recrimination and guilt' following sexual risk may play in triggering depression, and even suggested a possible cycle involving sexual risk-taking and depression.

> *"PEP may save them from an unintended exposure to HIV, but not from the self recriminations and guilt, which are clear triggers for depression. In this case, there may be a cycle of risky behaviour and guilting over it."*
>
> PROUD PPI responses

The possibility of cyclical causation of depression and CLS is discussed in more detail in the thesis conclusion (Chapter 9).

8.4 Discussion

8.4.1 Summary of results

There was little support from the data for an association of depressive symptoms with CLS measures and partner numbers in the PROUD sample of men who, at enrolment, were required to report CLS in the past three months. The study trial arm was not found to moderate the association. There was also no evidence to suggest that antidepressant use was associated with sexual behaviour measures at baseline. Depressive symptoms were, however, associated with use of PEP in the past year at baseline, including after adjustment for socio-demographic factors and additional adjustment for higher-risk drinking and number of recreational drugs used. This relationship was also observed amongst men who did not report: (i) poly-drug use, (ii) chemsex-drug use, and (iii) club-drug use. It was not possible to investigate associations with PEP use at subsequent time-points. However, associations with PEP were broadly consistent across different definitions of depressive symptoms on PHQ-9.

There was some evidence to suggest that depressive symptoms were associated with lower self-efficacy for sexual safety. Depressive symptoms were independently associated with difficulty saying no to unwanted sex and unhappiness with one's sex life, as well with the following reasons for non-condom-use at last CLS; being under the influence of drugs/alcohol, not having any condoms, and not liking condoms. Finally, there was some evidence to suggest that lower self-efficacy for sexual safety and difficulty saying no to unwanted sex was associated with report of an unknown or HIV-positive status partner at last CLS. Measures of self-efficacy for sexual safety were not associated with any of the (other) sexual behaviour measures.

8.4.2 Prevalence of sexual behaviour

Given the inclusion criteria for enrolment in the PROUD trial, the prevalence of CLS measures found was much higher compared to the 68 surveys of sexual behaviour among UK MSM identified in review (ii) of this thesis (section 2.5.2). For instance, the prevalence of CLS with two or more partners in the past three months at baseline of the PROUD trial was 75.9%, and among UK studies identified in review (ii), the highest prevalence observed of CLS with two or more partners in the past year was 38.1% [(144)].

8.4.3 Depressive symptoms and sexual behaviour

For the main measure of depressive symptoms used in this thesis, no associations were found between depressive symptoms and higher levels of CLS, or partner numbers, in the PROUD trial of MSM at high-risk for HIV acquisition, despite the evidence for a relationship in AURAH (Chapters 5 and 6) and other studies of HIV-negative MSM (see section 2.4.5 of Chapter 2). The following sections consider possible explanations for this.

8.4.3.1 Participant involvement in PROUD study findings: depression not associated with sexual behaviour

Participants identified three main reasons why an association between depressive symptoms and report of a higher number of sexual partners or more sex without a condom may not have been found. The first was that past sexual behaviour may have been underreported on study questionnaires, either as a result of embarrassment or an inability to recall sexual practices. Emphasis was placed on the effect chemsex and group sex may have on one's ability to accurately recall sexual risk behaviour. Responses may have implied that if past sexual risk-taking had been more accurately reported, and perhaps particularly by men with depressive symptoms, an association may have been detected. The second was that depression may actually lead to less sexual activity, rather than increased sexual risk-taking. The third was that a difference was not detected between men reporting depressive symptoms and men who did not, in terms of sexual risk behaviour, since all men enrolled in PROUD were reporting CLS.

8.4.3.1 Depression, self-efficacy, drug use, and CLS: comparing PROUD findings to AURAH, and other studies investigating depression and CLS in review (i)

In this section, possible interpretations as to why depressive symptoms were not found to be associated with sexual risk behaviours in PROUD are further explored. The following reasons given take into account the causal pathways between depression and CLS that were found to be consistent with AURAH data, see Figure 19c in Chapter 6.

In PROUD, the prevalence of self-efficacy for sexual safety was low and the prevalence of recreational drug use was high, mirroring the high prevalence of multiple CLS partners reported by all men. However, this was not reflected by an equivalently high prevalence of depressive symptoms, thus depression does not appear to fit in to the hypothesized conceptual model when looking at PROUD data. The increase in depressive symptoms observed from baseline of PROUD (see section 7.3.1) may indicate a problem with the measurement of depression in this trial setting. Furthermore, the prevalence and impact of depression may differ in a PrEP trial population compared to an observational study. In addition to depression, other psychosocial factors may also explain recreational drug use (e.g. 'outness', minority stress, frequency of gay scene use, CSA, and IPV) and low self-efficacy for sexual safety (e.g. drug use, CSA, and IPV), and these factors may be particularly relevant to the PROUD RCT, for which men with depression may not choose to participate in.

Furthermore, in the AURAH study, 27% of all MSM and 32% of MSM reporting recent sex reported CLS with two or more partners in the past three months. In AURAH, depressive symptoms were associated with all measures of CLS. The PROUD trial included a unique self-selecting sample of men who reported high levels of CLS partners. Around three-quarters of men reported CLS with two or more partners in the past three months, across time-points, a much higher proportion than AURAH. Unlike in AURAH, in PROUD, levels of recreational drug

use rather than self-efficacy appeared to more consistently explain differences in high versus lower levels of CLS (as discussed in section 8.4.6 below). This may also explain why an association was not observed in PROUD, since findings from AURAH suggest that the main mechanism of effect between depressive symptoms and CLS is low self-efficacy for sexual safety. It may be that recreational drug use, and other factors with greater disinhibiting effects (including personality traits associated with sexual compulsivity/sensation seeking), better explain sexual behaviour among a sample of men predominantly reporting multiple CLS partners. Of note, of the studies presented in Table 1 of review (i) that have investigated the association between depressive symptoms and sexual risk behaviour (including those that found such an association), the vast majority were based on samples that reported much lower levels of CLS than in PROUD; levels that were comparable to that in AURAH. There is some support from AURAH for the theory that the association between depression and level of CLS is diminished when considering very high levels of CLS versus lower levels of CLS. In AURAH, the association was somewhat weaker among the subgroup of men who reported recent CLS than among the larger subgroup who reported recent sex. Similarly, although the prevalence of depressive symptoms appeared to increase with increasing report of CLS partners, the relative increase was smaller at higher levels of CLS in AURAH. However, it may also be worth considering that the PROUD trial may have lacked power to detect a smaller difference between depressed and non-depressed men, as reflected in the width of the confidence intervals.

8.4.4 Depressive symptoms and PEP use

In the PROUD trial, depressive symptoms were independently associated with use of PEP in the past year at baseline, as was found to be the case in the AURAH study (see section 5.3.2).

8.4.4.1 Participant involvement in PROUD study findings: depression was associated with PEP use

Although a link between depression and CLS was not explicitly observed in PROUD, an association with PEP use was found. Some respondents clearly interpreted this as a link with CLS, either that depression leads to CLS (resulting in PEP use) or that CLS (resulting in PEP use) leads to depression. In this context the following interpretations were given; depression is associated with a lack of self-care and regulation that leads to CLS, sexualized drug use leads to depression, and a possible cycle involving depression and CLS. The notion that the relationship between depressive symptoms and CLS may be cyclical is discussed in the context of the findings of this thesis in the final conclusion chapter.

8.4.4.2 Depression, self-efficacy, CLS, and PEP use

There are further explanations for understanding the association between depressive symptoms and PEP use in PROUD, in light of the contradictory finding that depression was not associated with high levels of CLS. It may be that some individuals who engage in high-risk sexual behaviour, depending on personality type and the type of coping mechanism they employ, are

more likely to become anxious and depressed as a result of their behaviour, which may consequently result in more PEP use. Alternatively, reasons for sexual risk among depressed men may be different to men who are not depressed. If this is the case, subsequent attitudes to and perceptions of CLS and therefore subsequent PEP use, may differ. Some support for this comes from PROUD findings on self-efficacy and reasons for non-condom-use at last CLS. Compared to men who did not have depressive symptoms, those who did were more likely to report low self-efficacy and tended to be more likely to give alcohol/drugs as reasons for non-condom-use. This may suggest that the occurrence of CLS among men with depression tends to be more situational than intentional. Unplanned sexual risk-taking may be more likely to result in PEP use.

Finally, it is possible that the relationship observed between depression and PEP use operates in the opposite direction; i.e. PEP use itself leads to depression. There is no evidence to suggest a biological effect of the antiretrovirals used in PEP on depression (see section 7.3.8). However, there may be unmeasured mediators such as confrontation with one's sexual risk-taking history during the process of PEP prescription or stigma attached to PEP use. This was suggested by PROUD participants as to why depression prevalence increased over the course of the first year of the study, see section 7.3.8.

8.4.5 Socio-demographic factors associated with sexual behaviour

Although not established in the UK MSM literature identified in review (ii) of this thesis [509, 510, 512], there appears to be some evidence from the PROUD and AURAH studies, that not being in an ongoing relationship and reporting a bisexual or straight identity was associated with CLS with multiple partners (section 6.3.4 in Chapter 6 and Appendix Table 50 and Table 76). Although not observed in the PROUD trial, there does appear to be some evidence from AURAH (Appendix section 11.16 Table 76) and other UK studies identified in review (ii) [510, 512] that lower levels of educational attainment are associated with CLS with multiple partners.

8.4.6 Psychosocial factors associated with sexual behaviour

Findings from the PROUD trial suggest that use of recreational drugs, including chemsex-associated drug use in the past three months, may (at least) in part explain high levels of recent CLS and partner numbers, and as a result, PEP use and rectal STI diagnosis. This was also found to be the case in the AURAH study (Table 76 in Appendix section 11.16 and section 6.3.3 in Chapter 6), in other UK studies of MSM [478, 484, 509, 511, 515], and in high-income country studies of MSM [397, 585-600]. Higher-risk drinking was not associated with measures of CLS or partner numbers, nor PEP use or rectal STI diagnosis in the PROUD trial, in line with UK studies identified in review (ii) [478, 509]. However, higher-risk drinking has been found to be associated with CLS measures in the AURAH study (Appendix section 11.16 Table 76).

A meta-analysis of studies from 1980-2011 has been conducted, which pooled ORs from studies measuring HIV status and/or sexual risk behaviour among adult MSM with and without experiences of CSA. In fixed-effects meta-analyses of 4367 and 7796 MSM, CSA was associated with recent CLS (pooled OR: 1.85 95% CI: 1.36, 2.51) and HIV seropositivity (pooled OR: 1.54 95% CI: 1.22, 1.95) respectively [(604)]. Furthermore, a meta-analysis of studies published up to November 2013 pooled ORs from studies which measured IPV together with HIV status and/or sexual risk behaviour among samples including HIV-negative gay, bisexual and/or other MSM adults [(605)]. In random-effects meta-analyses of 4447 and 8835 MSM, exposure to any kind of IPV was associated with anal CLS (pooled OR: 1.72 95% CI: 1.44, 2.05) and HIV seropositivity (pooled OR: 1.46 95% CI: 1.26, 1.69) respectively.

In the PROUD trial, measures of IPV were associated with report of receptive CLS with an HIV-positive status partner not known to be on treatment and group sex at the 12-month questionnaire, including after adjustment for socio-demographic factors. Furthermore, reporting anal intercourse at age 12 or younger, which may include experiences of CSA, was associated with report of CLS with five or more partners at the 24-month questionnaire, including after adjustment for socio-demographics. However, with the exception of IPV victimization in the past year and group sex, these relationships were not observed in GEE models combining data from both follow-up time-points and incorporating greater statistical power. It may be that exposure to abuse in childhood and adulthood (in the context of an intimate partnership) is also not an effective means of distinguishing between individuals who report a higher number of CLS partners and individuals who report a lower number of CLS partners. In addition, a young age at anal sex debut may not reflect or pick up all sexual abuse experienced, as some participants may not have experienced forced/coerced sex and some CSA may occur at an older age. Unfortunately, it was not possible to investigate certain personality characteristics associated with sensation seeking and sexual compulsivity, as these factors may also be useful in understanding why some men who engage in CLS report a higher number of partners.

8.4.7 Limitations

The general methodological limitations of the PROUD trial are discussed in section 3.7.2 of Chapter 3. In this specific analysis, it is important to note that information on relationship status, the number and type of recreational drugs used in the past three months, higher-risk drinking, and PEP use and rectal STI diagnosis in the past year, was only available at the baseline questionnaire. It was not deemed appropriate to consider that these factors did not change over the course of the study. Accordingly, it was not possible to investigate these factors in GEE models, or even adjust for them at the 12- or 24-month questionnaires. It was also only possible to investigate group sex, self-efficacy for sexual safety, reasons for last CLS, and psychosocial factors in GEE models among the 436 men with data at the 12- and/or 24-month questionnaire, since information on these measures was not collected at baseline. Limitations with regards to the variable higher-risk drinking and extent to which age <13 years at anal sex debut may

indicate CSA, is described in detail in section 7.4.7. The proportion of missing responses recorded for rectal chlamydia, rectal gonorrhoea, syphilis, and LGV exceeded 5%. It was however, considered appropriate to continue to investigate these measures (and not apply multiple imputation techniques), given that the layout of the STI diagnosis question may have prompted participants to tick only those STIs that applied to them. Cross-sectional associations were investigated in this chapter, prohibiting us from making inferences about causality. Finally, as discussed in section 3.7.3, a large number of statistical tests were performed using PROUD data, due to analysis at each time-point. One measure of depression was positively associated with one CLS measure, but this was an isolated finding at one time-point, no associations were observed in any other analyses. Therefore, such a result could be due to chance.

8.4.8 Summary of discussion

Based on AURAH study findings and other studies in the literature, it appears that gay, bisexual, and other MSM with clinically significant depressive symptoms are more likely to engage in CLS than condom-protected sex even after adjusting for recreational drug use. However, based on PROUD trial findings and other studies in the literature, it appears that depressive symptoms do not explain why some men who engage in CLS have a high number of CLS partners (or a higher prevalence of more risky CLS). Higher levels of recreational and chemsex-drug use may better explain higher versus lower levels of CLS.

Depressive symptoms were associated with PEP use at baseline, even after adjusting for higher-risk drinking and number of recreational drugs used. It may be that some individuals who engage in sexual risk-taking develop symptoms of depression and/or anxiety, which then leads to PEP use. On the other hand, evidence from the PROUD trial suggests that sexual risk-taking among men with depression tends to be more situational than intentional, leading to more PEP use. Findings from AURAH support this notion, whereby the main mechanism through which depression might lead to sexual risk behaviour was lowered self-efficacy for sexual safety.

Chapter 9

9 Implications of thesis findings and final conclusions

9.1 Summary of thesis background, hypothesis, and structure

Depression is a psychological construct that is used to describe the co-occurrence of a number of symptoms, including feelings of worthlessness and hopelessness, anhedonia, sleep and appetite disturbance, and suicidal thoughts, which may be rooted in traumatic events (perhaps early on in life) [252, 257-266], and may reflect impaired neural functioning [265, 270-313]. This thesis addressed how these symptoms might affect sexual behaviour. The question was studied among gay- and, to a lesser extent, bisexual-identified men, and other MSM. In Chapter 1, the background to and rationale for this thesis was presented. Theoretical and epidemiological research was presented that suggests that the study of depression is particularly relevant among individuals of a sexual minority status as such status may induce high levels of stress as a result of a discriminatory social environment, which may lead to depression [211, 223-225, 227, 235-239, 242]. Epidemiological trends in HIV in the UK were presented, which suggest that HIV transmission remains ongoing among MSM [43]. Therefore, the hypothesis to investigate whether symptoms of depression are associated with sexual behaviour linked to increased risk of STI and HIV acquisition (in particular CLS) among sexual minority men in the UK was developed.

There was considerable evidence from the literature review presented in Chapter 2 of this thesis, for an association between depressive symptoms and increased sexual risk behaviour (and HIV seroconversion [369]) in high-income country studies of MSM (1996-2014) [353-368]. It was theorized in studies identified from the literature review that depressive symptoms may lead either to increased sexual risk-taking or to lowered libido/interest in sex and sexual inactivity. The direction of the association may depend on the severity of the symptoms and/or the type of coping mechanism employed by the individual. For instance, individuals who experience severe symptoms of depression may be more likely to withdraw from social and sexual activity, whereas, individuals who experience moderate symptoms may be more likely to engage in sexual risk behaviour [352]. Alternatively, more recent research suggests that it may be genetic and environmental influences that determine response to depression; some individuals may cope with depression with more externalizing responses such as substance use and sexual risk-taking, whereas, others may cope with more internalizing responses such as social withdrawal and other regressive behaviours [307, 362, 566, 568-573]. Theoretically, when studying the association between depression and sexual risk in a study sample, an overall lack of association may be due to opposing associations: depression linked to sexual risk but also to lack of sexual activity. Of the studies identified in the literature review, those that investigated a

sexually active sample appeared to consistently find an association between depressive symptoms and increased sexual risk-taking. An association was consistently found regardless of where the sample of men was recruited from, if the analysis was restricted to men who reported recent sex. Understanding at which recruitment sites men may be more likely to be engaging in sexual activity, may have implications for intervention. It was identified in the literature review that men attending sexual health clinics, as well as men recruited online, may report a higher prevalence of sexual risk behaviour compared to men recruited elsewhere (from community/commercial gay venues or the general population). Therefore, HIV prevention interventions focused on depression and targeted at sexual health clinic attendees (or possibly men using certain websites) may be more relevant and cost-effective. The vast majority of studies reviewed were conducted in the U.S. The implications of these findings in the UK/European context were unclear.

The hypothesized mechanism by which depressive symptoms lead to sexual risk behaviour, conceptualised in this thesis, was derived from findings in the literature review. Depressive symptoms were hypothesized to be associated with CLS indirectly via lowered self-efficacy for sexual safety. Self-efficacy is another psychological construct that, in a sexual context, is used to describe a perceived inability to exert control and keep oneself sexually safe (for example by condom-use). The association between depressive symptoms and sexual risk behaviour was also hypothesized to be partially confounded by recreational drug use, childhood sexual abuse (CSA), and intimate partner violence (IPV). The hypothesis was investigated in this thesis using data from the AURAH and PROUD studies of HIV-negative gay, bisexual, and other MSM in England. AURAH is an observational cross-sectional study that recruited men attending 20 GUM clinics. Analyses in this thesis were restricted to men in the AURAH sample who reported recent sex. PROUD recruited men who volunteered to participate in a randomised trial of PrEP efficacy, for which eligibility required that men reported ongoing CLS. The methodology of these studies was presented in Chapter 3 of this thesis.

In Chapter 4, using data from AURAH, the prevalence of depressive symptoms was examined and the association of demographic, socio-economic, and lifestyle factors with depressive symptoms was assessed. In Chapter 5, the thesis hypothesis was investigated. Chapter 6 extended the analyses presented in Chapters 4 and 5 by investigating in a single conceptual model, key hypothesized relationships with higher levels of depressive symptoms and CLS measures (including a number of complex mediational chains). In this chapter, the hypothesis that depressive symptoms would be associated with CLS indirectly via lowered self-efficacy for sexual safety was examined in more detail.

Using data from PROUD, Chapter 7 investigated the prevalence of depressive symptoms and associated factors. In Chapter 8, among the unique self-selecting sample of high-risk MSM in PROUD, the thesis hypothesis was investigated. Chapters 7 and 8 extended the AURAH

analyses, since information on age at anal sex debut (sex at a very young age may include experiences of CSA) and IPV, as well as other important psychosocial factors (markers of minority stress) was collected in PROUD.

Each of the results chapters provided a summary and interpretation of findings, in the context of existing literature, and assessed limitations of the analyses.

The findings presented in this thesis represent the largest study of the role of depression in sexual behaviour linked to STI/HIV transmission among sexual minority men in the UK to date. This final chapter draws together the results and considers implications for the epidemiological study of the link between depressive symptoms and sexual behaviour, as well as for clinical practice, and for possible interventions for HIV prevention.

9.2 Depression and sexual behaviour: interpretation of results

9.2.1 Link between depression and sexual behaviour in different samples of men

The relationship between depressive symptoms and sexual behaviour may be complex. It has been theorized that the prevalence of depressive symptoms may be elevated both among men who do not report recent sexual intercourse and men who report recent CLS, and lower among men who report condom-protected sex- creating a U-shaped relationship. Findings from the AURAH study (presented in Chapters 5, 6, and 8) support this theory. As described above, it is possible that some individuals may cope with depression with internalizing responses, whereas, others may cope with externalizing responses.

Among MSM reporting recent anal/vaginal sex in the AURAH study, in line with that hypothesized, symptoms of depression were strongly associated with markers of sexual risk: multiple CLS partners, unknown/HIV-positive status CLS partners, receptive CLS with unknown HIV status partners, bacterial STI diagnosis, and PEP use. Associations remained, although most were somewhat attenuated, after adjustment for regular smoking, higher-risk drinking, and number of recreational drugs used. The observed associations were also present among men who did not report drug use. Unfortunately, it was not possible to investigate the role of CSA and IPV in these relationships. However, AURAH findings in the UK add to substantial evidence (mainly from the U.S.) that sexually active men with depressive symptoms are more likely to engage in CLS versus condom-protected sex than are sexually active men without depressive symptoms, even after adjusting for recreational drug use.

In the PROUD trial of MSM reporting high levels of CLS, symptoms of depression were not associated with measures of CLS, including rectal STI diagnosis. It may be that symptoms of

depression do not distinguish between men reporting higher levels of CLS partners and lower levels of CLS partners- creating a plateauing effect in the U-shaped relationship. An additional exploration of data from AURAH provides some support for this theory: the association between depressive symptoms and higher levels of CLS appeared weakened among the subgroup of men with at least one CLS partner, although the association did remain. It may be that high levels of CLS partners are better explained by factors with greater disinhibiting effects and capacity for sexual arousal, such as personality traits associated with sensation seeking/sexual compulsivity and recreational drug use. This is supported by findings from the PROUD trial (Chapter 8), in which a higher number of recreational drugs used and chemsex-associated drug use were the only measures (for which data was available) found to be consistently associated with higher levels of CLS and partner numbers.

9.2.2 Mechanisms of association

In the AURAH study of sexually active men, depressive symptoms were associated with CLS measures indirectly via lowered self-efficacy for sexual safety (Chapter 6). In addition, reporting a higher number of recreational drugs used appeared to be another, distinct, pathway through which depressive symptoms might lead to CLS. However, in line with the hypothesis set forth in this thesis, self-efficacy appeared to be the most important factor leading to CLS in the SEM presented in Chapter 6. This is reflected by the fact that the link between depression and CLS measures was attenuated but remained after adjusting for drug use in modified Poisson regression models in Chapter 5. There was a greater degree of attenuation after adjusting for self-efficacy in regression models, most likely because the main indirect path was blocked.

It was assumed in this thesis that in order for men with depression to engage in CLS (have an externalized response to symptoms) a process of cognitive escape would most likely have to be enacted. Cognitive escape is a theoretical process whereby individuals turn their attention away from threatening cues in order to engage in a desired behaviour such as sex. Cognitive escape may take two forms: thought suppression or fatalistic beliefs. It was hypothesized in this thesis, that a perceived inability to maintain sexual safety (low self-efficacy) would for some individuals lead to fatalistic beliefs about HIV, with implications for sexual risk-taking. It was also hypothesized that recreational drug use may lead to CLS directly or indirectly via engagement in cognitive escape processes. Unfortunately, it was not possible to investigate the role of cognitive escape on the two causal pathways identified, since a measure of cognitive escape was not collected in AURAH or PROUD.

The finding that self-efficacy for sexual safety via condom-use, which requires exertion of control through discussion/negotiation in an interpersonal situation, may play an important role on the causal pathway between depression and CLS, may explain why a relationship was observed with CLS measures but not higher partner numbers in the AURAH study (Chapter 5).

Furthermore, there was some evidence to suggest that recreational drug use plays a role in the link between depression and high partner numbers.

In PROUD, although depressive symptoms were not associated with high levels of CLS, they were associated with PEP use (Chapter 8). When investigating reasons for non-condom-use, patterns of association suggested that men with depressive symptoms may be more likely to report measures of low self-efficacy for sexual safety and less likely to report CLS because they were intentionally seeking it and did not consider it placing them at risk. This may explain the observed relationship with PEP use. These findings lend some support to the conclusion that self-efficacy may be an important mechanism through which depression leads to CLS.

In addition to management of depressive symptoms, reducing sexual risk-taking among sexual minority men with depression may require interventions that address self-regulatory skills for sexual safety (including negotiation of condom-use) and integrate or offer referral to substance use services.

To conclude this section, it is necessary to acknowledge that CLS with a partner should not in itself be pathologized. The act of CLS will often occur within the context of loving and mutually supportive relationships. Strategies may also be used to try and reduce any perceived risk of HIV transmission such as use of PrEP, serosorting and seropositioning, or knowledge that an HIV-positive partner has a stably suppressed viral load. In the AURAH study, men who reported an ongoing relationship with a partner were more likely to report CLS, as has been found in other UK studies of MSM [482, 496, 510]. In AURAH, most CLS was CLS with a non-regular partner. The link found between depression and the act of CLS, may occur primarily within the context of non-regular partnerships. This may be supported by the finding that depressive symptoms were associated with CLS with two or more partners, CLS with an unknown/HIV-positive status partner (excluding reports of one long-term HIV-positive partner on ART), and receptive CLS with an unknown HIV status partner. These associations were mediated by low self-efficacy for sexual safety. CLS with one or more partners was the outcome focused upon in the SEM in this thesis, since depressive symptoms were hypothesized to lead to non-condom-use in itself. However, additional analyses suggested the same pattern of results for other CLS measures. The other measures of CLS described above could be considered to be the most important in terms of HIV prevention, as these in particular may confer more significant risk of HIV infection.

9.2.3 Temporality of association: investigating criteria for causality

The Bradford Hill Criteria for causality are presented in Chapter 3 (section 3.4.4). Each of the nine criteria are briefly evaluated based on findings from this thesis, in order to infer whether the

observed association between depressive symptoms and CLS measures (in the context of samples in which condom-protected sex and CLS is reported) is likely to be causal.

In terms of the consistency and strength of the association (criteria 1 and 2), the majority (68%) of studies that have investigated the link between depressive symptoms and measures of CLS among MSM samples including HIV-negative MSM, in high-income countries, have found a statistically significant positive association, including after adjusting for recreational drug use. Although it is unclear what the effect of adjusting for CSA and IPV might be. In particular, the association has been consistently demonstrated in samples of sexually active men, across geographical locations and study years, samples of differing age and ethnic profiles, and statistical methodologies. In this thesis, the association was consistently demonstrated in analyses based on AURAH, but not in those based on PROUD, possibly due to the selected high-risk sample recruited into the trial. In terms of strength of association, it is difficult to comment on the general magnitude of association given the investigation of different depression and sexual behaviour measures, using various statistical techniques, across studies. Logistic regression was the most common statistical technique utilized and reported ORs (adjusted for socio-demographics, alcohol, and drug use) ranged from 1.3 to 5.72. ORs adjusted for socio-demographics, for the association across different measures of sexual risk in the AURAH study, ranged from 1.80 to 2.13, suggesting a moderate to strong association. The finding of a statistically significant association in a number of studies (n=7) consisting of a small sample size (≤240 men) provides some further evidence in favour of a strong, and therefore perhaps more likely causal, relationship between depressive symptoms and sexual risk behaviour.

In addition, specificity (criterion 3) may be inferred by the apparent association between depressive symptoms and CLS measures, but not measures of high partner numbers in the AURAH study. These findings are in line with the hypothesized mechanism (reduced self-efficacy for sexual safety) leading to sexual risk behaviour set forth in this thesis.

In terms of criterion 4, temporality, evidence is limited, as most studies have been cross-sectional, with depression and CLS measured at the same time. It is not possible to comment on criterion 4 based on findings from AURAH and PROUD in this thesis, as AURAH was a cross-sectional study and the PROUD data were analyzed as cross-sectional. As all men in PROUD reported ongoing CLS at baseline, it was not possible to assess 'incidence' of CLS, and power was insufficient to analyze incident HIV infections. However, there does appear to be some evidence from U.S. studies for the temporality of the association. Two longitudinal studies have investigated the association between depressive symptoms and HIV incidence, whereby an association was observed in EXPLORE [367-369] but not MACS [361, 431]. However, in the latter study depressive symptoms did predict a higher sexual risk trajectory.

In terms of criterion 5, biological gradient, the prevalence of CLS increased with increasing severity of depressive symptoms in the AURAH study, as was the case in U.S. studies investigating categories of depressive symptom severity [357, 359, 360, 365, 367-369]. Furthermore, in terms of biological plausibility and coherence (criteria 6 and 7), evidence from across disciplines suggest that depression (or at least greater vulnerability towards depression) may precede the onset of risky sexual behaviour. Evidence from cognitive psychology suggests that depression may have strong roots in childhood and early adolescence. Its precursor is the meaning assigned to early/formative experiences and the subsequent formation of a systematic cognitive bias in the information processing system, which may affect responses to negative stimuli later on in life [252, 257-266]. Evidence from genetic and neurophysiological studies reiterate these findings [265, 270-313] and suggest that some individuals with depression react to symptoms with externalizing responses such as substance use and sexual risk-taking [307, 566, 568-573]. Furthermore, in the self-regulation and coping literature, social cognitive theory [256, 262, 381-387] has postulated that depressive symptoms may lead to a perceived inability to produce a desired outcome. This is particularly accurate in the context of interpersonal interactions extending to sexual situations. In addition, cognitive escape theory [396-399, 401-404] [397, 400] posits that symptoms of depression may lead to the notion that acquiring HIV is inevitable, with implications for sexual risk-taking. In the AURAH study, low self-efficacy for sexual safety was found to mediate the association between depressive symptoms and CLS, as has been observed in previous studies of sexually active U.S. MSM [362] and South African MSM [699]. In addition, in the AURAH study, high levels of recreational drug use were also found to mediate the association between depressive symptoms and CLS. Although this association was primarily investigated in the opposite direction in this thesis, in the cognitive escape model, men with depressive symptoms may engage in recreational drug use as a form of self-medication and/or in order to induce a state of cognitive release [397]. Recreational drug use may directly lead to sexual risk-taking via autonomic or central nervous system mechanisms which increase sexual arousal and disinhibition, or indirectly by inducing a state of cognitive release and escape from rational self-awareness [397, 597].

Further evidence in favour of a ‘coherent story’ comes from the associations observed between different measures of depressive symptoms, including suicidal ideation, with measures of CLS in the AURAH study. In addition to the associations observed between depressive symptoms and CLS, treatment for depression was also associated with CLS measures in AURAH, again providing some evidence in favour of coherence. However, the fact that, for some measures, CLS was elevated even among men who reported receiving treatment for depression and no current symptoms of depression, suggests that the effect on CLS was not reversed with the removal of symptoms as a result of treatment. Therefore, there is less support for criterion 8 of experimental manipulation- that reducing the exposure would reduce the occurrence of the outcome. However, as discussed in Chapter 5, the measure for treatment of depression may not capture all the necessary information. Criterion 9 (analogy) may be met, since symptoms of

generalized anxiety disorder (GAD), a common mood disorder for which there is overlap with depressive symptoms, were also associated with CLS measures in the AURAH study, and associations were found to be of a similar, albeit slightly weaker, magnitude.

Using the Bradford Hill Criteria to evaluate findings in this thesis provides some support in favour of a causal association between depressive symptoms and measures of CLS, but does not conclusively demonstrate that causation operates in one direction only. It is also plausible, however, that CLS may further perpetuate depression, perhaps making the symptoms worse, prolonging episodes, or even triggering the onset of depression. CLS may for some individuals reinforce a perceived inability to exert control in sexual situations, thereby lowering self-efficacy for sexual safety. It is theorized in social cognitive theory that low self-efficacy triggers depression and then depression further triggers low self-efficacy. Perhaps it is possible that depressive symptoms lead to CLS indirectly via low self-efficacy for sexual safety, which then leads to a cycle of associations, possibly involving self-efficacy. The interpretation of findings given by some of the PROUD participants supports this theory.

9.3 Implications for analysis of data from epidemiological studies investigating depression and sexual behaviour

Findings from this thesis suggest that when investigating the link between depression and sexual behaviour among sexual minority men in epidemiological studies, the behavioural profile of samples is important in explaining the presence/absence of an association. The U-shaped relationship between levels of sexual behaviour and depressive symptoms (see section 8.3.3.2) should, therefore, be taken into account when investigating the role of depression in sexual behaviour linked to STI/HIV acquisition. In other words, when investigating associations between depression and CLS, rather than comparing CLS to ‘no CLS’, it is important to separate out the group of men reporting condom-protected sex from those not reporting sex. At the same time, it is important to consider that the prevalence of depressive symptoms may begin to plateau among individuals reporting very high levels of CLS partners. Therefore, the relationship between depressive symptoms and increased sexual risk behaviour may be weaker among men reporting high levels of CLS. Among samples of men at high-risk of HIV infection, recreational drug use may be a more effective predictor of increased sexual risk-taking.

Furthermore, it may be beneficial to examine hypothesized relationships in a SEM framework, in order to assess possible indirect effects and better understand the mechanism of effect. SEM is also useful in allowing an investigation into whether alternative hypotheses are more consistent with the data, thereby generating further hypotheses. In the AURAH study, an alternative hypothesis, whereby depressive symptoms lead to CLS indirectly via low self-efficacy for sexual safety as well as indirectly via recreational drug use, was found to be slightly more consistent

with the data. These causal pathways should be investigated in epidemiological studies, together with alternative pathways via for instance IPV, in order to shed further light on the association between depression and sexual risk behaviour.

9.4 Implications of a possible causal link between depression and sexual risk behaviour for sexual health clinical practice

Clinical psychology service provision within GUM was introduced in the UK in the early 1980s in response to the onset of the HIV epidemic. The British Psychological Society dictates that the primary role of clinical psychologists within GUM settings is to address the psychological needs of individuals whose lives are affected by sexual health problems, including HIV infection, genital herpes, and genital warts [716]. In a recent survey conducted by the BASHH Special Interest Group in sexual dysfunction, some but not all of the 273 UK GUM clinics incorporated psychological interventions, including brief counselling, CBT, psychosexual therapy, integrated therapy, and hypnosis, into service provision (exact proportion not reported; 25% incorporated psychosexual therapy). The major barrier to integrating psychological interventions into GUM settings was reported to be funding [717]. The 2012 BASHH guidelines suggest that in order to reduce sexual risk-taking; intensive, multi-session, evidence-based behaviour change interventions, which may encompass safer sex advice and strategies to enhance communication skills and motivation to adopt safe sex practices[xli], should be offered either by trained clinic staff or by referral in all UK GUM clinics (where resources are available) [718]. It is recommended that interventions should be provided to attendees at greatest risk of STI/HIV transmission, including those with a history of bacterial STI diagnosis or substance abuse. BASHH states that although poor mental health may be useful in identifying individuals at high-risk of poor sexual health outcomes, there is not enough evidence to conclude an elevated risk of STI/HIV infection among those with psychological conditions [718]. Therefore, UK guidelines regarding GUM service provision have emphasized the need to address mental health in the context of the emotive significance attached to acquiring STIs and the lack of evidence, particularly among MSM, that those who disclose/screen positive for a mental health condition should be targeted for a sexual risk reduction intervention.

[xli] It is suggested that behaviour change interventions could take the form of motivational interviewing, which consists of a "collaborative, person-centred form of guidance aimed at eliciting and strengthening an individual's motivation for change". It is also suggested that behaviour change interventions should be incorporated within a combination approach to prevention, which may include referral to group and community-based behavioural interventions, as well as offering biomedical interventions (PEP, PrEP, and TasP). It is also suggested that computer assisted interventions should be considered as an alternative or adjunct to clinical staff delivered interventions, for instance videos shown in waiting rooms

718. Clutterbuck D, Flowers P, Barber T, Wilson H, Nelson M, Hedge B, et al. UK National Guidelines on safer sex advice. The Clinical Effectiveness Group of the British Association for Sexual Health and HIV (BASHH) and the British HIV Association (BHIVA). United Kingdom: British Association for Sexual Health and HIV (BASHH) and the British HIV Association (BHIVA), 2012..

In AURAH and PROUD, of HIV-negative MSM attending GUM clinics and/or reporting high levels of CLS and interest in PrEP, around half of those with evidence of current depression reported receiving medical treatment or therapy for depression. Although it is not known how many of those who were untreated had been offered treatment, the findings suggest that there is unmet need in terms of depression among MSM attending GUM clinics. Findings from this thesis suggest the need for a more integrated sexual health approach. This includes screening for depressive symptoms using brief instruments, such as the PHQ-9, which may be useful in identifying individuals who could be offered referral for interventions with proven efficacy such as psychotherapy and/or anti-depressant medication [719, 720]. In parallel, integration of substance use services or referral to such services could be used to the same effect- to alleviate symptoms and potentially reduce future sexual risk-taking.[721] Given the finding in this thesis that men attending GUM clinics may be more likely to cope with depressive symptoms with externalizing responses, due to their somewhat unique behavioural profile, it may be beneficial to offer attendees with depression referral to an HIV prevention intervention that specially addresses sexual risk-taking as a result of depressive symptomatology. A number of suggestions for developing an intervention addressing depression and sexual behaviour among sexual minority men are given below. A suggestion is given for a two stage group intervention. In the first stage, possible roots of depression among sexual minority men could be addressed and attempts made to ameliorate symptoms. In the second stage, attempts could be made to improve self-efficacy for sexual safety, potentially reducing sexual risk-taking.

9.4.1 Implications for intervention to ameliorate effects of depression among sexual minority men

In the PROUD trial, markers of internalized homophobia and concealment of one's sexual orientation to close family, friends, and work colleagues was strongly associated with depressive symptoms, including after adjustment for socio-demographic factors. In the AURAH study, concealment of sexual orientation was associated with higher levels of depressive symptoms indirectly via a strong association with less frequent visits to gay venues and lower levels of a supportive network. At the same time, reporting less frequent visits to gay venues was associated with lower levels of depressive symptoms via lower levels of recreational drug use. Throughout this thesis, recreational drug use was found to be associated with depressive symptomatology. In AURAH, the symptoms that predominate in depressive episodes differed between men who reported chemsex-drug use and men who did not. For men who reported chemsex-drug use, anhedonia and poor appetite/overeating were among the most important factors that explained the presence of depression, perhaps reflecting the direct psychological and physical effects of the drugs themselves. Furthermore, in PROUD, reporting IPV victimization and IPV perpetration was very strongly associated with depressive symptoms.

These findings lend support to the notion that addressing the potential root of mental health disorders among sexual minority individuals may be important in order to foster greater

community affiliation and support, and curtail stress. At the same time however, actively providing help to men, who may want it, who are active on the gay scene and may be using recreational drugs is vital as well in ameliorating the effects of depressive symptoms.

Although it is important to be cognizant of the unique forms of stress experienced by sexual minority men, it should not be forgotten that one's stress is often framed within one's socio-economic context. Therefore, emphasis on alleviating economic hardship together with efforts to promote self-acceptance and pride towards one's sexual orientation should be considered together when addressing depression among sexual minority men. In addition, addressing the damaging effect unhappy relationships may have on one's mental health may play an important role. Referral to services which provide individuals with the skills and advice needed to create and maintain successful relationships, and that encompass culturally appropriate structures set up to address IPV among same-sex male couples, may be useful.

Furthermore, in AURAH, older age was associated with being in an ongoing relationship with a partner and concealment of sexual identity. Younger age was associated with higher levels of recreational drug use via a greater tendency to be 'out' with one's sexual orientation and be active on the gay scene. These findings may suggest the need for separate interventions for younger and older sexual minority men. It may be that interventions focused on younger men should address recreational drug use on the scene and interventions focused on older men should address relationship counselling, community participation, and social support.

Care should be taken not to treat sexual minority men as a homogenous group, as gay-identified and plurisexual-identified men may have different needs. There is a growing body of evidence to suggest that bisexual-identified men experience a greater burden of depressive symptomatology than do gay-identified men [354, 415, 679, 680], as was found to be the case in the AURAH study, and for which there was some suggestion in PROUD. It is important to be cognizant of the heterogeneities present between sexual minority men and to tailor and target interventions carefully. Care should be taken to include bisexual and other men whose sexual identity is not based on attraction to one sex/gender, in efforts to promote social support and manage symptoms of depression.

Of note, although age at anal sex debut (sex at a very young age may include experiences of CSA) was incorporated into the PROUD questionnaire, reporting anal intercourse at age 12 or younger was not found to be associated with depressive symptoms. It is possible that this measure may not have fully captured experiences of CSA. There is some evidence to suggest that sexual abuse in childhood is associated with depressive symptomatology later on in life [41, 368, 610]. Addressing CSA associated trauma may be better conducted in one-to-one sessions with a psychotherapist. Finally, the above suggestions for intervention are given for ameliorating

symptoms of depression in adulthood. It is acknowledged that intervening with sexual minority individuals at a young age i.e. in schools and/or in LGBTQA youth groups, most likely will have positive effects on preventing the onset of mental health problems later on in life [343]. Public health emphasis should be placed both on preventing depression among sexual minority youth and ameliorating symptoms among sexual minority adults.

9.4.2 Implications for intervention to improve sexual safety

As described above, improved screening and referral of individuals with depressive symptoms to appropriate interventions is of public health importance. In the context of considering an intervention to improve sexual safety by managing depression, it is important however, to recognize the fact that treating/curing depression is challenging. Treatment most often requires therapy to re-wire faulty information processing and/or pharmacological intervention. The lack of ease of access (due to waiting times and financial constraints) to talk therapies, including various forms of psychotherapy and CBT, and lack of efficacy of anti-depressant medication add to the challenge that is treating depression. There is little dispute, if any, that lacking confidence in one's ability to produce a desired outcome goes hand-in-hand with depression. In order to reduce sexual risk-taking, what may be possible to suggest, given the findings of this thesis, together with those of Alvy et al (2011) [362], is to intervene upon beliefs of self-efficacy for sexual safety among individuals with depression, for which there does appear to be some evidence to suggest that self-regulatory programmes can greatly improve (see section 1.8.3.3 of Chapter 1).

Seminal work by Kelly (1995) [388] demonstrated the effectiveness of self-regulatory programmes for improved self-efficacy for sexual safety in the U.S. Similarly, Mpowerment, a community-level intervention that utilized a similar technique to Kelly and colleagues, was evaluated and found to be efficacious in reducing CLS among young U.S. sexual minority men in the 1990s [722]. Mpowerment encompassed peer-led meetings whereby the following topics were discussed: clearing up misconceptions about safer sex, eroticizing safer sex, promoting condom-use, and learning verbal and non-verbal safer sex strategies. This intervention has recently been re-evaluated among young BAME MSM in three CDC-funded community-based organizations (N=298) [723]. After adjusting for level of intervention exposure and socio-demographic factors, self-efficacy for sexual safety was found to increase significantly from baseline to the three and six month follow-up. The prevalence of CLS was found to decrease in the short-term but not longer-term. A control group was not included in this study. The authors suggested that a booster intervention would be needed to sustain behavioural changes in the long-term. Findings from Kelly (1995) [388] and the Mpowerment study [723] may be promising in terms of developing interventions that address self-regulatory skills among men with symptoms of depression, among whom self-efficacy for sexual safety may be lowered. It is of note, improving self-efficacy for sexual safety may also help in ameliorating symptoms of depression,

and hence have wider health benefits, especially if CLS does contribute to depressive symptoms in a cyclical manner involving self-efficacy, as discussed above in section 9.2.3.

It appears vital to remain aware and focus efforts on drug use, and chemsex-drug use in particular, in terms of reducing very high levels of sexual risk-taking. Furthermore, although the suggestions for intervention given are for GUM clinic attendees, they may also be useful for MSM who do not attend these services. Findings from the literature review in this thesis also suggest that men recruited online may be more likely to cope with depression with more externalizing responses, with implications for sexual risk-taking, given the levels of sexual risk behaviour noted among online samples. Recruitment of men online for intervention and/or online interventions may reach a broad cross-section of men, including individuals with little or no community attachment. However, it is of note that it is difficult to generalize about men recruited online since the sample depends on how exactly men were recruited i.e. via advertisement on dating apps/websites or on Facebook/social media.

9.5 Conclusions

In conclusion, findings from this thesis suggest that among sexually active men, management of depression alongside interventions surrounding self-efficacy for sexual safety may play an important role in HIV/STI prevention. A combination of efforts that address stress related to sexual minority status and socio-economic hardships common to the general population may be needed to alleviate depressive symptomatology. In particular, having a supportive network, which may be intricately linked to disclosure of one's sexual identity and community affiliation, appears to play an important protective role with regards to depression among sexual minority men. At the same time, in order to provide individuals with the tools needed to exercise self-protective control over interpersonal sexual situations, it may be useful to offer a guided self-enablement programme that simulates experiences of mastery in the exercise of personal control [256, 388]. Finally, addressing recreational drug use in both the context of mental health and sexual health remains an important issue. Integration of substance use services into GUM clinics or referral to such services may be useful in potentially reducing depressive symptomatology and future sexual risk-taking.

9.6 Recommendations for future research

Based on work conducted in this thesis, five manuscripts/reports have been published and three additional papers are in preparation at the time of submission (December 2017). Further work required is discussed below.

To date, there have been no UK survey studies of mental health and sexual behaviour that are tailored to sexual minority men at risk of HIV acquisition. Such a study would include a

comprehensive measure of sexual minority stress, religiosity, HIV-related worry, CSA, IPV, markers of sensation-seeking/sexual compulsivity, detailed substance use behaviour, frequency of gay scene use, and markers of self-efficacy for sexual safety and cognitive escape coping. This could be collected together with information on general factors known to be associated with poor mental health outcomes and sexual risk-taking (social support, socio-economic status, age, and relationship status). Future survey studies would be useful in investigating the conceptual model suggested in this thesis (Figure 8). Furthermore, respondent driven sampling (RDS), see section 2.2.4.2, has not been used to recruit gay, bisexual, and other MSM for survey participation in the field of sexual health in the UK. This method can be used to approximate a probability sample and may be useful for recruiting larger numbers of sexual and gender minority individuals, who may be difficult to reach through other sampling strategies. RDS may become especially useful in an era of social networking online, where it is easier for individuals to reach out to others in their network, and for researchers to get an idea of how many people are in the participant's network.

In addition, there have been no longitudinal studies in high-income countries that are designed and powered to investigate depression and sexual behaviour among MSM. Future longitudinal analyses would be useful in investigating the suggested causal pathways in this thesis. In particular, it would be useful to investigate in a randomized trial, the effect of an intervention to enhance depression treatment service provision on CLS measures and STI/HIV acquisition.

With the currently available evidence on efficacy of PrEP in preventing HIV transmission and with increasing use of PrEP among MSM, future studies of sexual risk behaviour in sexual minority men will need to account for PrEP use, rather than solely focusing on CLS. Condom-use is investigated as the preventative measure of HIV acquisition in this thesis. Whether an association between depression and (HIV) unprotected CLS is mediated by low self-efficacy for consistent PrEP use is very difficult to extrapolate, given the emphasis in this thesis on the link between depression and a behaviour (non-condom-use) that requires exertion of control in interpersonal interactions. In a sub-study of 334 MSM and transgender women in iPrEx OLE (an open-label extension to iPrEx), compared to men who reported no/mild symptoms of depression on CES-D, men who reported moderate levels of depressive symptoms were more likely to have protective levels of PrEP, and men who reported severe levels of symptoms were less likely to have protective levels of PrEP in dried blood spots [724]. However, the authors suggested that severe symptoms of depression did not play a major role in non-adherence to PrEP. Further investigation into the role of depression in PrEP adherence among sexual minority men in the UK is required.

Finally, it is important that future studies also address the role of depression in lowered libido and sexual inactivity among MSM, and investigate the complex role that antidepressants may

play in this relationship. There is a tendency of MSM studies to focus on risk behaviour when investigating the intersection of mental health and sexual behaviour, but outcomes related to personal wellbeing are also relevant.

In conclusion, the research agenda for 2018 onwards is clear. Mental health among sexual minorities in the UK needs to be more actively addressed. In 2015, Public Health England laid out a number of initiatives to develop the data sources needed to support the public health system in reducing mental ill health among sexual minorities, including the collection of sexual orientation data in mental health services and monitoring of homophobic incidents in schools [(725)]. In 2017, more attention has been given to the health and wellbeing of sexual and gender minorities in mainstream media. However, the scientific evidence base still urgently needs to be built up in the UK and elsewhere in Europe in order to inform interventions and prevention programmes.

10 Bibliography

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743. Desai M, editor Baseline predictors of HIV infection in the no-PrEP group in the PROUD trial. 22nd Annual Conference of British HIV Association (BHIVA); 2016 19-22 April; Manchester.

11 Appendices

11.1 Appendix 1: Publications and presentations arising from this thesis (July 2014-December 2017)

Publications:

Miltz A, Rodger AJ, Sewell J, Speakman A, Phillips AN, Sherr L, et al. (2017) Clinically significant depressive symptoms and sexual behaviour among men who have sex with men. BJPsych Open 3(3):127-37. http://bjpo.rcpsych.org/content/3/3/127.full-text.pdf+html

Miltz A, Cambiano V, Lampe FC, Sewell J, Speakman A, Phillips AN, et al. (2017) Eligibility for PrEP among MSM attending GUM clinics in the UK. Sex Transm Infect 93:571. http://sti.bmj.com/content/sextrans/93/8/571.full.pdf

Miltz A, Phillips AN, Speakman A, Cambiano V, Rodger A, Lampe FC. (2017) Implications for a policy of initiating antiretroviral therapy in people diagnosed with human immunodeficiency virus: the CAPRA research programme. Programme Grants Appl Res 5(18). https://www.journalslibrary.nihr.ac.uk/pgfar/pgfar05180/#/abstract

Sewell J, **Miltz A**, Lampe FC, Cambiano V, Speakman A, Phillips AN, et al. (2017) Poly drug use, chemsex drug use, and associations with sexual risk behaviour in HIV-negative men who have sex with men attending sexual health clinics. Int J Drug Policy 43:33-43. http://www.sciencedirect.com/science/article/pii/S0955395917300038?via%3Dihub

Sewell J, Speakman A, Phillips AN, Lampe FC, **Miltz A**, Gilson R, et al. (2016) A cross-sectional study on attitudes to and understanding of risk of acquisition of HIV: design, methods and participant characteristics. JMIR Res Protoc 5:e58. https://doi.org/10.2196/resprot.4873

Conference presentations:

Oral presentation (10.1136/sextrans-2015-052126.7, abstract book number 07): BASHH Spring Conference 2015 in Glasgow, June 1-3. Depression and sexual behaviour among men who have sex with men in the UK.

Poster (abstract number P_21): 11th International Workshop on HIV transmission, 15-16 October 2016, Chicago, IL, USA. Depression, self-efficacy, and sexual behaviour among men who have sex with men.

Working titles of papers in preparation at time of thesis submission (December 2017):

1. 'Intimate partner violence and sexual behaviour among men who have sex with men in the PROUD trial'
2. 'Investigating a conceptual model for the relationship between depression and condomless sex among gay, bisexual, and other men who have sex with men' (using data from AURAH)
3. 'Clinically significant depressive symptoms and sexual behaviour among men who have sex with men in the PROUD trial'

11.2 Appendix 2: Acknowledging AURAH study group members

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AURAH study nurse coordinator: Janey Sewell.
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11.4 Appendix 4: Prevalence of recreational drug use and intimate partner violence among sexual minority men and evidence for a link with sexual minority stress

11.4.1 Studies comparing the prevalence of recreational drug use between sexual minorities and their heterosexual counterparts in high-income countries

There is evidence to suggest that the prevalence of recreational drug use is elevated among sexual minority men compared to their heterosexual counterparts in high-income countries. In the National Well Being Study conducted in England and Wales between 2000 and 2002, described in section 1.8.1, the reported prevalence of recreational drug use in the past month was higher among gay-identified men compared to heterosexual-identified men (52% vs. 45%; χ^2 test p-value<0.05) [(726)]. In the national Crime Survey for England and Wales 2013/2014, gay- and bisexual-identified men were the group most likely to report having taken any illicit drug in the past year (at 33%) [(727)]. Similarly, in a recent systematic review of mostly U.S. samples, described in section 1.8.1, the vast majority of included studies (93%) reported an increased

risk of recent illicit drug use and drug dependency among lesbian-, gay- and bisexual-identified individuals compared to heterosexual-identified individuals. Elevated risk was observed across different orientations for both men and women [338].

In a random-effects meta-analysis of studies conducted from 1996-2005, gay, bisexual and other MSM (N=209) were found to report a higher prevalence of drug dependence in the past year compared to men who identified as heterosexual and did not report sexual attraction to or sex with men (N=7471), across three U.S. nationally representative household surveys (1996 National Household Survey of Drug Abuse, National Comorbidity Survey, McArthur Foundation National Survey of Midlife Development in the United States): pooled RR 2,41 95% CI: 1.48, 3.92 [332].

11.4.1.1 Recreational drug use on the gay 'scene': escape from minority stress

For many gay (and bisexual) men, the gay scene is an important social nexus and can represent a culturally-endorsed 'time-out' from stresses common to the gay community [601, 728]. Drug use often plays a key role in escaping self-awareness of social and sexual norms. Sexual minority men's use of drugs is potentially part of coping with minority stress [210, 229]. Of note, certain personality traits related to sensation-seeking and sexual compulsivity may be associated with the use of drugs, and one's ability to disengage from self-awareness [371, 612-614].

11.4.2 Studies comparing the prevalence of intimate partner violence between sexual minorities and their heterosexual counterparts in high-income countries

Evidence suggests that the prevalence of IPV is higher for men in same-sex couples than for men in opposite-sex couples and similar for same-sex male couples and women in opposite-sex couples. Four U.S. population-based studies have investigated the comparative prevalence among these population groups. In the 1995-1996 National Violence Against Women Survey, whereby 65 men and 79 women who reported a current or past same-sex cohabiting relationship were compared to randomly selected sub-samples of 300 men and 300 women who reported a current or past cohabitating relationship with an opposite sex partner (and no cohabitation with same-sex partner), lifetime IPV prevalence was significantly higher for men in same-sex cohabitating relationships compared to men in opposite-sex cohabitating relationships in unadjusted analysis (15.4% [95% CI: 10.9%, 19.9%] versus 7.7% [95% CI: 6.2%, 9.2%]). Lifetime IPV prevalence did not differ significantly for men in same-sex cohabitating relationships compared to women in opposite-sex cohabiting relationships in unadjusted analysis (15.4% [95% CI: 10.9%, 19.9%] versus 20.3% [95% CI: 18.0%, 22.6%]) [729].

In the UMHS, described in section 2.4.1.1, prevalence estimates of IPV in the past five years (39.2% 95% CI: 37.0%, 41.5%) were higher than those reported for men in opposite-sex

couples in the literature and as high, or higher, than those reported for women in opposite-sex couples. This comparative review was, however, limited by several factors including the differing IPV measures and recall periods, and the fact that the differences observed may have been confounded by socio-demographic factors, as only unadjusted analyses were presented (as was the case for the National Violence Against Women Survey) [730].

In the 2007-2008 California Health Interview Survey (N=13447 heterosexual-identified men, 415 gay-identified men, 135 bisexual-identified men, and another 92 MSM), after adjusting for socio-demographic, lifestyle, and psychological factors, the prevalence of lifetime IPV and IPV in the past year was found to be higher among gay, bisexual and other MSM compared to heterosexual-identified men who did not report sexual attraction to/sex with men, but the difference was only statistically significant for gay-identified men versus heterosexual-identified men (OR 2.68 [95% CI: 1.75, 4.11]; OR 2.41 [95% CI: 1.32, 4.40] respectively) [731].

In the 2010 National Intimate Partner & Sexual Violence Survey (N=9086 women and 7421 men), bisexual-identified men (N=89) reported a higher lifetime prevalence of rape, physical violence and/or stalking by an intimate partner compared to heterosexual-identified men (37.3% vs. 29.0%). Gay-identified men (N=148) reported a similar prevalence to heterosexual men (26.0%). Gay-identified men reported a higher prevalence of psychological IPV (specifically expressive aggression including name calling, insulting, or humiliating) compared to both bisexual-identified men and heterosexual-identified men (44.5%, 32.4%, 24.4% respectively) [732].

11.4.2.1 Minority stress and intimate partner violence

In line with the exosystem factor theory described in Textbox 4, the social pressure faced by sexual minority individuals to conform to heteronormative behaviours and the ensuing stress associated with homophobic discrimination and shaming, may trigger, depending on one's personal history, episodes of abuse in intimate partnerships. Evidence is gathering which suggests that among UK (N=398[733]), U.S. (N=1575 [734], N=750 [735]), and Canadian (N=186 [736]) samples of MSM, markers of internalized homophobia are associated with physical IPV perpetration[733, 736], emotional/psychological IPV perpetration[736], sexual IPV perpetration [734], physical IPV victimization [733], sexual IPV victimization [733], any IPV perpetration [735], and any IPV victimization [735], in unadjusted analysis [734, 736], and after adjusting for socio-demographic and lifestyles factors [733, 735].

It is of note, there is also some evidence to suggest that the prevalence of CSA is higher among gay, bisexual, and other MSM compared to heterosexual-identified men, including after adjustment for age and ethnicity [737]. In the 'Growing Up Today Study' (2005-2007 wave), a U.S. population-based longitudinal study of 16882 children (born of mothers who were enrolled in the Nurses' Health Study II), sexual minority individuals were more likely to screen positive for

a measure of childhood gender nonconformity. This measure included questions on favourite games and toys in childhood, which television characters were admired/imitated and feelings of masculinity or femininity. Gender nonconformity was found to partly explain the differences observed in CSA prevalence between gay, bisexual, and other MSM and heterosexual-identified men who did not report sexual attraction to/sex with men.

11.5 Appendix 5: Location of literature for thesis literature reviews

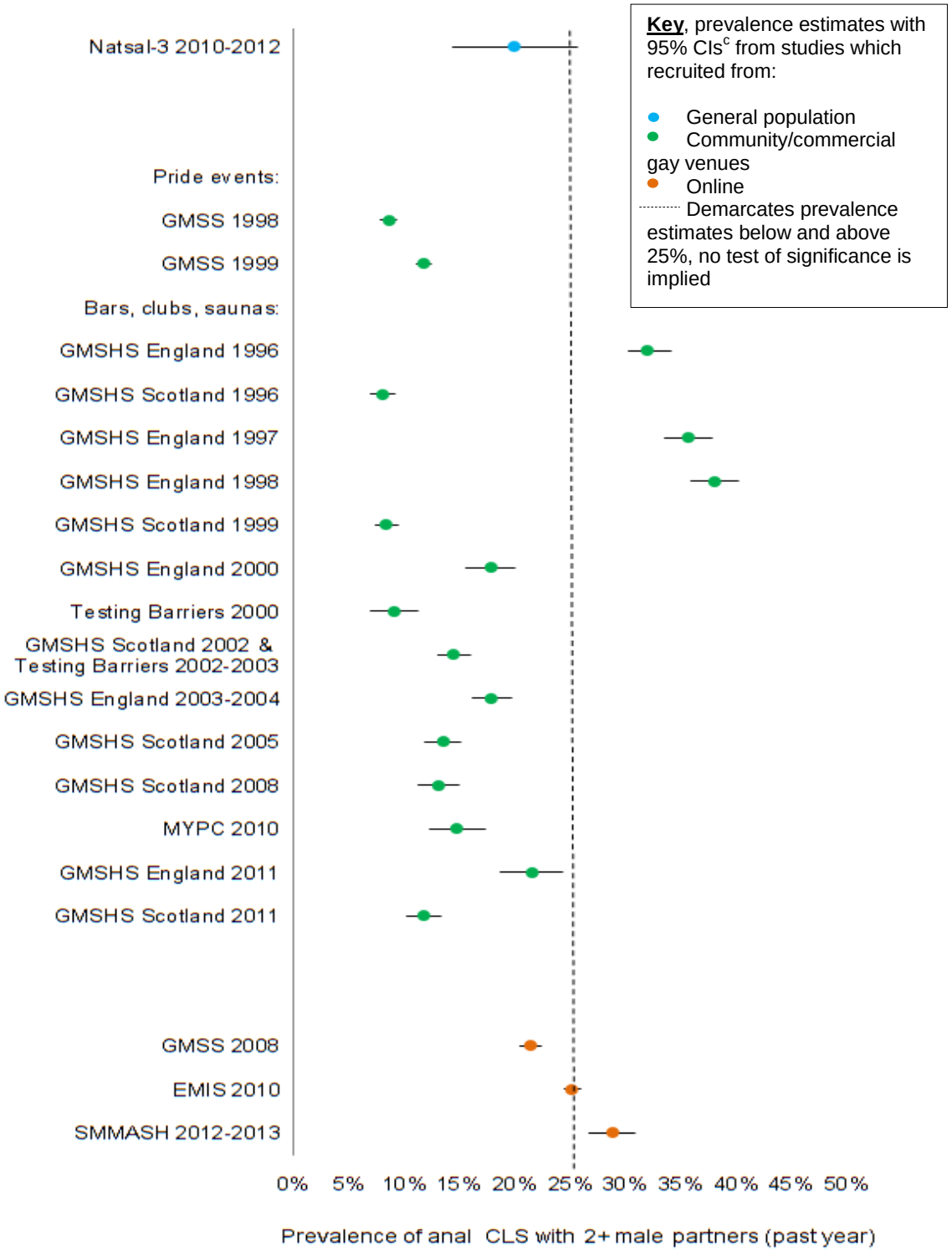
Table 45: Identification of publications for literature review

Database	MeSH terms- MSM sexual lifestyles/behaviour search	Limits
Pubmed	("men who have sex with men"[All Fields] AND ("HIV acquisition"[All Fields] OR "unsafe sex"[MeSH Terms] OR "HIV testing"[All Fields] OR "Pre-Exposure Prophylaxis"[All Fields] OR "Post-Exposure Prophylaxis"[All Fields])) AND (("1996/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang] AND "male"[MeSH Terms] AND (AIDS[sb] OR systematic[sb]) AND "adult"[MeSH Terms])	Publication date from 1996/01/01, Humans, English, Male
Cochrane Database of Systematic Reviews	"men who have sex with men" or gay next men or homosexual next men or bisexual next men or [mh "homosexuality male"] AND (HIV near acquisition or HIV near diagnos?s or positive HIV-test* or [mh "aids serodiagnosis"] OR high-risk sex* behaviour or condom-less next sex or unprotected next sex or unprotected next intercourse or "sex without a condom" or unsafe next sex or high-risk next sex or [mh "unsafe sex"] OR HIV next test* or late diagnos?s of HIV or delayed diagnos?s of HIV OR PrEP or "Pre-Exposure Prophylaxis" OR PEP or "Post-Exposure Prophylaxis"	/
Cochrane Central Register of Controlled Trials	"men who have sex with men" or gay next men or homosexual next men or bisexual next men or [mh "homosexuality male"] AND (HIV near acquisition or HIV near diagnos?s or positive HIV-test* or [mh "aids serodiagnosis"] OR high-risk sex* behaviour or condom-less next sex or unprotected next sex or unprotected next intercourse or "sex without a condom" or unsafe next sex or high-risk next sex or [mh "unsafe sex"] OR HIV next test* or late diagnos?s of HIV or delayed diagnos?s of HIV OR PrEP or "Pre-Exposure Prophylaxis" OR PEP or "Post-Exposure Prophylaxis"	/

11.6 Appendix 6: Prevalence of CLS across UK recruitment settings

Figure 29 presents the prevalence of CLS with two or more partners in the past year. The Natsal-3 estimate appears relatively high at 19.9%. However, as stated in section 2.5.2 of Chapter 2, the confidence interval is wide, reflecting the small sample size for MSM and therefore, relative imprecision of the prevalence. A similar pattern to that described for the measure of CLS with one or more partners in the past year (section 2.5.2) appears evident; on the whole, men recruited online appear to report a higher prevalence of multiple CLS partners in the past year (range from: 21.5%-28.8%) compared to men recruited from community and commercial gay venues (range form: 8.4%-38.1%). There are three exceptions to this pattern, where prevalence estimates from the GMSHS in England in 1996, 1997, and 1998 appear to be higher (32.0%, 35.7%, and 38.1% respectively). It is possible that differences observed between prevalence estimates may (in addition) reflect changes overtime, including city specific changes overtime.

Figure 29: Proportion of MSM reporting anal CLS with two or more male partners in the past year, from UK studies[a] which include HIV-negative men (1996-2014) and according to study recruitment site[b]



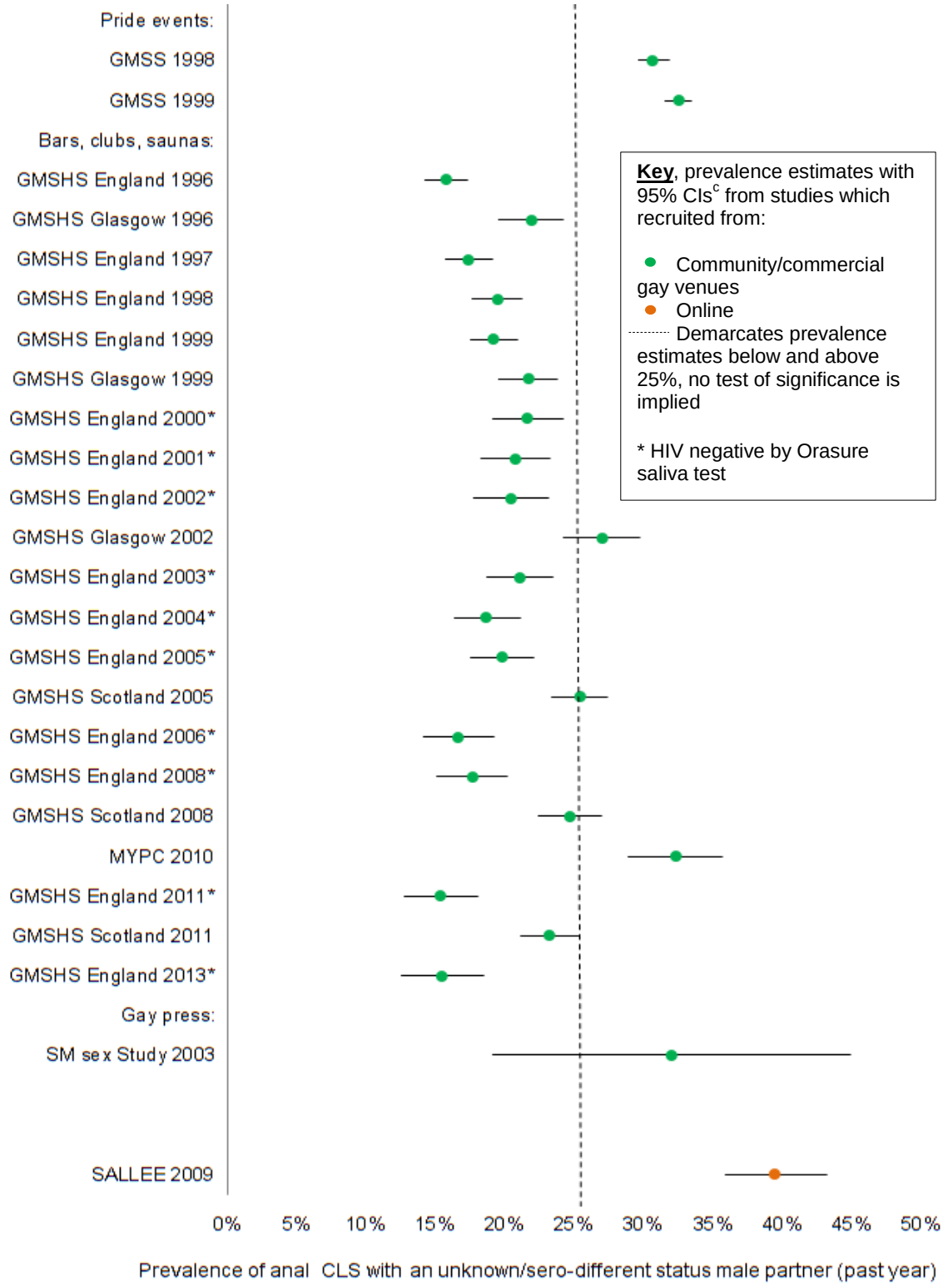
[a] In the GMSHS England 2011, the prevalence estimate pertains to men resident in London only.

[b] Studies that encompassed mixed approaches to sampling (i.e. from commercial venues, clinics, and online) were placed in the recruitment site category from which the largest proportion of the sample was selected.

[c] Binomial 95% confidence intervals using Wald test.

Figure 30 presents the prevalence of CLS with an unknown or sero-different HIV status partner in the past year. It was not possible to include an estimate for this measure of CLS from Natsal. Once again, a similar pattern may be evident; men recruited online appear to report a higher prevalence of CLS with an unknown/sero-different HIV status partner in the past year (39.5%) compared to men recruited from community and commercial gay venues (range from: 15.4%-32.6%). Unfortunately, for this measure of CLS it was only possible to compare the prevalence estimate from one online recruited sample. The seemingly higher prevalence reported in studies which recruited men from Pride events (30.7% and 32.6%), and lower prevalence of CLS with two or more partners in studies which recruited from Pride events (Figure 29), compared to bars, clubs, and saunas (range from: 15.4%-32.3%), may not be surprising. As suggested in section 2.5.2 of Chapter 2, the festive and temporary nature of Pride events may possibly facilitate risky sex with a partner, which may then be captured on a survey. As described in section 2.5.2, the high estimate and wide confidence interval observed for the SM sex Study may not be surprising given the sample size of this unique self-selecting sample.

Figure 30: Proportion of MSM reporting anal CLS with an unknown or HIV sero-different status partner[a] in the past year, from UK studies which include HIV-negative men (1996-2014) and according to study recruitment site[b]



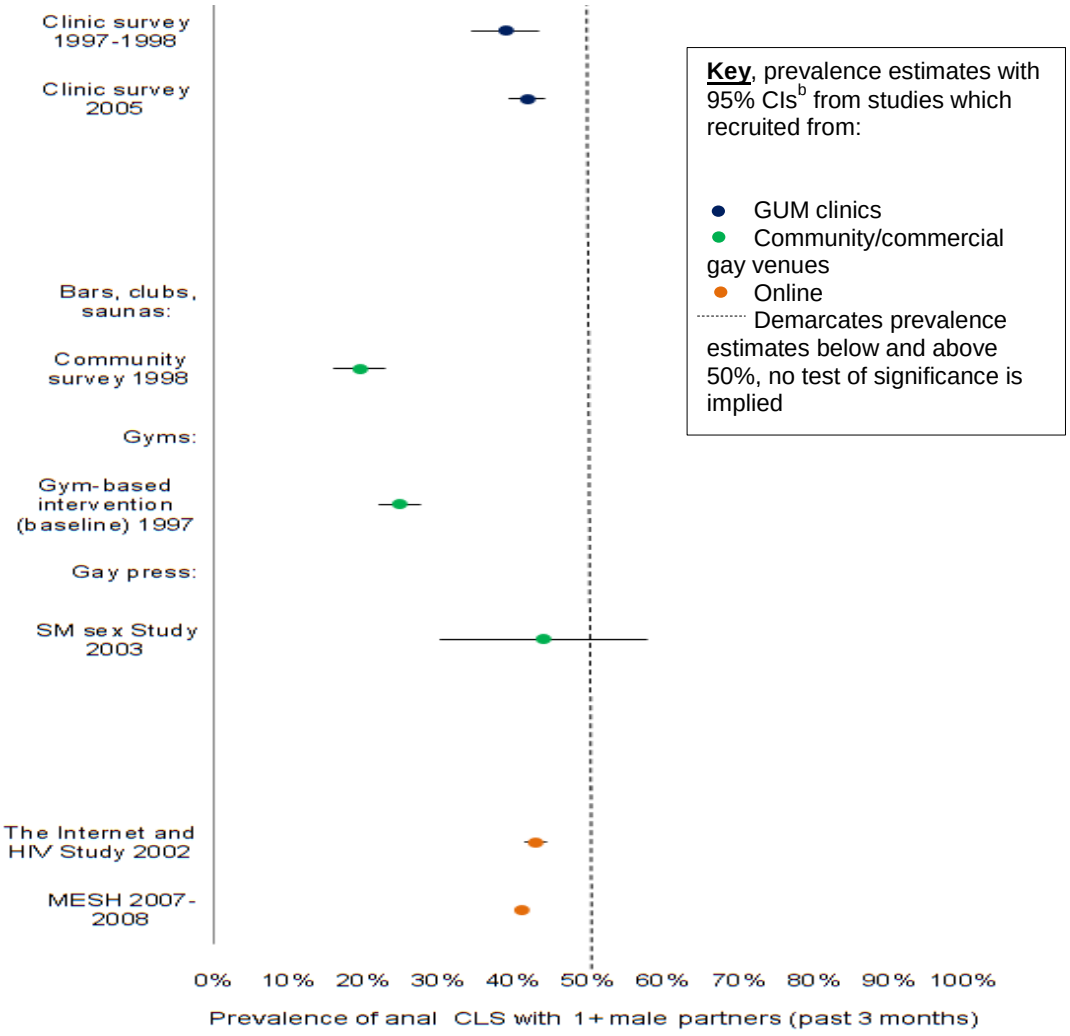
[a] In the GMSHS England 1999 and MYPC 2010, the prevalence estimate consists of men who reported CLS with a casual and/or unknown and/or HIV-positive status partner in the past year. Furthermore, in GMSHS England 2000-2013, the prevalence estimate pertains to men resident in London only.

[b] Studies that encompassed mixed approaches to sampling (i.e. from commercial venues, clinics, and online) were placed in the recruitment site category from which the largest proportion of the sample was selected.

[c] Binomial 95% confidence intervals using Wald test.

Figure 31 presents the prevalence of CLS with one or more partners in the past three months. In line with that observed for CLS measures reported in the past year, the reported prevalence of CLS in the past three months appears to be similar between GUM clinic samples (38.9% and 41.8%) and online samples (41.0% and 43.0%), and higher compared to community/commercial gay venue samples, excluding the somewhat difficult to compare estimate from the SM sex Study (19.6% and 24.9%).

Figure 31: Proportion of MSM reporting anal CLS with one or more male partners in the past three months, from UK studies which include HIV-negative men (1996-2014) and according to study recruitment site[a]

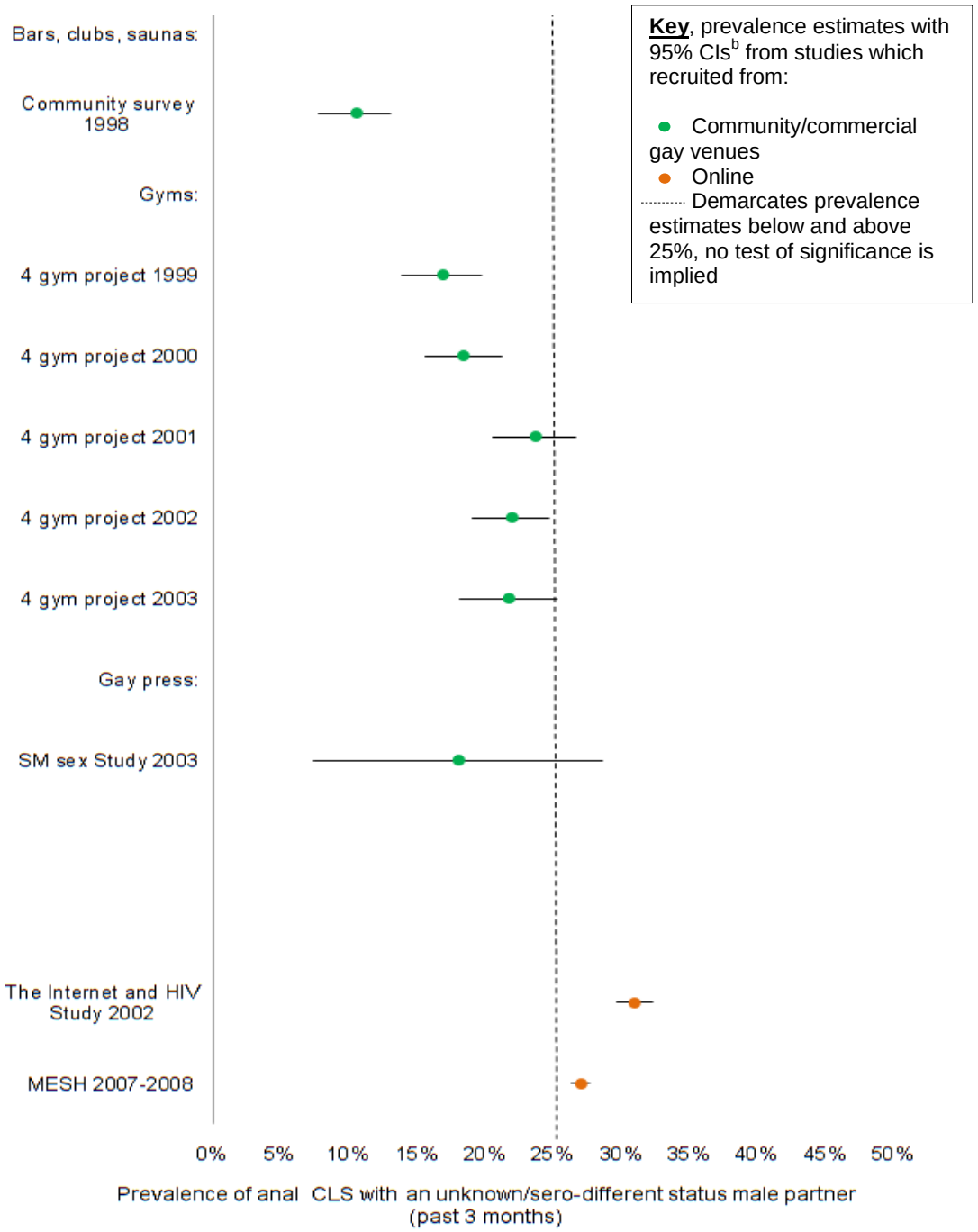


[a] Studies that encompassed mixed approaches to sampling (i.e. from commercial venues, clinics and online) were placed in the recruitment site category from which the largest proportion of the sample was selected.

[b] Binomial 95% confidence intervals using Wald test.

Finally, Figure 32 presents the prevalence of CLS with an unknown or HIV sero-different status partner in the past three months. This final figure again depicts that observed; the prevalence estimates of this CLS measure appear to be higher in studies of men recruited online (27.0% and 31.0%) versus from bars, clubs, saunas, or gyms (excluding SM sex Study, range from: 10.5%-23.7%). The confidence intervals are narrow for all online recruited samples, shown in each figure, given the large sample sizes of these studies. Within the community/commercial gay venue recruitment category, men recruited from gyms (most of which were reported to consist almost entirely of gay-identified male cliental [482-484]) appeared to report a higher prevalence (range from: 16.8%-23.7%) compared to men recruited from bars, clubs, and saunas (10.5%). However, only one study of commercial gay venues was available for comparison.

Figure 32: Proportion of MSM reporting anal CLS with an unknown or HIV sero-different status partner in the past three months, from UK studies which include HIV-negative men (1996-2014) and according to study recruitment site[a]



[a] Studies that encompassed mixed approaches to sampling (i.e. from commercial venues, clinics, and online) were placed in the recruitment site category from which the largest proportion of the sample was selected.

[b] Binomial 95% confidence intervals using Wald test.

11.7 Appendix 7: Relationship between socio-demographic and psychosocial factors with CLS measures among MSM in the UK

11.7.1 Age

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 66 collected data on age (Table 2). The association between age and common measures of CLS was investigated in nine publications, some of which combined a number of repeated surveys (across different studies) (Table 46) [118, 477, 482, 489, 509-512, 563]. In all nine studies, age was investigated in categories (of around five to ten year bands) and as a binary variable in two studies (using a cut-off of mid-twenties). Eight studies recruited men from community/commercial gay venues (including one gym sample and three Pride event samples) and the remaining study recruited men online. Four studies investigated CLS with one or more partners (with recall periods of three months in one study and the past year in three studies) and five studies investigated CLS with two or more partners in the past year as well as CLS with a partner of unknown/sero-different HIV status in the past year in two of these studies. Two studies found that the prevalence of CLS decreased with increasing age [482, 489] and two studies found no significant association in unadjusted analysis [510, 511]. One study investigated the association adjusted for relationship status and found that the significant unadjusted association remained [482]. Similarly, four studies found that older age was associated with lower levels of CLS with two or more partners in unadjusted analysis [512] and in adjusted analysis (for socio-demographic factors) [118, 477, 563]. One study investigated the association in unadjusted and adjusted analysis and did not find an association [509]. One study found that older age was associated with lower odds of CLS with a partner of unknown/sero-different HIV status adjusted for socio-demographic factors [563] and one study found that older age was associated with higher odds of this CLS measure in unadjusted analysis [509]. However, this latter association disappeared after adjusting for socio-demographic factors and recreational drug use.

Table 46: Unadjusted and adjusted associations found between age and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of age groups:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
Gym-based intervention baseline 1997 (N=1004)[482]	Gyms (N=1004)	20-24 25-29 30-34 35-39 40-44 45-49	CLS with 1+ partner (past 3 months)	χ^2 test for a linear trend	Lower CLS with older age	35.0% 29.0% 26.5% 23.9% 19.1% 14.3% *p<0.01*	OR per 5 year increase in age	Lower CLS with older age	0.80 [0.70, 0.90] *p<0.001*	Relationship status
GMSS 1998 (N=5065[a])[510]	Pride events (n=6315)	<20 20s 30s 40s 50+	CLS with 1+ partner (past year)	χ^2 test	None	48.1% 48.9% 45.7% 43.7% 44.8% *p>0.05*	/	/	/	/
GMSS 1999 (N=4025[a])[511]	Pride events (n=6612)	<20 20s 30s 40s 50+	CLS with 1+ partner (past year)	χ^2 test	None	58.4% 56.4% 53.9% 52.3% 51.9% *p>0.05*	/	/	/	/
GMSS 2000 (N=9789)[489]	Pride events (n=6624)	<20 20s 30s 40s 50+	CLS with 1+ partner (past year)	χ^2 test	Lower CLS with older age	49.0% 50.3% 43.9% 39.0% 34.5% *p<0.05*	/	/	/	/

Table 46: Unadjusted and adjusted associations found between age and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS (continued)

	Largest % recruited via:	Measure of age groups:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSS 2008 (N=7461)[512]	Online (N=4364)	<20 20s 30s 40s 50+	CLS with 2+ partners (past year)	χ^2 test	Lower CLS with older age	24.6% 24.1% 24.3% 23.8% 17.8% *p<0.05*	/	/	/	/
GMSHS Scotland 1996-2002 (N=6448)[118]	Gay bars (N=6448)	<26 26+	CLS with 2+ partners (past year)	/	/	/	OR	Lower CLS with older age	1 0.70 [0.58, 0.84]	Social class, education, area of residence, frequency of gay bar use, HIV optimism
GMSHS England 2003-2004 & GMSHS Scotland 2005 (N=3046)[563]	Commercial gay venues (N=3046)	15-25 26-35 36-45 46+	CLS with 2+ partners (past year)	/	/	/	OR	Lower CLS with older age	1 0.83 [0.65, 1.07] 0.64 [0.48, 0.85] 0.57 [0.38, 0.85] *p=0.003*	Education, employment status, HIV testing history
GMSHS Scotland 1996-2008, and Testing Barriers 2000-2003 (N=10223)[477]	Commercial gay venues (N=10223)	<25 25+	CLS with 2+ partners (past year)	/	/	/	OR	Lower CLS with older age	1 0.69 [0.60, 0.78] *p<0.001*	Survey year

Table 46: Unadjusted and adjusted associations found between age and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS (continued)

	Largest % recruited via:	Measure of age groups:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	16-25 26-35 36-45 45+	CLS with 2+ partners (past year)	OR	None	1 0.90 [0.59, 1.36] 0.97 [0.60, 1.58] 1.52 [0.84, 2.73] *p=0.392*	OR	None	1 0.96 [0.61, 1.52] 0.90 [0.51, 1.59] 1.46 [0.74, 2.89] *p=0.582*	Sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, popper, stimulant/recreatio-nal/illicit drug, Viagra use
GMSHS England 2003-2004 & GMSHS Scotland 2005 (N=3046)[563]	Commercial gay venues (N=3046)	15-25 26-35 36-45 46+	CLS with unknown/ sero-different partner (past year)	/	/	/	OR	Lower CLS with older age	1 0.81 [0.66, 1.00] 0.66 [0.52, 0.83] 0.50 [0.35, 0.70] *p<0.001*	Education, employment status, HIV testing history
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	16-25 26-35 36-45 45+	CLS with unknown/ sero-different partner (past year)	OR	Higher CLS with older age	1 0.93 [0.65, 1.35] 1.50 [0.96, 2.35] 1.93 [1.07,3.48] *p=0.029*	OR	None	1 0.89 [0.61, 1.32] 1.38 [0.85, 2.24] 1.78 [0.94, 3.37] *p=0.101*	Sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, popper, stimulant/recreatio-nal/illicit drug, Viagra use

[a] Men who reported anal sex with a man in the past year.
[b] Men who reported CLS with one or more partners in the past year, and did not have any missing data on any of the alcohol or drug use questions.

11.7.2 Ethnicity

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 52 collected data on ethnicity (Table 2). The association between ethnicity and common measures of CLS was investigated in seven publications (Table 47) [482, 489, 496, 498, 499, 510-512]. Four studies recruited men from community/commercial gay venues (including one gym sample and four Pride event samples) and three studies recruited men online. Ethnicity was not found to be associated with CLS with one or more partners or two or more partners, or partners of an unknown/sero-different HIV status in unadjusted analysis [482, 489, 496, 498, 510-512]. One study investigated the association between two measures of ethnicity with report of CLS with unknown/sero-different HIV status partners in the past three months adjusted for socio-demographic factors and recreational drug use, and found that the association remained non-significant [498].

Table 47: Unadjusted and adjusted associations found between ethnicity and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of ethnicity:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
Gym-based intervention baseline 1997 (N=1004)[482]	Gyms (N=1004)	White Non-white	CLS with 1+ partner (past 3months)	χ^2 test	None	It was reported: "There was no significant univariate association between UAI and ethnicity" (pg 1409). No estimate given	/	/	/	/
GMSS 1998 (N=5065[a])[510]	Pride events (n=6315)	White Black Asian[b] Other	CLS with 1+ partner (past year)	χ^2 test	None	46.4% 45.3% 48.0% 52.9% *p>0.05*	/	/	/	/
GMSS 1999 (N=4025[a])[511]	Pride events (n=6612)	White[e],UK White[f] Black[g] Asian[h] Other	CLS with 1+ partner (past year)	χ^2 test	None	54.7% 54.4% 53.9% 54.1% 0.7% *p>0.05*	/	/	/	/
GMSS 2000 (N=9789)[489]	Pride events (n=6624)	White[e],UK White[f] Black[g] Asian[h] Other	CLS with 1+ partner (past year)	χ^2 test	None	44.7% 44.2% 49.2% 47.0% 43.6% *p>0.05*	/	/	/	/
GMSS 2006 (N=12155)[496]	Online (n=8286)	White[e],UK White[f] Black Asian Mixed Other	CLS with 1+ partner (past year)	OR	None	It was reported: "no ethnic group was more or less likely to have had UAI than the White British men" (pg 28). No estimate given	/	/	/	/

Table 47: Unadjusted and adjusted associations found between ethnicity and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS (continued)

	Largest % recruited via:	Measure of ethnicity:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relatio-nship	Estimate	Measure of effect size	Relatio-nship	Estimate	Factors adjusted for
GMSS 2008 (N=7461)[512]	Online (N=4364)	White[e],UK White[f] Black Asian Mixed Other	CLS with 2+ partners (past year)	χ^2 test	None	23.0% 25.5% 26.4% 22.4% 20.8% 23.8% *p>0.05*	/	/	/	/
MESH 2007-2008 (N=13278) [498]	Online (N=12494)	White[e],UK Minorities SCA[c] CEE[c]	CLS with unknown/ sero-different partner (past 3 months)[d]	OR	None	1 0.95 [0.82, 1.10] 0.95 [0.63, 1.43] 0.96 [0.69, 1.34]	OR	None	1 0.99 [0.84, 1.16] 0.95 [0.62, 1.45] 0.91 [0.64, 1.29]	Age, place of residence, place of birth, education, employment, HIV treatment optimism, recreational drug use, HIV status
MESH 2007-2008 (N=13278) [498]	Online (N=12494)	White[e],UK Black Asian[h] Chinese Asian[i] Arab Other SCA[c] CEE[c]	CLS with unknown/ sero-different partner (past 3 months)[d]	OR	None	1 0.98 [0.75, 1.27] 1.01 [0.77, 1.31] 0.82 [0.54, 1.22] 0.87 [0.58, 1.30] 0.92 [0.48, 1.77] 1.15 [0.66, 2.02] 0.95 [0.63, 1.43] 0.96 [0.69, 1.34]	OR	None	1 1.00 [0.76, 1.31] 1.03 [0.78, 1.35] 0.97 [0.64, 1.47] 0.94 [0.62, 1.43] 0.97 [0.49, 1.91] 0.94 [0.53, 1.67] 0.95 [0.62, 1.45] 0.91 [0.64, 1.29]	Age, place of residence, place of birth, education, employment, HIV treatment optimism, recreational drug use, HIV status

[a] Men who reported anal sex with a man in the past year.
[b] South Asian.

[c] Men who were born in this region (SCA= South/Central America; CEE= Central/Eastern Europe)
[d] Includes men who reported CLS and had never tested for HIV.
[e] White British.
[f] Other white.
[g] Black or black British.
[h] Asian or Asian British.
[i] Asian other.

11.7.3 Sexual identity

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 30 collected data on sexual identity (Table 2). The association between sexual identity (gay- versus bisexual-identity) and common measures of CLS was investigated in two publications of data collected from men attending Pride events [510] or commercial gay venues [509] (Table 48). Sexual identity was not found to be associated with CLS with one or more partners or CLS with a partner of unknown/sero-different HIV status in the past year in unadjusted analysis [509, 510]. Bisexual men were more likely to report CLS with two or more partners in the past year in unadjusted analysis [509]. However, this association was investigated adjusted for socio-demographic factors and recreational drug use, and a significant relationship was no longer observed.

Table 48: Unadjusted and adjusted associations found between sexual identity and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of sexual identity:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSS 1998 (N=5065[a]) [510]	Pride events (n=6315)	Gay Bisexual	CLS with 1+ partner (past year)	χ^2 test	None	46.9% 40.3% *p>0.05*	/	/	/	/
GMSHS Scotland 2011 (N=639[b]) [509]	Commercial gay venues (N=1515, whole sample)	Gay Bisexual	CLS with 2+ partners (past year)	OR	Bisexual men more likely to report CLS	1 2.11 [1.05, 4.25] *p=0.037*	OR	None	1 1.81 [0.85, 3.86] *p=0.124*	Age, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, popper, stimulant/ recreational/illicit drug, Viagra use
GMSHS Scotland 2011 (N=639[b]) [509]	Commercial gay venues (N=1515, whole sample)	Gay Bisexual	CLS with unknown/ sero-different partner (past year)	OR	None	1 1.33 [0.66, 2.71] *p=0.429*	/	/	/	/

[a] Men who reported anal sex with a man in the past year.
[b] Men who reported CLS with one or more partners in the past year, and did not have any missing data on any of the alcohol or drug use questions.

11.7.4 Education

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 53 collected data on levels of educational attainment (Table 2). The association between educational levels and common measures of CLS was investigated in eight publications, some of which combined a number of repeated surveys (across different studies) (Table 49) [118, 482, 489, 496, 509, 510, 512, 563]. Six studies recruited men from community/commercial gay venues (including one gym sample and two Pride event samples) and the remaining two studies recruited men online. Four studies investigated CLS with one or more partners (with recall periods of three months in one study and the past year in three studies) and four studies investigated CLS with two or more partners in the past year as well as CLS with a partner of unknown/sero-different HIV status in the past year in two of these studies. One study found that the prevalence of CLS decreased with higher educational levels [510] and two studies found no significant association in unadjusted analysis [482, 489]. Another study only investigated the association adjusted for HIV status and found no association [496]. Similarly, one study found that the prevalence of CLS with two or more partners decreased with higher educational levels [512], however, another study did not [509], in unadjusted analysis. Two studies only investigated the association adjusted for socio-demographic factors, and again found no association [118, 563]. Educational attainment was not found to be associated with CLS with an unknown/sero-different HIV status partner in unadjusted or adjusted analysis [509, 563].

Table 49: Unadjusted and adjusted associations found between education and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of education levels:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
Gym-based intervention baseline 1997 (N=1004)[482]	Gyms (N=1004)	Univserity educated: Yes No	CLS with 1+ partner (past 3 months)	χ^2 test	None	It was reported: "No significant univariate association between UAI and education" (pg 1409). No estimate given	/	/	/	/
GMSS 1998 (N=5065[a])[510]	Pride events (n=6315)	O-level[b] A-level Degree	CLS with 1+ partner (past year)	χ^2 test	Lower CLS with higher levels of education	53.9% 46.1% 42.1% *p<0.01*	/	/	/	/
GMSS 2000 (N=9789)[489]	Pride events (n=6624)	Low Medium High	CLS with 1+ partner (past year)	χ^2 test	None	47.8% 48.3% 40.4% *p>0.05*	/	/	/	/
GMSS 2006 (N=12155)[496]	Online (n=8286)	Low Medium High	CLS with 1+ partner (past year)	/	/	/	OR	None	It was reported: "No differences in UAI across the education groups" (pg 28). No estimate given	Tested HIV-positive
GMSS 2008 (N=7461)[512]	Online (N=4364)	Low Medium High	CLS with 2+ partners (past year)	χ^2 test	Lower CLS with higher levels of education	27.5% 24.0% 21.3% *p<0.05*	/	/	/	/

Table 49: Unadjusted and adjusted associations found between education and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS (continued)

	Largest % recruited via:	Measure of education levels:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSHS Scotland 1996-2002 (N=6448)[118]	Gay bars (N=6448)	2ry[c] Further[d] Higher[e]	CLS with 2+ partners (past year)	/	/	/	OR	None	1 0.94 [0.74, 1.20] 0.94 [0.73, 1.21]	Social class, education, area of residence, frequency of gay bar use, HIV optimism
GMSHS England 2003-2004 & GMSHS Scotland 2005 (N=3046)[563]	Commercial gay venues (N=3046)	2ry[c] Higher[e]	CLS with 2+ partners (past year)	/	/	/	OR	None	1 0.98 [0.75, 1.28] *p=0.310*	Age, employment status, HIV testing history
GMSHS Scotland 2011 (N=639[f])[509]	Commercial gay venues (N=1515)	2ry[c] Further[d] Higher[e]	CLS with 2+ partners (past year)	OR	None	1.06 [0.62, 1.80] 1.37 [0.93, 2.02] 1 *p=0.441*	/	/	/	/
GMSHS England 2003-2004 & GMSHS Scotland 2005 (N=3046)[563]	Commercial gay venues (N=3046)	2ry[c] Higher[e]	CLS with unknown/ sero-different partner (past year)	/	/	/	OR	None	1 0.88 [0.70, 1.10] *p=0.454*	Age, employment status, HIV testing history
GMSHS Scotland 2011 (N=639[f])[509]	Commercial gay venues (N=1515)	2ry[c] Further[d] Higher[e]	CLS with unknown/ sero-different partner (past year)	OR	None	1.04 [0.65, 1.66] 1.13 [0.80, 1.61] 1 *p=0.240*	/	/	/	/

[a] Men who reported anal sex with a man in the past year.

[b] O-level or no formal education.
[c] Secondary school.
[d] Post-secondary schooling (including vocational training).
[e] Higher educational attainment (Degree/post-graduate).
[f] Men who reported CLS with one or more partners in the past year, and did not have any missing data on any of the alcohol or drug use questions.

11.7.5 Relationship status

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 28 collected data on relationship status (Table 2). The association between relationship status and common measures of CLS was investigated in four publications (Table 50) [482, 496, 510, 512]. Two studies recruited men from community/commercial gay venues and two studies recruited men online. Being in an ongoing relationship was found to be associated with CLS with one or more partners (in the past year and the past three months) in unadjusted analysis in three studies [482, 496, 510], one of which also investigated the association adjusted for age and found that the relationship remained [482]. However, relationship status was not associated with CLS with two or more partners in the past year in unadjusted analysis [512].

Table 50: Unadjusted and adjusted associations found between relationship status and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of relations-hip status:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSS 1998 (N=5065[a])[510]	Pride events (n=6315)	None[b] <1 year[c] >1 year[c]	CLS with 1+ partner (past year)	χ^2 test	Men in a relations-hip more likely to report CLS	34.8% 51.9% 55.2% *p<0.01*	/	/	/	/
GMSS 2006 (N=12155)[496]	Online (n=8286)	None[b] Partnered	CLS with 1+ partner (past year)	OR	Men in a relations-hip more likely to report CLS	1 2.29 [2.12, 2.47]	/	/	/	/
Gym-based intervention baseline 1997 (N=1004)[482]	Gyms (N=1004)	None[b] Partnered	CLS with 1+ partner (past three months)	χ^2 test	Men in a relations-hip more likely to report CLS	16.3% 32.1% *p<0.05*	OR	Men in a relations-hip more likely to report CLS	1 2.50 [1.80, 3.40] *p<0.001*	Age
GMSS 2008 (N=7461)[512]	Online (N=4364)	None[b] Partnered	CLS with 2+ partners (past year)	χ^2 test	None	23.5% 23.1% *p>0.05*	/	/	/	/

[a] Men who reported anal sex with a man in the past year.
[b] No regular partner.
[c] Length of regular partnership.

11.7.6 Recreational drug use

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 19 collected data on recreational drug use (Table 2). The association between recreational drug use and common measures of CLS was investigated in five publications, all of which recruited men from community/commercial gay venues (including two gym samples and one Pride event sample) (Table 51) [478, 484, 487, 509, 511]. Measures of recreational drug use investigated include: (i) any drug use, (ii) anabolic steroid use, (iii) use of poppers (inhaled drug consisting of nitrites, usually sold as cleaning products, with euphoria-inducing effects), (iv) Viagra use, (v) marijuana use, (vi) party drug use (ecstasy, LSD, amphetamine, and cocaine), and (vii) alcohol, poppers, marijuana, or any other recreational drug use. With the exception of one study [487], all studies found associations between measures of recreational drug use and measures of CLS, in unadjusted and/or adjusted analysis [478, 484, 509, 511]. In one study, use of any recreational drugs was found to be associated with CLS with two or more partners in the past year in unadjusted and adjusted analysis [509]. However, in the same study, recreational drug use was not found to be associated with report of CLS with a partner of unknown/sero-different HIV status in the past year in unadjusted analysis or adjusted for socio-demographic factors, alcohol, poppers, and Viagra use [509]. In this same study, use of poppers was associated with CLS with two or more partners and CLS with an unknown/sero-different HIV status partner (in the past year) in unadjusted analysis, but the association disappeared for both measures of CLS after adjusting for socio-demographic factors, alcohol use, and use of other recreational drugs (as well as Viagra) [509]. Similarly, in the same study, an identical pattern of associations was found with Viagra use [509]. Furthermore, in the two gym samples investigated, anabolic steroid use was found to be associated with CLS with one or more partners in the past three months in on study [484] but not the other, in unadjusted analysis [487]. In another study, use of marijuana, nitrites, and party drugs (in three separate measures) by either or both partners before or during sex in the past three months (during an episode of CLS with an unknown/sero-different status partner or during the last sexual encounter) was strongly associated with CLS with an unknown/sero-different HIV status partner (past three months) in unadjusted analysis [478]. In the final study, men who reported alcohol use, and recreational drug use, especially drugs other than poppers and cannabis, were more likely to report CLS with one or more partners in the past year compared to men who did not report alcohol or drug use, in unadjusted analysis [511].

Table 51: Unadjusted and adjusted associations found between recreational drug use and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of drug use:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
Gym-based intervention baseline 1997 (N=1004)[484]	Gyms (N=1004)	Anabolic steroids: Never Current user	CLS with 1+ partner (past three months)	χ^2 test	Men who use drugs more likely to report CLS	 22.2% 42.6% *p<0.001*	/	/	/	/
4 gym project 2000 (N=477[e])[487]	Gyms (N=477)	Anabolic steriods[h]: No Yes	CLS with 1+ partner (past three months)	χ^2 test	None	 34.8% 33.8% *p=1.000*	/	/	/	/
GMSS 1999 (N=4025[a])[511]	Pride events (n=6612)	None Alcohol[f] Poppers Cannabis Any other	CLS with 1+ partner (past year)	χ^2 test	Men who drink/use drugs more likely to report CLS	50.0% 53.0% 54.0% 49.9% 59.6% *p<0.001*	/	/	/	/
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	Used poppers: No Yes	CLS with 2+ partners (past year)	OR	Men who use drugs more likely to report CLS	 1 1.86 [1.31, 2.65] *p=0.001*	OR	None	 1 1.44 [0.96, 2.14] *p=0.076*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, stimulant/ recreational/illicit drugs, Viagra use

Table 51: Unadjusted and adjusted associations found between recreational drug use and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS (continued)

	Largest % recruited via:	Measure of drug use:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	Used drugs[g]: No Yes	CLS with 2+ partners (past year)	OR	Men who use drugs more likely to report CLS	1 3.20 [2.16, 4.73] *p<0.001*	OR	Men who use drugs more likely to report CLS	1 2.75 [1.74, 4.34] *p<0.001*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, poppers, Viagra use
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	Used Viagra: No Yes	CLS with 2+ partners (past year)	OR	Men who use drugs more likely to report CLS	1 2.49 [1.58, 3.94] *p<0.001*	OR	None	1 1.70 [0.97, 2.98] *p=0.062*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, poppers, stimulant/ recreational/illicit drugs,
Community-based survey 1998 (N=506)[478]	Commercial gay venues (N=506)	Marijuana before last (high-risk) sex[c]: No Yes	CLS with unknown/ sero-different partner (past three months)	OR	Men who use drugs more likely to report CLS	1 2.60 [1.24, 5.45]	/	/	/	/
Community-based survey 1998 (N=506)[478]	Commercial gay venues (N=506)	Nitrites before last (high-risk) sex[c]: No Yes	CLS with unknown/ sero-different partner (past three months)	OR	Men who use drugs more likely to report CLS	1 3.56 [1.78,7.13]	/	/	/	/

Table 51: Unadjusted and adjusted associations found between recreational drug use and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS (continued)

	Largest % recruited via:	Measure of drug use:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
Community-based survey 1998 (N=506)[478]	Commercial gay venues (N=506)	Party drugs[d] before last (high-risk) sex[c]: No Yes	CLS with unknown/ sero-different partner (past three months)	OR	Men who use drugs more likely to report CLS	1 2.93 [1.18, 7.28]	/	/	/	/
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	Used poppers: No Yes	CLS with unknown/ sero-different partner (past year)	OR	Men who use drugs more likely to report CLS	1 1.44 [1.04, 2.00] *p=0.029*	OR	None	1 1.27 [0.89, 1.82] *p=0.184*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, stimulant/ recreational/illicit drugs, Viagra use
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	Used drugs[g]: No Yes	CLS with unknown/ sero-different partner (past year)	OR	None	1 1.44 [0.98, 2.11] *p=0.062*	OR	None	1 1.23 [0.79, 1.89] *p=0.359*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, poppers, Viagra use
GMSHS Scotland 2011 (N=639[b])[509]	Commercial gay venues (N=1515, whole sample)	Used Viagra: No Yes	CLS with unknown/ sero-different partner (past year)	OR	Men who use drugs more likely to report CLS	1 1.98 [1.23, 3.19] *p=0.005*	OR	None	1 1.58 [0.92, 2.72] *p=0.097*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, alcohol, poppers, stimulant/ recreational/illicit drugs

[a] Men who reported anal sex with a man in the past year.
[b] Men who reported CLS with one or more partners in the past year, and did not have any missing data on any of the alcohol or drug use questions.
[c] Intake of marijuana/nitrites/party drugs by either or both partners immediately before sex, during sex or less than two hours before sex, during episode of CLS with an unknown or HIV sero-different partner in the past three months or at last sexual encounter in the past three months.
[d] Ecstasy, LSD, amphetamine, and cocaine.
[e] HIV-negative men.
[f] Alcohol use only.
[g] Stimulants, recreational drugs and/or illicit drugs.
[h] In the past year.

11.7.7 Alcohol use

Of the 68 UK studies (if repeated surveys are considered as separate studies) identified in this review, 10 collected data on alcohol use (Table 2). The association between alcohol use and common measures of CLS was investigated in two publications, both of which recruited men from community/commercial gay venues (Table 52) [478, 509]. Neither being drunk on alcohol (always/sometimes) nor alcohol use before/during sex was found to be associated with CLS with two or more partners in the past year or CLS with an unknown/sero-different HIV status partner (past year or past three months) [478, 509]. The associations remained non-significant after adjustment for socio-demographic factors and recreational drug use in one study [509].

Table 52: Unadjusted and adjusted associations found between drinking alcohol and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of alcohol use:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSHS Scotland 2011 (N=639[a])[509]	Commercial gay venues (N=1515, whole sample)	Drunk on alcohol: Never Yes[c]	CLS with 2+ partners (past year)	OR	None	1 1.25 [0.81, 1.91] *p=0.312*	OR	None	1 0.81 [0.49, 1.33] *p=0.397*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, popper, stimulant/ recreational/illicit drug and Viagra use
Community-based survey 1998 (N=506)[478]	Commercial gay venues (N=506)	Alcohol before last (high-risk) sex[b]: No Yes	CLS with unknown/ sero-different partner (past three months)	OR	None	1 1.02 [0.58, 1.80]	/	/	/	/
GMSHS Scotland 2011 (N=639[a])[509]	Commercial gay venues (N=1515, whole sample)	Drunk on alcohol: Never Yes[c]	CLS with unknown/ sero-different partner (past year)	OR	None	1 1.13 [0.77, 1.64] *p=0.538*	OR	None	1 1.10 [0.73, 1.66] *p=0.652*	Age, sexual orientation, area of residence, frequency of gay scene use, HIV/STI testing, HIV status, popper, stimulant/ recreational/illicit drug and Viagra use

[a] Men who reported CLS with one or more partners in the past year and did not have any missing data on any of the alcohol or drug use questions.
[b] Intake of alcohol by either or both partners immediately before sex, during sex, or less than two hours before sex, during episode of CLS with an unknown or HIV sero-different partner in the past three months or at last sexual encounter in the past three months.
[c] Always/sometimes.

11.7.8 CSA and IPV

Although the association between CSA and common measures of CLS was not investigated (as measures of CSA have not been explicitly collected), it was investigated whether sexual assualt and non-consensual sex in childhood and adulthood was associated with CLS with with one or more partners in the past year in two studies (Table 2 and Table 53) [355, 510]. Both studies investigated unadjusted associations only, one study finding that men who reported sexual assualt in childhood and/or adulthood were more likely to report CLS [510], and the other finding no association with non-consensual sex [355]. No UK studies of sexual behaviour among MSM have collected data on IPV (Table 2).

Table 53: Unadjusted and adjusted associations found between markers of CSA and sexual behaviour measures in UK studies of MSM (including HIV-negative MSM), by measure of CLS

	Largest % recruited via:	Measure of CSA:	Measure of CLS	Unadjusted association			Adjusted association			
Study:				Test/ measure of effect size	Relation-ship	Estimate	Measure of effect size	Relation-ship	Estimate	Factors adjusted for
GMSS 1998 (N=5065[a]) [510]	Pride events (n=6315)	Sexual assault: Never <16 years ≥16 years Both[b]	CLS with 1+ partner (past year)	χ^2 test	Men who report sexual assault in childhood and/or adulthood more likely to report CLS	 45.1% 46.7% 55.1% 60.4% *p<0.01*	/	/	/	/
Clinic survey 1999 (N=122)[355]	GUM clinic (N=122)	Non-consens-ual sex in childhood/ adulthood No Yes	CLS with 1+ partner (past year)	χ^2 test	None	 62.2% 59.4% *p=0.71*	/	/	/	/

[a] Men who reported anal sex with a man in the past year.
[b] Experienced sexual assualt both before & since the age of 16.

11.8 Appendix 8: Design and methods of the AURAH study

11.8.1 Identification of the sample population in AURAH

The AURAH study nurse coordinator (Janey Sewell) identified 15 clinical centres (comprising of 20 GUM clinic sites, see Table 54) for study participation based on previously successful research collaborations and on the understanding that the centre could facilitate access to large numbers of HIV-negative MSM and black African men and women.

Table 54: Number of MSM recruited from 20 GUM clinical sites for the AURAH study

Clinical centre	N=1340 MSM who reported anal/vaginal sex in the past three months n(%)
South East	
Claude Nicol Centre at Royal Sussex County Hospital (Brighton and Sussex University Hospitals NHS Trust)	173 (12.9%)
Florey Unit (Royal Berkshire NHS Foundation Trust)	32 (2.4%)
South West	
Brecon Unit at Southmead Hospital (North Bristol NHS Trust)	36 (2.7%)
London region	
Sydenham Centre at Barking Hospital (Barking, Havering and Redbridge University Hospitals NHS Trust)	8 (0.6%)
Barts Sexual Health Centre (Barts Health NHS Trust)	11 (0.8%)
Ambrose King Centre at The London Hospital (Barts Health NHS Trust)	10 (0.8%)
Greenway Centre at Newham Hospital (Barts Health NHS Trust)	7 (0.5%)
Whipps Cross Hospital (Barts Health NHS Trust)	6 (0.5%)
56 Dean Street (Chelsea and Westminster Hospital NHS Foundation Trust)	478 (35.7%)
John Hunter Clinic (Chelsea and Westminster Hospital NHS Foundation Trust)	43 (3.2%)
West London Centre for Sexual Health (Chelsea and Westminster Hospital NHS Foundation Trust)	90 (6.7%)
Clifden Centre (Homerton University Hospital NHS Foundation Trust)	33 (2.5%)
King's College Hospita (King's College Hospital NHS Foundation Trust)	29 (2.2%)
The Mortimer Market Centre (Central and North West London NHS Foundation Trust)	240 (17.9%)
Marlborough Clinic (Royal Free Hospital NHS Foundation Trust)	27 (2.0%)
Courtyard Clinic (St George's Healthcare NHS Trust)	35 (2.6%)
West Midlands	
Birmingham Heartlands Hospital (Heart of England NHS Foundation Trust)	7 (0.5%)
City of Coventry Healthcare Centre (Coventry and Warwickshire Partnership NHS Trust)	27 (2.0%)
East Midlands	
Leicester Royal Infirmary (University Hospitals of Leicester NHS Trust)	5 (0.4%)
Yorkshire and the Humber	
Princess Royal Community Health Centre (Calderdale and Huddersfield NHS Foundation Trust)	43 (3.2%)

11.8.2 Method of sample selection in AURAH

Recruitment to the study took place between June 2013 and November 2014 at different periods in the 20 clinic sites. At study start, all sites were asked to identify specific clinics each week for recruitment. Clinic attendees were consecutively sampled. After five months of

consecutive sampling, it became clear that the proportion of the populations of interest (MSM and black African men and women) was not reaching the targets set for analytic purposes. Accordingly, sampling switched to disproportionate quota purposive methods, in order to 'over represent' and recruit until the required proportion of the populations of interest were enrolled. Clinic staff was asked to identify and recruit only MSM or individuals of black ethnicity. Once the target sample population of 1000 MSM had been achieved, after ten months of recruitment, the five clinic sites that had recruited the highest numbers of MSM were asked to continue sampling and to focus solely upon the recruitment of MSM who were willing to participate in a follow-up longitudinal study commencing November 2014. The remaining 15 clinic sites were asked to focus solely upon the recruitment of men and women of black African ethnicity for a fixed period of four months before recruitment end.

11.8.3 Sample power calculation for the AURAH study

Determining the appropriate sample size for a particular research question, often requires a balance between accepting the limitations of resources available and the need to avoid error when concluding support for a null hypothesis: type I error is a false positive finding and type II error is a false-negative finding. A maximum probability of making a type I error, called alpha, is assigned. Alpha is usually set at 0.05, indicating that there is no greater than a 5% chance of making a type I error. A maximum probability for making a type II error, called beta, is assigned and referred to as the statistical power of the study. Statistical power depends on sample size. The larger the sample size the higher the level of statistical power. Beta is usually set at 20%, which means there is at least 80% chance of rejecting a false null hypothesis.

For the AURAH study, estimating the prevalence of the following three measures, was deemed vital: (i) CLS in the past three months with a partner of unknown or HIV-positive status and that one of the reasons for this was '*I knew there was a risk of acquiring HIV but I am not so concerned about having the disease that it made me want to have sex using a condom*' (where the denominator was all participants or all participants reporting CLS), (ii) CLS in the past three months with a positive partner who give a reason as '*I thought the risks of catching HIV were low because my partner was taking anti-retroviral therapy'*, and (iii) current depressive symptoms on the PHQ-9 scale, where the denominator was all MSM, heterosexual men and women, and black African men and women.

It was calculated that with a recruitment target of 2000 total sample size, 1000 MSM and 1000 heterosexuals (500 men and 500 women), of whom 600 are black African, the study would have sufficient power to estimate the three measures described above. This sample size enabled the estimation of proportions relating to measure (i), with the precision shown in Table 55, for estimated response proportions of 5%, 10%, 15%, and 20%, within the demographic subgroups.

Table 55: Precision for 95% confidence intervals for a single proportion according to major demographic subgroups, for the AURAH study

	Target number in AURAH	95% Confidence interval for prevalence of 5%	95% Confidence interval for prevalence of 10%	95% Confidence interval for prevalence of 15%	95% Confidence interval for prevalence of 20%
MSM	1000	+/- 1.35	+/- 1.86	+/- 2.22	+/- 2.48
All heterosexual men	500	+/- 1.90	+/- 2.63	+/- 3.15	+/- 3.51
Black African heterosexual men	300	+/-2.45	+/- 3.40	+/- 4.05	+/- 4.53
All women	500	+/- 1.90	+/- 2.63	+/- 3.15	+/- 3.51
Black African women	300	+/-2.45	+/- 3.40	+/- 4.05	+/- 4.53

For measure (ii), the denominator was the number of subjects who report CLS in the past three months (estimated to be 50% of the total number), and the estimated proportion was expected to be lower than for (i). Precision is shown in Table 56 for proportions of 5% and 10%. For measure (iii), the study has 80% power to detect the differences in prevalence of depression shown in Table 57 for the demographic subgroups, with a 2-sided alpha level set at 0.05.

Table 56: Precision for 95% confidence intervals for a single proportion according to major demographic subgroups[a], for the AURAH study

	Target number in AURAH	95% Confidence interval for prevalence of 5%	95% Confidence interval for prevalence of 10%
MSM	500	+/- 1.90	+/- 2.63
All Heterosexual men	250	+/-2.70	+/- 3.7
Black African heterosexual men	150	+/- 3.50	+/- 4.8
All women	250	+/-2.70	+/- 3.7
Black African women	150	+/- 3.50	+/- 4.8

[a] These estimates are based on Normal approximations but exact methods will be used to calculate 95% confidence intervals for proportions when the numerator is < 20.

Table 57: Differences between two proportions detectable with 80% power at 2-sided 5% significance level, according to major demographic subgroups, for the AURAH study

	Estimated final numbers in ASTRA	Target number in AURAH	Difference in prevalence of depression that could be detected, comparing HIV+ve with HIV-ve individuals, assuming 25% prevalence in HIV+ve people (in all groups)
MSM	2250	1000	4.5%
All Heterosexual men	400	500	7.5%
Black African heterosexual men	200	300	10.0%
All women	700	500	6.8%
Black African women	450	300	8.5%

11.8.4 AURAH questionnaire

An initial questionnaire was piloted at one study site in June 2013, using the recruitment procedures described above. Following feedback from participants and research staff, some revisions were made to the final questionnaire. These changes were submitted as amendments for ethical approval and were incorporated into the final version employed during the main recruitment period, which commenced in June 2013. The statement of ethical approval is presented in the following section.

The final questionnaire consisted of a printed A5 booklet, with versions for men (24 page questionnaire) and women (20 page questionnaire). The questionnaire sought detailed information on socio-demographic factors, health and well-being, lifestyle factors, HIV-related information, and sexual risk behaviour. A description of all questions asked is presented below. Of note, participants were made aware that their participation included supplying information on the results of any STI or HIV tests that took place in the clinic on the day they were enrolled in the study. Participants were given an envelope and asked to seal the completed questionnaire in it to ensure that their answers were kept confidential from clinic staff. Completed questionnaires were collected in the clinic and transferred regularly to the study management centre. If participants took the questionnaire off site to complete outside of the clinic area, they were supplied with a postage paid envelope to return the questionnaire to the study management centre.

Socio-demographic factors: Age, or year of birth, gender, ethnicity *(white British, Irish or other, black African, Caribbean or other, Indian, Pakistani, Bangladeshi or Asian other, white and black African, white and black Caribbean, white and Asian or mixed other, or Chinese or any other ethnic group)*, born in the UK, when moved to the UK *(born in the UK, moved >5 years ago, moved 1-5 years ago, or moved <1 year ago)*, education *(no qualifications, O levels/GCSEs, A levels, university degree, or other)*, employment *(employed full- or part-time, student, unemployed on benefits or not, permanently or temporarily sick, care, or other)*, housing *(own home, renting from council or private, temporary accommodation, staying with someone, homeless, or other)*, enough money to cover basic needs *(all of the time, most of the time, some of the time, or never)*, relationship status and HIV status of partner *(HIV-negative stable partner, HIV-positive stable partner, unknown status stable partner, or no stable partner)*, any children and sexuality *(straight/heterosexual, gay/homosexual, bisexual, or other)* and disclosure of 'MSM status' (*what proportion of the following groups (i) close family, (ii) friends and (iii) workmates, know that you are gay/bisexual/attracted to men [all/almost all, more than half, about half, less than half or few/none]).*

Health and well-being: Psychological and physical symptoms *(modified version of Memorial Symptom Assessment Scale Short-Form)* [738, 739], Depression *(PHQ-9)* [443], Anxiety *(GAD-7)* [629], Health-related quality of life *(EuroQoL 5D)* [628], Social support *(modified version of the*

Duke–UNC Functional Social Support Questionnaire – FSSQ) [631], ever been told that you have any major health condition *(cancer, diabetes, stroke, heart disease, high cholesterol, epilepsy, high blood pressure, mental health, or other)*, receiving medical treatment or therapy for depression, or any other mental health condition, diagnosed chronic Hepatitis B or C, diagnosed STI in the past year (with 11 individual options including other), symptoms of STI *(discharge, pain, or sores/rash)*, and finally, women were asked about being pregnant and men about circumcision.

Lifestyle factors: regular cigarette smoking, frequency of drinking alcohol *(never, monthly or less, 2-4 times a month, 2-3 times a week, or 4, or more times a week)*, usual alcohol intake in units on a typical day *(1-2, 3-4, 5-6, 7-9 or 10, or more)*, evidence of alcohol dependency *(the CAGE questionnaire)* [740], recent use of recreational drugs (with 19 individual drug options including other), recent use of injecting drugs, and gay scene frequency *(how often do you go to gay cafes, pubs, bars, nightclubs/discos [often, sometimes, occasionally, rarely, or never])*.

HIV related information: HIV-positive status *(no or don't know)*, HIV test on the day of the study, history of any HIV tests *(within the last six months, >six months and up to two years ago, >two years and up to five years ago, or >five years ago)*, beliefs about transmission risk in relation to ART and undetectable viral load *('I worry about getting HIV', 'If I had HIV and was being treated with modern HIV drugs I would expect to have a normal lifespan', 'If a person with HIV has an undetectable HIV VL this makes them less infectious to a sexual partner than if they had a high VL', 'when HIV VL is undetectable, a condom is not needed to prevent HIV transmission' [strongly agree, tend to agree, undecided/not relevant to me/no opinion, tend to disagree, or strongly disagree])*, knowledge and any history of post exposure prophylaxis (PEP) and pre-exposure prophylaxis (PREP), interest in PrEP, and attitudes to HIV self-testing and clinic based tests.

Sexual behaviour: Men were asked about anal sex with men, and anal or vaginal sex with women, in the past three months. Women were asked about anal or vaginal sex with a man in the past three months. Subsequent questions asked about condomless sex; the number of partners with whom they had condomless sex *(one, 2-4, 5-10, or >10)* and whether this partner or one of these partners were their long-term partner *(yes, no, or I don't have a long-term partner)*. If men reported condomless anal sex with a man, they were asked whether they had always been the receptive partner, always been the insertive partner or both. Regardless of the gender of the condomless sex partner, participants were further asked the reasons for non-condom-use *('Didn't think about using a condom/did not have one',' Don't like using a condom/more pleasurable without', 'Partner didn't want to use a condom', 'Felt unable to discuss condom-use', 'Got carried away/under the influence of alcohol or drugs', 'Difficult to keep erection for me or my partner', and just for sex with women; 'Trying for pregnancy')*, whether they considered the risks of HIV infection *('I thought there was a very low risk of being*

infected with HIV' and/or 'I knew there was a risk of getting HIV but I am not so concerned about HIV that it made me want to have sex using a condom'), whether they knew the HIV status of all of their partners *(no, yes all, or yes some)*, whether they had condomless sex with a person they knew had HIV, the number of HIV-positive condomless sex partners, whether this positive partner or one of these positive partners was their long-term partner *(yes, no, or I don't know)* and whether they agreed with the statement *'I thought the risks of catching HIV were low because my partner was taking anti-retroviral therapy'*. All participants were also asked about use of the Internet to find sexual partners, different sex practices *(fisting or use of sex toys)* and group sex, attitudes to disclosure of HIV status to sexual partners and negotiation of condom-use ('*I find it difficult to discuss condom-use with any new sexual partner', 'I am less likely to use a condom with a casual partner', 'I would expect a new partner to tell me if they're HIV-positive before we have sex', 'I'd expect to ask any new partner their HIV status before we have sex', and 'I feel confident that, if I want to, I can make sure a condom is used during sex with any partner, in any situation' (strongly agree, tend to agree, undecided/not relevant to me/no opinion, tend to disagree, or strongly disagree))*, and the number of new sexual partners in the past year.

A study website was set up (http://www.astra-study.org/aurah) providing access to full contact details, progress updates, background information, all the study documents and future results. PDF copies of the questionnaires are available on request from the study website (http://www.astra-study.org/aurah).

11.8.4.1 Statement of ethical approval for the AURAH study

The research protocol and all versions of the study documents (information sheet, consent form, questionnaires and insert) were approved by the designated research ethics committee (NRES committee London-Hampstead, ref: 13/LO/0246). Based on these documents, the study subsequently received permission for clinical research at all participating National Health Service sites.

11.8.4.2 Data processing in the AURAH study

An external data processing contractor digitised questionnaires received at the management centre. Each paper questionnaire was checked for legibility, digitally scanned and the resulting images were used as the source for two manual data entry rounds with subsequent quality checking. The completed data entry batches delivered by the contractor were checked for accuracy at the study management centre by fully examining a 5% sample. The original pseudonymised study datasets, including scanned images of the questionnaires were stored at the study management centre in encrypted digital form. They were preserved by being duplicated and stored on managed servers with regular backup and professional administration.

11.8.5 Data management in the AURAH study

11.8.5.1 Checking AURAH data for errors and inconsistencies

The data was checked for errors and inconsistences using the *'assert'* command in Stata. The assert command allows automation of the process of data checking within do-files. After the assert command a logical expression that should always be true of the data is described. For instance, the *'assert inlist(a3_ethnic,1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,.u)'* command and logical expression will be true if the variable ethnicity had values 1 to 16 or unknown (.u), and will be false otherwise. Furthermore, the *'assert a4_bornother==.n if a4_bornuk==1'* command and logical expression will be true when the response to 'having been born in the UK' is Yes (1) and the response to 'which other country were you born in' is Not applicable (.n), and will be false otherwise i.e. if a4_bornuk is coded as 1 (yes), then a4_bornother should always be coded as .n (not applicable). When the assert command fails the do-file stops and produces an error message describing the number of individuals in the dataset for whom the assertion has failed. Of note, as described below, local macros can be used to control how the assert command functions [616]. Where necessary a local macro (called 'run' and set to rc0) was used to determine whether the do-file should continue or stop upon encountering a false assertion. When an expression was followed by the option 'run', the do-file continued to run even if there was a false assertion. Table 58 and Table 59 outline the various assertions created.

Table 58: Strategy for creating assertions - individual variables and skip questions (data-management in the AURAH study)

For individual variables	For skip question variables[a] with one sub-group question	For skip question variables[a] with more than one sub-group question[b]	For skip question variables[a] with more than one false/true sub-group question[c]
1. Created one assertion based on the range of possible values/categories as indicated by the code book and 'all participants' study log.	1. Created one assertion which checked whether the sub-group variable is always .n if the skip question response renders the participant ineligible for the sub-group question (usually 'No').	1.Created two assertions for each sub-group question, the first checked whether the sub-group variable is always .n if the skip question response renders the participant ineligible for the sub-group question (usually 'No') and the second checked the reverse, whether the skip question response is always 'No' if the sub-group variable is coded as .n.	1.Created two assertions for each sub-group question, the first checked whether the sub-group variable is always .n if the skip question response renders the participant ineligible for the sub-group question (usually 'No') and the second checked the reverse, whether the skip question response is always 'No' if the sub-group variable is coded as .n.
	2. Created one assertion which checked whether the skip question response is always the eligible response (usually 'Yes') if the sub-group variable has a value i.e. is not missing (.u/.n). This second assertion was not included when the skip question was a scale of questions.	2. Created one assertion for each sub-group question, which checked whether the skip question response is always the eligible response (usually 'Yes') if the sub-group variable has a value i.e. is not missing (.u/.n).	2. Created one assertion for each sub-group question, which checked whether the skip question response is always the eligible response (usually 'Yes') if the sub-group variable has a value i.e. is not missing (.u/.n).
			3. Created two assertions for each sub-group question, the first checked whether the sub-group variable is always .u if the skip question is coded as .u. The second checked the reverse, whether the skip question is always .u if the sub-group question is coded as .u.

[a] Where a participant was asked to move to the next question if their response to this particular question was 'No'.

[b] If I recoded missing (i.e. coded as 0 in the raw dataset) on a variable into .n (not applicable) or a new category based on a skip question, then I checked to see whether there was more than one sub-group question following the skip question. If there was more than one, I included an additional assertion to pick up any changes from No to Yes. One of the sub-group variables may be coded as .n since they had a missing value and had ticked No for the skip question, however, if another sub-group variable contains a value that suggests that the skip question should be changed from No to Yes, then the previous sub-group would need to be recoded from .n into .u. A second assertion was needed to pick this up, asserting that the sub-group is always .n if the skip question is No was no longer enough, I needed to know whether the skip question was always coded as No if

the sub-group was coded as .n. Of note, if the .n category on a sub-group variable was based on gender, then a second assertion was not required since gender cannot be changed, regardless of the values on any of the sub-group variables. Of note, unlike all other skip questions in the questionnaire, insert variable categories (to attain further information on preferences for HIV testing) dictated whether participants should have values for the sub-group questions i.e. if someone had been placed in the completed insert category, then they should have at least one value for all questions in the insert i.e. they should not have all .u (whereas, this is not the case for other skip questions, where answering Yes and being eligible for the sub-group questions did not translate into having to have at least one value and not having all unknown). To account for this an extra assertion was created for the testing options variables, which checked whether the insert variable is always blank or no insert if the value for each testing option is greater than 4 i.e. was missing.

[c] Two additional assertions were required for false/true variables in this context, in order to take into account the fact that the sub-groups are coded 0 (false) and 1 (true) i.e. if someone had ticked Yes to the skip question and was eligible for the sub-group options, they would be coded as 0 if they did not tick a sub-group option and not .u. Therefore, it is necessary to assert here that the sub-group option is always .u if the skip question is .u and that the skip question is always .u if the sub-group option is .u, again this final assertion is used to pick up any changes from .u to Yes.

Table 59: Strategy for creating assertions- skip questions with multiple sub-group questions and implausible combinations of variables (data-management in the AURAH study)

For more than one skip question variable[a] with more than one sub-group question	For 'Other please specify' variables	For implausible combinations of variables
1. If gender is a skip question and the sub-group question is a skip question and again (although there might not always have been this third level or there might even have been more) its sub-group question is a skip question for multiple sub-group questions, then only gender was coded as .n for all these variables. For the remaining skip questions, the ineligible response was included as a new category in the sub-group variables i.e. two extra categories would have been added to the final level of sub-group questions, accounting for the two skip questions and the ineligible gender would have been coded as .n. Under these circumstances: Created assertions for each previous skip question until gender with each sub-group variable[b]. 1. Created two assertions for each sub-group variable, the first checked whether the sub-group question is always .n if gender is male/female (as appropriate). The second checked whether gender is always male/female if the sub-group question has a value i.e. is not missing (although .u would also be appropriate, but these assertions together cover the information we need).	1. Created one assertion which checked whether the categorical variable which included other please specify) always has a value i.e. is not missing (.u) if the encoded comments variable has a value i.e. is not missing.	1. Created two assertions, the first checked whether one variable is always a certain value if another variable is a certain value. The second checked whether the second variable is always a certain value if the first is a certain value.
2.Created two assertions for each sub-group variable, the first checked whether the sub-group question is always coded as a new category if the skip question response is ineligible i.e. usually 'No'. The second checked whether the skip question response is always 'No' if the sub-group question is coded as a new category (these two assertions would be repeated if there were more than one skip question following gender).		2. Created one assertion which checked whether a variable is .n if gender is male/female (as appropriate).
3.Created one assertion for each sub-group variable, which checked whether the skip question response is always the eligible response (usually 'Yes') if the sub-group variable has a value that does not include the new category (this assertion would be repeated if there were more than one skip question following gender).		

[a] Where a participant was asked to move to the next question if their response to this particular question was 'No'.

[b] Since all of these variables are linked and a change in one needs to be captured in all subsequent variables.

11.8.5.2 Correcting errors and inconsistencies in AURAH data

If errors in the range of variable categories were detected, where data entry personnel had coded a participant as 99 for a particular variable, indicating multiple responses, this was dealt with by investigating the participants' original scanned questionnaire and recoding using the criteria described in Table 60.

Table 60: Dealing with multiple responses (data-management in the AURAH study)

Likert scale variables	Yes/No & Don't know variables	Yes & No variables	Education levels	Ethnicity
Take the upper limit response i.e. if ticked quite a bit distressed and very much distressed, recode into very much. For frequency categories i.e. once, twice etc. if someone ticked once and twice, they were recoded into twice. If the scale includes undecided/not relevant to me in the middle either side of agree and disagree and someone ticked undecided and agree, then they were recoded into agree. If someone ticked tend to agree and strongly agree, they were coded as strongly agree, the same is true if someone wrote tend to agree and strongly disagree, they were recoded as the latter. If someone ticked tend to agree and tend to disagree, they were coded into undecided. If someone ticked almost all and more than half of a group knows you are gay, then they were recoded into almost all.	If ticked Yes & Don't know, recode as Don't know (do the same for No & Don't know).	If ticked Yes and No, create a new category that is Don't know/no preference. However, for treatment for depression and condomless sex, if someone had ticked yes & no, they were recoded into yes. If someone ticked I am an ex-smoker and I have never smoked, they were recoded as I am an ex-smoker.	Take the upper limit response i.e. if ticked O levels and A levels, recode into A levels	If ticked two ethnic groups, recode into the appropriate mixed category. If one of the two categories ticked includes a mixed group, recode into mixed other. If someone had ticked black African and another category or white and black African and another category, then they were kept in the category that included black African, since whoever ticked black African (regardless of whether it was mixed with white) are of interest.

Furthermore, if someone ticked No to a skip question (i.e. where a participant was asked to move to the next question if their response to this particular question was 'No') and was no longer eligible to answer the following question(s) but had ticked a response to at least one question, their sub-group questions were investigated. The following criteria were set out in order to deal with the various skip questions included:

1. If someone had only ticked No/Never to these questions, they were not recoded into Yes for the original skip question. Their values for the following variables were recoded into 'not applicable' (.n).
2. If someone had ticked No for the skip question and had ticked Yes/number of times/frequency to at least one question following, they were recoded into Yes for the original skip question and their values for the following variable(s) were changed accordingly, i.e. from not applicable to unknown (.u).
3. If someone had no values for the skip question but had indicated Yes/number of times/frequency to at least one question following, they were recoded into Yes for the original skip question.
4. If someone had no values for the skip question and had ticked No/Never only (and there is no other helpful information relating to these questions), they were not recoded, the skip question remained as unknown (a local macro was incorporated here to allow the Stata do-file to continue to run i.e. the file did not terminate once the assertion term relating to this variable failed but continued to check the data for errors).
5. If someone had ticked No to the skip but had ticked at least one false/true question following (i.e. one in which more than one option is possible), they were recoded into Yes for the original skip question and False to any false/true question that was not ticked.

Of note, if someone had ticked Yes to having been born in the UK but had values for the following questions, to which they were not eligible, they were recoded into Not applicable for these following questions. If someone had not ticked anything for born in the UK and had ticked that they had moved to the UK 1-5 years ago or less and had ticked an ethnicity other than white British, they were recoded into not born in the UK. However, if they had ticked white British ethnicity and had ticked having moved to the UK more than 5 years ago (or had not ticked this at all), they were recoded into born in the UK. If someone had ticked an ethnicity other than white British and they had ticked moved to the UK more than 5 years ago, they were kept as unknown for born in the UK and country born in.

11.8.5.3 Dealing with inconsistent responses to sexual behaviour in the AURAH study

The sexual lifestyle section in the AURAH questionnaire contained thirteen questions (for female and male partners separately), with an overall skip question 'In the past three months,

have you had sex (vaginal/anal sex) with a man/woman', and a number of subsequent questions to be answered if the response to the previous question was positive, including 'If Yes, did any of the sex within the last 3 months take place without a condom'. Unlike most other sections of the questionnaire, sexual behaviour is subject to social desirability bias. This was, however, probably limited by the AURAH study's attempt to assure participants of confidentiality of responses and data security issues. Instead of recoding individuals' responses as a matter of error and inconsistency, as described in the previous section, a different approach to highlighting and dealing with inconsistent responses was required.

Individuals who gave a positive response to a sub-group question(s) were not recoded into Yes for CLS if participants had said No to sex and/or CLS, instead they were recoded into a category called 'Possible'. In total, of MSM who reported anal/vaginal sex in the past three months and reported not having had CLS in the past three months, 3.3% (44/1340) and 0.03% (34/1340) were categorized as having 'possible CLS' with a man and woman respectively. The inclusion criteria for the 'Possible' group are described below. Of note, men who were placed in the 'possible' category of CLS were included in the 'no CLS' category for all analyses presented in this thesis.

1. If someone ticked No to the sub-skip question *'IF YES, did any of the sex within the last three months take place without a condom?'* and was no longer eligible to answer the following questions but had ticked Yes/number of times/True (including any anal position) to at least one question following, they were recoded into 'Possible' in the original sub-skip question (For condomless sex with a man n=43, and for condomless sex with a woman n=9). If they had missing values for one of the questions following, they were recoded into unknown.
2. If someone had ticked No to any sex in the past three months skip question and had no values for the CLS sub-skip question (i.e. they would have been coded as No sex), then if they ticked No/Never only for the questions following, their following questions were coded into No sex. If they had ticked at least one Yes/number of times/True to the questions following, then they were recoded into 'Possible' (For condomless sex with a man n=1, and for condomless sex with a woman n=25).
3. If someone had ticked Yes to any sex in the past three months skip question or had no values and if they had no values for the CLS sub-skip question (i.e. they would have been coded as unknown), then if they had ticked Yes/number of times/True to at least one question following, they were coded into Yes to the CLS sub-skip question. If they had ticked No/Never on a question following that was phrased as *'In the last three months, when you had sex without a condom...'*, they would be recoded into 'Possible', however, no one met this criteria. If someone had ticked No/Never on a question following that was not phrased in this way (including *'In the past three months, did you*

have anal sex with a woman without a condom' and *'In the past three months, did you have sex without a condom with a woman you knew was HIV-positive'*), they were not recoded into 'Possible', their value for the CLS sub-skip question remained as unknown and their value for the question following remained as No/Never (again, a local macro was incorporated here to allow the do-file to continue to run).

Further criteria were set forth to resolve other inconsistencies in the sexual lifestyle section. For instance, some participants had ticked *'Yes, I knew the HIV status of some of my partner(s)'* and had ticked one CLS partner. If someone had reported the profile of a partner that matched to their stable ongoing HIV-positive/negative status partner that they had reported, or if they had reported the profile of a partner whose status they knew to be positive and who they clearly stated was not their stable ongoing partner, then it was assumed that due to the wording of the status question, these people may have ticked 'Some' instead of 'All'. The wording of the 'some partners' option is confusing since partner(s) is specified instead of partners. The criteria for recoding these participants into *'Yes, I knew the HIV status of all of my partners'* are described in more detail below:

1. If they had reported being in a current stable relationship with an HIV-negative partner, and in the sexual behaviour section they had ticked 'Long-term CLS partner' and 'No' to having had an HIV-positive partner.
2. If they had reported being in a current stable relationship with an HIV-positive partner, and in the sexual behaviour section they had ticked 'Long-term CLS partner', 'Yes' to having had an HIV-positive partner, 'One' positive partner(s) and 'Yes' to long-term positive partner.
3. Regardless of whether they had reported being in a current stable relationship (*HIV-positive, HIV-negative, Don't Know status or missing response*) or having no current stable partner, if they had ticked 'No' to long-term partner, 'Yes' to having had an HIV-positive status partner, 'One' positive partner and 'No' to long-term positive partner.

Of note, for participants who had ticked no current stable partner, this included people who had ticked 'I don't have a long-term partner', 'Yes' to having had an HIV-positive partner, 'One' positive partner and 'I don't have a long-term partner'. Participants who did not meet these criteria were recoded into 2-4 CLS partners if they had indicated elsewhere that 2-4 partners is an appropriate assumption by looking at group sex, seeking sex on the Internet, acquisition of STIs, money or drugs for sex and number of new sexual partners. If someone had ticked group sex, they were recoded into 2-4 partners (regardless of what else they had ticked). If someone had not ticked group sex but they had ticked two or more new sexual partners and 'Yes' to at least one of the following; STI diagnosis, seeking sex on the Internet, or Money/drugs for sex, then they were again recoded into 2-4 partners. Those who had not were kept as they were.

11.8.5.4 Variables derived for analysis in AURAH

In short, date of birth and study clinic attendance date, which were originally stored as string variables (i.e. character variables, which permit storage of any combination of numbers and characters) in Stata, were converted into date variables. Stata stores each date as the number of days from January 1st 1960 (an arbitrary value), to facilitate calculations of the amount of time that has elapsed between two dates [616]. This made it possible to compute missing values for age by subtracting birth date from study clinic attendance date, see Table 61. In order to make the dates easier to read, I used the *%td* format, in order to produce variables with a two-digit day, three-letter month, and four-digit year.

Table 61: Dealing with date and other string variables (data-management in the AURAH study)

Date variable	Genuine string variable	
	'Other, please specify'	'Please specify' on a binary variable
1. Changed variable from *str* to *td*	1. The comments of participant's, who ticked the Other category of a categorical variable, were examined.	1. Created a sub-group variable, making sure, based on the comments, that participants were placed in the appropriate category of the original variable.
	2. New distinct categories were created from the comments (if appropriate) or participants were recoded into another category of the variable (if the comment clearly indicated another category should have been ticked). If neither of the above was appropriate, then participants were kept in Other.	2. No assertion was needed, since it was created.
	3. Created an assertion to check that everyone who has given a comment, has ticked a box i.e. a participant should not have a missing value if they wrote a comment.	

Furthermore, where appropriate, I distinguished between missing values (coded as .u ; "Unknown") and values which were not applicable i.e. when an individual had answered a previous question in such a way that they were not eligible for further questioning of this subject, their missing values should not be coded as unknown but as not applicable (.n), see Table 62. This was important in order to be able to clearly distinguish the proportion of individuals who had missing responses to questions.

A number of questions in the AURAH questionnaire included an 'Other, please specify' option, which included an allocated space for individuals to write their own response. In addition, a section was included at the end of the questionnaire which encouraged participants to write any comments/raise any issues. These responses were entered in the dataset, and as such, when imported in Stata, they were stored as string variables. It was necessary to convert these string variables into numeric variables in order to be able to utilize (i.e. code with) these variables when allocating individuals with certain responses into an appropriate category (be it of the

original variable asked or a new derived variable), see Table 61. In order to do this, I used the '*encode'* command in Stata to produce numeric variables that had value labels indicating which values correspond to which category. Of note, the variable pertaining to study clinic site was not entered into the original dataset and had to be imported from the clinic study log, as such it was imported as a string variable, and again had to be converted into a numeric variable in order for it to be included in analysis (i.e. as a predictor in a regression model). Each individuals specific study 'idcode' was also entered into the original dataset and as such was stored as a string variable in Stata, idcode was encoded into a numeric variable (this was vital during the data correcting stage, since errors were corrected based on idcode).

Table 62: Dealing with variables with missing values (data-management in the AURAH study)

Applicable to all participants	Applicable only to a sub-group of participants	Applicable only to a sub-group of participants (please tick all that apply)
1.Missing (i.e. 0) was recoded as .u.	1. Missing was dealt with making sure that only people who did not answer the sub-group question i.e. had a value of 0 (were missing) were recoded into .u/.n based on the original skip question. If someone was eligible for the sub-group question and had not answered it, they were recoded into .u (Unknown). If someone was not eligible for the sub-group question and had not answered it, they were recoded as .n (NA).	1.Missing was dealt with much in the same way as those questions which were not false/true (i.e. true if ticked and false otherwise), with the following exceptions: a) Participants who had ticked at least one option provided but had not specified yes/no on the original skip question, were recoded into yes. b) People who were eligible for the sub-group question and had not ticked an option were recoded from 0 (false) into 2. The remaining participants with a value of 0 for this option were recoded as .u. These people had not ticked yes or no for the skip question nor did they tick any of the sub-group options provided and were thus, unknowns. Two was recoded into 0 again and these people made up the false category.
2. No assertion was needed.	2. An assertion was included for each sub-group question of a skip variable that checked whether all participants who were not eligible had a value of .n for the sub-group question and that if someone had a value for the sub-group question, they were coded as Yes for the skip question.	2. An assertion was included for each sub-group option of a skip variable that checked whether all participants who were not eligible had a value of .n for the sub-group question and that if someone had a value for the sub-group question, they were coded as Yes for the skip question. It also checked whether all participants who were .u for the skip question had a value of .u for the sub-group options.
		3.If all the options were covered i.e. the sub-group options included other, then if someone had all 0 for all options provided, they were recoded into .u. Of note, the same coding here was also used for 'please tick all that apply' variables that were applicable to all participants. In that case, if everyone should give an answer (i.e. reason for attending clinic but not have you received a diagnosis of a major condition) and all options were covered, then again if someone had all 0 for each option provided then they were coded as .u.

Variables were then renamed (and derived variables labelled), values were labelled and variables were re-ordered appropriately in Stata. I also checked to see if someone had written a comment about having condomless sex/a broken condom (i.e. explicit comment about condomless sex), with a suggestion of it being within the past three months and an indication of the gender of their partner(s), for the reasons attending clinic variable. In anticipation, the following criteria for recoding were set forth: If a participant had made such a comment and had not said yes to CLS (in the sexual behaviour section of the questionnaire), then they were recoded. In addition, if a participant had written a comment about PEP use without indicating

the need for information or follow-up, then they were also recoded if appropriate (and if the gender of the partner was possible to deduce). Although a small number of participants had written that a condom had broken, no one specified a time frame and the gender of the partner. One male participant who did specify 'yesterday' had ticked yes to condomless anal sex. Another male participant specified a 'guy' but had not ticked condomless anal sex, but it would not have been appropriate to recode this participant into yes since it is possible that the broken condom occurred greater than three months ago and now they are here to screen (which may be synonymous with the HIV testing window period). Furthermore, I also checked all comments made throughout the questionnaires (these were documented in the original excel spread sheets). Of note, information on the results of an HIV test carried out on the day of the study questionnaire was imported into Stata from the study log.

11.8.5.5 Appending AURAH datasets

Finally, in order to append the 8 data batches together (each batch was cleaned individually), the following measures were taken: (i) I made sure that the order of the variables in all data batches were the same, (ii) I converted the encoded numeric variables back into string variables, so that upon appending they would fit into the right categories with the appropriate labels, (iii) I appended the datasets, using the most recent batch as the master dataset and the earlier batch as the using dataset, (iv) I generated a variable 'datasrc' that uniquely identifies which batch an idcode was from, (v) I checked whether there were any duplicates (specifically for idcode and then the remaining variables as well), and (vi) I encoded each of the string variables which had previously been decoded.

11.8.6 AURAH participants

11.8.6.1 Investigating response bias in the AURAH study

It appears that refusal to consent to study participation was significantly more common among attendees of London clinics, and to a lesser extent among clinic attendees in Yorkshire and the Humber region (sees Table 63). There could be a multitude of reasons for this; from living in a more busy/pressurized life in London, or being more overwhelmed by health promotion messages/requests for study participation, to the possibility that more staff in London create quicker 'in-and-out' services, and as such less time to focus upon a survey. There were however, a small number of attendees of clinics outside of London. Refusal to consent to study participation did not differ significantly by gender. Among those consenting however, men were more likely to not return a (usable) questionnaire compared to women. Furthermore, not returning a (usable) questionnaire was most common among participants attending a clinic in the East Midlands, followed by London, again however, the number of individuals participating in the East Midlands was small (n=66).

In total, 19 consenting individuals undertook an HIV test on the day of the questionnaire and received a positive HIV diagnosis (18 men and one woman). Participants who took an HIV test on the day of consenting to study participation and received a positive test result were more than twice as likely to not return a (usable) questionnaire, compared to participants who did not have an HIV test or received a negative test result (see Table 64). Of note, of the nine individuals who received an HIV-positive diagnosis and did not return a (usable) questionnaire, eight took the questionnaire offsite to be posted at their convenience, but never returned the questionnaire, leaving one individual who returned an unusable questionnaire (blank/no answers). Not all individuals who were aware (we can assume as a result of point-of-care screening) of an HIV-positive diagnosis, did not return a posted questionnaire (two individuals did so), however, it is more than understandable that the majority of these individuals did not return a questionnaire, as they would of course be entirely occupied by their diagnosis, and linkage to care. Although postage return questionnaires may have been a study limitation in this respect, as response bias would be introduced if all individuals who received a positive HIV diagnosis did not subsequently participate in the study, a study that primarily investigates behaviours that can lead to HIV acquisition, it must be emphasized that participants were asked to fill in the questionnaire and return it in the clinic- reflected in the fact that of the 10 participants who received a positive HIV test result and returned a (usable) questionnaire, eight did so in the clinic, we can justifiably assume prior to the consultation. It is also important to consider this significant result in terms of the small number of individuals who did receive a positive test result (n=19).

Table 63: Unadjusted associations of gender and study clinic region with refusal to consent to participation in the AURAH study

N=4380 GUM clinic attendees approached			Refusal to consent to study participation (n=1040; 23.7%)	
		N	%	*p-value* by χ^2 test
Gender	Female Male	1043 (24.0%) 3301 (76.0%)	21.8% 23.5%	*0.236*
Study clinic region	South East South West London West Midlands East Midlands Yorkshire & the Humber	325 (7.4%) 59 (1.4%) 3526 (80.5%) 309 (7.1%) 69 (1.6%) 92 (2.1%)	3.1% 1.7% 28.7% 1.3% 4.4% 10.9%	*<0.001*

Table 64: Unadjusted associations of gender, study clinic region, and HIV/STI information with unusable/unreturned questionnaires in the AURAH study

N=3340 clinic attendees consenting to study participation			Questionnaire not returned/unusable[a] (n=710; 21.3%)	
		N	%	*p-value* χ^2 test
Gender	Female Male	816 (24.4%) 2524 (75.6%)	17.2% 22.6%	*0.001*
Study clinic region	South East South West London West Midlands East Midlands Yorkshire & the Humber	315 (9.4%) 58 (1.7%) 2514 (75.3%) 305 (9.1%) 66 (2.0%) 82 (2.5%)	4.1% 5.2% 25.5% 8.5% 27.3% 11.0%	*<0.001*
HIV test undertaken on the day	Yes No	2546 (76.3%) 791 (23.7%)	20.7% 22.8%	*0.225*
HIV test result	No HIV test Negative result Positive result	791 (23.7%) 2527 (75.7%) 19 (0.6%)	22.8% 20.5% 47.4%	*0.012*[b]
STI test undertaken on the day	Yes No	2281 (87.0%) 341 (13.0%)	20.2% 23.5%	*0.161*

[a] Of note, 692 consenting individuals did not return a questionnaire, and 18 consenting individuals returned a questionnaire that did not contain any usable information (blank/no answers).
[b] p-value by Fisher's exact test.

11.9 Appendix 9: Design and methods of the PROUD trial

11.9.1 Identification of the PROUD sample population

The PROUD trial was coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London.Thirteen GUM clinics in England (eight in London [N=375, 69%] and five outside [Birmingham, Brighton, Manchester, Sheffield and York, N=165, 31%]) were identified for study participation.

11.9.2 Method of PROUD sample selection

Recruitment to the PROUD trial took place between November 2012 and April 2014. Men, and transgender women, aged 18 years or older who were attending the clinic for a routine visit and reported CLS on more than one occasion with a man in the past three months, were provided with information sheets on the PROUD trial if they were interested in PrEP. Furthermore, posters and electronic screens in participating GUM clinics, advertisements on social media, and distribution of business cards and leaflets by community organizations during outreach activities were also used to promote the study. Individuals who were interested (and recognized that they were eligible) in the study could download the information sheet from the study website. Potential participants were asked to make a note of their sexual behaviour and condom-use in preparation for enrolment. At the enrolment visit, HIV/STI test results and sexual behaviour were reviewed in order to confirm an HIV-negative status (confirmation was necessary within four weeks prior to or on the day of enrolment) and report of CLS on more

than one occasion within the past three months, and likely in the opinion of the participant, that CLS will occur in the next three months. Participants with an acute viral illness that could be due to HIV seroconversion, any contraindications to Truvada, treatment for Hepatitis B infection indicated or ongoing, and who were unlikely according to the opinion of the investigator, to comply with the randomized allocation, were not eligible.

11.9.3 Sample power calculation, randomization, and amendment to the PROUD study design

The purpose of the PROUD trial was to determine the feasibility of conducting a large trial to determine whether inclusion of PrEP as part of an HIV risk reduction package for MSM who are at risk of acquiring HIV is clinically effective and cost-effective. The PROUD trial was primarily designed to investigate the outcome of time to accrual of 500 participants and retention; the secondary outcomes consisted of: (i) HIV infection (ii) safety of PrEP, (iii) adherence to PrEP, and (iv) risk compensation as a result of PrEP use.

The PROUD trial was originally designed with an anticipated target sample size of 5000 participants (2500 per arm) in mind. Based on an estimated incidence of 3/100 person-years during the first 12 months in participants who were waiting to access PrEP and a 50% reduction in incidence in those offered PrEP; a sample size of 5000 would be adequately powered to detect a reduction in HIV incidence from 2.5 to 1.25 infections per 100 person-years. The initial pilot study used an arbitrary 10% target sample size of 500- a pragmatic choice which was to provide guidance as to whether 5000 participants could be enrolled over a two year study period. However, in April 2014, due to the very high incidence of HIV infection in the deferral arm of the study, it became apparent that a larger trial was not needed in order to investigate the effectiveness of PrEP on HIV incidence, and an Independent Data Monitoring Committee (IDMC) was set up to monitor key study outcomes [(80)].

11.9.4 PROUD questionnaire

Participants were asked to self-complete a paper questionnaire during clinic visits at baseline and on an annual basis thereafter. This was to occur in a private space. Participants were then asked to place the questionnaire in a sealed envelope, and hand it in to study clinic staff. Deferral of PrEP was initially set until the 12 month point, however, an unexpectedly high number of HIV infections were observed during the deferral period, which led to a recommendation from the Trial Steering Committee in October 2014 that all participants should be offered PrEP. Therefore, even participants who were still within the first 12 months of the study were asked to fill out their 12-month questionnaire and those in the deferred arm were offered PrEP. Of note, 25 men in the deferred arm were prescribed PrEP prior to completing their 12-month questionnaire. The surveys sought detailed information on socio-demographic and psychosocial factors, HIV/STI related information, and sexual behaviour. A description of all questions asked at each time-point is presented below. The statement of ethical approval is given in the following section.

Socio-demographic factors: At baseline only; date of birth, sexual identity *(gay/homosexual, straight/heterosexual, bisexual, or other)*, ethnicity *(white, Irish, Irish traveler, Chinese, Indian, Pakistani, Bangladeshi, black African, black Caribbean, black other, mixed ethnic group, or other)*, born in the UK, education *(no qualifications, O levels/GCSEs, A levels, university degree or above, still in full-time education, vocational training, or other qualifications)*, employment *(employed full- or part-time, student, unemployed , retired, or other)*, and relationship *status (yes, I am in a relationship and living with my partner; yes, I am in a relationship but not living with my partner, or; no, I am not currently in an ongoing relationship with a partner)*. At follow-up only; disclosure of 'MSM status' (*what proportion of the following groups (i) friends, (ii) work colleagues and (iii) close family, know that you are gay/transgender/have sex with men [all/almost all, more than half, less than half, few, or none]).*

Health and well-being: At baseline only; diagnosed STI in the past year *(with 13 individual STI options)*, and circumcision. At follow-up only; depression (PHQ-9) [443], and intimate partner violence *(experienced the following behaviours in relationships (i) Have you ever felt frightened of the behaviour of a partner, (ii) Have you ever needed to ask a partner's permission to work, go shopping, visit relatives, or visit friends i.e. beyond the usual of being considerate to and checking with a partner, (iii) Have you ever been hit, slapped, kicked or otherwise physically hurt by a partner, (iv) Have you ever been forced to have sex or made to engage in some sexual activity when you did not want to, (v) Have you ever been forced to have sex without a condom when you did not want to, (vi) Have you ever behaved in a manner that has made a partner feel frightened, (vii) Has a partner ever needed to ask your permission to work, go shopping, visit relatives, or visit friends i.e. beyond the usual of being considerate to and checking with a partner, (viii) Have you ever hit, slapped, kicked or otherwise physically hurt a partner, (ix) Have you ever forced a partner to have sex or engage in some sexual activity when he did not want to, (x) Have you ever forced a partner to have sex without a condom when he did not want to [never, yes-more than 1 year ago, yes within the last year with former partner, or yes within the last year with current partner])*, attitudes towards sexuality *('Obviously effeminate homosexual men make me feel uncomfortable', 'I feel comfortable in gay bars', 'Social situations with transgender/gay men make me feel uncomfortable', 'I feel comfortable being seen in public with an obviously transgender/gay person', 'I feel comfortable discussing homosexuality in a public situation', 'I feel comfortable being a transgender/gay man', 'Homosexuality is morally acceptable to me', 'Even if I could change my sexual orientation I wouldn't' [strongly agree, agree, neutral or uncertain, disagree, strongly disagree])*.

Lifestyle factors: At baseline only; frequency of alcohol drinking in the past three months *(daily, nearly every day, 3 or 4 times a week, once or twice a week, 2 or 3 times a month, once, or never)*, usual alcohol intake in units on a typical day, recent use of recreational drugs *(with 19 individual drug options including other)*, and at follow-up only; met new sexual partners in (i) gay

community centres, organisations, events or social groups, (ii) gay cafes, pubs and/or bars, (iii) gay nightclubs/discos, (iv) gay saunas, (v) backrooms, sex clubs or gay party, (vi) bareback parties, (vii) cruising areas were men meet for sex with men, (viii) gay social networking websites eg. Gay.com, gaydar.com, grindr, Manhunt, GayRomeo etc *(within the last 4 weeks, within the last 3 months, within the last 6 months, more than 6 months ago, or never)*.

HIV/STI related information: At baseline only; frequency of HIV testing at a sexual health clinic in the past year, frequency of STI testing at a sexual health clinic in the past year, frequency of PEP use in the past year, and beliefs about future PrEP adherence *(I will find it easy to remember to take my drug daily, I might forget to take my pill at my scheduled time but will remember to take it within a few hours, I might occasionally forget to take a dose, I might forget to take my drug once or twice a week, I will remember to take my pill if I know I am going to be having sex in a couple of days, or I will find a daily dosing schedule very difficult to follow)*. At follow-up only; concerns about transmission risk if having sex with a man whose HIV status was unknown and (i) no condom or PrEP was used during receptive anal sex, (ii) no condom or PrEP was used during insertive anal sex, (iii) no condom or PrEP was used but PEP was used after receptive anal sex, (iv) no condom was used during receptive anal sex but PrEP was being taken every day, (v) same as previous but tablets of PrEP were missed in the previous days, (vi) same as previous but several tablets were missed that week, and (vii) no condom or PrEP was used during receptive anal sex with a positive man who is on ART *(very worried, somewhat worried, or not worried)*, and use of PrEP before the study from (i) the Internet or elsewhere, (ii) someone else's Truvada, and (iii) someone else's antiretroviral tablets *(more than once, once, or never)*.

Sexual behaviour: Men were asked about number of sexual partners in the previous three months *(with how many different men have you been bottom [passive] and/or top [active] during anal sex in the last 90 days)*, the number of these partners with whom a condom was not used *('with how many were you bottom without using a condom' and 'with how many were you top without using a condom'; separate questions for receptive and insertive partners)*, the number of these partners who were known to be HIV-positive and known to be on treatment *('how many did you know were HIV-positive' and 'how many did you know were on HIV treatment'; separate questions for receptive and insertive partners)*, number of new anal sex partners in the past three months, perception of partner HIV status at last CLS act *(I don't know, I thought he was HIV-negative, I thought he was HIV-positive and on treatment, I thought he was HIV-positive and not on treatment, or I thought he was HIV-positive and did not consider whether he was on treatment)*, reasons for non-condom-use (*'I don't like using condoms'*, *'He doesn't like using condoms'*, *'Condoms weren't discussed'*, *'We don't use condoms with each other but do with other partners'*, *'Neither of us had any condoms'*, *'I didn't consider myself at risk of HIV'*, *'I was under the influence of alcohol'*, *'I was under the influence of drugs'*, *'I am faithful to him'*, *'He is faithful to me'*, *'It is more enjoyable without a condom'*, *'I was only dipping'*, *'I lose erections with*

condoms' [only asked in the follow-up questionnaire] and *'Other')*, and extent of feeling at risk when you have CLS *(not applicable, no risk, a little risk, somewhat at risk, large risk, or very large risk)*. At follow-up only; age at first sexual contact with a male, age at first act of anal intercourse with a male, attitudes towards ones sex life *('I am happy with my sex life', 'I am as sexually confident as I want to be', 'I find it easy to say 'no' to sex I don't want', 'The sex I have is always as safe as I want it to be', 'I would like to have more sex', 'I am usually sexually satisfied after sex', 'I would like to have a, or more, steady partner(s)', 'I would like to have a, or more, non-steady partner(s), 'I would like more intimacy in my life', 'I would like more love in my life' [strongly agree, agree, neutral or uncertain, disagree, or strongly disagree])*, sexualized drug use *(within the last 4 weeks, within the last 3 months, within the last 6 months, more than 6 months ago, or never)*, participated in group sex *(within the last 4 weeks, within the last 3 months, within the last 6 months, more than 6 months ago, or never)*, and received (i) money, (ii) drugs, or (iii) something else (such as a place to stay) for having sex *(within the last 4 weeks, within the last 3 months, within the last 6 months, more than 6 months ago, or never)*.

Of note, HIV and STI testing (urethral, rectal and pharyngeal swabs for *chlamydia trachomatis* and *Neisseria gonorrhoea*, serology for syphilis and Hepatitis C [when indicated]), was conducted on a three monthly basis. Hepatitis C screening was also conducted if the participant reported injecting or snorting drugs, fisting, or the use of sex toys. Serum creatinine was checked on an annual basis or more frequently if more than a trace of protein was detected by urine dipstick and could not be explained by infection. Finally, in depth interviews were also conducted as part of the PROUD trial.

A study website was set up (http://www.proud.mrc.ac.uk) providing access to full contact details, progress updates, background information, all study documents, and future results.

11.9.4.1 Statement of ethical approval for the PROUD trial

The study was reviewed and approved by London Bridge Research Ethics Committee.

11.9.4.2 Data processing in the PROUD trial

Details of all interested individuals were added to a pre-screening log. The log contained the names and GUM clinic numbers of all patients invited to participate in the study. This information together with sealed envelopes of the behavioural questionnaires was transferred securely to the MRC CTU for data entry. A computer generated randomization list with variable block sizes (of four, six, and eight; stratified by clinical site) was prepared by one of the trial statisticians, and incorporated into a database held securely at the coordinating centre.

11.9.5 Data management in the PROUD trial

11.9.5.1 Checking PROUD data for errors and inconsistencies

Variables of interest in this thesis were checked for errors and inconsistencies.

11.9.5.2 Correcting errors and inconsistencies in PROUD

In general, the policy adopted in PROUD analyses was to focus on the questions of interest and take what participants had reported for these questions, even if it was not completely in line with the other questions asked. Of note, this was only relevant for the sexual behaviour section, the question of recreational drug use and the subsequent drug options displayed, and the question of having been born in the UK and if not the subsequent 'which country born in' question. In addition, there were very few men who reported any inconsistencies.

11.9.5.3 Dealing with inconsistent responses to sexual behaviour in the PROUD trial

The sexual lifestyle sections in the PROUD questionnaires contained twelve questions. The first question asked participants to provide the number of men with whom they had had either receptive or insertive anal sex in the past three months. The subsequent questions were split into separate sets of questions regarding receptive and insertive partners, whether a condom was used with these partners, and the HIV and treatment status of these partners. Questions were phrased in such a way that participants were asked to write down a numerical response. Accordingly, inconsistencies could arise if a participant reported a higher number than previously recorded i.e. a higher number of receptive CLS partners than receptive anal sex partners. Previous PROUD data analyses have investigated given responses to the CLS questions [80, 615, 741-743]. As a result, the same was carried in this thesis; all responses to the CLS questions were analysed as they were, and changing an erroneous previous anal sex question response was not considered necessary.

Although imputing a 'correct' value for the anal sex questions is not possible since this value could be any higher number than that reported for the CLS questions, I have changed the responses to anal sex to be equal to that reported for CLS (only where a value was provided for the former i.e. the value for anal sex was not missing) in order to achieve consistency in the data. This was only relevant for a very small number of men (n=2 at baseline and n=0 at the 12- and 24-month questionnaires).

Of note, it was not necessary to solve any inconsistencies between report of CLS partners and report of HIV-positive CLS partners, since the sexual behaviour measures considered for analysis which included reporting an HIV-positive CLS partner, only required that one such partner be reported. Therefore, regardless of whether the number for HIV-positive CLS partners exceeded that for CLS partners did not affect which category the participant was placed in. No

men reported one HIV-positive (receptive or insertive) CLS partner and zero CLS (receptive or insertive) partners.

11.9.5.4 Variables derived for analysis in the PROUD trial

I derived a set of variables. Variables and their values were labelled and re-ordered as appropriate, comments made in the 'Other (please specify)' for sexuality were requested from the data managers and examined.

11.9.5.5 Merging PROUD datasets

I selected a set of derived variables of interest (together with the study identification number, date of randomization, trial arm, and date of follow-up visit) from the baseline and follow-up questionnaire datasets and created new, separate datasets. I then performed a 1:1 merge. The data were reshaped from a wide to long format, whereby Stata was informed which variable were time varying and time constant, in preparation for analysis.

11.10 Appendix 10: Socio-demographic and lifestyle factors associated with depressive symptoms (PHQ-9≥10) among all MSM in the AURAH study

Table 65: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with depressive symptoms on PHQ-9 (≥10) among all 1484 MSM in the AURAH study

N=1484 MSM participating in the AURAH study			PHQ-9 ≥10 (n=185; 12.5%)					
		N (%)	%	*p-value*[b]	Unadjusted PR[95% CI]	Overall *p-value*	Adjusted models PR[95% CI]	Overall *p-value*
Age (years)	<25 25-29 30-34 35-39 40-44 45+	254 (17.4%) 372 (25.4%) 277 (18.9%) 193 (13.2%) 143 (9.8%) 225 (15.4%)	19.7% 14.3% 8.3% 9.8% 7.7% 9.8%	*<0.001* *<0.001*[c]	2.01 [1.26, 3.22] 1.46 [0.91, 2.33] 0.85 [0.49, 1.48] 1.01 [0.56, 1.80] 0.79 [0.39, 1.57] 1	*<0.001* *0.001*[c]	1.72 [1.06, 2.79] 1.53 [0.95, 2.46] 0.95 [0.54, 1.65] 1.09 [0.61, 1.95] 0.88 [0.45, 1.74] 1	*0.033* *0.005*[c]
Born in the UK and white ethnicity	Yes, white Yes, BAME No, white No, BAME	759 (51.8%) 97 (6.6%) 437 (29.8%) 172 (11.7%)	12.8% 17.5% 10.3% 11.6%	*0.228*	1 1.37 [0.86, 2.19] 0.81 [0.58, 1.12] 0.91 [0.58, 1.43]	*0.222*	1 0.89 [0.53, 1.51] 0.91 [0.65, 1.29] 0.99 [0.62, 1.59]	*0.942*
Study region	London South Other	1112 (74.9%) 276 (18.6%) 96 (6.5%)	11.5% 13.0% 21.9%	*0.012*	1 1.13 [0.80, 1.60] 1.90 [1.26, 2.87]	*0.009*	1 1.07 [0.74, 1.53] 1.38 [0.88, 2.15]	*0.380*
University Education	Yes No/missing[a]	990 (66.7%) 494 (33.3%)	9.1% 19.2%	*<0.001*	1 2.12 [1.62, 2.76]	*<0.001*	1 2.00 [1.50, 2.66]	*<0.001*
Employment status	Employed Not employed/ missing[a]	1182 (79.7%) 302 (20.4%)	10.2% 21.5%	*<0.001*	1 2.12 [1.61, 2.79]	*<0.001*	1 1.52 [1.11, 2.09]	*0.010*
Money to cover basic needs (financial hardship)	Always Mostly At times/no	1062 (71.8%) 311 (21.0%) 107 (7.2%)	7.3% 16.7% 50.5%	*<0.001* *<0.001*[c]	1 2.31 [1.66, 3.20] 6.96 [5.23, 9.26]	*<0.001* *<0.001*[c]	1 1.95 [1.39, 2.74] 5.17 [3.71, 7.20]	*<0.001* *<0.001*[c]
Housing status	Home owner Renting Unstable/other	421 (28.8%) 832 (56.9%) 210 (14.4%)	4.0% 13.9% 21.4%	*<0.001* *<0.001*[c]	1 3.45 [2.10, 5.67] 5.31 [3.11, 9.04]	*<0.001* *<0.001*[c]	1 3.34 [1.99, 5.61] 4.05 [2.29, 7.17]	*<0.001* *<0.001*[c]

Table 65: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with current depressive symptoms on PHQ-9 (≥10) among all 1484 MSM in the AURAH study (continued)

N=1484 MSM participating in the AURAH study			PHQ-9 ≥10 (n=185; 12.5%)					
		N (%)	%	*p-value*[b]	Unadjusted PR[95% CI]	Overall *p-value*	Adjusted models PR[95% CI]	Overall *p-value*
Self-reported sexual identity	Gay Bisexual Straight	1313 (88.8%) 141 (9.5%) 25 (1.7%)	11.7% 20.6% 4.0%	*0.004*[d]	1 1.55 [1.09, 2.22][g]	*0.016*	1 1.45 [1.01, 2.07][g]	*0.042*
How many friends know you are gay/bisexual/attracted to men	All/almost all Some Few/none	1107 (76.1%) 271 (18.6%) 77 (5.3%)	11.3% 15.9% 16.9%	*0.059* *0.022*[c]	1 1.41 [1.02, 1.94] 1.50 [0.89, 2.52]	*0.057* *0.018*[c]	1 1.36 [0.96, 1.93] 1.18 [0.66, 2.11]	*0.230* *0.188*[c]
How many work colleagues know you are gay/bisexual/attracted to men	All/almost all Some Few/none	863 (60.1%) 308 (21.4%) 266 (18.5%)	12.1% 8.1% 17.7%	*0.002* *0.098*[c]	1 0.67 [0.44, 1.02] 1.47 [1.07, 2.01]	*0.003* *0.113*[c]	1 0.70 [0.45, 1.09] 1.40 [0.97, 2.00]	*0.016* *0.232*[c]
How many close family know you are gay/bisexual/attracted to men	All/almost all Some Few/none	954 (65.7%) 226 (15.6%) 273 (18.8%)	12.1% 13.3% 13.6%	*0.751* *0.464*[c]	1 1.10 [0.76, 1.60] 1.12 [0.80, 1.59]	*0.751* *0.461*[c]	1 1.05 [0.72, 1.54] 0.91 [0.61, 1.34]	*0.819* *0.703*[c]
'Out' to all/almost all friends, work colleagues and close family	Yes No	709 (47.8%) 775 (52.2%)	13.0% 11.9%	*0.490*	1 1.10 [0.84, 1.44]	*0.491*	1 1.10 [0.82, 1.48]	*0.527*
'Out' to few/no friends, work colleagues and close family	Yes No	65 (4.4%) 1419 (95.6%)	18.5% 12.2%	*0.135*	1.51 [0.89, 2.57] 1	*0.125*	1.13 [0.63, 2.01] 1	*0.684*
Ongoing relationship	Yes No/missing[a]	640 (43.1%) 844 (56.9%)	10.6% 13.9%	*0.062*	1 1.30 [0.99, 1.73]	*0.063*	1 1.27 [0.95, 1.69]	*0.107*
Supportive network	1: High levels 2 3 4 5: Low levels	440 (29.9%) 510 (34.7%) 317 (21.6%) 142 (9.7%) 62 (4.2%)	4.3% 7.3% 17.0% 31.7% 48.4%	*<0.001* *<0.001** 	1 1.68 [0.98, 2.88] 3.94 [2.39, 6.52] 7.34 [4.44, 12.12] 11.21 [6.73, 18.65]	*<0.001* *<0.001*[c]	1 1.49 [0.86, 2.58] 3.77 [2.27, 6.28] 6.54 [3.89, 10.98] 9.78 [5.77, 16.60]	*<0.001* *<0.001*[c]
Current smoker	Yes No/missing[a]	364 (24.5%) 1120 (75.5%)	18.4% 10.5%	*<0.001*	1.75 [1.33, 2.30] 1	*<0.001*	1.39 [1.04, 1.87] 1	*0.027*

Table 65: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with current depressive symptoms on PHQ-9 (≥10) among all 1484 MSM in the AURAH study (continued)

N=1484 MSM participating in the AURAH study			PHQ-9 ≥10 (n=185; 12.5%)					
		N (%)	%	*p-value*[b]	Unadjusted PR[95% CI]	Overall *p-value*	Adjusted models PR[95% CI]	Overall *p-value*
Higher-risk alcohol consumption	Yes No/missing[a]	288 (19.4%) 1196 (80.6%)	11.3% 17.4%	*0.005*	1.54 [1.14, 2.07] 1	*0.005*	1.44 [1.05, 1.96] 1	*0.023*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	672 (45.3%) 300 (20.2%) 319 (21.5%) 193 (13.0%)	9.4% 13.3% 13.2% 20.7%	*<0.001* *<0.001*[c]	1 1.42 [0.98, 2.06] 1.40 [0.97, 2.03] 2.21 [1.54, 3.18]	*<0.001* *<0.001*[c]	1 1.45 [0.99, 2.11] 1.49 [1.02, 2.18] 2.32 [1.60, 3.37]	*<0.001* *<0.001*[c]
Chemsex-associated drug use	No Yes	1160 (78.2%) 324 (21.8%)	11.3% 16.7%	*0.010*	1 1.60 [1.19, 2.17]	*0.002*	1 1.48 [1.10, 1.98]	*0.009*

[a] University Education: 0.3% (n=4) missing. Employed: 1.4% (n=20) missing. Ongoing relationship: 0.3% (n=4) missing. Smoke regularly: 0.4% (n=6) missing. Heavy drinking: 1.2% (n=18) missing. Recreational drug use: 1.3% (n=19) missing.
[b] Pearson χ^2 test
[c] Test for trend.
[d] Fisher's exact test.
Adjusted models: Each factor included in a separate model and adjusted for: age (included as four categories: <25, 25-29, 30-39, 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status and study region.

11.11 Appendix 11: Socio-demographic and lifestyle factors associated with other measures of depressive symptoms on PHQ-9 in AURAH

Table 66: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with other depression measures on PHQ-9 in AURAH

N=1340 MSM reporting sex in the past 3 months			Major depressive syndrome on PHQ-9 (n=85; 6.3%)			Major and other depressive syndromes on PHQ-9 (n=136; 10.2%)		
		N (%)	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*
Age (years)	<25 25-29 30-34 35-39 40-44 45+	235 (17.8%) 344 (26.0%) 255 (19.3%) 175 (13.2%) 125 (9.5%) 188 (14.2%)	13.6% 7.3% 3.1% 3.4% 5.6% 2.7% *<0.001* *<0.001*[c]	5.12 [2.03, 12.89] 2.73 [1.06, 7.02] 1.18 [0.39, 3.55] 1.29 [0.40, 4.15] 2.11 [0.68, 6.49] 1 *<0.001* *<0.001*[c]	4.22 [1.65, 10.8] 2.99 [1.16, 7.72] 1.36 [0.45, 4.11] 1.42 [0.44, 4.63] 2.46 [0.81, 7.48] 1 *0.004* *0.001*[c]	18.7% 11.1% 6.7% 6.9% 8.8% 5.9% *<0.001* *<0.001*[c]	3.20 [1.70, 6.02] 1.89 [0.99, 3.61] 1.14 [0.55, 2.38] 1.17 [0.53, 2.59] 1.50 [0.67, 3.36] 1 *<0.001* *<0.001*[c]	2.77 [1.46, 5.25] 2.00 [1.04, 3.85] 1.27 [0.60, 2.66] 1.16 [0.51, 2.62] 1.69 [0.76, 3.75] 1 *0.003* *0.001*[c]
Born in the UK and ethnicity	Yes, white Yes, BAME No, white No, BAME	676 (51.2%) 86 (6.5%) 408 (30.9%) 151 (11.4%)	6.5% 10.5% 4.7% 7.3% *0.195*	1 1.61 [0.81, 3.18] 0.72 [0.42, 1.21] 1.12 [0.59, 2.12] *0.200*	1 1.08 [0.52, 2.22] 0.90 [0.53, 1.53] 1.42 [0.72, 2.77] *0.678*	10.7% 12.8% 8.3% 10.6% *0.501*	1 1.20 [0.66, 2.17] 0.78 [0.53, 1.15] 0.99 [0.60, 1.66] *0.506*	1 0.85 [0.46, 1.58] 0.89 [0.60, 1.33] 1.16 [0.68, 1.97] *0.784*
Study region	London South Other	1017 (75.9%) 241 (18.0%) 82 (6.1%)	5.5% 7.1% 14.6% *0.004*	1 1.28 [0.76, 2.16] 2.66 [1.49, 4.75] *0.004*	1 1.13 [0.66, 1.94] 1.67 [0.86, 3.24] *0.314*	9.2% 11.2% 18.3% *0.028*	1 1.21 [0.81, 1.82] 1.98 [1.20, 3.25] *0.024*	1 1.13 [0.75, 1.70] 1.41 [0.83, 2.41] *0.431*
University Education	Yes No/missing[a]	891 (66.5%) 449 (33.5%)	3.9% 11.1% *<0.001*	1 2.83 [1.87, 4.30] *<0.001*	1 2.48 [1.58, 3.91] *<0.001*	7.4% 15.6% *<0.001*	1 2.10 [1.53, 2.89] *<0.001*	1 1.88 [1.34, 2.64] *<0.001*
Employment status	Employed Not employed/ missing[a]	1069 (79.8%) 271 (20.2%)	5.0% 11.8% *<0.001*	1 2.38 [1.57, 3.62] *<0.001*	1 1.43 [0.88, 2.32] *0.150*	8.3% 17.3% *<0.001*	1 2.08 [1.50, 2.89] *<0.001*	1 1.44 [0.99, 2.10] *0.057*

Table 66: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with other depression measures on PHQ-9 in AURAH (continued)

N=1340 MSM reporting sex in the past 3 months			Major depressive syndrome (n=85; 6.3%)			Major & other depressive syndromes (n=136; 10.2%)		
		N (%)	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*
Money to cover basic needs (financial hardship)	Always Mostly At times/no	958 (71.7%) 281 (21.0%) 97 (7.3%)	3.3% 8.2% 29.9% *<0.001* *<0.001*[c]	1 2.45 [1.46, 4.12] 8.95 [5.67, 14.1] *<0.001* *<0.001*[c]	1 1.91 [1.11, 3.27] 5.94 [3.54, 9.94] *<0.001* *<0.001*[c]	6.8% 12.8% 34.0% *<0.001* *<0.001*[c]	1 1.89 [1.28, 2.77] 5.01 [3.49, 7.21] *<0.001* *<0.001*[c]	1 1.60 [1.08, 2.37] 3.71 [2.46, 5.58] *<0.001* *<0.001*[c]
Housing status	Home owner Renting Unstable/ other	369 (27.9%) 764 (57.8%) 188 (14.2%)	1.9% 6.7% 13.3% *<0.001* *<0.001*[c]	1 3.52 [1.61, 7.68] 7.01 [3.09, 15.91] *<0.001* *<0.001*[c]	1 2.84 [1.26, 6.41] 3.86 [1.52, 9.82] *0.017* *0.005*[c]	5.2% 11.0% 16.0% *<0.001* *<0.001*[c]	1 2.14 [1.32, 3.46] 3.10 [1.79, 5.36] *<0.001* *<0.001*[c]	1 1.73 [1.04, 2.89] 1.87 [1.00, 3.48] *0.088* *0.058*[c]
Self-reported sexual identity	Gay Bisexual Straight	1190 (89.1%) 127 (9.5%) 19 (1.4%)	6.0% 9.5% 5.3% *0.302*[d]	1 1.49 [0.85, 2.63][f] *0.166*	1 1.34 [0.77, 2.34][f] *0.301*	9.6% 14.2% 10.5% *0.219*	1 1.43 [0.92, 2.23][f] *0.114*	1 1.34 [0.87, 2.07][f] *0.183*
How many friends know you are gay/bisexual/attracted to men	All/almost all Some Few/none	1006 (76.1%) 250 (18.9%) 66 (5.0%)	5.6% 8.4% 9.1% 0.130[d] 0.064[c]	1 1.53 [0.99, 2.39][f] *0.057*	1 1.51 [0.93, 2.44][f] *0.094*	9.2% 13.2% 12.1% *0.154* *0.090*[c]	1 1.43 [0.98, 2.07] 1.31 [0.67, 2.58] *0.151* *0.078*[c]	1 1.38 [0.94, 2.03] 1.14 [0.53, 2.46] *0.256* *0.263*[c]
How many work colleagues know you are gay/bisexual/attracted to men	All/almost all Some Few/none	794 (60.8%) 277 (21.2%) 236 (18.1%)	5.9% 3.3% 10.2% *0.005* *0.098*[c]	1 0.55 [0.27, 1.11] 1.72 [1.07, 2.75] *0.006* *0.124*[c]	1 0.63 [0.32, 1.27] 1.73 [1.02, 2.94] *0.020* *0.138*[c]	9.8% 6.9% 14.0% *0.027* *0.213*[c]	1 0.70 [0.43, 1.13] 1.42 [0.97, 2.08] *0.028* *0.233*[c]	1 0.73 [0.45, 1.20] 1.41 [0.91, 2.20] *0.086* *0.294*[c]
How many close family know you are gay/bisexual/attracted to men	All/almost all Some Few/none	869 (66.0%) 205 (15.6%) 242 (18.4%)	6.0% 5.9% 7.9% *0.548* *0.345*[c]	1 0.98 [0.53, 1.80] 1.31 [0.79, 2.18] *0.547* *0.351*[c]	1 0.92 [0.52, 1.65] 1.13 [0.65, 1.98] *0.855* *0.742*[c]	9.0% 11.7% 13.2% *0.114* *0.039*[c]	1 1.30 [0.85, 2.01] 1.47 [1.00, 2.17] *0.113* *0.036*[c]	1 1.28 [0.83, 1.97] 1.31 [0.85, 2.01] *0.327* *0.160*[c]

Table 66: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with other depression measures on PHQ-9 in AURAH (continued)

N=1340 MSM reporting sex in the past 3 months			Major depressive syndrome on PHQ-9 (n=85; 6.3%)			Major and other depressive syndromes on PHQ-9 (n=136; 10.2%)		
		N (%)	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*
'Out' to all/almost all friends, work colleagues and close family	Yes No	652 (48.7%) 688 (51.3%)	5.5% 7.1% *0.230*	1 1.29 [0.85, 1.96] *0.231*	1 1.40 [0.90, 2.17] *0.135*	8.9% 11.3% *0.139*	1 1.27 [0.92, 1.76] *0.141*	1 1.35 [0.96, 1.89] *0.089*
'Out' to few/no friends, work colleagues and close family	Yes No	56 (4.2%) 1284 (95.8%)	8.9% 6.2% *0.279*[d]	/[e]	/[e]	10.7% 10.1% *0.886*	1.06 [0.49, 2.29] 1 *0.886*	0.82 [0.36, 1.87] 1 *0.641*
Ongoing relationship	Yes No/missing[a]	579 (43.2%) 761 (56.8%)	4.8% 7.5% *0.048*	1 1.55 [1.00, 2.40] *0.051*	1 1.41 [0.90, 2.20] *0.135*	7.8% 12.0% *0.012*	1 1.54 [1.09, 2.16] *0.013*	1 1.40 [1.00, 1.98] *0.052*
Supportive network	1: High levels 2 3 4 5: Low levels	400 (30.1%) 464 (34.9%) 284 (21.3%) 130 (9.8%) 53 (4.0%)	1.0% 2.6% 9.2% 19.2% 34.0% <0.001[d] <0.001[c]	1 7.98 [4.69, 13.59][f] *<0.001*	1 7.19 [4.21, 12.28][f] *<0.001*	2.5% 6.3% 13.7% 26.9% 43.4% *<0.001* *<0.001*[c]	1 2.5 [1.23, 5.07] 5.49 [2.79, 10.82] 10.77 [5.49, 21.14] 17.36 [8.75, 34.44] *<0.001* *<0.001*[c]	1 2.33 [1.15, 4.74] 5.06 [2.53, 10.10] 9.31 [4.65, 18.64] 13.96 [6.71, 29.02] *<0.001* *<0.001*[c]
Current smoker	Yes No/missing[a]	334 (24.9%) 1006 (75.1%)	8.7% 5.6% *0.043*	1.56 [1.01 2.40] 1 *0.043*	1.13 [0.72, 1.77] 1 *0.607*	14.1% 8.9% *0.006*	1.59 [1.14 2.22] 1 *0.006*	1.30 [0.92, 1.84] 1 *0.135*
Higher-risk alcohol consumption	Yes No/missing[a]	259 (19.3%) 1081 (80.7%)	9.3% 5.6% *0.032*	1.64 [1.04, 2.58] 1 *0.032*	1.41 [0.87, 2.28] 1 *0.165*	14.7% 9.1% *0.007*	1.62 [1.14, 2.29] 1 *0.007*	1.47 [1.03, 2.10] 1 *0.033*

Table 66: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with other depression measures on PHQ-9 in AURAH (continued)

N=1340 MSM reporting sex in the past 3 months			Major depressive syndrome on PHQ-9 (n=85; 6.3%)			Major and other depressive syndromes on PHQ-9 (n=136; 10.2%)		
		N (%)	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*	% *p-value*[b]	Unadjusted PR[95% CI] Overall *p-value*	Adjusted models PR[95% CI] Overall *p-value*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	579 (43.2%) 269 (20.1%) 302 (22.5%) 190 (14.2%)	5.2% 6.7% 6.0% 10.0% *0.126* *0.048*[c]	1 1.29 [0.73, 2.28] 1.15 [0.65, 2.03] 1.93 [1.11, 3.35] *0.128* *0.053*[c]	1 1.19 [0.68, 2.09] 1.08 [0.60, 1.95] 1.81 [1.03, 3.18] *0.201* *0.105*[c]	8.5% 8.2% 10.3% 17.9% *0.001* *0.001*[c]	1 0.97 [0.60, 1.56] 1.21 [0.79, 1.86] 2.11 [1.41, 3.17] *0.001* *0.002*[c]	1 0.94 [0.58, 1.51] 1.21 [0.78, 1.87] 2.11 [1.39, 3.22] *0.002* *0.003*[c]
Chemsex-associated drug use	No Yes	1027 (76.6%) 313 (23.4%)	6.0% 7.4% *0.405*	1 1.22 [0.77, 1.93] *0.404*	1 1.27 [0.79, 2.06] *0.325*	8.9% 14.4% *0.005*	1 1.62 [1.16, 2.27] *0.005*	1 1.74 [1.23, 2.45] *0.002*

Adjusted models: Each factor included in a separate model and adjusted for: age (included as four categories: <25, 25-29, 30-39, 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status and study region.

[a] University Education: 0.3% (n=4) missing. Employed: 1.4% (n=19) missing. Ongoing relationship: 0.2% (n=3) missing. Smoke regularly: 0.4% (n=5) missing. Heavy drinking: 1.2% (n=16) missing. Recreational drug use: 0.8% (n=11) missing.

[b] Pearson χ^2 test

[c] Test for trend.

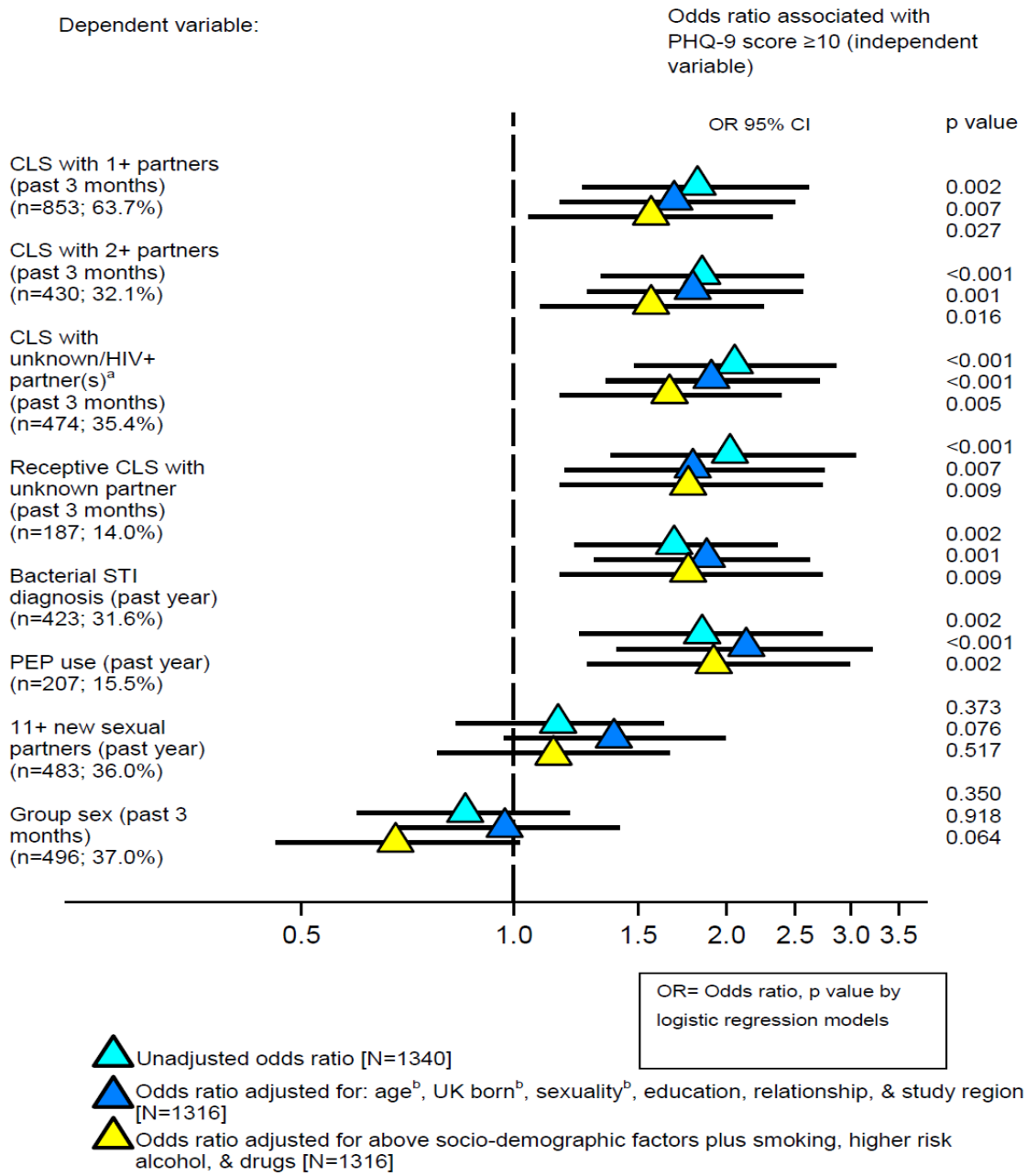
[d] Fisher's exact test.

[e] It was not possible to investigate this association due to small numbers.

[f] A Fisher's exact test p-value is presented for univariable comparison of the categories presented, however, in unadjusted and adjusted Poisson analyses; a dichotomized version of self-reported sexual identity (gay or bisexual/straight), disclosure of sexual orientation to friends (all/almost all or some/few/none), and social support score (highest score or otherwise) is investigated due to small numbers.

11.12 Appendix 12: Relationship between depressive symptoms and sexual behaviour measures in the AURAH study

Figure 33: Unadjusted and adjusted associations of depressive symptoms (PHQ-9≥10) with sexual behaviours among 1340 MSM who reported anal or vaginal sex in the past three months in AURAH using logistic regression



[a] Men who reported no CLS partners of unknown HIV status, and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.
[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+) and dichotomous UK born and self-reported sexual identity.

Table 67: Unadjusted and adjusted associations of depressive symptoms (PHQ-9≥10) with sexual behaviour measures among different samples of AURAH MSM according to report of recent sexual behaviour, in three sensitivity analyses

		PHQ-9 ≥10 n=166; 12.4% (independent variable)		
Dependent variables:	Modified Poisson models:	N=1304 MSM reporting anal sex in the past 3 months	N=853 MSM reporting anal/vaginal CLS in the past 3 months	N=815 MSM reporting anal CLS in the past 3 months
		PR[95% CI][a]; *p-value*[b]	PR[95% CI][a]; *p-value*[b]	PR[95% CI][a]; *p-value*[b]
CLS with 1+ partners (past 3 months)	Unadjusted	1.24 [1.12, 1.37]; *<0.001*	/	/
	Adjusted model (i)[c]	1.22 [1.10, 1.36]; *<0.001*	/	/
	Adjusted model (ii)[d]	1.18 [1.07, 1.31]; *0.002*	/	/
CLS with 2+ partners (past 3 months)	Unadjusted	1.48 [1.21, 1.80]; *<0.001*	1.22 [1.04, 1.44]; *0.016*	1.19 [1.00, 1.41]; *0.046*
	Adjusted model (i)[c]	1.46 [1.19, 1.80]; *<0.001*	1.22 [1.03, 1.43]; *0.020*	1.20 [1.01, 1.43]; *0.038*
	Adjusted model (ii)[d]	1.32 [1.07, 1.62]; *0.008*	1.14 [0.97, 1.34]; *0.122*	1.11 [0.93, 1.33]; *0.228*
CLS with unknown/HIV-positive status partners[e] (past 3 months)	Unadjusted	1.55 [1.30, 1.84]; *<0.001*	1.27 [1.10, 1.46]; *0.001*	1.25 [1.08, 1.44]; *0.002*
	Adjusted model (i)[c]	1.45 [1.21, 1.74]; *<0.001*	1.23 [1.06, 1.41]; *0.005*	1.20 [1.04, 1.38]; *0.014*
	Adjusted model (ii)[d]	1.31 [1.09, 1.57]; *0.003*	1.15 [1.00, 1.33]; *0.047*	1.12 [0.97, 1.29]; *0.131*
Receptive CLS with an unknown status partner (past 3 months)	Unadjusted	1.80 [1.31, 2.47]; *<0.001*	1.50 [1.11, 2.03]; *0.008*	1.45 [1.07, 1.96]; *0.015*
	Adjusted model (i)[c]	1.55 [1.11, 2.17]; *0.010*	1.37 [1.00, 1.88]; *0.049*	1.30 [0.95, 1.78]; *0.103*
	Adjusted model (ii)[d]	1.54 [1.10, 2.15]; *0.012*	1.41 [1.03,1.93]; *0.033*	1.33 [0.97, 1.81]; *0.076*
Bacterial STI diagnosis (past year)	Unadjusted	1.41 [1.16, 1.72]; *0.001*	1.31 [1.06, 1.62]; 0.014	1.30 [1.05, 1.61]; *0.016*
	Adjusted model (i)[c]	1.45 [1.18, 1.77]; *<0.001*	1.39 [1.12, 1.74]; *0.003*	1.37 [1.10, 1.71]; *0.004*
	Adjusted model (ii)[d]	1.30 [1.07, 1.58]; *0.010*	1.26 [1.01, 1.57]; *0.036*	1.24 [1.00, 1.53]; *0.050*
PEP use (past year)	Unadjusted	1.64 [1.20, 2.22]; *0.002*	1.61 [1.17, 2.22]; 0.004	1.55 [1.13, 2.14]; *0.007*
	Adjusted model (i)[c]	1.79 [1.30, 2.45]; *<0.001*	1.79 [1.29, 2.48]; *0.001*	1.71 [1.23, 2.37]; *0.001*
	Adjusted model (ii)[d]	1.64 [1.19, 2.26]; *0.002*	1.62 [1.16, 2.28]; *0.005*	1.55 [1.10, 2.17]; *0.011*
11+ new sexual partners (past year)	Unadjusted	1.09 [0.89, 1.34]; *0.412*	1.13 [0.90, 1.42]; *0.285*	1.09 [0.87, 1.38]; *0.447*
	Adjusted model (i)[c]	1.19 [0.97, 1.46]; *0.088*	1.24 [1.00, 1.54]; *0.054*	1.20 [0.97, 1.50]; *0.096*
	Adjusted model (ii)[d]	1.08 [0.89, 1.30]; *0.433*	1.09 [0.89, 1.33]; *0.408*	1.06 [0.86, 1.29]; *0.587*
Group sex (past 3 months)	Unadjusted	0.91 [0.73, 1.14]; *0.408*	0.95 [0.75, 1.21]; *0.695*	0.96 [0.76, 1.22]; *0.737*
	Adjusted model (i)[c]	0.99 [0.79, 1.24]; *0.928*	1.05 [0.83, 1.33]; *0.679*	1.07 [0.84, 1.35]; *0.595*
	Adjusted model (ii)[d]	0.84 [0.68, 1.04]; *0.113*	0.88 [0.71, 1.10]; *0.279*	0.89 [0.71, 1.11]; *0.313*

[a] Prevalence ratio associated with depressive symptoms on PHQ-9 (independent variable).
[b] p-value by Wald test using modified Poisson models.
[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.

[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.
[e] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

11.13 Appendix 13: Relationship between other depressive symptom measures on PHQ-9 and sexual behaviour measures in the AURAH study

Table 68: Unadjusted associations of other depression measures on PHQ-9 with sexual behaviour measures in AURAH

N=1340 MSM reporting sex in the past three months			CLS with 1+ partners	CLS with 2+ partners	CLS with unknown/ HIV-positive partner[b]	Receptive CLS with unknown status partner	Bacterial STI diagnosis (past year)	PEP use (past year)	11+ new sexual partners (past year)	Group sex (past 3 months)
		N (%)	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]
Major depressive syndrome on PHQ-9 (6.3%; n=85)	Yes No	85 (6.3%) 1255 (93.7%)	76.5% 62.8% *0.011*	44.7% 31.2% *0.010*	54.1% 34.1% *<0.001*	21.2% 13.5% *0.047*	34.1% 31.4% *0.601*	22.4% 15.0% *0.069*	34.1% 36.2% *0.702*	32.9% 37.3% *0.422*
Major and other depressive syndromes on PHQ-9 (10.2%; n=136)	Yes No	136 (10.2%) 1204 (89.9%)	75.7% 62.3% *0.002*	45.6% 30.6% *<0.001*	50.7% 33.6% *<0.001*	16.9% 13.6% *0.294*	39.7% 30.7% *0.031*	22.1% 14.7% *0.024*	37.5% 35.9% *0.709*	34.6% 37.3% *0.531*

[a] Pearson χ^2 test
[b] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

Table 69: Unadjusted and adjusted associations of other depression measures on PHQ-9 with sexual behaviour measures in AURAH

N=1340 MSM reporting sex in the past three months		Major depressive syndrome (6.3%; n=85)	Major & other depressive syndromes (10.2%; n=136)
Dependent variables:		PR[95% CI][a]; *p-value*[b]	PR[95% CI][a]; *p-value*[b]
CLS with 1+ partners (past 3 months)	Unadjusted	1.22 [1.07, 1.38]; *0.002*	1.22 [1.09, 1.35]; *<0.001*
	Adjusted model (i)[c]	1.18 [1.03, 1.35]; *0.014*	1.20 [1.08, 1.34]; *0.001*
	Adjusted model (ii)[d]	1.15 [1.01, 1.32]; *0.034*	1.16 [1.04, 1.29]; *0.009*
CLS with 2+ partners (past 3 months)	Unadjusted	1.43 [1.11, 1.84]; *0.005*	1.49 [1.22, 1.83]; *<0.001*
	Adjusted model (i)[c]	1.33 [1.03, 1.73]; *0.030*	1.46 [1.18, 1.80]; *<0.001*
	Adjusted model (ii)[d]	1.24 [0.96, 1.61]; *0.098*	1.31 [1.06, 1.60]; *0.012*
CLS with unknown/HIV-positive status partners[e] (past 3 months)	Unadjusted	1.59 [1.29, 1.96]; *<0.001*	1.51 [1.26, 1.81]; *<0.001*
	Adjusted model (i)[c]	1.43 [1.15, 1.79]; *0.001*	1.42 [1.18, 1.72]; *<0.001*
	Adjusted model (ii)[d]	1.34 [1.07, 1.67]; *0.010*	1.29 [1.07, 1.56]; *0.007*
Receptive CLS with an unknown status partner (past 3 months)	Unadjusted	1.57 [1.02, 2.43]; *0.041*	1.24 [0.83, 1.85]; *0.288*
	Adjusted model (i)[c]	1.30 [0.84, 2.03]; *0.242*	1.07 [0.71, 1.62]; *0.730*
	Adjusted model (ii)[d]	1.30 [0.83, 2.03]; *0.247*	1.05 [0.70, 1.59]; *0.798*
Bacterial STI diagnosis (past year)	Unadjusted	1.09 [0.80, 1.48]; *0.595*	1.30 [1.04, 1.62]; *0.023*
	Adjusted model (i)[c]	1.13 [0.82, 1.55]; *0.452*	1.33 [1.06, 1.67]; *0.015*
	Adjusted model (ii)[d]	1.04 [0.77, 1.41]; *0.781*	1.19 [0.95, 1.49]; *0.121*
PEP use (past year)	Unadjusted	1.49 [0.98, 2.27]; *0.060*	1.50 [1.06, 2.12]; *0.021*
	Adjusted model (i)[c]	1.63 [1.04, 2.55]; *0.034*	1.62 [1.14, 2.31]; *0.008*
	Adjusted model (ii)[d]	1.54 [0.97, 2.43]; *0.066*	1.45 [1.02, 2.07]; *0.041*
11+ new sexual partners (past year)	Unadjusted	0.94 [0.70, 1.28]; *0.706*	1.05 [0.83, 1.32]; *0.707*
	Adjusted model (i)[c]	1.03 [0.76, 1.40]; *0.826*	1.14 [0.91, 1.43]; *0.259*
	Adjusted model (ii)[d]	0.96 [0.73, 1.26]; *0.766*	1.03 [0.84, 1.27]; *0.792*
Group sex (past 3 months)	Unadjusted	0.88 [0.65, 1.21]; *0.436*	0.93 [0.73, 1.18]; *0.539*
	Adjusted model (i)[c]	1.02 [0.74, 1.39]; *0.923*	1.04 [0.82, 1.32]; *0.764*
	Adjusted model (ii)[d]	0.92 [0.68, 1.23]; *0.560*	0.89 [0.71, 1.12]; *0.315*

[a] Prevalence ratio associated with a major depressive syndrome on PHQ-9 or major and other depressive syndromes on PHQ-9 (independent variables).
[b] p-value by Wald test using modified Poisson models.
[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.
[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.
[e] Men who reported no CLS partners of unknown HIV status, and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

11.14 Appendix 14: Relationship between other depression measures on PHQ-9 and measures of self-efficacy for sexual safety in the AURAH study

Table 70: Unadjusted and adjusted associations of other depression measures on PHQ-9 with high self-efficacy for sexual safety in AURAH

N=1340 MSM reporting anal/vaginal sex in the past 3 months			High self-efficacy for sexual safety (n=900; 67.2%)							
		N (%)	%	*p-value*[a]	Unadjusted PR[95% CI]	Overall *p-value*[b]	Adjusted model (i)[c] PR[95% CI]	Overall *p-value*[b]	Adjusted model (ii)[d] PR[95% CI]	Overall *p-value*[b]
Major depressive syndrome	Yes No	85 (6.3%) 1255 (93.7%)	51.8% 68.2%	*0.002*	0.76 [0.62, 0.94] 1	*0.010*	0.75 [0.61, 0.92] 1	*0.007*	0.76 [0.61, 0.93] 1	*0.009*
Major and other depressive syndromes	Yes No	136 (10.2%) 1204 (89.9%)	55.9% 68.4%	*0.003*	0.82 [0.70, 0.95] 1	*0.010*	0.81 [0.70, 0.95] 1	*0.009*	0.82 [0.70, 0.96] 1	*0.015*

[a] Pearson χ^2 test

[b] p-value by Wald test using modified Poisson models.

[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.

[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.

Table 71: Unadjusted and adjusted associations of other depression measures on PHQ-9 with difficulty negotiating condom-use in AURAH

N=1340 MSM reporting anal/vaginal sex in the past 3 months			Difficulty negotiating condom-use (n=142; 10.6%)							
		N (%)	%	*p-value*[a]	Unadjusted PR[95% CI]	Overall *p-value*[b]	Adjusted model (i)[c] PR[95% CI]	Overall *p-value*[b]	Adjusted model (ii)[d] PR[95% CI]	Overall *p-value*[b]
Major depressive syndrome	Yes No	85 (6.3%) 1255 (93.7%)	14.1% 10.4%	*0.276*	1.36 [0.79, 2.36] 1	0.269	1.24 [0.71, 2.17] 1	*0.452*	1.22 [0.70, 2.12] 1	*0.480*
Major and other depressive syndromes	Yes No	136 (10.2%) 1204 (89.9%)	14.0% 10.2%	*0.178*	1.37 [0.87, 2.14] 1	0.172	1.30 [0.83, 2.05] 1	*0.253*	1.29 [0.82, 2.03] 1	*0.264*

[a] Pearson χ^2 test

[b] p-value by Wald test using modified Poisson models.

[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.

[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.

11.15 Appendix 15: Relationship of generalized anxiety disorder and suicidal ideation with sexual behaviour measures in the AURAH study

The prevalence of GAD on GAD-7 (≥10) was 10.2% (137/1340), see section 4.3.3.1 of Chapter 4. Compared to depressive symptoms on PHQ-9 (≥10) a similar pattern of associations was found between GAD on GAD-7 and sexual behaviour measures. Men with GAD were more likely than men without to report CLS with two or more partners, CLS with an unknown/HIV-positive status partner, receptive CLS with an unknown HIV status partner, and PEP use. Men with GAD were slightly less likely than men without to report eleven or more new sexual partners in the past year (Table 72). After adjusting for socio-demographic factors, all associations remained, with the exception of that with eleven or more new sexual partners. After adjusting additionally for smoking, drinking, and recreational drug use, associations with CLS measures and PEP use were attenuated but remained significant. GAD was not associated with CLS with one or more partners (although the unadjusted PR did appear to be of at least borderline significance), bacterial STI diagnosis, or group sex, in unadjusted or adjusted analysis (Table 73). Furthermore, men with GAD were less likely to report high self-efficacy for sexual safety and more likely to report difficulty negotiating condom-use than men without GAD (Table 74). Adjusted for key socio-demographic factors, GAD was inversely associated with high self-efficacy, and was associated with difficulty negotiating condom-use. These associations remained with some attenuation, after additional adjustment for smoking, alcohol, and recreational drug use (Table 75). GAD on GAD-7 was not associated with any reason for non-condom-use presented, in unadjusted or adjusted analysis (data not shown).

The prevalence of suicidal ideation on PHQ-9 was 11.7% (157/1340), see section 4.3.1 of Chapter 4. Compared to depressive symptoms on PHQ-9 (≥10) a similar pattern of associations was found between suicidal ideation on PHQ-9 with sexual behaviour measures. Men who reported suicidal ideation were more likely than men who did not to report all measures of CLS, as well as PEP use. Men who reported suicidal ideation were also slightly more likely than men who did not to report bacterial STI diagnosis (Table 72). After adjusting for socio-demographic factors, associations with all CLS measures, STI diagnosis, and PEP use remained. After adjusting additionally for smoking, drinking, and recreational drug use, most associations were attenuated but remained significant, with the exception of that with STI diagnosis, which was no longer associated with suicidal ideation. Suicidal ideation was not associated with report of eleven or more new sexual partners or group sex, in unadjusted or adjusted analysis. Suicidal ideation was not associated with high self-efficacy for sexual safety, in unadjusted or adjusted analysis (Table 73). Men who reported suicidal ideation were more likely to report difficulty negotiating condom-use than men who did not report suicidal ideation (Table 74). However, this relationship disappeared after adjustment (Table 75). Finally, indicating suicidal ideation on PHQ-9 was found to have a borderline association with a reason for non-condom-use being; my partner didn't want to use a condom, in unadjusted analysis, however, the association

disappeared after adjustment. Suicidal ideation on PHQ-9 was not associated with any of the other reasons for non-condom-use, in unadjusted or adjusted analysis (data not shown).

Table 72: Unadjusted associations of GAD and suicidal ideation with sexual behaviour measures in AURAH

N=1340 MSM reporting sex in the past three months			CLS with 1+ partners	CLS with 2+ partners	CLS with unknown/ HIV-positive partner[b]	Receptive CLS with unknown status partner	Bacterial STI diagnosis (past year)	PEP use (past year)	11+ new sexual partners (past year)	Group sex (past 3 months)
		N (%)	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]	% *p-value*[a]
Generalized anxiety disorder on GAD-7 (score of ≥10)	Yes No	137 (10.2%) 1203 (89.8%)	70.8% 62.8% *0.066*	43.1% 30.8% *0.004*	48.2% 33.9% *0.001*	22.6% 13.0% *0.002*	32.9% 31.4% *0.734*	22.6% 14.6% *0.014*	28.5% 36.9% *0.051*	30.7% 37.7% *0.104*
Suicidal ideation on PHQ-9 (final question)	Yes No	157 (11.7%) 1183 (88.3%)	77.1% 61.9% *<0.001*	45.2% 30.4% *<0.001*	52.9% 33.1% *<0.001*	25.5% 12.4% *<0.001*	38.2% 30.7% *0.056*	22.3% 14.5% *0.012*	38.9% 35.7% *0.435*	36.3% 37.1% *0.845*

[a] Pearson χ^2 test

[b] Men who reported no CLS partners of unknown HIV status and only one HIV-positive CLS partner who was a long-term partner and with whom they 'thought the risks of catching HIV were low because their partner was taking ART' were not counted as positive for this measure.

Table 73: Adjusted associations of GAD and suicidal ideation with sexual behaviour measures in AURAH

N=1340 MSM reporting sex in the past three months		GAD (GAD-7≥10)	Suicidal ideation on PHQ-9
Dependent variables:		PR[95% CI][a]; *p-value*[b]	PR[95% CI][a]; *p-value*[b]
CLS with 1+ partners (past 3 months)	Unadjusted	1.13 [1.00, 1.27]; *0.044*	1.25 [1.13, 1.37]; *<0.001*
	Adjusted model (i)[c]	1.11 [0.99, 1.25]; *0.079*	1.21 [1.09, 1.33]; *<0.001*
	Adjusted model (ii)[d]	1.08 [0.96, 1.22]; *0.182*	1.16 [1.06, 1.28]; *0.002*
CLS with 2+ partners (past 3 months)	Unadjusted	1.40 [1.13, 1.72]; *0.002*	1.49 [1.23, 1.81]; *<0.001*
	Adjusted model (i)[c]	1.39 [1.12, 1.74]; *0.003*	1.40 [1.14, 1.71]; *0.001*
	Adjusted model (ii)[d]	1.31 [1.05, 1.62]; *0.015*	1.27 [1.04, 1.56]; *0.019*
CLS with unknown/HIV-positive status partners[b] (past 3 months)	Unadjusted	1.42 [1.17, 1.72]; *<0.001*	1.60 [1.35, 1.89]; *<0.001*
	Adjusted model (i)[c]	1.36 [1.12, 1.67]; *0.002*	1.48 [1.24, 1.76]; *<0.001*
	Adjusted model (ii)[d]	1.28 [1.05, 1.55]; *0.015*	1.35 [1.13, 1.61]; *0.001*
Receptive CLS with an unknown status partner (past 3 months)	Unadjusted	1.74 [1.24, 2.46]; *0.001*	2.05 [1.51, 2.79]; *<0.001*
	Adjusted model (i)[c]	1.52 [1.05, 2.20]; *0.025*	1.81 [1.31, 2.49]; *<0.001*
	Adjusted model (ii)[d]	1.52 [1.05, 2.21]; *0.026*	1.80 [1.30, 2.48]; *<0.001*
Bacterial STI diagnosis (past year)	Unadjusted	1.05 [0.81, 1.35]; *0.732*	1.25 [1.00, 1.55]; *0.047*
	Adjusted model (i)[c]	1.10 [0.86, 1.42]; *0.441*	1.35 [1.09, 1.67]; *0.007*
	Adjusted model (ii)[d]	1.05 [0.82, 1.34]; *0.709*	1.23 [0.99, 1.51]; *0.061*
PEP use (past year)	Unadjusted	1.55 [1.10, 2.17]; *0.012*	1.53 [1.11, 2.12]; *0.010*
	Adjusted model (i)[c]	1.74 [1.23, 2.47]; *0.002*	1.68 [1.21, 2.33]; *0.002*
	Adjusted model (ii)[d]	1.71 [1.20, 2.43]; *0.003*	1.57 [1.13, 2.18]; *0.008*
11+ new sexual partners (past year)	Unadjusted	0.77 [0.59, 1.02]; *0.065*	1.09 [0.88, 1.34]; *0.427*
	Adjusted model (i)[c]	0.84 [0.64, 1.11]; *0.228*	1.19 [0.97, 1.46]; *0.105*
	Adjusted model (ii)[d]	0.80 [0.62, 1.04]; *0.099*	1.09 [0.89, 1.33]; *0.425*
Group sex (past 3 months)	Unadjusted	0.81 [0.62, 1.06]; *0.120*	0.98 [0.79, 1.22]; *0.846*
	Adjusted model (i)[c]	0.90 [0.69, 1.17]; *0.438*	1.04 [0.83, 1.29]; *0.741*
	Adjusted model (ii)[d]	0.83 [0.65, 1.06]; *0.133*	0.90 [0.73, 1.10]; *0.302*

[a] Prevalence ratio associated with a major depressive syndrome on PHQ-9 or major and other depressive syndromes on PHQ-9 (independent variables).
[b] p-value by Wald test using modified Poisson models.
[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.
[d] Adjusted models (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.

Table 74: Unadjusted and adjusted associations of GAD and suicidal ideation with high self-efficacy for sexual safety in AURAH

N=1340 MSM reporting anal/vaginal sex in the past 3 months			High self-efficacy for sexual safety (n=900; 67.2%)							
		N (%)	%	*p-value*[a]	Unadjusted PR[95% CI]	Overall *p-value*[b]	Adjusted model (i)[c] PR[95% CI]	Overall *p-value*[b]	Adjusted model (ii)[d] PR[95% CI]	Overall *p-value*[b]
Generalized anxiety disorder on GAD-7 (score of ≥10)	Yes No	137 (10.2%) 1203 (89.8%)	54.0% 68.7%	*0.001*	0.79 [0.67, 0.92] 1	*0.003*	0.78 [0.67, 0.92] 1	*0.002*	0.79 [0.67, 0.92] 1	*0.003*
Suicidal ideation on PHQ-9 (final question)	Yes No	157 (11.7%) 1183 (88.3%)	61.2% 68.0%	*0.087*	0.90 [0.79, 1.03] 1	*0.113*	0.92 [0.80, 1.04] 1	*0.192*	0.93 [0.81, 1.06] 1	*0.276*

[a] Pearson χ^2 test
[b] p-value by Wald test using modified Poisson models.
[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.
[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.

Table 75: Unadjusted and adjusted associations of GAD and suicidal ideation with difficulty negotiating condom-use in AURAH

N=1340 MSM reporting anal/vaginal sex in the past 3 months			Difficulty negotiating condom-use (n=142; 10.6%)							
		N (%)	%	*p-value*[a]	Unadjusted PR[95% CI]	Overall *p-value*[b]	Adjusted model (i)[c] PR[95% CI]	Overall *p-value*[b]	Adjusted model (ii)[d] PR[95% CI]	Overall *p-value*[b]
Generalized anxiety disorder on GAD-7 (score of ≥10)	Yes No	137 (10.2%) 1203 (89.8%)	18.3% 9.7%	*0.002*	1.88 [1.27, 2.78] 1	0.002	1.62 [1.06, 2.48] 1	*0.027*	1.62 [1.06, 2.49] 1	*0.027*
Suicidal ideation on PHQ-9 (final question)	Yes No	157 (11.7%) 1183 (88.3%)	16.6% 9.8%	*0.010*	1.69 [1.14, 2.50] 1	0.009	1.46 [0.97, 2.17] 1	*0.067*	1.45 [0.97, 2.16] 1	*0.067*

[a] Pearson χ^2 test
[b] p-value by Wald test using modified Poisson models.
[c] Adjusted model (i): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, and study region.

[d] Adjusted model (ii): Age in four categories (<25; 25-29; 30-39; 40+), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education, ongoing relationship status, study region, smoking, higher-risk drinking, and recreational drug use.

11.16 Appendix 16: Relationship of socio-demographic and lifestyle factors with sexual behaviour measures in the AURAH study

Table 76: Unadjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures (past three months) among 1340 MSM in AURAH who reported anal or vaginal sex in the past three months

N=1340 MSM reporting sex in the past 3 months			CLS with 1+ partners	CLS with 2+ partners	CLS with unknown/HIV-positive partner [l]	Receptive CLS with unknown status partner	Bacterial STI diagnosis (past year)	PEP use (past year)	11+ new sex partners (past year)	Group sex
		N (%)	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]
Age (years)	<25	235 (17.8%)	65.5%	28.5%	34.9%	15.3%	24.3%	14.5%	29.4%	28.1%
	25-29	344 (26.0%)	59.6%	26.2%	29.7%	11.9%	35.8%	14.0%	29.4%	30.2%
	30-34	255 (19.3%)	65.5%	32.6%	34.9%	11.8%	37.7%	17.7%	40.4%	39.2%
	35-39	175 (13.2%)	64.0%	37.7%	37.1%	17.1%	32.0%	20.0%	38.3%	46.9%
	40-44	125 (9.5%)	64.0%	36.8%	38.4%	15.2%	33.6%	13.6%	48.0%	45.6%
	45+	188 (14.2%)	65.4%	37.2%	43.6%	14.9%	22.9%	13.8%	41.0%	44.2%
			0.631	*0.023*	*0.046*	*0.499*	*0.001*	*0.396*	*<0.001*	*<0.001*
			0.565[c]	*0.002*[c]	*0.006*[c]	*0.483*[c]	*0.407*[c]	*0.859*[c]	*<0.001*[c]	*<0.001*[c]
Born in the UK and ethnicity	Yes, white	676 (51.2%)	66.3%	33.6%	37.7%	15.1%	30.5%	14.8%	36.8%	39.8%
	Yes, BAME	86 (6.5%)	68.6%	40.7%	34.9%	10.5%	29.1%	12.8%	27.9%	31.4%
	No, white	408 (30.9%)	57.1%	26.0%	31.9%	13.0%	35.8%	16.2%	39.5%	36.0%
	No, BAME	151 (11.4%)	66.2%	35.1%	34.4%	13.3%	26.5%	17.9%	28.5%	31.8%
			0.012	*0.010*	*0.273*	*0.577*	*0.123*	*0.674*	*0.037*	*0.150*
Study region	London	1017 (75.9%)	60.4%	29.3%	32.2%	12.6%	31.2%	14.6%	37.0%	37.0%
	South	241 (18.0%)	73.4%	40.7%	44.4%	15.4%	35.3%	20.3%	35.3%	39.4%
	Other	82 (6.1%)	75.6%	41.5%	48.8%	26.8%	25.6%	12.2%	26.8%	30.5%
			<0.001	*0.001*	*<0.001*	*0.001*	*0.229*	*0.058*	*0.177*	*0.351*
University Education	Yes	891 (66.5%)	60.5%	29.5%	32.0%	12.4%	29.0%	16.2%	37.2%	36.9%
	No/missing[a]	449 (33.5%)	69.9%	37.2%	42.1%	17.2%	36.8%	14.0%	33.9%	37.2%
			0.001	*0.004*	*<0.001*	*0.017*	*0.004*	*0.308*	*0.236*	*0.923*
Employment status	Employed	1069 (79.8%)	63.1%	31.1%	34.7%	13.5%	32.9%	15.3%	36.5%	38.4%
	Not employed/ missing[a]	271 (20.2%)	66.1%	36.2%	38.0%	15.9%	26.2%	16.2%	34.3%	31.7%
			0.359	*0.108*	*0.310*	*0.309*	*0.033*	*0.688*	*0.507*	*0.044*

Table 76: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures (past three months) among 1340 MSM in AURAH who reported anal or vaginal sex in the past three months (continued)

N=1340 MSM reporting sex in the past 3 months			CLS with 1+ partners	CLS with 2+ partners	CLS with unknown/HIV-positive partner [l]	Receptive CLS with unknown status partner	Bacterial STI diagnosis (past year)	PEP use (past year)	11+ new sex partners (past year)	Group sex
		N (%)	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]
Money to cover basic needs (financial hardship)	Always Mostly At times/no	958 (71.7%) 281 (21.0%) 97 (7.3%)	61.2% 68.0% 76.3% *0.003* *0.001*[c]	30.2% 34.2% 45.4% *0.007* *0.003*[c]	33.1% 38.1% 50.5% *0.002* *0.001*[c]	12.9% 15.3% 19.6% *0.149* *0.055*[c]	29.9% 36.3% 34.0% *0.106* *0.078*[c]	15.2% 13.9% 22.7% *0.109* *0.245*[c]	37.0% 35.2% 29.9% *0.366* *0.181*[c]	37.9% 35.2% 34.0% *0.585* *0.309*[c]
Housing status	Home owner Renting Unstable/other	369 (27.9%) 764 (57.8%) 188 (14.2%)	65.6% 62.0% 67.0% *0.306* *0.955*[c]	33.6% 30.4% 35.6% *0.284* *0.929*[c]	36.9% 34.0% 38.3% *0.437* *0.991*[c]	13.3% 13.6% 16.5% *0.543* *0.367*[c]	28.2% 32.9% 33.0% *0.258* *0.158*[c]	17.3% 14.9% 14.4% *0.512* *0.286*[c]	42.3% 34.6% 29.8% *0.006* *0.002*[c]	41.2% 35.9% 34.6% *0.161* *0.077*[c]
Self-reported sexual identity	Gay Bisexual Straight	1190 (89.1%) 127 (9.5%) 19 (1.4%)	63.1% 64.6% 94.7% *0.017*	31.8% 30.7% 57.9% *0.050*	35.0% 37.0% 52.6% *0.258*	13.8% 15.8% 15.8% *0.731*[d]	32.6% 27.6% 0.0% *0.006*	16.1% 11.0% 5.3% *0.200*[d]	38.0% 22.8% 5.3% *<0.001*	37.9% 30.7% 26.3% *0.174*
Ongoing relationship	Yes No/missing[a]	579 (43.2%) 761 (56.8%)	70.6% 58.3% *<0.001*	27.3% 35.7% *0.001*	30.7% 38.9% *0.002*	10.2% 16.8% *0.001*	29.0% 33.5% *0.080*	13.3% 17.1% *0.058*	27.3% 42.7% *<0.001*	34.9% 38.6% *0.160*
Supportive network	1: High levels 2 3 4 5: Low levels	400 (30.1%) 464 (34.9%) 284 (21.3%) 130 (9.8%) 53 (4.0%)	63.5% 61.0% 64.8% 66.2% 71.7% *0.494* *0.222*[c]	27.3% 29.1% 36.3% 41.5% 49.1% *<0.001* *<0.001*[c]	29.0% 34.9% 37.7% 43.1% 52.8% *0.001* *<0.001*[c]	10.3% 12.7% 16.2% 17.7% 32.1% *<0.001* *<0.001*[c]	30.3% 30.8% 30.3% 37.7% 39.6% *0.341* *0.104*[c]	11.3% 13.2% 16.9% 26.2% 32.1% *<0.001* *<0.001*[c]	31.5% 36.0% 37.0% 46.2% 41.5% *0.038* *0.004*[c]	35.0% 37.9% 37.3% 37.7% 43.4% *0.769* *0.290*[c]
Current smoker	Yes No/missing[a]	334 (24.9%) 1006 (75.1%)	71.9% 60.9% *<0.001*	40.1% 29.4% *<0.001*	46.7% 31.6% *<0.001*	15.3% 13.5% *0.424*	33.2% 31.0% *0.450*	14.7% 15.7% *0.650*	33.5% 36.9% *0.270*	40.7% 35.8% *0.106*

Table 76: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures (past three months) among 1340 MSM in AURAH who reported anal or vaginal sex in the past three months (continued)

N=1340 MSM reporting sex in the past 3 months			CLS with 1+ partners	CLS with 2+ partners	CLS with unknown/HIV-positive partner [l]	Receptive CLS with unknown status partner	Bacterial STI diagnosis (past year)	PEP use (past year)	11+ new sex partners (past year)	Group sex
		N (%)	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]	% *p-value*[b]
Higher-risk alcohol consumption	Yes No/missing[a]	259 (19.3%) 1081 (80.7%)	64.5% 63.5% *0.759*	39.0% 30.4% *0.008*	42.1% 33.8% *0.012*	15.4% 13.6% *0.441*	36.7% 30.3% *0.049*	18.9% 14.6% *0.085*	44.8% 34.0% *0.001*	44.0% 35.3% *0.009*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	579 (43.2%) 269 (20.1%) 302 (22.5%) 190 (14.2%)	58.4% 60.2% 68.5% 76.8% *<0.001* *<0.001*[c]	25.6% 25.3% 36.1% 55.3% *<0.001* *<0.001*[c]	27.6% 32.0% 39.4% 57.4% *<0.001* *<0.001*[c]	12.8% 12.3% 16.6% 15.8% *0.316* *0.123*[c]	22.6% 29.7% 34.4% 56.8% *<0.001* *<0.001*[c]	12.1% 11.2% 18.5% 26.8% *<0.001* *<0.001*[c]	24.9% 34.9% 39.7% 65.8% *<0.001* *<0.001*[c]	20.4% 32.0% 50.0% 74.2% *<0.001* *<0.001*[c]
Chemsex-associated drug use	No Yes	1027 (76.6%) 313 (23.4%)	60.7% 73.5% *<0.001*	26.9% 49.2% *<0.001*	30.4% 51.8% *<0.001*	12.9% 17.6% *0.035*	24.4% 55.0% *<0.001*	11.0% 30.0% *<0.001*	29.1% 58.8% *<0.001*	26.9% 70.3% *<0.001*

[a] University Education: 0.3% (n=4) missing. Employed: 1.4% (n=19) missing. Ongoing relationship: 0.2% (n=3) missing. Smoke regularly: 0.4% (n=5) missing. Heavy drinking: 1.2% (n=16) missing. Recreational drug use: 0.8% (n=11) missing.
[b] Pearson χ^2 test
[c] Test for trend.
[d] Fisher's exact test.

11.17 Appendix 17: Socio-demographic, lifestyle, and psychosocial factors associated with other depressive symptom measures on PHQ-9 at baseline, and the 12- and 24-month questionnaire in the PROUD trial

Table 77: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with a measure of major depression on PHQ-9 using baseline, 12-month follow-up, and 24-month follow-up data among all 540 men who participated in PROUD

					Major depression on PHQ-9			
N=540 men		Baseline [N=540] n(%)	12-month [N=410] n(%)	24-month [N=333] n(%)	Unadjusted PR [95% CI]	Overall p-value[a]	Adjusted[b] PR [95% CI]	Overall p-value[a]
Study time-point N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Baseline 12-month 24-month	/	/	/	1 1.79 [1.17, 2.73] 1.76 [1.12, 2.77]	*0.014* *0.010*[c]	1 1.82 [1.17, 2.81] 1.82 [1.14, 2.91]	*0.013* *0.009*[c]
Randomized to study trial arm N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	Immediate arm Deferred arm	/	216 (52.7%) 194 (47.3%)	182 (54.7%) 151 (45.4%)	1.64 [0.93, 2.88] 1	*0.086*	1.72 [0.97, 3.04] 1	*0.061*
Age N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	<25 25-29 30-34 35-39 40-44 45+	54 (10.0%) 96 (17.8%) 114 (21.1%) 97 (18.0%) 81 (15.0%) 98 (18.2%)	27 (6.6%) 56 (13.7%) 87 (21.2%) 78 (19.0%) 70 (17.1%) 92 (22.4%)	11 (3.3%) 35 (10.5%) 73 (21.9%) 66 (19.8%) 55 (16.5%) 93 (27.9%)	1.00 [0.45, 2.22] 0.71 [0.35, 1.43] 0.80 [0.43, 1.46] 0.33 [0.14, 0.77] 0.18 [0.06, 0.58] 1	0.017 0.721[c]	0.97 [0.44, 2.14] 0.72 [0.36, 1.43] 0.85 [0.46, 1.56] 0.36 [0.15, 0.84] 0.20 [0.06, 0.62] 1	*0.031* *0.803*[c]
Born in the UK and white ethnicity N=538[d], Obs=1279[e] ; N=534[f], Obs=1269[g]	Yes, white Yes, BAME No, white No, BAME	287 (53.4%) 35 (6.5%) 152 (28.3%) 64 (11.9%)	223 (54.7%) 22 (5.4%) 114 (27.9%) 49 (12.0%)	184 (55.3%) 17 (5.1%) 88 (26.4%) 44 (13.2%)	1 1.97 [0.88, 4.40] 0.80 [0.43, 1.51] 1.13 [0.53, 2.42]	0.261	1 1.63 [0.70, 3.77] 0.78 [0.41, 1.50] 1.02 [0.46, 2.23]	*0.506*
Self-reported sexual identity[d] N=536[d], Obs=1273[e] ; N=536[f], Obs=1273[g]	Gay Bisexual/straight	513 (95.7%) 23 (4.3%)	388 (95.6%) 18 (4.4%)	315 (95.2%) 16 (4.8%)	1 2.27 [0.98, 5.28]	0.057	1 2.25 [0.97, 5.24]	*0.060*
University Education N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Yes No/missing	327 (60.6%) 213 (39.4%)	256 (62.4%) 154 (37.6%)	204 (61.3%) 129 (38.7%)	0.68 [0.41, 1.12] 1	0.126	0.68 [0.41, 1.14] 1	*0.141*
Employed N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Yes No/missing	439 (81.3%) 101 (18.7%)	332 (81.0%) 78 (19.0%)	276 (82.3%) 57 (17.1%)	1 2.58 [1.57, 4.23]	<0.001	1 2.36 [1.41, 3.94]	*0.001*

Table 77: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with a measure of major depression on PHQ-9 using baseline, 12-month follow-up, and 24-month follow-up data among all 540 men who participated in PROUD (continued)

					Major depression on PHQ-9			
N=540 men		Baseline [N=540] n(%)	12-month [N=410] n(%)	24-month [N=333] n(%)	Unadjusted PR [95% CI]	Overall p-value[a]	Adjusted[b] PR [95% CI]	Overall p-value[a]
Study region N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	London Outside London	375 (69.4%) 165 (30.6%)	289 (70.5%) 121 (29.5%)	228 (68.5%) 105 (31.5%)	1 0.78 [0.44, 1.37]	0.385	1 0.62 [0.34, 1.12]	*0.113*
Had sexualized drug use (past three months) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	Yes No	/	224 (54.6%) 186 (45.4%)	159 (47.8%) 174 (52.3%)	1.25 [0.76, 2.08] 1	*0.377*	1.20 [0.72, 2.00] 1	*0.479*
Age≤15 years at anal sex debut N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Yes No	/	88 (22.3%) 307 (77.7%)	70 (21.8%) 251 (78.2%)	1.78 [1.02, 3.12] 1	*0.042*	1.71 [0.96, 3.06] 1	*0.068*
Age<13 years at anal sex debut N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Yes No	/	22 (5.6%) 373 (94.4%)	19 (5.9%) 302 (94.1%)	0.95 [0.30, 2.95] 1	0.927	0.95 [0.30, 3.00] 1	*0.937*
Time between any sexual contact and intercourse with a male N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Same time 1-2 years 3-4 years 5+ years	/	163 (41.3%) 90 (22.8%) 47 (11.9%) 95 (24.1%)	146 (45.5%) 67 (20.9%) 33 (10.3%) 75 (23.4%)	1 0.74 [0.38, 1.44] 0.79 [0.33,1.85] 0.85 [0.44, 1.63]	*0.815* *0.564*[c]	1 0.76 [0.39, 1.47] 0.75 [0.31, 1.77] 0.84 [0.43, 1.65]	*0.813* *0.548*[c]
Any IPV victimization N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	226 (55.1%) 184 (44.9%)	199 (59.8%) 134 (40.2%)	1 2.02 [1.22, 3.35]	*0.006*	1 2.15 [1.29, 3.58]	*0.003*
Any IPV victimization in the past year N=436[d], Obs=743[e] ; N=432[f], Obs=737 [g]	No Yes	/	346 (84.4%) 64 (15.6%)	284 (85.3%) 49 (14.7%)	1 3.08 [1.86, 5.10]	*<0.001*	1 3.18 [1.91, 5.29]	*<0.001*
Any IPV perpetration N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	330 (80.5%) 80 (19.5%)	273 (82.0%) 60 (18.0%)	1 2.29 [1.35, 3.89]	*0.002*	1 2.24 [1.31, 3.84]	*0.003*
Any IPV perpetration in the past year N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	378 (92.2%) 32 (7.8%)	310 (93.1%) 23 (6.9%)	1 3.08 [1.68, 5.67]	*<0.001*	1 3.07 [1.63, 5.78]	*0.001*
Bidirectional IPV (victimization and perpetration) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	341 (83.2%) 69 (16.8%)	277 (83.2%) 56 (16.8%)	1 2.23 [1.29, 3.82]	*0.004*	1 2.24 [1.29, 3.90]	*0.004*
Unidirectional IPV victimization (no reported perpetration) N=436[d], Obs=743[e] ; N=432[f],Obs=737[g]	No Yes	/	295 (72.0%) 115 (28.1%)	255 (76.6%) 78 (23.4%)	1 1.18 [0.70, 2.01]	*0.536*	1 1.28 [0.75, 2.19]	*0.357*
Any negative views about gay sexuality (marker of internalised homophobia) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No/missing Yes	/	239 (58.3%) 171 (41.7%)	195 (58.6%) 138 (41.4%)	1 2.01 [1.22, 3.31]	*0.006*	1 2.02 [1.22, 3.36]	*0.006*
'Out' to all/almost all friends, work colleagues and close family N=434[d], Obs=727[e] ; N=431[f], Obs=722[g]	Yes No	/	206 (51.6%) 193 (48.4%)	166 (50.6%) 162 (49.4%)	1 2.22 [1.29, 3.79]	*0.004*	1 2.24 [1.29, 3.88]	*0.004*

[a] p-value by Wald test using GEE models.

[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, and London study clinic site.
[c] Test for trend. Of note, findings were almost identical when adjusting additionally for study time-point.
[d] Number of men contributing observations to the unadjusted model.
[e] Number of observations examined in the unadjusted model.
[f] Number of men contributing observations to the adjusted model.
[g] Number of observations examined in the adjusted model.

Table 78: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with major & other depressive syndromes on PHQ-9 using baseline, 12-month follow-up, and 24-month follow-up data among all 540 men who participated in PROUD

					Major & other depressive syndromes on PHQ-9			
N=540 men		Baseline [N=540] n(%)	12-month [N=410] n(%)	24-month [N=333] n(%)	Unadjusted PR [95% CI]	Overall p-value[a]	Adjusted[b] PR [95% CI]	Overall p-value[a]
Study time-point N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Baseline 12-month 24-month	/	/	/	1 1.38 [0.98, 1.95] 1.33 [0.92, 1.93]	*0.141* *0.100*[c]	1 1.39 [0.98, 1.98] 1.36 [0.93, 1.99]	*0.134* *0.089*[c]
Randomized to study trial arm N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	Immediate arm Deferred arm	/	216 (52.7%) 194 (47.3%)	182 (54.7%) 151 (45.4%)	1.50 [0.93, 2.40] 1	*0.094*	1.51 [0.94, 2.42] 1	*0.085*
Age N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	<25 25-29 30-34 35-39 40-44 45+	54 (10.0%) 96 (17.8%) 114 (21.1%) 97 (18.0%) 81 (15.0%) 98 (18.2%)	27 (6.6%) 56 (13.7%) 87 (21.2%) 78 (19.0%) 70 (17.1%) 92 (22.4%)	11 (3.3%) 35 (10.5%) 73 (21.9%) 66 (19.8%) 55 (16.5%) 93 (27.9%)	1.13 [0.57, 2.24] 0.69 [0.37, 1.31] 1.05 [0.63, 1.76] 0.36 [0.17, 0.75] 0.53 [0.27, 1.03] 1	0.018 0.621[c]	1.08 [0.55, 2.13] 0.69 [0.37, 1.29] 1.09 [0.65, 1.81] 0.38 [0.18, 0.79] 0.56 [0.29, 1.08] 1	*0.025* *0.736*[c]
Born in the UK and white ethnicity N=538[d], Obs=1279 [e] ; N=534[f], Obs=1269[g]	Yes, white Yes, BAME No, white No, BAME	287 (53.4%) 35 (6.5%) 152 (28.3%) 64 (11.9%)	223 (54.7%) 22 (5.4%) 114 (27.9%) 49 (12.0%)	184 (55.3%) 17 (5.1%) 88 (26.4%) 44 (13.2%)	1 1.60 [0.78, 3.29] 0.90 [0.55, 1.49] 1.39 [0.78, 2.47]	0.345	1 1.41 [0.67, 2.96] 0.90 [0.54, 1.51] 1.36 [0.75, 2.46]	*0.518*
Self-reported sexual identity[d] N=536[d], Obs=1273[e] ; N=536[f], Obs=1273[g]	Gay Bisexual/straight	513 (95.7%) 23 (4.3%)	388 (95.6%) 18 (4.4%)	315 (95.2%) 16 (4.8%)	1 1.81 [0.85, 3.82]	0.122	1 1.76 [0.84, 3.72]	*0.136*
University Education N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Yes No/missing	327 (60.6%) 213 (39.4%)	256 (62.4%) 154 (37.6%)	204 (61.3%) 129 (38.7%)	0.66 [0.44, 0.99] 1	0.043	0.66 [0.44, 0.99] 1	*0.046*
Employed N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	Yes No/missing	439 (81.3%) 101 (18.7%)	332 (81.0%) 78 (19.0%)	276 (82.3%) 57 (17.1%)	1 1.97 [1.28, 3.02]	0.002	1 1.81 [1.16, 2.81]	*0.009*
Study region N=540[d], Obs=1283[e] ; N=536[f], Obs=1273[g]	London Outside London	375 (69.4%) 165 (30.6%)	289 (70.5%) 121 (29.5%)	228 (68.5%) 105 (31.5%)	1 0.83 [0.53, 1.30]	0.422	1 0.70 (0.44, 1.14]	*0.151*
Had sexualized drug use (past three months) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	Yes No	/	224 (54.6%) 186 (45.4%)	159 (47.8%) 174 (52.3%)	1.52 [0.99, 2.35] 1	*0.057*	1.48 [0.95, 2.29] 1	*0.080*

Table 78: Unadjusted and adjusted associations of socio-demographic and lifestyle factors with major & other depressive syndromes on PHQ-9 using baseline, 12-month follow-up, and 24-month follow-up data among all 540 men who participated in PROUD (continued)

					Major & other depressive syndromes on PHQ-9 on PHQ-9			
N=540 men		Baseline [N=540] n(%)	12-month [N=410] n(%)	24-month [N=333] n(%)	Unadjusted PR [95% CI]	Overall p-value[a]	Adjusted[b] PR [95% CI]	Overall p-value[a]
Age≤15 years at anal sex debut N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Yes No	/	88 (22.3%) 307 (77.7%)	70 (21.8%) 251 (78.2%)	1.40 [0.85, 2.29] 1	*0.184*	1.36 [0.82, 2.26] 1	*0.240*
Age<13 years at anal sex debut N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Yes No	/	22 (5.6%) 373 (94.4%)	19 (5.9%) 302 (94.1%)	1.03 [0.41, 2.61] 1	0.944	1.02 [0.41, 2.58] 1	*0.962*
Time between any sexual contact and intercourse with a male N=433[d], Obs=716[e] ; N=429[f], Obs=710[g]	Same time 1-2 years 3-4 years 5+ years	/	163 (41.3%) 90 (22.8%) 47 (11.9%) 95 (24.1%)	146 (45.5%) 67 (20.9%) 33 (10.3%) 75 (23.4%)	1 0.72 [0.41, 1.28] 0.89 [0.45,1.79] 0.88 [0.50, 1.53]	*0.734* *0.640*[c]	1 0.75 [0.42, 1.33] 0.90 [0.45, 1.80] 0.88 [0.50, 1.55]	*0.803* *0.656*[c]
Any IPV victimization N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	226 (55.1%) 184 (44.9%)	199 (59.8%) 134 (40.2%)	1 2.02 [1.32, 3.11]	*0.001*	1 2.18 [1.42, 3.34]	*<0.001*
Any IPV victimization in the past year N=436[d], Obs=743[e] ; N=432[f], Obs=737 [g]	No Yes	/	346 (84.4%) 64 (15.6%)	284 (85.3%) 49 (14.7%)	1 2.93 [1.91, 4.51]	*<0.001*	1 3.04 [1.97, 4.69]	*<0.001*
Any IPV perpetration N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	330 (80.5%) 80 (19.5%)	273 (82.0%) 60 (18.0%)	1 2.20 [1.40, 3.44]	*0.001*	1 2.21 [1.40, 3.49]	*0.001*
Any IPV perpetration in the past year N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	378 (92.2%) 32 (7.8%)	310 (93.1%) 23 (6.9%)	1 3.12 [1.87, 5.21]	*<0.001*	1 3.28 [1.92, 5.60]	*<0.001*
Bidirectional IPV (victimization and perpetration) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	341 (83.2%) 69 (16.8%)	277 (83.2%) 56 (16.8%)	1 2.26 [1.43, 3.57]	*<0.001*	1 2.33 [1.46, 3.71]	*<0.001*
Unidirectional IPV victimization (no reported perpetration) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No Yes	/	295 (72.0%) 115 (28.1%)	255 (76.6%) 78 (23.4%)	1 1.16 [0.74, 1.82]	*0.514*	1 1.25 [0.80, 1.97]	*0.331*
Any negative views about gay sexuality (marker of internalised homophobia) N=436[d], Obs=743[e] ; N=432[f], Obs=737[g]	No/missing Yes	/	239 (58.3%) 171 (41.7%)	195 (58.6%) 138 (41.4%)	1 2.05 [1.34, 3.14]	*0.001*	1 2.07 [1.35, 3.18]	*0.001*
'Out' to all/almost all friends, work colleagues and close family N=434[d], Obs=727[e] ; N=431[f], Obs=722[g]	Yes No	/	206 (51.6%) 193 (48.4%)	166 (50.6%) 162 (49.4%)	1 1.76 [1.13, 2.72]	*0.012*	1 1.75 [1.11, 2.74]	*0.015*

[a] p-value by Wald test using GEE models.

[b] Age (included as four categories: <25, 25-29, 30-39, 40+), born in the UK, sexual identity (gay or bisexual/straight), university education, and London study clinic site. Of note, findings were almost identical when adjusting additionally for study time-point.
[c] Test for trend.
[d] Number of men contributing observations to the unadjusted model.
[e] Number of observations examined in the unadjusted model.
[f] Number of men contributing observations to the adjusted model.
[g] Number of observations examined in the adjusted model.

11.18 Appendix 18: Changes overtime in screening positive for clinically significant depressive symptoms by PHQ-9 in the PROUD trial

Figure 34: Distribution of change in PHQ-9 depression score from baseline to the 12-month questionnaire in PROUD

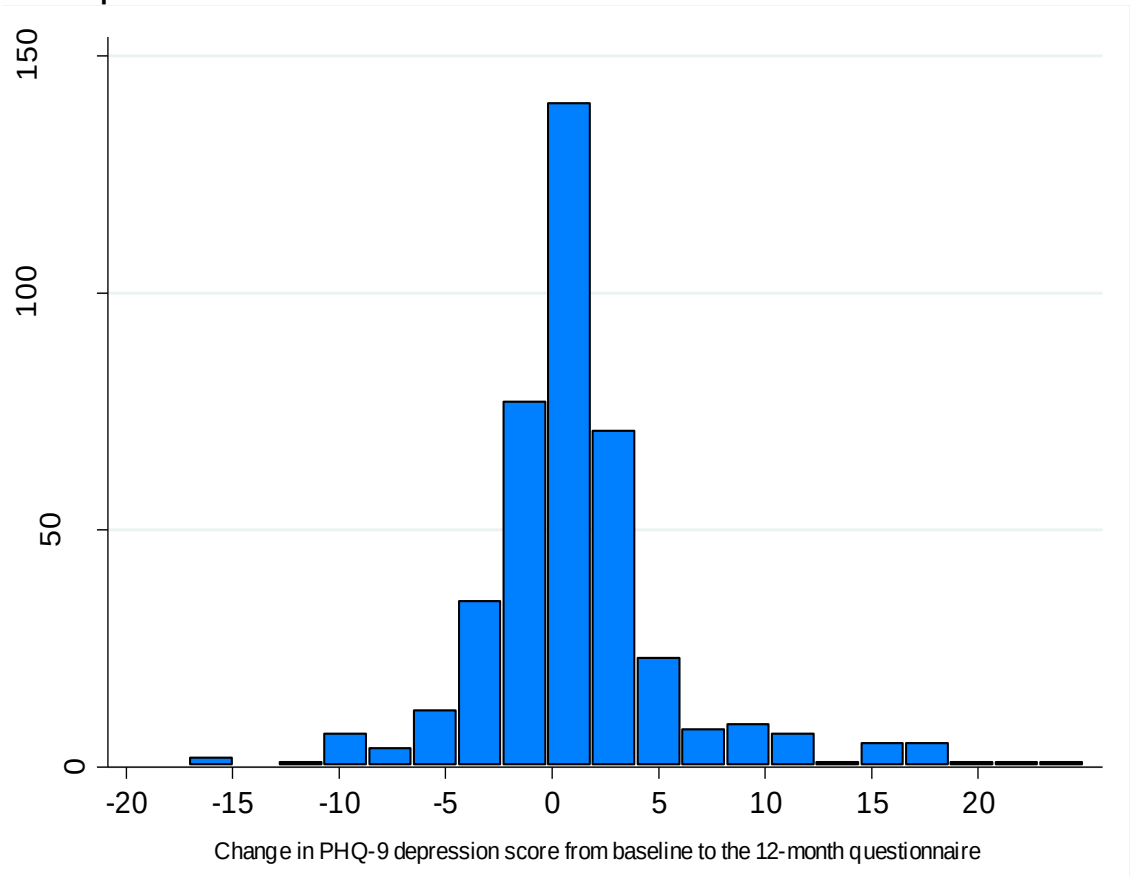


Table 79: Unadjusted associations of socio-demographic, lifestyle, and psychosocial factors with change in depression score from baseline to the 12-month questionnaire in PROUD

N=410 men with baseline and 12-month questionnaire data			Change in depression score [mean change=1, SD=4.9]	
		N (%)	Mean change scores [SD]	*p-value*[a]
Data collected at baseline:				
Age[c]	<25 25+	32 (7.8%) 378 (92.2%)	-2 [5.7] 1 [4.7]	*0.013*[b]
Born in the UK[e]	Yes No	245 (59.8%) 165 (40.2%)	1 [4.9] 1 [4.9]	*0.715*
Self-reported sexual identity	Gay Bisexual/straight	388 (95.6%) 18 (4.4%)	1 [4.9] 1 [5.4]	*0.927*[b]
University Education	Yes No/missing	256 (62.4%) 154 (37.6%)	1 [4.9] 1 [4.8]	*0.223*
Employed	Yes No/missing	332 (81.0%) 78 (19.0%)	1 [4.8] 0 [5.2]	*0.231*[b]
Ongoing relationship	Yes No/missing	182 (44.4%) 228 (55.6%)	1 [4.5] 1 [5.2]	*0.819*[b]
Study region	London Outside London	289 (70.5%) 121 (29.5%)	1 [5.1] 1 [4.4]	*0.441*[b]
Higher-risk drinking	Yes No/missing	129 (31.5%) 281 (68.5%)	0 [4.4] 1 [5.1]	*0.109*[b]
Recreational drug use (past 3 months)[e]	0/missing 1+	106 (25.9%) 304 (74.2%)	1 [4.6] 1 [5.0]	*0.909*
Data collected on/before 12-month questionnaire:				
Randomized to study trial arm	Immediate arm Deferred arm	216 (52.7%) 194 (47.3%)	1 [5.0] 1 [4.7]	*0.316*
Prescribed PrEP before 12-month questionnaire completion[d]	Yes No	241 (58.8%) 169 (41.2%)	1 [4.7] 1 [5.0]	*0.583*
Age≤15 years at anal sex debut	Yes No	88 (22.3%) 307 (77.7%)	2 [6.2] 1 [4.4]	*0.215*[b]
Age<13 years at anal sex debut	Yes No	22 (5.6%) 373 (94.4%)	2 [5.9] 1 [4.8]	*0.480*[b]
Any IPV victimization	No/missing Yes	226 (55.1%) 184 (44.9%)	1 [4.1] 1 [5.7]	*0.118*[b]
Any IPV victimization past year	No/missing Yes	346 (84.4%) 64 (15.6%)	1 [4.3] 3 [6.9]	*0.017*[b]
Any IPV perpetration	No/missing Yes	330 (80.5%) 80 (19.5%)	0 [4.3] 2 [6.4]	*0.014*[b]
Any IPV perpetration past year	No/missing Yes	378 (92.2%) 32 (7.8%)	1 [4.5] 4 [7.4]	*0.032*[b]
Any negative views about gay sexuality (marker of internalised homophobia)	No/missing Yes	239 (58.3%) 171 (41.7%)	0 [4.4] 1 [5.5]	*0.047*[b]
'Out' to all/almost all friends, work colleagues and close family	Yes No	206 (51.6%) 193 (48.4%)	1 [4.9] 1 [4.8]	*0.496*
'Out' to few/no friends, work colleagues and close family	Yes No	9 (2.3%) 390 (97.7%)	1 [6.4] 1 [4.8]	*0.971*[b]

[a] Two-sided p-value using two-sample t-test.
[b] Two-sample t-test with unequal variances.

[c] The choice of categories (<25; 25+) was driven by a previous examination of age in six categories (<25; 25-29; 30-34; 35-39; 40-44; 45+) in a one-way ANOVA, whereby it was clear that the mean change in depression score was different in the youngest age group. Due to the significant Bartlett's p-value, age was dichotomized was shown above and examined in a two-sample t-test with unequal variances.
[d] Twenty-five men were prescribed PrEP before the 12-month questionnaire.
[e] Due to a significant Bartlett's test p-value (indicating unequal variances) in a one-way ANOVA with change in depression score, this variable was dichotomized i.e. from UK born and ethnicity to UK born and from number of recreational drugs used to any drug use.

Table 80: Unadjusted associations of socio-demographic, lifestyle, and psychosocial factors with incidence of clinically significant depressive symptoms at the 12-month questionnaire in PROUD

N=372 men who scored <10 on the PHQ-9 at baseline			PHQ-9≥10 at month-12 [n=37; 10.0%]	
		N (%)	%	*p-value*[a]
Data collected at baseline:				
Age	<25 25-29 30-34 35-39 40-44 45+	21 (5.7%) 62 (16.7%) 74 (19.9%) 73 (19.6%) 59 (15.9%) 83 (22.3%)	4.8% 12.9% 12.2% 6.9% 1.7% 15.7%	*0.055*[c] 0.774[b]
Born in the UK and white ethnicity	Yes, white Yes, BAME No, white No, BAME	204 (55.1%) 18 (4.9%) 105 (28.4%) 43 (11.6%)	9.8% 22.2% 7.6% 11.6%	*0.286*[c]
Self-reported sexual identity	Gay Bisexual/straight	353 (95.9%) 15 (4.1%)	10.2% 6.7%	*0.543*[c]
University Education	Yes No/missing	232 (62.4%) 140 (37.6%)	9.1% 11.4%	*0.458*
Employed	Yes No/missing	308 (82.8%) 64 (17.2%)	9.7% 10.9%	*0.771*
Ongoing relationship	Yes No/missing	172 (46.2%) 200 (53.8%)	8.1% 11.5%	*0.280*
Study region	London Outside London	259 (69.6%) 113 (30.4%)	11.2% 7.1%	*0.222*
Higher-risk drinking	Yes No/missing	115 (30.9%) 257 (69.1%)	7.8% 10.9%	*0.361*
Recreational drug use (past 3 months)	0/missing 1 2-4 5+	95 (25.5%) 58 (15.6%) 119 (32.0%) 100 (26.9%)	13.7% 10.3% 5.9% 11.0%	*0.283* *0.338*[b]
Data collected on/before 12-month questionnaire:				
Randomized to study trial arm	Immediate arm Deferred arm	194 (52.2%) 178 (47.9%)	11.3% 8.4%	*0.348*
Prescribed PrEP before 12-month questionnaire completion[d]	Yes No	217 (58.3%) 155 (41.7%)	10.1% 9.7%	*0.884*
Age≤15 years at anal sex debut	Yes No	76 (21.2%) 282 (78.8%)	15.8% 8.5%	*0.061*
Age<13 years at anal sex debut	Yes No	20 (5.6%) 338 (94.4%)	10.0% 10.1%	*0.675*[c]
Any IPV victimization	No/missing Yes	212 (57.0%) 160 (43.0%)	5.7% 15.6%	*0.001*
Any IPV victimization past year	No/missing Yes	317 (85.2%) 55 (14.8%)	7.3% 25.5%	*<0.001*
Any IPV perpetration	No/missing Yes	305 (82.0%) 67 (18.0%)	7.2% 22.4%	*<0.001*
Any IPV perpetration past year	No/missing Yes	348 (93.6%) 24 (6.5%)	7.8% 41.7%	*<0.001*[c]
Any negative views about gay sexuality (marker of internalised homophobia)	No/missing Yes	226 (60.8%) 146 (39.3%)	7.1% 14.4%	*0.022*
'Out' to all/almost all friends, work colleagues and close family	Yes No	192 (53.0%) 170 (47.0%)	10.4% 10.0%	*0.896*
'Out' to few/no friends, work colleagues and close family	Yes No	8 (2.2%) 354 (97.8%)	12.5% 10.2%	*0.582*[c]

[a] Pearson χ^2 test
[b] Test for trend.
[c] Fisher's exact test.

[d] Twenty-five men were prescribed PrEP before the 12-month questionnaire.

11.19 Appendix 19: Patient and Public Involvement survey for PROUD participants

Textbox 7: Request for PROUD participants to comment on the prevalence and correlates of depression found during the study

To the participants of the PROUD study,

Our research group at UCL has been working with the PROUD team on a sub-study investigating depression among men who participated in PROUD. As part of this sub-study, we have found that the amount of men who reported symptoms of depression increased from 9% at the start of the PROUD study to 14% after about one year and remained the same at 14% after about two years. Men in the immediate PrEP group reported a similar amount of depression to men in the deferred PrEP group throughout the study. **We would like to ask you to help us understand why depression might have increased over the first year of the study among all men participating in PROUD.**

As part of this sub-study, we also investigated whether men with depression were more likely than men without depression to report a higher number of sexual partners, or sex without a condom. We found no link between depression and increased partner numbers or sex without a condom. We did find however, that men with depression were more likely to report PEP use in the past year than men without depression. **Again, we would like to ask you to help us interpret these findings.**

If you do have any comments on these findings then please click the link provided below to give your views.

https://www.surveymonkey.co.uk/r/XHTPTTV

Any thoughts you might have would be highly valued. We would appreciate any comments within the next month.

If you would like further information on this sub-study, please see the attached short report.

Textbox 8: Layout of survey monkey questions about the PROUD study findings

Depression increases after people join the PROUD study- what's happening?

Survey for PROUD participants about depression and the link between depression and sexual behaviour

1 **The amount of men reporting symptoms of depression increased from 9% at the start of the PROUD study to 14% after about one year and remained at 14% after about two years, men in the immediate PrEP group reported a similar amount of depression to men in the deferred PrEP group throughout the study. What do you think explains the increase in depression over the first year of the study among all men who participated in PROUD?**

2 **Throughout the PROUD study, men who were depressed did not report a higher number of sexual partners or more sex without a condom than men who were not depressed, what do you think explains this finding?**

3 **At the start of the PROUD study, men were asked about PEP use in the past year, and we found that men who were depressed reported more PEP use than men who were not depressed, what do you think explains this finding?**

11.20 Appendix 20: Prevalence of sexual behaviour measures in PROUD

Table 81: Proportion of missing values for sexual behaviour questions in PROUD

	Baseline [N=540]	12-month [N=410]	24-month [N=333]
	n (%) missing	n (%) missing	n (%) missing
'With how many different men have you been bottom (passive) during anal sex in the last 90 days?'	20 (3.7%)	6 (1.5%)	3 (0.9%)
'With how many were you bottom without using a condom?'[e]	5 (1.0%)[a]	1 (0.3%)[a]	0 (0.0%)[a]
'How many did you know were HIV-positive'[f]	19 (4.4%)[a]	8 (2.5)[a]	1 (0.4%)[a]
'How many did you know were on HIV treatment?'[g]	3 (1.5%)[a]	1 (0.6%)[a]	0 (0.0%)[a]
'With how many different men have you been top (active) during anal sex in the last 90 days?'	20 (3.7%)	12 (2.9%)	8 (2.4%)
'With how many were you top without using a condom?'[e]	3 (0.6%)[a]	3 (0.9%)[a]	1 (0.4%)[a]
'How many did you know were HIV-positive'[f]	22 (5.1%)[a]	10 (3.2%)[a]	2 (0.8%)[a]
'How many did you know were on HIV treatment?'[g]	0 (0.0%)[a]	1 (0.6%)[a]	0 (0.0%)[a]
'Of the men you've been either top or bottom with during anal sex in the last 90 days, how many were new partners?'	23 (4.3%)	6 (1.5%)	3 (0.9%)
'Think of the last time you had anal sex with a man without a condom. What was his HIV status?'	9 (1.7%)	11 (2.7%)	6 (1.8%)
Rectal Chlamydia diagnosis in the past year[b]	70 (13.0%)	/	/
Rectal gonorrhoea diagnosis in the past year[b]	62 (11.5%)	/	/
Syphilis diagnosis in the past year[b]	67 (12.4%)	/	/
LGV diagnosis in the past year[b]	82 (15.2%)	/	/
PEP use in the past year[b]	30 (5.6%)	/	/
Participated in group sex (sex with more than one other person on the same occasion)[c]	/	16 (3.9%)	14 (4.2%)

[a] The denominator is the number of men who responded to the previous question, providing a response greater than 0.
[b] Information on this measure was not collected at the 12- or 24-month questionnaire.
[c] Information on this measure was not collected at the baseline questionnaire.

11.21 Appendix 21: Relationship between other depressive symptom measures on PHQ-9 and sexual behaviour measures in the PROUD trial

Table 82: Unadjusted and adjusted associations of other depression measures with sexual behaviour measures in the past three months using baseline, 12- and 24-month questionnaire data among all 540 men who participated in PROUD

N=540 men (using data from baseline and follow-ups in GEE models) Dependent variables:	Major depressive syndrome on PHQ-9	Major & other depressive syndromes on PHQ-9	Suicidal ideation on PHQ-9
CLS with two or more partners			
PR [95% CI][c]	0.98 [0.77, 1.26]	1.00 [0.82, 1.23]	1.04 [0.86, 1.26]
p-value[a]	*0.896*	*0.999*	*0.691*
Adjusted PR[b] [95% CI][d]	0.99 [0.77, 1.26]	1.01 [0.82, 1.23]	1.04 [0.86, 1.26]
p-value[a]	*0.910*	*0.962*	*0.697*
CLS with five or more partners			
PR [95% CI][c]	1.04 [0.77, 1.42]	1.11 [0.86, 1.42]	1.10 [0.87, 1.40]
p-value[a]	*0.794*	*0.423*	*0.417*
Adjusted PR[b] [95% CI][d]	1.03 [0.76, 1.41]	1.10 [0.86, 1.41]	1.20 [0.86, 1.40]
p-value[a]	*0.831*	*0.445*	*0.444*
CLS with HIV+ partner not treated			
PR [95% CI][c]	0.54 [0.24, 1.22]	0.72 [0.40, 1.29]	0.87 [0.52, 1.47]
p-value[a]	*0.139*	*0.269*	*0.607*
Adjusted PR[b] [95% CI][d]	0.54 [0.24, 1.24]	0.72 [0.40, 1.30]	0.88 [0.52, 1.48]
p-value[a]	*0.145*	*0.275*	*0.619*
Receptive CLS with HIV+ partner not treated			
PR [95% CI][c]	0.67 [0.26, 1.75]	0.99 [0.50, 1.93]	0.93 [0.48, 1.79]
p-value[a]	*0.413*	*0.968*	*0.826*
Adjusted PR[b] [95% CI][d]	0.66 [0.25, 1.73]	0.98 [0.50, 1.94]	0.93 [0.48, 1.80]
p-value[a]	*0.394*	*0.965*	*0.825*
Unknown/HIV+ partner not treated at last CLS			
PR [95% CI][c]	1.35 [0.93, 1.97]	1.27 [0.92, 1.75]	1.12 [0.81, 1.56]
p-value[a]	*0.119*	*0.154*	*0.494*
Adjusted PR[b] [95% CI][d]	1.38 [0.94, 2.02]	1.29 [0.93, 1.78]	1.11 [0.80, 1.54]
p-value[a]	*0.096*	*0.131*	*0.524*
Ten or more new sex partners			
PR [95% CI][c]			
p-value[a]	0.99 [0.69, 1.43]	0.97 [0.72, 1.32]	1.04 [0.78, 1.39]
Adjusted PR[b] [95% CI][d]	*0.966*	*0.870*	*0.786*
p-value[a]	1.00 [0.69, 1.45]	0.99 [0.73, 1.34]	1.04 [0.78, 1.39]
	0.984	*0.935*	*0.785*
Receptive anal sex with ten or more partners			
PR [95% CI][c]	1.07 [0.75, 1.54]	1.18 [0.89, 1.58]	1.13 [0.85, 1.50]
p-value[a]	*0.699*	*0.256*	*0.413*
Adjusted PR[b] [95% CI[d]	1.08 [0.75, 1.56]	1.20 [0.90, 1.60]	1.13 [0.85, 1.50]
p-value[a]	*0.664*	*0.221*	*0.416*
Group sex			
PR [95% CI] [e]	0.97 [0.68, 1.38]	1.12 [0.84, 1.49]	1.04 [0.78, 1.40]
p-value[a]	*0.860*	*0.456*	*0.777*
Adjusted PR[b] [95% CI][e]	0.99 [0.69, 1.41]	1.13 [0.84, 1.52]	1.04 [0.77, 1.40]
p-value[a]	*0.935*	*0.413*	*0.812*

[a] p-value by Wald test using GEE models.

[b] Age (included as four categories: <25, 25-29, 30-39, 40), UK born (yes or no/missing), sexual identity (gay or bisexual/straight), university education (yes or no/missing), and London study clinic site (London or outside London).
[c] The number of men contributing observations to the unadjusted model was 540; The number of observations examined in the unadjusted model was 1283.
[d] The number of men contributing observations to the adjusted model was 536; The number of observations examined in the adjusted model was 1273.
[e] Men were asked whether they had engaged in group sex at the 12-month and 24-month follow-up questionnaires only. There were 104 men who did not fill out a questionnaire at either of these follow-up time-points, and therefore, 104 men for whom the question group sex had a missing value (since group sex was coded as yes; no or missing, everyone who filled out a questionnaire had a value). It is therefore of note, that the number of men contributing observations to the unadjusted model was 436; The number of observations examined in the unadjusted model was 743 and the number of men contributing observations to the adjusted model was 432; The number of observations examined in the adjusted model was 737.

11.22 Appendix 22: Relationship between socio-demographic and lifestyle factors with sexual behaviour measures at baseline of the PROUD trial

Table 83: Unadjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures in the past three months at baseline of PROUD

N=540 men at baseline									
		N (%)	CLS with 2+ partners [n=410;75.9%]	CLS with 5+ partners [n=221;40.9%]	CLS with HIV+ partner not treated [n=65;12.0%]	Receptive CLS with HIV+ partner not treated [n=35;6.5%]	Unknown/HIV+ partner not treated at last CLS [n=146;27.0%]	10+ new sex partners [n=200;37.0%]	Receptive anal sex with 10+ partners [n=175;32.4%]
			% *p-value*[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]
Age	<25	54 (10.0%)	77.8%	33.3%	11.1%	7.4%	22.2%	31.5%	31.5%
	25-29	96 (17.8%)	76.0%	41.7%	8.3%	5.2%	28.1%	44.8%	39.6%
	30-34	114 (21.1%)	74.6%	39.5%	13.2%	7.0%	26.3%	37.7%	30.7%
	35-39	97 (18.0%)	67.0%	35.1%	8.3%	6.2%	21.7%	34.0%	34.0%
	40-44	81 (15.0%)	76.5%	48.2%	13.6%	7.4%	25.9%	32.1%	28.4%
	45+	98 (18.2%)	84.7%	45.9%	17.4%	6.1%	35.7%	38.8%	29.6%
			0.127	*0.352*	*0.355*	*0.989*[c]	*0.312*	*0.471*	*0.624*
			0.315[b]	*0.125*[b]	*0.118*[b]	*0.967*[b]	*0.172*	*0.687*[b]	*0.274*
Born in the UK and white ethnicity	Yes, white	287 (53.4%)	78.1%	42.2%	12.2%	7.3%	25.1%	36.9%	35.2%
	Yes, BAME	35 (6.5%)	77.1%	37.1%	14.3%	5.7%	25.7%	34.3%	22.9%
	No, white	152 (28.3%)	71.1%	39.5%	14.5%	7.9%	29.6%	36.8%	34.2%
	No, BAME	64 (11.9%)	78.1%	42.2%	4.7%	0.0%	31.3%	39.1%	21.9%
			0.410	*0.906*	*0.192*[c]	*0.079*[c]	*0.645*	*0.973*	*0.115*
Self-reported sexual identity[j]	Gay	513 (95.7%)	75.4%	40.6%	12.3%	6.6%	26.5%	36.1%	32.8%
	Bisexual/ straight[g]	23 (4.3%)	87.0%	56.5%	8.7%	4.4%	39.1%	60.9%	30.4%
			0.206	*0.128*	*0.456*[c]	*0.548*[c]	*0.183*	*0.016*	*0.817*
University Education	Yes	327 (60.6%)	77.4%	42.2%	10.4%	6.1%	26.6%	39.1%	34.9%
	No/missing[a]	213 (39.4%)	73.7%	39.0%	14.6%	7.0%	27.7%	33.8%	28.6%
			0.331	*0.455*	*0.147*	*0.669*	*0.780*	*0.209*	*0.131*

Table 83: Unadjusted associations of socio-demographic and lifestyle factors with sexual behaviour measures in the past three months at baseline of PROUD (continued)

N=540 men at baseline									
		N (%)	CLS with 2+ partners [n=410;75.9%]	CLS with 5+ partners [n=221;40.9%]	CLS with HIV+ partner not treated [n=65;12.0%]	Receptive CLS with HIV+ partner not treated [n=35;6.5%]	Unknown/HIV+ partner not treated at last CLS [n=146;27.0%]	10+ new sex partners [n=200;37.0%]	Receptive anal sex with 10+ partners [n=175;32.4%]
			% *p-value*[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]	% p-value[a]
Employed	Yes No/missing[a]	439 (81.3%) 101 (18.7%)	75.6% 77.2% *0.734*	40.1% 44.6% *0.411*	12.1% 11.9% *0.957*	6.8% 5.0% *0.488*	27.6% 24.8% *0.566*	36.5% 39.6% *0.554*	32.6% 31.7% *0.863*
Ongoing relationship	Yes No/missing[a]	246 (45.6%) 294 (54.4%)	65.9% 84.4% *<0.001*	33.7% 46.9% *0.002*	12.2% 11.9% *0.918*	7.3% 5.8% *0.471*	24.8% 28.9% *0.284*	30.9% 42.2% *0.007*	30.1% 34.4% *0.291*
Study region	London Outside London	375 (69.4%) 165 (30.6%)	76.8% 73.9% *0.474*	42.1% 38.2% *0.390*	11.7% 12.7% *0.744*	6.9% 5.5% *0.520*	24.3% 33.3% *0.029*	38.4% 33.9% *0.323*	33.6% 29.7% *0.372*
Higher-risk drinking[g]	Yes No/missing[a]	173 (32.0%) 367 (68.0%)	79.2% 74.4% *0.223*	41.0% 40.9% *0.970*	13.3% 11.4% *0.537*	6.9% 6.3% *0.768*	26.6% 27.3% *0.872*	40.5% 35.4% *0.258*	37.0% 30.3% *0.118*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	148 (27.4%) 87 (16.1%) 159 (29.4%) 146 (27.0%)	67.6% 69.0% 74.8% 89.7% *<0.001* *<0.001*[b]	32.4% 31.0% 34.0% 63.0% *<0.001* *<0.001*[b]	10.8% 10.3% 10.1% 16.4% *0.269* *0.187*[b]	6.8% 4.6% 5.0% 8.9% *0.477* *0.510*[b]	27.0% 28.7% 31.5% 21.2% *0.242* *0.406*[b]	23.7% 24.1% 33.3% 62.3% *<0.001* *<0.001*[b]	18.9% 26.4% 27.0% 55.5% *<0.001* *<0.001*[b]
Chemsex-associated drug use	No Yes	309 (57.2%) 231 (42.8%)	69.9% 84.0% *<0.001*	32.0% 52.8% *<0.001*	11.3% 13.0% *0.557*	5.5% 7.8% *0.285*	28.5% 25.1% *0.383*	25.9% 52.0% *<0.001*	23.3% 44.6% *<0.001*

[a] Pearson χ^2 test
[b] χ^2 test for trend.
[c] Fisher's exact test.

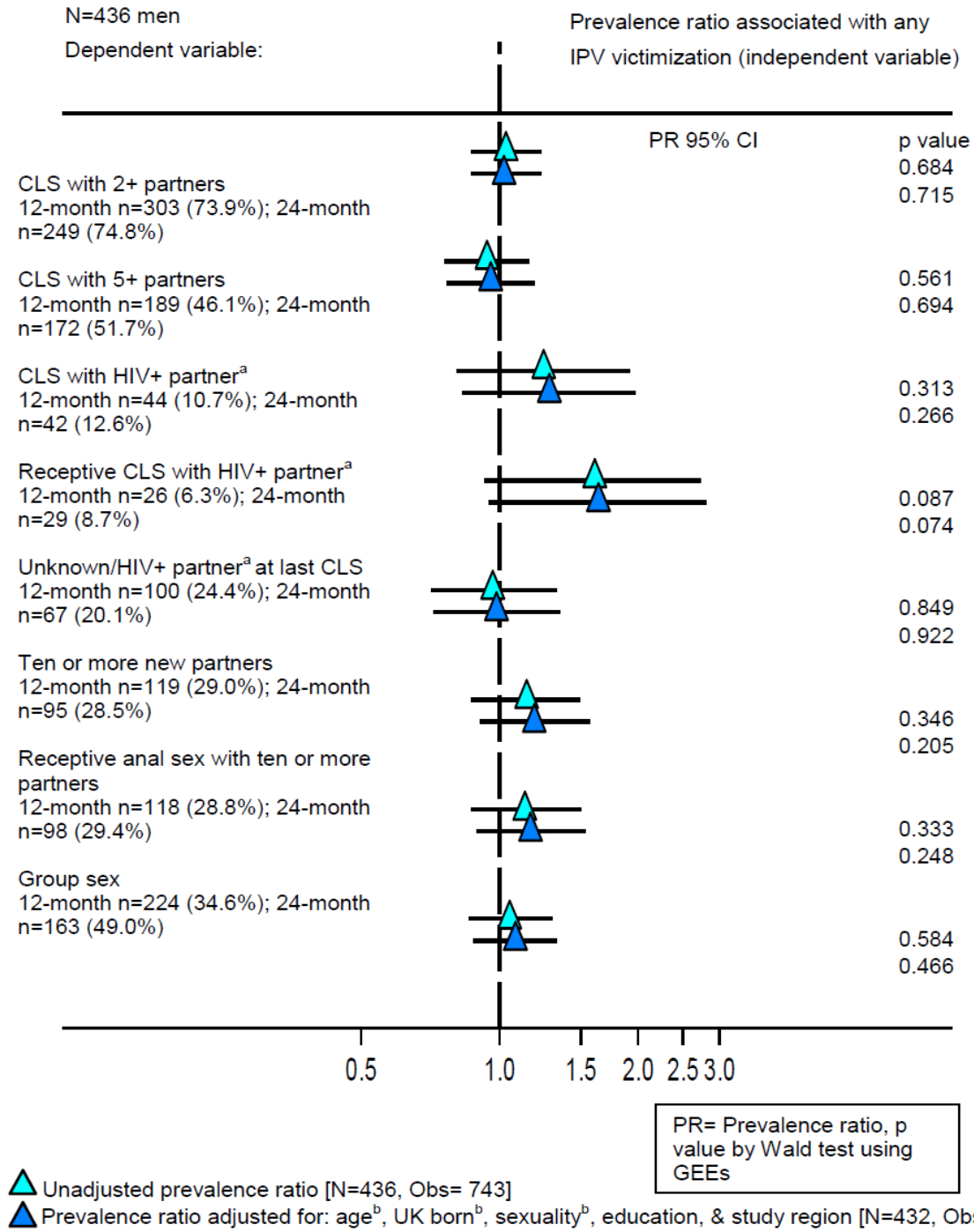
Table 84: Unadjusted associations of socio-demographic and lifestyle factors with PEP use and rectal STI diagnosis in the past year at baseline of PROUD

N=540 men at baseline				
		N (%)	PEP use [n=184;34.1%] % p-value[a]	Rectal STI diagnosis[c] [n=200;37.0%] % p-value[a]
Age	<25 25-29 30-34 35-39 40-44 45+	54 (10.0%) 96 (17.8%) 114 (21.1%) 97 (18.0%) 81 (15.0%) 98 (18.2%)	37.0% 37.5% 34.2% 39.2% 29.6% 27.6% *0.493* *0.114*[b]	35.2% 44.8% 38.6% 39.2% 38.3% 25.5% *0.131* *0.050*[b]
Born in the UK and white ethnicity	Yes, white Yes, BAME No, white No, BAME	287 (53.4%) 35 (6.5%) 152 (28.3%) 64 (11.9%)	31.7% 31.4% 35.5% 43.8% *0.305*	34.5% 37.1% 40.8% 37.5% *0.634*
Self-reported sexual identity[j]	Gay Bisexual/ straight[g]	513 (95.7%) 17 (3.2%) 6 (1.1%)	33.9% 39.1% *0.606*	37.4% 26.1% *0.270*
University Education	Yes No/missing[a]	327 (60.6%) 213 (39.4%)	35.8% 31.5% *0.300*	38.8% 34.3% *0.283*
Employed	Yes No/missing[a]	439 (81.3%) 101 (18.7%)	37.6% 33.3% *0.404*	37.1% 36.6% *0.926*
Ongoing relationship	Yes No/missing[a]	246 (45.6%) 294 (54.4%)	31.7% 36.1% *0.288*	32.5% 40.8% *0.047*
Study region	London Outside London	375 (69.4%) 165 (30.6%)	37.1% 27.3% *0.027*	39.2% 32.1% *0.117*
Higher-risk drinking[g]	Yes No/missing[a]	173 (32.0%) 367 (68.0%)	35.8% 33.2% *0.553*	37.6% 36.8% *0.860*
Recreational drug use (past 3 months)	0/missing[a] 1 2-4 5+	148 (27.4%) 87 (16.1%) 159 (29.4%) 146 (27.0%)	23.7% 25.3% 41.5% 41.8% *<0.001* *<0.001*[b]	27.7% 28.7% 37.7% 50.7% *<0.001* *<0.001*[b]
Chemsex-associated drug use	No Yes	309 (57.2%) 231 (42.8%)	25.2% 45.9% *<0.001*	28.8% 48.1% *<0.001*

[a] Pearson χ^2 test
[b] χ^2 test for trend.
[c] Rectal Chlamydia, rectal gonorrhoea, syphilis and/or LGV.

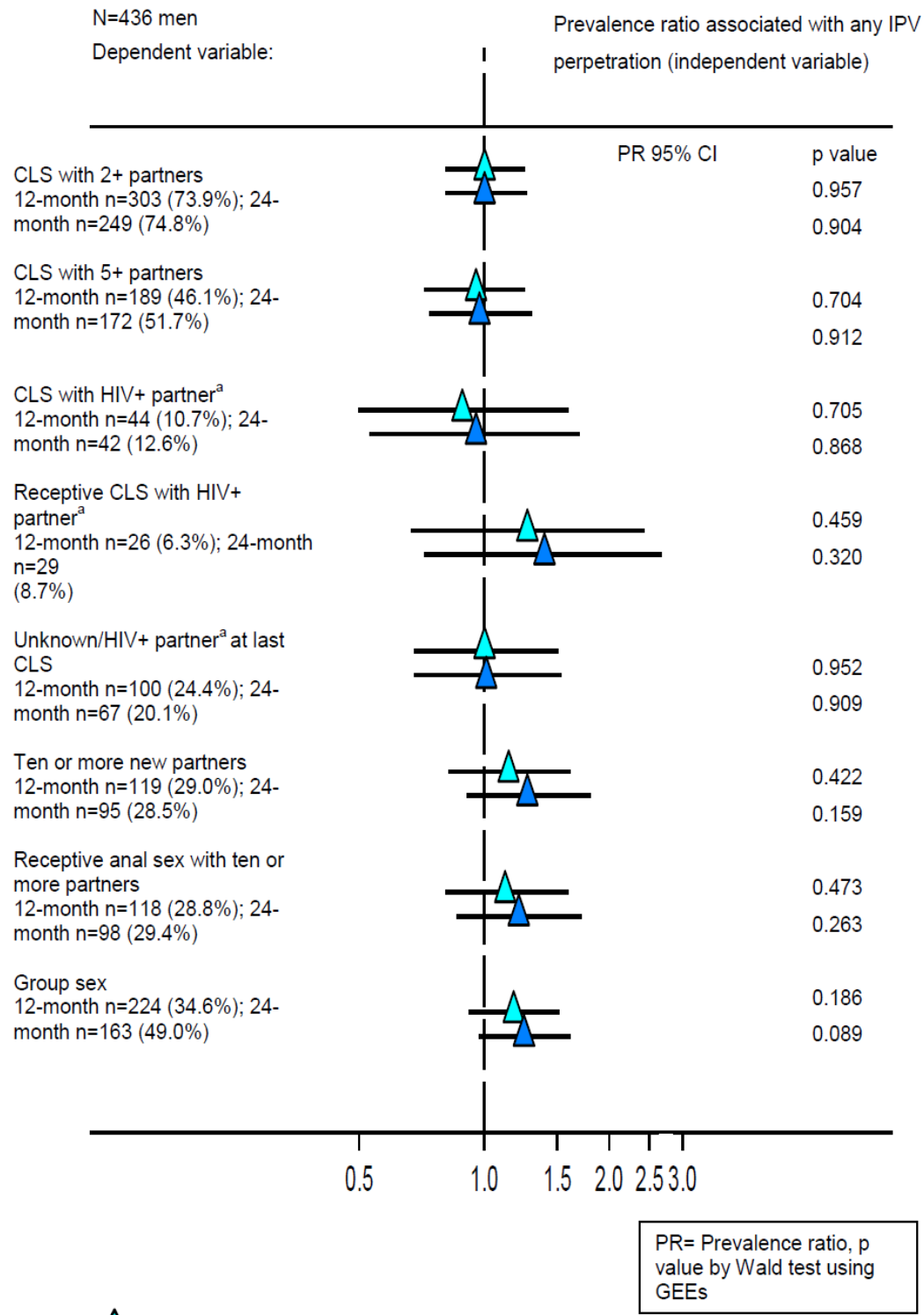
11.23 Appendix 23: Association between measures of IPV and sexual risk behaviour in the PROUD trial

Figure 35: Unadjusted and adjusted associations of any IPV victimization with sexual behaviours in the past three months among 436 men who participated in PROUD



[a] Not known to be on HIV treatment.
[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+), dichotomous UK born and self-reported sexual identity.

Figure 36: Unadjusted and adjusted associations of any IPV perpetration with sexual behaviours in the past three months among 436 men who participated in PROUD



[a] Not known to be on HIV treatment.
[b] The model was fitted to include age in four categories (<25; 25-29; 30-39; 40+), dichotomous UK born and self-reported sexual identity.