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Using Mendelian randomization to investigate causal relationships in evolutionary theories of development and behaviour

Using Mendelian randomization to investigate causal relationships in evolutionary theories of development and behaviour

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Abstract

There are multiple instances where standard methods in evolutionary approaches to studying human behaviour cannot easily test causality and/or examine the effects of psychological mechanisms on reproductive success. For example, research into life history theory, where manipulation of exposures is not typically possible, has previously been limited to standard analytical approaches that remain vulnerable to potential confounding bias. Additionally, although there has been a longstanding cliff-edge hypothesis for the maintenance of schizophrenia, investigation has been limited due to the constraints of family studies and the inability to manipulate the exposure or test long terms outcomes such as fitness.

Mendelian randomization combines genetic and phenotypic information to investigate psychological and key evolutionary traits with fitness outcomes using a causal framework that does not rely on manipulating the exposure. I applied Mendelian randomization and other related methods to these two areas of evolutionary human behaviour research. According to life history this theory, earlier age at menarche and age at first sexual intercourse can be viewed as directing effort towards reproductive goals as part of a fast life history strategy and therefore show causal effects on reproductive and behavioural outcomes. The schizophrenia paradox refers to the evolutionary conundrum for how schizophrenia, a heritable disorder, is maintained in the population despite being associated with lower reproductive success for those diagnosed.

I find some evidence that earlier age at menarche is causally related to traits that characterize a fast life history strategy, such as earlier age at first and last birth and lower educational attainment. Additionally, it appears that increased genetic liability for schizophrenia does not confer a fitness advantage and therefore the disorder is likely maintained through other explanations than cliff-edge effects. This thesis is novel in its application of epidemiological methods to test evolutionary theories of human behaviour and demonstrates the potential for evolutionary epidemiology.

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Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Publications

Lawn, RB, Lawlor, DA & Fraser, A, 2018, 'Associations between maternal pre-pregnancy body mass index and gestational weight gain and daughter's age at menarche'. *American Journal of Epidemiology*, 187: 4.

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Wootton, R, Lawn, R, Millard, L, Davies, N, Taylor, A, Munafò, M, Timpson, N, Davis, OS, Davey Smith, G & Haworth, C, 2018, 'Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: mendelian randomisation study'. *BMJ*, 362.

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Lawn, R, Sallis, H, Taylor, A, Wootton, R, Davey Smith, G, Davies, N, Hemani, G, Fraser, A, Penton-Voak, I & Munafò, M, 2019, 'Comment on the relationship between common variant schizophrenia liability and number of offspring in the UK Biobank'. *American Journal of Psychiatry*, 176: 7. (research letter with results)

Wootton, R, Richmond, R, Stuijfzand, B, Lawn, R, Sallis, H, Taylor, G, Jones, H, Zammit, S, Davey Smith, G & Munafò, M, 2018, 'Causal effects of lifetime smoking on risk for depression and schizophrenia: Evidence from a Mendelian randomisation study'. *Psychological Medicine*. E-pub ahead of print.

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List of Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
BMI	Body mass index
CI	Confidence interval
DNA	Deoxyribonucleic acid
EP	Evolutionary psychology
GWAS	Genome wide association study
HapMap	Haplotype map
HBE	Human behavioural ecology
HRC	Haplotype Reference Consortium
HWE	Hardy-Weinberg equilibrium
IBD	Identical by descent
InSIDE	Instrument strength independent of direct effect assumption
IVW	Inverse variance weighted
LD	Linkage disequilibrium
MAF	Minor allele frequency
MBE	Mode-based estimator
MBRN	Medical Birth Registry Norway
MoBa	Norwegian Mother, Father and Child Cohort Study
MR	Mendelian randomization
MRC IEU	Medical Research Council Integrative Epidemiology Unit
NOME	No Measurement Error
OR	Odds ratio
PCA	Principal component analysis
PGC	Psychiatric Genomics Consortium
PRS	Polygenic risk score
SE	Standard error
SD	Standard deviation
SIMEX	Simulation Extrapolation
SNP	Single nucleotide polymorphism
SSGAC	Social Science Genetics Association Consortium
ZEMPA	Zero Modal Pleiotropy Assumption

Chapter 1 Introduction

This chapter includes sections from the publications below

Lawn, R. B., Sallis, H. M., Wootton, R. E., Taylor, A. E., Demange, P., Fraser, A., Penton-Voak, I. S., & Munafò, M. R. (2019). The effects of age at menarche and first sexual intercourse on reproductive and behavioural outcomes: a Mendelian randomization study. bioRxiv; doi: https://doi.org/10.1101/423251.

Lawn, R. B., Sallis, H. M., Taylor, A. E., Wootton, R. E., Davey Smith, G., Davies, N. M., …Munafò, M. R. (2019). Schizophrenia risk and reproductive success: a Mendelian randomization study. *Royal Society Open Science*, *6*, 181049.

1.1 Thesis motivation and aim

There are multiple instances where standard methods in evolutionary approaches to studying human behaviour cannot easily test causality and/or examine the effects of psychological mechanisms on reproductive success. The ability to make stronger causal inference by using genetic variants as instrumental variables has resulted in the rapid uptake of this method, Mendelian randomization (MR), within epidemiology. For my doctoral work, I aimed to apply MR and other related methods to two areas of research – life history theory (concentrating on age at menarche and age at first sexual intercourse) and the schizophrenia paradox.

To my knowledge, my work here is the first to apply MR to these evolutionary questions. I was therefore highly motivated by the promise that this method holds to revolutionise evolutionary approaches and ultimately contribute to a better understanding of the causes and consequences of apparently maladaptive behaviour. I came to this PhD with an interest in evolutionary theory and approaches to behaviour, but with limited background in genetics or experience of statistical analysis and epidemiological methods for handling large, complex datasets. Due to this, I was grateful for the opportunity to conduct mini projects in the first year of this PhD programme and start the steep learning trajectory in order to gain these skills. I have since become very interested in the field of genetic epidemiology and hope to continue research in this area.

1.2 Evolutionary approaches to behaviour

Proposed in the mid-19th century, evolutionary theory describes the process of how traits change over time (Darwin, 1859). The main process described is natural selection, which

refers to individual differences in survival and reproduction due to differences in observable traits, termed phenotype (Darwin, 1859). Although natural selection acts on the phenotype, the genetic basis of these traits is passed on intergenerationally. The genetic basis of traits is termed the genotype, which increases or decreases in frequency over generations depending on the differential reproduction of individuals. Selection therefore gives rise to adaptive traits when a certain phenotype leads to a reproductive advantage and the genotype is therefore passed onto more offspring. Requirements for selection include variation between individuals, that this variation is heritable (a proportion is explained by genotype) and that it causes differential reproductive success (Darwin, 1859). Reproductive success is measured by how many of an individual's offspring also reproduce, although it is often proxied by the number of children that an individual has (Daly & Wilson, 1999). Fitness is a term also used to describe the number of children that an individual has.

Evolutionary theory can explain the existence of traits, both physical and behavioural, and has been successful in providing a framework for many areas of study, including mate choice, cooperation and individual differences (see Tooby & Cosmides, 1990, or Daly & Wilson, 1999). I focus on human traits in this thesis. There are two main evolutionary approaches to studying human behaviour: evolutionary psychology (EP) and human behavioural ecology (HBE). There is debate between these two approaches about how to define and measure adaptions, mainly due to each approach adopting a different level of explanation (Daly & Wilson, 1999). These levels of explanations were proposed by Tinbergen (1963) and provide distinct but complementary investigations of behaviour. According to Tinbergen (1963), for an integrative understanding of behaviour, investigations should include both 'proximate' and 'ultimate' (sometimes referred to as functional) levels of explanation. Proximate explanations incorporate how an individual's behaviour occurs, such as the psychological mechanisms that causes a behaviour within a specific immediate context (see section 1.2.2.1 for example). Ultimate explanations focus on why a trait has evolved, such as why a behaviour is adaptive and increases reproductive success (see section 1.2.1.1 for example). In order to have a complete understanding of behaviour, there should also be knowledge of ontogeny (proximate explanations over time) and phylogeny (ultimate explanations over time) of a behaviour rather than only investigation of individuals today (Tinbergen, 1963). See **Figure 1:1** for an illustrative summary.

I now discuss the EP and HBE approaches in turn, highlighting some limitations in their ability to test evolutionary hypotheses of human behaviour due to focusing on one level

of explanation and discussing whether the methods typically used in each approach allow for causal conclusions. I will then discuss the potential that MR may hold to overcome these limitations and provide a new form of evidence.

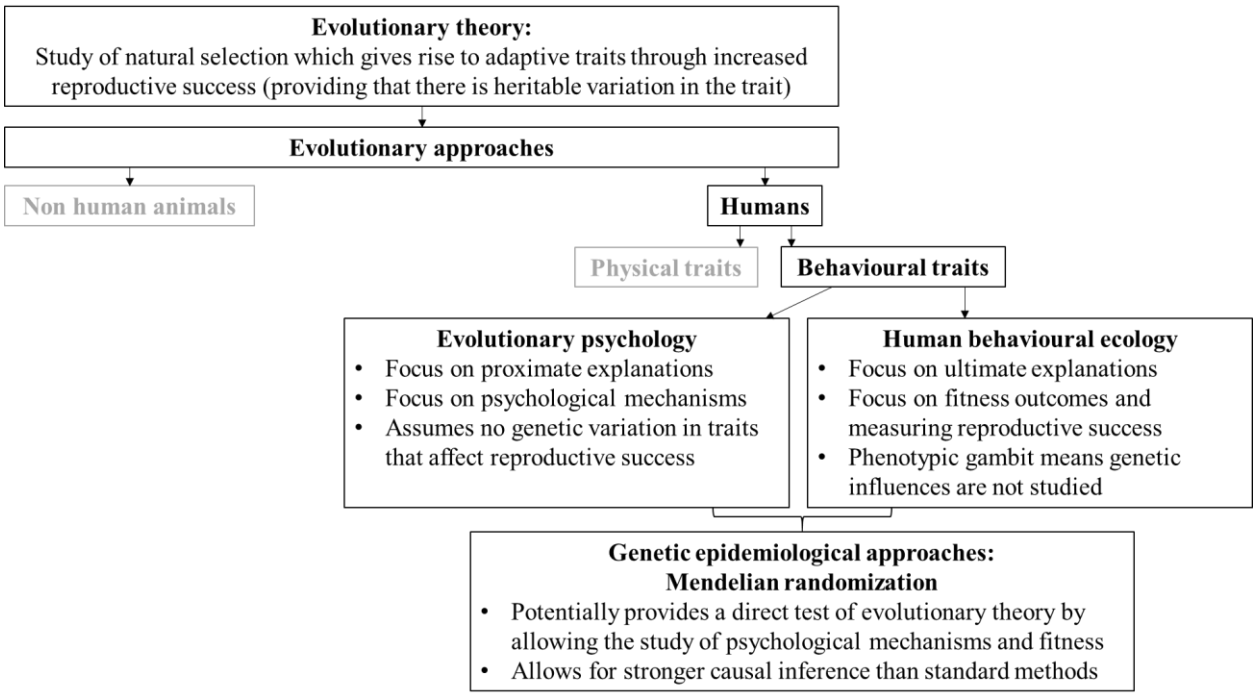

Figure 1:1 *Summary of introductory structure and thesis approach.*

1.2.1 Evolutionary psychology

The EP approach aims to investigate psychological mechanisms underlying human behaviour and their evolution (Ketelaar & Ellis, 2000). This approach assumes that the human brain is formed of specialized mechanisms to solve specific problems, particularly ones encountered in stable environments over the ancestral period (Tooby & Cosmides, 1990). These specialized mechanisms are thought of as evidence of 'good' design that we can examine today, where 'good' design would indicate selection for the trait through benefits to an individual's reproductive success and this successful design is therefore termed 'good' (Tooby & Cosmides, 1990). From this, EP focuses on whether psychological mechanisms demonstrate features expected of 'good' design to solve a past problem, arguing that such evidence is adequate for determining whether a trait is adaptive. By considering this evidence as adequate, the approach does not actually measure reproductive success and regards current fitness-associations as irrelevant to present design, with any environmental changes considered too recent for evolution (Symons, 1989; Tooby & Cosmides, 1990). Overall, EP is therefore mechanistic in that it

focuses on proximate explanations for behaviour although it assumes ultimate explanations led to the evolution of any given mechanism (Tinbergen, 1963).

1.2.1.1 Methodology

To investigate psychological mechanisms, EP relies on experiments and observational studies (particularly with self-report questionnaire data). For example, one area that has been widely investigated in EP is attractiveness, with many experimental studies on attractiveness evaluating whether mechanisms are in place to recognise facial cues as a signal of mate quality that could lead to increased reproductive success. One such study manipulated the exposure of male facial stimuli to be more masculine or feminine and assessed whether preferences change over the menstrual cycle to reflect a psychological mechanism designed to promote adaptive choices (Penton-Voak & Perrett, 2000). Again, whether these preferences actually result in increased reproductive success is not tested in EP investigations.

This narrow focus on mechanistic design characteristics as proxies for fitness is a limitation of the EP approach (Penton-Voak, 2011). Effects on reproductive success are required for selection to act and for a behaviour to be termed adaptive and the EP approach only assumes this. If attractiveness judgements are proposed as part of a suite of adaptive mechanistic behaviours that serve the ultimate goal of successful reproduction, possibly via health benefits, then it is important to actually empirically test the likelihood of a successful outcome (Penton-Voak, 2011). EP investigations do not therefore provide a direct test of selection.

A further limitation of EP methodology is the lack of ecological validity in experiments, where experiments do not approximate the real-world that is being examined and therefore the extent that findings can be generalized to a real-life setting is limited. For example, facial stimuli in attractiveness experiments are often manipulated composites of faces and may therefore not be generalizable to the mating decisions of real faces outside of experimental settings. On the other hand, this experimental methodology is also a strength of the EP approach as we can be more confident that a change in the outcome is due to the condition or exposure and assume exchangeability, meaning that the risk of an outcome in one group is the same as the risk in another group had they obtained the same value of the exposure (Hernán, 2004). Theoretically, we can never be completely certain about our causal conclusions as the counterfactual is, in reality, never observed (Hernán, 2004; Pingault et al., 2018); the counterfactual is the ‘other’ value of the exposure, that the individual does not experience (Hernán, 2004; Pingault et al., 2018). Randomization

allows for exchangeability by creating groups that are balanced for potential confounding factors (a common cause of the exposure and outcome that produces spurious associations) (Hernán, 2004). Due to this, randomized controlled experiments, as sometimes used in EP, are placed at the top of the evidence hierarchy for causal inference methodology (Davies, Holmes, & Davey Smith, 2018). Overall, it is therefore important to consider the ability of methods to provide causal evidence. Experiments, which are often used in EP, allow for causal inference but are limited in what exposures can be manipulated in an experimental setting and important evolutionary outcomes such as fitness cannot be measured. Therefore, although the experimental method tests causation, links between experimental evidence and evolution in this context are always indirect.

Another type of methodology used in EP is observational studies as there are circumstances where it is not possible to manipulate exposures for experimental designs (Rohrer, 2018). For example, standard analytical approaches applied to observational data have been used to examine life history theory in humans where it is not possible to manipulate developmental environments or reproductive behaviours (discussed further below) (Nettle, Frankenhuis, & Rickard, 2012; Richardson, Harrison, Hemani, & Davey Smith, 2018). These standard analytical approaches applied to observational data are likely to be affected by confounding bias, undermining causal inference (Webb, Bain, & Page, 2017). For this reason, these methods are placed lower down the hierarchy of causal inference ability (Webb et al., 2017). In traditional observational methods, attempts are made to adjust for confounders to try and achieve exchangeability (Webb et al., 2017). However, this requires adjustment of all confounders, which may or may not be measured (Webb et al., 2017). Furthermore, if a confounder is measured it is still possible that measurement error is present, leading to residual confounding (and even bias amplification) even if the variable is adjusted for in models, thus biasing causal estimates (Webb et al., 2017). In some instances, it is also possible that the outcome is in fact influencing the exposure, termed reverse causation (Webb et al., 2017). Reverse causation is difficult to address with cross-sectional data in which the temporal relationship between the exposure and outcome is less clear than in longitudinal studies (Webb et al., 2017). Overall, this means that EP hypotheses that cannot be tested in an experimental setting, and therefore use observational data instead, can be limited in the ability for causal conclusions.

1.2.1.2 Genetics

Some evolutionary psychologists argue that fitness-relevant traits will not show heritable variation due to the narrowing effect of selection which would remove all but the highest-

fitness genetic variant over time (Tooby & Cosmides, 1990). Therefore, any heritable variation indicates no selection acting and a lack of adaptive significance (Tooby & Cosmides, 1990). From this, EP regards genetic influences as redundant when studying behaviour and focus has been on similarities across humans rather than observed variation (Nettle, 2006; Tooby & Cosmides, 1990). If heritable individual variation is discussed, such as frequency dependent selection where optimum phenotypes depend on the proportion of that phenotype in a population, then this is given very low significance (Nettle, 2006). Conversely, others argue that more weight should be given to interindividual variation at the genotypic level in humans as this variation is frequently observed (see Nettle, 2006). Behaviour geneticists have shown that many important fitness traits are highly heritable, demonstrating that the population contains genetic variation. For example mental health disorders (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and personality (Nettle, 2006) are heritable traits that do show fitness-associations (Nettle, 2006; Nettle & Clegg, 2006).

This heritable variation can arise through multiple means, such as genetic mutations and cost-benefit trade-offs. For example, EP hypothesizes that facial symmetry is used as a cue for mate quality. Genetic mutations can cause heritable variation in symmetry and therefore have effects on attractiveness and subsequent fitness (Nettle, 2006). For personality traits investigated in EP, it is likely that heritable variation persists from trade-offs of the costs and benefits of behaviours in certain contexts where at any point in space and time there is an optimum value of the trait for fitness (Nettle, 2006). These costs and benefits therefore have effects on reproductive success, meaning fitness-relevant traits can show heritable variation as optimal values differ contextually (Nettle, 2006). If there is no cost then selection would act to narrow heritable variation (Nettle, 2006). In this thesis, I leverage this heritable variation of evolutionary relevant traits to investigate causal effects of age at menarche, age at first sexual intercourse, schizophrenia liability and educational attainment on fitness (and other behavioural) outcomes.

1.2.2 Human behavioural ecology

Behavioural ecology combines the study of animal behaviour with evolutionary theory to study the fitness consequences of a behaviour (Daly & Wilson, 1999; Winterhalder & Smith, 2000). When applied to the study of human behaviour, the field is termed HBE and was introduced in the mid-1970s (Daly & Wilson, 1999; Winterhalder & Smith, 2000). In this approach, complex decisions are broken down into a set of rules or conditions and individuals are construed as fitness-maximisers (Daly & Wilson, 1999; Tooby & Cosmides, 1990; Winterhalder & Smith, 2000). Through comparing the

reproductive success of individuals, this approach mainly provides ultimate level explanations for human behaviour (Tooby & Cosmides, 1990).

1.2.2.1 Methodology

HBE originated through applying models from behavioural ecology in the biological sciences to humans via the study of hunter-gatherer optimal foraging models for resources. These studies remain at the heart of the approach's methodology (Daly & Wilson, 1999; Winterhalder & Smith, 2000). Contemporary hunter-gatherer societies offer natural 'experimental' settings for research to investigate how humans have evolved (Mulder, 2006). As an example, Mulder (1990, 2006) investigated the fitness-maximizing decision making of marital choices among the Kipsigis people of Kenya when considering prospective husbands' resources (land ownership) and their number of existing wives. It was found that although women prefer bachelors over polygynists, they appear to incorporate a potential husbands' resources to provide for multiple wives which impacts reproductive success (Mulder, 1990, 2006). Again, for an integrative understanding of behaviour, investigations should include both proximate and ultimate levels of explanation. As these studies only examine differential reproduction today, they therefore provide ultimate level explanations (Mulder, 2006). The proximate mechanisms underlying how humans reach such an adaptive strategy is often disregarded in HBE (Mulder, 2006).

Through studying individuals in society via natural experiments, the HBE approach uses ecologically valid methods. However, by doing so, experimental control is sacrificed and confidence in identifying a true causal effect may be diminished compared to a randomized experiment. As discussed above, without randomization and manipulation of exposures it is difficult to conclude that confounding factors are not causing spurious results.

The focus on ultimate explanations, rather than also incorporating possible mechanisms for an integrative understanding of behaviour (discussed in section 1.2), and the lack of ability for causal inference are limitations of the HBE approach that I have attempted to address in this thesis (Mulder, 1990, 2006).

1.2.2.2 Genetics

Evolutionary theory centres around genetic processes yet rarely is genetic data used to inform the research (Hadfield, Nutall, Osorio, & Owens, 2007). This applies to the HBE approach whereby focusing on measurable fitness-maximizing behaviours, and not their

underlying mechanisms, genetic influences are ignored (Hadfield et al., 2007; Rubin, 2016). The HBE approach does not consider this a limitation in determining the evolutionary dynamics of a population (Hadfield et al., 2007; Rubin, 2016). This focus on the fitness of phenotypes is termed the phenotypic gambit under the assumption that phenotypic patterns can be used as predictors of genetic patterns (Hadfield et al., 2007; Rubin, 2016). Although the phenotypic gambit does simplify investigations, as behaviours are regulated by numerous genes as well as environmental factors and their interactions, this deterministic view can lead to false predictions of evolutionary hypotheses for human behaviour (Hadfield et al., 2007; Rubin, 2016). Recently, there has been increasing recognition that many traits relevant to HBE show polygenic inheritance that can be exploited in quantitative genetic methodology to overcome the phenotypic gambit and allow for causal conclusions of evidence (Hadfield et al., 2007; Rittschof & Robinson, 2014).

1.3 Mendelian randomization

Epidemiology is the study of the aetiology, distribution, and control of disease. Instrumental variable analysis is a method developed in economics and used within epidemiology. An instrument is a variable that robustly predicts the exposure of interest and shows no independent association with the outcome that does not act via the exposure (Lousdal, 2018). Recently, with the availability of genetic data, genetic variants are increasingly used as instruments in epidemiology to estimate causal effects of a phenotype of interest on an outcome, termed Mendelian randomization (Davies, Holmes, et al., 2018; Kaprio, 2000). The underlying principle of MR is that alleles should be randomly distributed within a population and if an allele is also associated with a trait of interest then we can look for outcomes that covary with the presence or absence of that allele (Conley, 2009). Therefore, by using genetic variants as instruments, MR can mimic a randomized experiment and allow for stronger causal inference than standard analytical methods by exploiting genetic information to attain reasonable approximation of the counterfactual scenario and estimate causal effects (Pingault et al., 2018) (Davey Smith & Ebrahim, 2003). It can be therefore be helpful to think of MR as ‘nature’s randomized controlled experiment’ in which participants are allocated to different exposure levels due to their genetic liability, randomized at conception.

Genetic variants in MR can be used to instrument or proxy environmental, molecular or physiological traits that are affected by the genetic variant (Hemani, Zheng, et al., 2018). MR was developed by epidemiologists to strengthen causal inference for risks of disease

(Davey Smith & Ebrahim, 2003). Early applications therefore focused on health traits, such as C-reactive protein, however the method has more recently been used to investigate some psychological traits and/or reproductive behaviours as both exposures and outcomes (Day, Helgason, et al., 2016; Gage, Davey Smith, Ware, Flint, & Munafò, 2016; Gage et al., 2017; Taylor et al., 2016; Wootton, Lawn, et al., 2018). Incorporating genetic factors into methodology through MR can also overcome some of the limitations discussed above for evolutionary approaches to human behaviour; as MR allows investigation of both psychological phenomena (proximate explanations) and fitness outcomes (ultimate explanations) it therefore potentially provides a direct test of evolutionary hypothesis by empirically testing the likelihood of increasing reproductive success for any given mechanism or trait. In this way, MR can help to integrate EP and HBE approaches and their levels of explanation for more satisfactory evolutionary accounts of behaviour and provide a new form of evidence (Tinbergen, 1963). Attempts to reconcile these approaches have been done previously (see Smith, 2000, for review) and there has been a growth of interest in providing ultimate explanations alongside proximate mechanisms in recent years (Nettle, 2006). I therefore propose that MR should be employed within evolutionary approaches to studying human behaviour with its potential to revolutionise the field. Additionally, MR overcomes issues of confounding and reverse causation in non-experimental designs to provide stronger causal inference than standard analytical approaches using observational data. A more detailed discussion of MR methods is provided in Chapter 2.

1.3.1 Applying Mendelian randomization

In this thesis, I used MR to investigate two areas of evolutionary theory relevant to human behaviour – life history theory and the schizophrenia paradox.

1.3.1.1 Life history theory

Life history theory addresses how organisms differ in allocation of limited resources to growth and reproductive efforts, characterizing species into those on ‘fast’ or ‘slow’ life history strategies (Ellis, 2004; Ellis & Bjorklund, 2012). A ‘fast’ life history strategy is characterised by more effort directed towards reproduction such as earlier puberty and sexual activity, whereas a ‘slow’ life history strategy can be described by later maturity and proportionally greater investment in a smaller number of children (Ellis, 2004; Ellis & Bjorklund, 2012). For example, rabbits undergo rapid sexual development, short interbirth intervals and various other traits demonstrating short-term goals that characterize a fast life history strategy (Figueredo et al., 2005). Conversely, elephants show delayed sexual development and long interbirth intervals and are considered to be

on a slow life history strategy (Figueredo et al., 2005). The shorter life expectancy of rabbits than elephants increases the adaptive benefits of taking a fast life history strategy (Figueredo et al., 2005). Furthermore, within-species variation in life history strategy has been proposed. For example, in developmental environments characterized by harsh conditions and high extrinsic mortality, adopting a fast life history strategy may increase reproductive success in comparison to a slower strategy with delayed reproduction (Belsky, Steinberg, & Draper, 1991; Ellis, 2004; Ellis & Bjorklund, 2012; Figueredo et al., 2005).

For humans, life history theory has been applied to characterize individuals into those on relatively faster or slower strategies (Figueredo et al., 2005), with substantial variation between humans in the timing of significant reproductive life events such as age at menarche (the start of a woman's sexual maturity and reproductive potential) and first sexual intercourse (Belsky et al., 1991; James, Ellis, Schlomer, & Garber, 2012). Life history theory explains this variation as an adaptive response to an individual's developmental environment and adverse childhood experiences have been shown to associate with earlier age at menarche (Magnus et al., 2018). Adverse childhood environments are also associated with earlier age at first sexual intercourse (Lenciauskiene & Zaborskis, 2008; Richardson et al., 2018; Waldron et al., 2015). Life history strategies consist of a suite of adaptations and whilst adopting a fast life history strategy evolved due to reproductive advantages in certain conditions, it may also have costs to an individual in modern environments. Such costs include those associated with teenage pregnancy and risky behaviours like violence, criminality, and substance abuse (Ellis & Bjorklund, 2012; Hawes, Wellings, & Stephenson, 2010; Simpson, Griskevicius, Kuo, Sung, & Collins, 2012). Therefore, as well as previous research into the causes of earlier age at menarche and sexual intercourse (Lenciauskiene & Zaborskis, 2008; Magnus et al., 2018; Richardson et al., 2018; Waldron et al., 2015), it is also important to examine how traits within life history strategies affect each other, especially as starting menarche is necessary for reproduction and age at first sexual intercourse may be modifiable via policy and environmental changes. Previous research has framed later traits such as age at first birth within a life history perspective (Nettle, 2011). I address this in the present study by examining the effects of two reproductive traits (age at menarche and age at first sexual intercourse) on other reproductive and behavioural outcomes including age at first birth, age at last birth and educational attainment. By looking at these traits that occur later in life, and assuming age at menarche can somewhat proxy early life adversity and a fast life history strategy, I take a life course approach to examine causal pathways in life history theory.

Standard analytical approaches applied to observational data have been used to examine life history strategies in humans as it is not possible to manipulate developmental environments in experimental settings (Nettle et al., 2012; Richardson et al., 2018). However, as discussed above, inferring causality in studies using such approaches is difficult and likely to be affected by confounding bias (Davey Smith & Ebrahim, 2003). For example, structural equation modelling has been proposed to investigate life history theory. One study investigated lifetime allocation of resources to reproduction, proxied by number of offspring that survived to 18 years, mean inter-birth interval and age at last birth (Helle, 2018). Although the author stresses the benefits that an SEM framework provides in handling measurement error of exposure variables, the potential for confounding is always a concern as these methods allow for the control of measured but not for unmeasured confounders (Helle, 2018; Warrington, Freathy, Neale, & Evans, 2018). Even though it is difficult to manipulate reproductive timings, particularly age at menarche but also age at first sexual intercourse (Helle, 2018), we can apply MR to investigate causal relationships between these traits and outcomes of interest. Although MR has been used to previously investigate age at menarche with many later life health outcomes (e.g., Sequeira, Lewis, Bonilla, Davey Smith, & Joinson, 2017), the study here will provide stronger causal inference for age at menarche and evolutionarily relevant outcomes.

1.3.1.2 The schizophrenia paradox

Schizophrenia is a severe and debilitating mental disorder that is substantially heritable (Van Dongen & Boomsma, 2013). The prevalence of schizophrenia remains stable over populations and time, and yet is associated with lower reproductive success for those diagnosed (Bundy, Stahl, & MacCabe, 2011; Essen-Möller, 1959; Jablensky et al., 1992; Nettle & Clegg, 2006; Van Dongen & Boomsma, 2013). This creates an evolutionary puzzle: how is schizophrenia maintained in the population despite apparent negative selection? Multiple theories have been proposed to explain this paradox (Essen-Möller, 1959; Huxley, Mayr, Osmond, & Hoffer, 1964; Power et al., 2013; Shaner, Miller, & Mintz, 2004). One is mutation-selection balance, which suggests that selection against detrimental genetic variants is counteracted by the continuous occurrence of new mutations (Mullins et al., 2017; Rees, Moskvina, Owen, O'Donovan, & Kirov, 2011). Another is that effects over many common genetic variants are individually too weak to be under negative selection (Loh et al., 2015; Mullins et al., 2017; Van Dongen & Boomsma, 2013).

Another popular theory is that stabilizing selection operates. Stabilizing selection is where the optimum fitness level for a trait is approximately at the mean of the trait and fitness declines along a normal distribution on either side of this optimum (Essen-Möller, 1959; Huxley et al., 1964; Lewis, 1958; Nesse, 2004). Within this, 'cliff-edge' effects on fitness hypothesize that fitness increases with increased expression of the trait until a threshold, where increased expression then results in a steep decline in fitness for some individuals (Nesse, 2004; Van Dongen & Boomsma, 2013). It has been suggested that schizophrenia-related traits may demonstrate 'cliff-edge' effects on fitness (Nesse, 2004; Nettle, 2001; Shaner et al., 2004; Van Dongen & Boomsma, 2013). Some have suggested that this peak occurs at levels of symptoms that could result in a diagnosis of schizophrenia, with a reproductive advantage among healthy individuals with an increased liability for the disorder (such as genetic liability and in the absence of the disorder itself) compensating for the lower reproductive success of those with the disorder itself (Keller & Miller, 2006; Nesse, 2004; Nettle & Clegg, 2006; Van Dongen & Boomsma, 2013). It is suggested that this reproductive advantage is maintained by sexual selection and mediated via creativity and/or risky behaviour (Del Giudice, Angeleri, Brizio, & Elena, 2010; Nettle, 2006; Nettle & Clegg, 2006; Shaner et al., 2004; Wang et al., 2016). Behaviourally, it is possible that higher genetic liability for schizophrenia may be associated with attractive traits (e.g., creativity) and therefore also with a greater number of children (Del Giudice et al., 2010; Nettle & Clegg, 2006). For example, schizotypy, a personality measure of schizophrenia-proneness, has been shown to be associated with creativity, short term mating interest and mating success (Crow, 2008; Del Giudice et al., 2010; Nettle & Clegg, 2006). Additionally, genetic liability for schizophrenia is associated with increased risk of unprotected sex (Wang et al., 2016).

Relatives of people with schizophrenia are assumed to have an intermediate level of genetic liability for the highly heritable disorder (Del Giudice, 2010). Studies into whether cliff-edge fitness maintains the prevalence of schizophrenia have therefore largely focused on family studies. However, despite extensive research, there is no clear evidence of increased fecundity in relatives of individuals with schizophrenia (Bundy et al., 2011; Del Giudice, 2010; Power et al., 2013). Del Giudice argued that family studies underestimate the reproductive benefits of schizophrenia-proneness in the general population (Del Giudice, 2010). He highlights that relatives not only share genetic liability for schizophrenia but also their environments, which may hinder fitness and result in apparent negative selection (Del Giudice, 2010). These family studies also suggest that optimum fitness could occur before the appearance of symptoms that might result in a diagnosis of schizophrenia and there therefore may be a peak in fitness even

within a non-case sample. It is therefore important to investigate a potential reproductive advantage of schizophrenia-proneness in the wider population, rather than relying on family studies alone. Moreover, it is important to investigate causal relationships between schizophrenia risk and reproductive success, rather than relying on observational methods.

The recent developments in genetic epidemiology, discussed throughout this thesis, mean that it is now possible to investigate the fitness effects of genetic liability for schizophrenia in the wider population. Genetic variants associated with schizophrenia have been used to show that genetic liability for schizophrenia (using a score comprising of these individual genetic variants) is positively associated with creativity and risk-taking (Power et al., 2015; Richardson et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Evidence for associations between genetic liability for schizophrenia and age at first birth is mixed. Higher genetic liability for schizophrenia was found for those with a young age at first birth (e.g., below 20 years) compared to those with an intermediate age at first birth (Mehta et al., 2016; Ni, Gratten, Wray, Lee, & Science, 2017). Another study found no clear evidence for linear or quadratic associations between a genetic liability for schizophrenia and age at first birth (Mullins et al., 2017). Two previous studies also used schizophrenia-associated genetic variants to investigate whether genetic liability for schizophrenia is associated with number of children but results were again inconclusive, perhaps due to limited power (Beauchamp, 2016; Mullins et al., 2017). The studies showed estimates in the direction of a reproductive advantage but confidence intervals were typically wide and consistent with no effect (Beauchamp, 2016; Mullins et al., 2017). Nevertheless, these studies demonstrate how genetic liability for schizophrenia can be measured in the wider population.

In this thesis (Chapter 5), I applied a range of methods with roots in genetic epidemiology to test part of the cliff-edge hypothesis. I examined whether increasing genetic liability for schizophrenia increases reproductive success in multiple population-based samples which are not selected on schizophrenia status and therefore include very few cases. This linear increase is predicted for part of cliff-edge fitness where a reproductive advantage among healthy individuals with higher genetic liability for the disorder compensates for lower reproductive success of those with the disorder itself.

1.4 Chapter summary

This thesis is novel in its application of epidemiological methods to test evolutionary hypotheses of human behaviour. These methods, such as MR, combine genetic and phenotypic information to investigate psychological and key evolutionary traits with fitness outcomes using a causal framework. I applied such methods to understand the causal relationships in evolutionary theories of life history and the maintenance of schizophrenia in the population. Research into life history theory, where manipulation of exposures is not typically possible, has previously been limited to standard analytical approaches that include possible confounding bias. Although there has been a longstanding cliff-edge hypothesis for the maintenance of schizophrenia, investigation has been limited due to the constraints of family studies and the inability to manipulate the exposure or test long terms outcomes such as fitness. The genetic methodologies applied begin with a MR study testing the life history theory. According to this theory, earlier age at menarche and age at first sexual intercourse can be viewed as directing effort towards reproductive goals as part of a fast life history strategy and therefore show causal effects on reproductive and behavioural outcomes (Chapter 4). In Chapter 5 I use MR, Linkage disequilibrium (LD) score regression and polygenic risk score (PRS) analysis to investigate the schizophrenia paradox (Chapter 5). I discuss these methods in full in the following chapter.

Chapter 2 Genetic epidemiological methods

This chapter includes sections from the publication below

Lawn, R. B., Sallis, H. M., Wootton, R. E., Taylor, A. E., Demange, P., Fraser, A., Penton-Voak, I. S., & Munafò, M. R. (2019). The effects of age at menarche and first sexual intercourse on reproductive and behavioural outcomes: a Mendelian randomization study. *bioRxiv*; doi: https://doi.org/10.1101/423251

Table 2:1 *is adapted from the publication below*

Wootton, R. E., Richmond, R. C., Stuijfzand, B. G., **Lawn, R. B.**, Sallis, H. M., Taylor, G. M. J., Jones, H. J., Zammit, S., Davey Smith, G., & Munafò, M. R. (2018). Causal effects of lifetime smoking on risk for depression and schizophrenia: Evidence from a Mendelian randomisation study. *Psychological Medicine*. E-pub ahead of print.

2.1 Chapter overview

As discussed in Chapter 1, this thesis addresses evolutionary questions using MR methods. In this chapter, I first provide a brief overview of MR. I then describe the assumptions, instruments and various 'methods' of MR in detail. Although I use the term 'methods' as is usual in the field, these are simply variants of MR. Here, I have attempted to amalgamate the theoretical concept of MR with some practical details for carrying out analysis. For a full theoretical review see Davey Smith and Ebrahim (2003), for more of a practical guide see Davies et al. (2018) and for a full glossary of MR see Lawlor et al. (2019). Lastly, I briefly discuss other genetic epidemiology methods used in my research, such as LD score regression and PRS analyses.

2.2 Mendelian randomization

As discussed in Chapter 1, MR employs an instrumental variable analysis framework, with the instrument specifically being genetic variants known as single nucleotide polymorphisms (SNPs) (Davey Smith & Ebrahim, 2003). MR can be employed using any heritable exposure, assuming a SNP produces an outcome that could equally be produced by an environmental exposure (Gage, Davey Smith, et al., 2016; Hemani, Zheng, et al., 2018). For a graphical illustration of MR see **Figure 2:1**. Here, Z denotes the genetic instrument, X the exposure of interest and Y the outcome. I further use 'SNP-exposure' to signify the Z-X relationship and 'SNP-outcome' to indicate the Z-Y relationship.

To illustrate an analysis, one example of using MR to overcome biases when manipulation of the exposure is not practical is the study of alcohol consumption effects on blood pressure and, ultimately, cardiovascular disease (previously described in Davey Smith & Ebrahim, 2003 and Davies et al., 2018). Individuals who consume more alcohol may differ from individuals who consume less alcohol for other cardiovascular risk factors, such as by smoking more heavily. This could therefore introduce spurious associations due to bias from confounding by smoking heaviness. Using SNPs associated with metabolite responses to alcohol consumption as an instrument for alcohol intake is akin to randomizing individuals into higher or lower drinking conditions and MR can therefore be used to estimate a causal effect of alcohol consumption (Davey Smith, 2006; Lawlor, 2016) (see **Figure 2:2**). This causal effect is obtained through calculating a Wald ratio where the SNP-outcome estimate is divided by SNP-exposure estimate ($\frac{ZY}{ZX}$) and forms the basis for all MR methods discussed below.

For all MR methods in this thesis, the SNP-exposure and SNP-outcome associations should ideally be derived in distinct non-overlapping samples of participants and can be taken from genome-wide association studies (GWAS) estimates, termed GWAS summary level data, or derived from individual level cohort data (see Chapter 3) (Lawlor, 2016). Estimates from SNP-phenotype regressions are then considered SNP-level, rather than individual-level, and can also be termed 'summary data'. It is preferable for the SNP-exposure and SNP-outcome GWAS to be adjusted for the same standard covariates to minimize bias (Davies, Holmes, et al., 2018). Although I do not use the term here, MR with non-overlapping samples has often been called 'two sample MR' or 'two sample summary data MR'. Using overlapping samples in the MR methods that I use can produce bias towards the observational association estimate, which may be biased by confounding (Davies, Holmes, et al., 2018; Hemani, Bowden, & Davey Smith, 2018). However, the SNP-exposure and SNP-outcome samples should come from the same underlying population (Lawlor, 2016). An additional benefit to using non-overlapping samples, is it allows the investigation of relationships where the exposures and outcomes of interest have not been measured in the same sample (Gage, Jones, et al., 2016). In using non-overlapping samples, data should be harmonized to ensure that the SNP-exposure and SNP-outcome estimates correspond to the same allele with particular attention required for palindromic SNPs. Palindromic SNPs contain alleles represented by the same pair of letters on both the forward and reverse DNA strands, therefore causing ambiguity when aligning SNPs across samples.

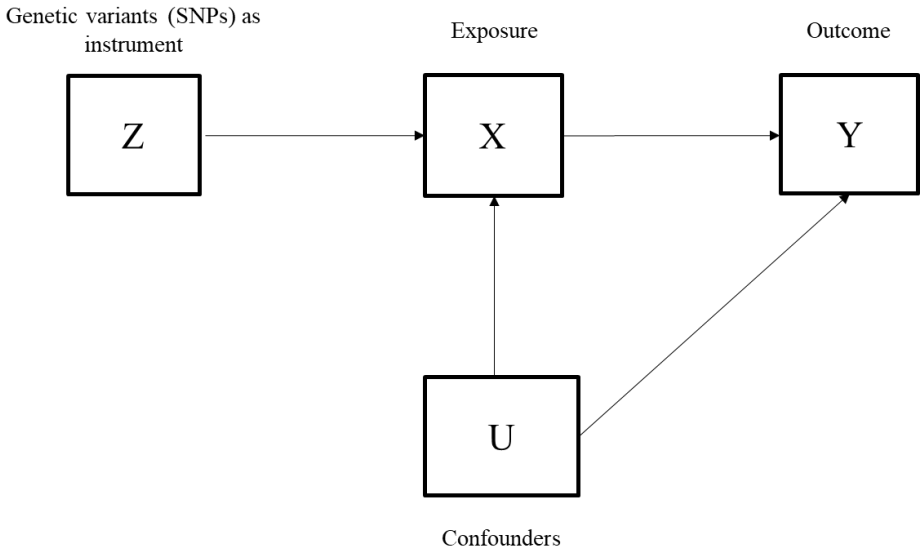

Figure 2:1 *Diagram representing a valid MR analysis based on an instrumental variable framework.*

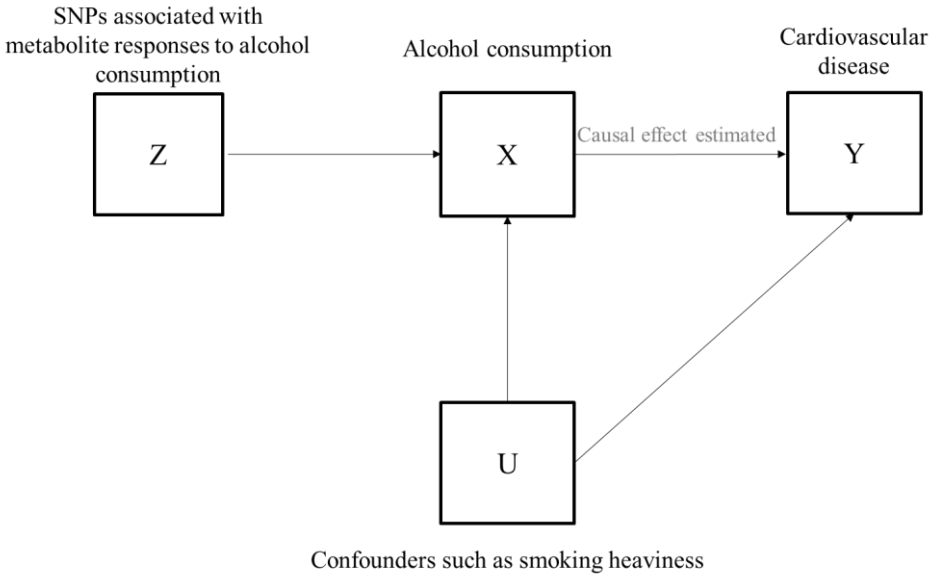

Figure 2:2 *Diagram representing a valid MR analysis for the above example investigating the effect of alcohol consumption on cardiovascular disease.*

2.2.1 Assumptions of Mendelian randomization

MR analysis relies on three main assumptions (Lawlor, Harbord, Sterne, Timpson, & Davey Smith, 2008). See **Figure 2:1** for a diagram illustrating a valid MR analysis in terms of these 3 assumptions. Assumption 1 is signified by the arrow between Z and X. Assumptions 2 and 3 are represented by the absence of arrows. Here, U denotes the combined influence of unmeasured confounders. If measured covariates are included then the assumptions are conditional on these (Bowden et al., 2017; Palmer et al., 2011).

2.2.1.1 Assumption 1: The relevance assumption: the instrument is robustly associated with the exposure used in analysis

In line with this assumption, SNPs used as instrumental variables in MR are identified in GWAS to be significantly and independently associated with the exposure at a *p*-value less than 5×10^{-8} and must be found to replicate in an independent sample (or at least explain a significant proportion of the variance in an independent sample). This is discussed further in the section on instruments below.

2.2.1.2 Assumption 2: The independence assumption: the instrument is not associated with confounding factors

By using SNPs as instruments, MR exploits Mendel's laws of segregation and independent assortment by which the inheritance of genetic variants is determined mostly independently of other genetic variants and the environment through random allocation at conception (Davey Smith & Ebrahim, 2003). This independence has been demonstrated through pairwise correlations between nongenetic variables and genetic variables, with genetic variants showing little association with each other and non-genetic confounders (Davey Smith et al., 2007). This highlights the advantages of using genetic variants as proxies of environmental exposure levels to overcome bias due to confounding, to which non-genetic observational studies are prone (Davey Smith et al., 2007). However it should be noted that this assumption can be affected by ancestry (Davies, Holmes, et al., 2018) and is more likely to be violated when traits are highly polygenic, as complex polygenic traits can be instrumented by many SNPs which may also associate with other traits (see below section on instruments) (Pingault et al., 2018). Since genotype is determined at conception and fixed for the lifetime, the risk of reverse causality is removed in MR (Davey Smith & Ebrahim, 2003; Lawlor et al., 2008).

2.2.1.3 Assumption 3: The exclusion restriction assumption: the instrument only affects the outcome through its effect on the exposure

This third assumption is violated when the SNP has an effect on the outcome through alternative pathways, instead or in addition to, through the exposure and is termed horizontal pleiotropy (Bowden et al., 2017; Davey Smith & Hemani, 2014). Horizontal pleiotropy is tested for in analyses and can be out ruled further by functional knowledge of a SNP (although SNPs are most often selected on the basis of having achieved genome-wide significance) (Bowden et al., 2017; Davey Smith & Hemani, 2014). In contrast, vertical pleiotropy is used to refer to the effect of a SNP on the outcome via a trait that is on the pathway under investigation (Davies, Holmes, et al., 2018; Hemani, Bowden, et al., 2018). Vertical pleiotropy is the principle of MR, whereby one factor

affects a downstream outcome, and does not violate the exclusion restriction assumption (Davey Smith & Davies, 2016; Hemani, Bowden, et al., 2018). It is possible that this assumption is violated through dynastic effects whereby a parents' genotype creates an environment via the parents' phenotype that affects an individual's outcome being measured, opening a pathway between instruments in the individual and their outcome via parental environments (Pingault et al., 2018).

2.2.1.4 Assumption 4: Homogeneity and monotonicity

If these assumptions are met, effects estimated using MR should be free from bias due to confounding and therefore the associations between ZX and ZY (i.e., SNP-exposure and SNP-outcome) can be used to estimate the causal effect of X on Y (Bowden et al., 2017; Davey Smith & Ebrahim, 2003; Lawlor, 2016). However, there is a fourth assumption of instrumental variable analysis that has received little attention for its application to MR and is an area under active research (Lawlor et al., 2019; Swanson & Hernán, 2018). This fourth assumption refers to homogeneity and monotonicity. For homogeneity, it is assumed that the instrument does not modify the causal effect of the exposure on the outcome between the exposed and unexposed and, by extension, that this causal effect is the same in all individuals (Lawlor et al., 2019; Swanson & Hernán, 2018). This can be relaxed so that the effect is only held constant within subgroups, such as the exposed or non-exposed for a binary exposure measure (Lawlor et al., 2019). Due to the strength of the homogeneity assumption, monotonicity is used instead. For this, it is assumed that there is a monotonic relationship between the instrument and exposure and it therefore has the same direction of effect across individuals (i.e., the instrument does not increase the exposure in some individuals and decrease it in others) (Lawlor et al., 2019). Again, the application of this assumption to MR is under active research and currently this assumption is rarely considered in analysis.

2.2.1.5 Summary of assumptions

It is clear that instrumental variable analysis such as MR relies on strong assumptions and unverifiable conditions (Labrecque & Swanson, 2018). Subject knowledge is the most common method for concluding that assumptions hold although there are multiple ways to further strengthen or refute these assumptions and I discuss these below, such as adjusting for principal components of ancestry and triangulating across multiple MR methods. For a full review of assessing assumptions see Labrecque and Swanson (2018).

2.2.2 Instruments for Mendelian randomization

As discussed, MR uses SNPs as instruments in analysis. Humans share 99.9% of their genetic sequence across the 14.8 billion base pairs of the genome with SNPs contributing to part of the non-shared genome (Frazer, Murray, Schork, & Topol, 2009; Venter et al., 2001). Variation in SNPs can be used in MR analyses to proxy or instrument environmental exposures of interest and to investigate the effect of these exposures on outcomes. SNPs can proxy directly measured phenotypes (e.g., body mass index (BMI)) and in some cases can proxy phenotypes that themselves are proxies for environmental exposures (e.g., cortisol for stress). Instruments might predict differing levels of the exposure because of direct genetic effects or because of the association with related environments. Either way the instrument must robustly predict the environmental exposure. Therefore, MR is not usually used to assess the specific effects of a genetic variant (Davey Smith & Ebrahim, 2003; Gage, Davey Smith, et al., 2016; Lawlor et al., 2008). As discussed, identification of SNPs robustly associated with an exposure of interest, and hence appropriate for use as instruments to study a given exposure, are identified in GWAS. The GWAS is ideally conducted in independent samples from those used for the MR analyses (Gage, Davey Smith, et al., 2016). See **Figure 2:3** for how instruments are selected.

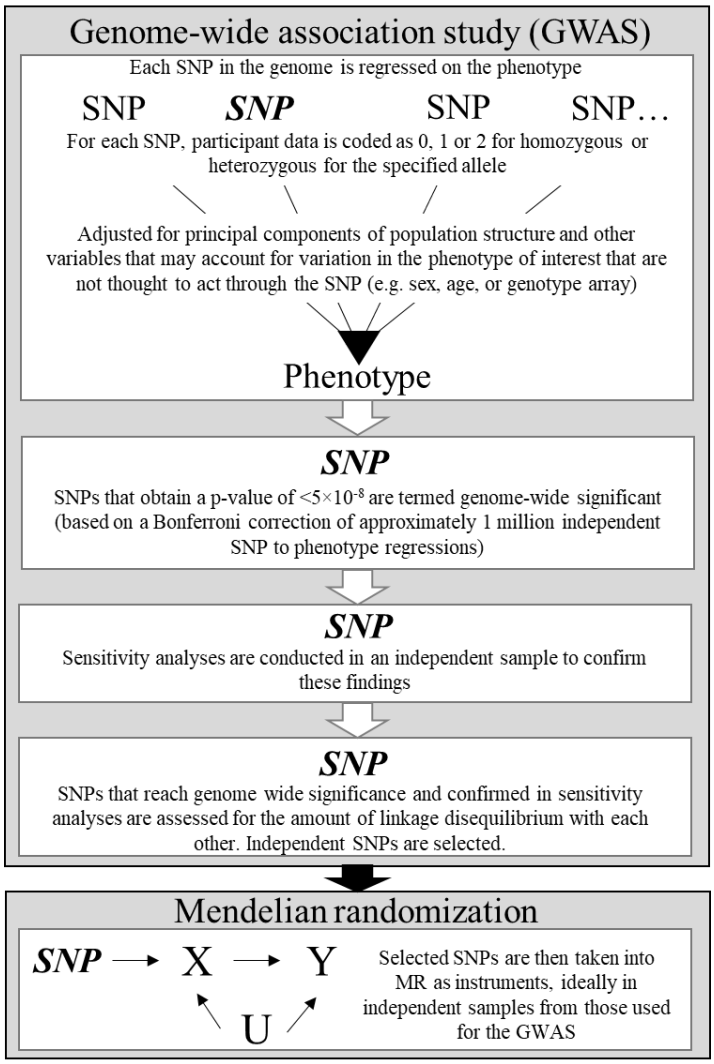

Figure 2:3 *Flow chart for how SNPs are selected as instruments for MR. For the methods used in this thesis, SNP-outcome estimates can then be taken from a publicly available GWAS for the outcome trait or derived from individual level data.*

It is assumed that a SNP that best proxies the exposure, sometimes termed a causal SNP, will either be genotyped, imputed, or captured through LD with another SNP included in the instrument. LD is defined as non-random correlations between alleles at different loci due to the disproportionate co-inheritance of alleles, through their proximity or population structure (Lawlor et al., 2019; Pingault et al., 2018). In this way, LD can be useful for MR analyses as instruments in MR do not have to be causally associated with levels of the exposure but only proxy them (Lawlor et al., 2008). This does not violate the assumptions of MR discussed. LD is also useful for identifying proxy SNPs if some instruments are unavailable in a sample. Additionally, LD is used to ensure that SNPs

used together as an instrument are independent of each other (see **Figure 2:3** and below for discussion on multiple SNP instruments).

Principal components are used in order to adjust for population structure as this can confound relationships between a SNP and a phenotype (Davies, Holmes, et al., 2018; Haworth et al., 2019; Timpson, Greenwood, Soranzo, Lawson, & Richards, 2017). Specifically, differences in allele frequencies across populations can generate spurious associations if in one population the allele is rare (e.g., minor allele frequency (MAF) below 1%) as any association between the SNP and outcome could be due to differences in ethnicity (Davies, Holmes, et al., 2018; Haworth et al., 2019; Schork, Murray, Frazer, & Topol, 2009; Timpson et al., 2017). Additionally, GWAS and MR studies typically restrict to populations of common ancestry to further address population structure (Davies, Holmes, et al., 2018), as I have done throughout this thesis.

Typically, a single SNP explains very little of the observed variation in the exposure, and most MR studies therefore use multiple genetic variants to increase power (Davies, Holmes, et al., 2018; Frazer et al., 2009). These multiple genetic variants can be analysed individually, meta-analysed for a single causal effect, or combined into a genetic score and then used as a single instrument (Davies, Holmes, et al., 2018). The statistical power of MR can be increased further by weighting each SNP by its association with the exposure, taken from the GWAS (Davies, Holmes, et al., 2018). Using a single SNP instrument is only appropriate if the SNP plays a known and specific role in the pathway of interest and has a large effect on the exposure (Gage, Davey Smith, et al., 2016). Throughout this thesis I use multiple SNPs as instruments.

Weak instrument bias may occur when a SNP or genetic score explains little of the observed variation in the exposure and/or is used in a study with a small sample size (Davies, Holmes, et al., 2018). In the MR methods used throughout this thesis, weak instrument bias attenuates results towards the null as SNP-exposure and SNP-outcome estimates are derived in non-overlapping samples and there is therefore no over-fitting of the data (Lawlor, 2016; Lawlor et al., 2019). The mean F statistic can determine the strength of an instrument to assess weak instrument bias, derived as the mean of the squared SNP-exposure association divided by the squared standard error (SE) of the SNP-outcome association for the MR methods here. A value above 10 indicates acceptable levels of relative bias (<10%) (Burgess, Butterworth, & Thompson, 2013; Pierce, Ahsan, & Vanderweele, 2011). The power of MR analyses is determined by this strength of association between the instrument and exposure as well as the sample size (Davies,

Holmes, et al., 2018). Using multiple SNPs to instrument an exposure is therefore important for complex polygenic traits where the effects of many common genetic variants are individually weak. However, each individual SNP must be a valid instrumental variable, defined by the three main assumptions above, to allow for unbiased causal inference (Lawlor et al., 2008).

2.2.3 Mendelian randomization methods

I will now discuss each of the MR methods used in this thesis: the inverse variance weighted (IVW), MR-Egger regression, weighted median, mode-based estimator (MBE) and additional sensitivity analysis methods (see **Table 2:1** and **Figure 2:5**). These methods are all extensions of the Wald ratio (defined above) to be used with multiple SNPs as instruments for the exposure. They first use the Wald ratio to estimate the causal effect per SNP before conducting a meta-analysis for the causal effect of an exposure on outcome across SNP instruments (see Bowden & Holmes (2019) for a recent review of meta-analyses for MR). Each method uses a varying number of the SNPs as instruments due to the different assumptions that each relies on. With these methods relying on different assumptions regarding directional horizontal pleiotropy, a consistent direction of effect across all methods for the same exposure and outcome relationship increases confidence in results, even if some SNPs are invalid instruments (Hemani, Bowden, et al., 2018). I use a consistent direction of effect to assess the robustness of results and not a formal statistical threshold as some methods have limited statistical power (Bowden, Del Greco M, et al., 2017; Lawlor, Tilling, & Davey Smith, 2016). As the IVW has the most statistical power, I focus on reporting these results throughout.

2.2.3.1 Inverse variance weighted

The IVW method is a meta-analysis of Wald ratios across all SNP instruments to provide a causal effect of the exposure of the outcome. **Figure 2:4** illustrates these ratio estimates per SNP from a fictional MR analysis where the slope is equivalent to a weighted average of the ratio estimates (Bowden et al., 2017; Pingault et al., 2018). As shown, an IVW approach is therefore similar to a weighted regression of SNP-outcome coefficients on SNP-exposure coefficients with the intercept constrained to zero (Burgess et al., 2013; Gage, Jones, et al., 2016). The gradient provides an estimate of the causal effect, indicating the increase in the outcome per unit increase in the exposure (Burgess et al., 2013). This method uses the inverse SE of the SNP-outcome association estimates as weightings (Bowden et al., 2017). By weighting the influence of each SNP by the inverse variance of the SNP-outcome association, stronger SNPs make a larger contribution to the estimate (Hemani, Zheng, et al., 2018).

The IVW is typically used as the main MR analysis as it has the most statistical power, due to using all SNP instruments. However, it therefore assumes that all SNP instruments are valid (Bowden et al., 2017). An IVW estimate is biased by any violation of the exclusion restriction assumption, such as due to heterogeneity or directional horizontal pleiotropy. As the gradient for the causal effect is taken from a line of best fit for all SNPs with the intercept constrained to zero, any heterogeneity or directional horizontal pleiotropy would draw the line away from the true slope (Bowden et al., 2017). Heterogeneity occurs when individual SNP estimates do not converge on the same causal estimate and may represent pleiotropy (Pingault et al., 2018). Cochran's Q is a measure of heterogeneity, derived as the weighted sum of squared differences between individual SNP effects and the pooled effect across SNPs, with the weights being those used in the MR method. The degrees of freedom are the number of SNPs minus 1. Overdispersion is a term used to indicate high heterogeneity and a Cochran's Q value greater than the degrees of freedom is considered evidence of this (Lawlor et al., 2008; Rees, Wood, & Burgess, 2017). However, Cochran's Q has very high statistical power if the number of SNPs is large, meaning that evidence of overdispersion is often found in MR studies, and therefore funnel plots are often used to assess heterogeneity and dispersion. Funnel plots provide an opportunity to assess if there is heterogeneity and if this heterogeneity is balanced across SNPs by plotting SNP estimates against the SE of their effect size (Hemani, Zheng, et al., 2018; Sterne et al., 2011). Even in the presence of heterogeneity by Cochran's Q, if symmetry is observed in the funnel plot then pleiotropy is considered balanced with a zero mean.

For an IVW meta-analysis, fixed or random effects methods can be used (Bowden et al., 2017; Burgess et al., 2013). A fixed effects method assumes all instruments are valid (such that none are pleiotropic), whereas a random effects method allows balanced horizontal pleiotropy if independent to the SNPs effects on the exposure - termed the Instrument Strength Independent of Direct Effect (InSIDE) assumption. This InSIDE assumption is not testable. If symmetry is observed in the funnel plot, a fixed effects or random effects IVW meta-analysis method should produce similar results (Bowden et al., 2017; Burgess et al., 2013). If asymmetry is observed in the funnel plot, then directional horizontal pleiotropy is likely present and a fixed or random effects method would produce different estimates. In this case, both fixed and random effect estimates would also differ to the other methods below which better account for directional horizontal pleiotropy (Bowden et al., 2017; Burgess et al., 2013).

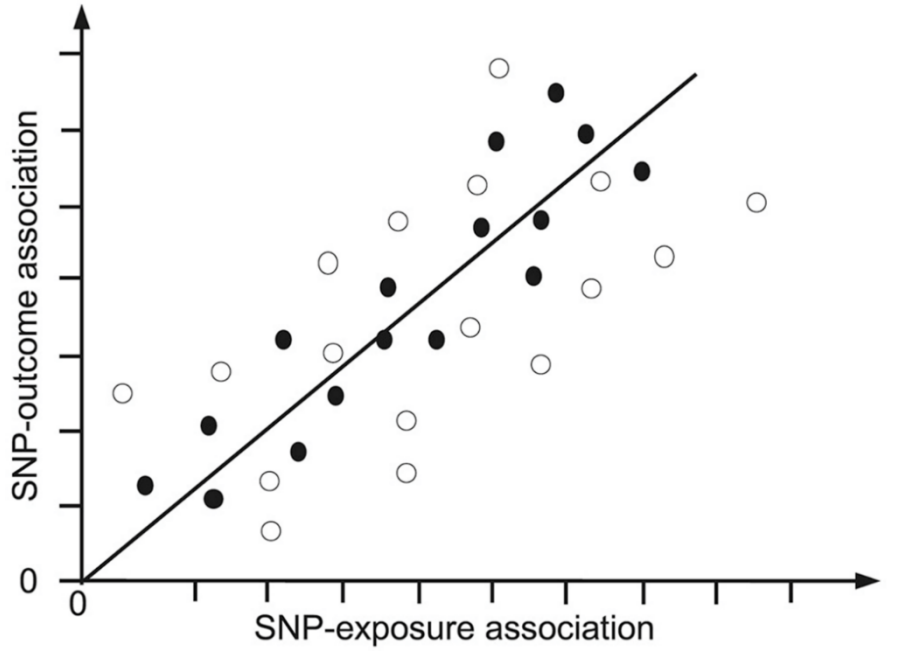

Figure 2:4 *Illustrative plot of SNP-outcome and SNP-exposure associations for an IVW approach. Solid dots represent no horizontal pleiotropy. Hollow dots represent balanced, as opposed to directional, horizontal pleiotropy. Both scenarios yield an unbiased IVW estimate. (credit Bowden et al., 2017).*

The IVW method further relies on the No Measurement Error (NOME) assumption where SNP-exposure associations are accurate to the true value and can be assessed by the mean F statistic value (Bowden et al., 2017).

In summary, the IVW includes all SNP instruments in a meta-analysis of Wald ratios with the intercept constrained to zero and is therefore perhaps the simplest MR method. Another strength of the IVW is that it has the most statistical power to detect causal effects. However, the method is strongly reliant on the assumption of no directional horizontal pleiotropy.

2.2.3.2 MR-Egger regression

MR-Egger is an extension of the IVW that also combines Wald ratios per SNP into a meta-regression to provide an estimate for the causal effect of the exposure on the outcome using the inverse SE of the SNP-outcome association estimates as weightings (Bowden et al., 2017). In addition, MR-Egger regression provides the causal estimate for the exposure on the outcome adjusted for directional horizontal pleiotropy (Lawlor et al., 2019). To do so, MR-Egger regression does not constrain the intercept to zero. The

intercept term therefore estimates the average pleiotropic effect across instrument SNPs and the gradient of the slope provides an estimate independent of the estimated directional horizontal pleiotropy (Bowden et al., 2017). This method therefore allows all SNPs to be invalid instruments in that they may have pleiotropic effects although pleiotropic effects must satisfy the InSIDE assumption (see above) (Bowden et al., 2017). A significant intercept term (using a *p*-value threshold of 0.05) suggests the presence of directional horizontal pleiotropy. The MR-Egger estimate and IVW estimate will converge if there is no directional horizontal pleiotropy as both intercepts would then be zero. However, if there is the presence of directional horizontal pleiotropy, then the slopes and causal effects will differ between these methods (see **Figure 2:5**).

MR-Egger further relies on the NOME assumption and failure to meet the NOME assumption is most extreme for MR-Egger compared to other methods (Bowden et al., 2017). It is possible to adjust for this dilution in MR-Egger by employing a Simulation Extrapolation (SIMEX) method (Bowden et al., 2017; Bowden, Fabiola Del Greco, et al., 2016; Hemani, Bowden, et al., 2018). The SIMEX model estimates what would have been obtained if NOME was met using information from a series of dummy datasets with increasing violations of NOME. The I^2_{GX} statistic quantifies the amount of dilution by dividing the true SNP-exposure associations by the variance of the SNP-exposure association (Bowden, Fabiola Del Greco, et al., 2016). An I^2_{GX} value of 0.9 or above indicates that a SIMEX adjustment is not required as the relative bias in the estimate is less than or equal to 10%, which is equivalent to the assurance given by an F statistic above 10 in other analyses (Bowden, Fabiola Del Greco, et al., 2016).

Overall, if InSIDE and NOME are perfectly satisfied, MR-Egger can provide an unbiased causal estimate with the presence of horizontal pleiotropy and this is therefore a key strength of the method. Whereas in a situation where InSIDE holds but NOME is violated, the estimate will be diluted rather than biased (Bowden, Fabiola Del Greco, et al., 2016). The main weakness of MR-Egger is that it suffers from the lowest power of all the MR methods discussed here as it requires variation between SNP-exposure estimates after all have been coded in the positive direction, and therefore requires a large number of SNP instruments (Bowden, Davey Smith, & Burgess, 2015). Additionally, it is less efficient than the IVW and also strongly relies on the InSIDE and NOME assumptions (Bowden et al., 2017).

2.2.3.3 Weighted median

The weighted median estimate is obtained by first calculating the Wald ratio causal estimate for each SNP and then taking the estimate with the median inverse variance weight. Whereas in an unweighted analysis it is assumed that at least 50% of the instruments are valid, in a weighted analysis it is assumed that instruments forming 50% of the weight in the analysis are valid (Bowden, Davey Smith, Haycock, & Burgess, 2016; Lawlor et al., 2008).

Overall, low false discovery rates are achieved with this approach (Bowden, Davey Smith, et al., 2016). This approach is more robust to directional horizontal pleiotropy than the IVW and more robust to outliers than the IVW and MR-Egger methods (Pingault et al., 2018). Additionally, the statistical power to detect causal effects is close to that of the IVW method, it does not require the InSIDE assumption to be met, and only half of the SNPs need to be valid instruments for an unbiased causal estimate (Hemani, Zheng, et al., 2018).

2.2.3.4 Mode-based estimator

The MBE finds the largest cluster of Wald ratios for a meta-analysis and uses inverse variance weightings. The simple MBE is an unweighted analysis however this thesis only uses the weighted MBE. The majority of instruments can be invalid providing that the Zero Modal Pleiotropy Assumption (ZEMPA) is satisfied. ZEMPA states that the largest subset of instruments with the same ratio estimate will contain valid instruments and therefore that invalid instruments have heterogeneous estimates. In other words, the MBE provides a causal estimate when the largest number of similar individual-instrument estimates come from valid instruments, even if the majority are invalid (Hartwig, Davey Smith, & Bowden, 2017). Benefits of this method is that it is more robust to directional horizontal pleiotropy than the IVW and more powerful than MR-Egger (Pingault et al., 2018).

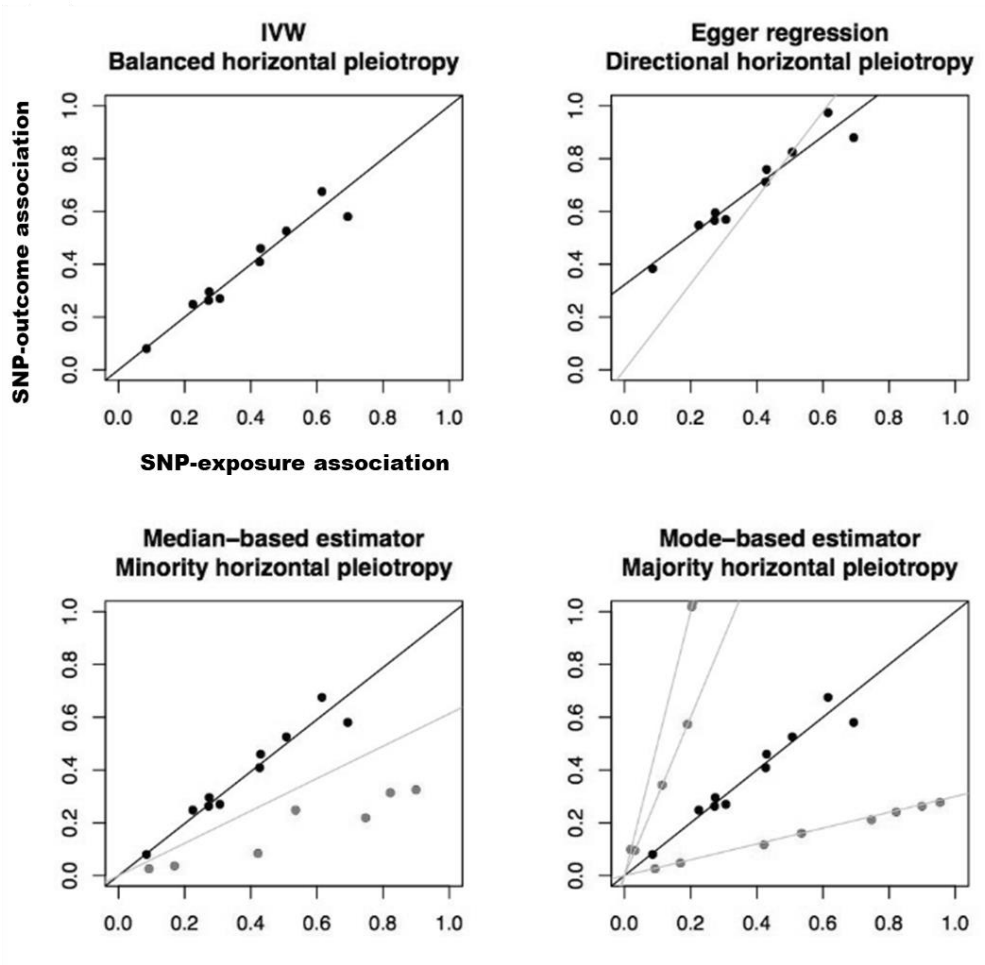

Figure 2:5 *Illustrative plot of MR methods used.*

The IVW estimate is not biased by balanced horizontal pleiotropy. If there is directional horizontal pleiotropy, then the MR-Egger estimate (black line) will be unbiased under the InSIDE assumption and differ from the IVW which constrains the intercept to zero (grey line). The weighted median will be unbiased if the majority of the instruments are valid (black points), with some invalid instruments (grey points) even though this indicates directional horizontal pleiotropy which biases the IVW (grey line). The MBE clusters SNPs based on their estimates (grey lines) and the cluster with the largest weight (black line) is selected as the causal estimate and is unbiased if the black dots are valid instruments. (credit Hemani et al., 2018)

2.2.3.5 Additional Mendelian randomization sensitivity methods

In Chapter 4, I also conducted radial MR-Egger regression and leave-one-out analysis to determine if outliers were present. Although similar to MR-Egger regression, the intercept is estimated on a scale so that the distance from a SNP estimate to the slope is equal to the square root of its contribution to the overall average heterogeneity (measured by Cochran's Q) after adjustment for directional horizontal pleiotropy. Therefore, radial MR-Egger regression can be used to assess outliers (Bowden et al., 2018). This method

will only estimate a causal effect providing that the InSIDE assumption is satisfied. A leave-one-out analysis can aid assessment of whether the MR estimate is driven or biased by a single SNP, perhaps due to a large horizontal pleiotropic effect. To do so, the method re-estimates the causal effect after systematically dropping one SNP at a time. A dramatic change in the estimate when one SNP is removed can highlight the sensitivity of the estimate to outliers and identify outliers to be investigated further (Hemani, Zheng, et al., 2018).

2.2.4 Specialist software

I use MR-Base and GitHub software within this thesis. MR-Base is an online platform (www.mrbase.org) that allows users to conduct the above MR methods with publicly available GWAS data (see Chapter 3) or with users own datasets using the R package (Hemani, Zheng, et al., 2018). For this thesis, I used the R package to derive some of the results in Chapter 5 as well as the leave-one-out analysis in Chapter 4. GitHub is another online platform where users can host analysis code. The analysis scripts for published results from this thesis are available on the MRC Integrative Epidemiology Unit's profile (MRC IEU) (www.github.com/MRCIEU).

Table 2:1 *A comparison of MR methods and their assumptions.*

MR method	Description	Additional assumptions	Power	Invalid variants allowed	Can be relaxed	
					A2	A3
IVW	A meta-analysis of the Wald ratios for each SNP ($\frac{ZY}{ZX}$) weighted by the inverse of the variance of the SNP-outcome association.	No pleiotropy or balanced pleiotropy conditional on the InSIDE assumption. NOME	Has the most power if the assumptions are satisfied.	100% but assumes 0%	✗	✗
MR-Egger regression	An extension of the IVW that relaxes the assumption that any pleiotropy must be balanced. A significant intercept term (p<0.05) suggests bias from directional horizontal pleiotropy, i.e., the average pleiotropic effect is not zero. MR-Egger regression provides consistent estimates even if all genetic instrumental variables are invalid as long as the INSIDE assumption is met.	Strong reliance on InSIDE. Strong reliance on NOME.	Has the lowest power.	100%	✗	✓
Weighted median	The weighted median estimate is obtained by first calculating the Wald ratio for each SNP and then taking the estimate with the median inverse variance weight.	Consistent when 50% of weight contributed by genetic variants is valid.	Similar to that of IVW method.	50%	✓	✓
MBE	Finds the largest cluster of Wald ratios. The majority of the genetic instruments can be invalid providing the ZEMPA assumption is satisfied. In the weighted mode method, the mode is calculated using the inverse variance weights of the Wald ratios.	ZEMPA	Less powerful than IVW and weighted median.	50%	✓	✓

A2 = assumption 2, that all instruments (Z) must not be associated with confounders. A3 = assumption 3, that all instruments (Z) must only be associated with the outcome (Y) through the exposure (X). These two columns have a cross if that method requires the assumption to be met and a tick if that assumption can be relaxed. Throughout the table, invalid refers to instruments that do not meet the three main assumptions of MR. The various methods can be more or less powerful under different models of pleiotropy.

2.3 Polygenic risk scores

Similar to the genetic scores described above, a PRS is a variable that combines SNPs associated with an exposure. Each of the risk alleles that a person has for the SNP is weighted by effect estimates from a GWAS (Euesden, Lewis, & O'Reilly, 2015). However, these scores are typically derived using lower *p*-value thresholds for the association between the SNP and trait of interest than instruments in MR in order to capture broader liability for a trait (Euesden et al., 2015; Mullins et al., 2017). This is especially useful in under-powered studies where few genome-wide significant SNPs are available or only a small sample is used (Euesden et al., 2015). PRSice is a dedicated PRS software for deriving scores across multiple *p*-value thresholds (www.prsice.info) (Euesden et al., 2015). I conduct analysis using PRSice in Chapter 5.

2.4 Linkage disequilibrium score regression

A final method that I use in this PhD is LD score regression (Chapter 5). This method identifies genetic correlations and can be useful for capturing the relationship between broader liability for traits of interest after MR analysis, or to highlight potential causal relationships between complex traits for further investigation with MR (Bulik-Sullivan, Finucane, et al., 2015). Genetic correlations represent shared genetic aetiology of two phenotypes which can then be further investigated using MR to assess whether the association is due to pleiotropy or a causal effect (Gage, Davey Smith, et al., 2016; Pingault et al., 2018). An LD score estimate for a genetic correlation is equivalent to the gradient when the product of the GWAS estimates (z-score standardized) of each trait is plotted against the LD score of each SNP (the sum of each SNPs LD with all other tagged SNPs). A positive value indicates that genetic effects tend to be shared genome-wide. LD score regression can be run using GWAS summary data and is not biased by sample overlap (Bulik-Sullivan, Finucane, et al., 2015). Instead of focusing on genome-wide significant SNPs as in MR analysis or a lower *p*-value threshold like PRS analysis, this method uses genome-wide data and the effects of all SNPs. This is particularly useful for complex traits where many common genetic variants have a small effect and the number of SNPs that reach genome-wide significance is small. However, for exposures where genome-wide significant SNPs explain a large proportion of the variance, then analysing the genome-wide significant SNPs will have less noise and can be more powerful (Bulik-Sullivan, Finucane, et al., 2015; Richardson et al., 2018). Furthermore, this method requires large sample sizes and a homogenous population in terms of ethnicity.

2.5 Chapter summary

In this chapter, I have described the instruments, assumptions, and various methods of MR. If the assumptions discussed hold (with focus on the relevance, independence and exclusion restriction), MR allows for stronger inferences of causality for associations between an exposure and outcome than standard analytical approaches applied to observational data. This is because MR estimates can then be interpreted as free from confounding or reverse causation (Lawlor et al., 2008). Different variations of MR rely on some additional assumptions for this to be possible: IVW (all instruments are valid and NOME), MR-Egger (all instruments may be invalid if InSIDE assumptions holds and NOME), weighted median (that a subset are valid instruments) and MBE (that a subset are valid instruments and ZEMPA holds). I have further described LD score regression and types of PRS that are genetic epidemiological methods used to assess broader liability for a trait of interest. In the next chapter I will describe the data that I use when applying these methods (Chapter 3).

Chapter 3 Cohort descriptions

3.1 Chapter overview

This thesis uses publicly available genome wide summary level data as well as participant data from three cohorts: UK Biobank, The Avon Longitudinal Study of Parents and Children (ALSPAC), and the Norwegian Mother, Father and Child Cohort Study (MoBa). In this chapter, I will briefly describe the publicly available data sources and then describe each of the cohorts in turn. In combination, these data offer the opportunity to conduct MR by providing phenotypic and genetic data on a large number of participants. Such large sample sizes are necessary to detect the small effect sizes common in MR and other genetic methods (Gage, Jones, et al., 2016).

3.2 Publicly available genome wide summary data

GWAS data is necessary for all analyses in this thesis and I was only able to conduct this research because the authors of each GWAS released their data publicly. I downloaded the discovery data for each GWAS from the relevant website (see **Table 3:1**). Using estimates from the discovery sample is common in genetic studies as sample sizes are smaller for replication analysis and typically only the genome-wide significant SNP estimates are published from combined data. Age at menarche data are published on the Reproductive Genetics Consortium website. For educational attainment, number of children and age at first birth the data was downloaded from the Social Science Genetic Association Consortium (SSGAC) website. For Schizophrenia, I used data from the Psychiatric Genomics Consortium (PGC). Further details of these GWAS and how they are used in my analyses are provided in **Table 3:1** and the relevant results chapter (Chapter 4 and Chapter 5).

Table 3:1 *Summary of GWAS used in thesis.*

Trait	N	Date	SNPs[a]	Website	Reference	Chapter
Age at menarche	182 416	2014	123	www.reprogen.org/data_download.html	(Perry et al., 2014)	4
Age at menarche	329 345	2017	389	www.reprogen.org/data_download.html	(Day et al., 2017)	4
Age at first sexual intercourse	125 667	2016	38	(N/A)	(Day, Helgason, et al., 2016)	4
Schizophrenia	36 989 cases and 113 075 controls (35 123 cases and 109 657 controls for Europeans only)	2014	128	www.med.unc.edu/pgc/results-and-downloads	(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014)	5
Educational attainment	293 793	2016	74	www.thessgac.org/data	(Okbay et al., 2016)	5
Number of children	343 072	2016	(N/A – used as outcome)	www.thessgac.org/data	(Barban et al., 2016)	Appendix

[a] *SNPs that reached genome-wide significance ($p<5\times10^{-8}$)*

3.3 UK Biobank

3.3.1 Overview and aim

UK Biobank was established by the Medical Research Council and Wellcome Trust with the aim of identifying risk factors for human diseases in middle to older aged individuals (Allen, Sudlow, Peakman, & Collins, 2014; Collins, 2012). In order to do so, a wide range of measurements were collected, including questionnaire responses, physical measurements and biological samples to create this phenotypically rich data source (Allen et al., 2014; Collins, 2012). UK Biobank is a population-based prospective cohort and therefore a large sample size was needed due to low likelihood of participants developing a particular disease (Collins, 2012). Consequently, approximately 500 000 participants were recruited (Collins, 2012). Volunteers provided electronic signed consent and UK Biobank received ethics approval from the Research Ethics Committee (Allen et al., 2014; Bycroft et al., 2018). UK Biobank is the largest sample used in this thesis. Further details and description are available on the website (www.ukbiobank.ac.uk) and in previous publications (Allen et al., 2012; Bycroft et al., 2018; Collins, 2012). Details of every available measure are provided at www.biobank.ndph.ox.ac.uk/showcase. Here I use the measures presented in **Table 3:2**, from data application number 6326.

3.3.2 Participants

Participants were invited if aged between 40 and 69 years during the recruitment period between 2006 and 2010, as well as being registered with the National Health Service and living within 25 miles of one of the 22 assessment centres across the UK (Allen et al., 2014; Collins, 2012; Fry et al., 2017). UK Biobank therefore consists of mostly post-reproductive participants within a population-based framework not selected on disease status. A total of 9.2 million individuals were invited with a response rate of less than 6% (Fry et al., 2017; Swanson, 2012).

3.3.3 Data collection

At the baseline assessment, participants completed a wide range of questionnaires related to their lifestyle, family and medical history as well as having blood samples taken (Allen et al., 2014). Repeat assessments for all baseline measures has been conducted on a subset of participants since (Allen et al., 2014). Participants also completed questionnaires using a computer and were allowed to click on various help prompts. In this thesis, I use data from the baseline assessment questionnaires, linkage to National Health Service medical records for schizophrenia diagnoses, and genetic data derived from blood samples. I use multiple measures from the baseline questionnaires and describe each in the relevant

results chapter (see Chapter 4 and 5 and **Table 3:2**). Below, I describe relevant methods pertaining to the genetic data that I use in this thesis.

3.3.4 Genetic data

Deoxyribonucleic acid (DNA) was extracted from the blood samples provided by participants at the baseline assessment and genotyping was conducted at the Affymetrix Research Services Laboratory (Bycroft et al., 2018). Genetic data for UK Biobank was released in two waves (May 2015 and July 2017) (Bycroft et al., 2018). The first release included ~150 000 participants genetic data (Bycroft et al., 2018). Of this first release, there were approximately 50 000 participants genotyped using the Applied Biosystems UK Biobank Lung Exome Variant Evaluation Axiom Array by Affymetrix array (Bycroft et al., 2018). The remaining participants of the first release and all participants of the second release were genotyped using the Applied Biosystems UK Biobank Axiom Array (~440 000 participants) (Bycroft et al., 2018). These arrays share 95% of markers (Bycroft et al., 2018). In total, the full release data contains 488 377 successfully genotyped samples.

Full details of the imputation as well as the pre-imputation quality control checks are published elsewhere (Bycroft et al., 2018). Briefly, multiallelic SNPs or SNPs with MAF ≤1% were removed. Imputation of genotypes was performed using a reference set of the UK10K haplotype and Haplotype Reference Consortium (HRC) (Howie, Marchini, & Stephens, 2011; Huang et al., 2015). The MRC IEU in-house team then restricted to autosomal variants within the HRC site list using stepwise filtering with changing imputation quality for different allele frequencies. This meant that rarer genetic variants were required to have a higher imputation info score with MAF and info scores recalculated within an in-house defined ‘European’ subset. The in-house ancestry restrictions consisted of those who self-report as ‘White British’ and who were shown to have similar ancestral backgrounds in a principal component analysis (PCA) (Bycroft et al., 2018). Estimated kinship coefficients identified 107 162 pairs of individuals (Bycroft et al., 2018; O’Connell et al., 2016) and in-house algorithms were applied to exclude individuals related to the greatest number of other individuals until no related pairs remain according to the algorithm. Individuals with sex-mismatch between genetic and reported sex or individuals with sex-chromosome aneuploidy were excluded. These in-house quality control procedures have been described elsewhere (Mitchell, Hemani, Dudding, & Paternoster, 2017).

Table 3:2 *Summary of measures used from UK Biobank data.*

Measure	Question	Chapter
Age at first birth	How old were you when you had your FIRST child?	4, 5
Number of sexual partners	About how many sexual partners have you had in your lifetime?	4, 5
Age at last birth	How old were you when you had your LAST child?	4, 5
Age when left education	At what age did you complete your continuous full-time education?	4
Educational attainment in years (derived)	Which of the following qualifications do you have? (You can select more than one)	4, 5
Alcohol intake	About how often do you drink alcohol?	4
Ever smoked	Derived by UK Biobank using: Do you smoke tobacco now?; In the past, how often have you smoked tobacco?	4, 5
Risk-taking	Would you describe yourself as someone who takes risks?	4

3.4 The Avon Longitudinal Study of Parents and Children (ALSPAC)

3.4.1 Overview and aim

ALSPAC is an ongoing population-based birth cohort that recruited 14 541 pregnancies in the greater Bristol area (Boyd et al., 2013; Fraser et al., 2013). An additional recruitment of children was later carried out, inviting those that were eligible to take part in the original effort, increasing the sample to 15,247 pregnancies (Boyd et al., 2013; Fraser et al., 2013). The aim of ALSPAC was to determine how genotype combines with environmental pressures to influence health and development and a wide range of measures has therefore been collected (Golding, Pembrey, & Jones, 2001). ALSPAC is described in detail in Boyd et al. (2013) and Fraser et al. (2013). These papers summarise the recruitment process, sample description, available data and measurement occasion. The ALSPAC website (www.bristol.ac.uk/alspac/), data dictionary (www.bristol.ac.uk/alspac/researchers/access/) and catalogue (www.variables.alspac.bris.ac.uk/) provide information on all available measures.

In this thesis, I use data on both the mothers and the children of the index pregnancy. I will refer to the two generations as ALSPAC G0 for the mothers and ALSPAC G1 for the children (who are now adults). For a summary of measures used in this thesis, see **Table 3:3**. Although not used here, data was also collected from the partners of ALSPAC G0 and, more recently, the children of ALSPAC G1. Participants provided informed consent

and ethical approval was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics committees.

3.4.2 Participants

Pregnant women living in Avon, United Kingdom were eligible if they were due to deliver between April 1, 1991, and December 31, 1992 (Boyd et al., 2013; Fraser et al., 2013). Approximately 85% of invited women enrolled into the study (Pembrey, 2004). If a woman was pregnant more than once during the recruitment period, it was possible to participate on each occasion.

3.4.3 Data collection

Data has been collected through self-completed questionnaires and assessment at designated research clinics. Data were collected on a wide range of phenotypes including physical and mental health, environmental factors, demographics and biological markers. ALSPAC G0 completed multiple questionnaires throughout pregnancy and post-pregnancy including information on themselves and their children and continue to do so. ALSPAC G1 were able to complete their own questionnaires during puberty if they wished to do so. Additionally, participants have attended clinics over the years where further assessments were carried out (see Boyd et al., 2013, and Fraser et al., 2013, for schedules of clinics). In this thesis, I use multiple phenotypic measures from various questionnaires and clinics, described in each results chapter (Chapter 4 and 5 and **Table 3:3**). I further use genetic data from cord blood samples for both ALSPAC G0 and G1, as described below.

3.4.4 Genetic data

ALSPAC G0 were genotyped using the Illumina Human660W-quad array conducted at the Centre National de Genotypage. ALSPAC G1 were genotyped with the Illumina HumanHap550 quad array at the Wellcome Trust Sanger Institute, Cambridge, United Kingdom and the Laboratory Corporation of America, Burlington, United States. Centrally performed quality control procedures were conducted on the raw genome-wide data, similarly for ALSPAC G0 and ALSPAC G1.

Participants were removed if there was a mismatch between genetic and reported sex, insufficient sample replication, minimal or excessive heterozygosity (0.34 and 0.36), disproportionate levels of individual missingness (>3%) or insufficient sample replication (identical by descent (IBD) < 0.8). Removal of SNPs was based on MAF < 0.01, SNP call rate < 0.95, individual call rate < 0.97, imputation info score < 0.80 and Hardy-Weinberg

equilibrium (HWE) $p< 5x10^{-7}$ for G1 and $p< 5x10^{-6}$ for G0. Cryptic relatedness was also measured (proportion of IBD>0.1 for G1 and >0.125 for G0). Population structure was assessed using multidimensional scaling of genome-wide identity by state pairwise distances using the four Haplotype map (HapMap) populations as a reference and samples showing evidence of population structure were excluded. Non-European individuals were removed. A total of 9048 for G0 and 9115 for G1 with 500 527 and 526 688 SNPs passed these quality controls and were included in phasing and imputation (Taylor et al., 2018). Genotype data for G0 and G1 were combined and then SNPs with genotype missingness above 1% (11 396 SNPs) were removed due to poor quality. Additionally, 321 participants with ID mismatches across G0 and G1 were removed. From this, 17 842 participants remained. Imputation of the target data was performed using the 1000 genomes reference panel (Phase 1, Version 3). There was 8237 eligible from G1 and 8,196 eligible from G0 with available genotype data after exclusion of related subjects, using cryptic relatedness measures described, that remained for genetic analysis (Taylor et al., 2018).

Table 3:3 *Summary of measures used from ALSPAC data.*

Measure	Question	Assessed at
G0		
Parity at 85 months post index child	Derived using: How many times have you been pregnant altogether before this time?; Since your study child was born, how many times have you been pregnant?	18 weeks gestation; 85 months post index child
Parity at 18 years post index child	Derived using: How many times have you been pregnant altogether before this time?; Since your study child was born, how many times have you been pregnant?; Since your study teenager's 7th birthday, how many times have you been pregnant?	18 weeks gestation; 85 months post index child; 18 years post index child
Age at first pregnancy	How old were you when you became pregnant for the very first time?	18 weeks gestation
Previous termination	Have you ever had any abortions or terminations?	18 weeks gestation
Covariables		
Education	Derived by ALSPAC using: What educational qualifications do you have? Please tick all that apply.	32 weeks gestation
Ever smoked	Have you ever been a smoker?	18 weeks gestation
Age at index delivery	Derived by ALSPAC using date of birth	N/A
G1		

Number of sexual partners	Altogether, in your life so far, how many people have you had sexual intercourse with?	21 years old; 23 years old
Had child	Derived using an ALSPAC measure for number of children in relation to: Date of birth of first child; Date of birth of fourth child	21, 22 years and 23 years old
Covariables		
Ever smoked	Have you ever smoked a whole cigarette?	23 years old

Note: ALSPAC data was only used in Chapter 5. Responses for G0 education were 1) certificate of secondary education, 2) vocational, 3) O level, 4) A level, 5) degree.

3.5 Norwegian Mother, Father and Child Cohort Study (MoBa)

3.5.1 Overview and aim

MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health and planned in the 1990s (Magnus 2006; 2016). The initial aim of the study was to detect causes of disease through investigating various risk factors however the aims have been widened since the study's conception (Rønningen et al., 2006). Recruitment for pregnant women was between 1999 and 2008 and data is still being collected. More than 95 200 mothers, 75 200 fathers and 114 500 children have participated. Throughout this thesis, I used data from the mothers only (see **Table 3:4** for summary). Informed consent was obtained from each MoBa participant upon recruitment. The study was approved by The Regional Committee for Medical Research Ethics in South-Eastern (or other, if applicable) Norway. Full details are available in Magnus et al. (2016, 2006) and on the study's website (www.fhi.no/en/studies/moba/).

3.5.2 Participants

There were no exclusion criteria for recruitment and all pregnant women in Norway were therefore eligible to participate, although the questionnaires were only available in Norwegian (Magnus et al., 2016, 2006). Participants were recruited from all over Norway and 50, out of a total of 52, hospitals with maternity units were involved by the end of the recruitment period. A postal invitation was sent to the mother and father prior to their routine ultrasound examinations at approximately 17 weeks gestation (Magnus et al., 2016, 2006). If a woman was pregnant more than once during the recruitment period, it was possible to participate on each occasion. Approximately 41% of those invited then enrolled into the study.

3.5.3 Data collection

This thesis is based on version 11 of the quality-assured data files and uses data from the first questionnaire sent to mothers, at 13-17 weeks gestation. This questionnaire related to previous pregnancies, medical history and medication, occupation, exposures in the work place and home, lifestyle habits and mental health (Magnus et al., 2006). As this was the first distributed questionnaire, there was little attrition, with 95% of mothers providing responses (Magnus et al., 2006).

In addition to questionnaire data, variables are available through data linkage to mandatory health registries in Norway. For every birth in Norway above 16 weeks gestation, a medical record is sent to the Medical Birth Registry Norway (MBRN) (Magnus et al., 2006). All MBRN records for the participants of MoBa are available, regardless of the number of questionnaires completed. Data from the MBRN was used in this thesis.

A blood sample was taken from participating mothers and fathers at the ultrasound assessment. More than 90% of fathers accompany their partner to the examination. At the birth, a blood sample was taken from the umbilical cord for mother and child. Blood samples were sent to a central biobank for genotyping (described below). Again, for this thesis, only the mother's genetic data was used.

3.5.4 Genetic data

As part of the HARVEST project, that includes other Norwegian cohorts, 11 000 randomly selected trios (mother, father and child) were genotyped from MoBa (Magnus et al., 2016). Individuals were only genotyped if they met these additional inclusion criteria: singletons, live births, linked with the MBRN and that mothers had completed the first questionnaire. Data has been deleted for participants who withdrew consent following genotyping. Genotyping was conducted using the Illumina Human Core Exome Beach Array and performed at the Norwegian University of Science of Technology Genotyping Core Facility. Two versions of the genotype array were used due to one version being discontinued during the genotyping period (termed MoBa12 and MoBa24). A batch effect was identified on MoBa12 (termed MoBa12-A and MoBa12-B) and I therefore adjust for the equivalent of 3 genotype arrays in all analysis.

Information on the centrally performed quality checks, performed separately for each genotype array, are described on the MoBa website (www.fhi.no/en/op/data-access-from-health-registries-health-studies-and-biobanks/data-from-moba/genetic-data-from-the-

norwegian-mother-and-child-cohort-study-mobagenetics/). Here, I use individuals from the 'core quality-controlled sample' of these quality checks (around 9400 mothers). These were identified as high-quality and ethnically homogenous samples (the HARVEST dataset is primarily ethnic Norwegians with approximately 5% from other ethnic backgrounds). High-quality samples were identified by genotyping call rate (below 95% and autosomal markers below 98%), relatedness (defined by IBD above 0.01 accumulated and overall IBD above 10%), and detection of ethnic outliers by PCA using HapMap samples. Filters for the markers included: genotyping call rate, HWE (p<0.0001), MAF (<5%), removal of ambiguous markers (A/T and C/G), removal of regions with high LD, and pruning. I conducted additional quality checks on just the mother's samples that I was using, ensuring that imputation quality was >0.8, MAF>0.05, SNP missingness <0.1, individual missingness <0.1 and HWE $p>5\times10^{-6}$.

Table 3:4 *Summary of measures used from MoBa data.*

Measure	**Question**
Age at first birth Age at first pregnancy Previous termination	For all earlier pregnancies. Include all pregnancies that ended in abortion, miscarriage or stillbirth as well as ectopic pregnancies. State the year the pregnancy began, how many kilos you gained during the pregnancy and the number of months you breast-fed each baby. State whether or not you smoked during earlier pregnancies.
Parity	Derived by the MBRN
Treated infertility	Have you ever been treated for infertility?
Relationship length	How long have you and the baby's father had a sexual relationship?
Pregnancy planned	Was this pregnancy planned?
Contraception was used	Did you become pregnant even though you or your partner used contraceptives?
Covariables	
Age at index delivery	Derived by MoBa using date of birth
Education	What education do you have? (Enter a cross indicating the highest level of education you have completed and current studies if you are still studying.)
Ever smoked	Have you ever smoked?

Note: MoBa data was only used in Chapter 5. Responses for education were 1) 9-year secondary school, 2) 1-2 year high school, 3) Technical high school, 4) 3-year high school general studies, junior college, 5) Regional technical college, 4-year university degree (Bachelor's degree, nurse, teacher, engineer), 6) University, technical college, more than 4 years (Master's degree, medical doctor, PhD)

3.6 Chapter summary

In this chapter, I have provided an overview of the data sources that I use in this thesis. These sources included publicly available genome wide summary level data as well as participant data from UK Biobank, ALSPAC, and MoBa. In the following two chapters, I will implement the methods from Chapter 2 using these data to investigate life history theory (Chapter 4) and the schizophrenia paradox (Chapter 5).

Chapter 4 Life History Theory: the effects of age at menarche and first sexual intercourse on reproductive and behavioural outcomes

This chapter is based on the publication below

Lawn, R. B., Sallis, H. M., Wootton, R. E., Taylor, A. E., Demange, P., Fraser, A., Penton-Voak, I. S., & Munafò, M. R. (2019). The effects of age at menarche and first sexual intercourse on reproductive and behavioural outcomes: a Mendelian randomization study. *bioRxiv*; doi: https://doi.org/10.1101/423251.

4.1 Background and chapter overview

In this chapter, I applied MR methods to investigate components of life history theory. Life history theory is characterized as a meta-theory and can therefore not be tested in its entirety but can generate testable predictions (Ketelaar & Ellis, 2000; Nettle & Frankenhuis, 2019). The literature on life history theory has become increasingly large and fragmented in recent years (Nettle & Frankenhuis, 2019). The most commonly tested prediction is that early life adversity is associated with earlier age at menarche and other reproductive traits. There is substantial variation in the timing of significant reproductive life events such as menarche and first sexual intercourse and life history theory explains this variation as an adaptive response to the developmental environment (Belsky et al., 1991). In environments characterized by harsh conditions, adopting a fast life history strategy, characterized by short term goals (e.g., earlier puberty and age at first child), may increase fitness (Belsky et al., 1991; Simpson et al., 2012). In line with this, there is evidence demonstrating that greater childhood adversity is associated with earlier age at menarche and age at first sexual intercourse (Carlson, Mendle, & Harden, 2014; Ellis, 2004; Henrichs et al., 2014; Magnus et al., 2018; Mishra, Cooper, Tom, & Kuh, 2009; Simpson et al., 2012).

It is also important to examine how traits within life history strategies affect each other, especially when traits such as age at first sexual intercourse may be modifiable via policy and environmental changes. I therefore examine another part to life history theory, that early menarche and sexual intercourse (markers or results of exposure to early life adversity) affect reproductive strategies to increase fitness in certain environments. Earlier age at menarche and age at first sexual intercourse can therefore be viewed as directing effort towards reproductive goals as part of a fast life history strategy. In line with this, I predict earlier menarche and age at first sexual intercourse to be causal

components of a suite of adaptations where the future is discounted relative to the present and effort is directed towards short-term reproductive goals and increased risky behaviour (Day, Helgason, et al., 2016; Ellis & Bjorklund, 2012). For example, short-term reproductive goals may include earlier age at first birth, earlier age at last birth, a shorter reproductive period, increased number of sexual partners and number of children, and less likelihood of being childless. Increased risky behaviour could manifest as increased likelihood of smoking and alcohol consumption in the modern day. On the other hand, investing in education, despite being evolutionarily novel, can be seen as a slow life history trait with delayed benefits.

Life history theory has previously been investigated in humans using standard analytical approaches applied to observational data as it is not possible to manipulate developmental environments (Nettle et al., 2012; Richardson et al., 2018). As discussed in Chapter 1, it is possible to apply MR to investigate causal associations even when it is impossible to manipulate reproductive timings such as age at menarche and age at first sexual intercourse. In this chapter, I therefore applied MR to investigate whether there is a causal effect of variation in age at menarche and age at first sexual intercourse on outcomes related to reproduction, education and risky behaviour within a life history framework. For this, I used instruments for age at menarche (and a separate instrument for age at first sexual intercourse) and UK Biobank data to independently investigate the effects of age at menarche and age at first sexual intercourse on several evolutionary relevant outcomes (see **Figure 4:1**).

A previous study that included a sub-sample of participants from UK Biobank showed a causal effect of earlier age at menarche on earlier age at first birth, earlier age at last birth, earlier age at leaving education, increased alcohol intake, lower likelihood of being childless, greater number of children (in combined sexes) and decreased likelihood of remaining in education after 16 years (Day, Helgason, et al., 2016). Additionally, earlier age at first sexual intercourse was causally related to earlier age at first birth, a greater number of children, increased likelihood of being an ever smoker, and decreased likelihood of attaining a degree. These findings suggest causal relationships between traits that characterize a life history strategy and support evolutionary explanations of variation in age at menarche and first sexual intercourse. I extend this work by using the full release of UK Biobank data (N = 114 883–181 255) and a suite of novel methods to more robustly test for horizontal pleiotropy, which would violate one of the key assumptions of MR (see Chapter 2 for details).

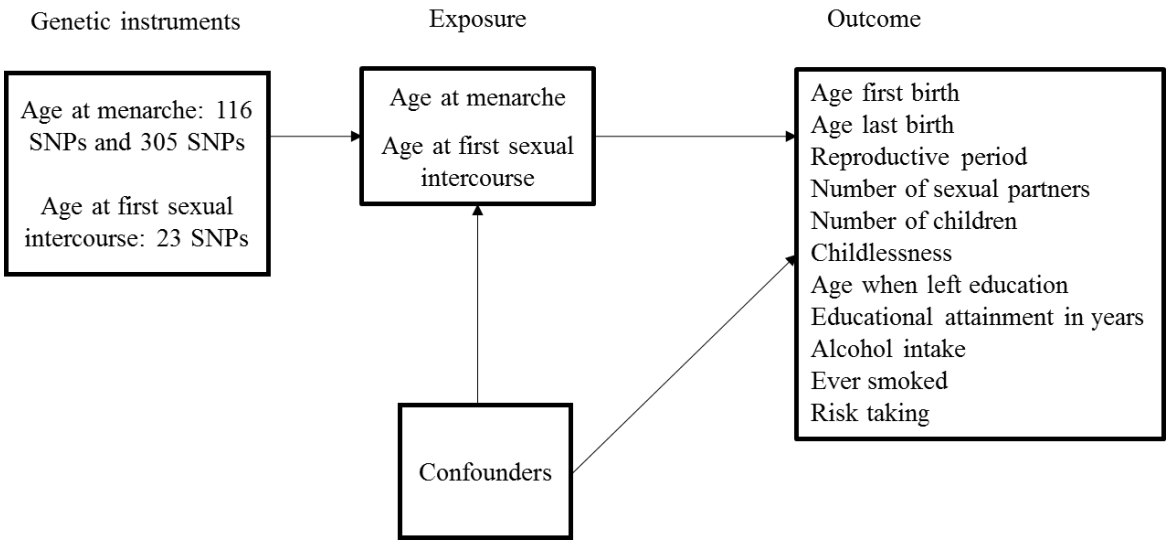

Figure 4:1 *Diagram representing MR analyses in this chapter. An example confounder in this case may be socioeconomic status which could be a common cause of age at menarche (James-Todd, Tehranifar, Rich-Edwards, Titievsky, & Terry, 2010; Mishra et al., 2009) and outcomes such as smoking status (Hiscock, Bauld, Amos, Fidler, & Munafò, 2012).*

4.2 Methods

4.2.1 Exposure instruments

For the age at menarche instruments, I used independent SNPs associated with age at menarche ($p<5\times10^{-8}$) from two GWAS separately (Day et al., 2017; Perry et al., 2014). The first identified 123 SNPs and explained approximately 3% of the observed variance in age at menarche (N = 182 416) (Perry et al., 2014). The second identified 389 SNPs which explained about approximately 7% of the variance (N = 329 345) (Day et al., 2017). I checked that there were no palindromic SNPs with MAF around 0.5 to ensure there were no issues with strand mismatches. I further used SNiPA (Arnold, Raffler, Pfeufer, Suhre, & Kastenmüller, 2015) with an LD threshold of 0.2 to check SNP independence. One of the 123 SNPs was removed due to high instability in its estimates. This resulted in 116 and 305 SNPs as instruments for age at menarche that were available in UK Biobank, excluding compound and tricyclic SNPs. The mean F statistic, indicating the strength of the instrument, was 60.98 for the 116 SNP instrument and 64.95 for the 305 SNP instrument. Mean differences and SEs for these SNPs and age at menarche associations in the GWAS discovery samples were recorded for each instrument and these became the exposure for age at menarche (see **Appendix 1** and **Appendix 2**).

For the instrument of age at first sexual intercourse, I used independent SNPs associated with age at first sexual intercourse ($p<5\times10^{-8}$) (Day, Helgason, et al., 2016) in both males and females. I recorded these GWAS associations, as done so for age at menarche, to be used as the instrument for age at first sexual intercourse (see **Appendix 3**). I used effect estimates identified in the pooled sex GWAS to increase statistical power. Of the 33 SNPs for the instrument of age at first sexual intercourse, there were 23 SNPs available in UK Biobank. These 23 SNPs passed all checks described above for age at menarche. The mean F statistic for the instrument was 39.22.

4.2.2 Outcomes

The outcome measures included were: age at first birth, age at last birth, reproductive period, number of children, childlessness, ever smoked, educational attainment in years, age when left education, alcohol intake, risk-taking and number of sexual partners for those that indicated they had had sex. These measures were derived similarly to previous research (Day, Helgason, et al., 2016; Okbay et al., 2016). I re-coded data as missing if age at first sexual intercourse was younger than age at menarche; if age at leaving education was answered as having never attended school; at the 99.99th percentile for number of children; at the 99.99th percentile for number of sexual partners. Reproductive period was derived as the difference between age at last birth and age at first birth for those that had more than one child. To account for non-normal or categorical data, I included binary measures of childlessness (childlessness coded as 1). I also included a measure for ever smoked (coded as 1 if participants had ever smoked in questions 'Do you smoke tobacco now?' or 'In the past, how often have you smoked tobacco?'). Alcohol intake was a categorical variable indicating 'never' (coded as 6), 'special occasions only', 'one to three times a month', 'once or twice a week', three to four times a week' and 'daily or almost daily' (coded as 1). Risk-taking was measured as 'yes' (coded as 1) or 'no' responses to 'Would you describe yourself as someone who takes risks?'. Only females were used for all outcome data.

4.2.3 Data analysis

The exposure associated SNPs described above were extracted from UK Biobank to derive SNP-outcome associations for the outcome data. Extraction was done using PLINK (v2.00) and best guess algorithms for determining alleles (further genotyping information in Chapter 3). Data were harmonized to ensure that the effect of the SNP on the exposure and the SNP on the outcome corresponded to the same allele. The age increasing allele was used in order to conduct MR analyses and results were then reversed to report the effect of earlier age at menarche and first sexual intercourse. To derive the

SNP-outcome associations for the outcome data, regressions were adjusted for birth year and the top 10 genetic principal components of population structure. In sensitivity analysis, I additionally adjusted SNP-outcome associations for genotype array.

I used the 116 SNPs for age at menarche (Perry et al., 2014) for the main analysis as this GWAS did not include any UK Biobank data. For the 305 SNP instrument which includes some individuals from the UK Biobank (Day et al., 2017), I calculated SNP-outcome associations and conducted analysis using outcome data from a UK Biobank sub-sample that did not overlap with the age at menarche GWAS. However, allocation into these sub-samples is related to smoking status (Wain et al., 2015) and division is therefore similar to stratifying on smoking. As smoking may be a collider (i.e., a common effect of the exposure and outcome) in this analysis then this stratification could introduce bias (see Chapter 5 for further discussion). I therefore also derived SNP-outcome estimates and conducted analysis for the 305 SNP age at menarche instrument using the full UK Biobank sample, which will suffer from bias towards the observational estimate due to sample overlap with the GWAS of the exposure (Burgess, Davies, & Thompson, 2016). It is also not possible to assess the suitability of one MR method, MR-Egger, with sample overlap as the suitability value (the I^2_{GX} value) cannot be reliably measured.

The age at first sexual intercourse GWAS (Day, Helgason, et al., 2016) was conducted solely in a sub-sample of UK Biobank data and I therefore conducted an unweighted analysis due to this sample overlap, using a fixed effects meta-analysis method. I conducted a fixed-effects meta-analysis of the SNP-outcome estimates in the full UK Biobank sample in addition to MR analysis in the non-overlapping sub-sample of UK Biobank. This fixed effects meta-analysis was only conducted for age at first sexual intercourse and not also for age at menarche. This fixed-effects meta-analysis is equivalent to performing an unweighted allele score analysis (Gill et al., 2018) and suffers from less bias than a weighted analysis with overlapping samples as it reduces the problem of overfitting and the estimate is therefore similar to one derived from distinct samples (Richardson et al., 2018). The units for this fixed effect meta-analysis therefore differs to the other MR methods as it is per increase in the number of effect alleles.

As discussed in Chapter 2, SNP-exposure and SNP-outcome data (i.e., SNP-exposure and SNP-outcome associations) were combined using IVW, weighted median, MBE and MR-Egger regression approaches. In addition to these analyses, I conducted Radial MR and a leave-one-out analysis for age at first sexual intercourse which helps to identify outlier

SNPs (see Chapter 2 for details) (Bowden et al., 2018). For binary outcomes, all MR results were transformed to odds ratios (ORs) by exponentiating them.

I calculated Cochran's Q for these IVW analyses to examine if effects differ across genetic variants (Davies, Holmes, et al., 2018). I further calculated the I^2_{GX} to assess the suitability of MR-Egger where above 0.9 is desired (Bowden, Fabiola Del Greco, et al., 2016).

Lastly, in an attempt to account for potential pleiotropic effects of age at menarche SNPs with BMI, age at menarche analysis using the 116 SNP instrument was repeated after removing SNPs associated with BMI at $p<5\times10^{-8}$ (Gill et al., 2018; Locke, Kahali, Berndt, Justice, & Pers, 2015; Sequeira et al., 2017). This resulted in 9 SNPs being removed: rs10938397, rs12446632, rs2947411, rs3101336, rs543874, rs7103411, rs7138803, rs7514705, rs8050136.

4.3 Results

4.3.1 Descriptives

Mean age in the UK Biobank sample was 57 years (standard deviation (SD): 7.91). Mean age at menarche and first sexual intercourse were 13 years (SD: 1.60) and 19 years (SD: 3.44), respectively. Further sample characteristics are given in **Table 4:1**.

Table 4:1 *Participant characteristics of UK Biobank sample.*

	Total N	**Mean (SD) or N (%)**
Age at assessment, years	181 358	56.67 (7.91)
Age at menarche, years	176 262	12.95 (1.60)
Age at first sex, years	154 599	19.02 (3.44)
Age first birth, years	124 093	25.39 (4.54)
Age last birth, years	123 926	30.15 (4.80)
Reproductive period, years	123 892	4.76 (3.65)
Number of sexual partners	149 902	4.63 (6.99)
Number of children	181 247	1.81 (1.15)
Childlessness		
Yes	181 255	33 242 (18.34)
No		148 013 (81.66)
Age when left education, years	124 279	16.63 (2.03)
Educational attainment, years	179 731	13.05 (4.32)
Alcohol intake		
Daily or almost daily		30 918 (17.06)
Three or four times a week		39 346 (21.71)
Once or twice a week	181 233	47 864 (26.41)
One to three times a month		23 723 (13.09)
Special occasions only		25 101 (13.85)
Never		14 281 (7.88)
Ever smoked		
Yes	180 751	101 112 (55.94)
No		79 639 (44.06)
Risk-taking		
Yes	174 718	31 973 (18.30)
No		142 745 (81.70)

4.3.2 Age at menarche

Further details of the instruments are provided in **Table 4:2**. Cochran's Q values indicate that most measures show evidence for overdispersion, although the dispersion appeared balanced when plotted (see **Appendix 4** and **Appendix 5**). The age at menarche 305 SNP instrument in **Table 4:2** is for the non-overlapping UK Biobank sample. For the age at menarche instruments, the I^2_{GX} values indicate that MR-Egger regression is appropriate.

Table 4:2 *Estimates for the I^2_{GX} and Cochran's Q*

	Age at menarche				**Age at first sexual intercourse**	
	116 SNPs		**305 SNPs**			
Unweighted I^2_{GX}	0.9		0.9		0.6	
	Q	***p***	**Q**	***p***	**Q**	***p***
Reproduction						
Age first birth	323.47	<0.001	575.69	<0.001	52.01	<0.001
Age last birth	273.22	<0.001	402.69	<0.001	41.96	0.01
Reproductive period	139.87	0.06	347.55	0.04	33.28	0.06
Number of sexual partners	178.63	<0.001	466.96	<0.001	23.87	0.35
Number of children	203.17	<0.001	414.35	<0.001	52.18	<0.001
Childlessness	187.30	<0.001	413.68	<0.001	53.89	<0.001
Education						
Age when left education	233.24	<0.001	442.82	<0.001	33.27	0.06
Educational attainment in years	259.91	<0.001	468.65	<0.001	30.53	0.11
Risky behaviours						
Alcohol intake	268.60	<0.001	565.41	<0.001	28.07	0.17
Ever smoked	227.40	<0.001	561.59	<0.001	67.12	<0.001
Risk-taking	146.57	0.03	392.27	<0.001	38.48	0.02

Using the 116 SNP instrument for age at menarche, there was consistent evidence of a causal effect of earlier age at menarche on earlier age at first birth across all MR methods. There was some evidence of an effect of earlier age at menarche on earlier age at last birth and all MR methods showed point estimates in a consistent direction. There was no clear evidence of an effect of age at menarche on duration of reproductive years, number of children, or number of sexual partners, and little evidence for an effect on likelihood of being childless with results showing confidence intervals consistent with the null and inconsistency for the direction of point estimates across MR methods. These results are presented in **Table 4:3** and **Table 4:4**.

Table 4:3 *Estimates of the causal effect of earlier age at menarche (116 SNP instrument) on life history outcomes using full UK Biobank data.*

		IVW		**MR-Egger regression**		**Weighted median**		**Weighted MBE**	
	N	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***
Reproduction									
Age first birth	115070 - 124093	-0.256 (-0.342, -0.171)	<0.001	-0.260 (-0.522, 0.002)	0.05	-0.325 (-0.471, -0.178)	<0.001	-0.362 (-0.722, -0.002)	0.05
Age last birth	114916 - 123926	-0.235 (-0.325, -0.144)	<0.001	-0.208 (-0.487, 0.07)	0.14	-0.241 (-0.391, -0.091)	0.002	-0.225 (-0.515, 0.066)	0.13
Reproductive period	114883 - 123892	0.018 (-0.053, 0.088)	0.62	0.040 (-0.175, 0.255)	0.71	0.015 (-0.09, 0.12)	0.78	-0.076 (-0.335, 0.184)	0.57
Number of sexual partners	138920 - 149902	-0.052 (-0.171, 0.067)	0.39	0.094 (-0.27, 0.459)	0.61	-0.030 (-0.235, 0.175)	0.77	-0.010 (-0.423, 0.403)	0.96
Number of children	168050 - 181247	-0.016 (-0.034, 0.002)	0.09	0.023 (-0.033, 0.078)	0.42	-0.022 (-0.052, 0.007)	0.14	0.020 (-0.042, 0.082)	0.53
Childlessness	168058 - 181255	1.060 (1.017, 1.105)	0.01	0.987 (0.869, 1.121)	0.84	1.047 (0.978, 1.121)	0.18	1.038 (0.905, 1.192)	0.59
Education									
Age when left education	115204 - 124279	-0.062 (-0.100, -0.024)	0.002	-0.153 (-0.27, -0.036)	0.01	-0.095 (-0.158, -0.031)	0.004	-0.126 (-0.283, 0.031)	0.12
Educational attainment in years	166640 - 179731	-0.072 (-0.139, -0.005)	0.04	-0.237 (-0.443, -0.03)	0.03	-0.128 (-0.253, -0.003)	0.05	-0.246 (-0.487, -0.005)	0.05
Risky behaviours									
Alcohol intake	168039 - 181233	0.059 (0.035, 0.083)	<0.001	-0.030 (-0.103, 0.044)	0.43	0.035 (-0.007, 0.077)	0.10	0.007 (-0.075, 0.089)	0.86

Ever smoked	167584 - 180751	1.002 (0.970, 1.034)	0.92	1.015 (0.921, 1.121)	0.76	0.994 (0.942, 1.049)	0.83	1.035 (0.924, 1.16)	0.55
Risk-taking	161994 - 174718	0.989 (0.949, 1.032)	0.61	1.092 (0.96, 1.242)	0.18	0.984 (0.916, 1.058)	0.67	0.979 (0.832, 1.153)	0.81

Note: CI: confidence interval

Table 4:4 *MR-Egger intercept values for age at menarche (116 SNP instrument) on life history outcomes using full UK Biobank data.*

	MR-Egger intercept		
	β or OR	**95% CI**	***p***
Reproduction			
Age first birth	0.0002	-0.011, 0.012	0.98
Age last birth	-0.001	-0.013, 0.011	0.84
Reproductive period	-0.001	-0.011, 0.008	0.82
Number of sexual partners	-0.007	-0.023, 0.009	0.40
Number of children	-0.002	-0.004, 0.001	0.15
Childlessness	1.003	0.998, 1.009	0.24
Education			
Age when left education	0.004	-0.001, 0.009	0.11
Educational attainment in years	0.008	-0.001, 0.017	0.10
Risky behaviours			
Alcohol intake	0.004	0.001, 0.007	0.01
Ever smoked	0.999	0.995, 1.004	0.77
Risk-taking	0.995	0.990, 1.001	0.11

For educational outcomes, there was evidence of an effect of earlier age at menarche on lower educational attainment and age at leaving education across most MR methods and consistent point estimates for all MR methods (see **Table 4:3** and **Table 4:4**). Alcohol intake appeared to decrease with earlier age at menarche, but the MR-Egger intercept indicated directional horizontal pleiotropy ($p = 0.013$), suggesting that this effect does not remain when horizontal pleiotropy is accounted for (see **Table 4:3** and **Table 4:4**). No clear evidence was found for effects of age at menarche on having ever smoked or risk-taking behaviour although these measures were binary and hence there was less statistical power to detect effects (see **Table 4:3**).

After removing SNPs also associated with BMI (Gill et al., 2018; Locke et al., 2015) from the genetic risk score, results were broadly similar to the main analysis although MR-Egger regression analysis showed decreased estimates and for many outcomes the *p*-values increased. This could be due to eliminating a possible pathway via BMI and/or reduced statistical power as a result of using fewer SNPs (see **Table 4:5** and **Table 4:6**). Note that for this age at menarche instrument after removal of BMI associated SNPs, the I^2_{GX} statistic was 0.9 and the mean F statistic was 61.07.

I repeated analyses using the 305 SNP instrument for age at menarche. Results were broadly similar to the main analysis (using the 116 SNP instrument) (see **Table 4:7**, **Table 4:8**, **Table 4:9**, and **Table 4:10**). There was slight increased evidence for an effect on number of sexual partners, ever smoked and childlessness. This analysis suffers from greater bias as it is uses a sub-sample of UK Biobank (described briefly above and further in Chapter 5) or alternatively, when using the entire UK Biobank sample in analyses, it results in overlap between the exposure and outcome datasets which has shown to bias results towards the observational estimate (Burgess et al., 2016).

Table 4:5 *Estimates of the causal effect of earlier age at menarche (116 SNP instrument) on life history outcomes using full UK Biobank data excluding SNPs associated with BMI at $p<5\times10^{-8}$ (9 SNPs excluded).*

	N	IVW		MR-Egger regression		Weighted median		MBE	
		β or OR (95% CI)	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***
Reproduction									
Age first birth	115070 - 124093	-0.244 (-0.333, -0.155)	<0.001	-0.215 (-0.479, 0.049)	0.11	-0.323 (-0.470, -0.176)	<0.001	-0.356 (-0.703, -0.009)	0.05
Age last birth	114916 - 123926	-0.225 (-0.319, -0.130)	<0.001	-0.188 (-0.469, 0.093)	0.19	-0.231 (-0.394, -0.068)	0.01	-0.205 (-0.500, 0.089)	0.17
Reproductive period	114883 - 123892	0.015 (-0.058, 0.087)	0.70	0.016 (-0.201, 0.232)	0.89	0.013 (-0.100, 0.126)	0.82	-0.074 (-0.328, 0.180)	0.57
Number of sexual partners	138920 - 149902	-0.084 (-0.208, 0.039)	0.18	0.101 (-0.266, 0.469)	0.59	-0.030 (-0.231, 0.170)	0.77	0.016 (-0.397, 0.428)	0.94
Number of children	168050 - 181247	-0.019 (-0.038, -0.0003)	0.05	0.016 (-0.040, 0.072)	0.58	-0.023 (-0.054, 0.008)	0.15	0.018 (-0.044, 0.080)	0.57
Childlessness	168058 - 181255	1.065 (1.020, 1.112)	0.004	0.994 (0.874, 1.130)	0.93	1.048 (0.978, 1.122)	0.19	1.034 (0.898, 1.189)	0.64
Education									
Age when left education	115204 - 124279	-0.061 (-0.101, -0.021)	0.003	-0.129 (-0.247, -0.011)	0.03	-0.102 (-0.165, -0.040)	0.002	-0.126 (-0.285, 0.033)	0.12
Educational attainment	166640 - 179731	-0.086 (-0.156, -0.016)	0.02	-0.242 (-0.451, -0.034)	0.02	-0.131 (-0.254, -0.009)	0.04	-0.232 (-0.475, 0.012)	0.07
Risky behaviours									
Alcohol intake	168039 - 181233	0.050 (0.025, 0.075)	<0.001	-0.041 (-0.115, 0.034)	0.28	0.020 (-0.022, 0.062)	0.34	0.006 (-0.077, 0.089)	0.88
Ever smoked	167584 - 180751	0.982 (0.950, 1.015)	0.28	0.995 (0.901, 1.098)	0.91	0.983 (0.931, 1.037)	0.53	0.966 (0.864, 1.080)	0.54
Risk-taking	161994 - 174718	0.985 (0.943, 1.029)	0.49	1.075 (0.944, 1.225)	0.27	0.983 (0.911, 1.062)	0.66	0.979 (0.835, 1.149)	0.80

Table 4:6 *MR-Egger intercept values for age at menarche (116 SNP instrument) on life history outcomes using full UK Biobank data and excluding SNPs associated with BMI at $p<5\times10^{-8}$ (9 SNPs excluded).*

	MR-Egger intercept		
	β or OR	**95% CI**	***p***
Reproduction			
Age first birth	-0.001	-0.013, 0.010	0.82
Age last birth	-0.002	-0.014, 0.011	0.78
Reproductive period	-0.0001	-0.010, 0.010	0.99
Number of sexual partners	-0.009	-0.025, 0.008	0.29
Number of children	-0.002	-0.004, 0.001	0.19
Childlessness	1.003	0.998, 1.009	0.26
Education			
Age when left education	0.003	-0.002, 0.008	0.23
Educational attainment	0.007	-0.002, 0.016	0.12
Risky behaviours			
Alcohol intake	0.004	0.001, 0.008	0.01
Ever smoked	0.999	0.995, 1.004	0.79
Risk-taking	0.996	0.990, 1.002	0.16

Table 4:7 *Estimates of the causal effect of earlier age at menarche (305 SNP instrument) on life history outcomes using non-overlapping UK Biobank data.*

		IVW		**MR-Egger regression**		**Weighted Median**		**MBE**	
	N	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***
Reproduction									
Age first birth	75469 - 90503	-0.286 (-0.361, -0.211)	<0.001	-0.342 (-0.540, -0.144)	0.001	-0.320 (-0.444, -0.195)	<0.001	-0.261 (-0.607, 0.086)	0.14
Age last birth	75366 - 90382	-0.255 (-0.335, -0.175)	<0.001	-0.224 (-0.435, -0.013)	0.04	-0.174 (-0.307, -0.041)	0.01	-0.119 (-0.434, 0.196)	0.46
Reproductive period	75343 - 90357	0.027 (-0.035, 0.089)	0.39	0.115 (-0.047, 0.278)	0.16	0.030 (-0.076, 0.136)	0.58	0.055 (-0.223, 0.332)	0.70
Number of sexual partners	90768 - 108801	-0.116 (-0.218, -0.015)	0.03	0.110 (-0.068, 0.467)	0.14	0.027 (-0.152, 0.206)	0.77	0.113 (-0.289, 0.515)	0.58
Number of children	109636 - 131506	-0.002 (-0.018, 0.014)	0.77	0.015 (-0.027, 0.057)	0.49	-0.003 (-0.029, 0.023)	0.80	0.067 (-0.019, 0.154)	0.13
Childlessness	109641 - 131512	1.036 (0.998, 1.075)	0.06	1.074 (0.974, 1.184)	0.15	1.028 (0.968, 1.091)	0.38	0.982 (0.841, 1.146)	0.82
Education									
Age when left education	75041 - 89959	-0.051 (-0.085, -0.017)	0.003	-0.012 (-0.101, 0.077)	0.80	-0.074 (-0.130, -0.018)	0.01	0.049 (-0.143, 0.241)	0.62
Educational attainment	108704 - 130387	-0.088 (-0.148, -0.029)	0.004	-0.207 (-0.364, -0.049)	0.01	-0.211 (-0.311, -0.111)	<0.001	-0.283 (-0.529, -0.037)	0.03
Risky behaviours									
Alcohol intake	109615 - 131487	0.051 (0.030, 0.073)	<0.001	0.037 (-0.019, 0.092)	0.20	0.040 (0.003, 0.077)	0.04	0.011 (-0.086, 0.107)	0.83
Ever smoked	109288 - 131109	0.970 (0.943, 0.998)	0.04	1.040 (0.964, 1.121)	0.31	0.963 (0.914, 1.014)	0.16	0.968 (0.861, 1.089)	0.59
Risk-taking	105717 - 126762	0.991 (0.955, 1.029)	0.65	1.057 (0.958, 1.166)	0.27	0.992 (0.929, 1.058)	0.80	1.035 (0.877, 1.222)	0.68

Table 4:8 *MR-Egger intercept values for age at menarche (305 SNP instrument) on life history outcomes using non-overlapping UK Biobank data.*

	MR-Egger intercept		
	β or OR	**95% CI**	***p***
Reproduction			
Age first birth	0.002	-0.005, 0.010	0.55
Age last birth	-0.001	-0.009, 0.007	0.76
Reproductive period	-0.004	-0.010, 0.003	0.25
Number of sexual partners	-0.013	-0.023, -0.003	0.01
Number of children	-0.001	-0.002, 0.001	0.39
Childlessness	0.999	0.995, 1.002	0.44
Education			
Age when left education	-0.002	-0.005, 0.002	0.35
Educational attainment	0.005	-0.001, 0.011	0.11
Risky behaviours			
Alcohol intake	0.001	-0.002, 0.003	0.57
Ever smoked	0.997	0.994, 1.000	0.05
Risk-taking	0.997	0.994, 1.001	0.17

Table 4:9 *Estimates of the causal effect of earlier age at menarche (305 SNP instrument) on life history outcomes using full UK Biobank data.*

	N	IVW		MR-Egger regression		Weighted median		MBE	
		β or OR (95% CI)	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***
Reproduction									
Age first birth	103472 - 124093	-0.325 (-0.390, -0.261)	<0.001	-0.263 (-0.433, -0.093)	0.003	-0.314 (-0.423, -0.205)	<0.001	-0.290 (-0.625, 0.044)	0.09
Age last birth	103332 - 123926	-0.287 (-0.356, -0.219)	<0.001	-0.176 (-0.357, 0.005)	0.06	-0.236 (-0.357, -0.115)	<0.001	-0.116 (-0.406, 0.175)	0.44
Reproductive period	103302 - 123892	0.034 (-0.019, 0.087)	0.21	0.084 (-0.056, 0.223)	0.24	0.025 (-0.063, 0.112)	0.58	0.034 (-0.232, 0.301)	0.80
Number of sexual partners	125058 - 149902	-0.089 (-0.179, 0.001)	0.05	0.006 (-0.231, 0.242)	0.96	-0.049 (-0.217, 0.118)	0.56	0.010 (-0.344, 0.363)	0.96
Number of children	151104 - 181247	-0.004 (-0.018, 0.010)	0.58	-0.010 (-0.045, 0.026)	0.60	-0.009 (-0.032, 0.015)	0.46	0.002 (-0.055, 0.060)	0.94
Childlessness	151111 - 181255	1.032 (1.000, 1.065)	0.05	1.096 (1.009, 1.190)	0.03	1.056 (1.001, 1.114)	0.05	1.076 (0.944, 1.227)	0.27
Education									
Age when left education	103643 - 124267	-0.060 (-0.089, -0.031)	<0.001	-0.065 (-0.141, 0.012)	0.10	-0.068 (-0.115, -0.020)	0.01	-0.022 (-0.185, 0.141)	0.79
Educational attainment	149833 - 179731	-0.048 (-0.099, 0.003)	0.06	-0.148 (-0.282, -0.013)	0.03	-0.126 (-0.220, -0.032)	0.01	-0.154 (-0.386, 0.077)	0.19
Risky behaviours									
Alcohol intake	151085 - 181233	0.052 (0.034, 0.070)	<0.001	0.050 (0.002, 0.097)	0.04	0.050 (0.018, 0.083)	0.002	0.010 (-0.080, 0.101)	0.82
Ever smoked	150677 - 180751	0.972 (0.949, 0.996)	0.02	1.027 (0.962, 1.094)	0.43	0.971 (0.929, 1.014)	0.19	0.976 (0.883, 1.078)	0.63
Risk-taking	145713 - 174718	0.999 (0.967, 1.031)	0.94	1.080 (0.993, 1.175)	0.07	0.989 (0.933, 1.048)	0.72	1.000 (0.855, 1.171)	0.10

Table 4:10 *MR-Egger intercept values for age at menarche (305 SNP instrument) on life history outcomes using full UK Biobank data.*

	MR-Egger intercept		
	β or OR	**95% CI**	***p***
Reproduction			
Age first birth	-0.003	-0.009, 0.004	0.44
Age last birth	-0.005	-0.011, 0.002	0.19
Reproductive period	-0.002	-0.007, 0.003	0.45
Number of sexual partners	-0.004	-0.013, 0.005	0.40
Number of children	0.0002	-0.001, 0.002	0.74
Childlessness	0.998	0.994, 1.001	0.12
Education			
Age when left education	0.0002	-0.003, 0.003	0.90
Educational attainment	0.004	-0.001, 0.009	0.12
Risky behaviours			
Alcohol intake	0.0001	-0.002, 0.002	0.92
Ever smoked	0.998	0.995, 1.000	0.07
Risk-taking	0.997	0.994, 1.000	0.05

4.3.3 Age at first sexual intercourse

Further details of the instrument are provided in **Table 4:2**. Again, Cochran's Q values indicate that most measures show evidence for overdispersion (see **Appendix 6**). The low I^2_{GX} value indicates that a SIMEX adjustment for MR-Egger should be conducted. I therefore performed and present the results for a SIMEX adjusted unweighted MR-Egger regression analysis of age at first sexual intercourse.

I conducted a fixed effects meta-analysis of the 23 SNP-outcome associations in UK Biobank and found evidence of relationships for earlier age at first sexual intercourse with earlier age at first birth, earlier age at last birth, a longer reproductive period, increased number of sexual partners, a greater number of children, decreased likelihood of being childlessness, earlier age at leaving education, lower educational attainment, increased likelihood of having ever smoked and increased likelihood of risk-taking behaviour (see **Table 4:11**).

Table 4:11 *Fixed effects meta-analysis of SNP-outcome associations using full UK Biobank and SNPs identified for age at first sexual intercourse.*

		Fixed effects meta-analysis		
	N	**β or OR**	**95% CI**	***p***
Reproduction				
Age first birth	109 021 – 124 093	-0.061	-0.069, -0.053	<0.001
Age last birth	108 873 – 123 926	-0.046	-0.055, -0.037	<0.001
Reproductive period	108 842 – 123 892	0.015	0.008, 0.022	<0.001
Number of sexual partners	131 643 – 149 902	0.019	0.007, 0.030	0.002
Number of children	159 140 – 181 247	0.006	0.004, 0.008	<0.001
Childlessness	159 147 – 181 255	0.986	0.982, 0.990	<0.001
Education				
Age when left education	109 137 – 124 279	-0.011	-0.015, -0.007	<0.001
Educational attainment in years	157 817 – 179 731	-0.015	-0.022, -0.008	<0.001
Risky behaviours				
Alcohol intake	159 137 – 181 233	0.001	-0.001, 0.003	0.409
Ever smoked	158 702 – 180 751	1.010	1.007, 1.014	<0.001
Risk-taking	153 432 – 174 718	1.011	1.006, 1.015	<0.001

There appeared to be a consistent effect of earlier age at first sexual intercourse on earlier age at last birth and increased likelihood of risk-taking behaviour across MR methods (see **Table 4:12**). In this MR analysis, I took SNP-exposure associations from a GWAS (Day, Helgason, et al., 2016) and SNP-outcome associations in a sub-sample of UK Biobank, therefore likely affected by selection bias (see Chapter 5 for further discussion).

The MR-Egger intercept showed evidence of directional horizontal pleiotropy for most outcomes (see **Table 4:13**) and, as discussed, this MR analysis may suffer from bias due to stratifying the UK Biobank sample. Overall, results for Radial MR and a leave-one-out analysis suggested no strong influence of outliers. Although there appeared to be a consistent outlier in age at first sexual intercourse analysis (rs538498277) when plotting (see **Appendix 7**), there was no formal evidence of this using radial MR, with second order modified weights and a *p*-value of 0.01 (Bowden et al., 2018), apart from in relation to ever smoked as an outcome (see **Appendix 8**). Another SNP (rs2188151) was most often identified as the top outlier in Radial MR (see **Appendix 8**). I therefore conducted a leave-one-out analysis to ensure that no outliers, including rs2188151, were having a relatively large effect on estimates (Hemani, Zheng, et al., 2018). This showed that estimates with a SNP removed were all within the confidence intervals for every other SNP, suggesting no strong influence of outliers (see **Appendix 9**).

Table 4:12 *Estimates of the causal effect of earlier age at first sexual intercourse on life history outcomes using non-overlapping UK Biobank data.*

		IVW		**SIMEX MR-Egger regression**		**Weighted median**		**MBE**	
	N	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***	**β or OR (95% CI)**	***p***
Reproduction									
Age first birth	79494 - 90503	-2.146 (-2.524, -1.768)	<0.001	0.738 (0.480, 0.996)	<0.001	-2.301 (-2.864, -1.739)	<0.001	-2.535 (-3.858, -1.211)	0.001
Age last birth	79387 - 90382	-1.687 (-2.090, -1.284)	<0.001	-0.611 (-0.883, -0.339)	<0.001	-1.546 (-2.143, -0.950)	<0.001	-1.567 (-2.855, -0.278)	0.03
Reproductive period	79365 - 90357	0.456 (0.146, 0.767)	0.01	-1.371 (-1.625, -1.118)	<0.001	0.341 (-0.086, 0.768)	0.13	0.403 (-0.569, 1.375)	0.43
Number of sexual partners	95510 - 108801	0.327 (-0.184, 0.838)	0.20	0.039 (-0.192, 0.269)	0.75	-0.155 (-0.828, 0.517)	0.66	-0.184 (-1.668, 1.301)	0.81
Number of children	115445 - 131506	0.223 (0.143, 0.303)	<0.001	-0.167 (-0.247, -0.086)	0.001	0.191 (0.067, 0.316)	0.006	0.044 (-0.276, 0.363)	0.79
Childlessness	115450 - 131512	0.605 (0.502, 0.728)	<0.001	1.021 (0.908, 1.147)	0.74	0.732 (0.557, 0.963)	0.04	0.905 (0.504, 1.625)	0.74
Education									
Age when left education	78953 - 89959	-0.285 (-0.456, -0.115)	0.002	0.596 (0.357, 0.835)	<0.001	-0.160 (-0.401, 0.081)	0.21	-0.112 (-0.648, 0.424)	0.69
Educational attainment	114477 - 130387	-0.484 (-0.784, -0.183)	0.003	0.109 (-0.036, 0.255)	0.15	-0.247 (-0.659, 0.164)	0.25	0.045 (-0.818, 0.907)	0.92
Risky behaviours									
Alcohol intake	115436 - 131487	0.026 (-0.081, 0.133)	0.62	-0.375 (-0.498, -0.252)	<0.001	0.049 (-0.102, 0.200)	0.53	0.077 (-0.256, 0.410)	0.66
Ever smoked	115090 - 131109	1.393 (1.206, 1.608)	<0.001	0.567 (0.492, 0.653)	<0.001	1.391 (1.103, 1.754)	0.01	1.425 (0.751, 2.704)	0.29

Risk-taking	111292 - 126762	1.348 (1.117, 1.626)	0.003	1.603 (1.297, 1.982)	<0.001	1.527 (1.177, 1.982)	0.004	1.523 (0.813, 2.851)	0.20

Table 4:13 *SIMEX unweighted MR-Egger intercept values for age at first sexual intercourse on life history outcomes using non-overlapping UK Biobank data.*

	MR-Egger intercept		
	β or OR	**95% CI**	***p***
Reproduction			
Age first birth	-0.082	-0.101, -0.063	<0.001
Age last birth	-0.030	-0.048, -0.013	0.002
Reproductive period	0.052	0.036, 0.069	<0.001
Number of sexual partners	0.009	-0.008, 0.027	0.30
Number of children	0.011	0.006, 0.015	<0.001
Childlessness	0.986	0.977, 0.995	0.01
Education			
Age when left education	-0.025	-0.034, -0.016	<0.001
Educational attainment in years	-0.017	-0.027, -0.006	0.01
Risky behaviours			
Alcohol intake	0.011	0.006, 0.017	0.001
Ever smoked	1.026	1.018, 1.035	<0.001
Risk-taking	0.995	0.985, 1.004	0.27

4.4 Discussion

4.4.1 Summary of results and previous literature

The results suggest that earlier age at menarche is causally related to some traits that characterize a fast life history strategy, such as earlier age at first birth, earlier age at last birth, lower educational attainment, and earlier age at leaving education. This is consistent with previous findings (Day, Helgason, et al., 2016; Gill et al., 2017). There was no clear effect of age at menarche on number of children in this female only sample (Day, Helgason, et al., 2016). Here, applying additional MR methods to those used previously, the effect of age at menarche on alcohol intake is not robust (Day, Helgason, et al., 2016).

Results show mixed evidence for age at first sexual intercourse on these life history traits, with results suggesting possible violation of the exclusion restriction assumption of no direct effects of the instrument on the outcome not acting through the exposure (i.e., the presence of directional horizontal pleiotropy) (Bowden et al., 2017; Davey Smith & Ebrahim, 2003). There is evidence for the presence of directional horizontal pleiotropy on multiple outcomes, suggesting that previous findings may have also included pleiotropic effects and may be questionable (Day, Helgason, et al., 2016). Results for age at first sexual intercourse are therefore not robust and our ability to infer causality is weakened.

4.4.2 Life history theory

The effects of earlier age at menarche on these reproductive and educational traits can be viewed as directing effort towards short-term reproductive goals and risky behaviour as an important part of a fast life history strategy (Ellis & Bjorklund, 2012). Variation in age at menarche may therefore represent an important causal component of a suite of adaptations (Belsky et al., 1991). Earlier age at first birth as part of a fast life history strategy can be considered an adaptive response to early life adversity and the present finding of an effect of earlier age at menarche on earlier age at first birth is therefore in line with this (Nettle, Coall, & Dickins, 2011). It is, however, interesting that there is an effect of earlier age at menarche on earlier age at last birth, with no clear effect on reproductive period. This suggests that individuals on a fast life history strategy are not just starting their reproductive life earlier but shifting their reproductive life forward in time. Nettle highlights that individuals in more deprived areas with short life expectancy, likely on a fast life history strategy, need to reproduce earlier than individuals in more affluent areas with higher life expectancy to be in good health for an equivalent period of care (Nettle, 2010). Education is a key predictor of positive later life outcomes in the UK,

and the present finding of a causal effect of earlier age at menarche on decreased educational attainment provides important information for determinants of educational attainment which should be independent from confounding (Gill et al., 2017). Investing in education can be seen as a slow life history trait with delayed benefits (Sng, Neuberg, Varnum, & Kenrick, 2017). The effect of age at menarche on educational attainment may be due to variation in cognition following variation in age at menarche and gonadal hormones, due to menarche, that may influence behaviour during schooling (Gill et al., 2017; Schulz & Sisk, 2016).

As a component of life history strategies, it is expected to see an effect of earlier age at menarche on increased number of children or likelihood of remaining childless, although access to contraception may influence this relationship. Number of sexual partners has previously been used as a proxy for reproductive success in a post-contraceptive environment, although it should be noted that contraception allows for the decoupling of sexual and reproductive partners (Nettle & Clegg, 2006). The present findings did not show a clear effect of age at menarche on number of sexual partners although female reproductive success is less dependent on number of sexual partners than males. It is further possible that the effect of age at menarche on number of children is masked by the detrimental effects of risky behaviours, such as substance use, on fertility in the modern environment (Anderson, Nisenblat, & Norman, 2010; Eggert, Theobald, & Engfeldt, 2004). Although these results show no clear evidence for an effect of earlier age at menarche on increased risky behaviours and substance use, binary measures of smoking and risk-taking were used, resulting in less statistical power. Furthermore, the measure of risk-taking was a single item asking whether participants would describe themselves as someone who takes risks and may not capture the full extent of risk-taking behaviour. There was no clear effect of age at menarche on alcohol intake, another form of substance use which has also been shown to be associated with decreased fertility (Anderson et al., 2010; Eggert et al., 2004). Further research should examine the mediating causal relationships between age at menarche and fertility in the modern environment using more detailed measures of substance use and larger samples.

4.4.3 Strengths

This study highlights how MR can be applied to test predictions within life history theory to provide evidence of causality and increase our understanding of health and social behaviour. A strength of the present study is the use of multiple MR methods. This allowed for extending upon the findings of previous research (Day, Helgason, et al., 2016) and for triangulation across methods, each with varying and orthogonal

assumptions, to provide greater confidence in results (Lawlor, Tilling, & Davey Smith, 2016). I was further able to compare evidence using two instruments for age at menarche. Additionally, I used a large population-based sample for the analysis to help identify the small effects common in genetic studies (Gage, Jones, et al., 2016), although I acknowledge that for binary outcomes power was more limited.

4.4.4 Limitations

There are also a number of limitations to consider. Most importantly, as there are currently no appropriate instruments for early life stress to be used within MR and it is therefore not possible to investigate early life stress using MR, I examined the effects of two intermediate reproductive traits (age at menarche and age at first sexual intercourse) on further reproductive and behavioural outcomes. Taking this life course approach to the causal pathways in life history theory by assuming earlier menarche is a proxy for early life adversity has limitations. Namely, early menarche is associated with both good condition and early life adversity, likely with different developmental pathways. I did not stratify analysis on any measure of adversity, or a proxy for adversity such as socioeconomic status. There has been a secular trend of decreasing age at menarche in recent times, perhaps due to obesity or improved living conditions (Ellis, 2004). This trend therefore also includes individuals that are assumed to be on a slow life history strategy. The present study therefore cannot fully disentangle those on a fast or slow life history strategy although it is assumed that earlier menarche and age at first sexual intercourse is a proxy for early life adversity and therefore an indicator of a fast life history strategy. I attempted to account for the possibility of effects of age at menarche acting via BMI in sensitivity analyses. The multiple possible interpretations of early age at menarche and age at first sexual intercourse are a strong limitation of this work however it is still important to examine all components of the life history theory framework, rather than to focus only on the effects of early life adversity on reproductive traits such as age at menarche.

Second, the age at first sexual intercourse GWAS was conducted in a sub-sample of UK Biobank data and I therefore conducted an unweighted analysis due to this sample overlap, using a fixed effects meta-analysis method. I additionally conducted MR by dividing the outcome sample to avoid overlap of participants, however this may have introduced bias as sub-division is related to smoking status and therefore akin to stratifying on smoking, which may be affected by the exposure and outcome (see Chapter 5 for further discussion) (Wain et al., 2015).

Third, I used SNPs for age at first sexual intercourse, and their associations, identified in a pooled sex GWAS, due to reductions in power of using SNPs identified in females only, and the exposure and outcome data therefore consist of different populations (not advised for MR studies) (Lawlor, 2016). Although most genetic variants showed sex-concordant associations in the GWAS, six genetic variants in the instrument for age at first sexual intercourse showed some evidence of sex-discordant associations (Day, Helgason, et al., 2016). The unweighted analysis for age at first sexual intercourse did not use GWAS estimates (Burgess & Thompson, 2013; Gill et al., 2018).

Fourth, UK Biobank data is unrepresentative of the population, with a 5% response rate, and therefore suffers from selection bias which may generate spurious associations (see Chapter 5 for further discussion) (Allen et al., 2014; Davey Smith & Davies, 2016; Munafò, Tilling, Taylor, Evans, & Davey Smith, 2018). Finally, genetic variants are non-specific and we cannot fully remove population structure, which can induce spurious associations through confounding, even within a sample of European ancestry and adjusting for principal components of population structure as done so here (Haworth et al., 2019).

4.4.5 Conclusions

I found some evidence that age at menarche is causally related to other life history traits and outcomes. Age at first sexual intercourse was also related to many life history outcomes, although there was evidence of directional horizontal pleiotropy which violates the exclusion restriction assumption of MR and results should therefore be treated with caution (Bowden et al., 2017; Davey Smith & Hemani, 2014). This study highlights how analyses techniques from genetic epidemiology can be used to answer how life history traits are related within life history strategies, and to better understand determinants of reproductive and social behaviour.

4.5 Chapter summary

In this chapter, I applied MR methods to investigate life history theory using instruments for age at menarche and age at first sexual intercourse and UK Biobank data. The results suggest that earlier age at menarche affects some traits that characterize life history strategies including earlier age at first and last birth, decreased educational attainment, and decreased age at leaving education. Unfortunately, due to evidence of directional horizontal pleiotropy, which violates an assumption of MR, the results for age at first sexual intercourse are less clear. An upcoming GWAS of age at first sexual intercourse

using multiple data sources will allow for this analysis to be conducted without stratifying UK Biobank data and introducing selection bias. Studies using this data will be better able to inform interventions on this potentially modifiable trait.

Overall, this study demonstrates how MR can be applied to test predictions of life history theory by providing an example of using MR within an evolutionary research field to better understand determinants of reproductive and social behaviour. There is an increasing number of GWAS being conducted on evolutionary relevant traits and future research could apply these MR techniques to further test predictions of life history theory, such as whether age at menarche is a mechanism between early life adversity and these evolutionary outcomes (Burgess et al., 2017).

Chapter 5 The Schizophrenia Paradox: schizophrenia risk and reproductive success

This chapter is based on the publications below

Lawn, R. B., Sallis, H. M., Taylor, A. E., Wootton, R. E., Davey Smith, G., Davies, N. M., …Munafò, M. R. (2019). Schizophrenia risk and reproductive success: a Mendelian randomization study. *Royal Society Open Science*, *6*, 181049.

Lawn, R. B., Sallis, H. M., Taylor, A. E., Wootton, R. E., Davey Smith, G., Davies, N. M., …Munafò, M. R. (2019). Comment on the relationship between common variant schizophrenia liability and number of offspring in the UK Biobank. *American Journal of Psychiatry*, 176(7), 573-574.

5.1 Background and chapter overview

In this chapter, I applied a range of methods rooted in genetic epidemiology (MR, LD score regression and PRS analysis) to investigate the schizophrenia paradox. Schizophrenia is a debilitating and heritable mental disorder associated with lower reproductive success (Bundy et al., 2011; Essen-Möller, 1959; Jablensky et al., 1992; Nettle & Clegg, 2006; Van Dongen & Boomsma, 2013). However, the prevalence of schizophrenia is stable over populations and time, resulting in an evolutionary puzzle: how is schizophrenia maintained in the population given its apparent fitness costs (Essen-Möller, 1959; Huxley et al., 1964; Power et al., 2013; Shaner et al., 2004)? One possibility is that increased genetic liability for schizophrenia, in the absence of the disorder itself, may confer some reproductive advantage (Essen-Möller, 1959; Huxley et al., 1964; Lewis, 1958; Nesse, 2004; Nettle, 2001; Shaner et al., 2004). A reproductive advantage among healthy individuals with higher genetic liability for the disorder may compensate for lower reproductive success of those with the disorder itself, termed cliff-edge fitness (see **Figure 5:1**) (Nesse, 2004; Van Dongen & Boomsma, 2013). It is suggested that this reproductive advantage is maintained by sexual selection and mediated via creativity and/or risky behaviour (Del Giudice et al., 2010; Nettle, 2006; Nettle & Clegg, 2006; Shaner et al., 2004; Wang et al., 2016). Genetic variants that have been associated with schizophrenia have also been associated with creativity and risk-taking (Power et al., 2015; Richardson et al., 2018; Strawbridge et al., 2018). In this chapter, I assess the correlation and causal effect of genetic liability for schizophrenia with a range of reproductive outcomes (such as number of children) in multiple population-based

samples which are not selected on schizophrenia status and therefore include very few cases.

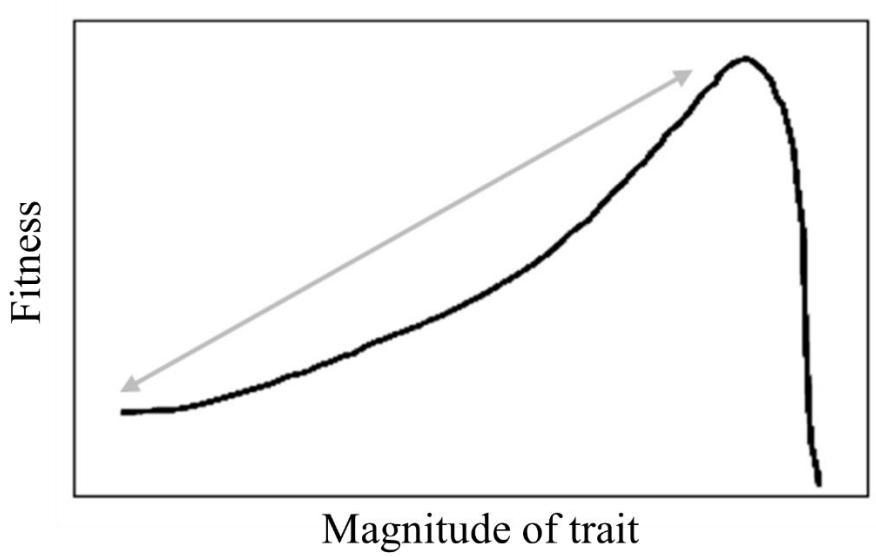

Figure 5:1 *Illustration of a cliff-edge fitness function where fitness increases with increasing levels of the trait until a peak followed by a steep decline. For schizophrenia this peak is estimated at diagnosis and a somewhat linear relationship is assumed up until this point (indicated by the grey arrow). (credit Nesse, 2004)*

In all main analyses of this paradox, I use genetic variants associated with schizophrenia within a MR framework to estimate the causal effect of genetic liability for schizophrenia on measures of reproductive success, overcoming some limitations of observational studies previously used to investigate this evolutionary paradox by reducing bias from confounding and reverse causation. To capture broader genetic liability, I additionally conduct LD score regression in UK Biobank and PRS analyses using varying *p*-value thresholds for genetic liability in MoBa and ALSPAC G0. As discussed in Chapter 2, these methods capture various aspects of genetic liability and can be used to gain a fuller understanding of the evolutionary processes involved. Cliff-edge fitness in those without a diagnosis of schizophrenia would predict a linear relationship (see **Figure 5:1**). However, given suggestions from family studies that there may be a fitness decline of healthy individuals with high genetic liability for the disorder, I conducted sensitivity analyses to investigate possible non-linear relationships where at very high levels of genetic score for schizophrenia liability there is decreased reproductive success in absence of schizophrenia itself (Bundy et al., 2011; Del Giudice, 2010; Power et al., 2013).

The principal measure of fitness in this chapter is number of children or parity. However, both earlier age at first birth and increased numbers of sexual partners have previously been used as indicators of reproductive success, particularly in developed populations in which contraception is commonly used to control family size (Mullins et al., 2017; Nettle & Clegg, 2006; Tropf, Stulp, et al., 2015; Westendorp & Kirkwood, 1998). Earlier age at first birth likely results in a longer reproductive period whereas number of sexual partners captures mating success and hence potential reproductive success (Nettle & Clegg, 2006). Additionally, earlier age at first pregnancy also captures potential reproductive success, similarly to age at first birth, in developed populations where terminations are available. Here, I use a range of these measures proxying reproductive success depending on data availability in the sample. Results in this chapter are presented in aggregate, by measure of reproductive success, however analyses using UK Biobank data was conducted first. Following this, I conducted analyses in MoBa and then ALSPAC data (both in ALSPAC G0 and ALSPAC G1).

5.2 Positive control

As the present studies applied MR in a novel context to this evolutionary paradox, I also included a positive control where the estimated relationship is known and I could therefore validate the approach to then conduct the analysis on genetic liability for schizophrenia. For this positive control, I estimated the effect of genetically predicted educational attainment on number of children and age at first birth in UK Biobank. Higher genetically predicted education is known to be associated with fewer children and delayed age at first birth (Barban et al., 2016; Beauchamp, 2016; Courtiol, Tropf, & Mills, 2016; Kong et al., 2017; Sanjak, Sidorenko, Robinson, Thornton, & Visscher, 2017). I therefore included educational attainment as an exposure with these two outcomes (using the same outcome datasets used for the schizophrenia analysis in UK Biobank) as a positive control. This positive control was only conducted in UK Biobank as UK Biobank was the first analysis that I conducted and therefore the point in time that I wanted to validate the approach, as well as having the largest sample size. As I aimed to conduct LD score regression in UK Biobank for genetic liability for schizophrenia, I also included LD score regression for educational attainment.

5.2.1 Positive control methods

5.2.1.1 Exposure instrument

SNPs associated with educational attainment ($p<5\times10^{-8}$) from a recent GWAS by the SSGAC were used (Okbay et al., 2016). As the GWAS conducted a replication in UK

Biobank, effect estimates from the pooled sex analysis of the discovery sample were used to avoid sample overlap. Sixty-seven SNPs were available in UK Biobank data and were eligible for inclusion. For exclusion criteria, I checked that there were no palindromic SNPs with MAF around 0.5 to ensure there were no issues with strand mismatches. I further used SNiPA (Arnold et al., 2015) with an LD threshold of 0.2 to check SNP independence. Of the 69 available SNPs in UK Biobank data, 2 palindromic SNPs with MAF close to 0.5 were excluded due to strand ambiguities. Effect estimates used for the remaining 67 educational attainment SNPs are listed in **Appendix 10** and showed a mean F statistic of 33.23.

5.2.1.2 Outcomes

Participants were either asked how many children they had given birth to or how many children they had fathered. I also derived a binary variable to indicate if participants were childless or not (childlessness coded as 1). Age at first birth was only measured in females in UK Biobank, with participants asked: "How old were you when you had your first child?". Although no age restrictions were applied in analyses, the nature of UK Biobank data meant that participants were aged towards the end of their reproductive lives.

5.2.1.3 Data analysis

I used LD score regression (Bulik-Sullivan, Finucane, et al., 2015; Bulik-Sullivan, Loh, et al., 2015) to calculate the genome-wide genetic correlation (r_g) between predicted educational attainment and number of children and age at first birth. Genome-wide associations were conducted for these outcomes using linear regression, implemented in PLINK v2.00 through the MRC IEU GWAS pipeline. In this, I adjusted for the top 10 principal components of population structure. For number of children, age and sex were also included as covariates. I then filtered results on MAF (>0.01) and imputation quality (>0.8) separately.

The exposure associated SNPs described above were extracted from UK Biobank to derive SNP-outcome associations for the outcome data. Extraction was done using PLINK (v2.00) and best guess algorithms for determining alleles (full genotyping information in Chapter 3). In MR analyses, data were harmonized to ensure that the effect of the SNP on the exposure and the SNP on the outcome corresponded to the same allele. The increasing allele for the exposure was used. Associations for exposure SNPs and all outcome measures were then calculated in R, fitting the same covariates as listed above. Effect sizes for number of children and age at first birth that were used in analysis are

listed in **Appendix 10**. As discussed in Chapter 2, SNP-exposure and SNP-outcome data (i.e., SNP-exposure and SNP-outcome associations) were combined using IVW, weighted median, MBE and MR-Egger regression. MR results of education on childlessness were converted to ORs by exponentiating log ORs. I calculated Cochran's Q and I^2_{GX} statistics to assess the suitability of an IVW and MR-Egger regression (see Chapter 2 for a description of these) (Bowden, Fabiola Del Greco, et al., 2016). All analysis was also conducted with SNP-outcome associations additionally adjusted for genotype array.

5.2.2 Positive control results

For sample descriptives see **Table 5:2** below. There was a modest negative genetic correlation between educational attainment and number of children (r_g = -0.35, p<0.001) and a strong positive genetic correlation between educational attainment and age at first birth (r_g = 0.81, p<0.001). There was a total of 1 117 154 SNPs included in this analysis.

Cochran's Q for an IVW approach of educational attainment and number of children was 199.54 (p<0.001), and 144.88 (p<0.001) for age at first birth, suggesting overdispersion although this appeared balanced (see **Appendix 11** for plot). Educational attainment had a negative effect on number of children (mean difference: -0.16, 95% CI: -0.21 to -0.12, p<0.001 per year increase in educational attainment) and a positive effect on age at first birth (mean difference 2.68, 95% CI: 2.40 to 2.95, p<0.001) per year increase in educational attainment (**Table 5:1**). There was also an effect of increased education on increased likelihood of being childless (OR: 1.60, 95% CI: 1.47 to 1.75, p<0.001 per year increase in educational attainment). Results for all educational attainment analysis with genotype array included as a covariate for outcome summary statistics are presented in **Appendix 12** and **Appendix 13**. It should be noted that the I^2_{GX} statistic for an unweighted MR-Egger regression was 0.3, which is deemed too low to conduct a SIMEX adjustment, and MR-Egger was therefore not appropriate to conduct (Bowden, Fabiola Del Greco, et al., 2016).

Table 5:1 *Estimates of the causal effect of genetically predicted educational attainment on number of children and age at first birth using IVW, MBE and weighted median MR methods.*

	No. of children[a]	**Age at first birth[b]**	**Childlessness[c]**
Method (67 SNPs[d])	**β (95% CI), *p***		**OR (95% CI), *p***
IVW	-0.162 (-0.206, -0.118), <0.001	2.677 (2.401, 2.952), <0.001	1.589 (1.446, 1.746), <0.001
Weighted median	-0.206 (-0.276, -0.135), <0.001	2.828 (2.387, 3.270), <0.001	1.567 (1.343, 1.829), <0.001
MBE	-0.249 (-0.478, -0.020), 0.04	1.649 (0.303, 2.995), <0.001	1.513 (0.952, 2.404), 0.09

[a] Number of children data from UK Biobank (N = 268 658 – 335 758). [b] Age at first birth data from UK Biobank (N = 99 317 – 124 093). [c] Childlessness data from UK Biobank (N = 268 658 – 335 758). [d] Educational attainment from the SSGAC GWAS (N = 283 723).

5.2.3 Positive control conclusion

Results of these positive control analyses were as expected and in line with previous genetic research, suggesting that educational attainment is under negative selection (Barban et al., 2016; Beauchamp, 2016; Courtiol et al., 2016; Kong et al., 2017; Sanjak et al., 2017). Finding results in a positive control analysis that are expected and in line with previous research suggests that the overall approach is valid, and I therefore carried forward these methods to test genetic liability for schizophrenia with the same outcome measures of reproductive success.

5.3 Methods

I will first outline methods that were common across all studies of genetic liability for schizophrenia using UK Biobank, MoBa and ALSPAC data. For example, the GWAS used, the MR methods applied and the non-linear analysis that I conducted. I will then outline any methods specific to each study in the order of UK Biobank, MoBa, ALSPAC G0 and ALSPAC G1.

For outcomes, number of children (or parity) was measured in UK Biobank, MoBa and ALSPAC G0. A binary measure of whether participants had had a child yet was used for ALSPAC G1. Number of sexual partners was included in UK Biobank and ALSPAC G1 analyses. For age at first pregnancy, data was available in MoBa and ALSPAC G0. Age at first birth was measured in UK Biobank and MoBa. Additionally, MoBa included multiple secondary outcomes such as whether the pregnancy was planned. Lastly, whether participants had previously had a pregnancy termination was available in MoBa and ALSPAC G0.

5.3.1 Across all studies

5.3.1.1 Schizophrenia GWAS

In all analyses, I used the PGC GWAS (N = 35 123 cases and 109 657 controls for Europeans) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In all MR analyses, independent SNPs associated with schizophrenia ($p<5\times10^{-8}$) were used. The 128 originally identified SNPs that reached this genome-wide significance threshold explained approximately 3.4% of the observed variance in schizophrenia risk. Estimates, on the log-odds scale, and SEs for the SNP and schizophrenia associations were recorded using GWAS data (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Again, for exclusion criteria, I checked that there were no palindromic SNPs with MAF around 0.5 to ensure there were no issues with strand mismatches. I further used SNiPA (Arnold et al., 2015) with an LD threshold of 0.2 to check SNP independence. If proxy SNPs were used when any originally identified GWAS SNPs were not available, I used a LD r^2 of 0.8 or above to search for proxies on SNiPA (Arnold et al., 2015) or proxies previously used (Gage et al., 2017).

5.3.1.2 MR methods used

I first conducted regressions between a genetic score for schizophrenia liability, including only genome-wide significant SNPs, and each outcome. This can provide evidence as to whether there is a causal effect but not the magnitude of this effect (Davies, Holmes, et al., 2018) and may suffer from some bias (Richardson et al., 2018). I therefore next conducted all MR methods described in Chapter 2 (IVW, weighted median, MBE and MR-Egger regression).

I created additive genetic scores for schizophrenia liability. Apart from in UK Biobank, weighted additive genetic scores were created using Plink (version 1.90 in MoBa and version 2.0 in ALSPAC) and then standardized. For this, I replaced any missing SNP data with the mean for that SNP across individuals in Plink. Due to the format of UK Biobank data, I created an unweighted genetic score in R with the same mean imputation for missing data. All scores counted the increasing allele. In sum, the Plink scores represent the per SD increase in liability for schizophrenia and the R score in UK Biobank represents the per allele increase in liability for schizophrenia. These scores are comparable and will differ only slightly, with minor increased power for the weighted scores (Burgess & Thompson, 2013). The units for the scores to outcome will therefore differ between UK Biobank and the remaining studies however the units for the main analysis, discussed below, are the same.

For all studies in this chapter, the I^2_{GX} statistic for an unweighted MR-Egger regression was below 0.5 which is deemed too low to conduct a SIMEX adjustment, and MR-Egger regression was therefore not appropriate to conduct (see Chapter 2) (Bowden, Fabiola Del Greco, et al., 2016). The IVW, weighted median and MBE were conducted and results were multiplied by 0.693 to represent the causal estimate per doubling in odds of schizophrenia risk (Burgess & Labrecque, 2018). For binary outcomes, MR results were multiplied by 0.693 on the log-odds scale, and then exponentiated. The reported estimates therefore indicate the effect of doubling the odds of schizophrenia on the odds of the binary outcome category that is coded as 1. In addition to the I^2_{GX} values, Cochran's Q and mean F statistics were calculated for all analyses. Acceptable mean F statistics (above 10) were obtained in all studies (see Chapter 2).

I included adjustment for the top 10 principal components of population structure and sex (in combined sex analysis). Genotype array and a measure of age were included where relevant. Some sex stratified analysis was conducted where data for both sexes were available. Results are presented per phenotype and a summary figure for the IVW results is presented at the end of each phenotype section.

5.3.1.3 Non-linear analysis

As an illustration of shape of the schizophrenia liability-reproductive success relationship, I plotted the relationship between the genetic score described above and each primary continuous outcome. For this, I divided the score into quintiles and plotted outcomes across these categories of the genetic score. Similarly, to further investigate a possible peak in reproductive success at intermediate-high genetic liability for schizophrenia, I conducted quadratic regression analysis of the genetic score for schizophrenia liability and outcomes (adjusted for the top 10 principal components of population structure and additionally adjusted for sex, genotype array and a measure of age where appropriate). Where a standardized genetic score for schizophrenia liability was used in analysis, the unstandardized score was used for the quadratic term. I repeated this quadratic analysis separately for each sex in data where data for both sexes were available. Lastly, I plotted the unadjusted quadratic regressions.

5.3.1.4 Covariables

There is a well-established association between smoking and schizophrenia liability (Wootton, Richmond, et al., 2018). I therefore regressed the genetic score in each sample with a binary measure for whether participants had ever smoked ('yes' coded as 1). This analysis was adjusted for the top 10 principal components of population structure and

genotype array if appropriate. In UK Biobank, ever smokers were identified from items asked at baseline assessment on whether participants were currently smoking tobacco most days or occasionally, had previously smoked tobacco most days or occasionally, or had tried smoking tobacco once or twice. In MoBa and ALSPAC G0, participants were asked whether they had ever smoked via questionnaire at approximately 18 weeks gestation. For ALSPAC G1, I used an item asked at approximately 23 years old on whether participants had ever smoked a whole cigarette.

5.3.2 UK Biobank

5.3.2.1 Exposure instrument

For genetic liability for schizophrenia, 75 of the 128 SNPs were not available in UK Biobank. I found proxies for 48 SNPs. After checking that all SNPs were eligible in regard to exclusion criteria, discussed above, a total of 101 SNPs remained. The final 101 SNPs and effect estimates are listed in **Appendix 14**. The mean F statistic for schizophrenia genetic liability was 35.15.

5.3.2.2 Outcomes

Number of children, childlessness and age at first birth were derived as they were in the positive control analysis for educational attainment. A measure of number of sexual partners was also included. If participants indicated that they had had sexual intercourse, they were asked “About how many sexual partners have you had in your lifetime?". Participants were given the information that “Sexual intercourse includes vaginal, oral or anal intercourse” if they activated the help button. I coded responses to missing if above the 99th percentile. I then derived a binary measure indicating if participants were in approximately the top 10th percentile for the highest number of sexual partners (equal to or above 12 partners coded as 1).

5.3.2.3 Data analysis

Data analysis for genetic liability for schizophrenia in UK Biobank followed the same processes as for the positive control. I used LD score regression (Bulik-Sullivan, Finucane, et al., 2015; Bulik-Sullivan, Loh, et al., 2015) to calculate the genome-wide genetic correlation between schizophrenia liability and number of children and age at first birth and number of sexual partners. For this, I used the same genome-wide associations that were calculated for number of children and age at first birth for positive control analyses. Genome-wide associations were also calculated for number of sexual partners using the same methods. For number of sexual partners analysis, the top 10 principal

components of population structure, age and sex were included as covariates, as done so for number of children.

I first regressed the genetic score for schizophrenia with the continuous outcomes. Effect sizes used in MR analysis for number of children, age at first birth, and number of sexual partners analysis are listed in **Appendix 14**. These regressions and the SNP-outcome associations for MR used the same models as the positive control and LD score regression above. The I^2_{GX} statistic for an unweighted MR-Egger regression was 0.2 for genetic liability of schizophrenia (Bowden, Fabiola Del Greco, et al., 2016). As done in the positive control, LD score regression and MR analysis was also conducted with SNP-outcome associations additionally adjusted for genotype array.

As well as the non-linearity plots discussed above, I additionally plotted the same relationships using deciles of the genetic score and with reproductive success on the x-axis. As further sensitivity analysis to assess if there was any decline in reproductive success within the sample at very high levels of genetic liability, I conducted a series of regressions between this genetic score for schizophrenia liability and outcomes, systematically removing cumulative centiles from the maximum. These regressions included adjustment for the top 10 principal components of population structure. Quadratic regression was adjusted for the top 10 principal components of population structure. Adjustment for age was also included for number of children and number of sexual partners. Lastly, sex was included as a covariate in combined sex analysis.

As there was an available measure on whether participants in UK Biobank had had a schizophrenia diagnosis, I repeated analysis after removing the few schizophrenia cases in the sample (maximum N = 207).

5.3.3 MoBa

5.3.3.1 Exposure instrument

There were 107 SNPs available in MoBa data and proxies were found for an additional 8 SNPs. A total of 10 SNPs did not meet additional quality checks and were therefore excluded (see Chapter 2 for details). I therefore included 105 SNPs in MoBa analysis (see **Appendix 15**). The mean F statistic for schizophrenia genetic liability was 36.36.

5.3.3.2 Outcomes

Primary outcomes in Moba were parity, age at first pregnancy and age at first birth. Parity was taken from the MBRN and represented parity to date (2018). Due to MoBa being a

pregnancy cohort, no binary measure of childlessness was derived. Age at first pregnancy was derived from age at pregnancy for the index child (taken from the MBRN) and questionnaire data for the earliest year of previous pregnancies. Age at first birth was similarly derived but restricted to pregnancies resulting in live births. As mentioned in Chapter 3, all questionnaire data was taken from the first questionnaire which was sent to mothers between 13 and 17 weeks gestation.

I also included a range of secondary outcomes. Whether the index pregnancy was planned was taken from questionnaire data. Mothers were also asked whether they had conceived the index pregnancy even though them or their partner used contraceptives. An item indicating if mothers had ever been treated for infertility was also taken from questionnaire data. These secondary outcomes were binary with 'yes' coded as 1. An additional secondary measure for the length of sexual relationship the mother had had with the index child's father was derived (coded as a continuous measure in months). I also included a binary measure of whether any previous pregnancy resulted in a termination ('yes' coded as 1).

5.3.3.3 Data analysis

There was no available measure for whether participants had been diagnosed with schizophrenia and therefore no exclusions were made for this. For regressions between the genetic score for schizophrenia liability and outcomes, I included covariates for the top 10 principal components of population structure and genotype array. I then further adjusted for birth year. I additionally included adjustment for age at delivery of the index child in analysis of whether any previous pregnancy had resulted in a termination. For all primary outcomes, I conducted MR analysis and used MR-Base to do so (Hemani, Zheng, et al., 2018). For this, I used Plink to calculate SNP-outcome associations (see **Appendix 15**), adjusted for the top 10 principal components of population structure, genotype array and birth year. The SNP-outcome associations were then taken into MR-Base, where they were harmonized with exposure SNPs to ensure that the effect of the SNP on the exposure and the SNP on the outcome corresponded to the same, increasing, allele. The I^2_{GX} value for this data was 0.2.

As additional sensitivity analyses, I assessed if there were associations between liability for schizophrenia and outcomes using genetic scores including SNPs with lower *p*-value thresholds from the schizophrenia GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). These scores were derived using PRSice software (Euesden et al., 2015) for schizophrenia-associated genetic variants using the

following *p*-value thresholds: 1×10^{-5}, 0.005, 0.05, 0.1, 0.5, 1. Of these, the threshold of 0.05 has been shown to be the best predictor of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) however I examined evidence across all included thresholds. Scores were weighted according to the association magnitude of each SNP in the GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and then averaged across SNPs to provide a score per individual. I standardized scores and then regressed each with the outcomes using the same models as for the regressions using the score with only genome-wide significant SNPs. For quadratic regression, genotype array, the top 10 principal components of population structure and additional adjustment for birth year were included.

5.3.4 ALSPAC G0

5.3.4.1 Exposure instrument

There was a total of 115 SNPs available in ALSPAC data (see **Appendix 16**). There were no available proxies for any missing genome-wide significant SNPs in ALSPAC. These 115 SNPs were eligible in regard to exclusion criteria. The mean F statistic for schizophrenia genetic liability was 37.16.

5.3.4.2 Outcomes

The primary measures in ALSPAC G0 were parity at 85 months post index child, parity at 18 years post index child, and age at first pregnancy. Parity measures were derived using questionnaire data for parity at 18 weeks gestation and any additional pregnancies reported until 85 months or 18 years later. As ALSPAC was also a pregnancy cohort, no binary measure of parity was derived. Age at first pregnancy was derived using questionnaire data for ALSPAC G0 age at first pregnancy, asked at approximately 18 weeks gestation, or the age at index pregnancy if they reported no previous pregnancies. I also included a secondary binary measure of whether any previous pregnancy resulted in a termination ('yes' coded as 1) from questionnaire data at 18 weeks gestation.

5.3.4.3 Data analysis

After conducting analysis with and without schizophrenia cases in UK Biobank, I decided to remove the few schizophrenia cases in ALSPAC G0 before analyses (maximum N = 7). For regression between the genetic score for schizophrenia liability and outcomes, I included covariates for the top 10 principal components of population structure and then further adjusted for birth year. I additionally included adjustment for age at delivery of the index child with whether any previous pregnancy had resulted in a termination.

I used Plink to calculate SNP-outcome associations for MR analyses (see **Appendix 16**), adjusted for birth year and the top 10 principal components of population structure. I then took these SNP-outcome associations into MR-Base and harmonized the data with exposure SNPs to ensure that the effect of the SNP on the exposure and the SNP on the outcome corresponded to the same, increasing, allele. The I^2_{GX} value for this data was 0.5.

I included the same additional sensitivity analyses in ALSPAC G0 as done so in MoBa data, regressing scores of the same varying *p*-value thresholds for liability to schizophrenia (derived using PRSice) on outcomes. These regressions used the same models as above with genome-wide significant SNPs. For quadratic regression, the top 10 principal components of population structure and birth year were included as covariates.

5.3.5 ALSPAC G1

5.3.5.1 Exposure instrument

As ALSPAC genetic data is similarly quality checked for ALSPAC G0 and ALSPAC G1, the SNPs available and those that passed exclusion criteria were the same. I therefore included the same 115 SNP list as for ALSPAC G0, with effect estimates for these listed in **Appendix 17**. The mean F statistic for schizophrenia genetic liability was 37.16.

5.3.5.2 Outcomes

I derived number of sexual partners using questionnaire data. The main measure was taken at 23 years old, and I replaced to missing if responses were above the 99.9th percentile. I additionally included a measure where I replaced any missing responses for the 23-year questionnaire with data from the same question asked at 21 years old if available. A binary measure indicating whether participants were in the top 10th percentile for number of sexual partners or not was derived from both the continuous measure of 23-year data and the continuous measure of 23-year plus 21-year data. Additionally, I included a binary measure of whether participants had had a child yet. This was coded as 1 if participants indicated that they had 1 child or more to questionnaires distributed at approximately 21, 22 and 23 years.

5.3.5.3 Data analysis

I firstly removed the one schizophrenia case. I then regressed the genetic score for schizophrenia liability against each outcome, adjusting for the top 10 principal components of population structure, sex and then additionally adjusting for age. For having ever had a child, I adjusted for at responding to the latest questionnaire, around 23

years. For number of sexual partners, I adjusted for age at answering the question that the data referred to.

I used Plink to calculate SNP-outcome associations for MR analyses (see **Appendix 17**) by regressing each measure of reproductive success on each SNP, adjusted for the top 10 principal components of population structure and age as above. For the binary measure of being in the highest number of sexual partners (plus 21-year data), the SNP rs1023500 could not be used to create a reliable association due to the rare outcome with one allele and was dropped from this analysis. The SNP-outcome associations were then taken into MR-Base (Hemani, Zheng, et al., 2018), where they were harmonized with exposure SNPs to ensure that the effect of the SNP on the exposure and the SNP on the outcome corresponded to the same, increasing, allele. Note that, again, the I^2_{GX} statistic for an unweighted MR-Egger regression was 0.5 for genetic liability of schizophrenia and MR-Egger regression was therefore not appropriate (Bowden, Fabiola Del Greco, et al., 2016). For quadratic regression, the top 10 principal components of population structure, age and sex (in combines sex analysis) were included as covariates.

5.4 Results

5.4.1 Descriptives

In the sample from UK Biobank, there were more females than males, a majority had children, and a minority had college or university degree qualifications. The mean age was 56.9 years (SD: 8.0) and the mean years of education was 13.3 (SD: 4.4). For the outcomes, the mean number of children was 1.8 (SD: 1.2), mean number of sexual partners was 5.8 (SD: 8.6) and the mean age at first birth was 25.4 years (SD: 4.5). See **Table 5:2** for all UK Biobank descriptives.

The mean age at delivery of the index child was 29.9 (SD: 4.4) in MoBa and 28.5 years (SD: 4.5) in ALSPAC G0. In MoBa, the mean age at first pregnancy was 25.8 years (SD: 4.7) and 25.5 years (SD: 4.9) in ALSPAC G0. Mean parity was 1.59 (SD: 0.9) in MoBa, 2.4 (0.9) at 85 months post index child in ALSPAC G0 and 2.5 (SD:4.9) at 18 years post index child in ALSPAC G0. In MoBa, mean age at first birth was 26.9 years (SD: 4.4). These descriptives are shown in **Table 5:3**.

Table 5:2 *Participant characteristics in UK Biobank sample.*

	Total N	**Mean (SD) or N (%)**
Sex		
Females	337 104	181 362 (53.80)
Males		155 742 (46.20)
Age at assessment, years	337 104	56.87 (8.00)
Educational attainment, years	333 975	13.34 (4.44)
College		
No	333 975	251 951 (75.44)
Yes		82 024 (24.56)
Number of children	335 758	1.79 (1.20)
Childless		
No	335 758	270 084 (80.44)
Yes		65 674 (19.56)
Age at first birth, years	124 093	25.39 (4.54)
Number of sexual partners	275 700	5.76 (8.63)
Highest number of sexual partners		
No	275 700	244 132 (88.55)
Yes		31 568 (11.45)

Table 5:3 *Participant characteristics in MoBa and ALSPAC G0 samples.*

	MoBa		ALSPAC G0	
	Total N	**Mean (SD) or N(%)**	**Total N**	**Mean (SD) or N(%)**
Age at index delivery	9444	29.94 (4.42)	7515	28.49 (4.76)
Age at first birth	9444	26.85 (4.41)	-	-
Age at first pregnancy	9444	25.80 (4.71)	7037	25.54 (4.89)
Parity	9444	1.59 (0.89)	-	-
Parity at 85 months post index child	-	-	4977	2.41 (0.89)
Parity at 18 years post index child	-	-	2562	2.54 (1.01)
Education	8940	4.57 (1.21)	6947	3.14 (1.26)
Ever smoked				
Yes	9360	4569 (48.81)	7188	3706 (51.56)
No		4791 (51.19)		43482 (8.44)
Infertility				
Yes	9354	769 (8.22)	-	-
No		8585 (91.78)	-	-
Relationship	9444	75.83 (48.88)		
Pregnancy planned				
Yes	9350	7800 (83.42)	-	-
No		1550 (16.58)	-	-
Contraception was used				
Yes	9132	396 (4.34)	-	-
No		8736 (95.66)	-	-
Previous termination				
Yes	9444	8161 (86.41)	7136	1008 (14.13)
No		1283 (13.59)		6128 (85.87)

In ALSPAC G1, the mean number of sexual partners was 8.6 (SD: 10.4) for 23-year data and 8.6 (SD: 10.7) for 23-year plus 21-year data. Approximately 11.5% of participants had had a child (see **Table 5:4**).

Table 5:4 *Participant characteristics in ALSPAC G1 sample.*

	Total N	**Mean (SD) or N(%)**
Sex		
Female	7749	3772 (48.68)
Male		3977 (51.32)
Age answering 23-year questionnaire	2743	23.86 (0.51)
Number of partners	2543	8.55 (10.41)
Number of partners plus 21 years	3032	8.62 (10.69)
Had child		
Yes	2546	292 (11.47)
No		2254 (88.53)

5.4.2 Ever smoked

Results for associations between the genetic scores for schizophrenia liability and whether participants had ever smoked are presented in **Appendix 18**. As expected, all ORs indicated an increased likelihood of having ever smoked with increased genetic liability for schizophrenia. There was clear evidence of an association when using genome-wide significant SNPs in UK Biobank and weak evidence in ALSPAC G1. For MoBa and ALSPAC G0, evidence became stronger with lower *p*-value thresholds for genetic liability than when using the genome-wide significant SNPs.

5.4.3 Number of children or parity

5.4.3.1 UK Biobank

Using LD score regression, I found little evidence of a genetic correlation between schizophrenia liability and number of children ($r_g = 0.002$, $p = 0.84$). The analysis included 1 114 456 SNPs. Results for these analyses with genotype array included as a covariate in generating outcome summary statistics are presented in **Appendix 19**.

There was little evidence of associations between the genetic score for schizophrenia liability and outcomes in regression analyses (see **Table 5:5**). Cochran's Q was 156.48 ($p<0.001$) for genetic liability of schizophrenia and number of children, suggesting overdispersion although this appeared balanced (see **Appendix 20**). Cochran's Q was 172.79 ($p<0.001$) for genetic liability of schizophrenia and childlessness with a similar pattern. There was little evidence that higher genetic liability for schizophrenia increased number of children (mean difference: 0.003 increase in number of children per doubling in the natural log OR of schizophrenia liability, 95% CI: -0.003 to 0.009, $p = 0.39$). I further tested childlessness as an outcome and found no strong evidence of an effect of genetic liability for schizophrenia on childlessness (see **Table 5:6**). When I repeated the MR analysis after removing the few schizophrenia cases in the sample, there was no clear change in results (see **Appendix 21**). Results for these analyses with genotype array included as a covariate in the outcome summary statistics are presented in **Appendix 22**.

Table 5:5 *Estimates of the association between the genetic score for schizophrenia liability and number of children in UK Biobank data.*

Genetic score for schizophrenia liability	**Number of children**	
	N	**β (95% CI), *p***
Combined sexes	335 758	0.0002 (-0.0004, 0.0008), 0.53
Females	181 255	0.0006 (-0.0002, 0.0014), 0.16
Males	154 503	-0.0003 (-0.0012, 0.0007), 0.60

Table 5:6 *Estimates of the causal effect of genetic liability for schizophrenia on number of children and childlessness using IVW, MBE and weighted median MR methods.*

	No. of children[b]	**Childlessness[c]**
Method (101 SNPs[a])	**β (95% CI), *p***	**OR (95% CI), *p***
IVW	0.003 (-0.003, 0.009), 0.39	0.998 (0.985, 1.012), 0.79
Weighted median	0.006 (-0.004, 0.015), 0.23	0.995 (0.975, 1.016), 0.65
MBE	0.020 (-0.012, 0.052), 0.22	0.992 (0.924, 1.065), 0.83

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Number of children data from UK Biobank (N = 318 921 – 335 758). [c] Childlessness data from UK Biobank (N = 318 921 – 335 758).

Sensitivity analysis investigating a possible non-linear relationship is presented in **Figure 5:2**, showing the mean number of children for quintiles of an unweighted additive genetic score for schizophrenia liability. As shown, there is little evidence of heterogeneity across values of the schizophrenia score. Similar patterns are seen across deciles of the genetic score for schizophrenia liability and when plotting these measures of reproductive success on the x-axis (see **Appendix 23** and **Appendix 24**). A series of regressions between the genetic score and number of children, systematically removing cumulative centiles, showed that estimates became slightly stronger although there was little statistical support (see **Table 5:7**). This analysis was repeated after removing the few schizophrenia cases, which did not alter results (see **Appendix 25**). Regression of the genetic score for schizophrenia liability and number of children further showed no clear evidence when including a quadratic term for genetic liability for schizophrenia and when stratified by sex (see **Table 5:8**). This quadratic relationship suggested a slight peak in fitness at intermediate levels of genetic liability, particularly for females, but again with little statistical support (see **Appendix 26**-**28**).

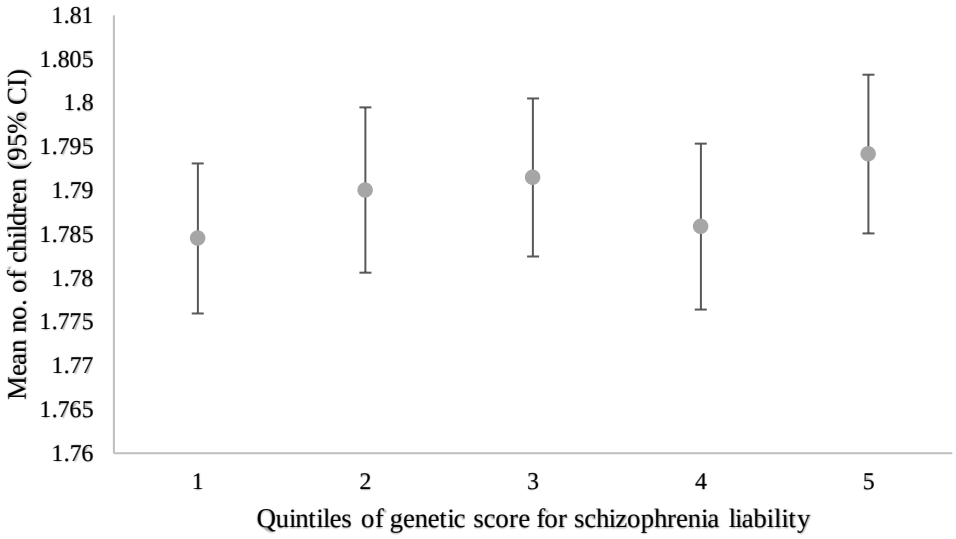

Figure 5:2 *Genetic score for schizophrenia liability (in quintiles) and mean number of children in UK Biobank data showing little evidence of heterogeneity across values of the score.*

Table 5:7 *Estimates of the association between the genetic score for schizophrenia liability and number of children removing cumulative deciles of the genetic score.*

Genetic score for schizophrenia liability	**Number of children**	
	N	**β (95% CI), *p***
Highest 10% removed	302 190	0.0005 (-0.0003, 0.0013), 0.19
Highest 20% removed	268 604	0.0002 (-0.0007, 0.0011), 0.70
Highest 30% removed	235 030	0.0005 (-0.0006, 0.0016), 0.35
Highest 40% removed	208 433	0.0006 (-0.0006, 0.0019), 0.30
Highest 50% removed	167 860	0.0008 (-0.0006, 0.0023), 0.27

Table 5:8 *Quadratic regression of the genetic score for schizophrenia liability with number of children in UK Biobank data.*

Genetic score for schizophrenia liability (including quadratic term for the score)	**Number of children**	
	N	**β (95% CI), *p***
Combined sexes	335 758	0.0025 (-0.0108, 0.0157), 0.72
Females	181 255	-0.0001 (-0.0174, 0.0172), 0.99
Males	154 503	0.0055 (-0.0149, 0.0259), 0.60

5.4.3.2 MoBa

There was a positive relationship between genetic liability for schizophrenia and parity using a genetic score consisting of genome-wide significant SNPs (see **Table 5:9**). Subsequently, MR results indicated a positive effect on parity with increasing genetic liability for schizophrenia in the IVW approach. The weighted median approach was also

in the positive direction although the MBE resulted in a small negative point estimate. The Cochran's Q for this IVW analysis was 79.74 (p = 0.96) (see **Appendix 29**). Conversely, associations did not remain in sensitivity analysis looking across p-value thresholds for genetic liability for schizophrenia although most point estimates were in the positive direction (see **Table 5:11**).

Table 5:9 *Estimates of the association between the genetic score for schizophrenia liability and number of children in MoBa data.*

	Parity (N = 9439)
Genetic score for schizophrenia liability	**β (95% CI), *p***
Model 1	0.021 (0.003, 0.039), 0.02
Model 2	0.021 (0.003, 0.039), 0.02

Model 1 is adjusted for the top 10 principal components of population structure and genotype array. Model 2 is additionally adjusted for mothers' birth year.

Table 5:10 *Estimates of the causal effect of genetic liability for schizophrenia on parity using IVW, MBE and weighted median MR methods.*

	Parity[b]
Method (105 SNPs[a])	**β (95% CI), *p***
IVW	0.031 (0.005, 0.057), 0.02
Weighted median	0.012 (-0.025, 0.049), 0.54
MBE	-0.001 (-0.093, 0.092), 0.98

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Parity data from MoBa (N = 9439).

Table 5:11 *Estimates for associations between genetic scores with varying p-value thresholds and parity in MoBa data.*

	Parity (N = 9439)
	β (95% CI), *p*
Genetic score for schizophrenia liability	
Model 1	
$p<1x10^{-5}$	0.010 (-0.008, 0.028), 0.29
$p<0.0005$	-0.0001 (-0.018, 0.018), 0.99
$p<0.005$	0.008 (-0.011, 0.027), 0.43
$p<0.05$	0.006 (-0.012, 0.024), 0.53
$p<0.1$	0.005 (-0.014, 0.024), 0.63
$p<0.5$	0.003 (-0.016, 0.022), 0.74
$p<1$	0.004 (-0.016, 0.023), 0.72
Model 2	
$p<1x10^{-5}$	0.010 (-0.008, 0.027), 0.29
$p<0.0005$	0.00004 (-0.018, 0.018), 0.99
$p<0.005$	0.007 (-0.011, 0.026), 0.44
$p<0.05$	0.006 (-0.013, 0.024), 0.55
$p<0.1$	0.004 (-0.015, 0.023), 0.65
$p<0.5$	0.003 (-0.016, 0.022), 0.77
$p<1$	0.003 (-0.016, 0.023), 0.75

Model 1 is adjusted for the top 10 principal components of population structure and genotype array. Model 2 is additionally adjusted for mothers' birth year.

As shown in **Figure 5:3**, the relationship between the genetic score for schizophrenia liability (using genome-wide significant SNPs) and parity suggests a somewhat linear relationship. In line with this, there was no clear statistical evidence for a relationship between genetic liability for schizophrenia and parity when including a quadratic term for the genetic score although the unadjusted quadratic plot suggested a possible J-shaped relationship (see **Table 5:12** and **Appendix 30**).

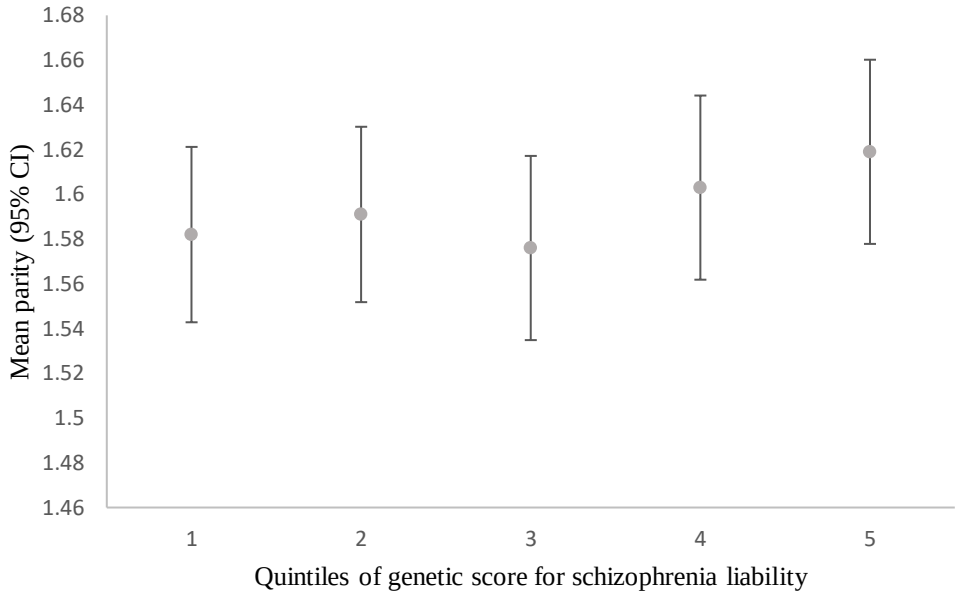

Figure 5:3 *Genetic score for schizophrenia liability (in quintiles) and mean parity in MoBa data showing a slight linear trend across values of the score.*

Table 5:12 *Quadratic regression of the genetic score for schizophrenia liability with parity in MoBa data.*

	Parity (N = 9439)
	β (95% CI), *p*
Genetic score for schizophrenia liability (including quadratic term for the unstandardized score)	
Model 1	-0.232 (-0.650, 0.185), 0.28
Model 2	-0.231 (-0.649, 0.187), 0.28

Model 1 is adjusted for the top 10 principal components of population structure and genotype array. Model 2 is additionally adjusted for mothers' birth year.

5.4.3.3 ALSPAC G0

There was no clear evidence for associations between liability for schizophrenia and parity using a genetic score consisting of genome-wide significant SNPs (see **Table 5:13**). In line with this, there was no clear effects across all MR methods (see **Table 5:14**). In sensitivity analyses using varying *p*-value thresholds for genetic liability, there was no clear evidence of associations with parity at 85 months or 18 years post index child (see **Table 5:15**). Cochran's Q for an IVW method for parity at 85 months post index child was 97.77 ($p = 0.86$) and 91.72 ($p = 0.94$) for parity at 18 years post index child (see **Appendix 31**).

Table 5:13 *Estimates of the association between the genetic score for schizophrenia liability and parity in ALSPAC G0 data.*

	Parity 85m post index child (N = 4977)	**Parity 18y post index child (N = 2562)**
	β (95% CI), *p*	
Genetic score for schizophrenia liability		
Model 1	0.008 (-0.016, 0.033), 0.51	0.003 (-0.035, 0.042), 0.86
Model 2	0.008 (-0.017, 0.032), 0.55	0.006 (-0.033, 0.044), 0.77

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for ALSPAC G0 birth year.

Table 5:14 *Estimates of the causal effect of genetic liability for schizophrenia on parity using IVW, MBE and weighted median MR methods*

	Parity at 85 months[b]	**Parity at 18 years[c]**
Method (115 SNPs[a])	**β (95% CI), *p***	
IVW	0.011 (-0.023, 0.045), 0.53	0.008 (-0.046, 0.062), 0.78
Weighted median	-0.004 (-0.054, 0.046), 0.86	0.012 (-0.064, 0.087), 0.76
MBE	-0.045 (-0.168, 0.078), 0.47	0.039 (-0.152, 0.230), 0.69

[a] Schizophrenia genetic data from the PGC GWAS (N = 35 123 cases and 109 657 controls); [b] Parity at 85 months post index child from ALSPAC G0 (N = 4977). [c] Parity at 18 years post index child from ALSPAC G0 (N = 2562).

Table 5:15 *Estimates for associations between genetic scores with varying p-value thresholds and parity in ALSPAC G0 data.*

	Parity at 85 months (N = 4977)	**Parity at 18 years (N = 2562)**
	β (95% CI), *p*	
Genetic score for schizophrenia liability		
Model 1		
$p<1x10^{-5}$	0.010 (-0.014, 0.034), 0.42	0.025 (-0.014, 0.064), 0.21
$p<0.0005$	0.004 (-0.020, 0.029), 0.74	0.033 (-0.006, 0.073), 0.10
$p<0.005$	0.013 (-0.012, 0.037), 0.32	0.035 (-0.004, 0.075), 0.08
$p<0.05$	0.022 (-0.003, 0.047), 0.08	0.033 (-0.007, 0.073), 0.11
$p<0.1$	0.018 (-0.007, 0.043), 0.15	0.025 (-0.015, 0.065), 0.21
$p<0.5$	0.012 (-0.013, 0.037), 0.36	0.025 (-0.015, 0.065), 0.22
$p<1$	0.011 (-0.014, 0.036), 0.40	0.019 (-0.020, 0.059), 0.34
Model 2		
$p<1x10^{-5}$	0.008 (-0.016, 0.033), 0.50	0.028 (-0.011, 0.068), 0.15
$p<0.0005$	0.002 (-0.022, 0.027), 0.84	0.036 (-0.004, 0.075), 0.08
$p<0.005$	0.012 (-0.013, 0.036), 0.35	0.035 (-0.004, 0.075), 0.08
$p<0.05$	0.021 (-0.004, 0.045), 0.10	0.035 (-0.005, 0.074), 0.09
$p<0.1$	0.017 (-0.008, 0.042), 0.19	0.028 (-0.012, 0.068), 0.17
$p<0.5$	0.010 (-0.015, 0.035), 0.42	0.027 (-0.013, 0.066), 0.19
$p<1$	0.009 (-0.015, 0.034), 0.46	0.021 (-0.018, 0.061), 0.29

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for ALSPAC G0 birth year.

There was little evidence of heterogeneity of mean parity across quintiles of the genetic score for schizophrenia liability when investigating the possibility of a non-linear relationship (see **Figure 5:4** and **Figure 5:5**). Although an unadjusted quadratic plot suggested a non-linear relationship for each measure of parity, there was no clear statistical support for these (see **Appendix 32** and **Appendix 33** and **Table 5:16**).

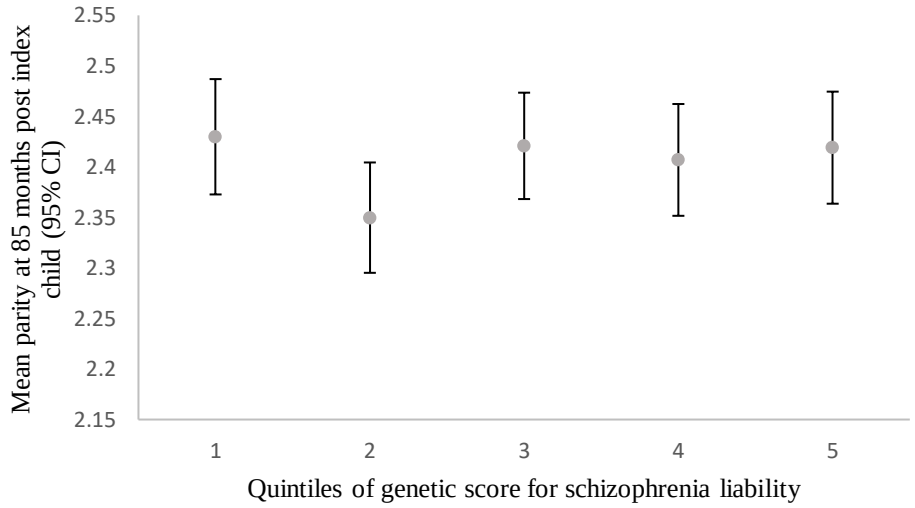

Figure 5:4 *Genetic score for schizophrenia liability (in quintiles) and mean parity at 85 months post index child in ALSPAC G0 data showing little evidence of heterogeneity across values of the score.*

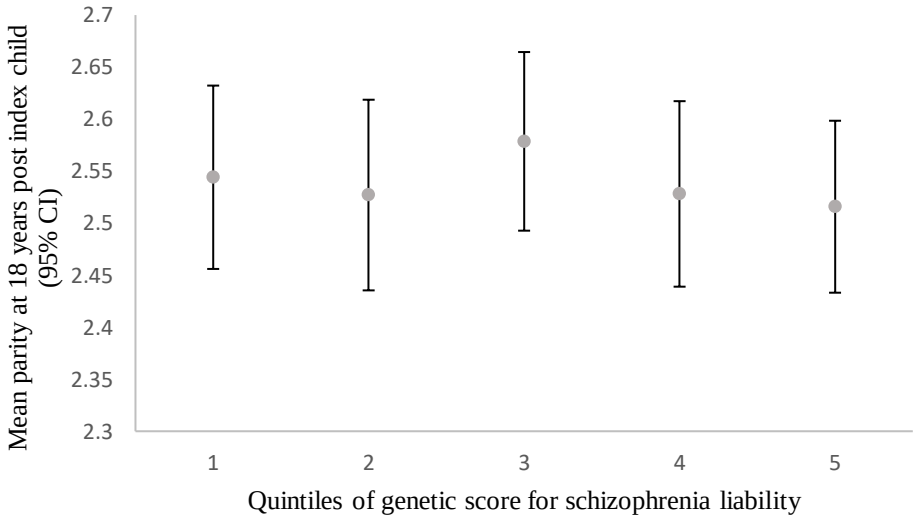

Figure 5:5 *Genetic score for schizophrenia liability (in quintiles) and mean parity at 18 years post index child in ALSPAC G0 data showing little evidence of heterogeneity across values of the score.*

Table 5:16 *Quadratic regression of the genetic score for schizophrenia liability with parity in ALSPAC G0.*

	Parity 85m post index child (N = 4977)	**Parity 18y post index child (N = 2562)**
	β (95% CI), *p*	
Genetic score for schizophrenia liability (including quadratic term for the unstandardized score)		
Model 1	-0.337 (-0.985, 0.312), 0.31	0.628 (-0.384, 1.639), 0.22
Model 2	-0.341 (-0.988, 0.307), 0.30	0.598 (-0.410, 1.607), 0.25

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for ALSPAC G0 birth year.

5.4.3.4 ALSPAC G1

As shown in **Table 5:17**, there was evidence of an effect in the positive direction for increasing genetic liability for schizophrenia on the likelihood of having had a child in females. However, in combined sexes or males only, there was no clear evidence of such an effect (see **Table 5:17** and **Table 5:18**). Cochran's Q values for the IVW method indicated only weak evidence for overdispersion (138.38, $p = 0.06$) (see **Appendix 34**).

Table 5:17 *Estimates of associations between the genetic score for schizophrenia liability and whether participants had had a child yet in ALSPAC G1 data.*

		Had child
Genetic score for schizophrenia liability	**N**	**OR (95% CI), *p***
Combined sexes	1956	1.123 (0.970, 1.301), 0.12
Females	1299	1.214 (1.027, 1.434), 0.02
Males	657	0.872 (0.639, 1.189), 0.39

Table 5:18 *Estimates of the causal effect of genetic liability for schizophrenia on whether participants had had a child yet using IVW, MBE and weighted median MR methods.*

	Had child[b]
Methods (115 SNPs[a])	**OR (95% CI), *P***
IVW	1.173 (0.948, 1.451), 0.14
Weighted Median	1.172 (0.875, 1.569), 0.29
MBE	0.937 (0.467, 1.881), 0.28

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Whether participants had had a child yet data from ALSPAC G1 (N = 1956).

5.4.3.5 Summary across all studies

All IVW point estimates for the effect of genetic liability for schizophrenia on number of children or parity were in the positive direction. There was statistical support for an effect in MoBa, whereas confidence intervals for the other studies included the null. For childlessness, there was no clear evidence in either UK Biobank or ALSPAC G1 and the point estimate for UK Biobank was very close to the null value, possibly due lower statistical power with using binary measures.

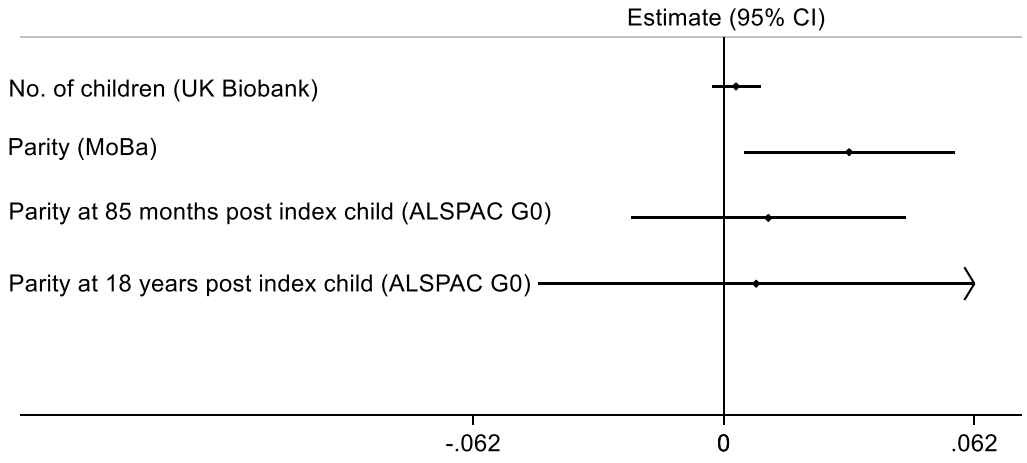

Figure 5:6 *IVW estimates for genetic liability for schizophrenia on number of children or parity across studies.*

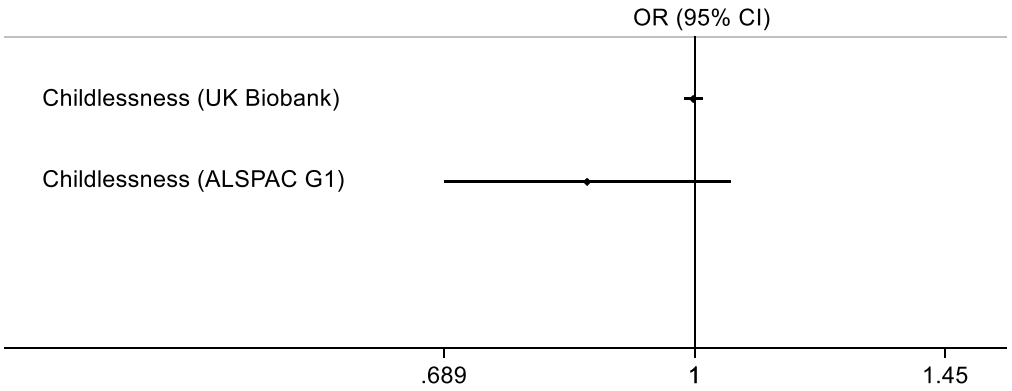

Figure 5:7 *IVW estimates for genetic liability for schizophrenia on likelihood of being childless across studies. ALSPAC G1 estimates are for the reverse coding of having had a child in the above analysis.*

5.4.4 Number of sexual partners

5.4.4.1 UK Biobank

There was no clear evidence of a genetic correlation between schizophrenia liability and number of sexual partners ($r_g = 0.007$, $p = 0.42$). Again, the analysis included 1 114 456 SNPs. Results for these analyses with genotype array included as a covariate in the outcome summary statistics are presented in **Appendix 19**.

There was clear evidence of a positive association between genetic liability for schizophrenia and number of sexual partners (see **Table 5:19**). Cochran's Q was 301.88 ($p<0.001$) for genetic liability of schizophrenia and number of sexual partner and 250.33 ($p<0.001$) for genetic liability of schizophrenia and being in the highest number of sexual partners for IVW analysis, again suggesting overdispersion although this also appeared balanced (see **Appendix 20** for an example). I found that higher genetic liability for schizophrenia had a positive effect on number of sexual partners (mean difference: 0.165 increase in number of sexual partners per doubling in the natural log OR of schizophrenia liability, 95% CI: 0.117 to 0.212, $p<0.001$) (see **Table 5:20**). A positive effect was also seen in analysis of the binary measure for the highest number of sexual partners (see **Table 5:20**). No clear change in results was seen when analysis was repeated without the few schizophrenia cases (shown in **Appendix 21**). Results for these analyses with genotype array included as a covariate in the outcome summary statistics are presented in **Appendix 22**.

Table 5:19 *Estimates of the association between the genetic score for schizophrenia liability and number of sexual partners in UK Biobank data.*

Genetic score for schizophrenia liability	**Number of sexual partners**	
	N	**β (95% CI), *p***
Combined sexes	275 700	0.016 (0.011, 0.021), <0.001
Females	148 630	0.005 (0.002, 0.009), 0.004
Males	127 070	0.029 (0.019, 0.038), <0.001

Table 5:20 *Estimates of the causal effect of genetic liability for schizophrenia on number of sexual partners and a binary measure of this using IVW, MBE and weighted median MR methods.*

	Number of sexual partners[b]	**Highest number of sexual partners[c]**
Method (101 SNPs[a])	**β (95% CI), *p***	**OR (95% CI), *p***
IVW	0.165 (0.117, 0.212), <0.001	1.057 (1.038, 1.077), <0.001
Weighted median	0.172 (0.092, 0.230), <0.001	1.034 (1.003, 1.066), 0.03
MBE	0.389 (-0.032, 0.810), 0.07	1.010 (0.884, 1.154), 0.88

[a] Schizophrenia genetic data from the PGC GWAS (N = 35 123 cases and 109 657 controls); [b] Number of sexual partners data from UK Biobank (N = 261 931- 275 700); [c] Highest number of sexual partners data from UK Biobank (N = 261 931- 275 700).

In sensitivity analysis, the relationship between the genetic score for schizophrenia liability and number of sexual partners appears linear (see **Figure 5:8**). Similar patterns are seen across deciles of the genetic score for schizophrenia liability and when plotting these measures of reproductive success on the x-axis (see **Appendix 35** and **Appendix 36**). Furthermore, a relationship was consistently shown when removing cumulative deciles from the maximum of the genetic score (see **Table 5:21** and **Appendix 25**). Furthermore, there was no clear evidence for a relationship between genetic liability for schizophrenia and number of sexual partners when including a quadratic term, again suggesting the relationship is linear (see **Table 5:22** and **Appendix 37-39**).

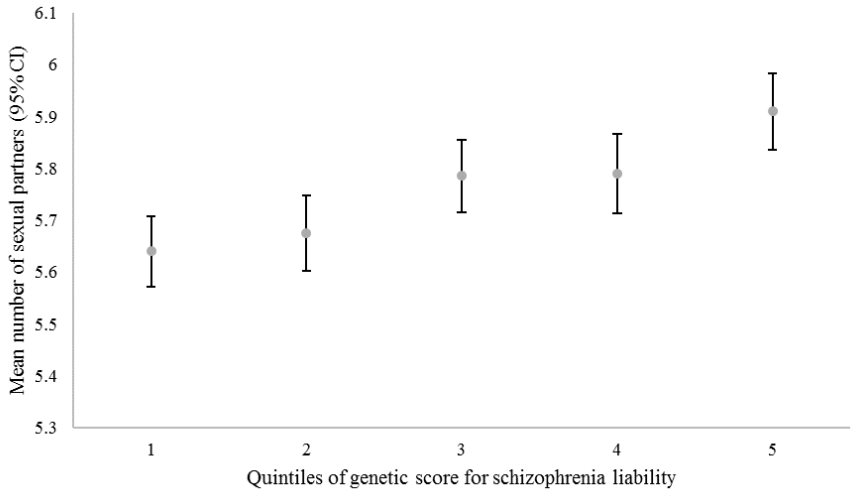

Figure 5:8 *Genetic score for schizophrenia liability (in quintiles) and mean number of sexual partners in UK Biobank data suggesting a linear relationship.*

Table 5:21 *Estimates of the association between the genetic score for schizophrenia liability and number of sexual partners removing cumulative deciles of the genetic score.*

Genetic score for schizophrenia liability	Number of sexual partners	
	N	**β (95% CI), *p***
Highest 10% removed	248 251	0.011 (0.005, 0.017), <0.001
Highest 20% removed	220 847	0.012 (0.005, 0.020), <0.001
Highest 30% removed	193 353	0.017 (0.008, 0.025), <0.001
Highest 40% removed	171 567	0.015 (0.006, 0.025), <0.001
Highest 50% removed	138 280	0.012 (0.001, 0.024), 0.04

Table 5:22 *Quadratic regression of the genetic score for schizophrenia liability with number of sexual partners in UK Biobank data.*

Genetic score for schizophrenia liability (including quadratic term for genetic score)	Number of sexual partners	
	N	**β (95% CI), *p***
Combined sexes	275 700	-0.046 (-0.148, 0.056), 0.38
Females	148 630	-0.017 (-0.092, 0.057), 0.65
Males	127 070	-0.085 (-0.289, 0.118), 0.41

5.4.4.2 ALSPAC G1

There was little evidence of associations between the genetic score for schizophrenia liability and outcomes in regression analyses (see **Table 5:23**). Cochran's Q values indicated little evidence for overdispersion across IVW analyses (see **Table 5:24** and **Appendix 34** for example plot). As shown in **Table 5:25**, there was little evidence for a causal effect of increasing genetic liability of schizophrenia on number of sexual partners across MR methods.

Table 5:23 *Estimates of the association between the genetic score for schizophrenia liability and number of sexual partners in ALSPAC G1 data.*

	Number of sexual partners		Number of sexual partners (plus 21-year data)	
	N	**β (95% CI), *p***	**N**	**β (95% CI), *p***
Combined sexes	2474	0.203 (-0.206, 0.613), 0.33	2963	0.219 (-0.169, 0.607), 0.27
Females only	1623	-0.050 (-0.443, 0.344), 0.81	1911	-0.064 (-0.433, 0.305), 0.73
Males only	851	0.636 (-0.285, 1.556), 0.18	1052	0.664 (-0.195, 1.524), 0.13

Table 5:24 *Cochran's Q values for an IVW approach.*

	Schizophrenia liability	
Outcome	**Q**	***p***
Number of sexual partners	130.14	0.14
Number of sexual partners (plus 21-year data)	122.33	0.28
Highest number of sexual partners	126.28	0.19
Highest number of sexual partners (plus 21-year data)	131.87	0.12

Table 5:25 *Estimates of the causal effect of genetic liability for schizophrenia on number of sexual partners and a binary measure of this using IVW, MBE and weighted median MR methods.*

	Number of sexual partners[b]	**Number of sexual partners (plus 21-year data)[c]**	**Highest number of sexual partners[b]**	**Highest number of sexual partners (plus 21-year data)[c]**
Method (115 SNPs[a])	**β (95% CI), *p***		**OR (95% CI), *p***	
IVW	0.293 (-0.301, 0.888), 0.33	0.313 (-0.231, 0.856), 0.26	1.066 (0.877, 1.296), 0.52	1.055 (0.888, 1.254), 0.54
Weighted Median	0.121 (-0.744, 1.278), 0.78	0.279 (-0.520, 1.077), 0.50	1.116 (0.849, 1.468), 0.43	1.017 (0.790, 1.307), 0.90
MBE	-0.382 (-2.238, 1.523), 0.40	0.343 (-1.374, 2.060), 0.70	1.216 (0.668, 2.204), 0.52	1.112 (0.655, 1.887), 0.92

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Number of sexual partners data from ALSPAC G0 (N = 2474); [c] Number of sexual partners (plus 21-year data) from ALSPAC G0 (N = 2963). The number of SNPs for [c] is 114.

In **Figure 5:9** and **Figure 5:10**, there is some suggestion of a peak in number of sexual partners even in this general population sample. Results from regression analysis including a quadratic term for the genetic score supported this peak, particularly in females (see **Table 5:26** and **Appendix 40-33**).

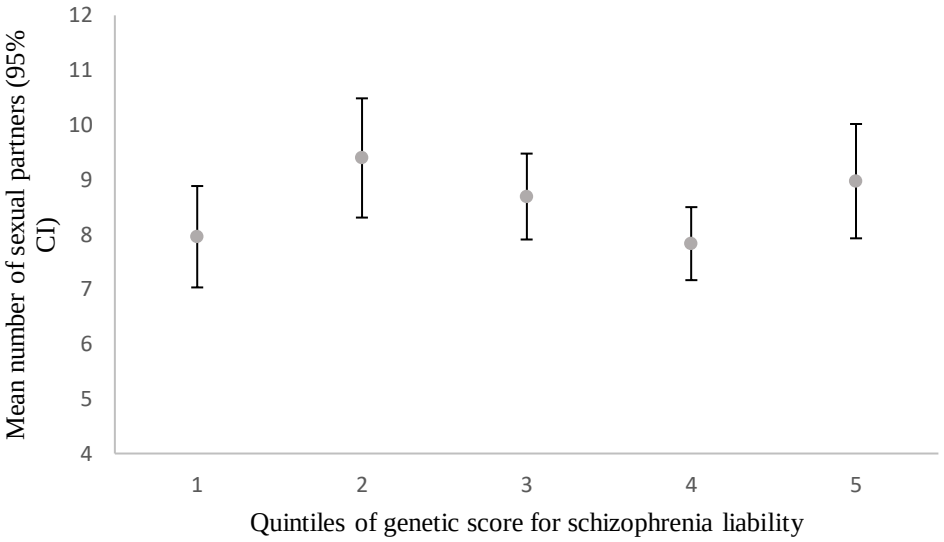

Figure 5:9 *Genetic score for schizophrenia liability (in quintiles) and mean number of sexual partners in ALSPAC G1 data suggesting a possible non-linear relationship.*

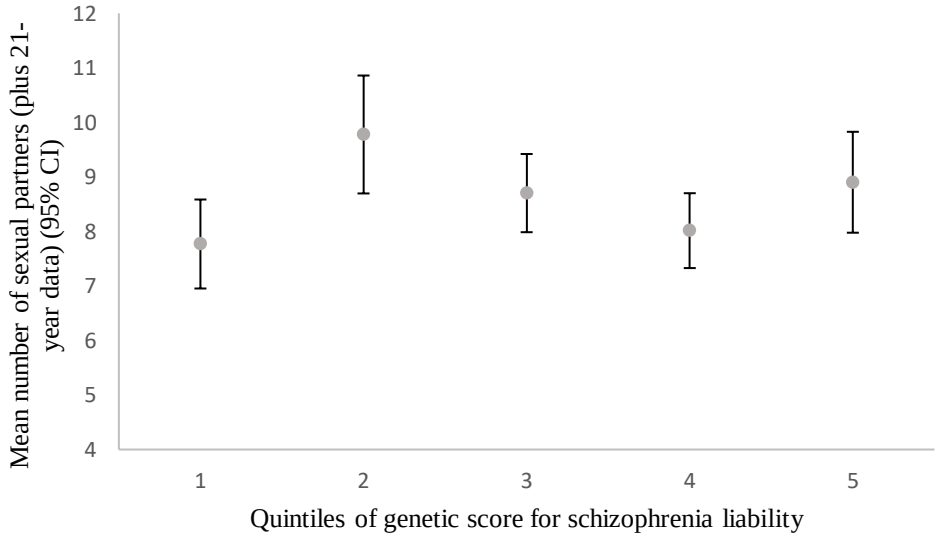

Figure 5:10 *Genetic score for schizophrenia liability (in quintiles) and mean number of sexual partners (plus 21-year data) in ALSPAC G1 data suggesting a possible non-linear relationship.*

Table 5:26 *Quadratic regression of the genetic score for schizophrenia liability with number of sexual partners in ALSPAC G1 data.*

Genetic score for schizophrenia liability (including quadratic term for the unstandardized score)	**Number of sexual partners**		**Number of sexual partners (plus 21-year data)**	
	N	**β (95% CI), *p***	**N**	**β (95% CI), *p***
Combined sexes	2474	6.264 (-3.852, 16.380), 0.23	2963	9.479 (-0.137, 19.094), 0.05
Females only	1623	10.824 (0.724, 20.924), 0.04	1911	9.983 (0.498, 19.468), 0.04
Males only	851	-3.171 (-24.57, 18.23), 0.77	1052	6.977 (-13.142, 27.096), 0.50

5.4.4.3 Summary across all studies

All IVW point estimates for the effect of genetic liability for schizophrenia on number of sexual partners were in the positive direction. There was a clear effect in UK Biobank, whereas confidence intervals for ALSPAC G1 results were wide and consistent with the null. It is likely that the smaller sample sizes for ALSPAC G1 data resulted in reduced power to clearly detect an effect, although sensitivity analysis also suggested a possible non-linear relationship (see above).

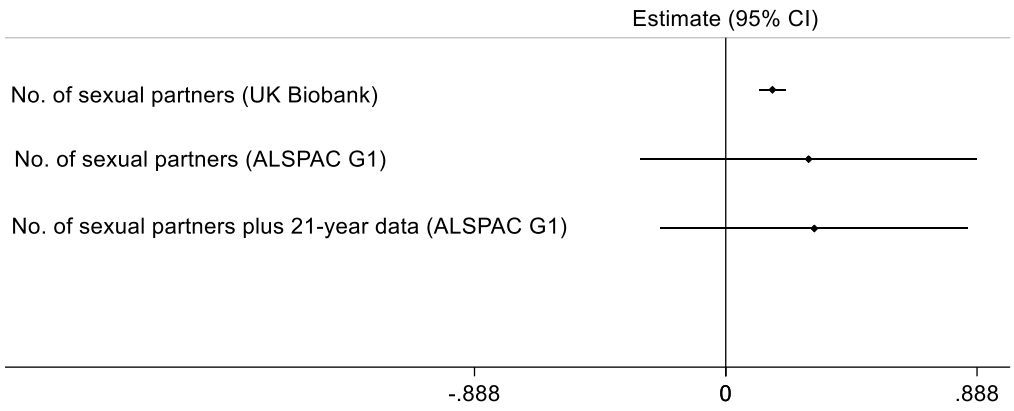

Figure 5:11 *IVW estimates for genetic liability for schizophrenia on number of sexual partners across studies.*

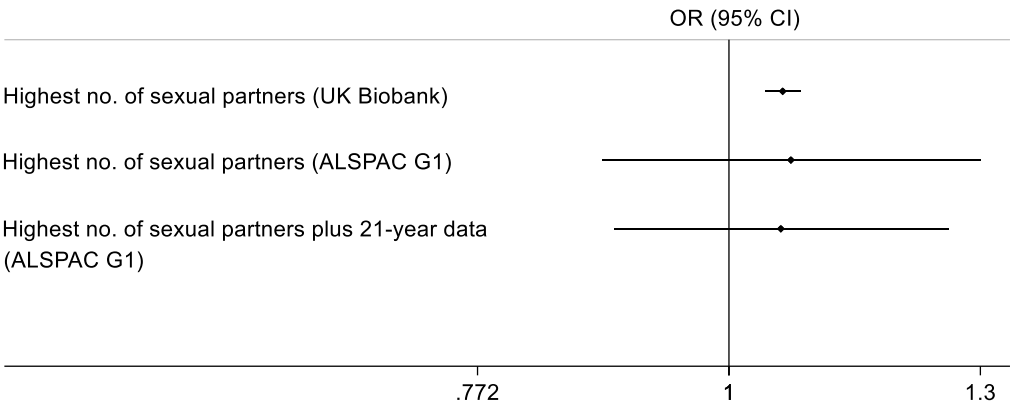

Figure 5:12 *IVW estimates for genetic liability for schizophrenia on a binary measure of number of sexual partners across studies.*

5.4.5 Age at first pregnancy and age at first birth

5.4.5.1 UK Biobank

Using LD score regression, there was little evidence of a genetic correlation between schizophrenia liability and age at first birth (r_g = -0.007, p = 0.45). Again, there were 1 114 456 SNPs included in this analysis. Results for these analyses with genotype array included as a covariate in the outcome summary statistics are presented in **Appendix 19**.

Regression of the genetic score for schizophrenia liability on age at first birth showed no clear evidence of an association (mean difference: -0.001 decrease in age at first birth per allele increase in genetic liability for schizophrenia, CI: -0.005 to 0.003, p = 0.54, N = 124 093). Cochran's Q was 286.64 for genetic liability of schizophrenia and age at first birth (p<0.001) which again suggests the presence of overdispersion although this did appear balanced (see **Appendix 20** for example). There was little evidence that higher genetic liability for schizophrenia decreased age at first birth (mean difference: -0.004 years lower age at first birth per doubling in the natural log OR of schizophrenia liability, 95% CI: -0.043 to 0.034, p = 0.82) (see **Table 5:27**). After removing the few schizophrenia cases in the sample, there was no clear change in results (as shown in **Appendix 21**). For results of these analyses with genotype array included as a covariate in outcome summary statistics, see **Appendix 22**.

Table 5:27 *Estimates of the causal effect of genetic liability for schizophrenia on age at first birth using IVW, MBE and weighted median MR methods.*

	Age at first birth[b]
Method (101 SNPs[a])	**β (95% CI), *p***
IVW	-0.004 (-0.043, 0.034), 0.82
Weighted median	0.023 (-0.042, 0.089), 0.49
MBE	0.060 (-0.175, 0.294), 0.62

[a] *Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls);* [b] *Age at first birth data from UK Biobank (N = 117 844 – 124 093).*

Sensitivity analysis investigating a possible non-linear relationship is presented in **Figure 5:13** and **Appendix 46**, showing the mean age at first birth for quintiles of an unweighted additive genetic score for schizophrenia liability. Although these figures are somewhat suggestive of a non-linear relationship between the genetic score for schizophrenia liability and mean age at first birth, there is little evidence of heterogeneity across values of the schizophrenia score. A series of regressions between the genetic score and age at first birth, systematically removing cumulative centiles from the maximum, suggests that the relationship is strongest at intermediate levels (see **Table 5:28**). This analysis was repeated after removing the few schizophrenia cases, which did not alter these results (see **Appendix 25**). There was a weak association when including a quadratic term for the genetic score, suggesting the lowest age at first birth was seen at intermediate levels of genetic liability (mean difference: -0.088 decrease in age at first birth per allele increase in genetic liability for schizophrenia, CI: -0.171 to -0.004, $p = 0.54$, N = 124,093) (also see **Appendix 47**).

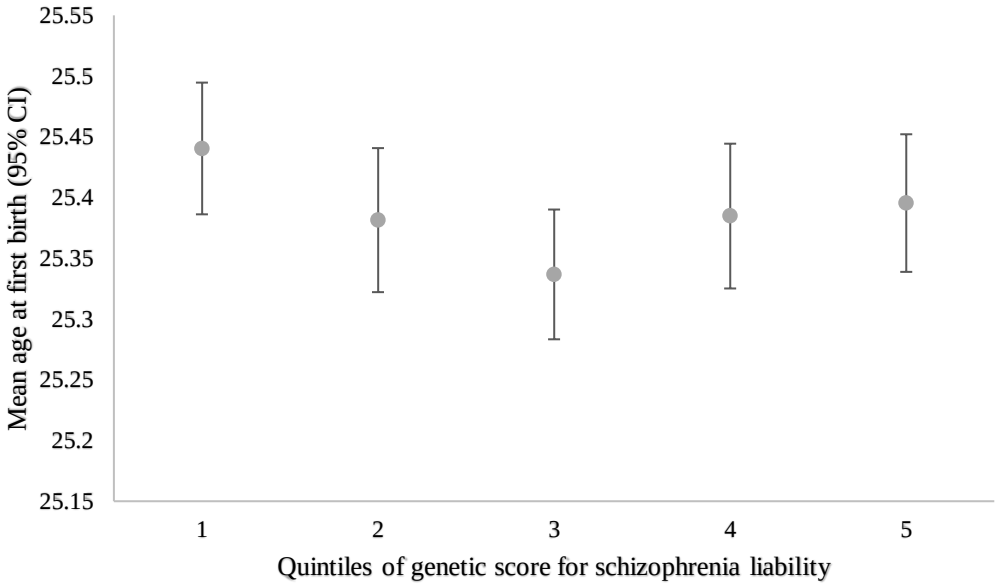

Figure 5:13 *Genetic score for schizophrenia liability (in quintiles) and mean age at first birth in women from UK Biobank data showing some evidence of a non-linear trend.*

Table 5:28 *Associations of the genetic score for schizophrenia liability and age at first birth removing cumulative deciles of the score.*

		Age at first birth
Genetic score for schizophrenia liability	**N**	**β (95% CI), *p***
Highest 10% removed	111 632	-0.004 (-0.009, 0.001), 0.15
Highest 20% removed	99 134	-0.005 (-0.010, 0.001), 0.11
Highest 30% removed	86 620	-0.008 (-0.014, -0.001), 0.03
Highest 40% removed	76 833	-0.009 (-0.016, -0.001), 0.02
Highest 50% removed	61 822	-0.008 (-0.018, 0.001), 0.08

5.4.5.2 MoBa

No clear associations were seen between genetic liability for schizophrenia and age at first pregnancy or age at first birth (see **Table 5:29**). Furthermore, there were no clear effects of genetic liability for schizophrenia on age at first pregnancy or age at first birth across MR methods (see **Table 5:30**). The Cochran's Q was 98.79 (p = 0.63) for age at first pregnancy and 89.67 (p = 0.84) for age at first birth (see **Appendix 29** for an example).

In sensitivity analysis varying the p-value threshold for genetic liability to schizophrenia, there was evidence of negative associations with age at first pregnancy (see **Table 5:31**). Point estimates were in a consistent negative direction although varying strengths of

evidence was seen. Evidence for age at first birth was weaker however results for a *p*-value threshold of 0.05 suggested a relationship when including adjustment for birth year.

Table 5:29 *Estimates of the association between the genetic score for schizophrenia liability and age at first pregnancy and age at first birth in MoBa data.*

	Age at first pregnancy (N = 9444)	**Age at first birth (N = 9444)**
Genetic score for schizophrenia liability	**β (95% CI), *p***	
Model 1	0.029 (-0.067, 0.124), 0.55	0.022 (-0.066, 0.111), 0.62
Model 2	0.006 (-0.079, 0.092), 0.88	-0.004 (-0.078, 0.071), 0.93

Model 1 is adjusted for the top 10 principal components of population structure and genotype array. Model 2 is additionally adjusted for mothers' birth year.

Table 5:30 *Estimates of the causal effect of genetic liability for schizophrenia on age at first pregnancy and age at first birth using IVW, MBE and weighted median MR methods.*

	Age at first pregnancy[b]	**Age at first birth[c]**
Method (105 SNPs[a])	**β (95% CI), *p***	
IVW	0.010 (-0.114, 0.133), 0.88	-0.006 (-0.114, 0.103), 0.92
Weighted median	-0.028 (-0.209, 0.155), 0.77	0.092 (-0.061, 0.245), 0.24
MBE	-0.067 (-0.610, 0.476), 0.81	0.202 (-0.171, 0.577), 0.29

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Age at first pregnancy data from MoBa (N = 9444); [c] Age at first birth data from MoBa (N = 9444).

Table 5:31 *Estimates for associations between genetic scores with varying p-value thresholds and age at first pregnancy and age at first birth in MoBa data.*

	Age at first pregnancy (N=9444)	**Age at first birth (N = 9444)**
	β (95% CI), *p*	**β (95% CI), *p***
Schizophrenia		
Model 1		
$p<1x10^{-5}$	-0.085 (-0.181, 0.010), 0.08	-0.060 (-0.149, 0.029), 0.19
$p<0.0005$	-0.107 (-0.203, -0.011), 0.03	-0.045 (-0.134, 0.045), 0.33
$p<0.005$	-0.126 (-0.225, -0.028), 0.01	-0.035 (-0.127, 0.057), 0.46
$p<0.05$	-0.145 (-2.45, -0.045), 0.004	-0.053 (-0.146, 0.040), 0.27
$p<0.1$	-0.156 (-0.258, -0.053), 0.003	-0.062 (-0.158, 0.034), 0.21
$p<0.5$	-0.132 (-0.234, -0.031), 0.01	-0.032 (-0.127, 0.063), 0.51
$p<1$	-0.125 (-0.229, -0.022), 0.02	-0.023 (-0.119, 0.074), 0.65
Model 2		
$p<1x10^{-5}$	-0.086 (-0.172, -0.001) 0.05	-0.060 (-0.135, 0.015), 0.11
$p<0.0005$	-0.098 (-0.184, -0.012), 0.03	-0.034 (-0.110, 0.041), 0.37
$p<0.005$	-0.140 (-0.228, -0.052), 0.002	-0.051 (-0.128, 0.027), 0.20
$p<0.05$	-0.184 (-0.274, -0.095), <0.001	-0.098 (-0.176, -0.019), 0.02
$p<0.1$	-0.187 (-0.279, -0.095), <0.001	-0.099 (-0.179, -0.018), 0.02
$p<0.5$	-0.171 (-0.262, -0.080), <0.001	-0.077 (-0.156, 0.003), 0.60
$p<1$	-0.170 (-0.262, -0.077), <0.001	-0.074 (-0.155, 0.008), 0.08

Model 1 is adjusted for the top 10 principal components of population structure and genotype array. Model 2 is additionally adjusted for mothers' birth year.

There appeared to be little evidence of heterogeneity for mean age at first pregnancy across quintiles of the genetic score for schizophrenia liability (see **Figure 5:14**) whereas a possible peak was observed for age at first birth (see **Figure 5:15**). Quadratic regression results showed no support for non-linearity (see **Table 5:32**, **Appendix 48** and **Appendix 49**).

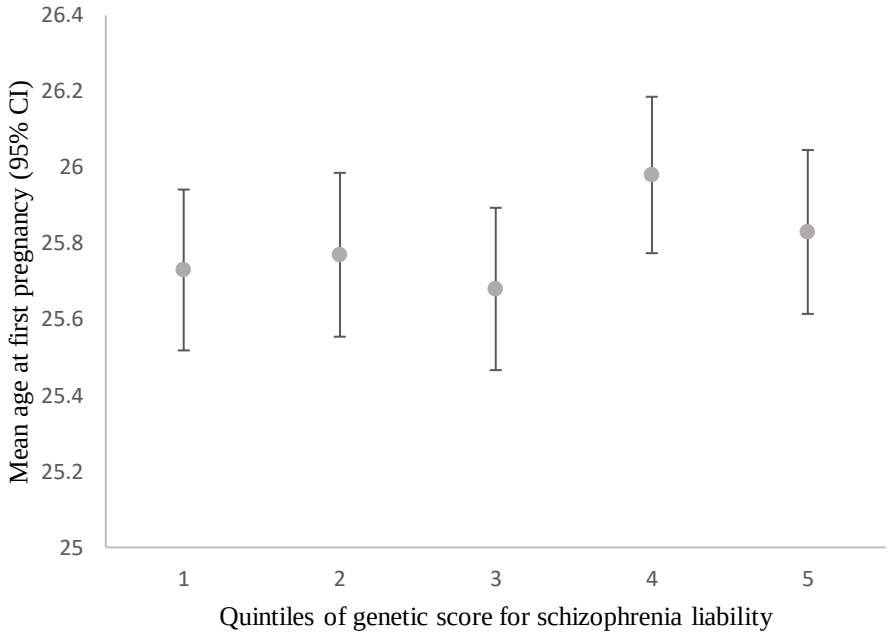

Figure 5:14 *Genetic score for schizophrenia liability (in quintiles) and mean age at first pregnancy in MoBa data showing little heterogeneity across values of the score.*

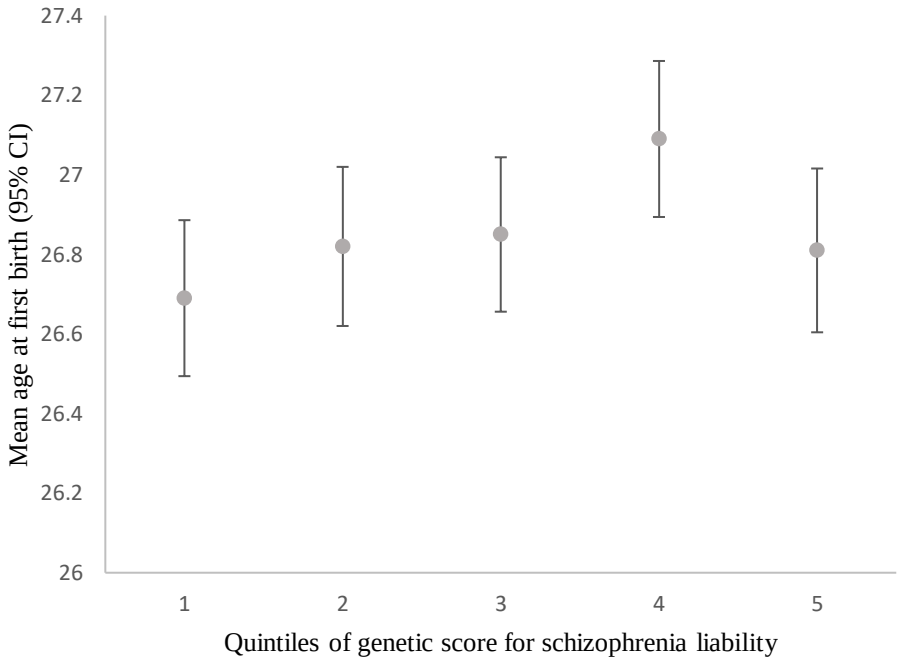

Figure 5:15 *Genetic score for schizophrenia liability (in quintiles) and mean age at first birth in MoBa data showing little heterogeneity across values of the score.*

Table 5:32 *Quadratic regression of the genetic score for schizophrenia liability with age at first pregnancy and age at first birth in MoBa.*

	Age at first pregnancy (N = 9444)	**Age at first birth (N = 9444)**
	β (95% CI), *p*	
Genetic score for schizophrenia liability (including quadratic term for the unstandardized score)		
Model 1	0.183 (-2.042, 2.408), 0.87	1.192 (-0.888, 3.273), 0.26
Model 2	0.342 (-1.658, 2.342), 0.74	1.375 (-0.376, 3.127), 0.12

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for mothers' birth year.

5.4.5.3 ALSPAC G0

There was no clear evidence for associations between liability for schizophrenia and age at first pregnancy using a genetic score consisting of genome-wide significant SNPs (see **Table 5:33**). Cochran's Q for this IVW analysis was 125.14 ($p = 0.22$) (see **Appendix 31** for an example). There was weak evidence for a negative effect of increasing liability for schizophrenia on age at first pregnancy using a weighted median approach (see **Table 5:34**).

Table 5:33 *Estimates of the association between the genetic score for schizophrenia liability and age at first pregnancy in ALSPAC G0 data.*

Genetic score for schizophrenia liability	**Age at first pregnancy (N = 7036)**
	β (95% CI), *p*
Model 1	0.033 (-0.081, 0.147), 0.57
Model 2	-0.028 (-0.117, 0.060), 0.53

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for ALSPAC G0 birth year.

Table 5:34 *Estimates of the causal effect of genetic liability for schizophrenia on age at first pregnancy using IVW, MBE and weighted median MR methods.*

	Age at first pregnancy[b]
Methods (115 SNPs[a])	**β (95% CI), *p***
IVW	-0.040 (-0.169, 0.089), 0.54
Weighted median	-0.184 (-0.373, 0.006), 0.06
MBE	-0.254 (-0.667, 0.159), 0.23

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Age at first pregnancy data from ALSPAC G0 (N = 7036).

In sensitivity analyses using a *p*-value threshold of below 0.05 for genetic liability, I found weak evidence for a negative association between liability for schizophrenia and age at first pregnancy. Results showed congruent direction of point estimates and varying strengths of evidence for this negative association across the varying *p*-value thresholds for genetic liability for schizophrenia (see **Table 5:35**).

Table 5:35 *Estimates for associations between genetic scores with varying p-value thresholds and age at first pregnancy in ALSPAC G0 data.*

	Age at first pregnancy (N = 7036)
	β (95% CI), *p*
Genetic score for schizophrenia liability	
Model 1	
$p<1x10^{-5}$	-0.045 (-0.158, 0.068), 0.44
$p<0.0005$	-0.038 (-0.152, 0.076), 0.51
$p<0.005$	-0.111 (-0.226, 0.003), 0.06
$p<0.05$	-0.099 (-0.214, 0.015), 0.09
$p<0.1$	-0.082 (-0.197, 0.032), 0.16
$p<0.5$	-0.084 (-0.199, 0.030), 0.15
$p<1$	-0.103 (-0.217, 0.012), 0.08
Model 2	
$p<1x10^{-5}$	-0.099 (-0.188, 0.011), 0.03
$p<0.0005$	-0.073 (-0.162, 0.016), 0.11
$p<0.005$	-0.107 (-0.196, -0.018), 0.02
$p<0.05$	-0.143 (-0.232, -0.053), 0.002
$p<0.1$	-0.138 (-0.228, -0.049), 0.002
$p<0.5$	-0.132 (-0.221, -0.043), 0.004
$p<1$	-0.142 (-0.232, -0.053), 0.002

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for ALSPAC G0 birth year.

Sensitivity analysis investigating a possible non-linear relationship between genetic liability for schizophrenia and age at first pregnancy showed little evidence when plotting the mean age across quintiles of the genetic score or in regression analysis including a quadratic term (see **Figure 5:16**, **Table 5:36** and **Appendix 50**).

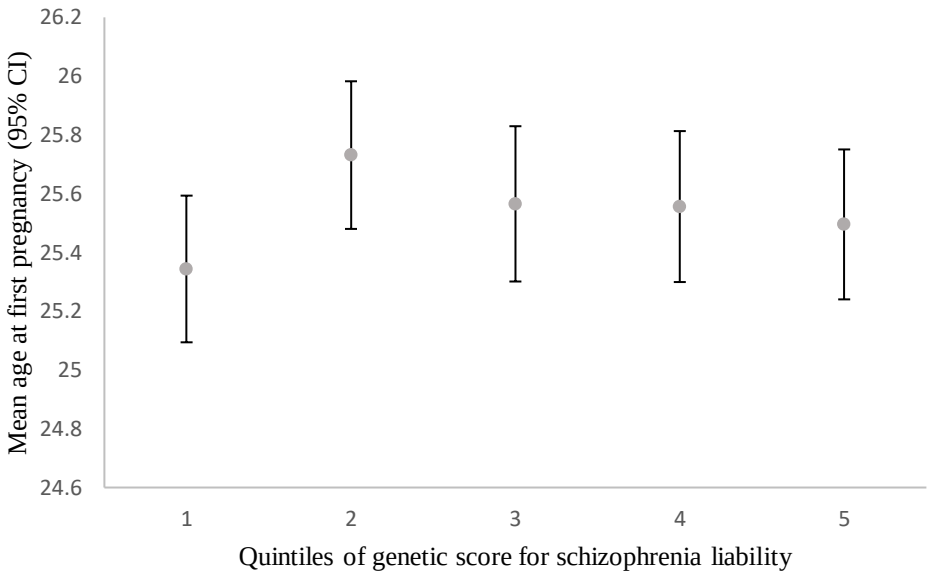

Figure 5:16 *Genetic score for schizophrenia liability (in quintiles) and mean age at first pregnancy in ALSPAC G0 data showing little heterogeneity across values of the score.*

Table 5:36 *Quadratic regression of the genetic score for schizophrenia liability with age at first pregnancy in ALSPAC G0.*

	Age at first pregnancy (N = 7036)
	β (95% CI), *p*
Genetic score for schizophrenia liability (including quadratic term for the score)	
Model 1	2.081 (-0.934, 5.096), 0.18
Model 2	1.398 (-0.952, 3.749), 0.24

Model 1 is adjusted for the top 10 principal components of population structure. Model 2 is additionally adjusted for ALSPAC G0 birth year.

5.4.5.4 Summary across all studies

Across all studies, the IVW results for a causal effect of genetic liability for schizophrenia on age at first pregnancy and age at first birth obtained confidence intervals consistent with the null (see **Figure 5:17**). For UK Biobank and ALSPAC G0 data, point estimates were in the negative direction.

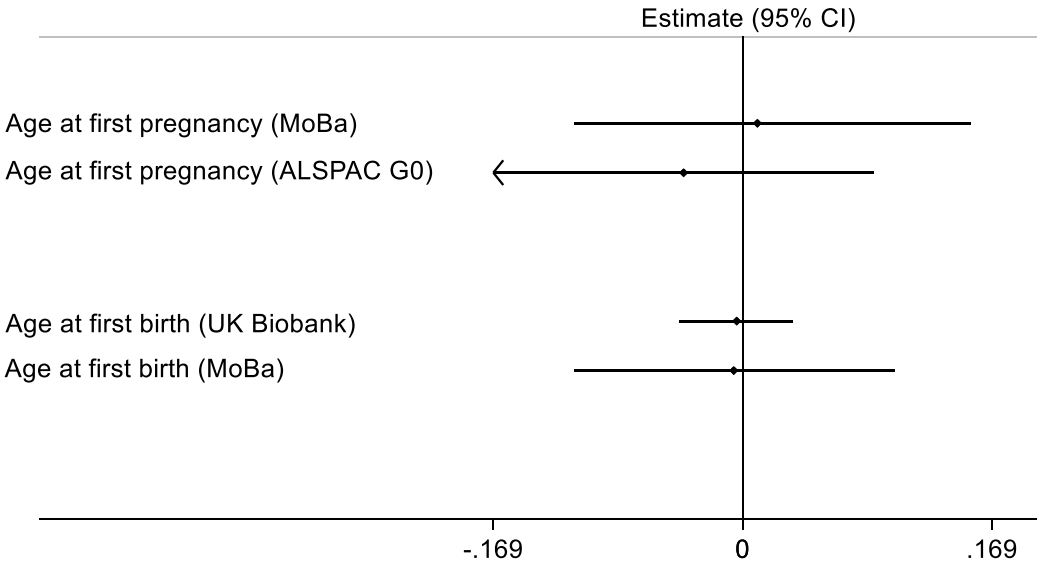

Figure 5:17 *IVW estimates for genetic liability for schizophrenia on age at first pregnancy and age at first birth across studies.*

5.4.6 Secondary measures of reproductive success in MoBa

When using a genetic score that included only genome-wide significant SNPs for schizophrenia liability, there was no clear evidence of associations between liability and any secondary outcome (whether the index pregnancy was planned, whether mothers had conceived the index pregnancy even though them or their partner used contraceptives, if mothers had ever been treated for infertility, and length of sexual relationship the mother had had with the index child's father) (see **Table 5:37**). However, there was evidence of an increased likelihood of having conceived the index pregnancy whilst them of their partner used contraceptives with increasing liability for schizophrenia across varying *p*-value thresholds for the SNPs included in the score (see **Table 5:37**). There was further weak evidence for a decrease in relationship length with the index pregnancies father with increasing genetic liability for the disorder using *p*-value thresholds of 0.005 and 0.1 with adjustment for birth year. There was no clear evidence that participants were less likely to be treated for infertility with increasing genetic liability for schizophrenia.

Table 5:37 *Estimates for associations between genetic scores with varying p-value thresholds and secondary measures of reproductive success in MoBa data.*

	Pregnancy planned (N = 9350)	**Contraception was used** (N = 9132) OR (95% CI), *p*	**Treated infertility** (N = 9354)	**Length of relationship with father** (N = 7134) β (95% CI), *p*
Genetic score for schizophrenia liability				
Model 1 - adjusted for the top 10 principal components of population structure and genotype array				
Plink score				
$p<5\times10^{-8}$	0.980 (0.928, 1.036), 0.48	0.979 (0.885, 1.083), 0.68	0.971 (0.902, 1.046), 0.44	0.123 (-0.873, 1.120), 0.81
PRSice scores				
$p<1x10^{-5}$	0.996 (0.943, 1.052), 0.88	1.013 (0.915, 1.121), 0.81	0.957 (0.889, 1.031), 0.25	-0.650 (-1.647, 0.348), 0.20
$p<0.0005$	0.959 (0.907, 1.013), 0.14	1.074 (0.969, 1.190), 0.18	0.986 (0.915, 1.063), 0.72	-0.748 (-1.754, 0.258), 0.15
$p<0.005$	0.949 (0.898, 1.005), 0.07	1.129 (1.016, 1.255), 0.02	1.017 (0.942, 1.098), 0.67	-0.819 (-1.852, 0.214), 0.12
$p<0.05$	0.968 (0.914, 1.025), 0.26	1.104 (0.993, 1.228), 0.07	0.989 (0.915, 1.068), 0.77	-0.482 (-1.529, 0.565), 0.37
$p<0.1$	0.974 (0.918, 1.033), 0.38	1.142 (1.023, 1.274), 0.02	0.989 (0.913, 1.071), 0.79	-0.653 (-1.730, 0.424), 0.24
$p<0.5$	0.972 (0.917, 1.031), 0.34	1.118 (1.004, 1.247), 0.04	0.996 (0.920, 1.078), 0.92	-0.456 (-1.521, 0.609), 0.40
$p<1$	0.978 (0.921, 1.037), 0.45	1.116 (0.100, 1.246), 0.05	0.998 (0.921, 1.082), 0.97	-0.457 (-1.541, 0.627), 0.41
Model 2 - additionally adjusted for mothers' birth year				
Plink score				
$p<5\times10^{-8}$	0.976 (0.924, 1.031), 0.39	0.983 (0.888, 1.088), 0.74	0.963 (0.894, 1.038), 0.33	-0.832 (-1.023, 0.856), 0.86
PRSice scores				
$p<1x10^{-5}$	0.996 (0.943, 1,053), 0.89	1.009 (0.911, 1.118), 0.86	0.953 (0.884, 1.026), 0.20	-0.700 (-1.641, 0.240), 0.14
$p<0.0005$	0.961 (0.909, 1.016), 0.158	1.068 (0.963, 1.184), 0.22	0.983 (0.912, 1.060), 0.65	-0.754 (-1.702, 0.195), 0.12
$p<0.005$	0.947 (0.894, 1.003), 0.07	1.130 (1.015, 1.258), 0.03	1.007 (0.932, 1.088), 0.86	-1.015 (-1.989, -0.042), 0.04
$p<0.05$	0.963 (0.909, 1.020), 0.20	1.110 (0.997, 1.236), 0.06	0.972 (0.899, 1.051), 0.48	-0.859 (-1.846, 0.128), 0.09
$p<0.1$	0.971 (0.914, 1.030), 0.33	1.145 (1.025, 1.278), 0.02	0.974 (0.898, 1.055), 0.52	-0.969 (-1.984, 0.047), 0.06
$p<0.5$	0.968 (0.912, 1.027), 0.28	1.122 (1.006, 1.252), 0.04	0.979 (0.904, 1.060), 0.60	-0.825 (-1.829, 0.179), 0.11
$p<1$	0.973 (0.916, 1.033), 0.36	1.121 (1.004, 1.253), 0.04	0.980 (0.903, 1.062), 0.62	-0.867 (-1.888, 0.155), 0.10

5.4.7 Previous pregnancy termination

In analysis of MoBa data using a genetic score of only genome-wide significant SNPs for schizophrenia liability, there was no clear statistical support for an increased likelihood of having had a previous termination, although estimates were in this direction (**Table 5:38**). In ALSPAC G0, there was weak evidence of an increased likelihood of having previously had a termination with increasing genetic liability for schizophrenia using genome-wide significant hits (see **Table 5:38**). In sensitivity analyses, clear associations for an increased likelihood of having had a previous termination with increasing genetic liability for schizophrenia were seen across all *p*-value thresholds for genetic liability in both studies apart from a threshold of $p<1$ in MoBa (see **Table 5:38**).

Table 5:38 *Estimates for associations between genetic scores with varying p-value thresholds and having ever had a previous termination.*

	Previously had termination	
	MoBa (N = 9444)	**ALSPAC G0 (N = 7134)**
	OR (95% CI), *p*	**OR (95% CI), *p***
Genetic score for schizophrenia liability		
Model 1		
Plink score		
$p<5\times10^{-8}$	1.023 (0.965, 1.086), 0.44	1.064 (0.996, 1.138), 0.07
PRSice scores		
$p<1x10^{-5}$	1.105 (1.041, 1.173), 0.001	1.098 (1.026, 1.176), 0.01
$p<0.0005$	1.138 (1.069, 1.212), <0.001	1.081 (1.011, 1.157), 0.02
$p<0.005$	1.137 (1.070, 1.209), <0.001	1.139 (1.065, 1.219), <0.001
$p<0.05$	1.144 (1.074, 1.218), <0.001	1.148 (1.074, 1.228), <0.001
$p<0.1$	1.146 (1.076, 1.220), <0.001	1.164 (1.088, 1.245), <0.001
$p<0.5$	1.151 (1.079, 1.228), <0.001	1.180 (1.104, 1.262), <0.001
$p<1$	1.054 (0.993, 1.119), 0.08	1.190 (1.114, 1.272), <0.001
Model 2		
Plink score		
$p<5\times10^{-8}$	1.021 (0.963, 1.083), 0.49	1.062 (0.994, 1.136), 0.08
PRSice scores		
$p<1x10^{-5}$	1.106 (1.042, 1.174), <0.001	1.096 (1.023, 1.173), 0.01
$p<0.0005$	1.136 (1.067, 1.210), <0.001	1.080 (1.009, 1.155), 0.03
$p<0.005$	1.134 (1.067, 1.205), <0.001	1.139 (1.065, 1.219), <0.001
$p<0.05$	1.141 (1.072, 1.215), <0.001	1.147 (1.072, 1.227), <0.001
$p<0.1$	1.143 (1.073, 1.217), <0.001	1.161 (1.086, 1.242), <0.001
$p<0.5$	1.147 (1.075, 1.224), <0.001	1.178 (1.102, 1.260), <0.001
$p<1$	1.054 (0.993, 1.119), 0.09	1.189 (1.112, 1.271), <0.001

Model 1 is adjusted for the top 10 principal components of population structure (and genotype array in MoBa). Model 2 is additionally adjusted for mothers' birth year.

Discussion

5.4.8 Summary of results and previous literature

I find some evidence that genetic liability for schizophrenia increases parity in MoBa using the IVW method, and further evidence of an association for increased likelihood of having had a child in ALSPAC G1 females. In UK Biobank, ALSPAC G0 and ALSPAC G1 (both sexes), results do not indicate a linear causal effect on number of children using MR techniques. In UK Biobank, results also do not indicate a genetic correlation between liability for schizophrenia and number of children using LD score regression. The majority of results are therefore inconsistent with cliff edge-fitness maintaining schizophrenia in the population, which would predict an increase in fitness with increased genetic liability in the general population. These results support previous research suggesting no strong evidence of a relationship between genetic liability for schizophrenia and number of children (Beauchamp, 2016; Mullins et al., 2017). In sensitivity analyses in UK Biobank, I found some suggestion of a possible peak in fitness at intermediate to high levels of genetic liability, but there was no statistical evidence for this, suggesting that if this non-linear association exists it is very weak, and not reliably detectable even in a large study such as UK Biobank. Hints of a non-linear relationship was seen across the datasets used here with no statistical support. A previous study also showed little evidence of quadratic associations between genetic liability for schizophrenia and number of children (Mullins et al., 2017).

For number of sexual partners, I find an effect of increasing genetic liability for schizophrenia on increasing number of sexual partners in UK Biobank, suggesting liability for the disorder increases mating success in the wider population and could reflect potential reproductive success (Nettle & Clegg, 2006). Although confidence intervals in ALSPAC G1 were consistent with the null, the IVW point estimate was also in the positive direction. Sensitivity analyses further suggest that the relationship between genetic liability for schizophrenia and number of sexual partners is linear in healthy populations although some evidence of non-linearity, particularly in females, was seen for ALSPAC G1.

Also consistent with previous research, I found no clear evidence for a linear association between genetic liability for schizophrenia and age at first birth (Mullins et al., 2017) and weak evidence of a non-linear association in UK Biobank (Ni et al., 2017). There was some evidence of a negative effect of increasing genetic liability for schizophrenia on age at first pregnancy in ALSPAC G0 using a weighted median MR approach. In sensitivity

analyses using MoBa and ALSPAC G0 data with lower *p*-value thresholds for genetic liability, there was evidence for associations between increasing liability and decreasing age at first pregnancy. The evidence was weaker for age at first birth in MoBa in this sensitivity analysis.

Sensitivity analysis results for secondary measures (in MoBa) further suggest that increased genetic liability for schizophrenia is associated with increased risky sexual behaviour indicated by the index pregnancy being more likely conceived on contraception and some evidence of a shorter length of relationship with the index pregnancy's father. Additionally, there was evidence for a positive effect of liability to the disorder and likelihood of having ever had a previous termination (in MoBa and ALSPAC G0). This may indicate potential reproductive success that is not captured by other measures and support previous suggestions of increased risky sexual behaviour, as well as help to explain stronger evidence for age at first pregnancy than age at first birth in MoBa.

5.4.9 Cliff-edge fitness

Cliff-edge fitness suggests that schizophrenia prevalence is sustained because the negative reproductive effects in those with an underlying genetic liability and the disorder are offset by a reproductive advantage to those who have an underlying genetic liability but do not develop the disorder (Mullins et al., 2017). This reproductive advantage may act via creativity or risky behaviour, with schizotypy in healthy adults predicting interest in short-term mating (Del Giudice et al., 2010) and overlapping genetic factors between schizophrenia and HIV infection, which are related to risky sexual behaviour (Wang et al., 2016). To note, I only examined part of the cliff-edge hypothesis as I use data that likely includes very few cases, and therefore I only investigate whether there is a linear effect on reproductive success with increasing genetic liability that could compensate for the negative reproductive effects in those with an underlying genetic liability and the disorder (Keller & Miller, 2006; Nesse, 2004; Nettle & Clegg, 2006; Van Dongen & Boomsma, 2013). I do not investigate these negative reproductive effects in those with the disorder. Although it is hard to estimate the size of effect on fecundity necessary to sustain the prevalence of schizophrenia (or indeed whether this effect size may fall within the confidence intervals of estimates across studies), these results overall provide little support for a cliff edge fitness effect maintaining schizophrenia prevalence with only an effect on parity found in one dataset using the IVW method. However, in the modern environment (with available contraception), there are limits to the conclusions we can make about historical evolutionary forces on schizophrenia-associated alleles from these present-day fitness associations. I do find evidence of increased mating success with

increasing genetic liability for schizophrenia in UK Biobank, and congruent estimates in ALSPAC G1. Mating success may proxy reproductive success in past environments and partly explain how the disorder has been maintained in the population. In both UK Biobank and ALSPAC G1, there was stronger evidence for a positive association between genetic liability for schizophrenia and number of sexual partners in males than females, in line with sex differences in reproductive strategies (Nettle & Clegg, 2006). As variance in reproductive success is higher in males than in females, it has been argued that males obtain higher reproductive benefits from additional mating's than females (Trivers, 1972). It has been suggested that creative displays are a form of sexual competition that reflect these evolutionary pressures (Miller, 1999; Nettle & Clegg, 2006). It is possible that the associations seen in females here are a by-product of male reproductive behaviour although there are of course also benefits to females of attracting additional mates, such as higher mate quality (Mullins et al., 2017). I assume that, on average, increasing numbers of sexual partners is a reasonable proxy for fitness however number of sexual partners has likely also undergone changes since the introduction of contraception, which has allowed for decoupling of sexual and reproductive partners. It therefore cannot be concluded that cliff-edge fitness has sustained the prevalence of schizophrenia within the population without clear effects on fecundity, for which I provide no clear evidence for a cliff edge effect on current fitness.

Two phenotypes colocalize in a genetic region when it contains variants that associate with both phenotypes, and can reflect causality (i.e., the SNP effect on one phenotype is mediated by its effect on the second phenotype), pleiotropy (the same SNP independently affects both phenotypes), or LD (two or more SNPs in LD affect different phenotypes) (Pingault et al., 2018). The sensitivity analysis lowering the *p*-value threshold for genetic liability can increase the power to detect small effects common in genetic analyses (Gage, Jones, et al., 2016). However, lowering the *p*-value threshold can also introduce horizontal pleiotropic effects, when genetic variants have an effect on the outcome through alternative pathways, instead or in addition to, through the exposure (Bowden et al., 2017; Davey Smith & Hemani, 2014). Using genome-wide significant SNPs as instruments is therefore the most suitable for causal inference whereas more lenient thresholds increase false discovery rates (Richardson et al., 2018). This has been demonstrated in recent simulations for liability for schizophrenia on multiple outcomes using the same schizophrenia GWAS as done so here (Richardson et al., 2018). Cliff-edge fitness maintaining the prevalence of schizophrenia suggests that an increased reproductive advantage is obtained through sexual selection, acting via creativity and/or risky behaviour (Nettle & Clegg, 2006; Shaner et al., 2004; Wang et al., 2016). Although

I find a trend for evidence of risky sexual behaviour, for sexual selection I argue that we should expect an effect specific to schizophrenia liability (Keller & Miller, 2006; Shaner et al., 2004) and relaxing the *p*-value threshold may therefore capture other forms of selection. A recent comment by Escott-Price and colleagues argue that a specific causal effect is not required when assessing whether schizophrenia is maintained through a reproductive advantage (Escott-Price et al., 2019b).

5.4.10 Alternative theories

This leaves two further main theories for how schizophrenia prevalence is maintained. One is that as schizophrenia is a highly heterogenous disorder and exhibits a highly polygenic architecture, with effects of genetic variants being individually too weak to be under negative selection (Loh et al., 2015; Mullins et al., 2017; Van Dongen & Boomsma, 2013). The present results are consistent with this possibility and suggest that identified schizophrenia genetic risk variants are not under strong selection in the general population. Another explanation is that mutation-selection balance maintains the prevalence of schizophrenia; rare recurrent DNA copy number variants which are also risk factors for schizophrenia are filtered out of the population by selection and replenished by de novo mutations (Rees et al., 2011). Rare copy number genetic variants conferring risk to psychiatric illness are under strong negative selection (Mullins et al., 2017; Rees et al., 2011), with most persisting in the population for only two generations (Rees et al., 2011). I used results from GWAS, which mainly detect common alleles and therefore cannot determine whether mutation-selection balance sustains the prevalence of schizophrenia through rare genetic variants, although schizophrenia-associated rare genetic variants have been shown to associate with number of children (Mullins et al., 2017; Van Dongen & Boomsma, 2013). Other explanations could include an increased likelihood of symptom diagnosis, changes in the environment (Gage et al., 2017; Weinstein et al., 2018) and/or selection bias (discussed below).

5.4.11 Strengths

The use of MR here can provide stronger evidence of causality than observational studies (Davey Smith & Ebrahim, 2003; Gage, Munafò, & Davey Smith, 2016). Firstly, I included a positive control analysis to confirm that this approach was valid. I evaluated results between various MR methods that rely on differing assumptions for agreement between methods providing greater confidence in the robustness of the results (Lawlor et al., 2016). Furthermore, I conducted multiple sensitivity analyses to capture broader genetic liability and investigate possible non-linearity in relationships. Additionally, this research offers large sample sizes which are necessary for investigating small effect sizes

common in such genetic analysis and I have conducted analysis across multiple cohort studies to compare results (Gage, Jones, et al., 2016).

5.4.12 Limitations

There are also some limitations that should be considered with the current evidence. First, MR relies on genetic variants naturally randomizing an exposure, and therefore inferring causality from genetic liability for schizophrenia as the exposure requires careful interpretation. The outcome sample was not selected on schizophrenia status, so it contained only few cases of diagnosed schizophrenia. Therefore, I assume that schizophrenia SNPs are associated with sub-diagnostic schizophrenia traits that could cause a reproductive advantage within the wider population (Crow, 2008; Del Giudice et al., 2010; Nettle & Clegg, 2006). Although debated (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; Zammit et al., 2013), schizophrenia symptoms have been suggested to exist on a continuum, and this assumption could therefore be met (Kendler et al., 1993; Poulton et al., 2000; Taylor et al., 2016; Van Os et al., 2009). Within this, I assume that the instrumental variable assumptions are satisfied for this continuous liability to provide a valid test of causality using the binary exposure (Burgess & Labrecque, 2018). Second, as genetic variants are non-specific, it is difficult to fully remove population structure which can induce spurious associations through confounding, even within a sample of European ancestry and adjusting for principal components of population structure as I have done (Curtis, 2018; Haworth et al., 2019). Third, the exposure and outcome samples were each quality controlled for relatedness however it is not possible to determine whether participants had relatives across the samples due to using summary level GWAS data for our exposures.

Fourth, age at first birth was only measured in females in all studies, and therefore consists of a different population to the exposure data (which includes data from both females and males). However, the correlation between male and female estimates for age at first birth in a recent GWAS was high (Barban et al., 2016). Similarly, the schizophrenia-associated genetic variants used in the sex stratified analyses were identified from a mixed sex population although in UK Biobank I used an unweighted genetic score which would also help to minimize any bias. Lastly, the present study uses data from the mothers of two pregnancy cohorts, therefore including only females that have also been pregnant which may affect the generalizability of findings to the wider population.

5.4.13 Selection bias and UK Biobank

As discussed in Chapter 3, genetic data for UK Biobank was released in two waves (May 2015 and July 2017). The first wave comprised ~150,000 participants in total, and was selected based on smoking behaviour (Wain et al., 2015). As previously demonstrated (Day, Loh, Scott, Ong, & Perry, 2016; Gkatzionis & Burgess, 2018; Hughes, Davies, Davey Smith, & Tilling, 2018; Munafò et al., 2018), this can yield biased estimates in analyses through collider bias. Collider bias occurs when a variable (termed the collider) is caused by each the exposure and the outcome and therefore controlling for the variable induces a spurious association between the exposure and outcome. Escott-Price and colleagues (2019) report an association between genetic liability for schizophrenia and number of children in UK Biobank. They interpret this as consistent with sexual selection. They used the most recent GWAS for schizophrenia, but the reported sample size suggests that only data from the first release was used. Further previous research also found evidence of an association between genetic liability for schizophrenia and age at first birth using the first release of data (Ni et al., 2017).

Initially, when using the first release of UK Biobank, I found results similar to those reported by Escott-Price and colleagues – a weak positive relationship between genetic liability for schizophrenia and number of children. However, given concerns about conditioning on this sub-sample (with well-established associations between smoking and both schizophrenia risk and fertility) (Wootton, Richmond, et al., 2018), I repeated the analyses in the full release. Strikingly, these results were quite different, with no clear evidence of a relationship between genetic liability for schizophrenia and number of children. The results for the two waves of UK Biobank data, and the full release as presented in the main results section, are shown in **Table 5:39**. Similarly, I did not support previous evidence for a relationship between genetic liability for schizophrenia and age at first birth in the full release (shown in the main results section **Table 5:27**). I also previously used GWAS summary data for number of children to conduct this analysis (methods and results are in **Appendix 51**, and tables are presented in **Appendix 52**). This data contained a substantial proportion of the first wave of UK Biobank data as well as some overlap between data in the schizophrenia and number of children GWAS, which biases the result towards the observational association (Burgess, Scott, Timpson, Davey Smith, & Thompson, 2015). Overall, it appeared that these results therefore supported balancing selection sustaining the prevalence of schizophrenia, likely due to bias (Courtiol et al., 2016; Huxley et al., 1964).

Table 5:39 *Estimates of the causal effect of genetic liability for schizophrenia on number of children using an IVW MR approach.*

	Number of Children	
	N	**β (95% CI), *p***
Genetic liability for schizophrenia[a]		
First release	90 058 to 94 792	0.012 (0.00003, 0.023), 0.05
Second release	228 863 to 240 966	-0.001 (-0.008, 0.006), 0.81
Full UK Biobank data (as above)	318 921 to 335 758	0.003 (-0.003, 0.009), 0.39

[a] *Schizophrenia genetic data from the PGC GWAS (N = 35 123 cases and 109 657 controls; 101 SNP instrument).*

It is possible that discrepancy between results are due to differences in the methodology, MR or a PRS analysis with varying *p*-value thresholds for genetic liability (discussed above), or an artefact of conditioning on the first, selective, release of UK Biobank data. A recent response by Escott-Price and colleagues suggests that their results differ due to using a lower *p*-value threshold (Escott-Price et al., 2019a, 2019b). It is still possible that the differences in **Table 5:39** are due to conditioning on the first, selective, release of UK Biobank data. On the other hand, UK Biobank data as a whole is unrepresentative of the population, given a response rate of approximately 5%, which may introduce selection bias in itself (Allen et al., 2014; Fry et al., 2017). This can generate spurious results in genotypic associations when selection is based on phenotypes associated with the genetic variants and could attenuate associations towards the null in the full release if schizophrenia-proneness and increased number of children reduced participation (Conde et al., 2017; Munafò et al., 2018; Taylor et al., 2018). Previous studies have found that higher genetic liability for schizophrenia is associated with lower participation in cohort studies which could bias estimates between genetic liability and traits that lead to nonparticipation in genetic associations and MR (Martin et al., 2016; Taylor et al., 2018). Therefore, it is possible that results in the first wave that is enriched for smokers are more representative of the general population.

It is therefore important that I conducted this study across multiple datasets. Although a smaller sample, MoBa had a response rate of 41% and this study used the first distributed questionnaire where 95% of mothers provided responses (Magnus et al., 2006). Moreover, all MBRN records for the participants of MoBa are available, regardless of the number of questionnaire data that was completed. This high response rate and mandatory health registries therefore mean that you can somewhat avoid the loss to follow up selection bias for some analyses (Magnus et al., 2016). ALSPAC also had a high response

rate (Fraser et al., 2013), although there was attrition for the measures used in the present study, particularly for parity measured 18 years post-recruitment for ALSPAC G0. Age at first pregnancy was derived from data collected at recruitment and 18 weeks gestation, leading to a much larger sample size, and one possibility for why I found more associations for age at first pregnancy than parity measures in ALSPAC G0. Data for ALSPAC G1 was asked at the last assessment (approximately 23 years) and therefore suffered attrition. Nevertheless, some argue that valid assessment of exposure-outcome relationships may be widely generalizable even if data is not representative of the population at large and these results are strengthened by assessing multiple datasets (Fry et al., 2017).

5.4.14 Conclusions

Whether genetic risk for psychiatric disorders is associated with a reproductive advantage is an important question, as it may explain the persistence of these disorders despite deleterious effects. The present study highlights the continued importance of investigating differential fertility and contributes to understanding the maintenance of schizophrenia, and educational attainment, in the population (Essen-Möller, 1959; Lewontin, 2016; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014; Tropf, Stulp, et al., 2015). It is important to consider that, in the modern environment, we can make limited conclusions about historical evolutionary forces on these schizophrenia-associated alleles from these present-day fitness associations. This is further highlighted by the present findings for increased liability to each disorder and increased likelihood of having had a termination. Educational attainment has previously been shown to predict human longevity (Marioni et al., 2016) and this work highlights how even traits with a positive effect on longevity can be maladaptive, although other influences on educational attainment in the population are also acknowledged (Sanjak et al., 2017). This work additionally demonstrates how epidemiological methods can be repurposed to study evolutionary theories. Future research should investigate causal methods for estimating non-linear relationships as well as other explanations for this evolutionary paradox, such as mutation-selection balance.

5.5 Chapter summary

In this chapter, I aimed to apply a range of methods with roots in genetic epidemiology (MR, LD score regression and PRS analysis) to investigate the schizophrenia paradox. I assessed the correlation and causal effect of genetic liability for schizophrenia with a range of reproductive outcomes, such as number of children, in multiple population-based samples which are not selected on schizophrenia status and therefore include very few

cases. MR indicated no robust evidence of a causal effect of genetic liability for schizophrenia on number of children across all but one cohort study. I find some evidence of a positive effect of genetic liability for schizophrenia on other measures of potential reproductive success such as number of sexual partners. These results suggest that, overall, increased genetic liability for schizophrenia does not confer a fitness advantage but does increase mating success and risky sexual behaviour. Results therefore suggest that schizophrenia may be being sustained in the population through other explanations than cliff-edge effects on fitness.

Chapter 6 Discussion

This thesis explored the application of MR and other related methods to two areas of evolutionary human behaviour research – life history theory and the schizophrenia paradox. Previous research has been limited as standard methods in evolutionary approaches to behaviour cannot easily test causality and examine both psychological mechanisms and reproductive success (which are required for a direct test of evolutionary hypotheses). I have demonstrated how epidemiological methods can be repurposed to study evolutionary theories and provide a new form of evidence. Specifically, MR combines genetic and phenotypic information to investigate psychological and key evolutionary traits with fitness outcomes using a causal framework that does not rely on manipulating the exposure. Genetic information has largely been ignored in tests of evolutionary hypotheses, through the phenotypic gambit and/or the assumption that fitness associated traits will not show heritable variation (Hadfield et al., 2007; Mills & Tropf, 2015; Nettle, 2006; Rubin, 2016). This thesis is novel in its application of epidemiological methods that support strong causal inference to test these hypotheses, and highlights the potential that incorporating genetic information and such methods has for evolutionary epidemiology (Pelletier et al., 2017). I believe that an integrative research approach from the fields of genetics and social sciences is important for predicting reproductive and other evolutionarily relevant outcomes.

As each results chapter included a discussion, here I summarise the main findings from this thesis before more broadly evaluating the potential for MR to test evolutionary hypotheses. Following this, I discuss the future for evolutionary epidemiology.

6.1.1 Summary of findings and implications

6.1.1.1 Life history theory

I applied MR to test for causal effects within a life history theory framework in Chapter 4. There are currently no appropriate instruments for early life adversity that can be used within an MR framework and hence it is not possible to investigate early life stress using MR. I therefore examined the effects of two intermediate reproductive traits (age at menarche and age at first sexual intercourse) on later reproductive and behavioural outcomes. Taking this life course approach to the causal pathways in life history theory by assuming that earlier menarche is a proxy for adversity has limitations. Namely, early menarche is associated with both markers that are associated with good phenotypic condition in many species (e.g., weight, size) and early life adversity with different developmental pathways, making interpreting the results more difficult.

Results showed that earlier age at menarche is causally related to some traits that characterize a fast life history strategy, such as earlier age at first birth, earlier age at last birth, lower educational attainment, and earlier age at leaving education. The effects of earlier age at menarche on these reproductive and educational traits can be viewed as directing effort towards short-term reproductive goals and risky behaviour as an important part of a fast life history strategy (Ellis & Bjorklund, 2012). There was no clear effect of age at menarche on number of children or alcohol intake. For age at first sexual intercourse, results were mixed and suggested violation of the exclusion restriction assumption of no direct effects of the instrument on the outcome not acting through the exposure (i.e., the presence of horizontal pleiotropy) (Bowden et al., 2017; Davey Smith & Ebrahim, 2003). Results for age at first sexual intercourse must therefore be treated with caution and causal inference is weakened.

This study highlights how analyses techniques from genetic epidemiology can be used to answer how life history traits are related within life history strategies, and to better understand determinants of health and social behaviour. Life history theory has implications for how we view apparently negative and assumingly maladaptive behaviour, such as decreased educational attainment. For example, the present finding of a causal effect of earlier age at menarche on decreased educational attainment suggests that decreased educational attainment may be considered a consequence of a suite of adaptive behaviours as part of a fast life history strategy. This finding therefore provides important information for determinants of educational attainment today, which is a key predictor of positive later life outcomes in the UK (Gill et al., 2017). The implications of a causal effect of earlier age at menarche on decreased educational attainment is particularly important due to secular trends of age at menarche decreasing in recent years (Ellis, 2004).

There have also been recent shifts in the timing of first birth in females to later ages with advanced age at first birth associated with health consequences for mother and offspring (Barban et al., 2016; Fall et al., 2015; Mills, Rindfuss, McDonald, & te Velde, 2011). The present finding of an effect of later age at menarche on later age at first birth and later age at last birth is therefore important for improving understanding of the causes in this reproductive delay in recent years (Mills et al., 2011; Pelletier et al., 2017).

6.1.1.2 The schizophrenia paradox

In Chapter 5, I applied a range of methods rooted in genetic epidemiology (MR, LD score regression and PRS analysis) to investigate the schizophrenia paradox. In assessing the

correlation and causal effect of genetic liability for schizophrenia on a range of reproductive outcomes in multiple population-based samples, I found no clear robust association or effect of genetic liability for schizophrenia on number of children. There was evidence of a positive causal effect of genetic liability for schizophrenia on other measures of potential reproductive success such as number of sexual partners. These results suggest that, overall, increased genetic liability for schizophrenia does not have a clear effect on fitness but does increase mating success and risky sexual behaviour. As discussed in Chapter 5, it is difficult to quantify the size of effect on fitness necessary to sustain the prevalence of schizophrenia and it is also possible that mating success may proxy reproductive success in past environments (pre-contraception) and partly explain how the disorder has been maintained in the population. However, number of sexual partners has likely also undergone changes since the introduction of contraception as sexual partners do not have to equate to reproductive partners. It is therefore difficult to conclude that cliff-edge fitness has sustained the prevalence of schizophrenia within the population without clear effects on fitness. Therefore, these findings suggest that it is possible that schizophrenia is sustained in the population through other explanations than cliff-edge effects on fitness (e.g., mutation-selection balance), which future research should focus on.

This research highlights the continued importance of investigating differential fertility. As schizophrenia is such a debilitating disorder, it is important to investigate how the prevalence is sustained (Essen-Möller, 1959; Lewontin, 2016; Polanczyk et al., 2014; Tropf, Barban, Mills, Snieder, & Mandemakers, 2015). The present results for educational attainment showing a negative effect on number of children (Chapter 5) also re-frame perceptions of maladaptive behaviour. Educational attainment has previously been shown to predict human longevity and is considered a predictor of positive later life outcomes in the UK (Gill et al., 2017; Marioni et al., 2016). This work therefore shows how even desirable traits with a positive effect on longevity can be maladaptive by having a negative effect on fitness (Sanjak et al., 2017).

6.2 Mendelian randomization to test evolutionary hypotheses

As discussed, I have attempted research within a novel field of evolutionary epidemiology for these hypotheses within life history theory (that earlier age at menarche and age at first sexual intercourse can be viewed as directing effort towards reproductive goals as part of a fast life history strategy and therefore show causal effects on reproductive and behavioural outcomes) and the schizophrenia paradox (schizophrenia, a

heritable disorder, is maintained in the population despite being associated with lower reproductive success for those diagnosed). Broadly, there are strengths and weaknesses to doing so. As MR was developed to test modifiable risk factors for disease outcomes, issues can arise when applying the method to social and psychological traits to test evolutionary questions. Here I will summarise the strengths of the method before discussing potential limitations of MR for testing evolutionary theories of human behaviour.

6.2.1 Strengths

MR allows investigation of psychological, behavioural and other trait and fitness outcomes. It therefore integrates both ultimate and proximate explanations and potentially provides a direct test of evolutionary hypotheses. Through using observational data, the method allows investigation of traits that cannot be manipulated, for ethical and other reasons, such as reproductive timing or measures of early life adversity. Even so, by using genetic variants that are fixed and randomized at conception, the ability to make causal inference is stronger than when applying standard analytical methods to observational data. Using genetic variants also allows investigation of genetic liability for a psychological trait in the wider population rather than only within families, in relation to fitness outcomes (as done so in Chapter 5). Furthermore, the availability of GWAS for evolutionary relevant traits is increasing, meaning that this method can be applied to test further hypotheses and possible mediating pathways. Online platforms such as MR-Base have also recently been introduced that make it easier to conduct these analyses (www.mrbase.org) (Hemani, Zheng, et al., 2018).

6.2.2 Weaknesses

As with most methods, it is first worth noting the strong assumptions underlying MR (discussed in detail in Chapter 2). If these assumptions do not hold, then confounding can be present and causal inference is weakened. MR is therefore plagued by the same biases as standard analytical approaches applied to observational data when assumptions break down. It is more difficult to meet the assumptions of MR with complex traits as complex traits are typically highly polygenic, and it is therefore possible that some of the genetic variants are pleiotropic (Pingault et al., 2018). Additionally, the biological pathways are not always known for complex social traits meaning it is more difficult to assess if assumptions are met (Conley, 2009). However, complex social traits such as educational attainment (which may proxy social status) are what evolutionary researchers are interested in investigating within an MR framework, particularly because they are not easy to intervene on for experimental designs. It is therefore important to have a well-

defined model and subsequent predictions, with knowledge of the genetic function and developmental pathways (Pingault et al., 2018). For the schizophrenia studies here, the biological function of the genetic variants has been thoroughly investigated and the model is well-defined (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). However, for age at first sexual intercourse the biological basis is less well known. Additionally, as discussed above, the age at menarche model is more difficult to interpret as early menarche is associated with both good condition and early life adversity. Overall, MR is therefore only as good as the likelihood of satisfying the assumptions, the instruments available and whether these instruments lead to strong models and predictions. Within this thesis, the work on schizophrenia meets the requirements and interpretations more easily.

Second, it is common that genetic instruments explain only a small proportion of variance in the exposure (Gage, Davey Smith, et al., 2016). This is particularly common for psychological traits such as schizophrenia used here, where only 3.4% of the variance was explained by genome-wide significant SNPs (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Without very large sample sizes as used in this thesis, which can be hard to obtain, this leads to low powered studies and makes it hard to assess whether a null result might reflect low power (Davey Smith & Ebrahim, 2004; Gage, Davey Smith, et al., 2016).

Third, genetic variants are randomized conditional on parental genotype. Therefore, assortative mating can violate the MR method (Hartwig, Davies, & Davey Smith, 2018). Assortative mating occurs when partners are chosen based on particular characteristics rather than at random (Lawlor et al., 2019). Assortative mating can be on the same trait (termed single trait) or when individuals with higher value for one trait mate with individuals that are higher (or lower) on another trait (termed cross-trait assortative mating) (Lawlor et al., 2019). Assortative mating on traits used within MR can lead to a spurious genetic correlation and subsequent bias (Lawlor et al., 2019). Hartwig and colleagues (2018) conducted simulations to estimate the bias in MR studies due to assortative mating. They found that assortative mating lead to bias that accumulated over generations, even for methods robust to horizontal pleiotropy (Hartwig et al., 2018). However, these simulations also showed that data from mother–father–offspring trios could be used to correct for this bias (Hartwig et al., 2018). It is likely that assortative mating is more of a problem for social traits that are evolutionarily relevant than for certain health traits which MR was originally developed for (e.g., C-reactive protein) and the application of MR to evolutionary hypotheses without trio data is therefore restricted

(Hartwig et al., 2018). For this thesis, considerable partner resemblances have been found for psychiatric disorders however no clear patterns of assortative mating has been seen for schizophrenia and any assortative mating is unlikely to balance the impact of reduced fecundity of patients with psychiatric disorders in the long term (Goddard et al., 2018; Peyrot, Robinson, Penninx, & Wray, 2016). Educational attainment does show evidence of assortative mating although it appears to be stable over generations (Conley et al., 2016; Goddard et al., 2018). For other evolutionary relevant traits, it is important to consider the potential for assortative mating and to use data from trios to account for this, although datasets with genetic data on trios are limited.

Fourth, population structure is a similar, although distinct issue in MR which can also lead to spurious associations and bias (discussed in Chapter 2) (Goddard et al., 2018). For testing evolutionary hypotheses, population structure becomes an issue when investigating traits that are associated with migration and selection into a dataset (Haworth et al., 2019). Selection on traits is more likely to occur for social traits than biological traits. In ALSPAC, for example, Haworth and colleagues (2019) found higher educational attainment in more geographically distant lineages to the study catchment area. They suggest that educational attainment of people who migrate for economic reasons likely differs from people who do not and this creates effects of ancestry even in a geographically and ethnically homogeneous sample (Haworth et al., 2019). In UK Biobank, genetic variants are associated with birth location and, given regional differences in traits, this can again cause covariance between genotypes and traits that can bias analyses (Haworth et al., 2019). The increasing sample sizes in GWAS increases the power to detect genetic instruments for MR studies however it also increases susceptibility to bias due to subtle population structure (Lawson et al., 2019). Adjusting for principal components may not be adequate for fully removing population structure (see Chapter 2) (Lawson et al., 2019). Studies typically also restrict to individuals of European ancestry to further address this, which can limit the study of evolutionary theories to human behaviour by restricting cross-cultural studies (Davey Smith & Hemani, 2014). The issue of population structure is highly topical and methods are being developed to overcome the biases, such as trans-ethnic modelling and chromosome painting which provide greater understanding of the traits-population structure relationship (Lawson et al., 2019).

Fifth, many GWAS are conducted in mixed sex samples to increase sample sizes. In MR, the SNP-exposure and SNP-outcome associations should be derived in similar underlying populations (see Chapter 2). Therefore, if the SNP-exposure relationships are taken from

a mixed sex GWAS this can limit the ability for sex stratified analysis. For many traits, the genetic correlation between sexes is likely high and therefore the instrument and SNP-exposure associations can be used for sex stratified analysis without much concern. However, investigating sex differences is a key aspect of many evolutionary hypotheses and that GWAS, and subsequently MR, are not always easily set up to do so is a limitation.

Sixth, MR relies on an instrumental variable framework which was developed to estimate the effect of an exposure at a point in time (Labrecque & Swanson, 2019). As MR utilises genetic variants that are fixed at conception it is said to estimate the 'lifetime effect', defined as the average change in outcome at time *t* when the entire exposure trajectory from conception to time *t* is shifted by 1 unit (Labrecque & Swanson, 2019). However, MR only estimates this 'lifetime effect' when the effect of the genetic variants on the exposure does not change over time such as when the trait is fixed over the life course (e.g., eye colour) (Labrecque & Swanson, 2019; Lawlor, 2016). Otherwise the denominator in the Wald ratio to derive a causal estimate varies depending on the timepoint measured and there is the potential for pleiotropy to occur via the exposure trait at another timepoint (Labrecque & Swanson, 2019). This becomes more complicated as GWAS studies often conduct meta-analysis over multiple samples with varying ages. This has implications for using MR to test evolutionary theories of human behaviour where exposure traits are unlikely to be fixed over the life course. Although this is said to affect the validity of findings, methods to overcome this issue are still under development and MR can still be used to provide a valid test of the null hypothesis with time-varying exposures.

Lastly, MR methods are typically designed to test linear relationships, as done so throughout this thesis, with continuous exposures. As discussed in Chapter 5, when using a binary exposure (e.g., schizophrenia status), the instrumental variable assumptions need to be satisfied for an underlying continuous liability (Burgess & Labrecque, 2018). As many psychological traits are binary measures in GWAS (e.g., diagnosis of a psychiatric disorder), then these additional assumptions will often have to be considered when testing evolutionary hypotheses that integrate psychological exposures with fitness outcomes.

6.3 The future of evolutionary epidemiology

Methods from genetic epidemiology, particularly MR, have great potential for testing evolutionary theories of human behaviour, health, and disease. Many evolutionary

relevant traits show heritable genetic variation and genetic variants can therefore be used to mimic these traits in analyses (Conley, 2009; Gage, Davey Smith, et al., 2016; Nettle, 2006). Here, I have successfully applied MR and related methods to test hypotheses within life history theory and the schizophrenia paradox. Recently, the number of evolutionary relevant traits that GWAS studies are being conducted on has increased exponentially (Gage, Davey Smith, et al., 2016). As examples, GWAS have now been conducted on risk-taking and personality measures which could be used to test evolutionary hypotheses of human behaviour (Karlsson Linnér et al., 2019; Nagel et al., 2018). The rapid increase in GWAS studies is in part due to the decreasing cost of genotyping and, subsequently, the availability of large datasets (Conley, 2009). However, GWAS on social traits must be well thought out for the results to be carried into MR analyses, such as knowledge of the possible biological pathways to the trait of interest (Conley, 2009). Moreover, phenotyping of social traits is often less precise as the traits are more difficult to measure and this measurement error can lead to noise in GWAS analyses (Karlsson Linnér et al., 2019; Tropf et al., 2017).

As discussed, MR was developed for health traits and there are additional considerations to be made when applying the method to social and evolutionarily relevant traits. However, new methods are under development to assess the potential bias of doing so (Brumpton et al., 2019; Hartwig et al., 2018; Labrecque & Swanson, 2019). Unfortunately, many of these methods require genetic data on mother-father-offspring trios which is less easily available (Hartwig et al., 2018). For example, family data is required to overcome bias from assortative mating or dynastic effects (when parental genotypes directly affect offspring phenotypes) (Brumpton et al., 2019; Hartwig et al., 2018; Kong et al., 2018; Pingault et al., 2018). For most cohorts with this trio data, such as MoBa, the offspring are still too young to investigate reproductive outcomes such as complete fitness and therefore many evolutionary hypotheses are not yet possible to test. However, when this data does become available, the wealth of prospective measures on these individuals during key developmental stages will be very valuable. As discussed in Chapter 5, it will still be important to think carefully about the representativeness and possible selection bias of the data, as well as the assumptions discussed above for MR analyses. In general, genetic research is in a period of rapid change with increasing data availability and methodological developments. Although this can make it challenging to keep up to date with these advances, it also means that it is an exciting time for a potential new field such as evolutionary epidemiology.

With the advances of many genetic epidemiological methods, it is crucial to again highlight that a single method for causal inference in observational settings will not provide a definitive causal effect (Pingault et al., 2018). Instead, genetic epidemiological methods, such as MR, can improve the strength of evidence on a continuum from association to causal effect and triangulation across multiple methods can increase confidence in these results (Lawlor et al., 2016; Pingault et al., 2018). For example, Davies et al. (2018) employed an MR framework for educational attainment alongside regression discordant analysis with a non-genetic instrument of policy change in age at leaving school to triangulate across results, tying together policy and genetics.

6.3.1 Conclusion

Causal inference using genetically informed designs has undergone rapid and exciting developments in recent years with potential for evolutionary approaches to human behaviour to reap these benefits (Pingault et al., 2018). The findings from this thesis suggest that MR can be applied to directly test evolutionary hypotheses of human behaviour by combining proximate and ultimate level explanations in a causal framework without the need to manipulate an exposure experimentally. There is some indication that earlier age at menarche is causally related to traits that characterize a fast life history strategy, such as earlier age at first birth, earlier age at last birth, lower educational attainment, and earlier age at leaving education. Additionally, it appears that increased genetic liability for schizophrenia does not confer a fitness advantage and therefore the disorder is likely sustained in the population through other explanations than cliff-edge effects. However, with additional considerations that need to be made when applying MR to evolutionary relevant social traits and the current lack of large samples with trio data on relevant measures to overcome some biases, the field of evolutionary epidemiology remains in infancy. Nevertheless, there is great potential for the application of MR within evolutionary research and it is an exciting time to be in such a fast-moving field.

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Appendices

Appendix 1 *List of SNPs ($p<5\times10^{-8}$) used in the 116 SNP analysis and their associations with age at menarche.*

	Age at menarche	
SNP	**β**	**SE**
rs10144321	0.04	0.006
rs1038903	0.04	0.006
rs10423674	0.04	0.005
rs10453225	0.09	0.005
rs10739221	0.08	0.006
rs10789181	0.03	0.005
rs1079866	0.07	0.007
rs10816359	0.04	0.008
rs10895140	0.04	0.005
rs10938397	0.04	0.005
rs10980854	0.06	0.011
rs10980921	0.09	0.009
rs11022756	0.05	0.006
rs11165924	0.03	0.006
rs11215400	0.04	0.006
rs1129700	0.03	0.005
rs11578152	0.03	0.005
rs11715566	0.05	0.005
rs11767400	0.04	0.006
rs11792861	0.04	0.005
rs12148769	0.05	0.008
rs12446632	0.04	0.007
rs12472911	0.04	0.006
rs1254337	0.04	0.005
rs12571664	0.04	0.006
rs12607903	0.04	0.005
rs12915845	0.03	0.005
rs13053505	0.04	0.007
rs13067731	0.04	0.007
rs13179411	0.06	0.007
rs13196561	0.04	0.006
rs1324913	0.03	0.005
rs1364063	0.05	0.005
rs1400974	0.05	0.005
rs1461503	0.05	0.005
rs1469039	0.05	0.007
rs1532331	0.03	0.005
rs16860328	0.04	0.005
rs16896742	0.04	0.005
rs16918254	0.05	0.009
rs16918636	0.03	0.006

rs17086188	0.07	0.013
rs17171818	0.04	0.006
rs17233066	0.09	0.014
rs17236969	0.05	0.008
rs17266097	0.04	0.005
rs1915146	0.03	0.005
rs1958560	0.03	0.005
rs2063730	0.05	0.007
rs2137289	0.05	0.005
rs2153127	0.08	0.005
rs2274465	0.03	0.005
rs239198	0.03	0.005
rs244293	0.03	0.005
rs246185	0.04	0.006
rs2479724	0.03	0.005
rs251130	0.04	0.006
rs2600959	0.04	0.005
rs268067	0.04	0.006
rs2687729	0.04	0.006
rs2688325	0.03	0.006
rs2947411	0.06	0.007
rs3101336	0.04	0.005
rs3733631	0.05	0.007
rs3743266	0.04	0.005
rs4369815	0.06	0.01
rs466639	0.08	0.007
rs4840086	0.04	0.005
rs4895808	0.03	0.005
rs543874	0.05	0.006
rs6009583	0.03	0.006
rs6427782	0.03	0.005
rs652260	0.03	0.005
rs6555855	0.04	0.006
rs6563739	0.03	0.005
rs6747380	0.07	0.007
rs6758290	0.04	0.005
rs6762477	0.04	0.006
rs6770162	0.04	0.005
rs6933660	0.03	0.005
rs6938574	0.04	0.007
rs6964833	0.04	0.006
rs7037266	0.03	0.005
rs7103411	0.04	0.006
rs7104764	0.03	0.006
rs7138803	0.04	0.005
rs7141210	0.03	0.005
rs7215990	0.04	0.006
rs7463166	0.03	0.005

rs7514705	0.04	0.005
rs7642134	0.04	0.005
rs7647973	0.05	0.006
rs7701886	0.03	0.005
rs7759938	0.12	0.005
rs7821178	0.04	0.005
rs7828501	0.04	0.005
rs7853970	0.03	0.005
rs7865468	0.03	0.005
rs7955374	0.04	0.008
rs8032675	0.04	0.005
rs8050136	0.04	0.005
rs852069	0.04	0.005
rs889122	0.04	0.006
rs900400	0.03	0.005
rs913588	0.03	0.005
rs929843	0.04	0.006
rs9321659	0.06	0.008
rs939317	0.04	0.006
rs9447700	0.03	0.005
rs9475752	0.04	0.006
rs951366	0.03	0.005
rs9560113	0.05	0.006
rs9635759	0.05	0.005
rs9647570	0.05	0.007
rs9849248	0.04	0.007
rs988913	0.04	0.005

Appendix 2 *List of SNPs ($p<5\times10^{-8}$) used in the 305 SNP analysis and their associations with age at menarche.*

	Age at menarche	
SNP	**β**	**SE**
rs10136330	-0.06	0.010
rs10138913	0.06	0.004
rs10143972	-0.04	0.005
rs10145469	-0.06	0.009
rs10156597	0.10	0.004
rs10175423	-0.02	0.004
rs10205969	-0.04	0.005
rs10237306	0.03	0.004
rs1023955	-0.03	0.004
rs10268051	0.02	0.005
rs1030015	-0.02	0.004
rs1032682	0.02	0.004
rs10400136	-0.03	0.004
rs10422323	0.04	0.006
rs10521021	-0.02	0.004
rs1054442	0.04	0.004
rs10750766	-0.03	0.004
rs10782777	-0.03	0.004
rs1079866	-0.07	0.006
rs10832021	-0.05	0.004
rs10885077	0.02	0.004
rs10906395	-0.02	0.004
rs10931831	-0.05	0.004
rs10933	-0.02	0.004
rs10934420	-0.05	0.004
rs10959016	-0.03	0.005
rs10959552	-0.04	0.006
rs10978641	-0.03	0.005
rs10992769	0.03	0.004
rs11031040	-0.04	0.005
rs11065822	0.03	0.004
rs11079810	0.04	0.006
rs11165924	0.03	0.004
rs11209331	0.02	0.004
rs11209943	0.04	0.004
rs11210871	0.04	0.004
rs11240695	-0.03	0.004
rs112991346	-0.04	0.006
rs113388806	-0.06	0.010
rs1148006	-0.03	0.004
rs115260227	-0.16	0.024
rs11534296	-0.04	0.004
rs115435316	0.11	0.011
rs11556924	0.02	0.004

rs11606190	0.04	0.006
rs11619721	-0.04	0.007
rs11668587	-0.03	0.004
rs11711674	0.02	0.004
rs117143374	-0.05	0.006
rs1172955	-0.04	0.004
rs117530880	-0.07	0.012
rs11756746	0.02	0.005
rs11767400	0.03	0.004
rs11786868	0.03	0.005
rs11792861	0.03	0.004
rs11852771	0.02	0.004
rs11873906	-0.05	0.004
rs12040029	-0.04	0.006
rs12125335	-0.05	0.006
rs12200565	0.03	0.004
rs12460047	-0.03	0.004
rs12467441	-0.04	0.006
rs12571664	0.04	0.005
rs12603280	-0.04	0.005
rs12663002	0.04	0.006
rs12894936	-0.05	0.004
rs12915845	-0.04	0.004
rs12937034	-0.03	0.004
rs13023912	-0.05	0.004
rs13043968	-0.04	0.006
rs13120031	0.03	0.004
rs13199764	0.04	0.005
rs13233916	-0.05	0.008
rs13278754	-0.03	0.004
rs13283567	-0.04	0.006
rs1329767	-0.03	0.004
rs13322435	0.04	0.004
rs1414186	-0.04	0.005
rs141847393	0.04	0.007
rs142058842	-0.07	0.005
rs142643995	0.06	0.012
rs1428120	0.03	0.004
rs1435753	-0.03	0.004
rs1449543	0.02	0.004
rs145438026	-0.07	0.008
rs1456031	0.02	0.004
rs150821390	0.07	0.012
rs1512238	-0.05	0.004
rs151680	0.03	0.004
rs1535252	-0.03	0.004
rs153793	-0.02	0.004
rs1539310	0.02	0.005

rs1566385	0.06	0.008
rs15671	-0.02	0.004
rs1571536	0.03	0.004
rs157877	-0.08	0.006
rs1601615	-0.03	0.004
rs16841867	0.05	0.006
rs169080	-0.03	0.004
rs16917237	0.04	0.005
rs16918378	0.05	0.006
rs16937956	-0.04	0.004
rs17035311	0.04	0.005
rs1704528	-0.05	0.004
rs17171852	-0.04	0.005
rs17390720	0.03	0.004
rs17563472	-0.06	0.011
rs17564430	-0.04	0.004
rs1815811	-0.03	0.004
rs184033703	-0.05	0.009
rs1885740	-0.03	0.005
rs1925047	-0.03	0.004
rs1971554	0.03	0.004
rs1984870	0.04	0.004
rs2066323	-0.02	0.004
rs2108753	0.03	0.004
rs222440	-0.03	0.005
rs2267812	0.04	0.005
rs2271758	-0.02	0.004
rs2295094	0.04	0.005
rs2300922	0.04	0.004
rs2312205	0.03	0.005
rs2343507	0.02	0.004
rs2378100	-0.02	0.004
rs2461794	0.03	0.004
rs247520	0.04	0.005
rs2546959	0.03	0.005
rs2558101	-0.02	0.004
rs256350	-0.02	0.004
rs2604265	0.04	0.004
rs2659007	-0.03	0.004
rs2661339	0.05	0.009
rs2679894	0.05	0.004
rs2688326	-0.04	0.004
rs2723065	-0.02	0.004
rs2724961	-0.05	0.004
rs2770957	0.03	0.005
rs2780243	-0.02	0.004
rs28757192	-0.06	0.011
rs2889128	0.02	0.004

rs29941	0.03	0.004
rs3021057	0.02	0.004
rs3113862	-0.04	0.004
rs34437050	0.24	0.020
rs34513772	0.02	0.004
rs35436838	-0.07	0.011
rs35485457	-0.04	0.004
rs35935052	0.04	0.005
rs360495	0.04	0.007
rs36093651	0.04	0.005
rs3733632	-0.05	0.005
rs3743266	0.04	0.004
rs3746037	0.04	0.005
rs3746619	0.05	0.007
rs3764002	-0.03	0.005
rs3782120	0.03	0.004
rs3809624	-0.03	0.004
rs3815212	0.03	0.005
rs395962	0.13	0.004
rs4303811	-0.04	0.006
rs4327718	-0.03	0.005
rs4340786	0.04	0.004
rs4359170	0.03	0.004
rs437836	0.04	0.005
rs443252	0.06	0.009
rs4448948	-0.04	0.008
rs446745	-0.03	0.005
rs4487799	0.02	0.004
rs4561063	0.03	0.004
rs4588499	-0.02	0.004
rs467379	0.02	0.004
rs4701140	0.02	0.004
rs474463	-0.03	0.005
rs4746113	-0.02	0.004
rs4751614	0.03	0.005
rs4778356	0.04	0.006
rs4801809	-0.04	0.007
rs4804025	-0.04	0.004
rs4813429	0.03	0.005
rs4836984	0.03	0.004
rs484353	0.03	0.004
rs4845364	0.02	0.004
rs4859001	0.04	0.006
rs4875424	-0.03	0.004
rs4877387	0.02	0.004
rs4886140	0.03	0.004
rs4945266	-0.04	0.005
rs4951261	0.03	0.004

rs4970598	0.06	0.011
rs4976623	0.03	0.005
rs506589	0.07	0.005
rs552491	-0.03	0.004
rs55680968	-0.05	0.008
rs55784701	0.03	0.005
rs56367141	-0.04	0.006
rs56409371	-0.03	0.005
rs5742915	-0.02	0.004
rs5753377	-0.03	0.004
rs582780	0.03	0.004
rs59246405	0.03	0.004
rs59543819	-0.03	0.004
rs59652033	-0.03	0.004
rs61817552	-0.03	0.005
rs61828391	-0.03	0.006
rs61846901	-0.03	0.004
rs6185	-0.03	0.004
rs62104180	0.11	0.010
rs62229372	0.05	0.006
rs62316795	0.04	0.005
rs62342064	0.06	0.007
rs62361685	0.05	0.009
rs62379978	-0.06	0.005
rs62391851	-0.06	0.009
rs6415872	0.02	0.004
rs6434162	-0.04	0.005
rs643428	-0.02	0.004
rs6439371	-0.03	0.004
rs6439713	0.03	0.004
rs6445624	0.04	0.006
rs6575806	-0.03	0.006
rs6590889	-0.04	0.004
rs660549	-0.02	0.004
rs66508321	-0.03	0.004
rs6661100	0.05	0.007
rs6678140	-0.03	0.004
rs6735626	0.02	0.004
rs68002803	0.03	0.004
rs6803264	0.03	0.005
rs6864818	0.04	0.005
rs6878910	0.04	0.006
rs6911407	0.03	0.004
rs6911527	0.03	0.005
rs6927679	0.03	0.004
rs6931884	0.06	0.006
rs6933660	-0.03	0.004
rs7072571	0.03	0.006

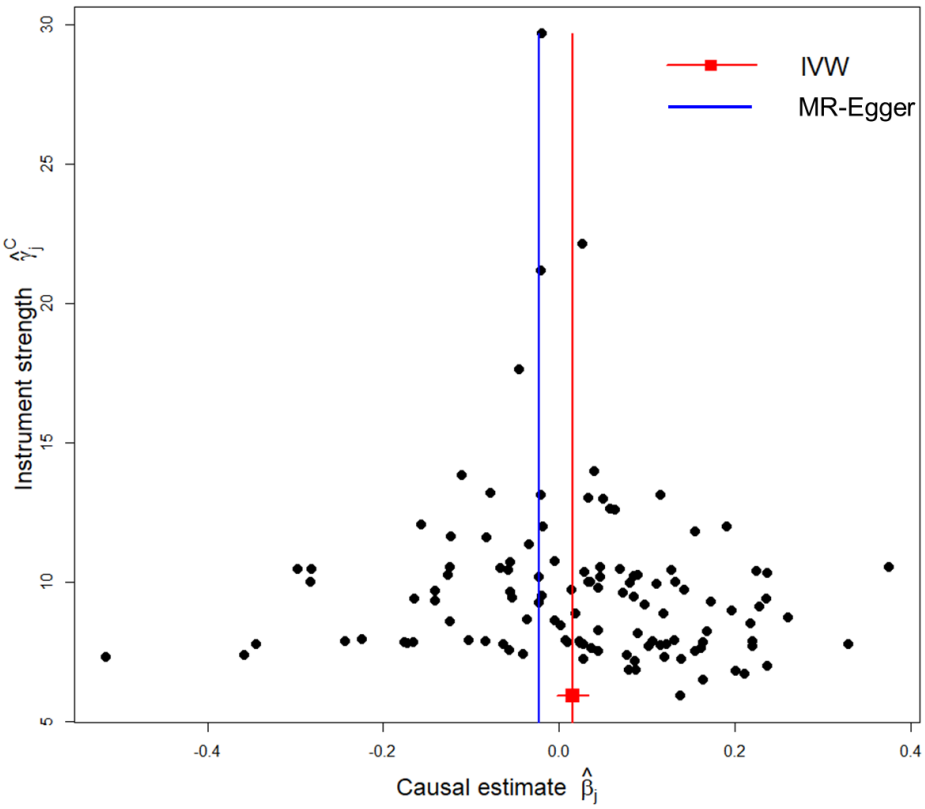
rs7077302	0.05	0.007
rs709488	-0.02	0.004
rs7108556	0.03	0.005
rs7115444	0.03	0.005
rs7132908	-0.04	0.004
rs7178532	0.04	0.004
rs7218751	0.03	0.005
rs7239114	-0.02	0.004
rs72756954	0.06	0.008
rs72787511	0.06	0.011
rs72842141	-0.06	0.009
rs73035994	-0.09	0.012
rs73187215	-0.04	0.007
rs73435048	-0.04	0.008
rs7359336	-0.05	0.004
rs73820560	-0.03	0.006
rs7426534	-0.02	0.004
rs7431217	0.02	0.004
rs74499585	0.06	0.008
rs7516763	0.02	0.004
rs7542538	0.03	0.005
rs7576624	-0.07	0.005
rs758747	-0.03	0.004
rs7587651	-0.02	0.004
rs7649124	0.03	0.005
rs7712046	-0.03	0.004
rs77530428	-0.12	0.017
rs77532868	0.06	0.010
rs7753896	0.03	0.004
rs7757654	-0.03	0.004
rs77955256	-0.04	0.006
rs7826872	0.03	0.004
rs7849973	0.02	0.004
rs7852169	-0.10	0.007
rs7853970	0.04	0.004
rs78928932	-0.06	0.009
rs7907759	0.04	0.004
rs79084266	-0.04	0.007
rs7912468	-0.02	0.004
rs79541760	0.04	0.005
rs7971408	0.05	0.006
rs7979001	0.02	0.004
rs80170948	-0.07	0.011
rs8040272	0.04	0.006
rs8051833	-0.04	0.004
rs813301	0.03	0.004
rs8136272	0.04	0.004
rs842567	-0.03	0.005

rs852061	-0.04	0.004
rs910425	-0.02	0.004
rs913588	-0.03	0.004
rs9330454	-0.03	0.004
rs9349203	-0.04	0.004
rs9382676	0.04	0.005
rs9403051	0.04	0.004
rs941520	-0.02	0.004
rs9427116	0.02	0.004
rs953230	0.03	0.004
rs9548873	-0.03	0.004
rs9568123	-0.03	0.005
rs9614460	-0.02	0.004
rs9635759	0.06	0.004
rs9647570	-0.04	0.006
rs970179	0.02	0.004
rs975642	-0.02	0.004
rs9758500	-0.05	0.004
rs9834893	-0.05	0.007
rs9972653	-0.05	0.004
rs999885	0.02	0.004

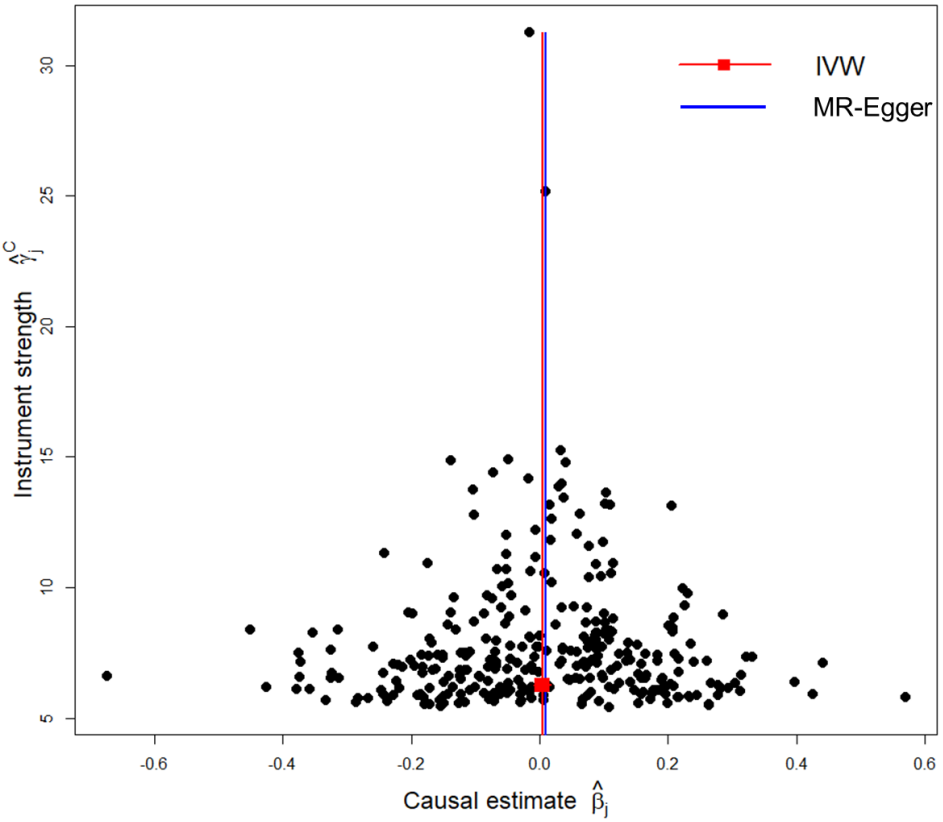
Appendix 3 *List of SNPs ($p<5\times10^{-8}$) used in analysis and their associations with age at first sexual intercourse.*

	Age at first sexual intercourse	
SNP	**β**	**SE**
rs10800813	0.02	0.004
rs115552537	0.03	0.005
rs12522910	0.04	0.005
rs1264194	0.03	0.004
rs12714592	0.03	0.004
rs1344293	0.03	0.004
rs2188151	0.03	0.004
rs2248699	0.02	0.004
rs341521	0.03	0.004
rs369230	0.03	0.004
rs4129322	0.04	0.007
rs4324362	0.03	0.004
rs4443996	0.02	0.004
rs4702	0.02	0.004
rs4840367	0.03	0.004
rs538498277	0.31	0.051
rs58749137	0.02	0.004
rs6058613	0.03	0.005
rs6549665	0.03	0.005
rs658385	0.02	0.004
rs726281	0.03	0.004
rs76513770	0.03	0.006
rs9516776	0.02	0.004

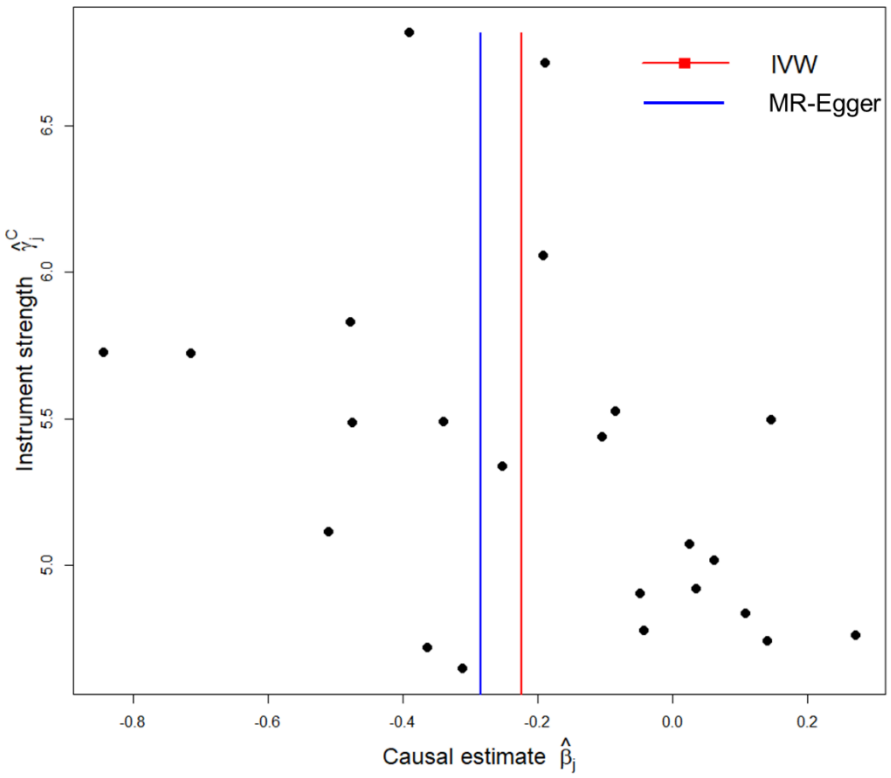
Appendix 4 *Funnel plot for Cochran's Q values using the age at menarche 116 SNP instrument. Here shown with number of children as an outcome for illustration.*



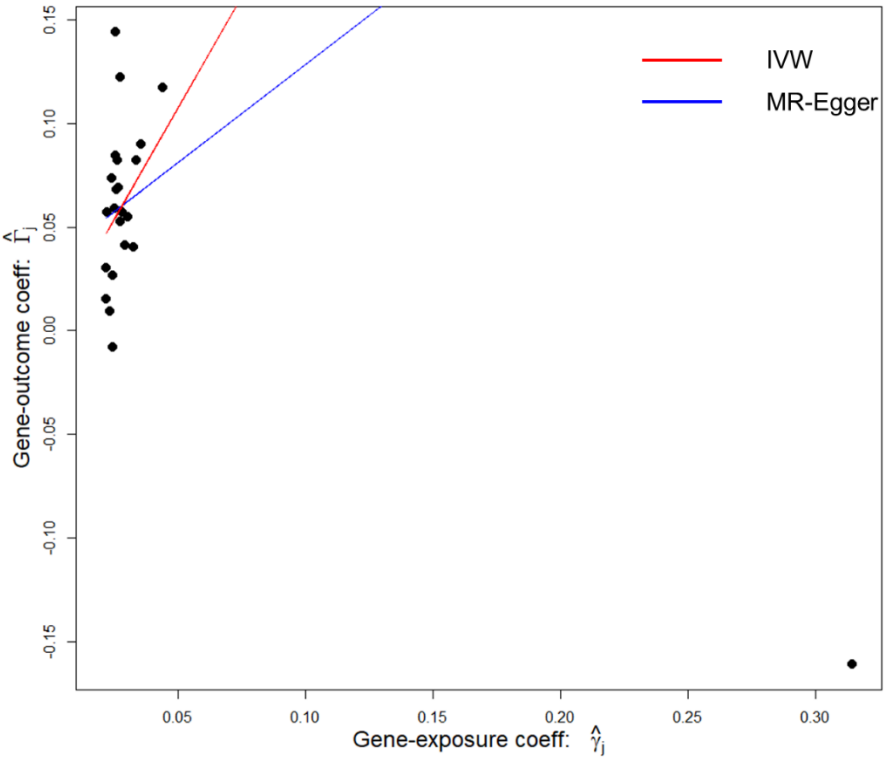
Appendix 5 *Funnel plot for Cochran's Q values using the age at menarche 305 SNP instrument. Here shown with number of children as an outcome for illustration, using non-overlapping UK Biobank data.*



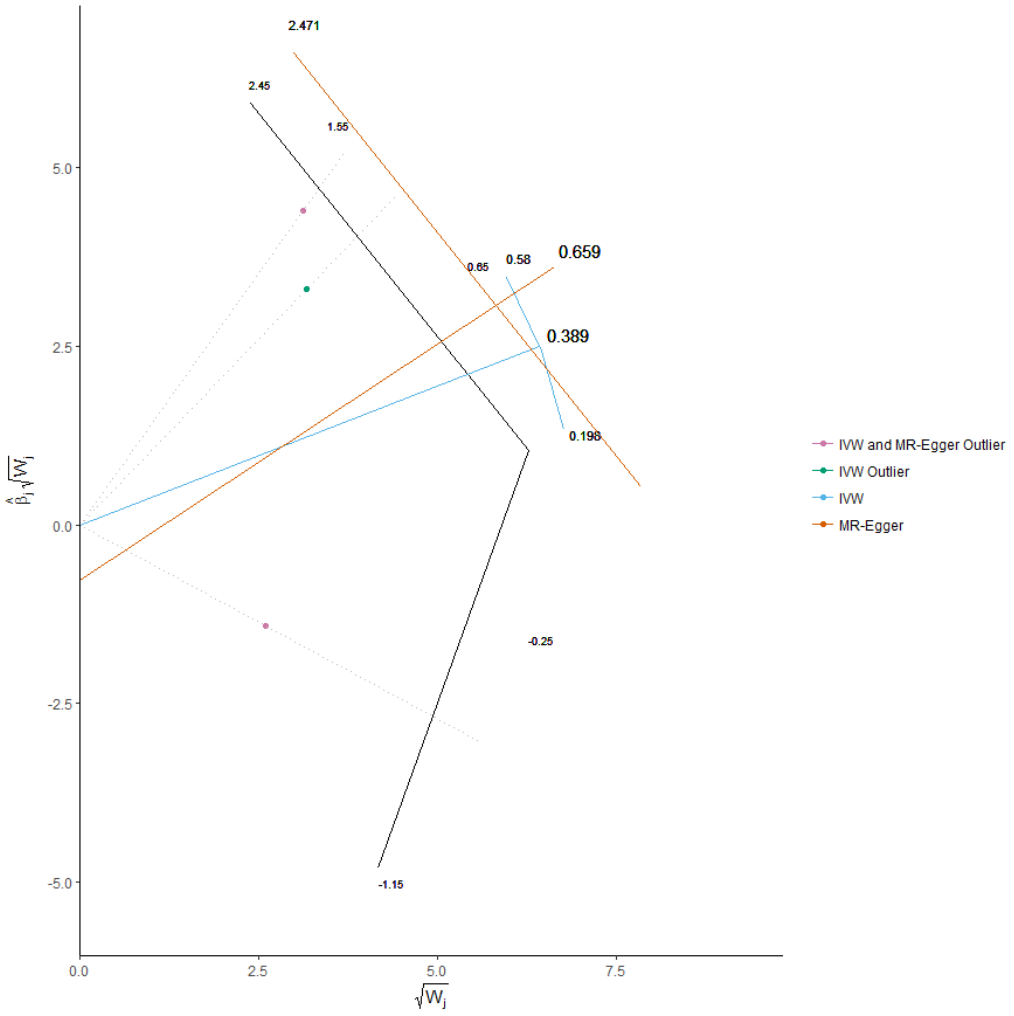
Appendix 6 *Funnel plot for Cochran's Q values using the age at first sexual intercourse instrument. Here shown with number of children as an outcome for illustration.*



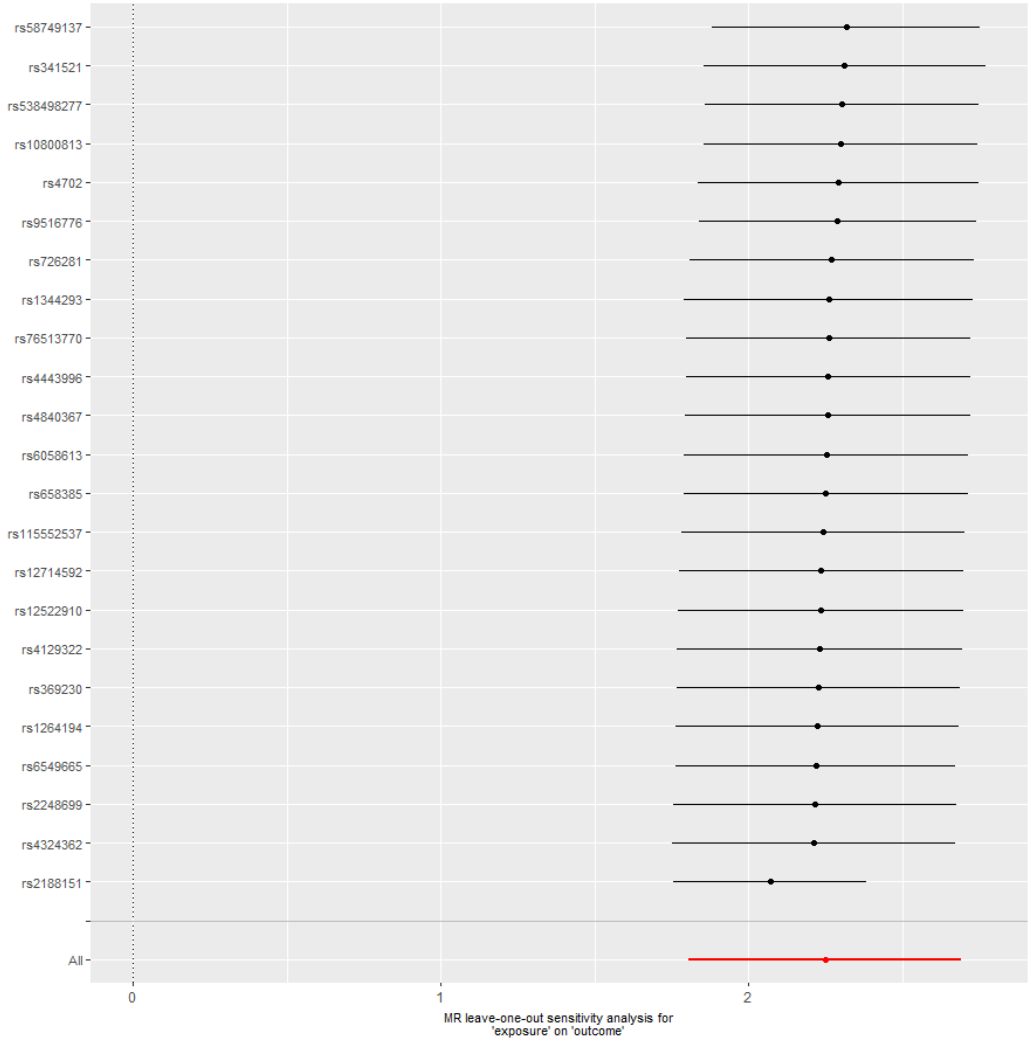
Appendix 7 *MR Plot illustrating rs538498277 as a potential outlier in analyses of age at first sexual intercourse. Here shown for increasing age at first sexual intercourse on age at first birth.*



Appendix 8 *Radial MR plot identifies rs2188151 as the strongest potential outlier. Here shown for increasing age at first sexual intercourse on age at first birth.*



Appendix 9 *Leave-one-out analysis indicates that all estimates were within the confidence intervals of all other estimates. Here shown for increasing age at first sexual intercourse on age at first birth.*



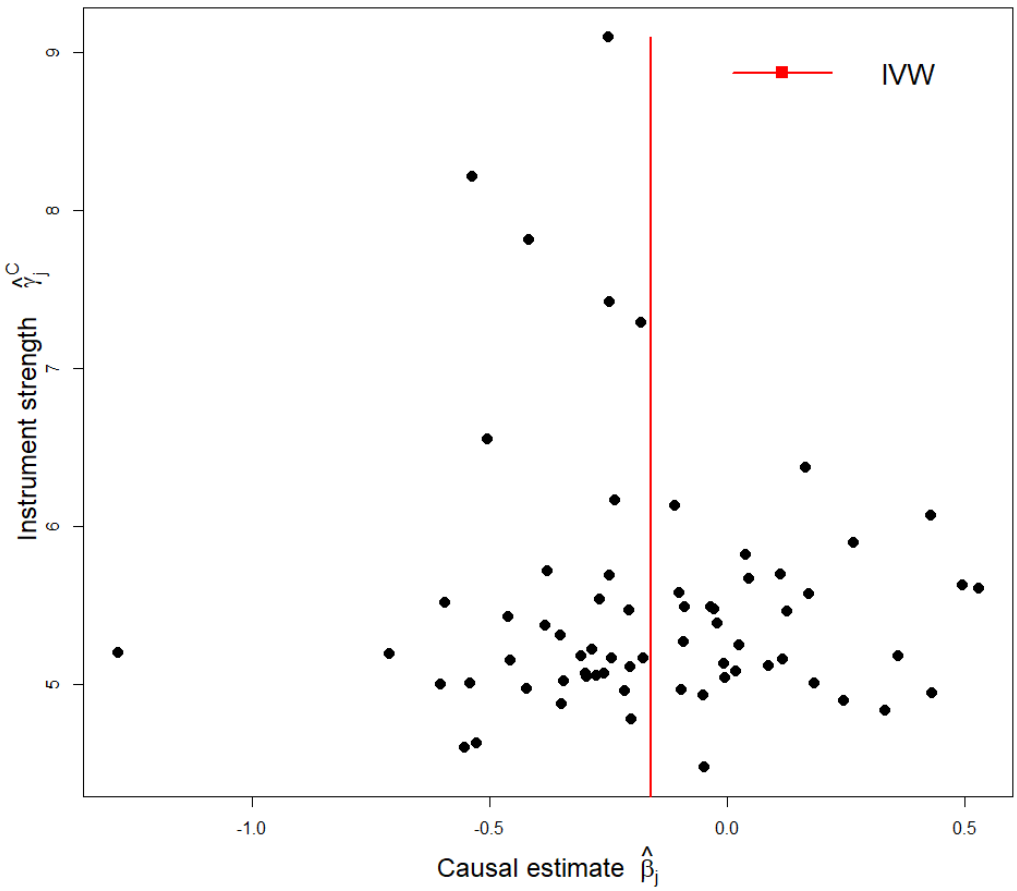
Appendix 10 *List of SNPs associated with educational attainment ($p<5\times10^{-8}$), number of children and age at first birth for UK Biobank analyses.*

SNP	Educational attainment[a]		Number of children[b]		Age at first birth[c]	
	β	SE	β	SE	β	SE
rs10061788	0.021	0.004	-0.002	0.004	0.033	0.025
rs1008078	-0.016	0.003	0.006	0.003	-0.077	0.019
rs1043209	0.018	0.003	0.008	0.003	0.052	0.019
rs10496091	-0.018	0.003	-0.003	0.003	-0.066	0.020
rs11191193	0.018	0.003	0.005	0.003	0.063	0.019
rs11210860	0.017	0.003	0.001	0.003	0.065	0.019
rs112634398	0.036	0.007	-0.013	0.007	0.069	0.046
rs113520408	0.017	0.003	0.000	0.003	0.023	0.020
rs11588857	0.020	0.003	0.011	0.004	0.034	0.022
rs11689269	0.016	0.003	-0.003	0.003	0.061	0.019
rs11690172	0.015	0.003	-0.004	0.003	0.027	0.019
rs11712056	0.024	0.003	-0.013	0.003	0.138	0.018
rs11768238	-0.017	0.003	-0.002	0.003	-0.010	0.020
rs12531458	0.014	0.003	-0.003	0.003	0.014	0.018
rs12646808	0.016	0.003	0.001	0.003	0.054	0.020
rs12671937	0.016	0.003	-0.003	0.003	0.034	0.018
rs12772375	-0.015	0.003	-0.003	0.003	0.006	0.019
rs12969294	-0.016	0.003	0.011	0.003	-0.063	0.019
rs12987662	0.027	0.003	-0.007	0.003	0.069	0.019
rs13294439	-0.023	0.003	0.010	0.003	-0.090	0.018
rs13402908	-0.018	0.003	0.002	0.003	-0.037	0.018
rs1402025	0.017	0.003	0.004	0.003	0.028	0.022
rs1606974	0.022	0.004	-0.008	0.004	0.091	0.028
rs165633	-0.018	0.003	0.000	0.004	0.004	0.022
rs16845580	0.016	0.003	-0.006	0.003	0.039	0.019
rs17119973	-0.019	0.003	0.005	0.003	-0.054	0.021
rs17167170	0.020	0.003	-0.005	0.004	0.073	0.023
rs1777827	0.015	0.003	-0.004	0.003	0.032	0.019
rs17824247	-0.016	0.003	0.007	0.003	-0.057	0.019
rs1871109	-0.016	0.003	0.000	0.003	-0.019	0.018
rs2245901	-0.016	0.003	0.000	0.003	-0.052	0.019
rs2431108	0.016	0.003	0.006	0.003	0.024	0.019
rs2456973	-0.020	0.003	0.010	0.003	-0.096	0.019
rs2457660	-0.017	0.003	0.002	0.003	-0.061	0.019
rs2568955	-0.017	0.003	0.009	0.004	-0.022	0.024
rs2610986	-0.016	0.003	-0.007	0.003	-0.014	0.020
rs2615691	-0.037	0.007	0.019	0.008	0.095	0.050
rs2837992	0.015	0.003	-0.006	0.003	0.050	0.019
rs2964197	0.015	0.003	-0.007	0.003	0.032	0.018
rs2992632	0.017	0.003	-0.005	0.003	0.047	0.020

rs301800	0.019	0.003	-0.004	0.004	0.058	0.024
rs3101246	-0.015	0.003	0.004	0.003	-0.024	0.019
rs324886	-0.015	0.003	0.009	0.003	-0.056	0.019
rs34072092	0.024	0.004	-0.007	0.005	0.074	0.029
rs34305371	0.035	0.005	-0.006	0.005	0.073	0.030
rs35761247	0.034	0.006	-0.020	0.006	0.197	0.039
rs4493682	0.019	0.004	-0.010	0.004	0.082	0.024
rs4500960	-0.016	0.003	0.001	0.003	0.021	0.018
rs4851251	-0.017	0.003	0.004	0.003	-0.067	0.021
rs4863692	0.018	0.003	0.001	0.003	0.090	0.019
rs55830725	-0.022	0.004	-0.011	0.004	-0.006	0.024
rs56231335	-0.017	0.003	0.001	0.003	-0.047	0.019
rs572016	0.014	0.003	0.005	0.003	0.042	0.018
rs61160187	-0.017	0.003	-0.002	0.003	-0.060	0.019
rs62259535	0.048	0.008	-0.011	0.008	0.251	0.049
rs62263923	-0.016	0.003	0.021	0.003	-0.052	0.019
rs62379838	0.016	0.003	-0.004	0.003	-0.007	0.020
rs6739979	-0.015	0.003	0.001	0.003	-0.048	0.019
rs7131944	0.015	0.003	-0.001	0.003	-0.015	0.019
rs7306755	0.023	0.003	0.004	0.004	0.039	0.023
rs76076331	0.020	0.004	-0.001	0.004	0.092	0.028
rs7767938	0.017	0.003	0.000	0.003	0.024	0.021
rs7854982	-0.015	0.003	0.000	0.003	-0.019	0.018
rs7945718	0.015	0.003	-0.003	0.003	0.021	0.019
rs7955289	0.017	0.003	-0.006	0.003	0.027	0.019
rs895606	0.015	0.003	0.002	0.003	0.075	0.018
rs9537821	0.024	0.003	-0.006	0.003	0.073	0.020

[a] Educational attainment from the SSGAC GWAS; [b] Number of children data from UK Biobank; [c] Age at first birth data from UK Biobank.

Appendix 11 *Funnel plot for Cochran's Q values for genetically predicted educational attainment in UK Biobank. Here shown with number of children as an outcome for illustration.*



Appendix 12 *Genetic correlations of genetically predicted educational attainment and number of children and age at first birth using LD score regression with outcome summary statistics also adjusted for genotype array (UK Biobank analyses).*

	No. of children[a]			Age at first birth[b]		
	r_g	SE	*p*	r_g	SE	*p*
Genetically predicted educational attainment[c]	-0.35	0.03	<0.001	0.81	0.02	<0.001

[a] *Number of children data from UK Biobank (N = 333 628);* [b] *Age at first birth data from UK Biobank (N = 123 310);* [c] *Educational attainment from the SSGAC GWAS (N = 283 723).*

Appendix 13 *Estimates of the causal effect of genetically predicted educational attainment on outcomes using IVW, MBE and weighted median MR methods with outcome summary statistics also adjusted for genotype array (UK Biobank analyses).*

	No. of children[a]	**Age at first birth[b]**	**Childlessness[c]**
Method (67 SNPs[d])	**β (95% CI), *p***		**OR (95% CI), *p***
IVW	-0.162 (-0.206, -0.118), <0.001	2.663 (2.388, 2.938), <0.001	1.590 (1.447, 1.747), <0.001
Weighted Median	-0.206 (-0.278, -0.134), <0.001	2.842 (2.378, 3.306), <0.001	1.570 (1.349, 1.828), <0.001
MBE	-0.249 (-0.477, -0.021), 0.04	1.621 (0.260, 2.981), <0.001	1.520 (0.964, 2.399), 0.08

[a] Number of children data from UK Biobank (N = 268 658 – 335 758). [b] Age at first birth data from UK Biobank (N = 99 317 – 124 093). [c] Childlessness data from UK Biobank (N = 268 658 – 335 758). Childlessness was coded as 1. Results were converted to ORs by exponentiating log ORs; [d] Educational attainment from the SSGAC GWAS (N = 283 723).

Appendix 14 *List of SNPs associated with schizophrenia ($p<5\times10^{-8}$) and associations with number of children, age at first birth and number of sexual partners for UK Biobank analyses.*

SNP	Original SNP if proxy used	r^2 for proxy	Schizophrenia[a]		Number of children[b]		Age at first birth[c]		Number of sexual partners	
			ln(OR)	SE	β	SE	β	SE	β	SE
rs1009080	rs1498232	0.99	-0.071	0.012	0.004	0.003	-0.018	0.020	-0.021	0.024
rs1023500			0.076	0.014	0.002	0.004	-0.024	0.023	-0.025	0.028
rs10412446	rs56873913	0.97	0.057	0.013	0.001	0.003	0.040	0.022	0.021	0.027
rs10503253			0.072	0.013	0.004	0.004	0.008	0.023	-0.030	0.028
rs10504857	rs7819570	1.00	-0.074	0.014	0.002	0.004	-0.018	0.024	-0.026	0.030
rs10520163			0.058	0.011	-0.004	0.003	0.007	0.018	0.019	0.022
rs10779702	chr1_8424984_D	0.97	0.063	0.011	0.002	0.003	-0.049	0.019	-0.021	0.023
rs10791097			0.077	0.011	0.007	0.003	-0.024	0.018	0.009	0.022
rs10803138			-0.072	0.013	0.006	0.003	-0.053	0.021	-0.086	0.026
rs10860964			0.063	0.011	0.005	0.003	-0.035	0.019	0.026	0.023
rs10900851	rs10043984	0.99	-0.064	0.012	0.008	0.003	-0.052	0.021	0.023	0.026
rs10933068	rs11685299	1.00	-0.063	0.012	-0.008	0.003	0.015	0.020	-0.083	0.024
rs11027857			0.064	0.011	0.005	0.003	0.007	0.018	-0.002	0.022
rs1106568			-0.069	0.013	-0.005	0.003	0.070	0.021	0.020	0.026
rs11139497			0.066	0.012	-0.005	0.003	-0.050	0.019	0.032	0.024
rs11210892			-0.068	0.012	-0.001	0.003	0.084	0.019	-0.083	0.024
rs1160682	rs12129573	1.00	-0.068	0.011	-0.003	0.003	0.053	0.019	-0.003	0.023
rs11632947	rs12903146	0.99	0.066	0.011	0.001	0.003	0.012	0.018	0.023	0.022
rs11682175			-0.073	0.011	0.002	0.003	-0.076	0.018	0.043	0.022
rs11683083	chr2_146436222_I	1.00	-0.078	0.014	0.007	0.004	-0.039	0.024	-0.043	0.029
rs12063329	rs140505938	1.00	0.088	0.015	-0.001	0.004	0.014	0.024	0.036	0.030
rs12148337			0.057	0.011	0.002	0.003	0.001	0.018	-0.028	0.022
rs12325245			-0.086	0.016	-0.001	0.004	-0.058	0.026	-0.019	0.032
rs12421382			-0.065	0.012	-0.004	0.003	-0.024	0.020	-0.029	0.024
rs12522290			0.082	0.015	0.008	0.004	-0.025	0.024	0.020	0.029

rs12619354	rs59979824	0.87	0.059	0.012	-0.004	0.003	0.040	0.019	0.062	0.024
rs12654855	rs79212538	0.95	-0.128	0.025	-0.010	0.007	0.023	0.043	-0.083	0.053
rs12659129	chr5_140143664_I	1.00	0.052	0.011	-0.002	0.003	-0.019	0.018	-0.037	0.022
rs12716972	rs12691307	0.98	0.063	0.011	-0.002	0.003	-0.0004	0.018	-0.014	0.023
rs13074054	chr3_180594593_I	0.99	0.077	0.014	0.008	0.004	-0.008	0.022	-0.041	0.027
rs13107325	rs35518360	0.85	0.152	0.022	0.001	0.006	-0.038	0.035	-0.134	0.043
rs1501357			-0.069	0.014	-0.002	0.004	0.050	0.024	-0.065	0.029
rs16867576			0.096	0.017	-0.009	0.004	-0.028	0.027	0.149	0.033
rs17049247	rs75575209	0.97	-0.103	0.019	0.008	0.005	-0.091	0.032	0.024	0.039
rs17149781	chr7_24747494_D	0.91	-0.086	0.017	0.004	0.005	-0.083	0.029	0.007	0.036
rs17194490			0.097	0.015	-0.003	0.004	0.034	0.025	0.048	0.030
rs17273111	rs4330281	1.00	0.056	0.011	-0.001	0.003	-0.025	0.018	0.020	0.022
rs17594526	rs78322266	1.00	0.169	0.031	-0.003	0.009	0.053	0.056	0.169	0.069
rs17602354	rs72934570	0.92	0.141	0.021	-0.001	0.005	0.010	0.033	0.188	0.040
rs1782810	rs1702294	0.99	0.118	0.014	0.003	0.004	0.004	0.023	0.000	0.029
rs2007044			-0.092	0.011	0.002	0.003	-0.015	0.019	-0.007	0.023
rs2053079			-0.072	0.013	0.004	0.003	-0.037	0.021	0.058	0.026
rs2057070	rs9607782	0.81	-0.068	0.012	0.006	0.003	-0.051	0.020	0.029	0.025
rs2068012			-0.070	0.013	-0.002	0.003	0.048	0.022	-0.007	0.027
rs211829			0.054	0.011	-0.005	0.003	0.001	0.019	0.022	0.023
rs215411			0.069	0.012	-0.002	0.003	0.003	0.020	0.017	0.024
rs2239063			0.069	0.012	-0.0002	0.003	0.003	0.020	0.053	0.025
rs2296569	rs55833108	0.83	-0.068	0.014	0.001	0.004	-0.007	0.023	0.074	0.028
rs2514218			-0.072	0.012	-0.0004	0.003	0.027	0.019	0.005	0.024
rs2535627			0.070	0.011	-0.0004	0.003	-0.019	0.018	-0.019	0.023
rs2693698			-0.062	0.011	0.001	0.003	0.025	0.018	-0.006	0.023
rs2796275	rs7523273	0.98	0.053	0.012	0.001	0.003	-0.002	0.019	0.037	0.024
rs2851447			-0.084	0.012	-0.002	0.003	-0.035	0.021	-0.048	0.026
rs2955357	rs8082590	1.00	0.064	0.012	-0.001	0.003	0.031	0.020	-0.038	0.024
rs2965180	rs2905426	0.97	0.063	0.011	0.009	0.003	-0.068	0.019	-0.006	0.023

rs2973161	rs2973155	0.97	-0.069	0.011	-0.006	0.003	0.006	0.019	-0.033	0.023
rs324015	rs324017	0.81	-0.069	0.013	0.003	0.003	0.005	0.021	-0.016	0.026
rs3802924	rs75059851	0.95	0.088	0.014	-0.0003	0.004	-0.041	0.023	0.005	0.029
rs3849046			0.062	0.011	-0.008	0.003	0.010	0.019	0.005	0.023
rs4128242	chr18_52749216_D	1.00	0.067	0.011	0.003	0.003	-0.024	0.019	0.021	0.023
rs4129585			0.079	0.011	0.003	0.003	-0.035	0.018	0.036	0.022
rs4240748			-0.057	0.011	0.009	0.003	0.030	0.019	-0.027	0.023
rs436124	rs679087	1.00	0.061	0.011	0.002	0.003	0.012	0.019	0.034	0.023
rs4388249			0.067	0.014	0.001	0.004	-0.037	0.025	0.104	0.031
rs4391122			-0.078	0.011	-0.001	0.003	0.068	0.018	0.027	0.023
rs4518583	rs3735025	1.00	0.061	0.011	-0.004	0.003	0.061	0.019	0.035	0.023
rs4523957			0.070	0.012	-0.005	0.003	-0.007	0.019	0.055	0.024
rs4648845			0.067	0.012	0.002	0.003	0.015	0.018	-0.010	0.023
rs4664442	rs2909457	0.98	0.059	0.011	0.002	0.003	0.029	0.018	0.017	0.022
rs4702			-0.081	0.012	-0.006	0.003	0.026	0.018	-0.132	0.022
rs6065094			-0.075	0.012	-0.003	0.003	-0.008	0.019	-0.062	0.024
rs6461049	chr7_2025096_I	0.93	0.080	0.011	0.006	0.003	0.033	0.018	0.077	0.023
rs6466056	rs6466055	1.00	0.068	0.011	-0.0005	0.003	-0.052	0.019	0.062	0.023
rs6579959	rs111294930	0.96	-0.067	0.012	-0.003	0.003	-0.018	0.020	-0.103	0.025
rs6670165			0.074	0.014	-0.001	0.004	0.004	0.023	0.066	0.029
rs6704641			0.075	0.015	0.006	0.004	0.008	0.023	-0.071	0.029
rs6704768			-0.077	0.011	-0.003	0.003	-0.051	0.018	-0.007	0.023
rs7085104	rs11191419	0.99	0.098	0.011	0.002	0.003	-0.001	0.019	-0.067	0.024
rs7140568	rs12887734	1.00	0.085	0.012	0.002	0.003	-0.004	0.020	0.036	0.025
rs715170			-0.067	0.012	-0.001	0.003	0.025	0.021	-0.061	0.025
rs7267348			-0.066	0.013	0.003	0.003	-0.003	0.021	-0.005	0.026
rs7432375			-0.071	0.011	-0.004	0.003	0.017	0.019	-0.006	0.023
rs7499750	rs7405404	1.00	0.077	0.013	-0.005	0.003	0.018	0.022	0.069	0.027
rs7730110	rs11740474	0.81	-0.059	0.011	0.002	0.003	0.021	0.019	-0.014	0.024
rs7801375			-0.083	0.015	0.0003	0.004	0.018	0.025	0.009	0.031
rs7815859	rs36068923	1.00	0.083	0.013	0.002	0.004	0.049	0.023	0.013	0.028

rs787983	rs6434928	0.98	-0.073	0.012	-0.004	0.003	-0.014	0.019	-0.019	0.024
rs7893279			0.112	0.018	0.008	0.005	0.083	0.029	0.106	0.035
rs7927176	rs77502336	0.96	-0.059	0.012	0.00001	0.003	0.017	0.019	0.053	0.024
rs8042374			0.090	0.013	-0.009	0.003	-0.005	0.022	-0.049	0.027
rs8044995			0.077	0.014	0.002	0.004	-0.022	0.025	0.017	0.030
rs832187			-0.070	0.011	0.0002	0.003	-0.037	0.019	0.021	0.023
rs867743	rs6984242	1.00	-0.062	0.011	-0.003	0.003	-0.029	0.019	0.020	0.023
rs884808	rs14403	0.86	-0.054	0.013	0.003	0.004	0.040	0.022	-0.058	0.027
rs9420			0.058	0.011	-0.002	0.003	-0.007	0.019	0.024	0.024
rs950169			-0.079	0.012	-0.003	0.003	0.038	0.021	-0.023	0.025
rs9636107			-0.080	0.011	-0.003	0.003	0.063	0.018	-0.034	0.023
rs982256	rs13240464	0.98	0.078	0.012	-0.001	0.003	0.030	0.019	-0.043	0.024
rs9841616			-0.074	0.015	-0.001	0.004	-0.021	0.024	-0.051	0.030
rs9876421	rs75968099	0.93	0.079	0.011	-0.007	0.003	0.021	0.019	0.043	0.024
rs9922678			0.068	0.012	-0.001	0.003	0.008	0.020	-0.008	0.025

[a] Schizophrenia genetic data from the PGC GWAS; [b] Number of children data from UK Biobank; [c] Age at first birth data from UK Biobank; [d] Number of sexual partners data from UK Biobank.

Appendix 15 *List of SNPs associated with schizophrenia ($p<5\times10^{-8}$) and associations with number of children, age at first birth and number of sexual partners for MoBa mothers analyses.*

				Schizophrenia[a]		Parity[b]		Age at first pregnancy[c]		Age at first birth[d]	
SNP	**Proxy for**	**Effect allele**	**Other allele**	**ln(OR)**	**SE**	**β**	**SE**	**β**	**SE**	**β**	**SE**
rs10043984		T	C	0.064	0.012	-0.003	0.013	0.070	0.073	-0.046	0.064
rs1023500		T	C	0.076	0.014	-0.015	0.015	0.063	0.080	0.147	0.070
rs10503253		A	C	0.072	0.013	0.024	0.014	-0.068	0.075	-0.056	0.066
rs10520163		T	C	0.058	0.011	0.010	0.011	-0.015	0.061	-0.030	0.053
rs10777339	rs4240748	A	G	0.056	0.011	0.030	0.012	0.017	0.064	-0.133	0.056
rs10779702		A	G	0.063	0.011	0.005	0.012	0.005	0.063	-0.009	0.055
rs10791097		T	G	0.077	0.011	-0.003	0.011	-0.083	0.062	-0.038	0.054
rs10803138		A	G	-0.072	0.013	0.009	0.013	-0.130	0.072	-0.147	0.063
rs10860964		T	C	0.063	0.011	0.009	0.012	-0.066	0.064	-0.021	0.056
rs11027857		A	G	0.064	0.011	0.015	0.011	-0.080	0.061	-0.051	0.054
rs1106568		A	G	-0.069	0.013	-0.008	0.013	0.028	0.070	0.053	0.061
rs111294930		A	G	0.088	0.014	-0.005	0.012	-0.008	0.067	0.024	0.059
rs11139497		A	T	0.066	0.012	-0.002	0.012	0.079	0.067	0.073	0.058
rs11191419		A	T	-0.102	0.012	-0.001	0.012	-0.074	0.065	-0.048	0.057
rs11210892		A	G	-0.068	0.012	-0.019	0.012	0.040	0.066	0.031	0.058
rs11682175		T	C	-0.073	0.011	0.005	0.011	0.027	0.062	0.009	0.054
rs11683083		A	G	-0.078	0.014	0.016	0.014	-0.047	0.078	-0.066	0.068
rs11693094		T	C	-0.074	0.011	0.023	0.011	-0.074	0.062	-0.055	0.054
rs12129573		A	C	0.069	0.011	0.014	0.012	-0.134	0.064	-0.142	0.056
rs12148337		T	C	0.057	0.011	0.004	0.011	-0.042	0.062	-0.048	0.054
rs12325245		A	T	-0.086	0.016	0.002	0.017	-0.040	0.092	0.023	0.080
rs12421382		T	C	-0.065	0.012	0.021	0.012	-0.079	0.064	-0.078	0.056
rs12522290		C	G	0.082	0.015	-0.008	0.015	0.119	0.082	0.047	0.072

rs12691307		A	G	0.072	0.011	-0.020	0.011	0.108	0.061	0.042	0.054
rs12704290		A	G	-0.106	0.017	0.026	0.017	0.025	0.095	-0.029	0.083
rs12826178		T	G	-0.168	0.024	-0.025	0.022	-0.202	0.122	-0.168	0.107
rs12903146		A	G	0.067	0.011	-0.011	0.011	0.079	0.062	0.016	0.054
rs13074054		A	G	0.077	0.014	0.028	0.015	-0.058	0.080	-0.078	0.070
rs13240464		T	C	0.081	0.012	0.002	0.012	-0.020	0.065	-0.042	0.057
rs1416544	rs1339227	A	G	-0.063	0.011	-0.003	0.012	0.055	0.063	0.002	0.055
rs14403		T	C	-0.067	0.013	0.0003	0.013	0.060	0.073	-0.007	0.064
rs1498232		T	C	0.072	0.012	-0.020	0.012	0.047	0.066	0.038	0.058
rs1501357		T	C	-0.069	0.014	0.008	0.015	-0.054	0.082	-0.009	0.072
rs16867576		A	G	0.096	0.017	-0.017	0.016	0.035	0.085	0.038	0.074
rs1702294		T	C	-0.118	0.014	-0.007	0.014	-0.116	0.076	-0.051	0.067
rs17149781		A	G	-0.086	0.017	-0.030	0.017	0.014	0.091	-0.026	0.080
rs17194490		T	G	0.097	0.015	-0.022	0.016	0.079	0.085	0.072	0.075
rs2007044		A	G	-0.092	0.011	-0.012	0.012	0.068	0.063	0.016	0.056
rs2053079		A	G	-0.072	0.013	0.007	0.013	-0.054	0.072	0.007	0.063
rs211829		T	C	0.054	0.011	0.006	0.012	0.051	0.064	-0.042	0.056
rs215411		A	T	0.069	0.012	0.005	0.012	-0.023	0.064	0.020	0.056
rs2239063		A	C	0.069	0.012	-0.014	0.013	0.145	0.068	0.096	0.060
rs2514218		T	C	-0.072	0.012	-0.010	0.012	0.110	0.066	0.050	0.058
rs2535627		T	C	0.070	0.011	-0.003	0.011	-0.053	0.062	0.049	0.054
rs2851447		C	G	-0.084	0.012	-0.022	0.013	-0.007	0.072	0.052	0.063
rs2905426		T	G	-0.068	0.012	0.0001	0.012	-0.018	0.064	-0.017	0.056
rs2909457		A	G	-0.060	0.011	-0.017	0.011	0.046	0.062	-0.0005	0.054
rs2973161	rs2973155	A	C	-0.069	0.011	-0.022	0.012	0.100	0.064	0.097	0.056
rs324017		A	C	-0.064	0.012	-0.010	0.013	-0.030	0.069	0.021	0.061
rs35518360		A	T	-0.145	0.020	-0.004	0.025	-0.037	0.138	-0.072	0.121

rs35672725	rs7819570	T	C	0.074	0.014	-0.022	0.016	0.103	0.086	0.089	0.075
rs36068923		A	G	-0.084	0.013	-0.002	0.014	0.101	0.074	0.045	0.065
rs3735025		T	C	0.063	0.011	-0.009	0.012	-0.024	0.065	-0.006	0.057
rs3768644		A	G	-0.094	0.018	0.013	0.019	-0.023	0.103	0.015	0.090
rs3845840	rs11685299	A	G	-0.062	0.012	-0.020	0.012	0.107	0.065	0.082	0.057
rs3849046		T	C	0.062	0.011	0.015	0.011	-0.032	0.062	-0.077	0.054
rs4128242		T	C	0.067	0.011	0.003	0.011	-0.006	0.062	0.023	0.055
rs4129585		A	C	0.079	0.011	-0.001	0.011	0.013	0.062	0.012	0.054
rs4330281		T	C	-0.058	0.011	0.006	0.011	0.049	0.062	-0.004	0.055
rs4388249		T	C	0.067	0.014	-0.018	0.015	0.010	0.081	0.017	0.071
rs4391122		A	G	-0.078	0.011	-0.008	0.011	0.049	0.062	0.034	0.054
rs4523957		T	G	0.070	0.012	-0.005	0.012	-0.006	0.063	-0.050	0.055
rs4648845		T	C	0.067	0.012	-0.008	0.011	0.043	0.061	0.025	0.054
rs4702		A	G	-0.081	0.012	-0.013	0.011	0.081	0.062	0.032	0.054
rs4766428		T	C	0.069	0.011	0.002	0.011	0.017	0.062	0.041	0.054
rs55661361		A	G	-0.079	0.012	0.004	0.012	-0.119	0.065	-0.089	0.057
rs55833108		T	G	0.074	0.014	0.005	0.013	0.009	0.073	-0.005	0.064
rs56205728		A	G	0.066	0.013	-0.001	0.013	0.070	0.068	0.042	0.060
rs59979824		A	C	-0.071	0.012	-0.002	0.012	-0.011	0.064	-0.008	0.056
rs6002655		T	C	0.069	0.011	0.007	0.011	0.059	0.062	0.058	0.054
rs6065094		A	G	-0.075	0.012	0.00009	0.012	0.001	0.067	0.009	0.059
rs6434928		A	G	-0.079	0.012	0.003	0.012	0.012	0.066	-0.014	0.057
rs6461049		T	C	0.080	0.011	-0.012	0.011	-0.017	0.062	0.041	0.055
rs6466055		A	C	0.069	0.011	-0.002	0.012	-0.011	0.066	-0.014	0.058
rs6670165		T	C	0.074	0.014	-0.009	0.015	0.075	0.082	0.011	0.071
rs6704641		A	G	0.075	0.015	0.013	0.016	-0.137	0.086	-0.102	0.076
rs6704768		A	G	-0.077	0.011	-0.011	0.011	0.003	0.062	0.022	0.054

rs679087		A	C	-0.064	0.012	0.011	0.012	-0.131	0.063	-0.017	0.055
rs6984242		A	G	-0.062	0.011	-0.006	0.012	-0.005	0.063	0.032	0.055
rs715170		T	C	-0.067	0.012	-0.011	0.013	-0.079	0.069	-0.030	0.060
rs7267348		T	C	-0.066	0.013	0.0004	0.013	-0.048	0.072	-0.017	0.063
rs72934570		T	C	-0.145	0.021	0.006	0.020	0.098	0.108	-0.045	0.095
rs73229090		A	C	-0.099	0.018	-0.012	0.018	0.119	0.096	0.083	0.084
rs7405404		T	C	0.077	0.013	0.013	0.014	0.089	0.076	0.091	0.067
rs7432375		A	G	-0.071	0.011	-0.009	0.012	-0.020	0.063	0.059	0.055
rs75059851		A	G	0.091	0.014	0.014	0.013	-0.095	0.072	-0.092	0.063
rs7523273		A	G	0.060	0.012	-0.001	0.012	0.026	0.063	-0.032	0.055
rs75968099		T	C	0.080	0.011	0.003	0.012	0.023	0.065	0.017	0.057
rs7730110		T	C	-0.059	0.011	-0.007	0.012	0.085	0.063	0.061	0.055
rs77447799	rs75575209	T	G	0.106	0.019	-0.002	0.020	-0.057	0.107	0.059	0.094
rs77502336		C	G	0.062	0.012	-0.001	0.012	-0.003	0.067	0.003	0.059
rs7801375		A	G	-0.083	0.015	0.011	0.016	-0.073	0.085	-0.071	0.075
rs7893279		T	G	0.112	0.018	-0.008	0.018	-0.120	0.098	0.007	0.086
rs79212538		T	G	0.141	0.026	-0.003	0.024	-0.019	0.133	-0.118	0.116
rs8042374		A	G	0.090	0.013	-0.003	0.014	0.057	0.075	0.030	0.065
rs8044995		A	G	0.077	0.014	-0.004	0.015	-0.123	0.082	-0.058	0.072
rs8082590		A	G	-0.066	0.012	-0.006	0.012	0.036	0.067	0.084	0.059
rs8113357	rs56873913	T	C	0.062	0.013	-0.004	0.013	-0.058	0.073	-0.009	0.064
rs832187		T	C	-0.070	0.011	-0.0002	0.012	-0.082	0.065	-0.038	0.057
rs9420		A	G	0.058	0.011	0.019	0.012	-0.072	0.065	-0.072	0.057
rs950169		T	C	-0.079	0.012	0.017	0.013	0.034	0.070	-0.033	0.061
rs9607782		A	T	0.089	0.013	0.001	0.013	0.069	0.071	0.052	0.062
rs9636107		A	G	-0.080	0.011	-0.004	0.011	0.027	0.062	-0.015	0.054
rs9841616		A	T	-0.074	0.015	-0.006	0.016	0.074	0.085	0.157	0.074

rs9922678	A	G	0.068	0.012	0.005	0.012	-0.116	0.068	-0.093	0.059

[a] Schizophrenia genetic data from the PGC GWAS; [b] Parity data from MoBa; [c] Age at first pregnancy data from MoBa; [d] Age at first birth data from MoBa.

Appendix 16 *List of SNPs associated with schizophrenia ($p<5\times10^{-8}$) and associations with number of children, age at first birth and number of sexual partners for ALSPAC G0 analyses.*

			Schizophrenia[a]		**Parity at 85 months[b]**		**Parity at 18 years[c]**		**Age at first pregnancy[d]**	
SNP	**Effect allele**	**Other allele**	**ln(OR)**	**SE**	**β**	**SE**	**β**	**SE**	**β**	**SE**
rs10043984	T	C	0.064	0.012	0.0003	0.021	0.025	0.033	0.114	0.075
rs1023500	T	C	0.076	0.014	-0.027	0.022	-0.002	0.036	-0.004	0.082
rs10503253	A	C	0.072	0.013	-0.004	0.023	0.010	0.036	0.030	0.081
rs10520163	T	C	0.058	0.011	0.051	0.018	0.056	0.029	-0.024	0.064
rs10779702	A	G	0.063	0.011	-0.017	0.019	0.001	0.030	0.049	0.068
rs10791097	T	G	0.077	0.011	-0.023	0.018	0.007	0.028	-0.046	0.064
rs10803138	A	G	-0.072	0.013	0.025	0.020	0.036	0.032	-0.067	0.074
rs10860964	T	C	0.063	0.011	0.011	0.019	0.0005	0.029	-0.039	0.067
rs11027857	A	G	0.064	0.011	0.018	0.018	0.038	0.028	-0.106	0.064
rs1106568	A	G	-0.069	0.013	-0.025	0.021	0.054	0.033	0.061	0.074
rs111294930	A	G	0.088	0.014	-0.004	0.024	-0.020	0.037	0.035	0.085
rs11139497	A	T	0.066	0.012	0.017	0.019	0.022	0.031	-0.084	0.070
rs11191419	A	T	-0.102	0.012	-0.012	0.019	-0.001	0.031	0.122	0.070
rs11210892	A	G	-0.068	0.012	-0.029	0.019	-0.063	0.030	0.074	0.068
rs115329265	A	G	0.196	0.016	0.030	0.023	0.038	0.038	-0.055	0.085
rs11682175	T	C	-0.073	0.011	-0.015	0.018	-0.014	0.028	0.074	0.066
rs11683083	A	G	-0.078	0.014	0.010	0.023	0.004	0.037	-0.056	0.084
rs11685299	A	C	-0.066	0.012	0.006	0.019	0.003	0.030	-0.013	0.068
rs11693094	T	C	-0.074	0.011	0.011	0.018	0.013	0.028	-0.076	0.065
rs117074560	T	C	-0.157	0.028	-0.006	0.046	-0.057	0.075	-0.052	0.166
rs12129573	A	C	0.069	0.011	0.017	0.019	0.016	0.030	-0.094	0.067
rs12148337	T	C	0.057	0.011	0.025	0.018	-0.007	0.028	-0.051	0.065

rs12325245	A	T	-0.086	0.016	-0.002	0.026	-0.014	0.043	-0.130	0.094
rs12421382	T	C	-0.065	0.012	0.012	0.019	-0.022	0.030	0.089	0.069
rs12522290	C	G	0.082	0.015	-0.025	0.023	-0.034	0.037	-0.032	0.085
rs12659129	T	C	0.052	0.011	0.024	0.018	-0.010	0.028	0.043	0.065
rs12691307	A	G	0.072	0.011	-0.014	0.018	-0.015	0.029	0.203	0.066
rs12704290	A	G	-0.106	0.017	-0.027	0.028	-0.059	0.044	0.127	0.102
rs12887734	T	G	0.088	0.012	0.017	0.020	-0.038	0.032	-0.079	0.073
rs12903146	A	G	0.067	0.011	0.022	0.018	0.052	0.029	-0.048	0.064
rs13074054	A	G	0.077	0.014	-0.033	0.022	-0.062	0.035	0.088	0.079
rs13240464	T	C	0.081	0.012	0.021	0.019	0.001	0.030	0.004	0.068
rs1339227	T	C	-0.063	0.011	0.002	0.019	-0.013	0.030	-0.019	0.068
rs140505938	T	C	-0.090	0.015	0.036	0.024	-0.035	0.038	-0.047	0.086
rs14403	T	C	-0.067	0.013	-0.012	0.022	-0.013	0.034	-0.035	0.079
rs1498232	T	C	0.072	0.012	-0.013	0.020	0.005	0.031	0.005	0.071
rs1501357	T	C	-0.069	0.014	0.001	0.023	0.022	0.037	-0.025	0.082
rs16867576	A	G	0.096	0.017	-0.033	0.026	-0.017	0.042	-0.098	0.096
rs1702294	T	C	-0.118	0.014	0.011	0.023	0.067	0.037	0.004	0.084
rs17149781	A	G	-0.086	0.017	-0.028	0.028	0.027	0.045	-0.152	0.102
rs17194490	T	G	0.097	0.015	-0.023	0.024	-0.014	0.038	0.070	0.088
rs190065944	A	G	0.077	0.014	-0.016	0.019	0.001	0.031	0.043	0.069
rs2007044	A	G	-0.092	0.011	0.001	0.018	0.006	0.030	0.003	0.067
rs2053079	A	G	-0.072	0.013	-0.008	0.021	0.067	0.034	0.135	0.076
rs2068012	T	C	-0.070	0.013	-0.042	0.021	-0.043	0.032	0.096	0.076
rs211829	T	C	0.054	0.011	-0.015	0.019	0.003	0.029	0.065	0.067
rs215411	A	T	0.069	0.012	0.016	0.019	-0.002	0.030	-0.036	0.069
rs2239063	A	C	0.069	0.012	-0.024	0.020	-0.033	0.032	-0.005	0.072

rs2332700	C	G	0.077	0.013	0.003	0.020	-0.017	0.032	0.053	0.074
rs2514218	T	C	-0.072	0.012	-0.016	0.019	-0.003	0.030	0.104	0.069
rs2535627	T	C	0.070	0.011	-0.006	0.018	-0.025	0.028	-0.029	0.064
rs2693698	A	G	-0.062	0.011	0.008	0.018	0.019	0.028	-0.042	0.064
rs2851447	C	G	-0.084	0.012	0.046	0.021	0.026	0.033	-0.162	0.075
rs2905426	T	G	-0.068	0.012	0.014	0.019	0.029	0.030	0.092	0.069
rs2909457	A	G	-0.060	0.011	0.006	0.018	0.016	0.028	-0.059	0.064
rs2973155	T	C	-0.067	0.011	0.014	0.018	0.026	0.029	0.027	0.067
rs324017	A	C	-0.064	0.012	0.008	0.019	-0.007	0.032	0.032	0.071
rs35518360	A	T	-0.145	0.020	-0.023	0.037	-0.051	0.058	-0.077	0.132
rs36068923	A	G	-0.084	0.013	-0.008	0.022	-0.055	0.035	0.041	0.079
rs3735025	T	C	0.063	0.011	-0.001	0.019	-0.019	0.030	-0.072	0.067
rs3768644	A	G	-0.094	0.018	0.023	0.028	0.098	0.045	0.005	0.102
rs3849046	T	C	0.062	0.011	-0.007	0.018	-0.017	0.028	0.025	0.064
rs4128242	T	C	0.067	0.011	0.029	0.018	0.031	0.029	-0.079	0.066
rs4129585	A	C	0.079	0.011	-0.009	0.018	-0.011	0.028	0.034	0.065
rs4240748	C	G	-0.057	0.011	-0.028	0.018	-0.051	0.029	0.033	0.066
rs4330281	T	C	-0.058	0.011	0.003	0.018	0.019	0.028	0.015	0.064
rs4388249	T	C	0.067	0.014	0.018	0.025	0.011	0.040	0.168	0.089
rs4391122	A	G	-0.078	0.011	0.020	0.018	0.056	0.029	0.033	0.066
rs4523957	T	G	0.070	0.012	0.006	0.019	-0.023	0.030	-0.095	0.069
rs4648845	T	C	0.067	0.012	0.003	0.019	0.030	0.031	-0.095	0.070
rs4702	A	G	-0.081	0.012	-0.018	0.018	-0.031	0.029	0.130	0.065
rs4766428	T	C	0.069	0.011	0.001	0.019	0.048	0.030	-0.072	0.070
rs55661361	A	G	-0.079	0.012	0.001	0.019	-0.023	0.030	-0.140	0.069
rs55833108	T	G	0.074	0.014	-0.005	0.021	-0.037	0.034	-0.091	0.077

rs56205728	A	G	0.066	0.013	0.026	0.022	-0.043	0.034	0.072	0.078
rs56873913	T	G	0.066	0.013	0.003	0.022	-0.032	0.035	-0.007	0.079
rs59979824	A	C	-0.071	0.012	-0.023	0.020	-0.002	0.031	0.027	0.070
rs6002655	T	C	0.069	0.011	-0.022	0.019	0.016	0.029	0.064	0.067
rs6065094	A	G	-0.075	0.012	-0.0004	0.019	-0.013	0.030	0.001	0.069
rs6434928	A	G	-0.079	0.012	-0.012	0.019	-0.026	0.030	-0.103	0.069
rs6461049	T	C	0.080	0.011	-0.012	0.018	-0.005	0.029	0.120	0.065
rs6466055	A	C	0.069	0.011	0.009	0.019	0.030	0.030	0.005	0.067
rs6670165	T	C	0.074	0.014	0.024	0.023	0.019	0.036	-0.042	0.083
rs6704641	A	G	0.075	0.015	-0.024	0.024	-0.003	0.038	0.177	0.086
rs6704768	A	G	-0.077	0.011	0.010	0.018	-0.015	0.028	0.054	0.065
rs679087	A	C	-0.064	0.012	-0.018	0.019	-0.012	0.031	-0.061	0.070
rs6984242	A	G	-0.062	0.011	0.021	0.018	0.008	0.029	-0.133	0.066
rs715170	T	C	-0.067	0.012	-0.015	0.020	0.011	0.032	0.041	0.072
rs7267348	T	C	-0.066	0.013	-0.002	0.021	-0.009	0.034	0.026	0.076
rs72934570	T	C	-0.145	0.021	-0.031	0.032	-0.040	0.051	0.070	0.117
rs73229090	A	C	-0.099	0.018	0.024	0.028	0.013	0.045	0.014	0.101
rs7405404	T	C	0.077	0.013	0.001	0.021	0.009	0.034	-0.112	0.076
rs7432375	A	G	-0.071	0.011	0.010	0.018	0.023	0.030	0.034	0.066
rs75059851	A	G	0.091	0.014	-0.015	0.023	-0.034	0.036	0.198	0.083
rs7523273	A	G	0.060	0.012	0.0003	0.019	-0.041	0.030	0.019	0.069
rs75575209	A	T	-0.112	0.019	0.030	0.032	0.019	0.050	0.030	0.115
rs75968099	T	C	0.080	0.011	-0.006	0.019	-0.018	0.029	0.065	0.068
rs7730110	T	C	-0.059	0.011	0.029	0.019	-0.004	0.030	-0.043	0.069
rs77502336	C	G	0.062	0.012	-0.011	0.019	-0.018	0.030	0.144	0.070
rs7801375	A	G	-0.083	0.015	0.003	0.024	-0.023	0.039	0.088	0.087

rs7819570	T	G	0.076	0.014	0.032	0.025	-0.002	0.039	0.037	0.089
rs78322266	T	G	0.177	0.031	0.079	0.061	0.054	0.090	-0.032	0.217
rs7893279	T	G	0.112	0.018	-0.020	0.028	0.005	0.045	-0.027	0.100
rs7907645	T	G	0.144	0.022	-0.052	0.041	-0.030	0.063	-0.134	0.146
rs79212538	T	G	0.141	0.026	-0.016	0.045	0.062	0.071	-0.128	0.163
rs8042374	A	G	0.090	0.013	0.030	0.021	0.064	0.034	-0.027	0.076
rs8044995	A	G	0.077	0.014	0.018	0.024	0.009	0.037	-0.093	0.086
rs8082590	A	G	-0.066	0.012	0.0001	0.019	-0.007	0.031	0.130	0.070
rs832187	T	C	-0.070	0.011	0.001	0.019	0.006	0.030	0.040	0.068
rs9420	A	G	0.058	0.011	0.019	0.019	0.008	0.030	0.001	0.069
rs950169	T	C	-0.079	0.012	-0.014	0.020	-0.031	0.032	0.073	0.073
rs9607782	A	T	0.089	0.013	0.006	0.021	-0.004	0.034	0.043	0.076
rs9636107	A	G	-0.080	0.011	-0.029	0.018	-0.048	0.029	0.046	0.065
rs9841616	A	T	-0.074	0.015	0.030	0.023	0.049	0.037	-0.069	0.084
rs9922678	A	G	0.068	0.012	-0.002	0.019	0.002	0.030	0.033	0.070

[a] Schizophrenia genetic data from the PGC GWAS; [b] Parity at 85 months post index child data from ALSPAC G0; [c] Parity at 18 years post index child data from ALSPAC G0; [d] Age at first pregnancy data from ALSPAC G0.

Appendix 17 *List of SNPs associated with schizophrenia ($p<5\times10^{-8}$) and associations with number of number of sexual partners and having had a child yet in ALSPAC G1 data.*

			Schizophrenia[a]		No. of sexual partners[b]		No. of sexual partners with 21-year data[c]		Had child[d]	
SNP	**Effect allele**	**Other allele**	**ln(OR)**	**SE**	**β**	**SE**	**β**	**SE**	**ln(OR)**	**SE**
rs10043984	T	C	0.064	0.012	-0.132	0.337	0.123	0.317	0.107	0.115
rs1023500	T	C	0.076	0.014	-0.534	0.365	-0.509	0.345	0.143	0.131
rs10503253	A	C	0.072	0.013	0.194	0.368	0.081	0.348	-0.297	0.142
rs10520163	T	C	0.058	0.011	-0.209	0.292	0.145	0.275	0.229	0.101
rs10779702	A	G	0.063	0.011	0.183	0.302	0.180	0.286	-0.208	0.108
rs10791097	T	G	0.077	0.011	-0.123	0.290	0.035	0.274	0.025	0.100
rs10803138	A	G	-0.072	0.013	-0.199	0.334	-0.026	0.316	-0.020	0.114
rs10860964	T	C	0.063	0.011	-0.098	0.307	-0.267	0.287	0.071	0.109
rs11027857	A	G	0.064	0.011	0.018	0.294	0.033	0.276	0.092	0.102
rs1106568	A	G	-0.069	0.013	0.292	0.338	0.283	0.319	0.130	0.120
rs111294930	A	G	0.088	0.014	-0.264	0.403	-0.537	0.372	-0.050	0.136
rs11139497	A	T	0.066	0.012	-0.063	0.315	0.215	0.298	-0.072	0.111
rs11191419	A	T	-0.102	0.012	-0.220	0.313	0.000	0.300	-0.029	0.109
rs11210892	A	G	-0.068	0.012	-0.117	0.312	0.048	0.294	0.139	0.111
rs115329265	A	G	0.196	0.016	-0.233	0.379	-0.012	0.357	-0.111	0.127
rs11682175	T	C	-0.074	0.011	-0.491	0.296	-0.336	0.279	-0.039	0.104
rs11683083	A	G	-0.078	0.014	-0.369	0.380	-0.208	0.357	-0.209	0.127
rs11685299	A	C	-0.066	0.012	-0.328	0.316	-0.243	0.297	-0.039	0.108
rs11693094	T	C	-0.074	0.011	-0.045	0.293	-0.190	0.277	0.103	0.102
rs117074560	T	C	-0.157	0.028	-0.824	0.723	-1.081	0.679	0.240	0.235

rs12129573	A	C	0.069	0.011	-0.141	0.305	-0.226	0.285	0.143	0.105
rs12148337	T	C	0.057	0.011	-0.081	0.294	-0.235	0.276	0.054	0.102
rs12325245	A	T	-0.086	0.016	0.216	0.434	0.046	0.407	0.136	0.155
rs12421382	T	C	-0.065	0.012	-0.014	0.322	0.154	0.304	-0.076	0.111
rs12522290	C	G	0.082	0.015	0.041	0.378	0.048	0.356	-0.008	0.133
rs12659129	T	C	0.052	0.011	-0.023	0.294	-0.220	0.276	0.160	0.102
rs12691307	A	G	0.072	0.011	-0.045	0.296	-0.043	0.281	-0.056	0.106
rs12704290	A	G	-0.106	0.017	-0.755	0.451	-0.562	0.427	0.259	0.147
rs12887734	T	G	0.088	0.012	0.282	0.327	0.146	0.306	0.320	0.110
rs12903146	A	G	0.067	0.011	0.057	0.290	0.093	0.274	0.171	0.103
rs13074054	A	G	0.077	0.014	0.005	0.354	-0.064	0.336	0.046	0.123
rs13240464	T	C	0.081	0.012	-0.064	0.312	0.142	0.295	0.005	0.109
rs1339227	T	C	-0.063	0.011	-0.410	0.305	-0.220	0.286	-0.107	0.108
rs140505938	T	C	-0.090	0.015	-0.050	0.392	0.348	0.366	0.129	0.133
rs14403	T	C	-0.067	0.013	0.175	0.355	0.356	0.332	0.032	0.124
rs1498232	T	C	0.072	0.012	-0.352	0.319	-0.556	0.301	0.123	0.110
rs1501357	T	C	-0.069	0.014	0.500	0.382	0.515	0.359	-0.018	0.132
rs16867576	A	G	0.096	0.017	-0.212	0.430	-0.305	0.402	-0.119	0.145
rs1702294	T	C	-0.118	0.014	0.098	0.379	0.100	0.361	0.029	0.130
rs17149781	A	G	-0.086	0.017	0.396	0.474	0.268	0.448	0.108	0.172
rs17194490	T	G	0.097	0.015	-0.549	0.395	-0.799	0.375	0.276	0.133
rs190065944	A	G	0.077	0.014	0.358	0.309	0.464	0.293	-0.103	0.110
rs2007044	A	G	-0.093	0.011	-0.084	0.304	-0.066	0.289	-0.190	0.102
rs2053079	A	G	-0.072	0.013	0.456	0.343	0.268	0.322	-0.150	0.116
rs2068012	T	C	-0.070	0.013	0.276	0.356	0.415	0.335	-0.069	0.121
rs211829	T	C	0.054	0.011	-0.580	0.299	-0.526	0.282	0.112	0.107
rs215411	A	T	0.069	0.012	-0.040	0.311	0.030	0.291	0.103	0.106

rs2239063	A	C	0.069	0.012	0.307	0.328	0.343	0.308	0.001	0.113
rs2332700	C	G	0.077	0.013	-0.177	0.338	-0.116	0.319	-0.014	0.118
rs2514218	T	C	-0.072	0.012	-0.241	0.315	-0.231	0.296	-0.149	0.111
rs2535627	T	C	0.070	0.011	-0.260	0.295	-0.183	0.279	-0.096	0.103
rs2693698	A	G	-0.062	0.011	0.086	0.290	-0.114	0.273	-0.084	0.102
rs2851447	C	G	-0.084	0.012	0.373	0.340	0.475	0.320	-0.055	0.118
rs2905426	T	G	-0.068	0.012	0.453	0.313	0.403	0.295	-0.245	0.107
rs2909457	A	G	-0.060	0.011	-0.561	0.292	-0.547	0.275	-0.037	0.102
rs2973155	T	C	-0.067	0.011	-0.146	0.299	-0.244	0.283	0.107	0.104
rs324017	A	C	-0.064	0.012	0.068	0.328	-0.045	0.306	0.206	0.110
rs35518360	A	T	-0.145	0.020	-0.165	0.578	0.097	0.555	-0.052	0.205
rs36068923	A	G	-0.084	0.013	0.552	0.362	0.420	0.339	0.017	0.125
rs3735025	T	C	0.063	0.011	0.073	0.300	0.216	0.284	0.119	0.106
rs3768644	A	G	-0.094	0.018	-0.616	0.472	-0.258	0.441	-0.219	0.175
rs3849046	T	C	0.062	0.011	0.253	0.296	0.303	0.277	0.122	0.104
rs4128242	T	C	0.067	0.011	-0.061	0.297	0.092	0.280	0.105	0.104
rs4129585	A	C	0.079	0.011	-0.345	0.294	-0.180	0.276	-0.072	0.102
rs4240748	C	G	-0.057	0.011	-0.256	0.299	-0.340	0.282	0.030	0.103
rs4330281	T	C	-0.058	0.011	0.234	0.290	0.204	0.274	-0.039	0.101
rs4388249	T	C	0.067	0.014	-0.539	0.401	-0.412	0.381	-0.037	0.141
rs4391122	A	G	-0.078	0.011	-0.524	0.299	-0.345	0.285	0.011	0.107
rs4523957	T	G	0.070	0.012	-0.868	0.316	-0.622	0.298	0.126	0.111
rs4648845	T	C	0.067	0.012	0.723	0.309	0.712	0.288	-0.071	0.114
rs4702	A	G	-0.081	0.012	-0.290	0.297	-0.292	0.279	-0.056	0.104
rs4766428	T	C	0.069	0.011	0.727	0.314	0.440	0.300	0.026	0.111
rs55661361	A	G	-0.079	0.012	0.159	0.313	0.205	0.293	0.007	0.110
rs55833108	T	G	0.074	0.014	-0.100	0.352	-0.161	0.334	0.112	0.120

rs56205728	A	G	0.066	0.013	0.948	0.376	0.728	0.354	0.050	0.126
rs56873913	T	G	0.066	0.013	-0.075	0.351	0.157	0.330	-0.011	0.122
rs59979824	A	C	-0.071	0.012	0.227	0.323	0.255	0.302	-0.063	0.112
rs6002655	T	C	0.069	0.011	0.080	0.314	0.177	0.296	-0.023	0.109
rs6065094	A	G	-0.075	0.012	0.665	0.305	0.575	0.290	0.180	0.105
rs6434928	A	G	-0.079	0.012	0.100	0.311	-0.021	0.295	0.078	0.111
rs6461049	T	C	0.080	0.011	0.026	0.304	0.028	0.286	-0.085	0.106
rs6466055	A	C	0.069	0.011	0.328	0.305	0.476	0.288	0.228	0.106
rs6670165	T	C	0.074	0.014	0.837	0.365	0.632	0.349	-0.086	0.132
rs6704641	A	G	0.075	0.015	-0.693	0.393	-0.560	0.372	-0.039	0.135
rs6704768	A	G	-0.077	0.011	-0.125	0.295	-0.225	0.276	0.096	0.103
rs679087	A	C	-0.064	0.012	0.159	0.311	0.079	0.296	-0.105	0.110
rs6984242	A	G	-0.062	0.011	0.134	0.297	0.026	0.280	0.035	0.104
rs715170	T	C	-0.067	0.012	-0.293	0.329	-0.321	0.310	-0.072	0.119
rs7267348	T	C	-0.066	0.013	-0.330	0.338	0.110	0.316	0.047	0.116
rs72934570	T	C	-0.145	0.021	-0.194	0.521	-0.515	0.496	-0.123	0.185
rs73229090	A	C	-0.100	0.018	-0.352	0.454	-0.426	0.426	-0.151	0.162
rs7405404	T	C	0.077	0.013	0.774	0.349	0.559	0.329	0.013	0.121
rs7432375	A	G	-0.071	0.011	-0.042	0.299	-0.109	0.281	-0.191	0.109
rs75059851	A	G	0.091	0.014	-0.618	0.376	-0.397	0.354	0.061	0.135
rs7523273	A	G	0.060	0.012	-0.095	0.307	-0.290	0.291	-0.086	0.105
rs75575209	A	T	-0.112	0.019	-0.706	0.519	-0.584	0.487	-0.452	0.161
rs75968099	T	C	0.080	0.011	-0.044	0.309	0.154	0.291	0.032	0.106
rs7730110	T	C	-0.059	0.011	-0.519	0.310	-0.349	0.293	-0.286	0.105
rs77502336	C	G	0.062	0.012	-0.036	0.319	-0.226	0.301	-0.139	0.111
rs7801375	A	G	-0.083	0.015	0.733	0.395	0.384	0.376	0.211	0.132
rs7819570	T	G	0.076	0.014	-0.007	0.402	0.425	0.379	0.077	0.143

rs78322266	T	G	0.177	0.031	-0.790	0.921	-0.927	0.870	-0.127	0.342
rs7893279	T	G	0.112	0.018	0.370	0.448	0.665	0.424	-0.114	0.149
rs7907645	T	G	0.144	0.022	0.400	0.637	-0.332	0.609	0.095	0.235
rs79212538	T	G	0.141	0.026	0.124	0.788	-0.140	0.729	0.126	0.251
rs8042374	A	G	0.090	0.013	0.335	0.342	0.399	0.320	-0.147	0.116
rs8044995	A	G	0.077	0.014	0.187	0.387	-0.045	0.365	-0.304	0.148
rs8082590	A	G	-0.066	0.012	-0.803	0.318	-0.670	0.298	-0.166	0.109
rs832187	T	C	-0.070	0.011	-0.439	0.303	-0.200	0.287	0.090	0.106
rs9420	A	G	0.058	0.011	0.237	0.310	0.340	0.292	-0.076	0.111
rs950169	T	C	-0.079	0.012	-0.259	0.335	-0.261	0.312	0.113	0.114
rs9607782	A	T	0.089	0.013	0.476	0.340	0.577	0.322	0.169	0.117
rs9636107	A	G	-0.080	0.011	0.043	0.291	0.091	0.276	-0.056	0.103
rs9841616	A	T	-0.074	0.015	-0.126	0.394	-0.041	0.371	0.142	0.134
rs9922678	A	G	0.068	0.012	-0.435	0.324	-0.088	0.306	-0.190	0.117

[a] Schizophrenia genetic data from the PGC GWAS; [b] Number of sexual partners data from ALSPAC G1; [c] Number of sexual partners with 21-year data from ALSPAC G1; [d] Had child data from ALSPAC G1.

Appendix 18 *Estimates for associations between genetic scores with varying p-value thresholds and whether participants had ever smoked.*

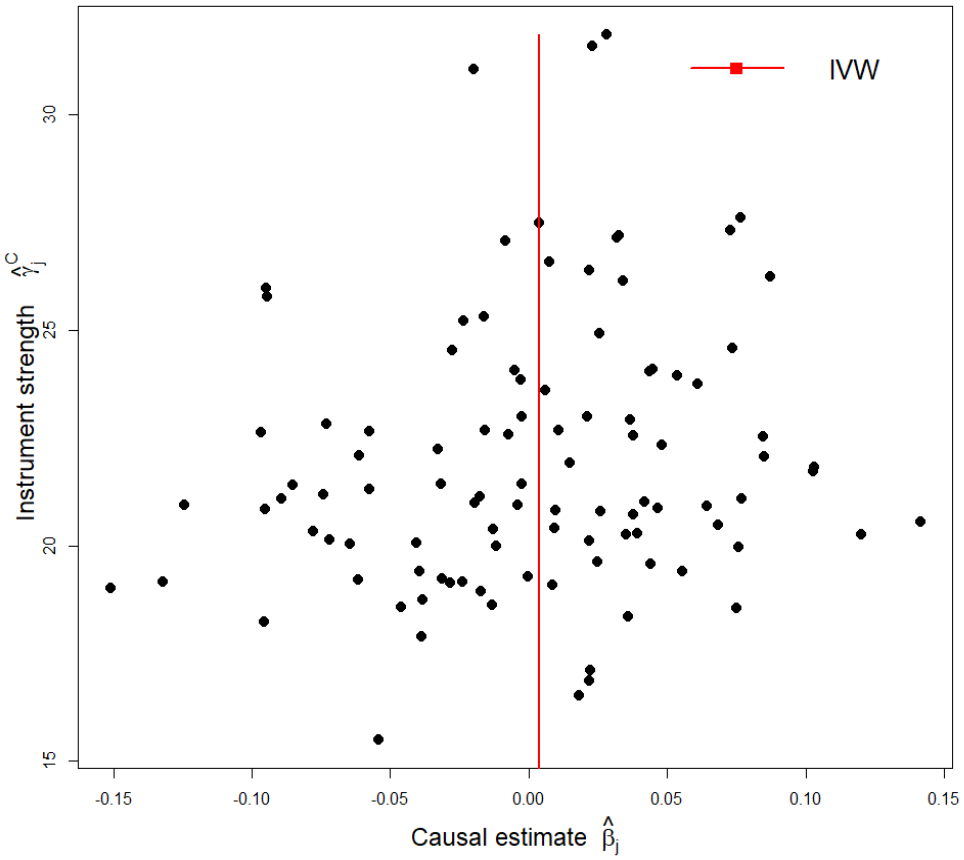
	UK Biobank (N = 335 957)	**ALSPAC G0 (N = 7188)**	**MoBa (N = 9360)**	**ALSPAC G1 (N = 2760)**
Genetic score for schizophrenia liability	**OR (95% CI), *p***			
Plink score				
$p<5\times10^{-8}$	1.002 (1.001, 1.003), 0.002	1.004 (0.958, 1.051), 0.87	1.011 (0.971, 1.053), 0.60	1.076 (0.995, 1.164), 0.07
PRSice score				
$p<1\times10^{-5}$	-	1.061 (1.013, 1.111), 0.01	1.025 (0.984, 1.068), 0.24	-
$p<0.0005$	-	1.069 (1.021, 1.120), 0.005	1.048 (1.006, 1.092), 0.03	-
$p<0.005$	-	1.086 (1.037, 1.137), 0.001	1.059 (1.015, 1.104), 0.01	-
$p<0.05$	-	1.107 (1.056, 1.159), <0.001	1.084 (1.039, 1.131), <0.001	-
$p<0.1$	-	1.106 (1.056, 1.159), <0.001	1.100 (1.053, 1.15), <0.001	-
$p<0.5$	-	1.113 (1.062, 1.166), <0.001	1.097 (1.05, 1.146), <0.001	-
$p<1$	-	1.104 (1.054, 1.157), <0.001	1.098 (1.05, 1.148), <0.001	-

Appendix 19 *Genetic correlations of genetic liability for schizophrenia and number of children, age at first birth and number of sexual partners using LD score regression with outcome summary statistics also adjusted for genotype array (UK Biobank analyses).*

	No. of children[a]			**Age at first birth[b]**			**Number of sexual partners[c]**		
	r_g	**SE**	***p***	**r_g**	**SE**	***p***	**r_g**	**SE**	***p***
Genetic liability for schizophrenia[d]	0.002	0.01	0.84	-0.007	0.01	0.44	0.007	0.01	0.43

[a] Number of children data from UK Biobank (N = 333,628); [b] Age at first birth data from UK Biobank (N = 123 310); [c] Number of sexual partners data from UK Biobank (N = 273 970); [d] Schizophrenia data from the PGC GWAS (N= 35 123 cases and 109 657 controls).

Appendix 20 *Funnel plot for Cochran's Q values for genetic liability for schizophrenia in UK Biobank. Here shown with number of children as an outcome for illustration.*



Appendix 21 *Estimates of the causal effect of genetic liability for schizophrenia on outcomes using IVW, MBE and weighted median MR methods with cases of schizophrenia removed (UK Biobank analyses).*

	No. of children[b]	**Age at first birth[c]**	**Number of sexual partners[d]**
Method (101 SNPs[a)])	**β (95% CI), *p***		
IVW	0.003 (-0.003, 0.009), 0.33	-0.004 (-0.043, 0.035), 0.83	0.166 (0.118, 0.213), <0.001
Weighted Median	0.006 (-0.004, 0.016), 0.23	0.027 (-0.036, 0.090), 0.41	0.179 (0.099, 0.258), <0.001
MBE	0.021 (-0.011, 0.053), 0.21	0.063 (-0.169, 0.295), 0.60	0.261 (-0.024. 0.546), 0.08

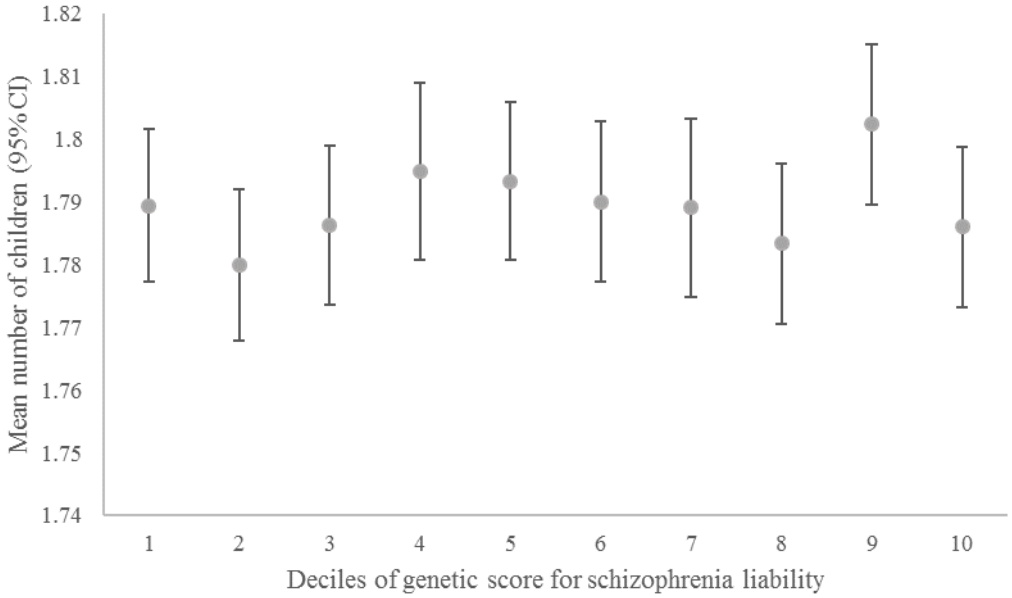
[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Number of children data from UK Biobank (N = 318 735 - 335 562). [c] Age at first birth data from UK Biobank (N = 117 822 - 124 069). [d] Number of sexual partners data from UK Biobank (N = 261 931 - 275 586).

Appendix 22 *Estimates of the causal effect of genetic liability for schizophrenia on outcomes using IVW, MBE and weighted median MR methods with outcome summary statistics also adjusted for genotype array (UK Biobank analyses).*

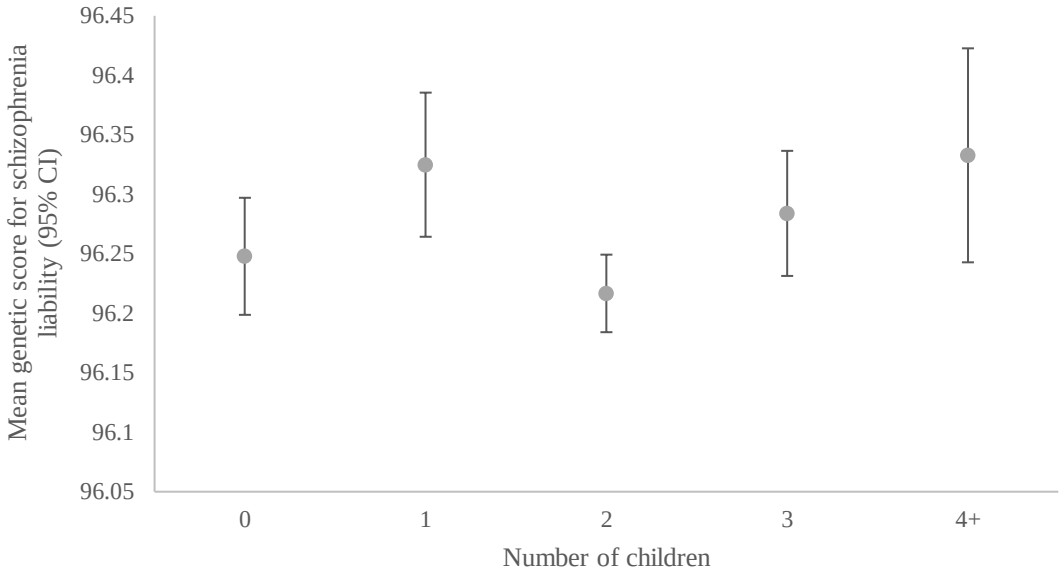
	No. of children[b]	**Age at first birth[c]**	**Number of sexual partners[d]**	**Childlessness[e]**	**Highest number of sexual partners[f]**
Method (101 SNPs[a)]	**β (95% CI), *p***			**OR (95% CI), *p***	
IVW	0.003 (-0.003, 0.009), 0.39	-0.004 (-0.043, 0.035), 0.84	0.165 (0.117, 0.212), <0.001	0.998 (0.985, 1.012), 0.79	1.057 (1.038, 1.077), <0.001
Weighted Median	0.006 (-0.003, 0.015), 0.22	0.018 (-0.047, 0.083), 0.59	0.171 (0.091, 0.250), <0.001	0.996 (0.975, 1.017), 0.68	1.035 (1.003, 1.068), 0.04
MBE	0.020 (-0.011, 0.052), 0.21	0.050 (-0.175, 0.275), 0.66	0.385 (-0.034. 0.805), 0.08	0.993 (0.924, 1.068), 0.85	1.011 (0.884, 1.155), 0.88

[a] Schizophrenia genetic data from the PGC GWAS (N= 35 123 cases and 109 657 controls); [b] Number of children data from UK Biobank (N = 318 921 – 335 758). [c] Age at first birth data from UK Biobank (N = 117 844 – 124 093). [d] Number of sexual partners data from UK Biobank (N = 261 931- 275 700); [e] Childlessness data from UK Biobank (N = 318 921 – 335 758); [f] Highest number of sexual partners data from UK Biobank (N = 261 931- 275 700).

Appendix 23 *Genetic score for schizophrenia liability (in deciles) and mean number of children in UK Biobank data.*



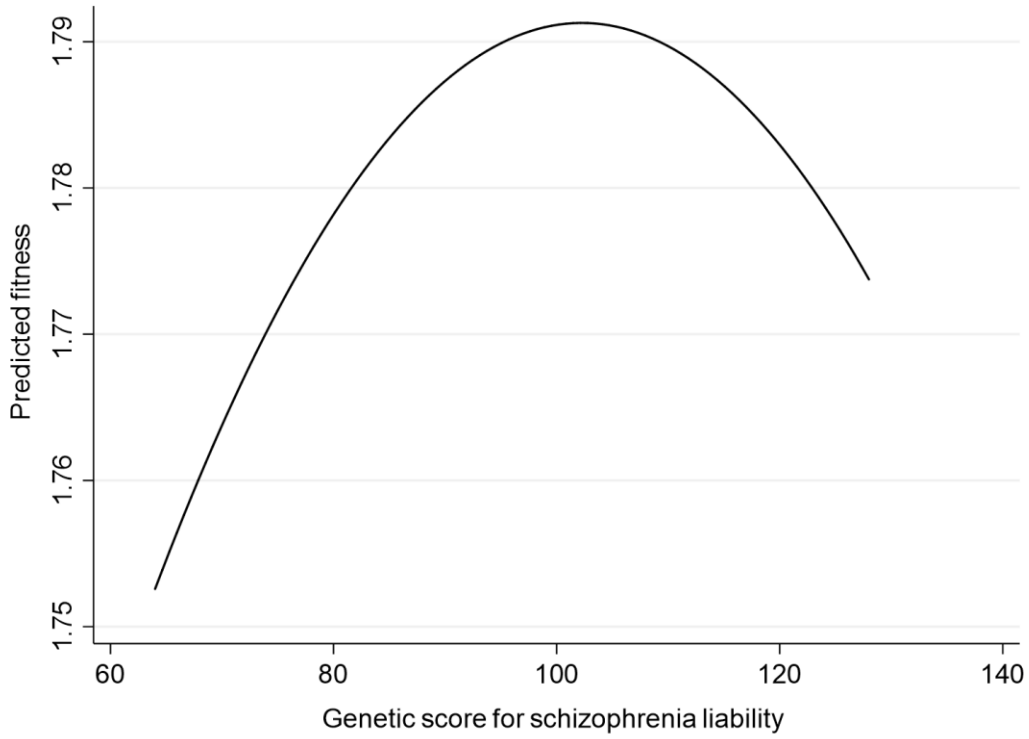
Appendix 24 *Number of children and mean genetic score for schizophrenia liability in UK Biobank data.*



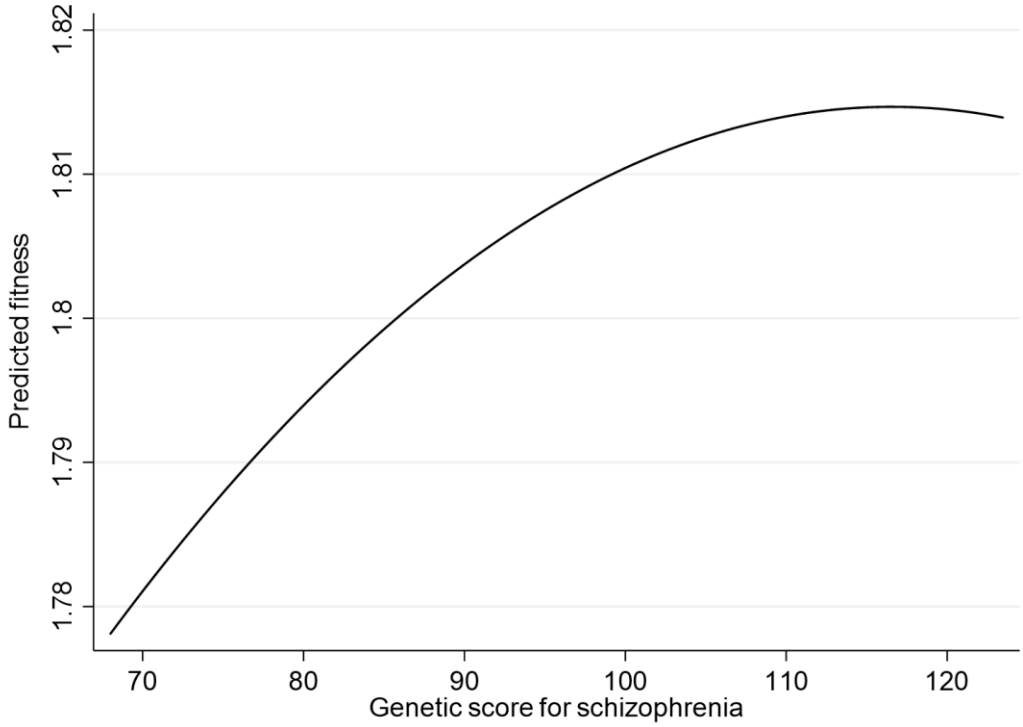
Appendix 25 *Associations of the score for genetic liability for schizophrenia and outcomes removing cumulative deciles of the score, with cases of schizophrenia removed in UK Biobank data.*

	Number of children	**Age at first birth**	**Number of sexual partners**
Schizophrenia genetic score		**β (95% CI), *p***	
Highest 10% removed	0.0005 (-0.0002, 0.0013), 0.18 N = 302 011	-0.004 (-0.008, 0.001), 0.15 N = 111 599	0.011 (0.005, 0.017), <0.001 N = 248 143
Highest 20% removed	0.0002 (-0.0007, 0.0011), 0.69 N = 268 439	-0.005 (-0.010, 0.001), 0.15 N = 99 106	0.012 (0.005, 0.019), <0.001 N = 220 745
Highest 30% removed	0.0005 (-0.0006, 0.0016), 0.37 N = 234 886	-0.008 (-0.014, -0.001), 0.03 N = 86 593	0.017 (0.008, 0.025), <0.001 N = 193 259
Highest 40% removed	0.0006 (-0.0006, 0.0019), 0.32 N = 208 339	-0.009 (-0.016, -0.001), 0.02 N = 76 821	0.015 (0.006, 0.025), <0.001 N = 171 511
Highest 50% removed	0.0008 (-0.0006, 0.0023), 0.29 N = 167 780	-0.008 (-0.018, 0.001). 0.08 N = 61 811	0.012 (0.001, 0.024), 0.03 N = 138 230

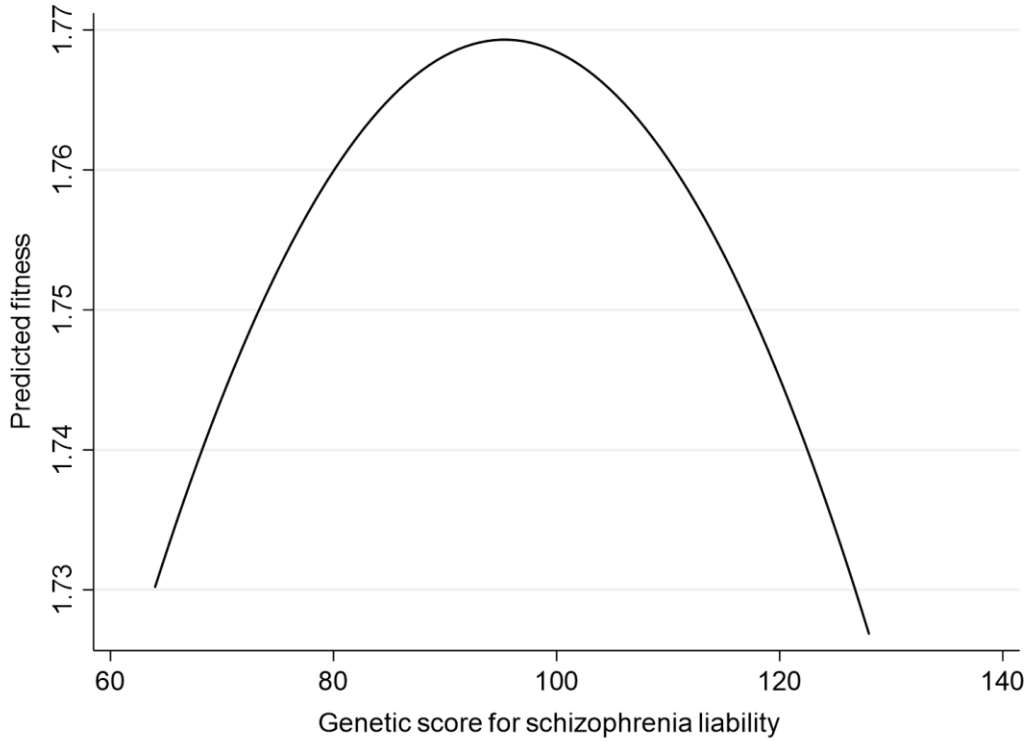
Appendix 26 *Curve for prediction for fitness from a linear regression of a genetic score for schizophrenia liability on number of children and a squared genetic score for schizophrenia liability in both sexes in UK Biobank data.*



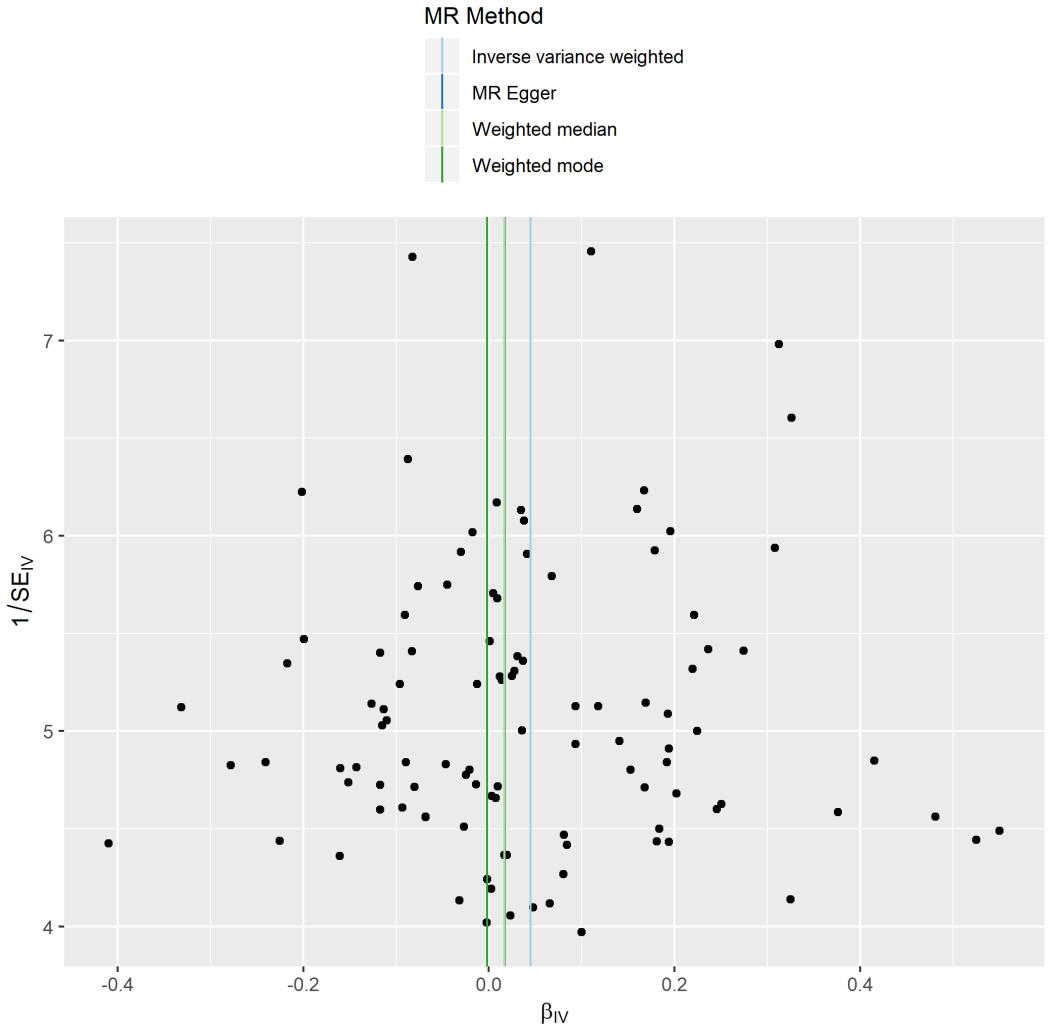
Appendix 27 *Curve for prediction for fitness from a linear regression of a genetic score for schizophrenia liability on number of children and a squared genetic score for schizophrenia liability in females in UK Biobank data.*



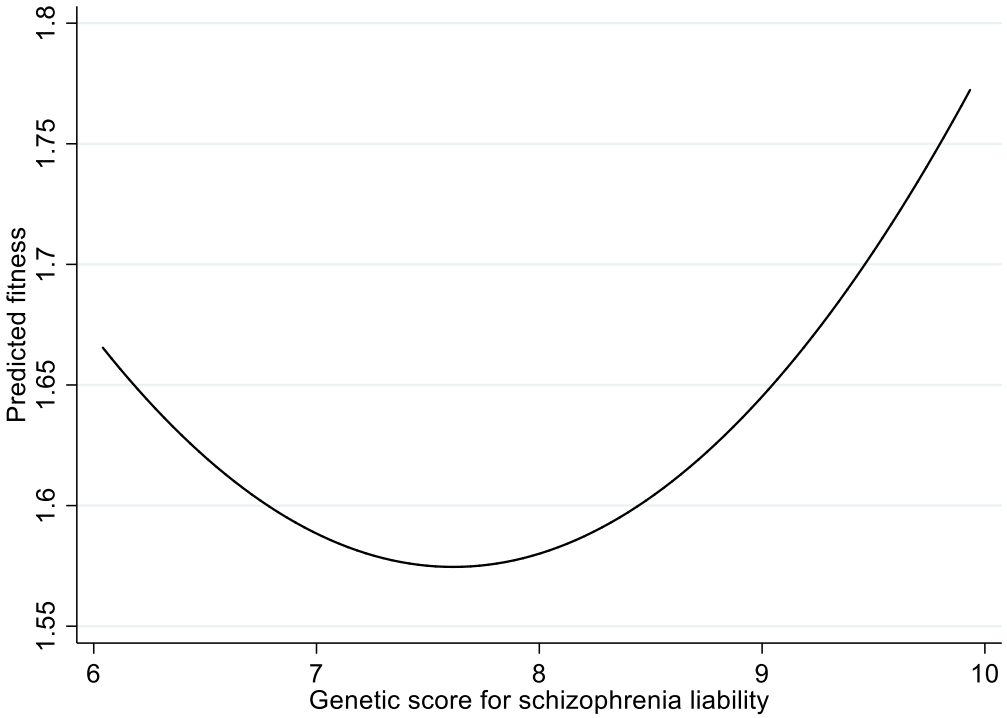
Appendix 28 *Curve for prediction for fitness from a linear regression of a genetic score for schizophrenia liability on number of children and a squared genetic score for schizophrenia liability in males in UK Biobank data.*



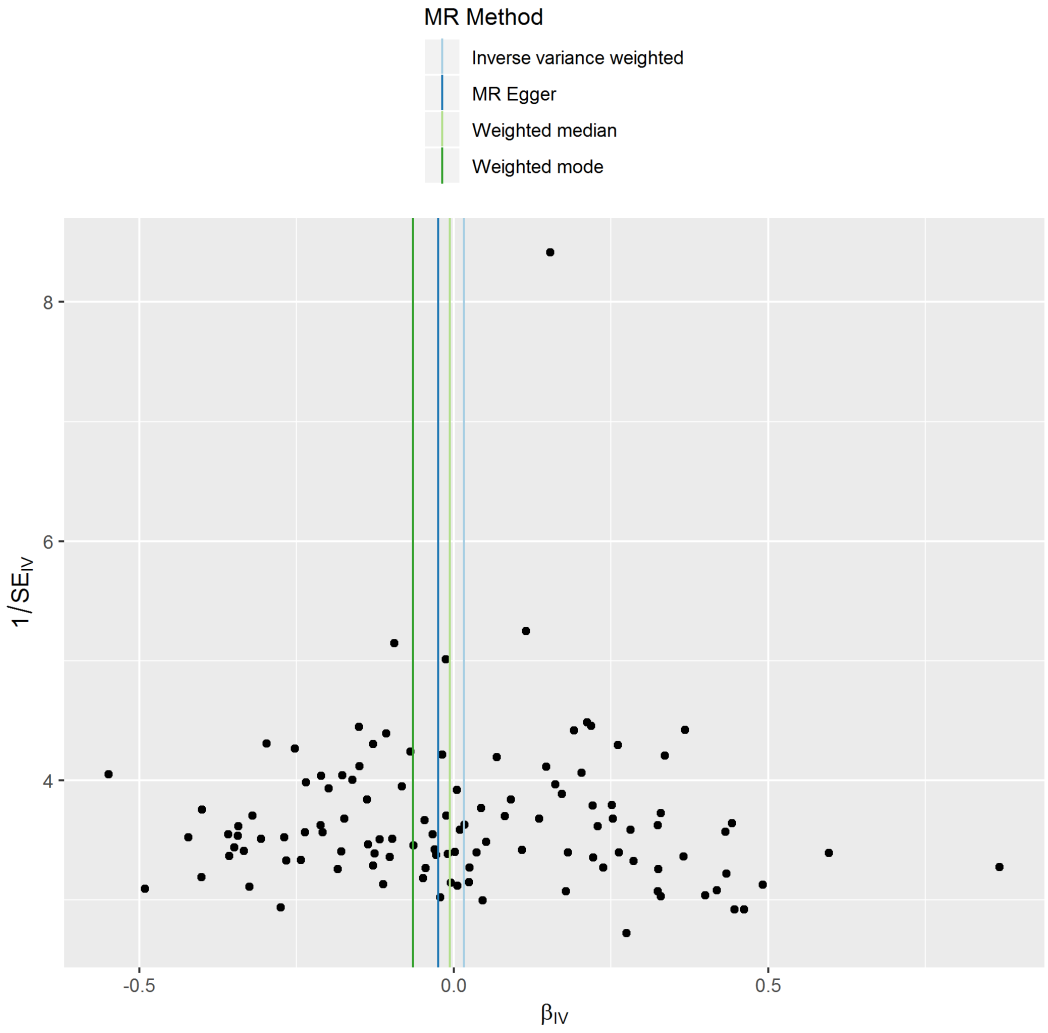
Appendix 29 *Funnel plot for Cochran's Q values for genetic liability for schizophrenia in MoBa. Here shown with parity as an outcome for illustration.*



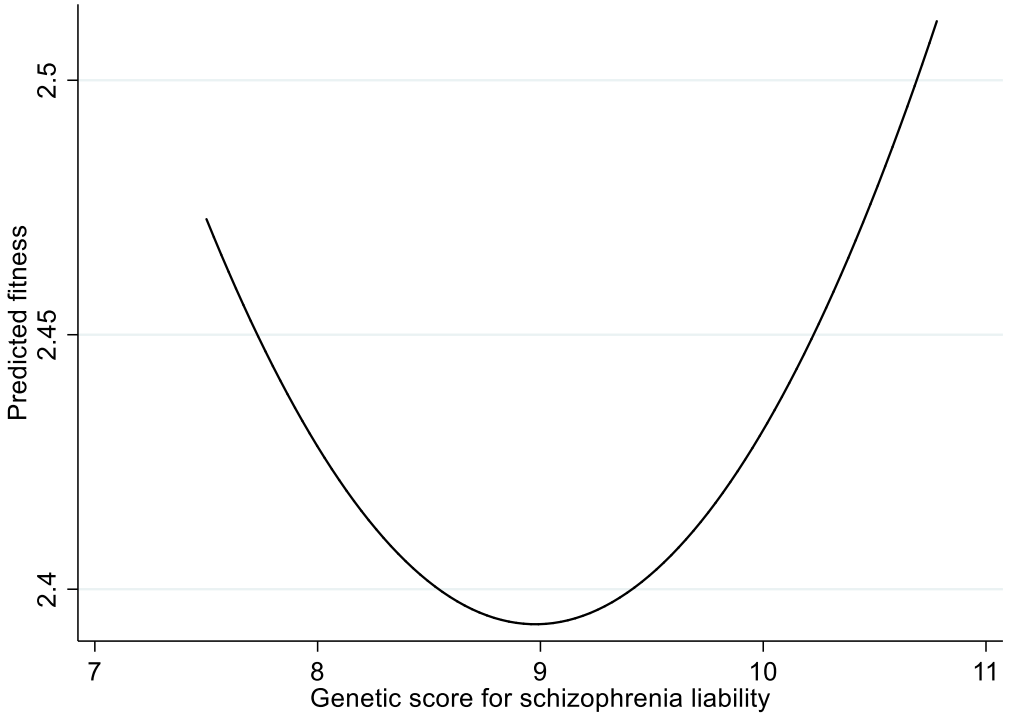
Appendix 30 *Curve for prediction for fitness from a linear regression of a genetic score for schizophrenia liability on parity and a squared genetic score for schizophrenia liability in MoBa data.*



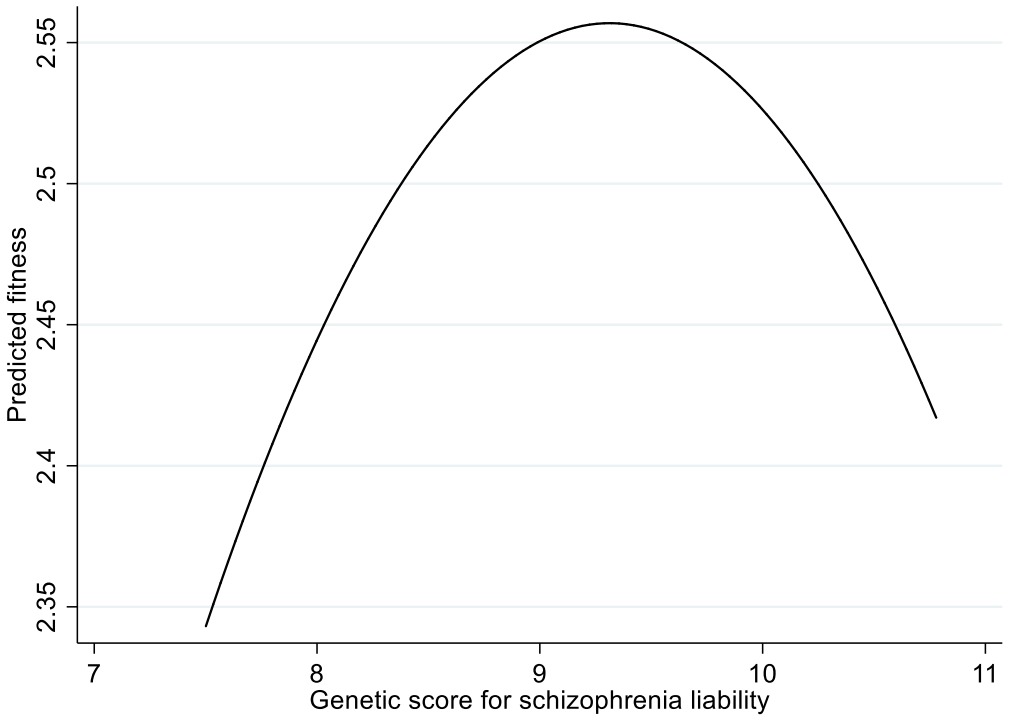
Appendix 31 *Funnel plot for Cochran's Q values for genetic liability for schizophrenia in ALSPAC G0. Here shown with parity at 85 months post index child as an outcome for illustration.*



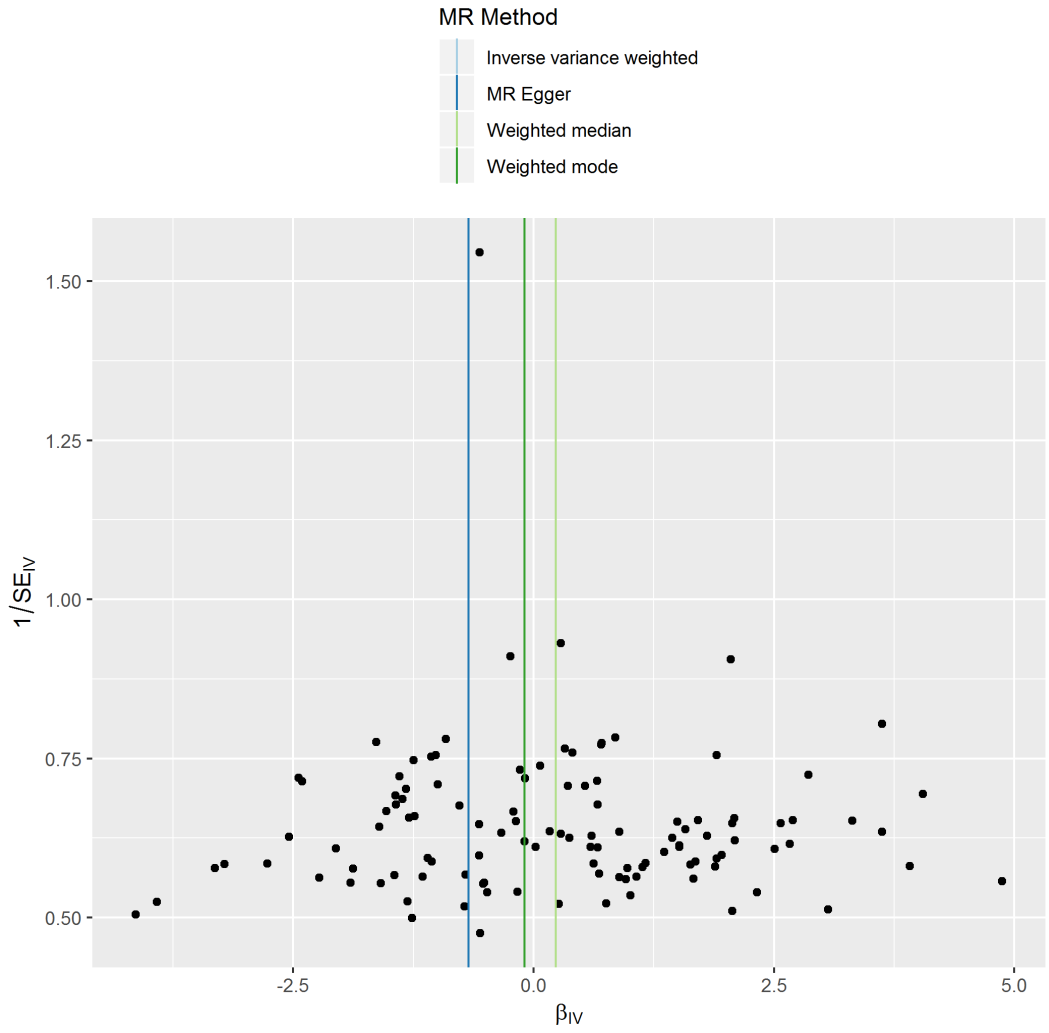
Appendix 32 *Curve for prediction for fitness from a linear regression of a genetic score for schizophrenia liability on parity at 85 months post index child and a squared genetic score for schizophrenia liability in ALSPAC G0 data.*



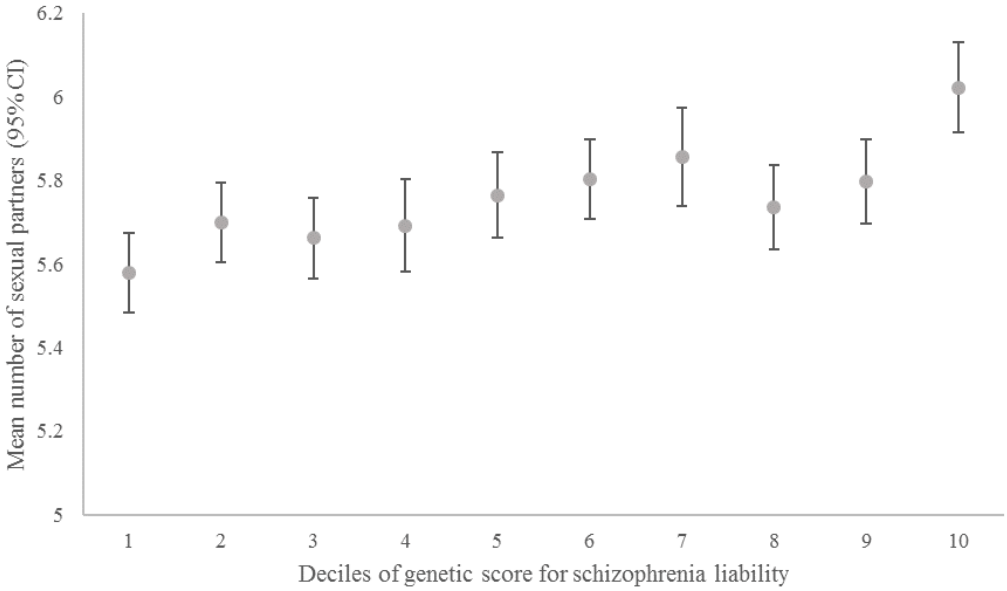
Appendix 33 *Curve for prediction for fitness from a linear regression of a genetic score for schizophrenia liability on parity at 18 years post index child and a squared genetic score for schizophrenia liability in ALSPAC G0 data.*



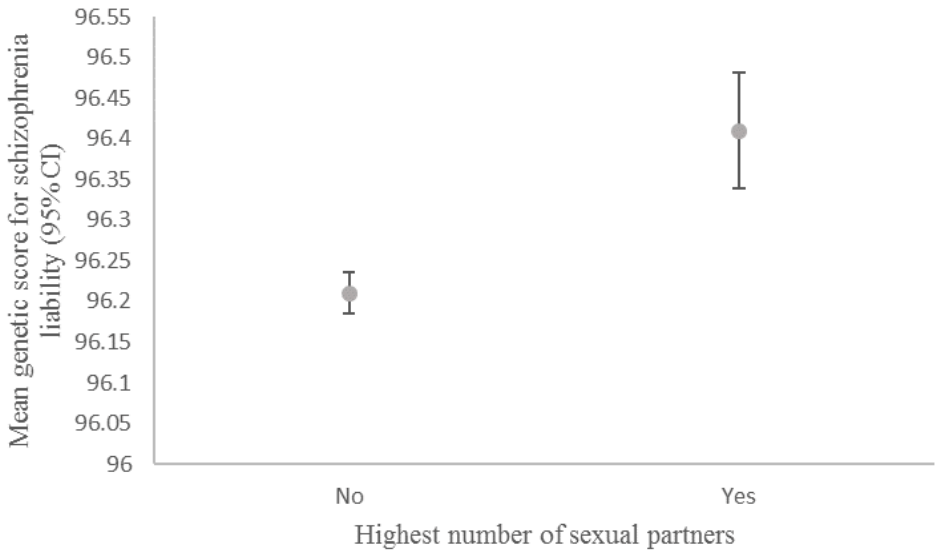
Appendix 34 *Funnel plot for Cochran's Q values for genetic liability for schizophrenia in ALSPAC G1. Here shown with whether participants had had a child as an outcome for illustration.*



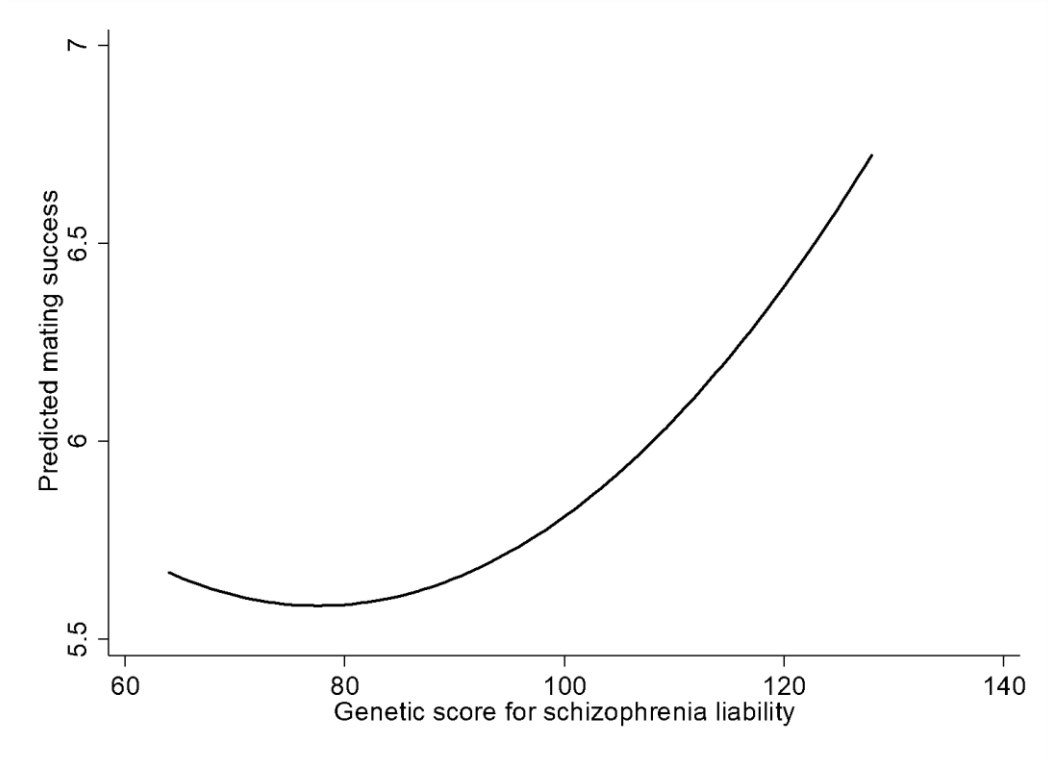
Appendix 35 *Genetic score for schizophrenia liability (in deciles) and mean number of sexual partners in UK Biobank data.*



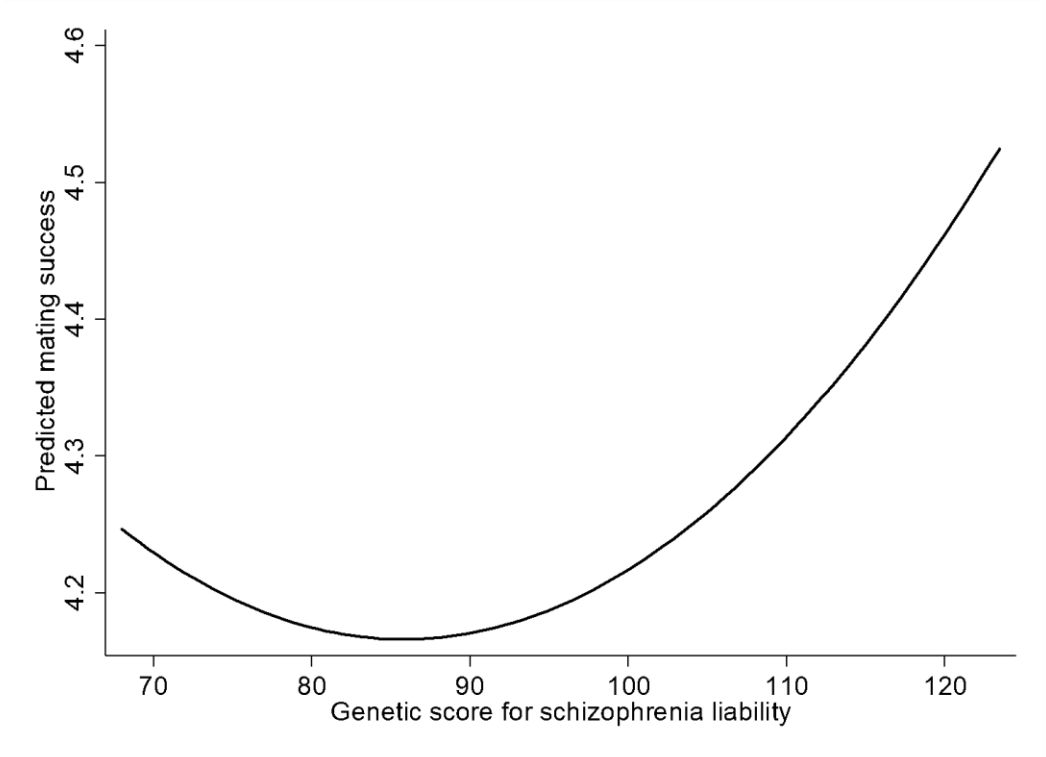
Appendix 36 *Whether individuals had the highest number of sexual partners and mean genetic score for schizophrenia liability in UK Biobank data.*



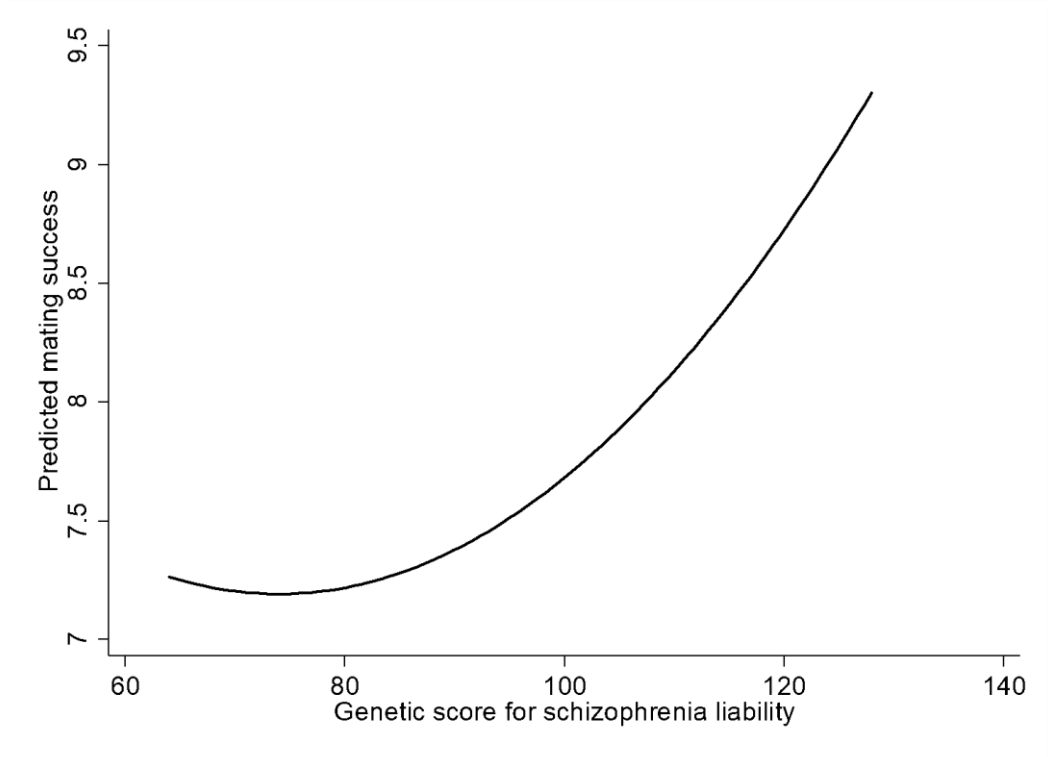
Appendix 37 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners and a squared genetic score for schizophrenia liability in both sexes in UK Biobank data.*



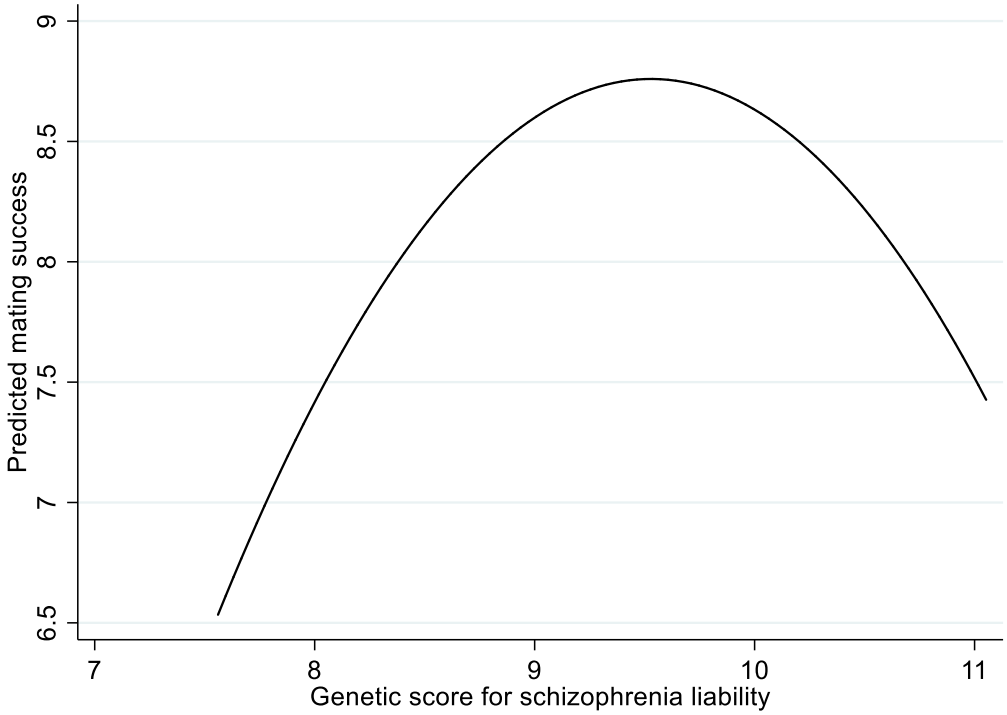
Appendix 38 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners and a squared genetic score for schizophrenia liability in females in UK Biobank data.*



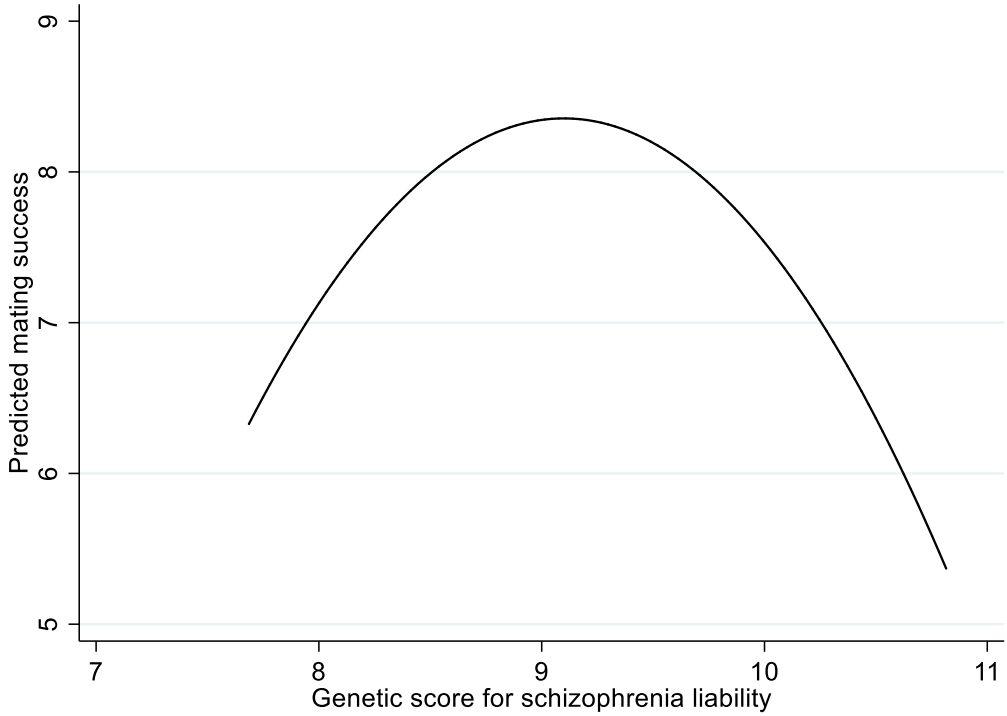
Appendix 39 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners and a squared genetic score for schizophrenia liability in males in UK Biobank data.*



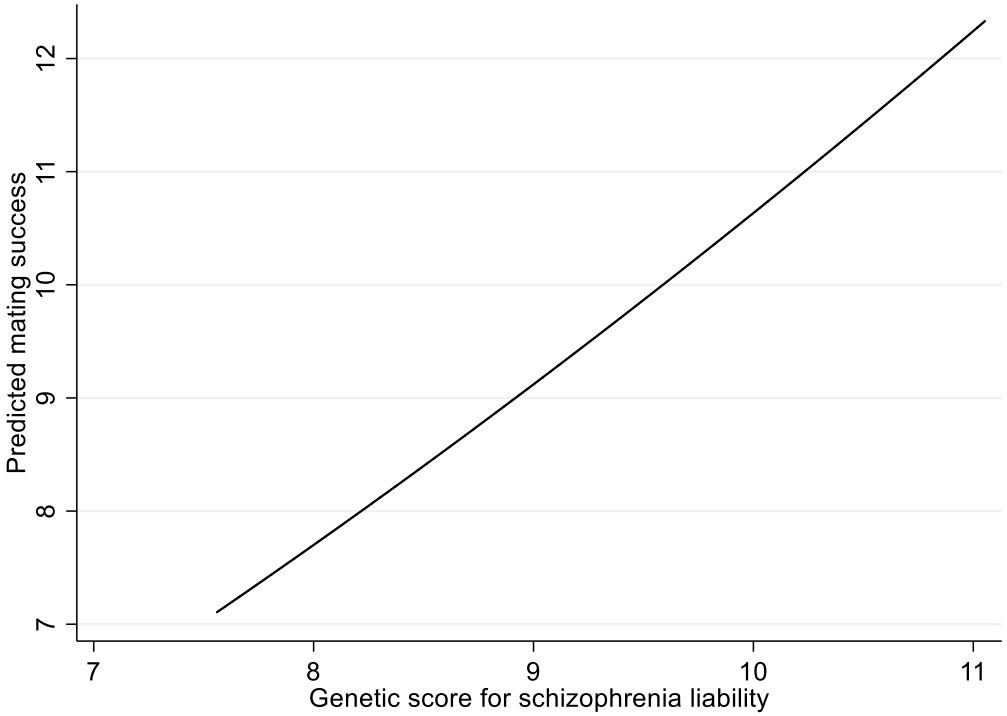
Appendix 40 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners and a squared genetic score for schizophrenia liability in ALSPAC G1 data.*



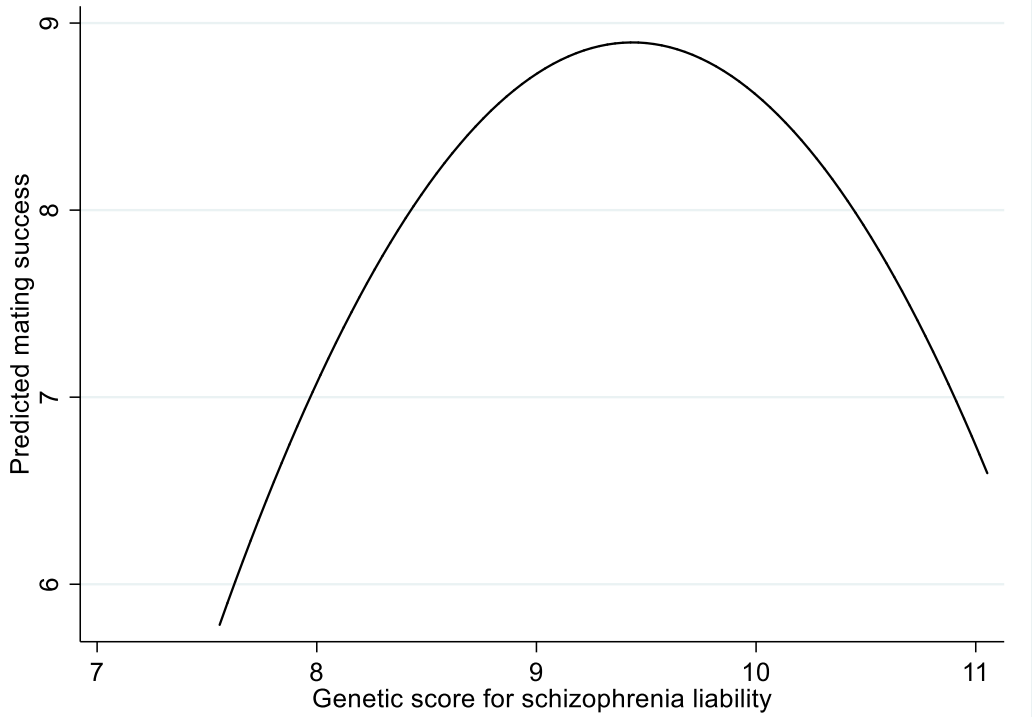
Appendix 41 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners and a squared genetic score for schizophrenia liability in females in ALSPAC G1 data.*



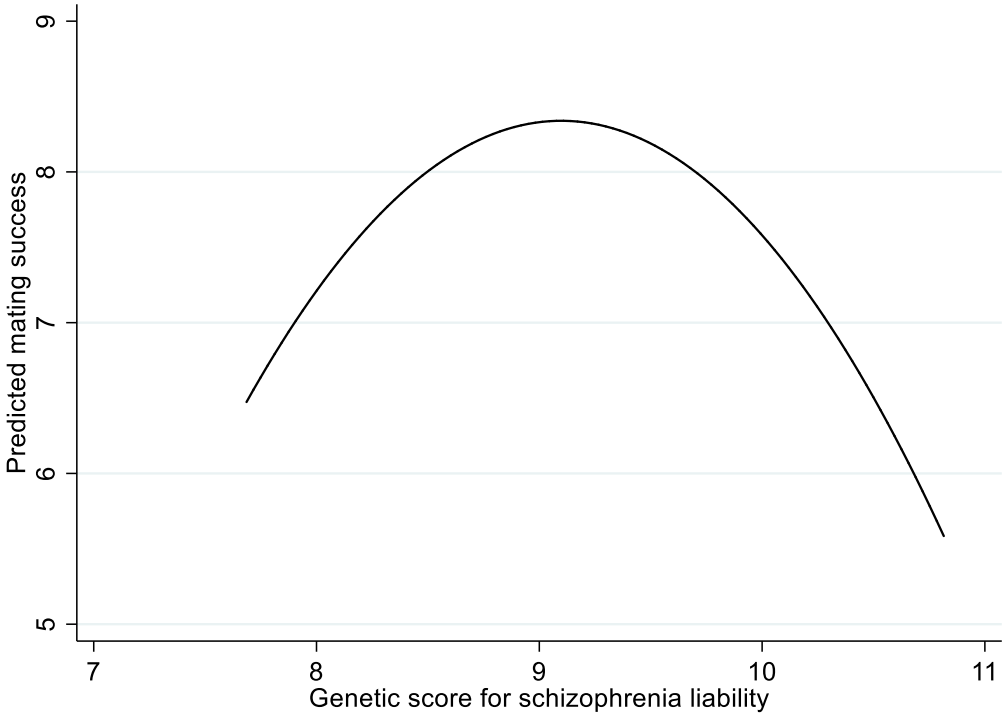
Appendix 42 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners and a squared genetic score for schizophrenia liability in males in ALSPAC G1 data.*



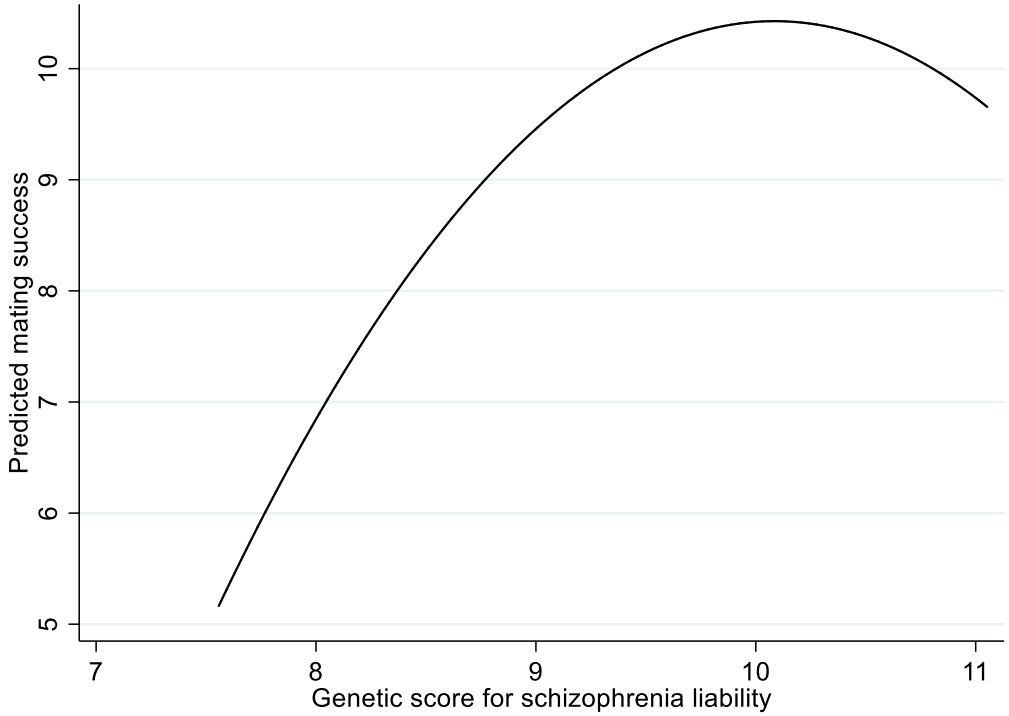
Appendix 43 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners (plus 21-year data) and a squared genetic score for schizophrenia liability in ALSPAC G1 data.*



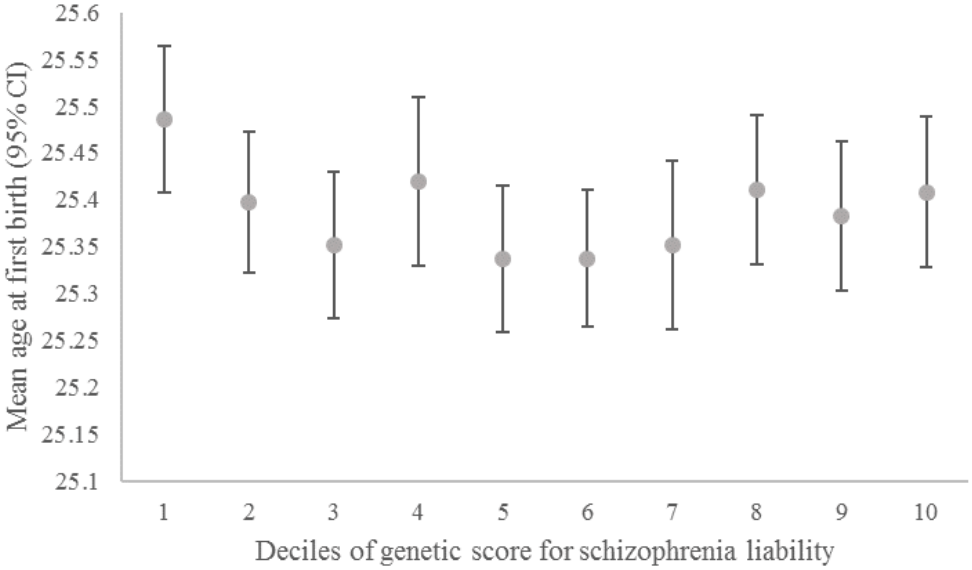
Appendix 44 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners (plus 21-year data) and a squared genetic score for schizophrenia liability in females in ALSPAC G1 data.*



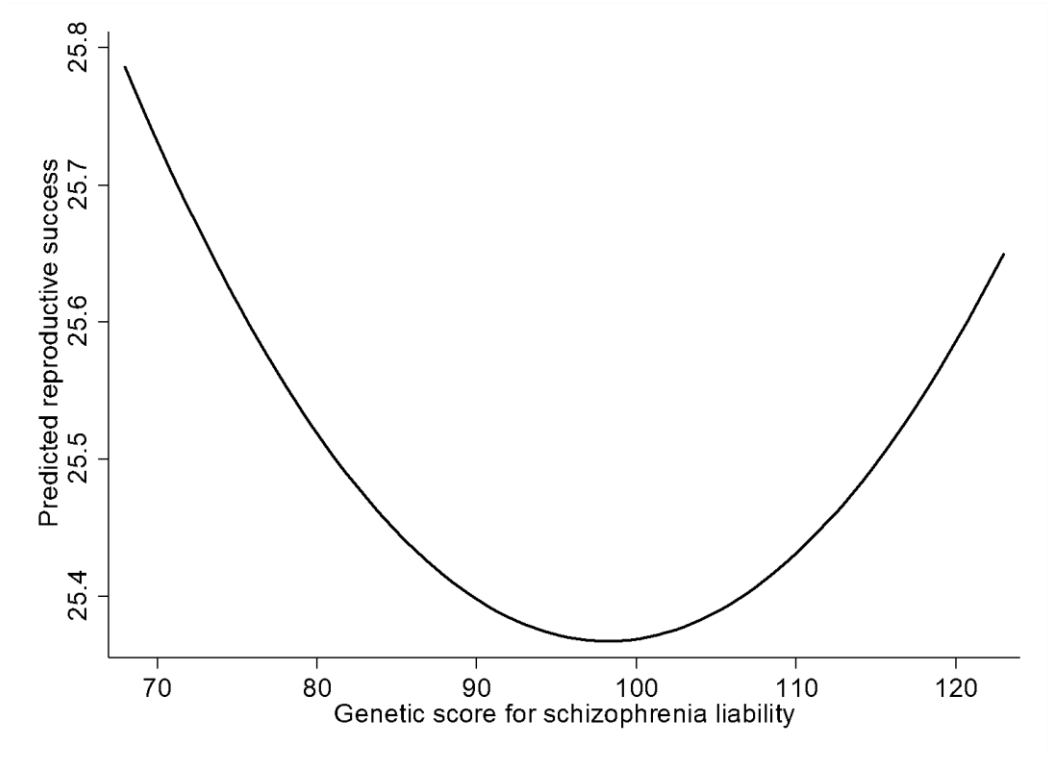
Appendix 45 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on number of sexual partners (plus 21-year data) and a squared genetic score for schizophrenia liability in males in ALSPAC G1 data.*



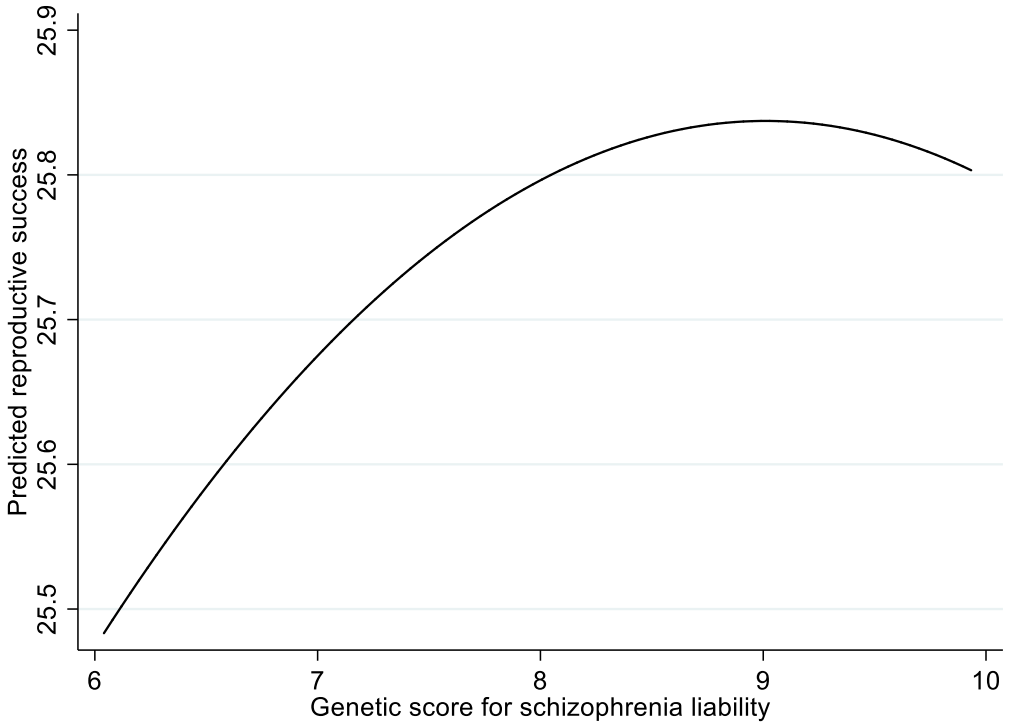
Appendix 46 *Genetic score for schizophrenia liability (in deciles) and mean age at first birth in women from UK Biobank data.*



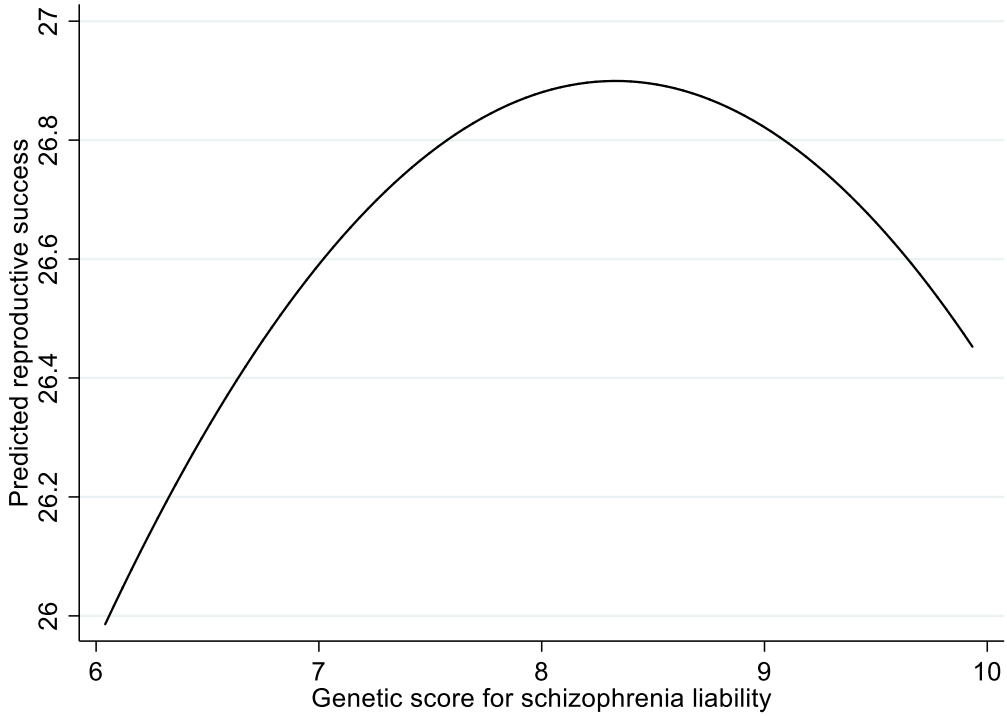
Appendix 47 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on age at first birth and a squared genetic score for schizophrenia liability in females in UK Biobank data.*



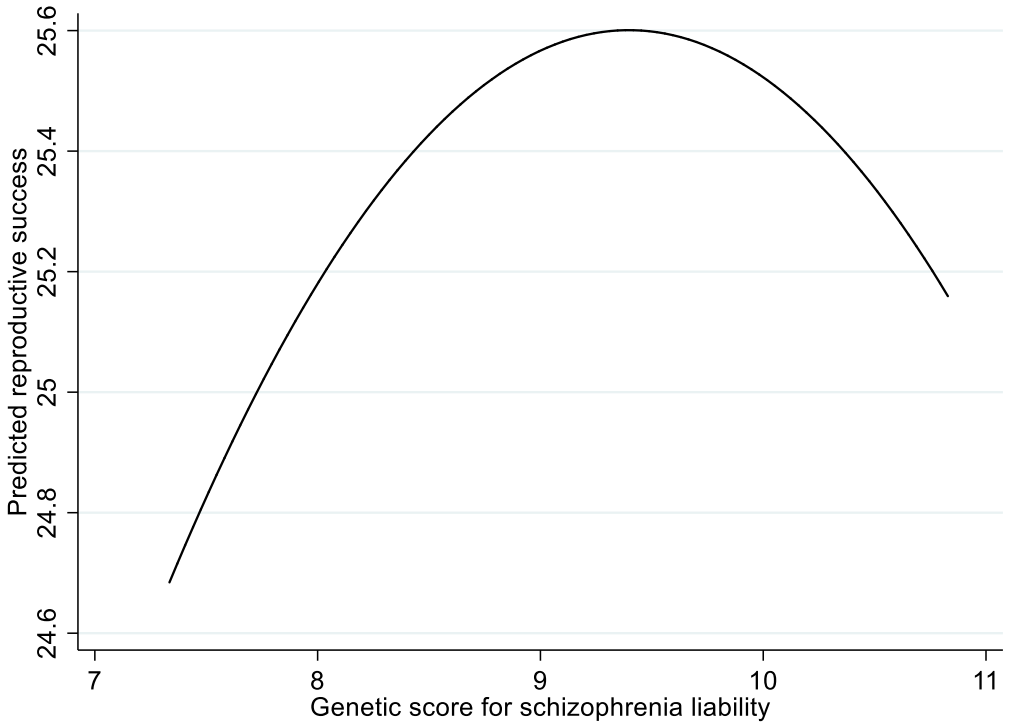
Appendix 48 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on age at first pregnancy and a squared genetic score for schizophrenia liability in MoBa data.*



Appendix 49 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on age at first birth and a squared genetic score for schizophrenia liability in MoBa data.*



Appendix 50 *Curve for prediction from a linear regression of a genetic score for schizophrenia liability on age at first pregnancy and a squared genetic score for schizophrenia liability in ALSPAC G0 data.*



Appendix 51 *Analyses using publicly available GWAS outcome data.*

Genetic liability for schizophrenia

I used MR analyses of summary level results from GWAS to assess causal associations between genetic liability for schizophrenia and number of children. Here, I used SNPs associated with schizophrenia ($p<5\times10^{-8}$) from the PGC GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and extracted the SNPs, or available proxy SNPs for them, from the SSGAC meta-analysis GWAS for number ever born (i.e., number of children) in combined sexes (N= 279 161 to 343 033) (Barban et al., 2016). This analysis used GWAS estimates that were not restricted to the European sample for schizophrenia. Seventy-four SNPs were not available in the number of children data. Of these, I found proxies for 48 unavailable SNPs, using a LD r^2 of 0.8 or above, through SNiPA or proxies used previously (Arnold et al., 2015; Gage et al., 2017). Where palindromic SNPs were used, the MAF was checked to ensure there were no issues with strand mismatches. There were no palindromic SNPs with MAF around 0.5. The final 102 SNPs and effect sizes for the schizophrenia risk and number of children analysis are listed in **Appendix 52**. These associations for SNP-number of children were recorded, taking the standardized beta coefficients and the corresponding SEs. The SEs for number of children were based on MAF and phenotypic variance (Barban et al., 2016). Data were harmonized to ensure that effect of SNP on the exposure and the SNP on the outcome corresponded to the same allele. SNP-exposure and SNP-outcome data were combined using an IVW, MBE and weighted median regression to give causal estimates.

Results

There was some evidence that higher genetic liability for schizophrenia increased number of children (mean difference: 0.008 SD increase in number of children per doubling in the natural log OR of schizophrenia liability, 95% CI: 0.001 to 0.015) using an IVW approach. The Cochran's Q for this analysis was 160.36 ($p<0.001$). Weighted median estimates were consistent with the main findings. An MBE approach showed no effect of risk of schizophrenia on number of children, although again estimates were in the direction of a reproductive advantage (see **Appendix 53**). It must be noted that the I^2_{GX} statistic for an unweighted MR-Egger regression in schizophrenia risk and number of children analysis was 0.2 and MR-Egger regression could not be conducted (Bowden, Fabiola Del Greco, et al., 2016). The mean F statistic for MR-Egger regression of schizophrenia risk and number of children was 36.13.

Appendix 52 *List of SNPs associated with schizophrenia ($p<5\times10^{-8}$) and proxies where used for GWAS summary data outcome analysis.*

SNP	Original SNP if proxy used	r^2 for proxy	Schizophrenia		Number of children	
			β	SE	β	SE
rs1009080	rs1498232	0.99	-0.069	0.012	0.006	0.004
rs1023500			0.074	0.014	0.000	0.004
rs10503253			0.071	0.013	-0.006	0.004
rs10504857	rs7819570	1.00	-0.075	0.014	0.003	0.005
rs10520163			0.061	0.011	0.000	0.003
rs10779702	chr1_8424984_D	0.97	0.064	0.011	0.002	0.004
rs10791097			0.074	0.011	0.007	0.003
rs10803138			-0.071	0.013	0.002	0.004
rs10860964			0.059	0.011	-0.001	0.004
rs10900851	rs10043984	0.99	-0.067	0.012	0.002	0.004
rs10933068	rs11685299	1.00	-0.062	0.011	-0.007	0.004
rs11027857			0.063	0.011	0.007	0.003
rs1106568			-0.069	0.012	-0.010	0.004
rs11139497			0.068	0.012	-0.008	0.004
rs11210892			-0.070	0.011	-0.006	0.004
rs1160682	rs12129573	1.00	-0.069	0.011	-0.005	0.004
rs11632947	rs12903146	0.99	0.065	0.011	0.004	0.003
rs11682175			-0.074	0.011	0.000	0.003
rs11683083	chr2_146436222_I	1.00	-0.079	0.014	0.004	0.005
rs12063329	rs140505938	1.00	0.088	0.015	-0.004	0.005
rs12148337			0.057	0.011	0.000	0.003
rs12325245			-0.087	0.015	-0.001	0.005
rs12421382			-0.059	0.011	0.000	0.004
rs12522290			0.082	0.015	0.009	0.005
rs12619354	rs59979824	0.87	0.056	0.011	-0.001	0.004
rs12654855	rs79212538	0.95	-0.112	0.024	-0.020	0.008
rs12659129	chr5_140143664_I	1.00	0.052	0.011	0.003	0.003
rs12716972	rs12691307	0.98	0.062	0.011	-0.002	0.003
rs13074054	chr3_180594593_I	0.99	0.081	0.013	0.004	0.004
rs13107325	rs35518360	0.85	0.152	0.022	0.004	0.007
rs1339227			-0.060	0.011	-0.001	0.004
rs1501357			-0.077	0.013	-0.001	0.005
rs16867576			0.096	0.017	-0.009	0.005
rs17049247	rs75575209	0.97	-0.103	0.019	0.009	0.006
rs17149781	chr7_24747494_D	0.91	-0.081	0.017	0.001	0.005

rs17194490			0.097	0.015	-0.006	0.005
rs17273111	rs4330281	1.00	0.057	0.011	-0.004	0.003
rs17594526	rs78322266	1.00	0.169	0.031	0.013	0.010
rs17602354	rs72934570	0.92	0.141	0.021	-0.001	0.006
rs1782810	rs1702294	0.99	0.115	0.014	0.008	0.004
rs2007044			-0.092	0.011	0.004	0.004
rs2053079			-0.073	0.012	-0.003	0.004
rs2057070	rs9607782	0.81	-0.066	0.012	0.002	0.004
rs2068012			-0.069	0.013	0.005	0.004
rs211829			0.055	0.011	0.003	0.004
rs215411			0.065	0.011	-0.009	0.004
rs2239063			0.069	0.012	0.006	0.004
rs2514218			-0.072	0.012	-0.001	0.004
rs2535627			0.070	0.011	0.007	0.003
rs2693698			-0.063	0.011	-0.004	0.004
rs2796275	rs7523273	0.98	0.054	0.012	-0.002	0.004
rs2851447			-0.091	0.012	0.001	0.004
rs2965180	rs2905426	0.97	0.061	0.011	0.000	0.004
rs2973161	rs2973155	0.97	-0.065	0.011	-0.008	0.004
rs324015	rs324017	0.81	-0.064	0.012	0.001	0.004
rs3802924	rs75059851	0.95	0.089	0.013	0.006	0.004
rs3849046			0.063	0.011	0.000	0.003
rs4128242	chr18_52749216_D	1.00	0.070	0.011	-0.001	0.004
rs4129585			0.078	0.011	-0.005	0.003
rs4240748			-0.059	0.011	0.002	0.004
rs436124	rs679087	1.00	0.059	0.011	-0.002	0.004
rs4388249			0.072	0.014	-0.009	0.005
rs4391122			-0.079	0.011	-0.002	0.003
rs4518583	rs3735025	1.00	0.061	0.011	-0.005	0.004
rs4523957			0.068	0.011	-0.004	0.004
rs4648845			0.069	0.012	0.009	0.004
rs4702			-0.078	0.011	-0.002	0.004
rs6065094			-0.074	0.011	-0.002	0.004
rs6461049	chr7_2025096_I	0.93	0.078	0.011	0.003	0.004
rs6466056	rs6466055	1.00	0.066	0.011	0.003	0.004
rs6670165			0.071	0.014	0.004	0.004
rs6704641			0.076	0.014	0.005	0.005
rs6704768			-0.074	0.011	-0.001	0.004
rs7085104	rs11191419	0.99	0.094	0.011	0.003	0.004
rs7140568	rs12887734	1.00	0.083	0.012	0.009	0.004

rs715170			-0.066	0.012	0.002	0.004
rs7267348			-0.064	0.012	0.006	0.004
rs7432375			-0.071	0.011	-0.001	0.004
rs7499750	rs7405404	1.00	0.078	0.013	-0.005	0.004
rs7730110	rs11740474	0.81	-0.057	0.011	-0.003	0.004
rs7801375			-0.083	0.015	-0.001	0.005
rs7815859	rs36068923	1.00	0.084	0.013	-0.001	0.004
rs7893279			0.113	0.017	-0.005	0.005
rs7927176	rs77502336	0.96	-0.064	0.011	0.000	0.004
rs8042374			0.087	0.012	-0.004	0.004
rs8044995			0.078	0.014	-0.005	0.005
rs832187			-0.061	0.011	-0.003	0.004
rs867743	rs6984242	1.00	-0.064	0.011	-0.003	0.004
rs884808	rs14403	0.86	-0.052	0.013	0.002	0.004
rs9420			0.061	0.011	-0.004	0.004
rs950169			-0.079	0.012	-0.009	0.004
rs9636107			-0.076	0.011	-0.010	0.003
rs982256	rs13240464	0.98	0.077	0.011	0.000	0.004
rs9841616			-0.081	0.014	-0.009	0.005
rs9876421	rs75968099	0.93	0.078	0.011	-0.013	0.004
rs9922678			0.067	0.012	0.004	0.004
rs6579959	rs111294930	0.96	-0.064	0.012	0.000	0.004
rs4664442	rs2909457	0.98	0.058	0.011	0.000	0.003
rs2296569	rs55833108	0.83	-0.068	0.014	0.001	0.004
rs10412446	rs56873913	0.97	0.056	0.013	0.001	0.004
rs787983	rs6434928	0.98	-0.072	0.011	-0.012	0.004
rs2955357	rs8082590	1.00	0.064	0.011	0.004	0.004

Appendix 53 *Estimates of the causal effect of genetic liability for schizophrenia on number of children using IVW, MBE and weighted median MR methods in combined sexes.*

Method	**β**	**95% CI**	***p***
Number of children: 102 SNPs			
IVW	0.008	0.001, 0.015	0.03
Weighted median	0.008	-0.003, 0.020	0.14
MBE	0.008	-0.036, 0.051	0.99