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Comorbid alcohol and mental health disorders: A longitudinal analysis of development to young adulthood

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Abstract

Background:

Alcohol is the most widely consumed of the psychoactive substances and was responsible in 2012 for nearly 6% of all global deaths. Disorders of alcohol use are highly comorbid with mental health disorders and create a significant health burden: the two are responsible for 183.9 million DALYs annually. The majority of this burden of disease falls on young adults, and despite the poorer prognosis and more frequent relapse that characterise this condition, information on early life factors associated with its development is limited. Data provided by large scale population studies and reports on clinical samples are valuable but are limited by the lack of prospective measures or cannot be generalised due to sample specificity. Although predictors of alcohol use disorders and mental health disorders have separately been widely studied, their application to comorbidity is not straightforward.

Aims:

This study has three main aims:

1. To describe the prevalence, types and onset of comorbidities of mental health and alcohol use disorders in young Australians;
2. To understand factors from different phases of the life span which may predict the onset of comorbidity or be affected by it, and which may present targets for intervention; and
3. To consider the role of alcohol in the context of illicit substance and mental health comorbidities.

In this context, this research program aims to explore factors which may distinguish comorbidity from its constituent disorders.

Methods:

Data from this study were drawn predominantly from the Mater-University of Queensland Study of Pregnancy (MUSP), a pre-birth linked cohort of mothers and children begun in 1981. The baseline sample of 7223 pregnancies comprising the original cohort was followed for twenty-one years, providing prospective measures of health and related factors for both mother and child. At twenty one years, structured psychiatric interviews of the offspring provided lifetime DSM-IV diagnoses of mental health, alcohol and other substance use disorders. The condition of interest, alcohol and mental health disorders which co-occurred within a 12-month period, was examined in light of important developmental factors ranging from pre-birth to late adolescence, using primarily

multinomial logistic regression analyses. Additional data from the Healthy Neighbourhoods Study were analysed to examine potential markers of early-emerging co-occurring conditions in pre-adolescent students.

Key findings:

Comorbid alcohol and mental health disorders are highly prevalent at young adulthood, occurring in 12% of this representative sample. Indicators of this comorbidity may be detected in children as young as 10-14 years old. A number of factors distinguish the risk of comorbidity from that of single disorders. Socio-economic disadvantage derived from the family of origin contributes significantly to the risk of comorbidity, with risk increasing in a dose-response manner for multiple dimensions of disadvantage. Maternal smoking during pregnancy is also implicated, independent of its socio-economic aspect, as is low mother-child warmth. In pre-adolescent years, co-occurring depressive symptoms and drinking were associated with low school commitment and family substance problems, while good adaptive coping skills were linked to a lower risk of this co-occurrence. During adolescence, child smoking, drinking and attention and/or thought disorders may be seen as early indicators of developing comorbidity. During adulthood, individuals with comorbid disorders are more likely to exhibit behavioural problems, particularly aggression and delinquency, but are also more vulnerable to experiencing psychological or physical forms of interpersonal violence. We also confirm that the antecedents of alcohol/mental health comorbidity differ from illicit substance/mental health comorbidity, and that common mental health disorders are strongly associated with poly-substance use disorders in young adults.

Conclusions:

This study extends our knowledge of comorbid alcohol use and mental health disorders by characterising the prevalence and the predictors of comorbidity for young adults in the general population. In addition to the health burdens, individuals with comorbid disorders are more likely to exhibit problematic behaviours at youth and adulthood which may leave them vulnerable to engagement with the judicial system. Features of the family environment, starting pre-birth, distinguish comorbid alcohol use and mental health disorders from single disorders and several predictors distinguish this comorbidity from that with illicit substance use disorders. Early identification is possible, and intervention with this group may help reduce the burden on both health and justice systems, but such interventions must also take into consideration the multiple socio-economic disadvantages experienced by this group.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Peer reviewed papers included in thesis

1. Salom, C. L., Betts, K. S., Williams, G. M., Najman, J. M., Scott, J. G. and Alati, R., 2014. Do young people with comorbid mental and alcohol disorders experience worse behavioural problems? Psychiatry Research 219(2), 372-379.
2. Salom, C. L., Williams, G. M., Najman, J. M. and Alati, R., 2014. Does early socio-economic disadvantage predict comorbid alcohol and mental health disorders? Drug and Alcohol Dependence 142, 146-153.
3. Salom, C. L., Williams, G. M., Najman, J. M. and Alati, R., 2015. Familial factors associated with development of alcohol and mental health comorbidity. Addiction 110(2), 248-257.
4. Salom, C. L., Kelly, A. B., Alati, R., Williams, G. M., Patton, G. C. and Williams, J. W., 2015. Individual, school-related and family characteristics distinguish co-occurrence of drinking and depressive symptoms in very young adolescents. Drug and Alcohol Review (E-pub 29/06/15).
5. Salom, C. L., Williams, G. M., Najman, J. M. and Alati, R., 2015. Substance use and mental health disorders are linked to different forms of intimate partner violence victimisation. Drug and Alcohol Dependence 151, 121-127.
6. Salom, C.L., Betts, K.S., Williams, G.M., Najman, J.M. and Alati, R., 2015. Childhood drinking predicts young adult poly-substance use. Addiction (E-pub 26/08/15).

Publications additional to this thesis

In addition to the publications listed above, I have been involved in collaborative studies with other researchers. For each of these studies I have made a substantial contribution to development of the idea, statistical analyses and/or the first draft of the manuscript.

1. Betts, K.S., **Salom, C.L.,** Williams, G.M., Najman, J.M. and Alati, R., 2015. Associations between self-reported symptoms of prenatal maternal infection and post-traumatic stress disorder in offspring: evidence from a prospective birth cohort study. Journal of Affective Disorders 175(0), 241-247.

2. **Salom, C.L.,** Holman, A., Connor, J.P., Toumbourou, J.W. and Kelly, A.B., 2012. Evidence that community-based prevention reduces adolescent alcohol use: A commentary on Gilligan et al. Drug and Alcohol Review 31(7), 930-931.
3. Quek, L.-H., White, A., Brown, J., Low, C., Dalton, N., **Salom, C.** and Connor, J., 2011. An evaluation of the *Choices* Schoolies program in North Queensland. Drug and Alcohol Review 30(S1), 49-49.

Conference abstracts

1. Poster presentation, Australasian Epidemiology Association Annual Scientific Meeting 2013: Salom, C.L., Williams, G.M., Najman, J.M., Alati, R. Is there an association between prenatal socio-economic disadvantage and comorbid alcohol/mental health problems?
2. Accepted for poster presentation at the WASP 2014 Jubilee Congress, London, UK, November 13-15, 2014: Salom, C. L., Betts, K. S., Williams, G. M., Najman, J. M., Scott, J. G., Alati, R. Young people in the general population with comorbid alcohol/mental health disorders also experience worse behaviour problems
3. Accepted for poster presentation at the WASP 2014 Jubilee Congress, London, UK, November 13-15, 2014: Salom, C.L., Williams, G.M., Najman, J.M., Alati, R. Early socio-economic disadvantage predicts comorbid alcohol and mental health disorders.
4. Presentation at UQ School of Population Health Research Higher Degree Conference 2014 (People's Choice award for presentation): Salom, C.L., Williams, G.M., Najman, J.M., Alati, R. What is different about comorbid alcohol and mental health disorders? A life course model.
5. Oral presentation at the 7th Australasian Drug and Alcohol Strategy Conference, Brisbane, 2015: Salom, C. L., Betts, K. S., Williams, G. M., Najman, J. M., Scott, J. G., Alati, R. Adding alcohol to mental health issues means behaviour problems.
6. Oral presentation at the IV International Congress on Dual Disorders, Barcelona, 2015: Salom, C.L., Williams, G.M., Najman, J.M., Alati, R. Familial factors associated with development of alcohol and mental health comorbidity.
7. Poster Presentation at the IV International Congress on Dual Disorders, Barcelona, 2015 (poster prize): Salom, C.L., Williams, G.M., Najman, J.M., Alati, R, Predictors of poly-substance use in young adults – a latent class analysis.
8. Accepted for oral presentation at the Australian and New Zealand Addiction Conference, Gold Coast, 2015: Salom, C.L., Williams, G.M., Najman, J.M., Alati, R. Comorbid alcohol and mental health disorders: a life course approach.

Publications included in this thesis

1. Salom, C. L., Kelly, A. B., Alati, R., Williams, G. M., Patton, G. C. and Williams, J. W. 2015. Individual, school-related and family characteristics distinguish co-occurrence of drinking and depressive symptoms in very young adolescents. Drug and Alcohol Review (e-pub 29/06/15). *Incorporated in Chapter 5*

Contributor	Statement of contribution
SALOM (Candidate)	Conceived research question, designed & undertook analyses (90%); interpreted results (90%); wrote manuscript (100%)
KELLY	Advised on analysis (5%); edited manuscript
ALATI	Edited manuscript
G. WILLIAMS	Advised on analysis (5%); interpreted results (10%)
PATTON	Critical review of manuscript
J. WILLIAMS	Critical review of manuscript

2. Salom, C. L., Betts, K. S., Williams, G. M., Najman, J. M., Scott, J. G. and Alati, R., 2014. Do young people with comorbid mental and alcohol disorders experience worse behavioural problems? Psychiatry Research 219(2), 372-379. *Incorporated in Chapter 5*

Contributor	Statement of contribution
SALOM (Candidate)	Conceived research question (80%), designed & undertook analyses (90%); interpreted results (80%); wrote manuscript (100%)
BETTS	Assisted with analysis (10%); critical review of manuscript
WILLIAMS	Advised on analyses; interpreted results (20%)
NAJMAN	Critical review of manuscript
SCOTT	Conceived research question (20%); critical review of manuscript
ALATI	Advised on analyses; critical review of manuscript

3. Salom, C. L., Williams, G. M., Najman, J. M. and Alati, R., 2014. Does early socio-economic disadvantage predict comorbid alcohol and mental health disorders? Drug and Alcohol Dependence 142, 146-153. *Incorporated in Chapter 6*

Contributor	Statement of contribution
SALOM (Candidate)	Conceived research question (100%); designed & undertook analyses (90%); wrote manuscript (100%)
WILLIAMS	Advised on analyses (5%)
NAJMAN	Critical review of manuscript
ALATI	Advised on analyses (5%); critical review of manuscript

4. Salom, C. L., Williams, G. M., Najman, J. M. and Alati, R., 2015. Familial factors associated with development of alcohol and mental health comorbidity. Addiction 110(2), 248-257. *Incorporated in Chapter 6*

Contributor	**Statement of contribution**
SALOM (Candidate)	Conceived research question (100%); designed & undertook analyses (90%); wrote manuscript (100%)
WILLIAMS	Advised on analyses (5%); Critical review of manuscript
NAJMAN	Critical review of manuscript
ALATI	Advised on analyses (5%); Critical review of manuscript

5. Salom, C. L., Williams, G. M., Najman, J. M. and Alati, R. 2015. Substance use and mental health disorders are linked to different forms of intimate partner violence victimisation. Drug and Alcohol Dependence 151, 121-127. *Incorporated in Chapter 6*

Contributor	**Statement of contribution**
SALOM (Candidate)	Conceived research question (100%), designed & undertook analyses (90%); wrote manuscript (100%)
WILLIAMS	Advised on analyses (5%); critical review of manuscript
NAJMAN	Critical review of manuscript
ALATI	Advised on analyses (5%); critical review of manuscript

6. Salom, C. L., Betts, K.S., Williams, G. M., Najman, J. M. and Alati, R., 2015. Predictors of comorbid poly-substance use and mental health disorders in young adults – a latent class analysis. Addiction (e-pub 26/08/15). *Incorporated in Chapter 7*

Contributor	**Statement of contribution**
SALOM (Candidate)	Identified research question, designed & undertook analyses (80%); wrote manuscript (90%)
BETTS	Undertook Latent Class Analysis (20%); wrote manuscript (10%)
WILLIAMS	Advised on analyses; critical review of manuscript
NAJMAN	Critical review of manuscript
ALATI	Advised on analyses; critical review of manuscript

Contributions by others to the thesis

The contribution of others to this thesis is detailed in the above section concerning co-author contribution to published journal articles. Of note is the assistance of Kim Betts in the Latent Class Analysis used for paper #6 listed above.

Statement of parts of the thesis submitted to qualify for the award of another degree

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Keywords

Alcohol, mental health disorders, comorbidity, longitudinal, illicit substance use disorders, adolescence, socio economic disadvantage, behaviour, intimate partner violence, family

Australian and New Zealand Standard Research Classifications (ANZSRC)

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ANZSRC code: 110319 Psychiatry, 20%

Fields of Research (FoR) Classification

FoR code: 1117 Public Health and Health Services, 80%

FoR code: 1103 Clinical Sciences, 20%

Contents

List of Tables

List of Figures

List of abbreviations used in the thesis

ABS	Australian Bureau of Statistics
ALSPAC	Avon Longitudinal Study of Parents and Children
AUD	Alcohol use disorder
AR	Attributable risk
AUDIT	Alcohol Use Disorder Identification Tool
CAMHD	Comorbid Alcohol and Mental Health Disorder
CBCL	Child Behaviour Check List
CIDI	Composite International Diagnostic Interview
CI_{95}	95% confidence interval
CTC	Communities That Care
DALY	Disability Adjusted Life Year
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSSI	Delusions Symptoms States Inventory
FCV	First clinic visit during pregnancy
GAD	Generalised anxiety disorder
GWAS	Gene-wide association studies
HPA	Hypothalamic-Pituitary-Adrenal (Axis)
IPV/IPA	Intimate Partner Violence/Intimate Partner Abuse
IPW	Inverse probability weighting
LCA	Latent class analysis
LFU	Loss to follow up
MDD	Major depressive disorder
MHD	Mental health disorder
MI/MICE	Multiple imputation/ by chained equations
MUSP	Mater-University of Queensland Study of Pregnancy
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiological Study of Alcohol and Related Conditions
NESDA	Netherlands Study of Depression and Anxiety
NLAES	National Longitudinal Alcohol Epidemiology Survey
NHMRC	National Health & Medical Research Council
NSC/NSC-R/NSC-A	National Study of Comorbidity/Replication/Adolescent Supplement
NSMHWB	National Study of Mental Health and Well Being
OR	Odds ratio
PTSD	Post-traumatic stress disorder
SES/SEP/SEIFA	Socio-economic status/position/indicator for area
SMFQ	Angold Short Moods & Feelings Questionnaire
SUD	Substance use disorder
WHO	World Health Organisation
WRAT	Wide Range Achievement Test
YASR	Young Adult Self Report
YSR	Youth Self Report

Chapter 1: Introduction

Perspective

Alcohol is the most widely-consumed psycho-active substance in the world. Though its moderate use is generally considered to be positive to health and social wellbeing, excessive alcohol consumption is associated with considerable harm. In 2012, 5.9% of all global deaths and 5.1% of the global burden of disease were attributable to alcohol consumption (1). This burden is not equally shared. The World Health Organisation recently reported that 62% of the world's adult population does not consume alcohol (1), thus concentrating the harms attributable to alcohol, typically in higher-income countries. In Australia, drinking is culturally accepted, resulting in widespread use but also high levels of abuse and disorder (2). Young people in particular may be heavy, often problematic drinkers, with their alcohol use affecting not only their own health and well-being but also that of the families and communities around them (3, 4).

Mental health disorders are also common (5-8) and contribute substantially to the global burden of disease, accounting for some 146 million Disability Adjusted Life Years (DALYs) annually (9). These disorders tend to first arise during adolescence and young adulthood, the period in which problematic drinking also typically begins (10). This age group experiences the greatest burden of disease from mental health and substance use disorders (9). Conversely, these disorders are the greatest cause of disability in young people (11). The early onset predicts greater severity and stability of symptoms for both conditions, and highlights adolescence/young adulthood as a formative period for the development of comorbidity (12). Over the last two decades, researchers have become more aware that alcohol and other substance use issues often involve co-occurring mental health problems, with implications for both for the individual and for the services treating them. Although concerted efforts are underway to better manage comorbidity (13), this requires an improved understanding of comorbidity as an entity, rather than as an accumulation of symptoms. Hence this body of research focuses on comorbidity of alcohol use and mental health disorders.

Comorbidity or Dual Diagnosis: a definition

The term comorbidity was coined by Feinstein in 1970 (14) and is defined as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." As such, this definition may apply to any

pair (or more) of disorders, for example asthma and anaemia. In the case of mental health disorders, the Diagnostic and Statistical Manual of Mental Disorders [Fourth edition; DSM-IV] presents disorders separately, with no defined categories of comorbidity. Thus, comorbidity may be homologous, i.e. reflecting multiple diagnoses within a diagnostic spectrum such as depression and dysthymia, or heterologous, i.e. diagnoses across spectra such as depression and substance use. Concern has been expressed that homologous comorbidity may merely be a reflection of severity of shared symptoms (15). Recently, criticism has been levelled at the use of the term 'comorbidity' to describe the presence of multiple common mental disorders such as depression and anxiety as diagnosed using the DSM-V, again due to the shared nature of symptoms (16). Heterologous comorbidity however may reflect either etiologically independent conditions or a manifestation of shared underlying factors, whether these are genetic or environmental. It is on heterologous comorbidity that this thesis focusses.

The term dual diagnosis is also used, particularly in clinical settings, referring specifically to the combined presence of any psychiatric disorder (identified on Axis I or II of the DSM-IV) and a substance abuse disorder. In Australia, Dual Diagnosis guidelines issued in 2008 (17) define "dual diagnosis or co-occurring conditions … as the co-occurrence of two or more disorders or problems, at least one of which is a mental health problem and at least one of which relates to the use of alcohol and other drugs." However, the wider literature refers predominantly to the term comorbidity. For the purpose of this thesis, the terms will be used interchangeably.

Of interest from an epidemiological perspective is the idea of synchronous occurrence or overlap. This does not refer to a specific time of overlap, only the existence of multiple conditions in one person. These may be concurrent (overlapping in time) or successive (18). This latter has also been described (19) as "cumulative comorbidity": both disorders occur during a lifetime but not necessarily simultaneously. This measure has been used in a number of large population-based studies (20-22). However, the issue of timing of disorder is important. The experience of two disorders that are temporally distant from one another may involve significant abatement of one disorder before emergence of the other, allowing the two to be considered as separate issues. In contrast, where the disorders are concurrent, or occur in closer temporal proximity, they are more likely to have a shared aetiology, to interact, or to have a distinct combined impact (18). It is on such co-occurring disorders that these studies focus.

Adolescence/young adulthood is a formative period for the development of alcohol and mental health problems, and although these disorders may not always be concurrent, their co-occurrence within this limited timespan is likely to involve interaction between the disorders. Thus a lifetime diagnosis at age 21, for example of both alcohol use disorder and a depressive disorder, is likely to involve both disorders being active within a 4-5 year period, allowing this to be regarded as dual diagnosis. In contrast, restricting diagnosis of comorbidity to last-12-month prevalence data as in some reports (18, 23) may under-estimate the extent to which an individual at this age experiences two (or more) disorders.

The concept of ordered disease is widely discussed in the literature – which disorder is primary, or occurred first. This has been primarily of interest in clinical discussions, specifically in the instance of substance-induced mental health disorders, where it was judged that abatement of the substance misuse would ameliorate the mental health symptoms. It was considered that treating the primary disorder afforded an opportunity to prevent the secondary; this approach has since been criticised as less than cost effective (24), particularly as a minority of cases were found to have clearly causal pathways. More recently, treatment settings have been less concerned about primary versus secondary disease as simultaneous therapies become more widely practiced (25-29). Of greater interest is identifying the presence of multiple morbidities which will impact on the severity of symptoms and consequently on treatment efficacy.

Opportunity

The co-occurrence of mental health and alcohol use disorders has been described in large cross-sectional studies, and a number of cohort studies have provided information on the separate development of alcohol problems and mental health issues. These are discussed in depth in Chapter 2 (Review of the Literature). Despite this, we have limited knowledge of the development of comorbidity in younger individuals, the risk factors at epidemiological level which may highlight those likely to develop this combined disorder and the impact that family may have on dual diagnosis.

The Mater University Study of Pregnancy (MUSP) pre-birth cohort has been followed at various intervals over 21 years, with the availability of data on biological, psychological, family and social factors over the study. This provides an opportunity to examine the relationships between these factors from before birth, through childhood and adolescence and the development of the comorbid condition in young adults. In addressing these relationships, we hope to identify opportunities to intervene early, to work effectively in prevention, or to better engage people in treatment services.

Aims and objectives of the present work

Overview of research aims

Within the direction of generating a better understanding of comorbid alcohol and mental health conditions, this body of research has three main aims:

1. To describe the prevalence, types and onset of comorbidities of mental health and alcohol use disorders in young Australians;
2. To understand factors from different phases of the life span which may predict the onset of comorbidity or be affected by it, and which may present targets for intervention; and
3. To consider the role of alcohol in the context of other substance and mental health comorbidities.

In this context, this research program aims to explore factors which may distinguish comorbidity from its constituent disorders.

Thesis structure

This project was structured to follow human development from gestation through to young adulthood, examining factors across the lifetime of participants that may contribute to the comorbidity of alcohol and mental health disorders at age twenty-one. The literature review (Chapter 2) follows this pattern, describing very early life factors through to adolescence which may affect development, then considering the impact of comorbid conditions on the individual and those around them. In the Methods section (Chapter 3), an overview is given of the data and methodologies used, with more specific detail in the relevant manuscripts which comprise the results (Chapters 4-7) and in Appendix 2.

The results section follows on from this. Chapter 4 details a characterisation of the cohort at 21 years, describing the prevalence and types of comorbid alcohol and mental health disorders and demographic factors associated with this comorbid condition. Chapter 5 discusses cross-sectional associations which examine a) how early we can detect indications of comorbidity, and b) if young people in the general population with comorbid disorders experience more difficulties than those with single conditions. Chapter 6 examines factors across the life course which may precede the development of this comorbidity or be affected by its development. Finally, Chapter 7 investigates whether the comorbidity of mental health disorders with substances other than alcohol has different antecedents.

Table 1: Thesis structure

Results Chapter	Content	Description
4	Preliminary examination of cohort	Prevalence, comorbidities, temporal overlap, attrition, demographics (unpublished data)
5	Cross-sectional associations	Manuscript under review: Individual, school-based and family characteristics distinguish co-occurrence of drinking and depressive symptoms in very young adolescents
		Published paper: Do young people with comorbid mental and alcohol disorders experience worse behavioural problems?
6	Life course predictors	Published paper: Does early socio-economic disadvantage predict comorbid alcohol and mental health disorders?
		Associations of birth-weight, IQ, maternal health and parenting behaviours at 5 years with comorbidity (unpublished data)
		Published paper: Familial factors associated with development of alcohol and mental health comorbidity
		Accepted manuscript: Substance use and mental health disorders are linked to different forms of intimate partner violence victimisation
7	Other substance use comorbidities	Submitted manuscript: Predictors of comorbid poly-substance use and mental health disorders in young adults: a latent class analysis

Chapter 2: Review of the literature

This review of the literature on comorbidity will first discuss what is known about the prevalence of comorbid conditions and the impact of comorbidity for those who experience this condition. It will then examine factors likely or known to predict its development. Finally it will address the impact of comorbidity on behaviour and relationships with others.

Please note that for each of the papers included in this thesis, the literature specific to that particular topic is included in the relevant manuscript, rather than being duplicated here. This review is intended to supplement rather than duplicate those papers.

Prevalence and characteristics of comorbidity in populations

A variety of data types has been used to estimate the prevalence of comorbid disorders. Although clinical cohort studies indicate a high degree of comorbidity, these typically capture only a subset of those affected, usually severely so, and thus may not accurately reflect the extent of this comorbidity in the community. In Australia, accurate estimates from treatment services have been further hampered by the lack of uniformity of data collection and the absence of a central analysis and reporting focus for these disorders (30).

Large national studies in a number of countries have estimated the prevalence of mental health and substance use disorders in general populations. The World Mental Health Survey Initiative compared findings from such surveys in 28 countries, including the USA, France, India, Ukraine, Israel, China, Australia and New Zealand. Australia was found to have very high rates of mental disorders. In its most recent National Study of Mental Health and Wellbeing (2007 NSMHWB), 14.4% of the cohort reported an anxiety disorder, 6.2% an affective disorder, and 5.3% a substance use disorder in the preceding 12 months (31). Absolute levels of mental disorder were slightly lower than in the US, where 18.1% and 9.5% reported anxiety and mood disorders respectively; substance use disorders were somewhat higher than the US, which reported a prevalence of 3.8% (32). The rank order of disorder prevalence was similar to national studies from the US, Europe and New Zealand (33).

Of the substance use disorders, alcohol was the most common: 81% of the substance use disorders reported above involved alcohol (23). It is Australia's most widely used substance: 78% of Australians consumed alcohol in the last year and 7% reported drinking daily (34). Those in late adolescence/early adulthood (aged 14-19) are often regular

drinkers (54% in the last year, 12% being weekly drinkers), with significant numbers (15%) drinking at levels consistent with immediate risk or with potential to develop dependence (35). The primacy of alcohol among substance use disorders in adolescence has been widely reported in other developed countries (36), with increasing prominence noted in many less-developed regions (37).

Combinations of disorder conditions

High levels of alcohol and mental health disorder comorbidity have been described worldwide. Three large US studies, the National Epidemiological Study of Alcohol and Related Conditions (NESARC), its predecessor the National Longitudinal Alcohol Epidemiological Survey (NLAES) and the National Study of Comorbidity (38), the Netherlands Study of Depression & Anxiety (39), the Adult Psychiatric Morbidity Study in the UK (6) and international comparisons (40) all suggest that alcohol use disorders are commonly associated with anxiety, mood and conduct disorders. The 2007 NSMHWB reported that, among those with alcohol dependence in the last 12 months, 52% also met criteria for an anxiety disorder and 34% for an affective or mood disorder in the last year (41), or approximately 159,000 and 101,000 persons respectively.

Generalized anxiety disorder is highly associated with substance use disorders (23, 42), with high disability and vulnerability to further comorbid conditions. Alcohol dependence specifically is strongly associated with depression and mood disorders, more so than is alcohol abuse (39, 40). Stronger again are the associations of alcohol use disorders (AUD) with mania/hypomania (43) and specific phobias (44), with some gender differences. Strong associations have also been seen between alcohol use disorders and conduct disorders and adult antisocial behaviour (40). A link between increased severity of alcohol problems (i.e. from use to abuse to dependence) and the magnitude of comorbidity (i.e. the number of comorbid conditions) (15, 21, 40) suggests a strong interplay between the two.

Although homotypic comorbidity (e.g. anxiety and depression) is extremely common, the second most frequent comorbidity is anxiety with substance use (1.3% for males and 0.8% for females). For Australia, with a current population of 23,426,000 persons (45), this indicates a potential clinical load of over 245,000 persons with a twelve-month substance-anxiety comorbidity. Therefore, comorbid alcohol and mental health disorders are indeed a significant, ongoing concern in Australia. However, rates of comorbidity reported for Australia are for the general adult population. We do not have prevalence estimates for the

young-adult group, and these may differ from US reports (22) due to the lower legal drinking age in Australia.

The variations in onset age for disorder subtypes and a lack of consistent unidirectional pattern between alcohol and mood disorders question the ordering that support causality models for comorbidity, although a subgroup may exist for which this causality applies (43, 46-48). The remainder may however be of more interest for this study, with the potential to share common causal pathways (49), aetiology and risk factors which may be used to predict comorbidity. The specifics of common pathways are however still strongly debated. Several large twin studies (50, 51) have shown the presence of common genetic predisposing factors between GAD and MDD, including personality factors such as neuroticism (52), suggesting that expression of a specific disorder is determined by environmental factors not shared between GAD & MDD. Young-Wolff, reviewing twin studies examining alcohol problems found less consistency: the level of importance of genetic influences appeared to vary across populations and environmental conditions (53).

In light of the lack of agreement as discussed here, the idea that multiple causal pathways may coexist with shared diathesis (18, 25, 40) is gaining currency. To date co-occurring disorders have largely been investigated in terms of compared disorders, rather than in terms of comorbidity as a distinct outcome. Regardless of the mechanism by which comorbidity develops, it is clear that late adolescence/early adulthood is a critical period for its emergence (32), and that disorders which may be mild at younger ages tend to progress to greater severity over time (32), and thus young adulthood is an important time for early detection and investigation of comorbidity as an entity (18).

Impact of comorbidity

The impact of comorbid substance use disorders and mental health disorders is felt at individual, community and service levels. This section suggests why the impact of comorbidity is distinct from each of its contributing conditions and provides an important target for study.

For communities and individuals

Individually, mental health and alcohol use each place a major burden of disease on the population; the combined global burden for 2010 was estimated at 184 million disability adjusted life-years (DALYs) (9). According to the Australian Burden of Disease and Injury Study, mental disorders contribute more to disability than any other disorder for young (10

– 24 year old) Australians (54). Alcohol misuse disorders explain more prevalent years lost to disability for this group than any other substance use disorder. This aligns with global estimates for this age group: neuropsychiatric disorders contribute 45% of all years lost to disability, and mental disorders and alcohol constitute four of the top six causes of DALYs (55). Population based studies such as the 2007 NSMHWB showed that persons with comorbid disorders experienced significantly more impairment as a result of their illness than those with single disorders (56). Other national studies have shown similar results (32, 57), but this increased impairment uses measured such as days out of role in the last month and this gives little indication of the social and relational impacts of comorbidity.

Economic costs of this are high. Estimates of workplace costs including absenteeism, loss of productivity, and increased load to 'cover' others show a strong impact of mental health, alcohol problems and comorbidities of the two, both in Australia (2, 58-61) and overseas (62, 63). Treatment and disease management are also expensive. Charlson and colleagues (64) estimated the management costs for chronic diseases and found them to be exponentially related to the number of comorbidities, while others estimated at least a doubling over single disorders (65).

For individuals who experience comorbidity, the symptoms of each type of disorder are more severe across clinical and psychological domains than if each was present alone (25, 66). In a large clinical study, Davis showed that comorbid depression and substance use clients had more severe symptoms, more impairment and were more likely to have other co-occurring mental health issues (28).

Disorder development can be accelerated and prognosis worse. Much of this literature comes from clinical reports. Farris showed that treatment outcomes were poorer for comorbid clients, both in completion of treatment and in post-treatment follow up (67). Bruce and colleagues in a 12-year prospective study showed that patients with a pre-existing generalized anxiety disorder progressed more quickly from substance use to dependence, and patients with a substance use disorder were less likely to recover from their anxiety disorder (68). More recently Samet and colleagues showed that comorbid depressive disorders increased the likelihood of relapse into substance use (69) and in a population based study, Tuithof and colleagues reported that alcohol use disorders were more likely to persist if comorbid with anxiety (70). Likewise, a series of longitudinal studies reviewed by Moffitt (19) showed that comorbid symptoms are more likely to persist, despite treatment, than those of a single disorder. These agree with an extensive literature

reviewed by Merikangas (40) and Kessler (32) showing worsened clinical courses, higher suicide risk and greater impairment. Congruent with these, analyses of large population data have shown comorbid disorders to be associated with lower quality of life (71) and increased risk of suicide (72).

For services and systems

Comorbid conditions may not be immediately diagnosed on presentation to a service. In Australia, the overwhelming majority of mental health treatment occurs at community based mental health services, rather than at hospitals (73). Due to the frequent separation of substance and mental health treatment services (74), expertise in diagnosis and facility to treat may also be segregated between these sectors (75, 76). The Australian Bureau of Statistics reported from the MHWB07 survey that of those with comorbid disorders, 42% sought help from a GP and 24% from "other health professionals", compared to only 23% from a psychologist and 14.5% from a psychiatrist (5). Unless those at the presenting service are aware of the potential for comorbidity, diagnoses may be incomplete, focussing on either substance or mental health issues, depending on service expectations. This is particularly common for younger patients who make limited disclosures (77). This may result in initial treatment plans which do not account for both conditions, which may thus limit effectiveness and efficient use of resources (78). This becomes more important as uptake of mental health treatment increases across the board via increased government subsidy (79).

Although it is now believed that comorbid disorders can be treated concurrently (25, 26, 80), therapies have until very recently been more complex (27, 81), or less developed. Reviews in the last five years by Baillie (82) and Teesson (23) both noted a paucity of well conducted evaluations of therapies for comorbid disorders, noting the importance of understanding particular combinations of comorbidities. There is concern about interactions between patients' substance use and pharmacotherapies used to treat mental health conditions, as well as the potential for misuse of these drugs (26) or the development of additional dependencies (83). Issues also arise of compliance with treatment conditions due to intoxication and/or mental health impairment (81, 84). More recently, some success has been demonstrated with concurrent treatments (29, 85-87), but these rely on accurate identification of the comprising disorders.

There is disagreement about whether those with comorbid conditions are more likely to seek treatment. Although large national surveys like NSMHWB and NESARC show reasonable levels of service use (31, 57, 88), and some studies (19, 89) show adults with

multiple disorders were more likely to have engaged with services than those with a single condition, Teesson and colleagues noted that this did not apply where one of the disorders was substance related (23), and others reported “equally low service use” for single and comorbid disorders (42, 90, 91).

In the US, those with comorbid alcohol and mental disorders were more likely to report barriers, particularly financial barriers, to accessing treatment (89). This may particularly affect younger persons, who are less likely to seek treatment (92-96). In the US Comorbidity Study, fewer than one in five affected adolescents had sought treatment (97). Young people are generally under-represented in service profiles, not seeking help in early stage conditions (98), with the result that they are more likely to develop further conditions (i.e. become comorbid), to experience negative functional outcomes such as educational failure, family disengagement, unemployment and criminal activities (99-101), and are more likely to be seen by a service ill-equipped to respond appropriately to their multiple conditions (32, 74, 94).

In conjunction with the high prevalence of multiple morbidities (5, 32, 88) and the longer persistence of comorbid disorders, this information places comorbid alcohol and mental health disorders at the very costly end of the spectrum.

Summary - prevalence and impact of comorbidity

In Australia and overseas, comorbidity between alcohol and mental health disorders is common and may be increasing in prevalence. There is evidence to suggest that key symptoms emerge largely in late adolescence and early adulthood, which makes young adults a prime target for investigating the features of comorbidity. It can also be seen that dual diagnosis represents a very significant burden at individual, community and at systemic levels, despite being under-treated, and that knowledge of comorbidity beyond information about separate disorders is necessary to inform the generation of targeted interventions. However our knowledge of the prevalence and social impacts of comorbidity in young adults is limited for Australia.

Very early life factors affecting comorbidity

In order to understand the underlying mechanisms associated with comorbidity, it is necessary to examine factors in earlier life which are related to mental health disorders, alcohol use disorders or both. Due to the limited number of studies on the antecedents of comorbid alcohol and mental health disorders, particularly from prospective studies, this

review of factors which contribute to the development of this comorbidity draws necessarily upon the literature regarding the individual constituent disorders.

Gestation is a period of development very sensitive to environmental influences, but its involvement in comorbidity is not known. The developmental origin of disease model, or "Barker's Hypothesis", proposes that some risks of disease are initially introduced during foetal growth and development, potentially in response to environmental "challenges" to the mother (102). The foetus adapts to these challenges by differently expressing its genotype to prepare for the post-natal environment. These changes may include metabolism, hormone production and tissue sensitivity to hormones which direct organ development.

For example, a mother experiencing low nutrition may produce a child whose metabolism has slowed (become "thrifty") *in utero*, in order to better survive a low-food environment after birth. One physical manifestation of this may be a child of lower birth weight or a pre-term birth. Longer-term consequences of this developmental change may not manifest until later in life, when subsequent environmental challenges reveal limitations in the response pathways established for such low birth weight children (103).

This is exemplified by cases where low birth-weight children show accelerated growth in early childhood in response to favourable nutrition, but then exhibit a greater risk for diseases such as obesity, chronic heart disease, Type II diabetes and hypertension(102). The reduced response to insulin, which *in utero* made economical use of available nutrition, was insufficient to cope with a plentiful environment. One well-known manifestation of this paradigm was the 1944 Dutch "Hunger Winter", where the blockade of food supplies to the Netherlands during World War II exacerbated existing food shortages and resulted in a famine. The children of women pregnant in the Netherlands during this time were found to be susceptible to diabetes, obesity, and cardiovascular disease (102), but also (and more relevant to this study) to mental disorders such as antisocial personality disorders (104) and schizophrenia (105, 106).

Animal models have shown a response, similar to that of nutritional limitation, to stress, where maternal exposure to glucocorticoids in pregnancy produces offspring with increased hypertension and alterations in the hypothalamus-pituitary-adrenal (HPA) axis (107). The HPA axis modulates hormonal and behavioural responses to stress and reward pathways and is implicated in the development of coping mechanisms and depression (108), providing a biological link between prenatal stress and the development of depression. In a review of the role of stress in the development of depression/addictive

comorbidities, Rao (109) suggests that interaction of the HPA with the limbic system may also be involved. Although much of this evidence is from animal studies, current research on differential expression of phenotypes using human twins may provide more direct evidence of these pathways in humans.

Birth weight

Following on from this, birth weight may be regarded as a marker of altered development during pregnancy as a response to adversity. As such, the place of birth weight in the causal pathways to comorbidity bears investigation, but this is not expected to be straightforward. Birth weight has been linked with adolescent psychological distress and adult depression, but not directly with substance use disorders.

Gale and Martyn (110), analysing data from the British Birth Cohort, suggested that lower birth weight may increase susceptibility to depression. This was confirmed by a report from Patton and colleagues (111) on a large Australian cohort study, and a later study by Costello (112). Interestingly, in this latter study, birth weight did not predict other psychiatric disorders for either sex, but high levels of comorbidity between anxiety and depression were seen. However, most of these studies had limitations with respect to recall bias or imprecise measures of birth weight and/or gestational age.

More complete accounts of birth weight relationships are available using prospective data from the MUSP study. Alati and colleagues (113) found that very low birth weight, but also the highest quintile of birth weight, was associated with behavioural problems in adolescence. This was however independent of socio-economic factors, mothers' alcohol and tobacco use in pregnancy and maternal anxiety/depression in pregnancy, which may indicate that birth weight was in fact directly associated with behaviour, rather than being an indicator of *in utero* stress.

Betts and colleagues (114) noted that lowest quintile birth weights were associated with a lifetime diagnosis of post-traumatic stress disorder (PTSD) in young adults, but not with other anxiety disorders. A subsequent analysis found that birth weight was associated only with comorbid anxiety/depressive disorders, not single disorders (115). Earlier, Hayatbakhsh and colleagues had examined childhood predictors of early substance use in this cohort and found no direct association with birth weight (116), but none of these studies examined substance-based comorbidity.

Intellectual Quotient (IQ)

IQ is often taken as a marker of the ability to cope with one's surrounds, with higher IQ reported as one of several markers of resilience in children (117). In turn, intelligence has been shown to be associated with mood, behaviour, learning ability, socio-economic position and substance use, but the mechanisms for this are not clear. Associations with specific mental health disorders and alcohol use disorders are not consistent, and the relationship with comorbidity is not well understood. In addition to this, instruments measure cognition in different domains including visual and verbal, with the robustness of some measurements debated due to their reliance on literacy, such that IQ is potentially underestimated in disadvantaged groups.

Development of IQ may be impacted *in utero*. Although the impact of severe and prolonged alcohol use on cognition as seen in Foetal Alcohol Spectrum Disorder (FASD) is well documented, the effect of exposure appears to be a continuum, with non-FASD children also showing IQ deficits after prenatal alcohol exposure but relative to amounts consumed (118). The pattern of *in utero* exposure also appears important; binges of at least 4 drinks in a day (separate to regular drinking) were related to inattention and hyperactivity (119).

Socio-demographic factors may confound this relationship, and the directionality of these relationships is unclear (120, 121). Fergusson and colleagues (122) found an association between low childhood IQ and the appearance up to age 25 of some mental health disorders: anxiety and suicidality but not major depression. However, socio-economic factors accounted for most of this relationship. There is a strong link between a subject's IQ and his/her socio-economic standing via education. The IQ of a child may be thus apparently influenced by parental SES, where this is more likely to be due to some heritability of IQ. This is also confirmed by two studies of Scandinavian men, where a link between IQ and drinking problems was accounted for by socio-economic factors (123, 124).

Maternal drinking in pregnancy

A recent article by Sawada Feldman and colleagues (125) showed the direct impact of prenatal alcohol exposure on physical features such as microcephaly (associated with impaired intellectual development and hyperactivity) and birth weight, with effects strongest in the first trimester of pregnancy. Several studies have been published also linking it directly to the development of behavioural patterns and alcohol problems in the

offspring. Alati and colleagues (126) linked prenatal alcohol exposure to alcohol use disorders at young adulthood; drinking in early pregnancy led to both early (before 17) onset and late (18 and older) onset disorders in the offspring.

In another longitudinal study, Larkby (127) showed that prenatal alcohol exposure was significantly associated with increased rates of conduct disorder during adolescence. This involved only mild exposure (anything over 1 glass per day), again during the first trimester, and was independent of the mother's psychopathology, the home environment and other prenatal substance exposures. Other behavioural issues such as hyperactivity and attention problems (including Attention Deficit Hyperactivity Disorder) are reported to increase in prevalence in children with prenatal alcohol exposure (118). More recently, one longitudinal study has shown that binge drinking during pregnancy, independent of regular drinking, was linked to the development of hyperactivity and inattention problems in children (128). Such child attention problems are themselves linked to the development of alcohol use disorders. Very early alcohol exposure may thus have multiple pathways to impact on the development of comorbid mental health and alcohol use disorders, but this link has not been established.

Summary – very early life factors

From the above discussions it is apparent that very early life may be important in the development of both alcohol and mental health disorders, with some indications that this begins during prenatal development. In light of the conflicting literature, it is no surprise that a model for perinatal factors predicting comorbidity has not emerged. The MUSP study provided an opportunity to examine the association of IQ, birth weight, maternal drinking and socio-economic factors with comorbid alcohol and mental health disorders in young adults, and to produce a model showing how these factors interact.

The impact of maternal disorders and behavioural factors during early years

Characteristics of the family during childhood and adolescence may impact on the development of comorbidity. Once again, limited information has been published on the effect of these factors on comorbid conditions. As a result, this review draws necessarily upon studies of mental health and alcohol conditions separately to build a picture of the influences at play.

Family behavioural factors (substance use, mental health, stress and coping) have been shown to be strongly predictive of problem drinking and mental health issues

separately in the offspring. The mechanisms appear to be complex and inter-related, reflecting commonalities between substance, depressive and anxiety disorders. In addition the impact may involve heritable or genetic components, environmental or culturally transmissible components, and variation of the impacts of these across the ages of the child.

In order to disentangle these effects, a number of different study types have been helpful. Large scale epidemiological studies have yielded information on the association of disorders across generations, and allowed for assessment of potentially confounding factors. Longitudinal studies have provided evidence of temporality of effects, but have in some cases been limited by the scale of the study and the analytical power provided. High risk studies, selecting cases and controls, have assisted with this, providing information on familial associations of disorders. However, to distinguish between genetic (heritable) traits and the outcomes of shared environments, twin and adoption studies have been required as well as the more recent gene-wide association studies (GWAS). This section reviews evidence from all of these sources.

Parental alcohol use

A family history of alcohol (substance) disorders is one of the strongest predictors for the development of substance use disorders (129) but the mechanism for this is complex. Although prenatal exposure to alcohol may affect the foetus and several candidate genes have been identified as involved in predisposal to alcohol use disorder (130), other familial alcohol exposure has distinct effects. As an example, parental drinking during the child's early years may model alcohol use for the child, providing an environmental effect that is distinct from use during pregnancy or inherited disorders (131). This is referred to as cultural transmission. In a review of twin studies, Hopfer (132) found that both genetic and shared environmental influences on adolescent substance use are moderated by age, gender and specific contexts.

Exposure to parental use of alcohol (as distinct from disorders) has been shown to predict the onset of alcohol use in their children (133-135) and the risk of drinking problems in young adulthood (136), but less so the progression to disorders. These effects are stronger for biological than adopted offspring (137), suggesting at least some genetic component is involved. Disorders of parental alcohol use are strongly predictive of disorders in their children, with recent gene-wide association studies showing alcohol dependence to have a heritability of approximately 50% (138). However environmental

factors may influence this; as an example, analysis of recent Australian drinking (139) showed that parents are less likely to drink at risky levels than non-parents.

Cohort studies have shown that parental alcohol use disorders are associated with earlier onset of use, and children's progression from alcohol use to misuse and disorders (140), with some gender related differences. A large cross sectional study found that boys with a dependent parent were likely to develop mania (if father had an alcohol use disorder) and panic (if the mother). Girls were likely to develop mania and schizophrenic disorders (mother), as well as alcohol abuse (either parent), and were more at risk than boys, particularly if the alcohol use disorder was maternal (141).

It is also suggested that parental alcohol use disorders are associated with the development of mental health disorders in their offspring. Brook's longitudinal study (although focussed on African Americans and Puerto Ricans) suggests that early offspring alcohol use, related to parental alcoholism, links with use in late adolescence and then psychological problems in young adulthood (134). Avenevoli's high risk family study supports this, suggesting that parental alcohol use disorders increase the risk of offspring depression, potentially via the associated conduct disorders, but also via reduced family cohesion (142). In a recent review, Saraceno (143) also suggests that the increased risks of alcohol problems, anxiety, depression and comorbidities of these experienced by the children of alcoholics may be due to increased disturbances in family relationships, rather than the disorders themselves.

Maternal depression and anxiety

Parental histories of anxiety and depression have been shown to predict development of these disorders in their offspring as children or adolescents, even more so when both parents are involved (129, 144-146). Although these disorders are very commonly found together and share some risk markers, the presence of risk factors specific to each disorder suggests that at least parts of the etiological pathways are different (19). Similarly, although depression and alcohol use disorders tend to co-occur in families, transmission to offspring appears to operate differently.

In both cases, patterns of transmission may be sub-type specific. One prospective community family study has shown specific associations of maternal social phobia and generalised anxiety disorder with development of the child's anxiety (147). Another prospective study of high-risk families showed specificity in the familial expressions of anxiety and depression, with depression following later than the onset of most subtypes of

anxiety in comorbid subjects (148). The appearance of depression may also depend on the subtype: at least one longitudinal study showed bipolar depressive disorder emerging before alcohol problems, with non-bipolar depression developing later (149). Alcohol may also associate differently with anxiety subtypes, showing common pathways with panic disorders but not social phobias (144).

Maternal depression has been linked to both alcohol misuse and depression in the offspring (143). During the perinatal period, it has been suggested that the mother's depression contributes to this effect via the disruption of prenatal and postnatal bonding, but depression present at other times may act via other pathways later in childhood. Where paternal depression and substance use are also present, the links to offspring depression (150) may be acting through disruption of family cohesion and the development of child conduct issues (142).

Twin studies suggest there is a moderate degree of genetic influence for child depression, which becomes more prominent into adolescence (151) and particularly later adolescence (152). As with discussion of alcohol use, it is more likely that the genetic influence remains constant, while the influence of the family environment is strongest in childhood and wanes in later life.

As to a family history of depression, parental anxiety may be linked to child depression through conduct disorders (142). Alternatively, parental anxiety may be related to child depression via its impact on the risk of (concurrent) child anxiety (129). It has been suggested that this is via parental modelling of anxious behaviour (153). Instead, children of anxious parents may have temperamental vulnerability factors such as a higher stress reactivity (145), which may be 'activated' by their experience of stress.

Similar to alcohol use disorders, the transmissions of anxiety and depression may have some genetic components. Certainly genomic studies have identified variants linked to major depression (154). The two disorders may differ in the involvement of the behavioural side of familial mental disorders, but the impact of non-genetic factors appears strongest in childhood. As with other discussions, the impact on combined alcohol and mental disorders has not been studied, and due to the variations noted, it is not immediately inferable.

Summary – the impact of maternal disorders

Although there is evidence for parental anxiety, depression and alcohol use disorders predicting each of these in their offspring, and some of the pathways appear to have

common elements, few studies have examined the effect of parental conditions on comorbidity in the children. Merikangas (145) suggests that patterns of co-aggregation of disorders depend on the subtypes of disorder, and Marquenie (155) argues that family histories of anxiety and substance use disorders do not predict comorbidity of these conditions in offspring. Stressors, either intra- or extra-familial as discussed below, may modulate any relationship seen, but few studies have accounted for this. Further discussion of the role of parental disorders is included in the paper "*Familial factors associated with development of alcohol and mental health comorbidity*" which is incorporated in Chapter 6.

The MUSP study provided the opportunity to examine the effects of maternal anxiety, depression and alcohol use disorders during the childhood and adolescence of their offspring on the emergence of comorbidity in the offspring at age 21. Although the MUSP cannot account for genetic transmission of disorders, it is possible to evaluate the effects of maternal disorders at different times across child development. If temporal variation is seen, this may suggest cultural transmission and account for important influences such as *in utero* exposure to alcohol and stress experienced during childhood and adolescence.

Parenting and family environment

In addition to the genetic transmission factors and behavioural modelling discussed in previous sections, the structure and function of the family have been shown to impact on facets of the development and course of both mental health and substance use disorders in the offspring. Several major reviews and meta-analyses have described the associations between parenting and anxiety, depression and alcohol use disorders in offspring. In a meta-analysis of 45 studies, McLeod and colleagues found that parenting accounted for 8% of the variance in child depression (156). In a second meta-analysis, of 47 studies, parenting was found to account for 4% of the variance in child anxiety (157). Another meta-analysis examined the effects on delinquency, which is often associated with alcohol problems, particularly in adolescence, finding that 11% of the variance was accounted for by parenting factors (158). Saraceno and colleagues in their 2009 review found that adverse family environmental factors were linked with an increased risk of adolescent alcohol problems and with internalising symptoms in both adolescents and adults (143).

Family structure and function

The environment in which parenting operates also impacts on the outcomes of practices used. Measures of family function vary, and the directionality of effect between function or dysfunction and disorders are not clear. In one adoption study, designed to distinguish environmental factors from heritable indicators, family function measures showed an effect on adolescent drinking levels, although this was less than the effect of sibling-related environmental factors (137). More recently, youth with comorbid anxiety and depression were found to have similar levels of family dysfunction to those with depression alone, but more than those with anxiety alone(159), but this was a cross sectional clinical sample, so the causal direction of the association could not be addressed.

Warmth and closeness

Warmth has been less often considered in studies than some other aspects of parenting (as noted in the Hoeve meta-analysis(158)), but a number of reviews have shown it to be linked with alcohol problems, depression and anxiety. Some evidence has been shown that rejection and hostility (or lack or warmth) from parents are involved in the development of child delinquency, which is related to alcohol problems (158). McLeod's review showed that parental hostility and rejection also had an effect on child depression, greater in fact than that of parental control (156). Consistent with these findings, Saraceno's review showed that lack of warmth, along with parental neglect, was linked with increased risks of adolescent alcohol problems and internalising symptoms in both adolescents and adults (143), while de Vore noted that increased warmth was related to decreased anxiety in children (153).

It has been suggested that a lack of warmth from parents leads to underdevelopment of control by the child of arousal and impulsivity. Lack of parental reaction can result in the child not developing a desire to control their externalizing behaviour in order to elicit a more positive response from the parent. Similarly, low levels of warmth can promote avoidant behaviour in the child, which can then develop into internalising disorders (160).

Closeness, or bonding between parent and child, has also been shown to lead to greater uptake of parental behavioural norms, and protect against association with deviant peers and initiation of substance use (161). A sound parent-child relationship has been found to predict resilience in children and adolescents (117). Conversely, negative communication has been linked to higher drug use. More recently, using Australian data, emotional closeness to the opposite-sex parent has been found to be protective (162, 163)

against the development of high risk behaviours, including problematic alcohol use. These findings have been repeatedly replicated and are the basis for many youth prevention programs (164-167).

Conflict

It has been suggested that disruption of the family environment by conflict and divorce may impact on child disorders through a number of mechanisms: the modelling of poor conflict resolution by parents, less consistent discipline or parenting practices, disruption of bonds between parent and child, and stress placed on the child (168). Several of these may hold, as this disruption is associated with disorders of both parents and children.

More marital discord and conflict was observed within the families of depressed women as reviewed by Burke (169); the conflict and discord were recently found to mediate (at least partially) the relationship between parental and child depression, as well as acting as an independent risk factor (170). Family conflict and divorce have been associated with both adolescent alcohol problems and internalising disorders for adolescents and young adults across a number of studies (143), with conflict having more influence on drug use than structural change (divorce or separation) (161). One study has shown family conflict to be related to comorbid alcohol use and mental health disorders, but this analysis did not account for parental disorders (171) of either type. It is also possible this effect may be gender related: Kelly and colleagues showed recently that family conflict was associated with early drinking of girls but not boys (162), but did not consider mental health problems.

Others have suggested that conflict between the parents may be created by trying to deal with the child's symptoms, such as anxiety (168). However, this directionality does not appear to hold for all disorders. The results of a longitudinal study suggest that although parent-child conflict predicted the development of conduct problems (a risk factor for substance use disorders) and antisocial behaviour in adolescents, the conduct problems did not predict increases in parent-child conflict (172, 173). This effect was confirmed as purely environmental, rather than genetic: similar effects were seen for biological and adopted adolescents.

Family Structure

Although it has been suggested that family structure *per se* may be related to substance use and mental health disorders, potentially via the lower socio-economic status related to single parent families, more evidence points to changes in family structure as being directly relevant to increased risk of comorbidity. A review by Saraceno and

colleagues indicated that adverse family conditions such as divorce were linked to higher risks of adolescent alcohol problems and internalising symptoms (143).

However a review by Nunes-Costa suggested that the effect of divorce on child adjustment stems less from the divorce itself, working instead through the factors such as inter-parental conflict, parent disorders and parenting inconsistencies that arose from the divorce (174). In another study, Alati and colleagues found that frequent partner changes, interacting with low maternal control, was the strongest tested predictor for the development of alcohol problems at age 14 (175), and that this potentially acted through lower levels of monitoring. Adding detail, a birth cohort study in Rhode Island showed that family disruption prior to child's age 7 increased the risk of depression, most markedly adolescent-onset depression, and that this effect was stronger in females (176). The effect of family structure on comorbidity has not yet been reported in prospective studies.

Stress

Stress has been shown to impact on the expression of other disorders, with both intra-familial and external stressors influencing the development of comorbidity. For example, children of depressed parents were more likely to show depressive symptoms where high parental expressed emotion acted as a stressor for the child (150, 177). However, contrary to the evidence above about conflict, a recent analysis of data from the Minnesota Twin study suggested that life stressors outside the family (so excluding divorce) were more likely to be associated with internalising disorders at age 17 than were problematic parent relationships (178). Similarly, other studies have associated stressful life events beyond the family with drinking among adolescents with depression (179), and childhood trauma appears to account at least partially for comorbid anxiety and alcohol problems in adolescence (155).

These stress-responses may have less to do with learned reactions to stress and coping styles than with genetically determined biochemical responses which describe a stress-sensitivity (109, 180, 181). It has been suggested that exposure to major negative life events can activate genetic risks for child and adolescent depression (182). Internalising disorders in adolescents (143) and young adults (183), specifically those in response to stress (184), have been shown as associated with the activation of specific brain regions (109) and specific alleles of the serotonin transporter, monoamine oxidase A and dopamine receptor genes, which are implicated in the regulation of mood. Development of effective coping skills has been suggested as effective in enhancing resilience to stressors and the associated disorders (185).

The role of stressors and the capacity to cope with these is discussed in the paper "*Individual, school-based and family characteristics distinguish co-occurrence of drinking and depressive symptoms in very young adolescents*", which forms part of Chapter 5.The relationship between family environment and the early stages of development of comorbid alcohol and mental health disorders is discussed in the paper "*Individual, school and family characteristics distinguish co-occurrence of drinking and depression in very young adolescents*" which is incorporated in Chapter 6.

Poverty or socio-economic stress

Poverty, a more continuous external stressor which acts on both mother and child, has also been shown using the MUSP data to increase the development of both depression and anxiety (186). Other aspects of low socio-economic status have also been associated with comorbid alcohol and mental health disorders, although the heterogeneity of measures used make comparisons challenging (12). Indicators of SES such as low family income (187-189), restricted education (190, 191) and limited social support (179) are all arguably continuous stressors which contribute to the development of comorbidity.

The role of socio-economic factors and disadvantage in the development of comorbid alcohol and mental health disorders is discussed in the paper "*Does early socio-economic disadvantage predict comorbid alcohol and mental health disorders?*" which is included in Chapter 6.

Parenting Practices

Three major styles of parenting have been widely described in the literature: authoritative, permissive and authoritarian. The authoritative style involves strict boundaries but also high levels of warmth, whereas a permissive parenting style involves high levels of warmth but low levels of control and limit setting. The third, authoritarian style is typified by strict boundaries, high levels of control and low levels of warmth.

Authoritative parenting has been associated with fewer negative behavioural outcomes and is regarded as a factor protecting against the development of alcohol use problems in adolescence (153, 161, 192). It has also been associated with less anxiety in pre-adolescents (9-14 year-olds), than are authoritarian or permissive styles. It has also been associated with lower levels of alcohol and drug use (193-196).

The setting of boundaries and expectations for acceptable behaviour ("norming") is a central parenting practice. Inconsistent or unclear behaviour limits and parental

permissiveness have been strongly associated with substance use and delinquency (161) and externalising behaviour as discussed above (158). Parental norms regarding alcohol use are more likely to be adopted by children in warm, supportive environments, and although norming effects are strongest in young children, they have been demonstrated to persist into adolescence (192). Unsupportive or inconsistent parenting has been linked with both anxiety and aggression (168), possibly by generating a sense of insecurity in the child, as does inconsistency between parents. A link has also been shown between inconsistent discipline and persistent externalising behaviours, potentially due to reinforcement of early behaviours, or rather lack of corrective action.

Although comorbidity was associated with poor family management in one study (171), and with maternal inconsistency with rules in another (197), the literature on parenting is muddied by inconsistent methods of measuring facets of family and parenting environments. In addition to this, factors may be defined by parental report, child report or observational studies. Child reports are limited by the age at which a child can adequately describe parenting styles or practices. However, child reports reflect their *perception* of the parenting style, and have been congruent with the more broadly accepted observational studies of examining anxiety (193) and drinking disorders (196). The use of observational studies for large cohorts may be limited by resources, and parental reports, although convenient, may however be biased by the social desirability element of responses. The use of retrospective reporting of parenting may also introduce recall bias, particularly where adults are recounting parental practices from early childhood.

Summary – contributions of the family environment

The literature describing the impacts of parenting and the family environment on the development of alcohol use disorders and of mental health disorders is sometimes contradictory, but it appears that the parenting relationship has, at very least, the potential to modulate the impact of other factors (such as parent disorders) on child well-being. This potential, in addition to the limited literature on the impact of parenting on comorbidity, indicates that parenting practices and family function may be important in its development. The complex interplay between family environmental factors and parental disorders in the development of comorbidity will require careful modelling.

The impact of comorbidity on other persons

Comorbidity may also impact on those beyond the comorbid person. Treatment literature shows clearly that persons with comorbid mental health and substance use issues experience worse health outcomes than those with single conditions. Disorders persist longer, require more intensive treatment, and some established treatments such as pharmacotherapies for depression and anxiety are complicated by substance use issues of drug interaction and lack of compliance. There is a need to also focus on personal relationship outcomes, for which less information is available.

Mental health disorders are well documented as impacting on inter-personal relationships (142, 169, 186). There is also growing literature on the outcome of problematic alcohol consumption on others: on inter-personal relationships, interpersonal violence and inappropriate public behaviour involving accidents and injury to others (198, 199). It is possible that the behavioural under-control associated with alcohol use disorders (192) may interact with underlying mental health problems to reduce barriers to violence. Aspects of these issues are discussed below.

Antisocial behaviour, aggression and violence

Aggression is examined here as a specific aspect of antisocial behaviour; it has a strong association with alcohol use disorder, also characterised by disinhibition, suggesting the potential for interactions, or possibly common predictive factors (200). Aggression is commonly regarded as a male trait, with most studies focussing on males. Early (pre-adolescent) aggression in boys has been shown to predict involvement in alcohol, drugs and delinquency in adolescence, as well as internalising and externalising behaviours (201).

Several twin studies have found that aggression or aggressive antisocial behaviour is a stable, heritable trait, which is likely to persist over time and be less influenced by environmental factors (202, 203). Longitudinal studies, including the MUSP, the Dunedin cohorts and the Australian Temperament Study, have shown that antisocial behaviours persist into adulthood. Those who manifest these from childhood and adolescence exhibit higher levels of substance abuse, poorer adjustment in relationships (204) and elevated symptoms of anxiety and depression (205, 206). Interestingly, antisocial behaviour has not however been shown to predict alcoholic bingeing (205), which is commonly associated with acts of violence; it is possible that other temporalities apply. In the following section, the associations between alcohol and violence and mental health and

violence will first be considered separately, after which commonalities and any literature on comorbidity and violence will be discussed.

The nexus between behavioural problems and comorbid alcohol and mental health disorders is further discussed in the paper "*Do young people with comorbid mental and alcohol disorders experience worse behavioural problems?*" which is included in Chapter 5.

Mental health, alcohol and violence

The combination of alcohol use and mental health disorders exacerbates the risk of violence. Several studies of schizophrenia patients showed that their odds of violent behaviour increased if alcohol was used (207); the odds were higher again if poly-substance use was involved (208). Similarly, patients with early psychosis reported high levels of perpetrating verbal or physical aggression, and were more likely to report violent behaviour if there was a history of substance misuse (209). A systematic review and meta-analysis by Fazel showed that the presence of schizophrenia and other psychoses markedly increase the odds of interpersonal violence or violent crime, with greater odds for women, but noted substantial heterogeneity across studies. Comorbid substance abuse increased these odds approximately four-fold (210). Common findings that the risk of substance use disorders (SUD) alone was similar to that of comorbid schizophrenia and SUD, but greater than for schizophrenia alone, suggest that most of the excess risk is mediated by the substance misuse rather than the mental health disorder.

In a more detailed study, Mulvey and colleagues followed mentally ill patients up weekly for six months, showing that violence was more likely to occur on the day of or after alcohol intoxication. The reverse order did not hold. The authors suggested that alcohol may have been functioning as a disinhibitor of violent tendencies, but allowed that some situational violence may have been associated with the place of alcohol consumption. The study did not distinguish the effects for different disorders, noting only that 76% were diagnosed with affective disorders, 45% with substance use disorders and 45% were comorbid (211). A review by Davis of depression and alcohol use disorders noted a similar increase in violence for comorbid conditions, as well as greater intensity of depressive and anxious symptoms (28). However this evidence linking violence and comorbidity is drawn from clinical samples, often with very severe disorders, rather than samples representing the general population.

Alcohol and violence

In the 2010 Australian National Household Drug Survey, 8.1% of respondents reported being victim of physical abuse from an intoxicated person in the last 12 months. 24.7% had experienced verbal abuse and 14.3% had been put in fear of abuse (3), and these figures showed an increase on those reported in 2007. In the US, the National Longitudinal Study of Adolescent Health (US) also showed strong cross sectional associations between alcohol use and violent behaviour among young drinkers, but longitudinal associations have also been found between high-volume drinking and violence (212) and between alcohol use disorders and violence (213). In a separate study of comorbidity in young adults, 8.7% of participants self-reported substance use and violent behaviours; the link was again stronger among males, with sensation seeking and the perception of antisocial rewards increasing the risk of violence among drinkers (214).

The mechanism of this association is still not entirely clear although some research points to a causal association. In laboratory simulations, alcohol consumption has been shown to increase aggressive behaviour in both men and women. Men were likely to express alcohol related aggression in direct and indirect forms, and were more aggressive to other men. Women were more likely to use indirect forms of aggression, and were equally aggressive to men and women (215). A more recent study, again using laboratory simulations, has shown that a failure to consider future consequences exacerbates this effect of alcohol on violent behaviour (216), with gender effects again noted (217).

Mental health and violence

In a large review, Dubreucq and colleagues noted that although a large proportion of violent offenders are not mentally ill, mental disorders represent a risk for violence against others that is significantly higher than that of the general population. A greater risk of assault was associated with non-compliance with medications, acute psychotic symptoms and alcohol or drug abuse (218).

Schizoid disorders in particular have been extensively investigated for links with violent behaviour. A significant literature base including clinical, epidemiological and longitudinal studies links schizophrenia and schizoid disorders with violence and aggression. In a 2000 review, male gender, non-compliance with medication and repeat intoxication were found to be linked to violent behaviour (219). A later series of studies from the same authors followed large cohorts of adult psychiatric patients after release from treatment, using national crime records to track offences committed. Nearly 4% of schizophrenia patients

and 5% of affective disorder patients committed violent offences in the 7-12 year period post release. These offenders were more likely to be male and have hostility syndromes (220, 221).

More common disorders such as depression have been linked with violence and aggression in larger population-based samples. Analysis of a subsample of depressed mothers has shown that maternal depression, fully mediated by adolescent depression, predicted aggression at age 20 in the MUSP study (222). Similarly, a subgroup from the Dunedin longitudinal study showed that men who self-reported violent episodes were more likely than non-violent men to have depressive disorder or anxiety disorders, or to be alcohol dependent.

In seeking to understand the mechanisms underlying these relationships, serotonin levels were monitored in the Dunedin study. Violent men were found to have higher levels of serotonin than non-violent men. In other studies, variations in the serotonin transporter gene (5-HTTLPR) have been seen to moderate the stress/aggression association. Those with a shortened allele of the gene's promoter region show a more aggressive response to chronic stress, but without a gender difference (223). However, the observed association between violence and serotonin, which held only for men, appeared to be independent of any relationship between the violence and alcohol dependence, depressive or anxiety disorders, mania and IQ (224).

In one of the few studies examining comorbidity, a patient study of post-traumatic stress disorder (PTSD) sufferers with comorbid substance use disorders showed that higher levels of alcohol use exacerbated their risk of violent behaviour. A specific correlation was shown between the hyper-arousal symptoms of PTSD and violence (225), possibly related to the functionality of serotonin in modulating the response to environmental stressors.

Relationship violence

Relationship violence, or intimate partner violence, is a specific case of interpersonal aggression. Some associations are similar: In two sets of case reviews, one of primary care patients, the other more extreme of homicides, each noted a high proportion of cases involving mental illness, as well as substance use disorders among perpetrators (226, 227).

Moffitt and colleagues however show that intimate partner abuse is a specific construct distinct from other antisocial behaviours (228). General violence was linked to weak

constraint or low self-control, whereas intimate partner violence was not. In a study based on a subsample of the MUSP, being depressed predicted being a victim of intimate partner violence at age 20. This relationship was partially mediated by social functioning at adolescence, potentially suggesting that negative outcomes could be ameliorated by learned coping skills. This is supported by a later analysis which showed that depression at 15 which later resolved was associated with better outcomes at adulthood (229).

One final study illustrates cyclic behavioural links. Adolescents with a psychiatric disorder were more likely to become involved in abusive relationships as young adults, as either aggressor or victim. Although this held for both men and women, some gender differences were seen. Those in abusive relationships were more likely to then develop later psychiatric disorders, independent of any history of mental illness (230, 231).

The links between substance use and mental health disorders and relationship violence are further discussed in the paper "*Substance use and mental health disorders are linked to different forms of intimate partner violence*" which is incorporated in Chapter 6.

Summary – impact of comorbidity on others

The studies above suggest that complex relationships may exist between mental health, alcohol use disorders and violent or aggressive behaviour, but the specific relationships with comorbidity are not well-documented. Relationship violence as a specific subset of such behaviour is also linked, but the causal direction of the association between the disorders is not clear.

Literature Overview

Comorbidity between alcohol and mental health disorders is common and may be increasing in prevalence. It has a significant impact on individuals, health services and communities, and is often under-treated. There is evidence to suggest that key symptoms emerge largely in late adolescence and early adulthood, which makes young adults a prime target for investigating the features of comorbidity.

Very early life is important in the development of both alcohol and mental health disorders, with some studies, though not all, suggesting that this begins during prenatal development. There is also some evidence for the effect of parental anxiety, depression and alcohol use disorders on comorbidity in the children and that stress and parenting behaviours may each have an impact on these relationships. Lastly, complex relationships

exist between mental health, alcohol use disorders and violent or aggressive behaviour, with implications for relationships at adulthood. However, there are notable gaps in the literature on these factors as they relate to comorbid, rather than single, disorders. Additionally, very few studies have attempted to explain the interplay between these domains and their associations with the development of comorbidity.

Data from the prospective MUSP study present a number of opportunities. In this study, it has been possible to model the associations of very early life factors such as IQ, birth weight, maternal drinking and socio-economic factors with comorbid alcohol and mental health disorders. Thence data from childhood and adolescence have been investigated to provide information on later family-related influences, evaluating the effects at different periods of child development. Finally, links between comorbid conditions and behaviours such as aggression and violence at young adulthood have been explored, and the role of illicit substance use disorders in alcohol/mental health comorbidity also examined. In this way, it has been possible for the first time to build a comprehensive picture of factors across the life span which influence the development of comorbidity, and of the debilitation associated with this condition, even as early as young adulthood.

Chapter 3: Methods

Introduction

The majority of this research program uses data from the Mater-University of Queensland Study of Pregnancy (MUSP), a longitudinal pre-birth cohort of mothers and their children followed from early pregnancy to 21 years. The use of this cohort has allowed the assessment of a broad range of demographic, lifestyle, physical health and anthropometric measures which may be related to the development of alcohol and mental health disorders at young adulthood. In particular, the longitudinal nature of this study, with most measures collected prospectively, has allowed the investigation of temporal pathways and reduced reliance on retrospective assessments and the introduction of bias due to recall. However, the nine-year gap between follow-ups at early childhood (5 years) and adolescent (14 years) for this cohort meant that information on the very early adolescent years (10-14 years), a developmentally sensitive period, was not available.

Another large Australian sample of children, the 2006 Healthy Neighbourhoods Study, which covered this period, was also included. Although this latter sample was cross-sectional, it comprised children between ten and fourteen years old from communities across three states and provided data on individual, family, school and community dimensions of potential importance to the development of comorbidity.

This chapter gives an overview of the datasets and discusses the choice of analytical strategies. The MUSP study is described first, followed by the Healthy Neighbourhoods study. A copy of the Ethics Approval granted for this study by the School of Population Heath Research Ethics Committee is included as Appendix 1. Detailed information regarding specific factors used in each analysis can be found in the individual manuscripts which comprise the Results section, with further detail on each variable contained in Appendix 2.

MATER-UNIVERSITY OF QUEENSLAND STUDY OF PREGNANCY (MUSP)

Background, participants and phases of the MUSP

The Mater-University Study of Pregnancy (MUSP) is a longitudinal pre-birth cohort study of mothers and their children. Mothers were recruited between 1981 and 1984 at very first clinic visits for obstetric care to the Mater Misericordiae Hospital in Brisbane, Australia. Consecutive public patients were approached, with 8458 women agreeing to participate. Of these women, 7223 gave birth at the Mater Hospital to singleton progeny who survived to discharge. Two cohorts, mothers and children, were established. Some 520 women had more than one pregnancy during the recruitment period, but a separate questionnaire was completed about each child within the cohort. Mothers were re-interviewed at 3-5 days and 6 months after the child's birth, and then followed up at 5, 14 and 21 years. Data were collected on both mother and child at each time point, including obstetric data, physical measures, questionnaires and diagnostic psychiatric interviews. The development of the cohort is shown diagrammatically in Figure 1 (Chapter 4).

The MUSP was approved by the Behavioural and Social Sciences Ethics Review Committee at the University of Queensland and the Mater Health Services Human Research Ethics Committee and has been extensively described elsewhere (232).

At the five-year follow up, 5259 mothers provided information on their child and 5234 on their own health. Physical and developmental measures were collected for 4000 children. At 14 years, 5185 mothers remained in the study and completed interviews and questionnaires about their own health and that of their children. A subset of the mothers (n=3700), selected for ongoing contact with the child's biological father, completed an additional questionnaire about the child's father. The child cohort (n=5170) completed questionnaires about their own health and behaviour. Of these, approximately 3800 also completed physical and developmental testing.

A total of 3778 offspring participated in the 21-year follow up, providing physical measures and completing questionnaires. A subset of these (2539 participants) also completed the Composite International Diagnostic Interview (CIDI (233)) in order to generate DSM-IV diagnoses of mental health and substance use disorders.

At the time of recruitment, the MUSP cohort was found to be representative of the lower-middle range of SES in Brisbane. Attrition analysis has shown that mothers lost to follow up are more likely to have been younger and un-partnered at childbirth, to exhibit depressive and anxious symptoms, and come from a lower family income family. Loss to

follow up has been affected by participants changing residence and contact details or no longer being interested in continuing with the study. This became more pronounced with later follow ups at which more complex and time consuming data were collected. These effects have been exacerbated by the length of time between later follow ups (e.g. 5 to 14 years, and 14 to 21 years). In addition, use of the CIDI at 21 years added considerably to the cost of data collection and limited the number of participants able to be examined. However, the remaining sample provided sufficient power to examine complex constellations of precursors. Retention of participants and the data provided are outlined in the table below.

Summary of data from each phase of the MUSP and response rates

Study stage	Data type	Mothers	Response rate %	Children	Response rate %
FCV*	Questionnaire	8458	-	n/a	-
Birth	Obstetric	7223	100	7223	100
5 years	Questionnaire	5234	72	5259	73
	Developmental	n/a	-	4010	56
14 years	Questionnaire	5185	72	5171	72
	Paternal	3734	52	-	-
	Developmental	n/a	-	3798	53
21 years	Questionnaire	3692	51	3778	52
	CIDI	n/a	-	2551	35
	Physical	n/a	-	2666	37

* FCV = first antenatal clinic visit

Measures

Substance and mental health disorder measures

DSM-IV diagnoses

At 21 years, 2551 offspring were administered the mental health and substance use modules of the Composite International Diagnostic Interview. Responses were coded to yield last-twelve-month and lifetime DSM-IV diagnoses of a range of substance and mental health disorders. These were grouped into alcohol, mental health and other-substance use disorders. The ‘any alcohol use disorder’ diagnostic group included alcohol abuse and dependence, whereas ‘any mental health disorder’ included all participants reporting an anxiety, affective, eating or psychotic disorder. The ‘illicit substance use disorder’ group included abuse and/or dependence for all illicit substances, i.e. excluding alcohol and

nicotine. These groups were non-exclusive, and within each group, the presence of multiple homotypic disorders was possible. The majority of analyses for this research program were conducted using lifetime diagnoses, in order to maximise the sample size.

Substance use disorders

CIDI responses at 21 years were used to generate two further substance use variables. One was a dichotomous variable indicating a lifetime diagnosis of ANY substance use disorder, **including** alcohol. This variable was used in Chapter 6, paper 6.2, examining the relationship between substance use disorders and intimate partner violence. The second considered lifetime diagnoses of substance use disorder/s **other than** alcohol. This category included cannabis, opiates such as heroin, stimulants including amphetamines and ecstasy, hallucinogens including LSD and prescription sedatives. For the purpose of latent class analysis (Chapter 7), these substance use disorders were further grouped into cannabis, stimulants, depressants and hallucinogens.

Inclusion/exclusion of illicit substance use disorders in modelling

For the majority of analyses, modelling focussed on alcohol use and mental health disorders such that illicit substance use diagnoses were not assessed. In order to then characterise any impact of illicit substance use disorders on the relationships under consideration, sensitivity analyses were then conducted a) without inclusion of illicit-substance using participants, and b) adjusting for illicit substance use disorders. Where a direct comparison was desired between alcohol use disorders and illicit substance use disorders, as for Chapter 6, paper 6.3, participants were grouped into exclusive categories.

Temporal overlap of disorders to confirm comorbidity

A number of studies have used lifetime diagnoses of each component disorder as the basis of assessing comorbidity (20-22, 39). In older adults, there is a significant chance that this may represent sequential disorders rather than co-occurring symptoms, and may thus provide limited information about the interaction between disorders. In younger persons, mental health and substance use disorders are commonly episodic (18), suggesting that the use of lifetime diagnoses may be similarly inconclusive. For the purpose of this study, I have used a classification of comorbidity which requires that participants report episodes of both alcohol use disorder and mental health disorder within a 12-month period, to indicate temporal overlap. The use of last-12-month diagnoses has been used by other studies to adhere to this criterion (18). However by using lifetime diagnoses, but testing whether the onset of each individual's most recent alcohol use and

mental health disorder episodes occurred within 12 months of each other, we have been able to increase the size of our comorbid sample, and include co-occurrences prior to the year before assessment.

Disorder categories

For the majority of analyses, a four-category variable "Comorbidity Group" was used as the outcome: No (DSM-IV) disorder; mental health disorder but no alcohol use disorder (MHD); alcohol use disorder but no mental health disorder (AUD) and Comorbid ('any alcohol use disorder' plus 'any mental health disorder').

For a subset of analyses, a seven-category variable "Disorder Group" was created: No (DSM-IV) disorder; mental health disorder but no alcohol or illicit-substance use disorder (MHD); alcohol use disorder but no mental health or illicit substance use disorder (AUD); illicit substance use disorder but no alcohol use or mental health disorder (SUD); alcohol use or mental health disorder but no illicit substance use disorder (AUD/MHD); substance and mental health but no alcohol use disorder (SUD/MHD); alcohol or illicit substance use disorder but no mental health disorder (AUD/SUD) or all three disorder types (AUD/SUD/MHD).

Latent classes of substance use and mental health disorders

In order to categorise young adults by poly-substance use disorders, latent class analysis (LCA) was undertaken, using seven binary DSM-IV diagnoses as indicator variables (any anxiety disorder, any depressive disorder, alcohol abuse/dependence, cannabis abuse/dependence, stimulant (amphetamine or cocaine) abuse/dependence, depressant (opiate or sedative) abuse/dependence and hallucinogen (LSD) abuse/dependence.

Impairment

In order to assess the impact of disorders on a participant's life, two impairment scales were created. At 21 years, participants reported separately on how their alcohol or substance use had affected their life during the past four weeks. Eight items asked whether they felt troubled, frustrated or controlled by their use; if they worried about present or future health, or whether use limited their work or study performance, social life, or ability to go places. For each question a scale from one to five indicated increased severity. Item scores were summed to give an "alcohol problems" score (Cronbach's α=0.92) and a "substance problems" score (α=0.99). These were then categorised such that the top 10% of scores was positive for alcohol problems or substance problems.

Non-disorder substance use

In addition to the information on substance and mental health disorders generated by the CIDI, the following information on substance use was self-reported by participants through the main study questionnaires.

Smoking

At 14 and 21 years, participants self-reported the number of cigarettes smoked during the previous week. This was dichotomised (no smoking/smoking), or categorised to yield a 4-level smoking intensity scale (nil/1-9 cigarettes per day/10-19 cigarettes per day/20+ cigarettes per day).

Drinking alcohol

At 14 and 21 years, participants reported how often they consumed alcohol, and how many drinks per occasion. Adolescent (14 years) drinking was dichotomised such that drinking at least "a few times a year" and more than "1 or 2 glasses per occasion" was classed as positive. Young adult drinking (21 years) was categorised using NHMRC low-risk drinking guidelines (234) into non-drinkers, regular drinkers who did not binge (more than a few times/month, but never >5 drinks/session) and drinkers who did binge (>5 drinks/session). Age of first use was self-reported at 21.

Cannabis use

Cannabis use was self-reported at 21 years and dichotomised such that use "at least every few days" was classified as regular. Age of first use was self-reported.

Family factors

Parent health

Smoking

At FCV, mothers self-reported the number of cigarettes smoked daily prior to and during pregnancy. Similar reports of daily smoking were made at 5 and 14 years. For dichotomous variables, any smoking was deemed positive.

At 14 years, mothers reported on smoking by their partner (smoker/non-smoker).

Drinking alcohol

These measures differentiated between regular drinking and binge drinking. At FCV, 5 years, 14 years and 21 years, mothers reported how often they drank alcohol and how many drinks they consumed per occasion. These were combined to generate three

categories, using the 2009 NHMRC low-risk drinking guidelines (234): non-drinkers, regular drinkers (more than a few times/month) who did not binge (never >5 drinks/session) and drinkers who did binge (>5 drinks/session).

At 14 years, a subsample of mothers was asked "Has [the child's natural father] ever had an alcohol problem?" 'Paternal alcohol problems' was coded positive if this item was endorsed.

Mental health

Maternal mental health was assessed at FCV, 5, 14 and 21 years using the Delusions-Symptoms-States Inventory (DSSI (235)), which contains anxiety and depression subscales. The depression subscale has been found to correlate strongly with other depression scales, including Beck's Depression Inventory (236). Anxiety and depression are typically recorded as cases (235) where at least four of seven symptoms from that subscale are endorsed (depression α=0.88; anxiety α=0.84). A combined DSSI score summing all symptoms endorsed has been used to indicate mental distress (237). We dichotomised this score as positive for the highest 10% of scores (α=0.90).

At 14 years, a subsample of mothers was asked whether [the child's natural father] had ever had severe depression, difficulties concentrating when a child, overactivity when a child, a schizophrenic episode or panic attacks. 'Any paternal mental health problems' was coded positive if any item was endorsed.

Family environment

Mother-child warmth

The Parker Bonding instrument was used at 21 years to record offspring perception of maternal warmth and involvement during childhood (238). As parental warmth is a defining component of authoritative parenting practices, we used that subscale in our analyses (α=0.88); the lowest 10% of scores were coded as low warmth (238).

Parent-child communication

Open family communication was reported by mothers at 14 years using Barnes and Olson's Open Family Communication scale (239). This is a 10-item composite with higher scores indicating worse communication (α=0.85). The highest 10% were coded as poor communication as described (239).

Parental intimate partner violence

Mothers reported at 14 years on any experience of violence within their relationship during the past seven years; this was dichotomised (yes/no).

Residential area problems

Residential area problems (240, 241) were reported by the mother at 14 years. Vandalism, burglary, car theft, drug abuse, street violence, unemployment, driving offences, alcohol abuse and school truancy in the residential area were recorded as being no problem, moderate or a major problem. These items were summed to give a 'residential problems' score (α=0.93); the highest 10% of scores were categorised as 'problematic'.

Parenting practices

AT 5 years, mothers self-reported on parenting practices. The maternal control scale (α=0.64) comprised five items and was categorised into low, moderate and high using 10th and 90th percentile cut-offs. Disciplinary practices were also assessed using five items, each coded as always, sometimes or never: use of physical punishment (α=0.61); reasoning with the child (α=0.82) and applying consequences (α=0.73).

Family of origin socio-economic factors

Family income, employment and education were reported by the mother at baseline (first clinic visit; FCV) and coded binomially for disadvantage as below.

Family income

Family income at FCV was recorded as less than $2600pa, <$5200pa, < $10,400pa, <$15,600pa, <$20,80pa, <$26000pa or >$26000pa. The 1982 minimum wage was $7857; unemployment benefits were $6427 (married) or $3856 (single with dependents) (242). To account for the number of persons supported by the recorded family income, we conservatively coded un-partnered mothers as disadvantaged if family income was < $5200 and married/de facto participants as disadvantaged if < $10,400.

Parental employment

Maternal pre-pregnancy employment was coded as disadvantaged if recorded as 'unemployed', or 'on benefits'. A small proportion of women who reported 'studying' (0.64%) were also classed as 'disadvantaged', as this was presumed to have limited their

employment at that time. 'Home duties' was not coded as disadvantaged as this represented participation in home-based (although unpaid) work.

Partner employment was reported by the mother at FCV. This was coded as disadvantaged if 'unemployed', 'studying', 'on benefits', 'in prison' or 'no partner'.

Parental education

Education completed by the mother and the father were recorded at FCV as <Year 10, <Year 12, post-high school qualification or university qualification. Each was coded as disadvantaged if less than Year 12.

Marital status

Maternal marital status was self-reported at FCV, 5 and 14 years. This was dichotomised as partnered (married/living together) or un-partnered (single, divorced/separated/widowed).

At 14 years, mothers also reported on cohabitation with the child's natural father (yes/no) and the number of times they had changed partners since the child's birth (0-5).

Mother's age at birth

Mother's age at birth was calculated from mother's and child's date of birth as extracted from hospital obstetric records.

Racial background

Mother's and fathers' ethnicities were recorded at baseline as Caucasian, Asian or Aboriginal/Islander.

Offspring characteristics

Gender and age

Offspring gender and date of birth were extracted from hospital obstetric records at birth.

Birth weight and gestational age

Gestational age in weeks (GA) was extracted from hospital obstetric records at birth; this was used initially as a continuous variable.

Birth weight (in grams) was extracted from hospital obstetric records at birth. Birth weight was internally adjusted for gestational age and gender to give a z score as

previously described (113, 114, 243). This was then categorised by quintiles, with one being the lowest z-score and five the highest.

IQ

IQ was measured at age 5 using the Peabody instrument and at 14 using the Raven Progressive Matrices and the Wide Range Achievement Test (WRAT). Each yielded a score which was considered as a continuous variable, or categorised into normal, below normal and above normal or by percentiles. Peabody scores of 85-115 are considered "normal range". Scores were also categorised into quintiles as for birth weight.

Behaviour problems

Behaviour problems were assessed using Achenbach's Child Behavior Check List (maternal report) at 5 years, the Youth Self Report (YSR) at 14 years, and the Young Adult Self Report (YASR) at 21 years (244, 245). These scales comprise 114 items describing a range of behaviour problems experienced over the 6 months prior to assessment. The YASR was developed for use with young adults aged 18-30 years in clinical settings (246) but has been validated in large population samples (247).

The Youth Self Report comprised eight sub-scales (withdrawn, somatic, anxious/depressed, social, thought, attention, delinquency and aggression). These were grouped into internalising (anxiety/depression, somatic and withdrawn; α=0.87), externalising (aggression 0.84 and delinquency 0.71; combined α=0.87), a combined attention and/or thought subscale (α=0.81), and a total problems score.

The Young Adult Self Report had internal reliability scores of 0.91 in this sample (248). The total problems score comprised the internalizing (anxiety/depression; α=0.91 and withdrawn; α=0.72) and externalizing (intrusive α=0.72, aggression (α=0.81) and delinquency (α=0.72)) scales plus the somatic (α=0.81), thought (α=0.61) and attention (α=0.70) subscales.

Each scale or subscale was used as a continuous variable, or categorised using a 90th percentile cut-off to indicate case-ness (246, 248).

Young adult demographic factors

Education

At 21 years, participants recorded the highest level of education completed. This was dichotomised such that completion of less than Year 12 (high school) constituted lower education. Education achievement was reported as the participant's Overall Position (OP),

which ranged from 1 (highest) to 25 (lowest). The Overall Position is a bell-curved tertiary entrance rank used in Queensland which summarises a student's performance over the last two years of high school, relative to other tertiary-eligible students.

Employment

At 21 years, participants reported whether they were in paid employment. This was dichotomised such that less than part-time employment was deemed not employed.

Family structure

Cohabitation with a partner (249) (no/yes) and the number of children in care of the participant were self-reported at 21 years (250).

Socio-economic disadvantage

Children's socio-economic disadvantage at 21 years was estimated using the level of education completed. As many offspring were still studying at that time (37%) or living with their parents (65%), income and employment were not considered measures that would accurately reflect socio-economic disadvantage.

Significant experiences

Experience of childhood sexual abuse

At 21 years, participants self-reported whether they had experienced sexual abuse and at what age this had occurred. Abuse before the age of 16 was dichotomised (no/yes). (251)

Initiating independence

At 21 years, participants reported at what age they had left the family home. This was dichotomised such that leaving before the age of 17 (when most Queensland children complete Year 12) was classed as early.

Intimate partner violence

Intimate partner abuse was assessed at 21 years using a modified Composite Abuse Scale (252, 253), comprising 20 items which assessed frequency of ever experiencing emotional abuse (12 items; α=0.92), physical abuse (5 items; α=0.93) and severe combined abuse (3 items; α=0.75; included sexual abuse and use of a weapon). For each item, higher scores indicated more frequent occurrence. For each scale, both total scores and the number of items endorsed were recorded to describe severity and diversity of abuse, respectively. Scales were also dichotomised such that for physical and severe

combined abuse, endorsement of any single item was positive (213, 254, 255). For emotional abuse, endorsement of two items was required (254).

Analytical approaches

Descriptive statistics

In initial analyses, the distribution of comorbidity groups at child age 21 was determined across each factor under consideration, using a proportion of respondents where factors were categorical or a mean score where continuous. Variation across the comorbidity categories was tested using ANOVA, with post-hoc pair-wise t-tests used to examine differences between categories. Where distributions were positively skewed, ANOVAs were performed using transformed scores (e.g. square root of score). Where results (in terms of levels of significance of differences) did not differ from those for untransformed scores, the effect estimates from the latter were presented for ease of interpretation.

Prediction models

Multinomial logistic regression

As the DSM-IV yields dichotomous diagnoses, and the central interest was a direct comparison between comorbid alcohol/mental health disorders and each single disorder, or no disorder (i.e. a total of four mutually-exclusive categories), multinomial logistic regression modelling was used (256). This extension of logistic regression analyses estimates the relationship between independent variables X_1 to X_k and the odds that the outcome variable Y will belong to a particular category j compared to the odds that it will belong to reference category j'. This is shown using the equation

$$\log \frac{(\text{odds } Y = j)}{(\text{odds } Y = j')} = \alpha_j + \beta_j X_1 + \beta_j X_2 + \ldots + \beta_j X_k + e$$

For the purpose of these analyses, the outcome variable ranges from Y_0 (no disorder) to Y_3 (comorbid alcohol and mental health disorders). The reference category can thus be altered as appropriate to reflect the comparison required.

Univariable relationships were initially generated to yield Odds Ratios (OR) with 95% confidence intervals (CI_{95}) using the No Disorder group as reference. Multivariable regression models were then constructed, typically incorporating factors which had reached statistical significance (P<0.05) in bivariate associations. Where suggested by

the literature, interactions such as gender were examined. Analyses were then stratified by factors whose interaction terms reached statistical significance ($P<0.05$).

In order to directly compare comorbid group or co-occurring groups with single disorder groups, regression models were repeated, using each single-disorder group in turn as reference. This approach was used for the four-level comorbidity group outcomes (Chapters 4-6) and the four-class poly-substance use outcomes (Chapter 7).

When examining the association of different disorder/groupings with the experience of different forms of intimate partner violence (IPV), the risk of each form of violence was assessed individually, using disorder/groupings as predictors, and adjusting the models for other forms of IPV (Chapter 6, paper 6.3).

Lastly, where only alcohol use disorders were included in the outcome variable, potential confounding by illicit substances was assessed by repeating the main analyses, firstly excluding participants with illicit substance use disorders, then adjusting for substance use disorders.

Factor analysis

Details of the factor analysis undertaken to generate the socio-economic disadvantage scale are described in the manuscript which forms paper 6.1 (Chapter 6).

Latent class analysis

Latent class analysis (LCA) is a technique used to identify unobserved heterogeneity in a population, assigning individuals to empirically derived classes, with the number of classes determined by a combination of the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC), the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (A-LMRT), and the bootstrap likelihood ratio test (BLRT) (257). This analysis was undertaken in Mplus version 6.

We used seven binary DSM-IV diagnoses as indicator variables (any anxiety disorder, any depressive disorder, alcohol abuse/dependence, cannabis abuse/dependence, stimulant (amphetamine or cocaine) abuse/dependence, depressant (opiate or sedative) abuse/dependence and hallucinogen (LSD) abuse/dependence) for the LCA. After determining the 'best' fitting model which ranged from 2 to 5 classes (no more than 5 classes were tested as we included only 7 indicator variables), individuals' posterior probabilities (i.e., the probabilities of each individual belonging to each of the classes)

were then exported to Stata version 12.1 for regression analysis in which the class variable was used as a multinomial outcome. To account for the uncertainty in the class membership we used 100 random draws of each participant's posterior probability to create 100 datasets, with the variability across these datasets reflecting the uncertainty (258).

Attrition

As with all longitudinal studies, loss to follow up is a significant consideration. Over the twenty-one years of the MUSP study, considerable attrition has occurred, with participants unable to be contacted or no longer wishing to be involved. Typically, those lost to the study by 21 years were more likely to be male, with younger mothers who were less educated, un-partnered at pregnancy and reported anxiety, depression and smoking at baseline. In order to assess how attrition may have affected the results, a multivariable regression model of attrition by 21 years was created using baseline predictors (maternal age, marital status, education, anxiety, depression, drinking and smoking and offspring gender).

Accounting for attrition used two procedures: multiple imputations by chained equations (MICE), and inverse probability weighting (IPW). Where it was appropriate to start from a Missing at Random assumption (259), the STATA procedure was used to impute missing data to create multiple imputed datasets. Imputation models used baseline factors above, in addition to variables used in the regression models. Missing data were imputed from both predictors and outcomes; this has been suggested as appropriate if a stable imputation model can be achieved which is not determined solely by analytical factors (259). For most analyses, 20 cycles of imputation were used in accordance with suggestions by Enders to minimise the increase in standard errors generated (260), after which the final analysis was repeated for each imputed dataset and the individual effect estimates pooled to obtain the final estimate. Sensitivity analysis used 50 cycles, with and without imputation of the outcome variable. Imputed results were then compared to those from the complete case analyses.

Where the Missing at Random assumption could not be justified, i.e. the subsample was not randomly selected (as for the maternal reports of paternal health and behaviours at 14 years), inverse probability weighting with robust estimates for standard errors was used to account for those lost to follow-up from the 7223 original cohort members,

according to recommendations (261, 262). Baseline predictors were fitted in a logistic regression model (response vs nonresponse as outcome) to determine weights for each individual using the inverse probability of response. The multivariable analyses were then repeated, including the weighting adjustments, and weighted results compared to the complete case analyses.

Unless otherwise indicated, all analyses were undertaken using STATA 12.1 (StataCorp, USA).

HEALTHY NEIGHBOURHOODS STUDY

Background and participants

In order to identify indications of early-emerging comorbidity, a large sample with detailed data on alcohol use and mental health in early adolescence was sought. Although cross-sectional, the 2006 Healthy Neighbourhoods (HN) Study can be considered as broadly representative of young adolescent Australian students. This study assessed risk and protective factors associated with alcohol and other substance use in school children across three Australian states (Victoria, Queensland and Western Australia). Ethics approval for the study was obtained from the University of Melbourne Human Research Ethics Committee.

The sample comprised 8001 students enrolled in late primary school (n = 4370, modal age = 11) and early secondary school (n=3631, modal age = 12). Thirty-one communities were randomly selected across quartiles of socio-economic disadvantage, using the Australian Bureau of Statistics Socio-Economic Indexes For Areas (SEIFA) to stratify the sample (263). Within each community, schools were randomly selected, with 231 electing to participate (61% government, 17% Catholic, 22% independent; 52% response). Consent to participate was given by government and Catholic Education bodies in each jurisdiction, or directly by principals of independent schools. Within each school, all students of the appropriate grade were invited to participate. Student participation was dependent on written parental consent, attendance on day of survey administration and student assent (67% response). Data were collected by student self-report during school time using a web-based questionnaire, the Communities That Care (CTC) Youth Survey, which was developed in the United States and adapted for use in Australia (164, 264,

265). All responses were coded for anonymity. The HN study protocol has been extensively described in other publications (162, 266).

Measures

Outcomes: depressive symptoms and drinking

Depressive symptoms in the two weeks prior to survey were measured using the Angold Short Moods & Feelings Questionnaire (SMFQ; α=0.91 in this sample) and dichotomised such that scores above 10 were coded positive, as correlating with clinically significant depression in adolescents (267, 268). Other CTC Youth Survey items asked participants about recent (past 30-day) and lifetime (ever tried more than a few sips) alcohol consumption; both were dichotomised as no/yes. Co-occurrence was recorded where participants were positive for both drinking in the previous month and depressive symptoms during the past two weeks. Respondents were grouped into four exclusive categories: control, depressive only, drinking only, and co-occurrence. In alignment with several other analyses published using these data, we also considered lower cut-off outcomes. Scores above seven for the SMFQ were considered indicative of emerging depressive symptoms (267, 269, 270), and lifetime drinking was included, as any consumption of alcohol at ages 11-14 can be considered risky according to National Health & Medical Research guidelines on alcohol (234, 271).

Risk and protective factors

A large range of risk and protective factors was also assessed by the CTC survey. The factors considered for this study are detailed below.

School based factors

School-based dimensions were used as examples of extra-familial stressors. Students recorded the number of school moves experienced since kindergarten: this was categorised as none, 1-2, 3-4 and 5+ moves. Composite items measured academic achievement (two items examined students' perception of overall grades and comparison to peers; α=0.68), and commitment to school (6 items measured truancy, effort, interest, enjoyment and perceived importance of schoolwork; α=0.77) over the last 12 months. Higher scores indicated low achievement or low commitment.

Family factors

Familial factors included composite measures of family conflict (three items examined family arguments and yelling; α=0.79) and family closeness (four items examined closeness and sharing with mother/father; α=0.77) (162). For these, higher scores

indicated more conflict or stronger family closeness, respectively. A family history of substance problems was reported via a single item and dichotomised as no/yes.

Individual factors

Individuals' adaptive stress-coping skills were measured using four items examining self-blame and self-efficacy (α=0.59); a higher score indicated good coping skills. All composite indicators were dichotomised as per previous research on this sample, such that the highest 15% of scores were positive. Demographic controls recorded on the CTC survey included gender, age, school level (primary/secondary) and sector (government/non-government), and cultural background (language/s spoken at home and Indigenous status). Socioeconomic status (SES) was estimated from the student's home postcode, using Australian Bureau of Statistics data to generate a SEIFA score (263).

Analytical approach

A four-group outcome was derived: Co-occurring, Depressive Only (i.e. non-drinking); Drinking Only (i.e. no depressive symptoms) and Control. Assessment of co-occurrence required a measure of recent alcohol use that was likely to overlap with the past-two-week measure used to report depressive symptoms; hence the last-30-days measure of drinking was used. Distribution of these groups was examined across participant demographics and key measures.

Multinomial logistic regression models were created to examine relationships between outcome groups and school-level, family-level and individual-level factors. The multivariable model incorporated factors with significant bivariate associations. Clustering at school level was incorporated as a random effect. As student age per grade was not constant between states, models were adjusted for age rather than grade, as well as gender and SES. This gave a final sample of 7000 for whom complete data on variables of interest were held.

Interactions with gender and school-level were examined, stratifying models where these were significant. The Control group was used as the initial reference category, but in order to directly compare the Co-occurring group to Drinking Only or Depressive Only conditions, the regressions were repeated using each group in turn as reference. Attributable Risks were calculated for the risk and protective factors identified in the models. Sensitivity analyses were undertaken using (i) a lower cut-off for depressive symptoms (SMFQ score >7) and (ii) any life-time drinking. All analyses were undertaken using STATA Version 12.1 (StataCorp, USA).

Results Section

These chapters describe the results obtained through a number of studies conducted. It is broken into four chapters, which examine: 1) preliminary characterisation of comorbidity in the MUSP offspring cohort; 2) the age at which early indications of comorbidity may be detected; 3) factors across the course of life which are associated with the development of comorbidity and 4) the place of alcohol/mental health comorbidity in relation to other substances.

In the case of preliminary studies, comment is made in these chapters on the relationship of these findings to other reports. The majority of the findings are discussed in the papers in which these studies have been published, with a summative discussion of the findings and implications being presented in Chapter 8.

Chapter 4: Preliminary characterisation of comorbid conditions in the MUSP cohort

Prevalence of DSM-IV diagnoses in young adults

This preliminary study identified DSM-IV diagnoses of disorders in the MUSP offspring cohort at 21 years (Table 2). Over half of the MUSP-21 cohort reported a lifetime mental health disorder at 21 years. Approximately one in four young adults reported an alcohol use disorder, with a similar proportion having experienced an anxiety disorder. One in four reported an affective disorder. Roughly half of these had occurred within the previous year, and of those, a third to one half in the preceding month.

Table 2: Lifetime, 12-month and 1-month diagnoses of DSM-IV disorders in MUSP-21 young adults

Diagnosis	**Lifetime**		**12-month**		**1-month**	
	N	*%*	*N*	*%*	*N*	*%*
Any affective disorder	**550**	**21.5**	**274**	**10.7**	**83**	**3.2**
any major depression	504	19.7	239	9.3	67	2.6
any mania	44	1.7	34	1.3	14	0.6
dysthymia	40	1.6	15	0.6	10	0.4
Total affective disorders§	588	23.0	288	11.2	91	3.6
Any anxiety disorder	**641**	**25.0**	**489**	**19.0**	**329**	**12.8**
any panic	92	3.6	68	2.7	30	1.2
agoraphobia	91	3.5	63	2.5	42	1.6
social phobia	204	7.9	106	4.1	65	2.5
GAD†	114	4.4	61	2.4	35	1.4
specific phobia	321	12.5	264	10.3	178	6.9
PTSD†	161	6.3	111	4.4	68	2.7
Total anxiety disorders§	983	38.31	673	26.2	418	16.3
Any alcohol use disorder	**712**	**27.9**	**359**	**14.1**	**131**	**5.1**
alcohol abuse	640	25.1	302	11.8	114	4.5
alcohol dependence	229	9.0	102	4.0	23	0.9
Total alcohol use disorders§	869	34.0	404	15.8	137	5.4
any psychosis*	36	1.4	19	0.7	13	0.5
Any DSM-IV diagnosis**	**1,479**	**58.5**	**1,036**	**41.0**	**625**	**24.7**

† GAD = generalised anxiety disorder; PTSD = post-traumatic stress disorder
§ Participants could be diagnosed with more than one disorder
* This category includes schizophrenia and schizophreniform disorders
**This category also includes eating disorders and other substance use disorders

In order to establish the MUSP birth cohort as a representative sample with regard to alcohol and mental health disorders, these diagnoses were compared with findings from other large national studies (Table 3). Prevalences for the MUSP offspring were consistent with reports on comparable age groups from large population-based studies in Australia (the 2007 National Survey of Mental Health and Wellbeing) and the USA (the National Comorbidity Study Replication and the National Epidemiologic Survey on Alcohol and Related Conditions).

Table 3: Mental health disorder prevalence in the MUSP-21 cohort and other population studies

Disorder	MUSP-21		Australia § (16-24yo)	Australia total § (16-85yo)		USA † (18-29yo)
	12m %	LT %	12m %	12m %	LT%	LT %
Any affective disorder	10.7	21.5	6.3	6.2	15.0	21.4
any major depression	9.3	19.7	-	4.1	11.6	15.4
any mania	1.3	1.7	-	1.8	2.9	5.9
dysthymia	0.6	1.6	-	1.3	1.9	1.7
Any anxiety disorder	19.0	25.0	12.2	14.4	26.3	30.2
any panic	2.7	3.6	-	2.6	5.2	4.4
agoraphobia	2.5	3.5	-	2.8	6.0	1.1
social phobia	4.1	7.9	-	4.7	10.6	13.6
generalized anxiety	2.4	4.4	-	2.7	5.9	4.1
specific phobia	10.3	12.5	-	n/r	n/r	13.3
PTSD	4.4	6.3	-	6.4	12.2	6.3
Any alcohol use disorder	14.1	27.9	11.1	n/r	n/r	30.3¥
alcohol abuse	11.8	25.1	8.3	2.9	18.9	17.8¥
alcohol dependence	4.0	9.0	2.7	1.4	3.8	12.5¥
Any MH diagnosis	-	58.5	26.4	20.0	45.0	-

§ Australian National Survey of Mental Health and Wellbeing 2007 (MHWB07) (5)
† National Comorbidity Study Replication (NSC-R) 2001 (32)
¥ National Epidemiologic Survey on Alcohol and Related Conditions 2001-2002 (88)

In the MUSP offspring cohort, 4% of participants recorded diagnoses of both an alcohol use disorder and a mental health disorder in the 12 months prior to assessment and 12% over their lifetime (Table 4). Of the lifetime comorbid group, all 305 experienced both disorder types within a twelve month period, fulfilling the criterion set for temporal overlap (Table 5).

Table 4: Allocation of MUSP-21 participants to comorbidity groups according to DSM-IV diagnoses

Diagnosis period	No disorder	MHD only	AUD only	Comorbid AUD/MHD
	N (%)	N (%)	N (%)	N (%)
12 months	1793 (71%)	388 (15%)	263 (10%)	95 (4%)
Lifetime	1237 (49%)	592 (23%)	405 (16%)	305 (12%)

Table 5: Overlap of disorder timings within the Comorbid group

Overlap type	N	%
Both AUD and MHD within last 12m according to CIDI	95	31.2
Recency of alcohol dependence & MHD within 12m of each other	26	8.5
Recency of alcohol abuse & MHD within 12m of each other	184	60.3
Total	**305**	**100**

Alcohol use disorders were significantly associated with both depressive and anxiety disorders, particularly mania and PTSD, but not with psychoses or eating disorders (Table 6). These figures were again consistent with large population studies in the US (NESARC(88), NCS(22)), the UK (Mental Health(6)), the Netherlands (NESDA(190)) and other European countries (40).

Table 6: Bivariate associations of alcohol use disorders with different mental health disorders in young adults, for lifetime and last-12-month diagnoses

Mental Health Disorder	Lifetime		12-month	
	OR	CI_{95}	OR	CI_{95}
Any affective	**1.64**	(1.34, 2.00)	**1.85**	(1.36, 2.54)
Major depression	**1.45**	(1.18, 1.79)	**1.61**	(1.15, 2.27)
Mania	**3.49**	(1.91, 6.38)	**2.00**	(1.45, 6.19)
Dysthymia	1.52	(0.78, 2.95)	2.73	(0.84, 8.93)
Any anxiety	**1.48**	(1.22, 1.80)	**1.53**	(1.17, 1.98)
Panic	1.26	(0.80, 1.98)	0.73	(0.33, 1.62)
Agoraphobia	0.86	(0.52, 1.40)	1.08	(0.53, 2.21)
Social phobia	1.17	(0.86, 1.61)	1.14	(0.66, 1.97)
GAD	**1.74**	(1.18, 2.57)	1.28	(0.64, 2.55)
Specific phobia	**1.35**	(1.05, 1.74)	**1.43**	(1.02, 2.00)
PTSD	**2.04**	(1.47, 2.82)	**1.73**	(1.09, 2.76)
Any psychosis	0.93	(0.43, 1.99)	1.31	(0.37, 4.57)
Eating disorder	1.73	(0.77, 3.87)	1.84	(0.50, 6.71)
Any MH disorder	**1.57**	(1.32, 1.88)	**1.67**	(1.29, 2.16)

Characteristics of DSM-IV diagnosed disorders in the MUSP-21 cohort

Descriptive statistics presented here indicate gender, socio-demographic and health indicator differences, as well as ages of disorder onset and some measures of complexity and severity. Participants who completed the Composite International Diagnostic Interviews (CIDI) to provide DSM-IV diagnoses at 21 years were compared to members of the original cohort, according to baseline features such as gender and socio-economic status.

Examination of demographic characteristics of the MUSP-21 young adult sample showed that although the alcohol use disorder group comprised more males (80% male) and the mental health disorder group, more females (75% female), the comorbid group did not have a gender bias (Table 7). More of the comorbid group smoked, they seemed to have started smoking earlier, and more of them reported other substance use disorders.

Table 7: Socio-economic and health characteristics of the MUSP young adult sample in each comorbidity group

Factor	Category	No disorder	MHD only	AUD only	Comorbid
		N (%)	**N (%)**	**N (%)**	**N (%)**
Total		1237 (48.7%)	592 (23.3%)	405 (16.0%)	305 (12.0%)
Gender	Female	624 (50.4%)	444 (75%)	79 (19.5%)	152 (49.8%)
Education [a]	Low	171 (14.0%)	135 (23.0%)	112 (28.4%)	96 (31.9%)
Employed	No	214 (17.5%)	166 (28.3%)	54 (13.7%)	89 (29.7%)
Income [b]	Low	387 (31.3%)	211 (35.6%)	47 (11.6%)	83 (27.2%)
Smoking	Yes	307 (25.1%)	227 (38.9%)	194 (49.1%)	118 (62.5%)
Other SUD [c]	Yes	128 (10.4%)	118 (19.9%)	192 (47.4%)	182 (59.9%)
Cohabitation	Yes	277 (22.7%)	168 (28.6%)	84 (21.1%)	63 (21%)
		Mean (CI_{95})	**Mean (CI_{95})**	**Mean (CI_{95})**	**Mean (CI_{95})**
Age	Years	20.4 (20.3, 20.4)	20.4 (20.3, 20.5)	20.5 (20.5, 20.6)	20.6 (20.5, 20.6)
Drinking age	Years	15.3 (15.0, 15.5)	14.9 (14.5, 15.2)	15.1 (14.9, 15.3)	15.2 (15.0, 15.4)
Smoking age	Years	15.9 (15.7, 16.0)	15.6 (15.4, 15.8)	15.3 (15.1, 15.6)	15.0 (14.7, 15.3)
OP [d]	1-25	7.6 (7.2, 8.1)	6.8 (6.2, 7.5)	5.7 (4.9, 6.6)	4.90 (4.0, 5.8)

[a] Low education: less than Year 12 had been completed
[b] Low income: less than $200/week
[c] DSM-IV diagnosis of a lifetime illicit substance use disorder (i.e. excluding alcohol or tobacco)
[d] OP=overall academic position at completion of Year 12; ranges from 25 (lowest) to 1 (highest)

Bivariate associations (Table 8) showed that only unemployment (29.7% of the comorbid group) and smoking (62.5% of comorbid group, younger age of onset) distinguished the comorbid group from both the MHD and AUD groups.

Table 8: Bivariate relationships between demographic and health characteristics of MUSP offspring participants and comorbidity group at 21 years

Factor	Category	MHD only	AUD only	Comorbid
		OR (CI_{95})	**OR (CI_{95})**	**OR (CI_{95})**
Gender	Female	**2.95** (2.37, 3.66)	**0.24** (0.18, 0.31)	0.98 (0.76, 1.26)
Education	Low	**1.83** (1.43,2.36)	**2.44** (1.86, 3.20)	**2.88** (2.15, 3.86)
Employed	No	**1.17** (1.09, 1.26)	**1.16** (1.07, 1.26)	**1.33*** (1.21, 1.45)
Income	Low	1.22 (0.99, 1.50)	**0.29** (0.21, 0.41)	0.82 (0.62, 1.09)
Smoking	Yes	**1.90** (1.54, 2.34)	**2.87** (2.27, 3.63)	**4.95*** (3.79, 6.46)
Other SUD	Yes	**2.15** (1.64, 2.83)	**7.80** (5.97, 10.19)	**12.90*** (9.62, 11.30)
Cohabit	Yes	**1.36** (1.09, 1.71)	0.91 (0.69, 1.20)	0.91 (0.67, 1.23)
Age	Per year	1.05 (0.93, 1.18)	**1.26** (1.10, 1.44)	**1.30** (1.11, 1.52)
Drinking age	Per year	**0.91** (0.85, 0.98)	**0.67** (0.62, 0.72)	**0.68** (0.63, 0.74)
Smoking age	Per year	**0.93** (0.86, 1.00)	**0.88** (0.81, 0.95)	**0.80*** (0.74, 0.87)
OP	Per point	0.99 (0.97, 1.00)	**0.97** (0.95, 0.98)	**0.95** (0.94, 0.97)

* $OR_{comorbid} > OR_{AUD}$ and OR_{MHD} ($P<0.05$)

Although some very early episodes of anxiety and depression were recorded in this cohort, the mean ages of onset for were very similar for all four disorder types (Table 9), highlighting adolescence and late teen years as important.

Table 9: Age of disorder onset for each disorder type

Age (years)	AUD	Depression	Anxiety	Psychosis
Mean onset age for cohort	18.9	19.1	19.0	18.7
Youngest recorded episode	14	9	6	13
Most recent episode	22	22	21	21

Disorder severity was estimated using two measures: 1) the number of separate mental health disorder diagnoses recorded for each participant by 21 years (Table 10); and 2) the impairment perceived by each individual as a result of their alcohol and other substance use (Table 11). The mean number of mental health disorders recorded by members of the MHD only and Comorbid groups were very similar. However the Comorbid group appeared to have somewhat more participants with high levels of multi-morbidity (four disorders or more).

Table 10: Number of lifetime mental health disorder diagnoses (excluding alcohol use disorders) per individual at young adulthood, by comorbidity group

No. of disorders	MHD only		AUD only		Comorbid	
	N	(%)	N	(%)	N	(%)
1	333	56%	(342	84%)	160	52%
2	150	25%	(63	16%)	79	26%
3	64	11%	-	-	40	13%
4	25	4%	-	-	16	5%
5	13	2%	-	-	7	2%
6	4	0.7%	-	-	3	1%
7	1	0.2%	-	-	0	-
4+ disorders	**43**	**7.3%**	-	-	**26**	**8.5%**
Mean disorders (CI_{95})	1.73	(1.65-1.82)	0	-	1.82	(1.70-1.94)

Additionally, impairment scores appeared higher for the comorbid group than for those with mental health disorders alone (Table 11). At bivariate level, those with comorbid disorders perceived themselves to be more impaired by their alcohol problems than those with either alcohol only or mental health only disorders. The comorbid group also perceived themselves as more impaired by their substance use problems than either single disorder group. This is consistent with reports from clinical samples (28, 66).

Table 11: Impairment due to their alcohol or substance use problems as perceived by MUSP offspring at 21 years, by comorbidity group

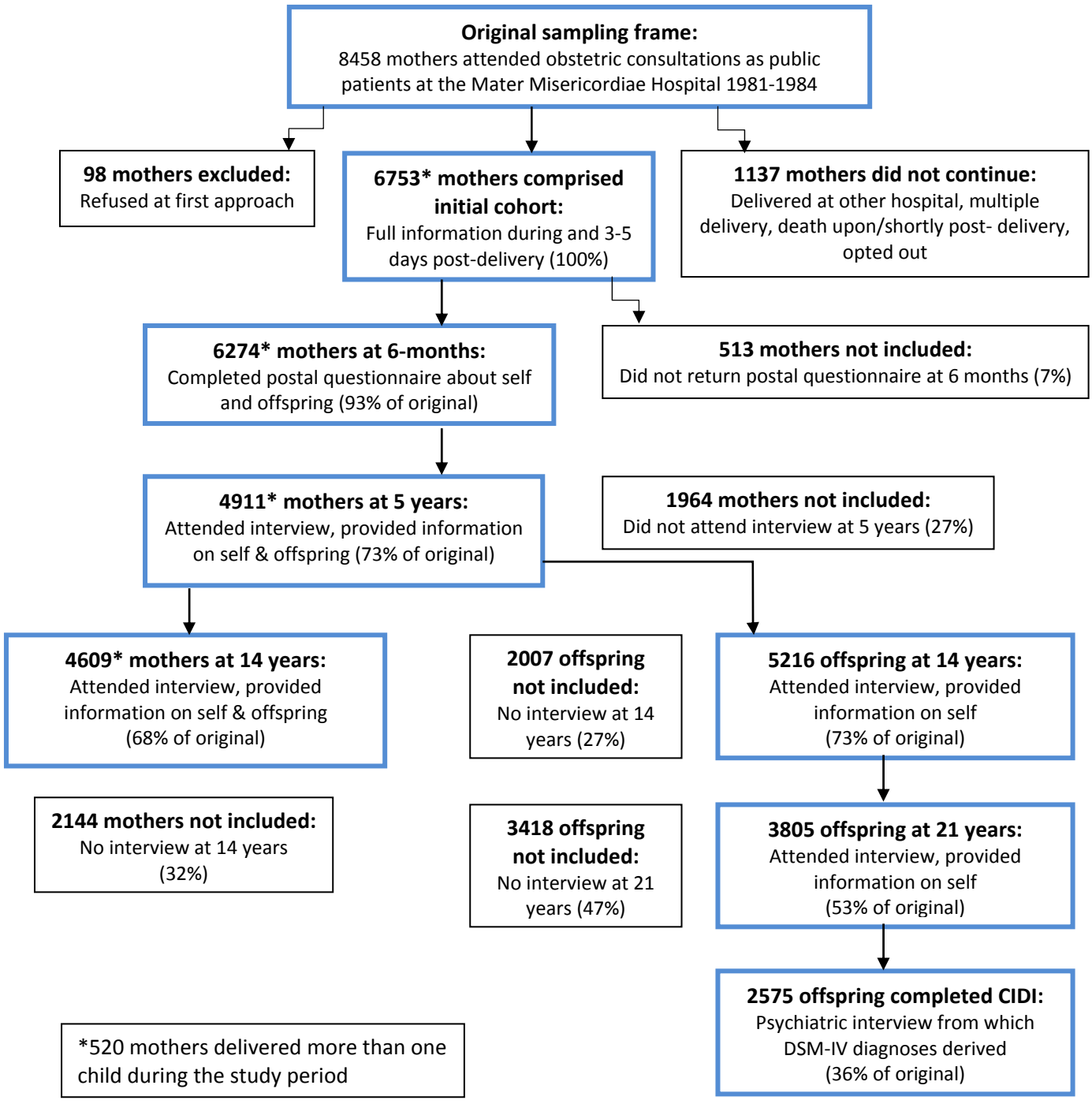
	MHD only		AUD only		Comorbid	
Mean impairment score						
	Mean	**(CI_{95})**	**Mean**	**(CI_{95})**	**Mean**	**(CI_{95})**
Alcohol problems	15.75	(15.57, 15.93)	16.88	(16.68, 17.08)	17.20	(16.90, 17.50)
Substance problems	11.92	(11.46, 12.38)	14.49	(13.90,15.09)	15.75	(15.06, 16.44)
Bivariate association of impairment score with comorbidity group						
	OR	**(CI_{95})**	**OR**	**(CI_{95})**	**OR**	**(CI_{95})**
Alcohol problems	1.40	(0.74, 2.66)	**6.48**	(3.90, 10.76)	**10.63***	(6.44, 17.54)
Substance problems	**1.84**	(1.19, 2.83)	**4.40**	(2.94, 6.57)	**8.03*****	(5.42, 11.89)

$OR_{Comorbid} > OR_{AUD}$ or OR_{MHD}; *** P<0.005, *P<0.05

Attrition in the MUSP offspring sample

As with many longitudinal studies, attrition in the MUSP sample has been significant. Of the 7223 live singleton offspring at baseline, only 3805 (53%) participated in the 21 year follow up. Of those, 2575 completed the CIDI to yield diagnoses for comorbidity categorisation, giving a final sample constituting 36% of the original cohort. This is shown diagrammatically in Figure 1.

Figure 1: Recruitment and attrition from the MUSP study



Bivariate and mutually adjusted associations between gender, baseline maternal characteristics and the odds of being lost to follow up by young adulthood showed that attrition was differential (Table 12). Those lost by 21 years were more likely to be male, with younger mothers who were un-partnered at pregnancy and reported anxiety, depression and smoking at baseline, representing a significantly disadvantaged group.

Table 12: Association between baseline factors and loss to follow up (LFU) of MUSP offspring by 21 years

Covariate	Category	Odds of being LFU	
		Unadjusted	Adjusted
		OR (CI_{95})	OR (CI_{95})
Participant gender	Female	**0.83** (0.75, 0.91)	**0.82** (0.74, 0.91)
Maternal age at FCV[$]		**0.98** (0.97, 0.98)	**0.98** (0.97, 0.99)
Mother's marital status at FCV[$]	No partner	**1.58** (1.35 1.84)	**1.34** (1.13, 1.58)
Mother's education at FCV[$]	< Year 12	**1.16** (1.04, 1.29)	1.08 (0.97, 1.21)
Maternal binge in pregnancy	Yes	**1.30** (1.05, 1.61)	1.01 (0.86, 1.18)
Maternal smoking in pregnancy	Yes	**1.22** (1.10, 1.34)	**1.14** (1.02, 1.27)
Mother depressed at FCV[$]	Depressed	**1.52** (1.17, 1.99)	**1.50** (1.15, 1.96)
Mother anxious at FCV[$]	Anxious	**1.29** (1.08, 1.53)	**1.30** (1.09, 1.54)

[$] FCV = First clinic visit in pregnancy (baseline)

Summary of Chapter 4

There was a significant association between alcohol and mental health disorders in this cohort. Twelve percent of the cohort reported both lifetime alcohol and mental health disorders by 21 years. All of these showed temporal overlap within 12 months and so could be considered comorbid. There was no gender bias in the comorbid group.

The comorbid group considered themselves to be more impaired by their alcohol or other substance use than the mental health disorder group, and tended to have a greater degree of mental health multi-morbidity. The comorbid group also appeared to have lower rates of employment and higher rates of smoking and illicit substance use than either the MHD or AUD groups.

Considerable loss to follow up had occurred between enrolment and completion of the CIDI at 21 years. Those lost were more likely to be male, and have younger, un-partnered mothers who smoked, and who were depressed and anxious during pregnancy. These factors will be important to consider in adjusting relationships for attrition.

Chapter 5: How early does comorbidity emerge, and can we distinguish comorbid participants from those with single disorders?

Characterisation of the MUSP young adults indicated that comorbid alcohol and mental health disorders were experienced by 12% of our cohort. The mean age of onset for the disorder groups was 18-19 years, but disorders emerged for some as early as 9 years (for depression) and 14 years (for alcohol use disorders). This suggested that comorbidity may develop earlier than late adolescence in some cases. It was possible to identify a small group in this cohort who at 14 years were drinking alcohol and exhibited internalising behaviour problems (n=68; 1.4%). These adolescents were likely to develop alcohol use (OR 5.76; CI_{95} 1.68, 19.81 compared to no disorder) and comorbid disorders (OR 12.82; CI_{95} 4.10, 40.10) by young adulthood, but low numbers precluded further analysis.

In the sample of pre-adolescent school children from the Healthy Neighbourhoods Study, it was possible to examine depressive symptoms as a pre-disorder indicator of mental distress, and the co-occurrence of these with early onset alcohol use, which has been linked to an increased risk of later alcohol use disorders (272). Links to a number of risk and protective factors from the individual, school and family domains were also assessed. This is described in paper 5.1.

The preliminary studies also suggested that the comorbid group may experience more impairment due to their substance use, and were more likely to suffer from multi-morbid mental health disorders, than the single-disorder groups. Clinical studies have described more severe symptoms among comorbid patients (28), but the impact on functionality of comorbid disorders is less clear for the general population. Using behavioural problems as a measure of social functioning, and taking a dimensional rather than categorical approach, we were able to examine whether comorbidity was associated with more debilitation than single disorders across a range of behaviours. This is described in paper 5.2.

5.1 Detection in very early adolescence

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Supplementary materials published online in support of this paper appear in Appendix 3 of this thesis.

Title

Individual, school-related and family characteristics distinguish co-occurrence of drinking and depressive symptoms in very young adolescents

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Running head:

Co-occurrence of pre-disorder drinking/depressed mood in pre-teens

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Abstract

Introduction and aims: Alcohol misuse and depressed mood are common during early adolescence, and comorbidity of these conditions in adulthood is associated with poorer health and social outcomes, yet little research has examined the co-occurrence of these problems at early adolescence. This study assessed risky and protective characteristics of pre-teens with concurrent depressed mood/early alcohol use in a large school-based sample.

Design and methods: School children aged 10-14 years (n=7289) from late primary and early secondary school classes in government, Catholic and independent sectors participated with parental consent in the cross-sectional Healthy Neighbourhoods Study. Key measures included depressed mood, recent alcohol use, school mobility, family relationship quality, school engagement and coping style. Multinomial logistic regression analyses were used to identify school and family-related factors that distinguished those with co-occurring drinking and depressive symptoms from those with either single condition. Gender and school level interactions for each factor were evaluated.

Results: Co-occurring conditions were reported by 5.7% of students (CI_{95} 5.19, 6.19). Recent drinkers were more likely than non-drinkers to have symptoms consistent with depression (OR 1.80; CI_{95} 1.58, 2.03). Low school commitment was associated with co-occurring drinking/depressive symptoms (OR 2.86; CI_{95} 2.25, 3.65 compared to null condition). This association appeared to be weaker in the presence of adaptive stress-coping skills (OR 0.18; CI_{95} 0.14, 0.23).

Conclusions: We have identified factors which distinguish pre-teens with very early co-occurrence of drinking and depressed mood, and protective factors with potential utility for school-based prevention programs targeting these conditions.

Keywords: Adolescence; co-morbidity; alcohol; depression; prevention; risk factors

Introduction

Comorbidity of alcohol and mental health disorders adds complexity to problematic diagnoses. In adults and adolescents, comorbidity predicts poorer functioning, worse prognosis and non-response to treatment (1-3), and this co-occurrence is not uncommon, with population reports of 16% in adults and 12% for younger adults (4). For the component disorders, early onset of symptoms is a risk for disorder and increased severity (5-8) but this phenomenon is not described for co-occurrence. Each of these individual conditions is notable in pre-teens; 8% of British 10 year olds reported alcohol use and 18% depressed mood (9), while 9% of Australian 12 year olds drank and 10% of US 14 year olds reported major depression (10, 11). Population estimates of co-occurring conditions in the pre-teen group are not however widely reported, and little is known about factors associated with early-emerging co-occurrence.

If there are factors underlying the development of comorbid alcohol and mental health problems, we would expect these to be apparent early in its course (12). As such, these factors and how they relate to co-occurrence of alcohol and depressive symptoms in the pre-teen years merit investigation. It has been suggested that, as for other problems that cluster in youth such as delinquency and sexual behaviours (13), there may be common factors that underlie the co-occurrence of alcohol and mental health problems (14). For example, retrospective reports of poor family connection, academic difficulty and adverse childhood events have all been associated with alcohol and mental health comorbidity in adults (1, 2, 15). Family alcohol problems and stress have also been implicated (8, 16), and each of these has been linked to the contributing single disorders (9, 16-20).

As a specific concern, comorbidity may however be distinguished by specific contributing factors. In recent reports, socio-economic disadvantage, family conflict, poor parental relationships and maternal smoking during adolescence were shown to be

more strongly associated with comorbidity than either alcohol or mental health disorders in adults (21-23). Gender differences have been found for single conditions, in that depressed mood is more common among girls (18, 24) while alcohol problems develop earlier in boys, but reports of gender balance in comorbidity are equivocal (1, 15, 25, 26).

Less is known about factors associated with emergence in the pre-adolescent years of co-occurring drinking and depression. While other literature reports on factors in individual and family domains such as conflict, attachment and parent substance or mental health problems (2, 23, 27), the school environment may provide new opportunities for indicators to be identified. Little attention has been paid to the impact on comorbidity of common but unsettling events such as changes of school, which may give rise to stress, and academic failure which may indirectly drive early alcohol use and affect depressed mood (28). This is surprising, given that school-associated factors such as truancy and low commitment to school are associated individually with adolescent alcohol use and depression (28, 29).

Protective factors which assist young people to cope with these separate vulnerabilities may also be important for co-occurring drinking and depressed mood, but have not been widely studied in this context. Emotional closeness to family is a protective factor for both depression and drinking, and there is some evidence to suggest that young people's capacity to adapt or cope with stressors is important in building the resilience which reduces later disorders (24, 30). Their relationship to co-occurring conditions is thus of interest.

In this study, we aim to address three gaps in the literature. Firstly, we determine the prevalence of co-occurring alcohol use and depressive symptoms in a population of very young adolescents, as this has not previously been reported. Secondly, we

compare for the first time the characteristics across school-based and family domains of young people with co-occurring drinking and depressive symptoms to those who report either drinking or depressive symptoms alone. We hypothesize that there may be factors which distinguish young people who report co-occurring drinking and depressive symptoms. Importantly, we account for the impact of family conflict and substance problems on these associations and examine gender differences. Lastly, we assess whether protective factors such as family closeness and adaptive stress-coping skills alter the relationships between these characteristics and drinking/depressive symptoms, as has been shown for drinking and depressive disorders individually (24, 31, 32) but not for co-occurrence.

Methods:

Participants:

The sample was drawn from the 2006 Healthy Neighbourhoods Study which comprised 8093 Australian students aged 10-14 years (87% aged 12 or younger), enrolled in late primary school (n = 4426, modal age = 11) and early secondary school (n=3667, modal age =12). Thirty-one communities were randomly selected across quartiles of socio-economic disadvantage using the Australian Bureau of Statistics *Socio-Economic Indexes For Areas* (SEIFA) to stratify the sample (33). Schools were randomly selected within each community, with 231 schools electing to participate (61% government, 17% Catholic, 22% independent; 52% response). All students of the appropriate grade in each school were invited to participate (67% response). The study protocol has been extensively described elsewhere (24, 34).The final sample comprised only students for whom complete data on the factors of interest were available (n=7289).

Procedure:

Ethics approval for the study was obtained from the University of Melbourne Human Research Ethics Committee (Approval #050016). Consent to participate was obtained from government and Catholic Education bodies in each jurisdiction, or directly from principals of independent schools. Student participation was dependent on written parental consent, attendance on survey administration day and student assent. Data were collected in classrooms during school time using a web-based questionnaire. Average completion time was 39 minutes (range 22-110 minutes).

Measures:

Measures discussed below were self-reported by participants using the Communities That Care (CTC) Youth Survey, which has been used extensively in the United States and validated with Australian young people (35-37).

Depressive symptoms and drinking

Depressive symptoms in the previous two weeks were measured using the Angold Short Moods & Feelings Questionnaire (SMFQ; α=0.91 in this sample) and dichotomised such that scores above 10 were coded positive, as correlating with clinically significant depression in adolescents (38, 39). CTC Youth Survey items asked participants about recent (last 30-day) and lifetime (ever) alcohol consumption (had more than a few sips of alcohol at one time); both were dichotomised as no/yes. Co-occurrence was recorded where participants were positive for both drinking in the last month and depressive symptoms during the last two weeks. Sensitivity analyses were undertaken using SMFQ scores above seven as indicative of emerging depressive symptoms (9, 38, 40), and using lifetime drinking, as any consumption of alcohol at ages 11-14 is considered risky (41, 42). Although binge drinking (more than five

alcoholic drinks at one time in the last 2 weeks) as an indicator of problematic drinking was measured, the prevalence (5%) was too low to allow further analysis.

Risk and protective factors

Risk and protective factors were self-reported by students. The CTC survey recorded the number of school moves experienced since kindergarten: this was categorised as none, 1-2, 3-4 and 5+. Composite items measured perceived academic achievement (two items examined students' perception of their overall grades and comparison to peers; α=0.68), and commitment to school (6 items measured truancy, effort, interest, enjoyment and perceived importance of schoolwork; α=0.77) over the last 12 months. Higher scores indicated lower achievement or lower commitment. Other composites measured family conflict (three items examined family arguments and yelling; α=0.79), family closeness (four items examined closeness and sharing with mother/father; α=0.77) (24) and adaptive stress-coping skills (four items examining self-blame and self-efficacy; α=0.75). For these, higher scores indicated more conflict, stronger family closeness and better stress-coping skills, respectively. All composite indicators were dichotomised as per previous studies using this survey (35, 37, 43) such that the highest 15% of scores for each indicator were recorded as positive for that characteristic. Family history of substance problems was reported by participants via a single item ("anyone in your family ever had a severe drug or alcohol problem?") and dichotomised as no/yes. Participants' perception of the proportion of their close friends who drank ("Of your four best friends, how many have tried alcohol?") was dichotomised such that more than two (>50%) was positive.

Demographic controls included gender, age, school level (primary/secondary) and sector (government/non-government), and cultural background (language/s spoken at home and Indigenous status). Socioeconomic status (SES) was estimated from the

student's home postcode, using Australian Bureau of Statistics data to generate a SEIFA score (33).

Analysis:

A four group design was used: *Co-occurring, Depressive Only*; *Drinking Only* and *Norms*. Assessment of co-occurrence required a measure of recent alcohol use that was likely to overlap with the last-two-week measure used to report depressive symptoms; hence the last-30-days measure of drinking was used. Distribution of these groups was examined across participant demographics and key measures. We used multinomial logistic regression to examine relationships between groups and school-level or individual-level factors, with the *Norms* group as reference. To compare the *Co-occurring* group to *Drinking Only* or *Depressive Only*, we repeated the regressions, using each group in turn as reference. Our multivariable model incorporated factors identified as significant in univariate regressions as well as gender and SES, and incorporated clustering at school level as a random effect. As student age per grade was not constant between states, we adjusted for age rather than grade. This gave a final sample of 7000 for whom we had complete data on variables of interest. Finally, we examined school-level (i.e. primary vs secondary) and gender interactions for each factor, stratifying models where these were significant, and calculated Attributable Risks for risk and protective factors in the sample. In sensitivity analyses, we adjusted for peer drinking, and assessed our models using (i) a lower cut-off for depressive symptoms (SMFQ score >7) and (ii) any life-time drinking. All analyses were undertaken using STATA Version 12.1 (StataCorp, USA).

Results

Emergence of drinking and depressive conditions:

Drinking without depressive symptoms was reported by 11.1% (CI_{95} 10.5, 11.8) of students, and depressive symptoms but no drinking by 14.6% (CI_{95} 13.8, 15.3). Nearly six percent (5.7% CI_{95} 5.2, 6.2) of all students reported co-occurring conditions; 7.8% (CI_{95} 6.9, 8.6) of high school and 4.2% (CI_{95} 3.6, 4.8) of primary students (Table 1). Gender and school sector proportions in the co-occurrence group were not different to the normative group, but fewer students spoke a language other than English at home.

Substantial initiation to alcohol use had occurred in the primary school group: 30.2% (CI_{95} 28.8, 31.5) reported ever drinking more than a few sips of alcohol and 14.8% (CI_{95} 13.7, 15.8) had consumed alcohol in the last month. Both alcohol initiation (52.3%; CI_{95} 50.6, 53.9) and recent drinking (26.7%; CI_{95} 25.3, 28.2) were common in students who had begun high school. Depressive symptoms were common in both primary (20.1%; CI_{95} 18.9, 21.3) and high school students (22.8%; CI_{95} 21.4, 24.1). Recent drinkers were more likely than non-drinkers to have symptoms consistent with depression (OR1.80; CI_{95}1.58, 2.03), but severity of depressive symptoms did not differ greatly between the *Depressive Only* and *Co-occurring* groups. A greater proportion of the *Co-occurring* group reported recent binge drinking (43%) than did those in the *Drinking Only* group (30%).

Associations:

At bivariate level, all factors except gender and SES were more strongly associated with the *Co-occurring* group than the normative*, Drinking Only* or *Depressive Only* groups (Table 2, Part A). In the fully adjusted model (Table 2, Part B), low commitment to school and family substance problems were significantly more likely to be associated with co-occurrence than with drinking or depressive symptoms alone. Similarly, the protective relationship with adaptive stress-coping skills was significantly stronger for the *Co-occurring* group than with *Depressive Only* and *Drinking Only* groups.

Both family closeness and adaptive stress-coping skills showed significant gender interactions. In the resulting gender-stratified models (Table 3), the link between low school commitment and co-occurrence remained stronger than with single conditions for boys and girls. However, the 'protective' relationship between good stress coping skills and co-occurrence was stronger than for drinking or depressive symptoms in girls only. Interactions with school level did not reach statistical significance (P>0.05 for all terms); hence we did not stratify our models by school level.

Attributable risk calculations showed that low stress coping skills were associated with 10.5% of the risk of co-occurrence in this population (Supplementary Table 1). Family conflict and substance problems were linked to almost 9% and 10% respectively. More school moves, low academic achievement and school commitment and poor family closeness were associated with 6-7% each. Gender, school level and school sector showed weaker links.

In sensitivity analysis, peer drinking was associated with the *Drinking only* (OR 5.36, CI_{95} 4.41, 6.52) and *Co-occurring* groups (OR 4.76, CI_{95} 3.69, 6.13) but not the *Depressive only* group, and did not substantively alter the relationships reported (results available from author). Sensitivity analyses using alcohol initiation rather than last-month drinking increased the proportion of students in the *Drinking Only* group to 28.6% (from 11.1%) and in the *Co-occurring* group to 9.8% (from 5.7%; Supplementary Table 2), but produced similar relationships to those reported here (Supplementary Table 3). Analyses using a lower cut-off for depressive symptoms (score of >8), as suggested for this age group, increased the proportion of students in the *Depressive Only* group to 23% (from 14.6%) and the *Co-occurring* group to 8.3% (from 5.7%), but did not meaningfully alter any of the relationships shown here (Supplementary Table 4).

Discussion

To our knowledge, this is one of the first reports on the rates of co-occurring drinking and depressed mood in pre-teens and of risky and protective characteristics which distinguish this co-occurrence from either single condition. The co-occurrence of drinking and depressed mood was evident in 5.7% of students, and the likelihood of depressive symptoms among drinkers was nearly twice that among non-drinkers. This likelihood is similar to UK and NZ studies (9, 25) and indicates the co-occurrence is not a chance event. Importantly, rates of depressive symptoms (21%) and recent alcohol use (20%) in this student group were consistent with other national and international data (9-11, 44), with drinking more common in older students as expected (45, 46), suggesting our findings may be generalizable to other samples.

In the school domain, low commitment to school distinguished co-occurrence from the single conditions, but academic difficulties were associated with all three conditions, and neither link was gender-specific. More school movement, which has not previously been reported on, appeared to be more important for co-occurrence in girls although the *p* value for a gender interaction test did not reach statistical significance. Studies with greater capacity to assess gender interactions are needed to assess whether girls who experience numerous school changes are more susceptible to co-occurrence than boys. Consistent with previous research, family conflict and substance problems also appeared to be related to co-occurrence (1, 2, 26, 47), but these factors did not account for the relationships above, suggesting that these intra-family stresses are not solely responsible for the school-based manifestations. As to protective factors, emotional closeness to family was associated with lower odds of co-occurrence, but only for girls. This is a new finding which is supported by existing work showing family closeness having more impact on girls' drinking (24). In contrast, the protective association of

adaptive stress-coping skills with co-occurrence, another new finding, was not gender specific.

Despite higher prevalence of co-occurring drinking/depressive symptoms in high school students, school-level interactions did not reach statistical significance, which may have been due to age variation between states at each grade. In Victoria, Grade 6 is the final year of primary school, whereas in the other states sampled (Queensland/Western Australia), Grade 6 is the penultimate year. As a result, Victorian students in Grades 6 and 8 were on average six months older than their counterparts.

Our study adds to the existing evidence as we have identified that low school commitment and family substance problems were importantly associated with very early indications of co-occurring alcohol use and depressive symptoms, while accounting for a range of individual, demographic and school domains, with statistical evidence of a difference to the relationships with drinking or depressive symptoms alone. Additionally, we have shown that some factors associated with co-occurring drinking and depressive symptoms are different for boys and girls at this age, even though the prevalence of co-occurrence does not differ by gender. This information has the potential to inform activities to improve the resilience of young people. Despite some successes, prevention programs for alcohol have had limited effect (48-50). It may be that young people experiencing co-occurring depressive disorders are less responsive to these efforts (51-53). Similarly, co-occurrence may reduce the benefits seen from programs which only target youth depression. Intervention modalities with efficacy for both conditions may be most useful, as may be screening for both conditions in adolescents referred for either condition.

Our Attributable Risk (AR) analyses suggest that poor coping skills were related to nearly 10.5% of the co-ocurring depressive symptoms and early alcohol use in this

group. Although cross-sectional data such as ours cannot infer causal relationships, others have shown that early interventions using cognitive and skills training have been effective at separately reducing drinking and depression even in the very young (52, 53). Addressing low school commitment, although the AR was smaller, may potentially have broader impact, as it was related to all three conditions and was not gender-sensitive.

At least one intervention has demonstrated reductions in low school commitment, with some associated reductions in cannabis use (54). Importantly, the relationships shown here did not vary by school sector, school level or SES, suggesting that if our findings are supported by longitudinal studies, strategies aimed at improving coping skills in young adolescents may be useful across a broad demographic range to address the co-occurrence of early alcohol use and depressive symptoms.

This paper has a number of strengths. The sample is large and can be considered broadly representative of Australian students, as source communities were selected to reflect the range of SES represented in the Australian census (24). The survey uses valid and reliable scales and has been shown to have strong similarities to cross-sectional and longitudinal associations for both Australian and American students (55). The scope of information gathered has allowed us to examine associations in school-based domains and protective factors, which is novel for co-occurrence, while controlling for known contributors to youth problems. Depression, alcohol use and some risk factors for these in very young adolescents have been described before (26, 56, 57), but our paper is the first to describe the prevalence of early co-occurrence of these conditions in a large community sample, with the added value of a robust analysis of associated risk and protective factors.

Our findings must be seen in light of some limitations. This study is cross-sectional and so causal inferences cannot be drawn. It is possible that some factors considered (school movement, family closeness and coping skills) are likely to have been present before the onset of drinking and depressed mood, but depressed mood may also reduce coping skills and/or school commitment, therefore longitudinal research is needed to clarify temporal relationships for the very early co-occurrence.

Our measure of drinking may be more indicative of initiation rather than problematic alcohol use, as highlighted recently (58), but 43% of our *Co-occurring* group reported recent binge drinking, suggesting a risk of later disorder for this group (5). Our data are also limited by self-report, but items within the CTC questionnaire have been found to indicate truthful reporting (34, 56). Despite this, the ability of 11-14 year olds to knowledgeably report on family substance misuse problems may be limited. There may also be other factors associated with development of depressed mood and early drinking in young people which were not available for this analysis. However, we note that the inclusion in our model of family conflict and parental substance problems, both strongly associated with adolescent difficulties, did not substantively alter the distinguishing associations of co-occurring drinking/depressive symptoms with low school commitment and adaptive stress coping skills.

Some bias may have been introduced during the parental consent process (67% response rate), but we are unable to estimate the effect of this on our sample. Typically non-participation is associated with lower SES; however this factor was not significant in the relationships we describe. Data missing through non-response to some items may also have affected our results; those with poor academic achievement and high family conflict were less likely to have been included in the final analysis. However, as these factors were associated with co-occurrence, this is most likely to have led us to underestimate the contribution of these factors to our models. Finally, it is possible that

the presence of depressive symptoms has introduced bias in the reporting by some students, which may have affected the prevalence of both *Depressive Only* and *Co-occurring* groups.

In summary, co-occurrence of alcohol use and depressed mood emerges very early in or prior to adolescence. It is associated with considerable disruption of education, but is less prevalent in students, particularly girls, who have good adaptive coping skills. If longitudinal research confirms our findings, school-based interventions targeting the factors identified in this study may be recommended.

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Contributors

CLS conceived the study, designed and undertook the analysis and wrote the first draft of the manuscript. ABK, RA and GMW provided input into the analytical design and contributed significantly to discussions and to the manuscript; GCP contributed to preparation of the manuscript; JWW is Chief Investigator on the Healthy Neighbourhood Study and contributed to preparation of the manuscript.

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comments and discussion during the development of the paper. All authors declare no conflict of interest.

Table 1: Characteristics of the sample of Australian school students

(continued on following page)

	Total	Norm	Depressive only [a]	Drinking only [b]	Co-occurrence
	N **(%)**	**%**	**%**	**%**	**%**
Overall prevalence	8524	5662 (69)	1203 (15)	919 (11)	470 (6)
INDIVIDUAL FACTORS					
Gender					
Female	4177 (52)	2863 (53)	740 (62)	330 (36)	244 (52)
Indigenous status					
Indigenous	252 (3)	163 (3)	50 (4)	30 (3)	9 (2)
Home language					
Other than English	122 (2)	91 (2)	26 (2)	3 (0)	2 (0)
English + other	810 (10)	584 (11)	128 (11)	62 (7)	36 (8)
SES					
Mean SEIFA decile+/- SE	5.2±.03	5.3±.03	4.8±.07	5.3±.08	4.8±.11
Age					
Mean years +/-SE	11.6±.01	11.5±.01	11.5±.02	11.9±.03	11.8±.04
Depressive severity					
Mean score +/- SE	8.13±0.07	6.15 ± 0.07	16.05±0.12	5.93±0.14	15.92±0.18
Adaptive stress coping style					
Good	5443 (68)	4178 (77)	475 (40)	651 (71)	139 (30)
FAMILY FACTORS					
Family conflict					
Present	2288 (31)	1144 (23)	586 (51)	280 (32)	278 (61)
Family substance problem					
Present	576 (8)	270 (5)	133 (12)	87 (10)	86 (19)
Family closeness					
Good	6524 (83 **)**	4645 (88)	865 (74)	714 (79)	300 (66)

	Total	Norm	Depressive only [a]	Drinking only [b]	Co-occurrence
SCHOOL RELATED FACTORS					
School sector					
Non-Government	3234 (39)	2256 (40)	439 (37)	373 (41)	166 (35)
School level					
High school	3367 (45)	2307 (42)	531 (44)	544 (59)	285 (61)
School moves					
1-2	3376 (42)	2285 (42)	491 (41)	406 (45)	194 (42)
3-4	1373 (17)	879 (16)	215 (18)	179 (20)	100 (21)
5+	469 (6)	257 (5)	112 (10)	50 (5)	50 (11)
Commitment to school					
Low	3581 (45)	2025 (37)	680 (57)	529 (58)	347 (74)
Academic achievement					
Low	1203 (15)	659 (12)	226 (19)	175 (19)	143 (31)

[a] Depressive = SMFQ score ≥11, last 2 weeks

[b] Drinking = recent (last month) alcohol consumption

Table 2: Multinomial logistic regression models of co-occurring drinking/depressive symptoms in young Australian students, comparing co-occurring with norms, depressive only and drinking only

A: Unadjusted associations		**vs Norm**		**vs Depressive**		**vs Drinking**	
Factor		**OR**	**CI_{95}**	**OR**	**CI_{95}**	**OR**	**CI_{95}**
School moves	1-2	**1.36*****	1.08, 1.72	1.18	0.95, 1.46	1.01	0.79, 1.28
	3-4	**1.83*****	1.39, 2.41	**1.34****	1.04, 1.72	1.16	0.87, 1.54
	5+	**3.13*****	2.20, 4.45	**1.44****	1.03, 2.02	**1.81*****	1.20, 2.75
Academic achievement	Low	**3.14*****	2.54, 3.88	**1.86*****	1.46, 2.38	**1.85*****	1.43, 2.39
School commitment	Low	**4.73*****	3.82, 5.86	**2.16*****	1.71, 2.73	**2.06*****	1.62, 2.63
Family conflict	Present	**5.32*****	4.36, 6.40	**1.48*****	1.19, 1.85	**3.27*****	2.59, 4.15
Family substance problems	Present	**4.31*****	3.31, 5.62	**1.78*****	1.32, 2.39	**2.12*****	1.53, 2.92
Family closeness	Good	**0.28*****	0.23, 0.34	**0.68*****	0.54, 0.87	**0.51*****	0.40, 0.66
Adaptive stress coping skills	Good	**0.12*****	0.10, 0.15	**0.64*****	0.51, 0.80	**0.17*****	0.13, 0.22
Gender	Female	0.97	0.80, 1.17	**0.68*****	0.54, 0.84	**1.93*****	1.54, 2.41
SES		**0.93*****	0.90, 0.96	1.00	0.96, 1.04	**0.92*****	0.89, 0.97

B: Fully adjusted model		vs Norm		vs Depressive		vs Drinking	
Factor		**OR**	**CI_{95}**	**OR**	**CI_{95}**	**OR**	**CI_{95}**
School moves	1-2	1.28	0.98, 1.66	1.16	0.88, 1.54	1.02	0.76, 1.38
	3-4	**1.41****	1.03, 1.92	1.29	0.92, 1.81	0.98	0.69, 1.41
	5+	**1.91*****	1.25, 2.91	1.14	0.74, 1.75	1.61	0.96, 2.68
Academic achievement	Low	**1.57*****	1.22, 2.03	**1.49*****	1.14, 1.96	1.26	0.94, 1.70
School commitment	Low	**2.86*****	2.25, 3.65	**1.81*****	1.39, 2.34	**1.60*****	1.22, 2.11
Family conflict	Present	**3.29*****	2.64, 4.10	1.23	0.97, 1.56	**2.45*****	1.90, 3.17
Family substance problems	Present	**2.51*****	1.85, 3.40	**1.59*****	1.16, 2.18	**1.50****	1.05, 2.14
Family closeness	Good	**0.61*****	0.48, 0.78	0.85	0.66, 1.10	0.88	0.66, 1.16
Adaptive stress coping skills	Good	**0.18*****	0.14, 0.23	**0.75****	0.58, 0.96	**0.20*****	0.15, 0.26
Gender	Female	1.07	0.86, 1.33	**0.69*****	0.55, 0.87	**1.96****	1.53, 2.52
SES		0.96	0.92, 1.00	1.01	0.97, 1.06	0.95	0.91, 1.00

Model has also been adjusted for age, SES and for clustering at school level.

Asterisks indicate that the OR for co-occurrence is significantly different to that for the reference group (*P<0.05; **P<0.01; ***P<0.005).

Differences between the *Co-occurring* group and either *Drinking Only* or *Depressive Only* group were evaluated by repeating the regression using each group in turn as reference.

Table 3: Multinomial regression models of co-occurring drinking/depressive symptoms in Australian students, stratified by gender (fully adjusted models)

BOYS		**vs Norm**		**vs Depressive**		**vs Drinking**	
Factor		**OR**	**CI_{95}**	**OR**	**CI_{95}**	**OR**	**CI_{95}**
School moves	1-2	1.06	0.74, 1.51	1.33	0.89, 1.99	0.93	0.63, 1.39
	3-4	1.31	0.85, 2.02	1.37	0.84, 2.23	0.88	0.55, 1.43
	5+	1.14	0.56, 2.34	0.65	0.31, 1.38	1.35	0.58, 3.12
Academic achievement	Low	**1.55****	1.09, 2.08	**1.63****	1.09, 2.42	1.34	0.90, 1.98
School commitment	Low	**2.55*****	1.78, 3.64	**1.49****	1.01, 2.23	**1.62****	1.10, 2.39
Family conflict	Present	**3.15*****	2.31, 4.30	1.03	0.73, 1.47	**2.25*****	1.59, 3.19
Family substance problems	Present	**1.95*****	1.24, 3.07	1.31	0.79, 2.15	**2.03*****	1.19, 3.48
Family closeness	Good	0.77	0.53, 1.11	0.83	0.56, 1.23	0.93	0.64, 1.37
Adaptive stress-coping skills	Good	**0.21*****	0.15, 0.29	0.81	0.57, 1.15	**0.24*****	0.16, 0.34

GIRLS		**vs Norm**		**vs Depressive**		**vs Drinking**	
School moves	1-2	1.61	1.09, 2.37	1.15	0.77, 1.73	1.15	0.73, 1.83
	3-4	**1.60****	1.02, 2.51	1.31	0.82, 2.10	1.20	0.70, 2.07
	5+	**2.71*****	1.56, 4.71	1.54	0.88, 2.68	1.73	0.87, 3.43
Academic achievement	Low	**1.64*****	1.13, 2.38	1.39	0.96, 2.04	1.11	0.70, 1.75
School commitment	Low	**3.12*****	2.24, 4.34	**2.05*****	1.45, 2.89	**1.48****	1.00, 2.19
Family conflict	Present	**3.35*****	2.44, 4.60	1.38	0.99, 1.91	**2.68*****	1.81, 3.96
Family substance problems	Present	**3.17*****	2.09, 4.82	**1.76*****	1.17, 2.65	1.02	0.63, 1.66
Family closeness	Good	**0.51*****	0.37, 0.70	0.82	0.59, 1.14	0.67	0.44, 1.00
Adaptive stress-coping skills	Good	**0.16*****	0.11, 0.22	**0.68****	0.48, 0.96	**0.17*****	0.11, 0.26

Co-occurring drinking/depressive symptoms = SMFQ score ≥11 (last 2 weeks) plus recent (last month) alcohol consumption.

Model has also been adjusted for age, SES and clustering at school level.

Asterisks indicate that the OR for co-occurrence is significantly different to that for the reference group in each case (**P<0.05; ***P<0.01).

Differences between the *Co-occurring* group and either *Drinking Only* or *Depressive Only* group were evaluated by repeating the regression using first the *Drinking Only* then the *Depressive Only* group as reference.

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5.2 Association of comorbidity with behaviour problems

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Title

Do young people with comorbid mental and alcohol disorders experience worse behavioural problems?

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Abstract

This article examines whether young individuals in the general population with comorbid alcohol use and mental health disorders experience worse internalising and externalising behaviour problems than those with single disorders. A large cohort of women at the Mater Misericordiae Hospital in Brisbane, Australia, was enrolled during pregnancy in a longitudinal study. Mother/offspring dyads were followed over twenty-one years. At age 21, offspring behaviour problems were examined using the Young Adult Self Report, alcohol and mental health disorders with the Composite International Diagnostic Interview. Associations between comorbidity and behaviour problems were assessed using multinomial logistic regression, accounting for life-course factors. Twelve percent of young adults had alcohol/mental health DSM-IV disorders with significant temporal overlap. A further 16% had alcohol disorders only and 23% mental health disorders only. The comorbid group scored significantly higher on total and externalizing behaviour problems but not internalizing behaviour problems. Stronger associations of aggression/delinquency with comorbidity were not fully accounted for by factors known to influence separate development of mental health and alcohol disorders. Young adults with comorbid alcohol/mental health disorders experience more, and more severe, behavioural problems than those with single disorder types, indicating an increased burden from comorbidity, with implications for treatment and public order.

Keywords

Comorbidity; epidemiology; alcohol-related disorders; behaviour; mental health

1. Introduction

There is increased interest in co-occurring disorders of substance use, mental health and behaviour (Boden et al., 2012; Balan et al., 2013; Heron et al., 2013; Kidorf et al., 2013; Terry-McElrath et al., 2013). Mental health and alcohol use disorders frequently co-occur in clinical settings (Hirschfeld et al., 1989; Swendsen and Merikangas, 2000; Kessler, 2004; Teesson et al., 2009; Alegria et al., 2010). It is becoming increasingly apparent that in addition to integrated care requirements (Davis et al., 2008; Carroll et al., 2009; Kidorf et al., 2013), patients with comorbid alcohol and mental health disorders (CAMHD) are characterised by more severe clinical outcomes (Hirschfeld et al., 1989; Bruce et al., 2005) and specific social difficulties (Merikangas et al., 1998b; Swendsen and Merikangas, 2000; Davis et al., 2008; Kessler and Wang, 2008b; Jaworski et al., 2011).

Comorbid alcohol and mental health problems are also prevalent in the general population: in 2007, 22% of the Australian population with a lifetime alcohol use disorder (AUD) (Teesson et al., 2010) also reported a co-occurring mental health disorder (Teesson et al., 2009). Similar findings are seen elsewhere (Merikangas et al., 1998b). In the National Longitudinal Alcohol Epidemiologic Survey (NLAES), those with comorbid depression and alcohol problems tended to have more severe alcohol use disorders (AUD) than those without depression (Grant et al., 1996). At population level, It is unclear whether alcohol and mental health comorbidity is linked with poorer functioning in other areas although some initial evidence suggests this is the case. The Australian National Survey of Mental Health and Wellbeing (NSMHWB) and US national studies showed that those with comorbid anxiety and alcohol disorders experienced significantly more days out of role as a result of their illness than those without comorbidity (Merikangas and Kalaydjian, 2007; Kessler and Wang, 2008a; Slade et al., 2009). More recently, longitudinal studies have suggested that social functioning may also be affected, manifesting as relationship difficulties and intimate partner violence (Boden et al., 2012; 2013; Heron et al., 2013).

One marker of decreased functioning which may be associated with CAMHD is behaviour problems. This area has been less examined to date. Yet individuals with problematic behaviour such as aggression and delinquency experience substance use and mental health disorders during their lifetime as well as poorer social and economic position (Achenbach et al., 1995; Bor et al., 2010). Additional evidence suggests that behaviour problems often cluster with substance use disorders (Helstrom et al., 2004; Heron et al.,

2013), as do personality disorders (PD) such as Antisocial PD (Regier et al., 1990) and Borderline PD (Bornovalova et al., 2005) although this may be due in part to diagnostic overlap (Regier et al., 1990) or shared traits such as impulsivity and disinhibition (Bornovalova et al., 2005). In contrast however, latent class analysis of disorders in the National Comorbidity Study – Adolescent Supplement (NCS-A) (Kessler et al., 2012b) ascribed behaviour disorders and substance disorders to separate classes, with the suggestion that the two have unique underlying psychopathological processes in younger persons, and that these may vary across the life course (Kendler et al., 2008). Existing studies have tended to focus on childhood or adolescent behaviour problems, as predictors of later substance use or mental disorders (Becker et al., 2012; Kessler et al., 2012a), and suicidal behaviours (Matsumoto et al., 2011). As to comorbid mental health and alcohol problems, most (Regier et al., 1990; Merikangas et al., 1998b; Teesson et al., 2009), though not all (Kessler et al., 2012b) population studies have investigated CAMHD in adults, therefore describing comorbidity years after its initial development. Occurring on a backdrop of anxiety and behaviour problems in childhood and adolescence, with depression developing through late teenage years to early adulthood (Merikangas et al., 1998b; Marquenie et al., 2007; McEvoy et al., 2011), early adulthood is arguably a sensitive period for the development of CAMHD (Cerda et al., 2010), as well as for determining trajectories of social functioning. In this respect, it is surprising that little research attention has been paid to the role of behaviour problems and how these may be associated with CAMHD in young adults.

Finally, methodological weaknesses in the existing literature are worth noting. Firstly, assessment of CAMHD has often relied on lifetime diagnoses, with little validation of disorder overlap to ensure co-occurrence of the disorders of interest (Grant et al., 1996; Kessler, 2004; Kessler et al., 2012b). The use of shorter diagnostic periods (i.e. last twelve months (Hall et al., 2009; Teesson et al., 2009)) has been advocated, but this method also has disadvantages as it may miss earlier co-occurrences. Secondly a dimensional approach to behaviour problem assessment, using continuous rather than categorical diagnostics, is not typically used in studies of adults despite being common in studies of children. Yet treating each behaviour problem dimension as a continuum is arguably a more powerful approach. Compared to a categorical diagnostic approach, a dimensional approach permits identification of sub-threshold behaviour patterns and provides more information on wellbeing, with details of behaviour problems, severity and impact on

functioning that are more indicative of the range of issues experienced by the general population (Achenbach, 2005; Brauner and Stephens, 2006; Hudziak et al., 2007).

In summary, there is a notable gap in research on the relationship between behaviour problems and the highly prevalent combination of alcohol problems and common mental disorders in young adults. We hypothesize that comorbidity of alcohol and mental health disorders is associated with greater behaviour problems compared with single disorder types. The purpose of this study was to evaluate this association, accounting for early individual and environmental factors, and using both categorical and dimensional diagnostic instruments to assess disorders and behaviours at age 21.

2. Methods

2.1 Study design and participants

The Mater University Study of Pregnancy (MUSP) is a birth cohort study of mothers and their children, enrolled at the mothers' first clinical visit during pregnancy to the Mater Misericordiae Hospital in Brisbane during the 1980s. Both dyads were followed up at birth, 5 days and 6 months, then 5, 14 and 21 years after birth. At the time of enrolment and at follow ups, all participants gave their signed, informed consent. The MUSP study was approved by the Behavioural and Social Sciences Ethics Review Committee at the University of Queensland and has been extensively described elsewhere (Najman et al., 2005). At the 21–year follow up, 3801 members of the offspring cohort participated; 3778 completed a self-report questionnaire including the Young Adult Self Report (YASR) (Achenbach, 1997). Of these, 2539 participants (67%) were also administered the mental health and substance use disorders modules of the Composite International Diagnostic Interview (CIDI). Only participants for whom complete data on mental health, substance use and behaviour disorders are available (2314) were included in the current analyses.

2.2. Measures

2.2.1: Comorbidity categories

Data from CIDI responses were coded to yield DSM-IV disorder diagnoses for occurrence over the lifetime (LT) of the participant. For the purpose of this study, both alcohol abuse and dependence were included in 'any alcohol use disorder' (AUD). Participants

diagnosed with any DSM-IV disorder/s were defined as having 'any mental health disorder' (MHD) (including any anxious, affective, psychotic or eating disorder).

A four-category variable "Comorbidity Type" was created. Participants were classified as having 'no (DSM-IV) disorder'; a 'mental health disorder only' (MHD only, i.e. no alcohol disorder); an 'alcohol use disorder only' (AUD only, i.e. no mental health disorder) or 'comorbid (CAMHD) alcohol and mental health disorders' (i.e. 'any alcohol use disorder' plus 'any mental health disorder'). Rather than using last-12-month diagnoses to ensure temporal overlap of disorders for comorbidity (Hall et al., 2009; Teesson et al., 2009), which missed earlier disorder episodes, we examined ages of onset of most recent episodes for the disorders comprising each individual's lifetime comorbid status. All participants within this classification were found to have episodes of the alcohol use disorder and the mental health disorder occurring within 12 months of each other, indicating temporal overlap of these disorders.

2.2.2: Behavioural problems

The YASR is a self-report scale developed for use with young adults aged 18-30 years in clinical settings (Achenbach, 1997) but validated in large population samples (Achenbach et al., 1995). It comprises 114 items describing a range of behaviour problems experienced over the previous 6 months using eight subscales. It has achieved internal reliability scores of 0.91 in this sample (Dingle et al., 2011). The Total Problems score comprises the Internalizing (anxiety/depression and withdrawn) and Externalizing (intrusive, aggression and delinquency) scales plus the somatic, thought and attention subscales. For the main regression models, each scale or subscale was used as a continuous variable. For supplementary analyses, the dimension score was categorised, using a 90th percentile cut-off to indicate case-ness for each dimension (Achenbach, 1997; Dingle et al., 2011).

2.2.3: Covariates

Covariates included participants' demographics (age, gender, maternal marital status and maternal education) and factors previously found to be associated with CAMHD and behaviour problems in adults. Maternal smoking, drinking, anxiety, depression were also included in the multivariable models, since previous studies have shown these factors to be associated with development of both mental health and substance use problems in their offspring (Merikangas et al., 1998a; Alati et al., 2006; Saraceno et al., 2009).

Maternal education level was recorded at the first clinic visit during pregnancy (FCV) and was categorised to less than high school, completed high school or completed post-high school study. Maternal marital status, drinking and smoking at the 14-year follow up were assessed using maternal self-reports; these were categorised as partner (married/living together) or no partner (single, divorced, or separated); smoker or non-smoker*;* and non-drinker, occasional drinker (less than weekly) or regular drinker (weekly or more). Maternal anxiety and depression were assessed at the 14-year follow-up using the Delusions-Symptoms-States Inventory (DSSI; (Bedford and Foulds, 1977)). The DSSI contains both anxiety and depression subscales; the depression subscale has been found to correlate strongly with other scales of depression, including the Beck's Depression Inventory (Najman et al., 2000) and achieved Cronbach's α values of 0.88 in the maternal sample at the 14-year follow up. The internal consistency of the anxiety subscale reached 0.84 in this sample. Maternal anxiety and depression were recorded as a case if the individual was positive for at least four of the seven symptoms from that subscale (Bedford and Foulds, 1977).

2.3. Statistical analyses

2.3.1: Main analysis

Although both major measures (DSM-IV diagnoses and YASR behaviour problems) were assessed at the 21-year follow up, for the purposes of these analyses, DSM-IV diagnosed comorbidity categories were used as the outcome variable. To discern whether worse behaviour was more likely to indicate comorbid alcohol and mental health disorders, we generated a mean score, by comorbidity category, for each YASR subscale. Variation of subscale scores across the comorbidity categories was tested using ANOVA, with post-hoc paired t-tests used to examine differences between categories. To account for skewed distribution, ANOVAs were performed using transformed scores (square root of score). The results did not differ significantly from those for untransformed scores, so the latter are presented here for ease of interpretation. In order to compare the magnitude of change across comorbidity categories between YASR dimensions, change as a percentage of the total score range was calculated for each dimension (data not shown).

Multinomial logistic regression analyses were performed to examine the relationships between comorbidity category and YASR subscale scores, with the No Disorder category as reference. Models were adjusted for covariates as described above. Regressions were

then repeated with the AUD and MHD categories as reference in order to establish differences between these and the CAMHD group.

To assess the association of comorbidity class with severe behaviour problems, we examined the number of individuals whose YASR behaviour problem reached case level. As a measure of behaviour problem complexity, we then assessed the number of case-level behaviour problems per individual, by comorbidity category. For each, we used multinomial regressions and adjusted for covariates as described above. Regressions were performed with alternate reference groups as described above to compare comorbidity categories with the no-disorder control, and to describe differences between single-disorder groups and the CAMHD group.

In sensitivity analyses, to ascertain the specificity of alcohol effects versus other substances, we adjusted for offspring smoking (smoker or non-smoker) and regular marijuana use (occasional/no use or use every day/few days), self-reported at the 21-year follow-up (data not shown).

2.3.2: Attrition analysis

Finally, we used two methods to assess how loss to follow up (LFU) may have affected our results. Firstly, to determine whether differential attrition introduced bias to our results, we fitted a multivariate logistic regression model to compare a number of baseline factors between those retained and those lost to follow up. Secondly, starting from a missing at random assumption (Sterne et al., 2009), we used the STATA procedure of multiple imputation, using 10 cycles of regression to generate 10 data sets; our analysis was repeated using these data. Variables used for the imputation models included maternal age, education, marital status, anxiety and depression at first clinical visit during pregnancy and maternal pre-pregnancy drinking and smoking, in addition to those listed above. All analyses were undertaken using the STATA 11 statistical package (StataCorp, USA).

3. Results

Of the original birth cohort (7223), 3801 MUSP offspring completed the YASR at age 21, with 2515 providing complete information on both CIDI and YASR. Some differences emerged between those lost to follow up (LFU) and those included in this study. In the multivariate model of loss to follow up, participant male gender, maternal anxiety, depression and smoking, un-partnered marital status and lower education significantly predicted loss to follow up (Table 1). These factors were then used in the multiple imputation process.

Of those remaining in the study, 48.7% had no lifetime DSM-IV disorder, 23.3% had a lifetime mental health disorder but no alcohol disorder (MHD only), 16% had a lifetime alcohol disorder but no mental health disorder (AUD only), and 12% had comorbid lifetime alcohol and mental health disorders (CAMHD) (Table 2). Analysis of episode recency for each individual's disorders showed that all members of the CAMHD group experienced co-occurrence of the disorders within 12 months, allowing the disorders to be considered comorbid. Although the MHD only group comprised more females (75%) and the AUD only group more males (80%), both the no-disorder and CAMHD groups had similar proportions of male and female members (Table 2).

In exploratory analyses, significant differences were found by ANOVA between disorder groups for the total problems scale; paired t-tests showed the mean score was significantly higher for the CAMHD group than for either single-disorder group (). We therefore examined each subscale separately. Similar results were seen for all but the withdrawn and anxiety/depression subscales (Table 2). Considering the score difference between the CAMHD group and the single-disorder groups as a proportion of score ranges, the greatest increments were seen for aggression and delinquency subscales (data not shown).

All covariates found to be related to at least one disorder category (Table 3) were retained in the final models (Table 4). After excluding individuals with data missing for variables of interest, a final sample of 2314 remained. Participants' age, smoking, regular marijuana use, lower maternal education, and maternal smoking, depression, anxiety and un-partnered marital status were all associated with CAMHD, but only participant and maternal smoking and depression were more strongly associated with CAMHD than with

either single disorder (P-value for all covariates <0.05). No gender interactions were found for the behaviour problems in the comorbid group.

Table 4 shows the unadjusted and fully adjusted models of comorbidity class with individual problem subscales as predictors (composite scales are not shown). The adjusted models differ little to the univariable analyses. Other than the anxiety/depression and withdrawn subscales, for each subscale, those with higher behaviour problem scores were more likely to be in the CAMHD group than to have single disorder types only. Further adjustment for participant smoking and marijuana use produced negligible change (data not shown). When we repeated the regressions using the MHD or AUD group as reference, odds ratios showed that, for each point increase in YASR behaviour score, there was roughly a 10% increase in the likelihood of the person having comorbid alcohol and mental health disorders over a single disorder. Aggression, somatic, thought and attention disorders appear to contribute more through the mental health disorders, whereas delinquency associates more strongly via the alcohol disorders. Multiple imputation analysis yielded very similar results to those shown here (Supplementary Table 3).

In additional analyses, we found that those in the CAMHD group were more likely to have a subscale score reaching case level for somatic, thought, intrusive, aggression or delinquency problems than those with single disorders (Supplementary Table 1). Individuals with comorbid alcohol and mental health conditions also tended to have more case-level problem behaviours (Supplementary Table 2). Having a larger number of case-level problem behaviours was associated with a significant increase in the likelihood of comorbidity, a trend which was unaltered by adjustment (Supplementary Table 2).

4. Discussion

In this research we aimed to investigate whether behaviour problems were more strongly associated with comorbid alcohol and mental health problems than they were in those with the constituent disorder types alone. This study extends clinical evidence, confirming that CAHMDs emerge early in adulthood, suggesting that the associated behaviour problems are likely to be more complex and more severe than in those with either single disorder type.

We found that the significant comorbidity between alcohol and mental health disorders, reported in adults by a number of large population studies, is apparent by early adulthood. Any functional deficit will thus affect a crucial developmental stage in the life course. Although some identification of the functional impact of comorbidity in younger people was undertaken in the National Comorbidity Study Replication – Adolescents (NCS-A) (Merikangas et al., 2009), these specific analyses have not yet been published. We provide the first report of population-level associations with behaviour at age 21; those in the CAMHD group experienced significantly more numerous and more severe problems than those with alcohol or mental health disorders alone. Within this, our study found that the relationship of comorbidity with internalizing behaviour problems was no stronger than that reported with constituent disorders. However, this may be due to a ceiling effect, whereby the constructs measuring the internalising disorders and internalising behaviour problems overlap such that the addition of AUD contributes little extra to the internalising behaviour problem score in those with internalising disorders. More importantly, those with CAMHD were more likely to externalize their distress. Behaviour scores on the aggressive, intrusive and delinquent subscales were more elevated for the CAMHD group, consistent with extensive evidence associating externalizing, conduct and disruptive behaviour problems separately with alcohol (Fergusson et al., 1993; Alati et al., 2005; Boden et al., 2012; Heron et al., 2013) and mental health disorders (Alegria et al., 2010).

Some links between behaviour problems and comorbidity have been reported in clinical samples (Fazel et al., 2009), but these focused on severe disorders such as schizophrenia and other psychoses. This is the first study suggesting that the same associations are found to be true for more common mental health disorders, such as mood and anxiety disorders. It is likely that similar associations may be found with other substance use disorders, potentially via the associated disinhibition (Bornovalova et al., 2005). This is beyond the scope of this paper, but future studies should expand our findings to other, less prevalent, substance use disorders to investigate possible links with behaviour. The increases in severity of behavioural problems for those with CAMHD (10-15% over single disorder groups) are smaller than those observed in clinical samples (Swendsen and Merikangas, 2000; Davis et al., 2008), but this is to be expected; firstly because our study is based on a population rather than a clinical sample, and secondly because participants are young adults, who are likely to have been assessed at early stages of their disorders.

What is however notable is that even by this early stage, important increases in severity of behaviour problems are already apparent.

Our finding that comorbid alcohol dependence is associated with increased externalising behaviour problems among individuals with mental health problems has several implications. For individuals, the presence of externalizing behaviour problems in particular may exacerbate the severity of alcohol problems and hasten progression from the alcohol abuse disorders that are typical of this age group, to alcohol dependence (Behrendt et al., 2011), or further undermine chances of recovery from CAMHD (Grella and Stein, 2013). The complexity of problems may explain the increased days-out-of-role reported by comorbid persons (Slade et al., 2009; Teesson et al., 2009), and dovetails with reports of increased disorder severity for comorbid groups (Merikangas and Kalaydjian, 2007; Kessler and Wang, 2008a). More importantly, it is possible that higher externalizing behaviour problems will increase the risk of exposure to the criminal system for individuals with CAMHD. There are well-documented links between alcohol, violence, involvement with the justice system and recidivism (Sly et al., 2009; Boden et al., 2012; O'Driscoll et al., 2012) and the economic costs of these (Bouchery et al., 2011). Younger persons engage less with treatment services, whether for alcohol or mental health disorders (Cohen et al., 2007), so these associated behaviour problems are likely to manifest as public order problems (Hingson et al., 2009; Laslett et al., 2011). As a result, comorbid conditions may be highly prevalent in those engaged with the criminal system, and conversely, behaviour problems may act as indicators of underlying alcohol/mental health disorders in offenders. Co-occurrence of mental health disorders has been noted in reoffending substance users (O'Driscoll et al., 2012), but the full impact of comorbid disorders on rehabilitation and reoffending in offenders is unknown. Future research should investigate this likelihood and any associated social and individual implications.

Finally, our findings may also have implications for early intervention. The externalizing behaviour problems associated with CAMHD are likely to be challenging in mainstream service environments and hence alienate this group of people from care when they do present for treatment (Alegria et al., 2010). Although current service-level initiatives regarding comorbidity recommend routine screening for both substance and mental health disorders on presentation (Mills et al., 2009), our findings suggest that the presence of externalizing behaviours on presentation should highlight the need for dual disorder screening, and management practices should be implemented for the externalizing

behaviours associated with this comorbidity. Our findings underline the need for adequate measures to be routinely employed in expectation of such behaviour problems, as opposed to being regarded as an extreme and uncommon occurrence.

This paper has significant strengths. It describes effects in a large and non-selected community sample, allowing conclusions to be generalized to the population, and is able to adjust the associations seen for a number of relevant longitudinal covariates. Ours is one of the first studies to use a rigorous method to assess comorbidity. Using the onset of most recent episodes, we were able to demonstrate that the entire group reporting comorbid alcohol and mental health disorders showed co-occurrence of the two classes within a 12 month period. Most previous large scale national studies have used lifetime reporting of two disorders as their criterion for comorbidity (Swendsen and Merikangas, 2000; Kessler, 2004). With variation in ages of onset (Merikangas et al., 1998b; McEvoy et al., 2011), and the episodic rather than chronic nature of such disorders during youth development, our more stringent approach gives us greater confidence that the constituent disorders were temporally comorbid, in order to show the impact of their co-occurrence. Additionally, we have been able to provide more detailed information on the range of behavioural problems associated with CAMHD by using continuous measures rather than categorical diagnostics.

Our findings should be seen in the context of some limitations. Firstly, our data were cross-sectional, and so have limited predictive value. However, the reporting periods for behaviour and CIDI-diagnosed comorbidity may not overlap. Behaviour problems are reported for the six months immediately prior to interview, whereas 69% of comorbidity cases were not within the 12 months preceding interview, so may have preceded the behaviour problems. From this information we may suggest that, for those in whom the comorbid disorder episodes may have subsided, the more severe behaviour problems with which they are associated persist.

Secondly, the loss to follow up in our study may have introduced bias to our results. Only 2575 of the original birth cohort were administered the CIDI at the 21-year follow up, resulting in 32% of the original birth cohort being available for this analysis. Some differences have emerged between those represented her and the original sample. Those lost to this group were more likely to have mothers who smoked and were depressed. Maternal smoking remained a significant factor in the relationships between the externalizing behaviour problems and comorbidity, and maternal depression in the

relationship between aggression and comorbidity, as well as with single disorders. Thus, the relationship strengths described here may have been underestimated as a result of loss to follow up. In addition, despite the limitations of imputations analysis in dealing with attrition bias, the results of our MI analysis were virtually identical to those in our main analysis, giving further confidence to the robustness of our findings in the face of attrition.

In conclusion, we found that CAMHD emerge at young adulthood in significant numbers in the general population, and that this comorbidity is strongly associated with increases in internalising and externalizing behaviour problems. If our findings are replicated in similar studies, future intervention strategies will need to include behavioural management practices.

Author disclosures

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Contributors

Authors Salom, Alati, Williams and Scott designed the study; author Salom wrote the protocol and managed the literature searches. Authors Salom and Betts undertook the statistical analysis. Author Salom wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare there are no conflicts of interest.

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Table 1: Multivariable attrition analysis showing the likelihood of being lost to follow up (LFU) according to baseline factors, expressed as Odds Ratios (OR) with 95% Confidence Intervals (CI_{95})

Covariate	Category	Odds of being LFU at 21 years	
		OR	CI_{95}
Participant gender	Female	0.81	(0.74, 0.90)
Mother's education at FCV[$]	Completed Year 12	**1.39**	(1.13, 1.69)
	Less than Year 12	**1.21**	(1.06, 1.38)
Mother's marital status at FCV[$]	No partner	**1.40**	(1.19, 1.65)
Mother smoking pre-pregnancy	Smoker	**1.22**	(1.10, 1.36)
Mother drinking pre-pregnancy	Occasionally	0.86	(0.77, 0.97)
	Regularly	0.97	(0.83, 1.13)
Mother depressed at FCV[$]	Depressed	**1.52**	(1.17, 1.99)
Mother anxious at FCV[$]	Anxious	**1.29**	(1.08, 1.53)

[$] FCV = first clinic visit during pregnancy

Model is fully adjusted for all covariates; significant (P<0.05) ORs are shown in bold

Reference categories for the covariates above are: male; completed post-Year 12 study; married/living together; non-smoker; non-drinker; not depressed; not anxious

Table 2: Mean YASR dimension scores for MUSP offspring participants at age 21, by comorbidity category

	No disorder	MHD only [a]	AUD only [b]	CAMHD [c]	
No of participants:	1226 (49%)	589 (23%)	398 (16%)	302 (12%)	
Male	606	146	319	152	
Female	620	443	79	150	
YASR dimension	**Mean score** (CI_{95})	**Mean score** (CI_{95})	**Mean score** (CI_{95})	**Mean score** (CI_{95})	**F** [d] (*P*-value)
Total problems	22.05 (21.28,22.81)	36.27 (34.74, 37.79)	27.84 (26.18,29.49)	42.76[§] (40.42, 45.10)	184.1 (<0.001)
Internalizing	8.17 (7.80, 8.54)	14.77 (14.05, 15.50)	8.12 (7.47, 8.78)	14.76 (13.76, 15.77)	148.3 (<0.001)
Anxiety/ depression	6.08 (5.80, 6.37)	11.53 (10.95, 12.11)	5.89 (5.38, 6.39)	11.43 (10.64, 12.21)	163.5 (<0.001)
Withdrawn	2.10 (1.98, 2.21)	3.22 (3.01, 3.42)	2.23 (2.03, 2.44)	3.31 (3.02, 3.59)	48.0 (<0.001)
Externalizing	7.33 (7.03, 7.62)	10.37 (9.83, 10.91)	11.45 (10.74,12.16)	14.95[§] (14.01, 15.88)	138.0 (<0.001)
Intrusive	2.49 (2.36, 2.61)	3.12 (2.92, 3.32)	3.07 (2.83, 3.31)	3.69[§] (3.38, 4.00)	25.6 (<0.001)
Aggression	3.29 (3.13, 3.45)	5.24 (4.94, 5.53)	4.55 (4.18, 4.91)	6.83[§] (6.33, 7.33)	108.5 (<0.001)
Delinquency	1.60 (1.50, 1.70)	2.02 (1.85, 2.19)	3.80 (3.52, 4.07)	4.41 (4.07, 4.75)	193.1 (<0.001)
Somatic	3.43 (3.27, 3.60)	6.13 (5.81, 6.44)	4.12 (3.79, 4.45)	6.87[§] (6.36, 7.38)	129.5 (<0.001)
Thought	0.45 (0.40, 0.50)	1.02 (0.91, 1.13)	0.76 (0.64, 0.87)	1.40[§] (1.21, 1.59)	70.5 (<0.001)
Attention	2.82 (2.70, 2.94)	3.91 (3.70, 4.11)	3.37 (3.13, 3.62)	4.54[§] (4.25, 4.83)	58.1 (<0.001)

[a] Mental Health Disorders (MHD) included any lifetime DSM-IV disorder; inc psychoses, eating disorders & substance use disorders
[b] Alcohol Use Disorders (AUD) included lifetime DSM-IV alcohol abuse and alcohol dependence disorders.
[c] CAMHD participants were diagnosed with any lifetime MHD plus any lifetime AUD.
[d] ANOVA results confirmed significantly different mean scores between the categories
[§] Post-hoc paired T-tests showed mean score for dimension was significantly higher for comorbid group than for AUD or MHD (p<0.05)

Table 3: Univariate relationships between covariates and comorbidity categories a

Covariate	No of cases (%)	Comorbidity category: MHD only OR (CI_{95})	AUD only OR (CI_{95})	CAMHD OR (CI_{95})
Gender				
male	1790 (47%)			
female	1988 (53%)	**2.97** (2.38, 3.69)	**0.24** (0.18, 0.32)	0.96 (0.75, 1.24)
Age (years)	3778	1.05 (0.93, 1.18)	**1.26** (1.10, 1.44)	**1.30** (1.11, 1.52)
Maternal education [b]				
Post Year 12 study	1252 (17%)			
Completed Year 12	689 (10%)	0.99 (0.66, 1.49)	**1.58** (1.01, 2.48)	**1.85** (1.09, 3.13)
Did not complete Year 12	5229 (73%)	**1.31** (1.02, 1.68)	**1.62** (1.20, 2.20)	**2.07** (1.44, 2.98)
Maternal drinking [c]				
Non-drinker	2436 (47%)			
Occasional drinker	1657 (32%)	1.02 (0.81, 1.27)	**1.35** (1.03, 1.76)	0.84 (0.62, 1.14)
Regular drinker	1079 (21%)	0.88 (0.67, 1.15)	**1.48** (1.10, 1.99)	1.23 (0.89, 1.69)
Maternal smoking [c]				
Non-smoker	3570 (69%)			
smoker	1602 (31%)	**1.51** (1.21, 1.89)	**1.46** (1.13, 1.88)	**2.19**[§] (1.67, 2.87)
Maternal depression [c]				
Non-depressed	6789 (94%)			
Depressed	434 (6%)	1.15 (0.75, 1.78)	1.35 (0.85, 2.16)	**2.62**[§] (1.71, 4.02)
Maternal anxiety [c]				
Not anxious	6250 (86%)			
Anxious	973 (14%)	**1.44** (1.11, 1.87)	1.21 (0.89, 1.65)	**1.75** (1.28, 2.41)
Maternal marital status [c]				
Married/living together	4184 (81%)			
No partner	983 (19%)	**1.52** (1.17, 1.97)	1.18 (0.86, 1.62)	**1.43** (1.03, 1.99)
Participant smoking [d]				
Non-smoker	2396 (64%)			
smoker	1362 (36%)	**1.90** (1.54, 2.34)	**2.87** (2.27, 3.36)	**4.95**[§] (3.79, 6.46)
Participant marijuana use [d]				
Non/occasional use	3289 (88%)			
Regular use	465 (12%)	**1.56** (1.07, 2.28)	**5.95** (4.28, 8.28)	**6.68** (4.72, 9.47)

[a] Multinomial logistic regression models, unadjusted, using No Disorder as reference

[b] Measured at first clinical visit during pregnancy (FCV)

[c] Measured at 14 year follow up

[d] Measured at 21 year follow up

[§] Association of covariate with comorbid group is significantly greater than with either single disorder group (P<0.005)

Table 4: Multinomial logistic regression models of comorbidity category at age 21, with YASR dimensions as predictors

YASR Dimension	Unadjusted models [a]			Fully adjusted models [a, b]			Comparisons [c]	
	MHD only OR (CI_{95})	**AUD only** OR (CI_{95})	**CAMHD** OR (CI_{95})	**MHD only** OR (CI_{95})	**AUD only** OR (CI_{95})	**CAMHD** OR (CI_{95})	**CAMHD vs MHD** OR (CI_{95})	**CAMHD vs AUD** OR (CI_{95})
Internalizing								
Anxiety / depression	**1.16**(1.14, 1.18)	0.99(0.97, 1.02)	**1.15** (1.13, 1.18)	**1.15**(1.13, 1.18)	1.01.(0.98, 1.03)	**1.16** (1.13, 1.18)	1.00 (0.98, 1.01)	**1.15** (1.11, 1.18)
Withdrawn	**1.24**(1.19, 1.30)	1.03(0.98, 1.09)	**1.26** (1.19, 1.33)	**1.26**(1.20, 1.32)	0.99 (0.94, 1.05)	**1.25** (1.18, 1.33)	0.99 (0.93, 1.05)	**1.27** (1.18, 1.35)
Externalizing								
Intrusive	**1.12**(1.08, 1.17)	**1.11**(1.06, 1.17)	**1.23**[§](1.17, 1.29)	**1.15**(1.10, 1.21)	**1.09**(1.04, 1.15)	**1.23**[§] (1.17, 1.30)	**1.08** (1.01, 1.14)	**1.14** (1.06, 1.20)
Aggression	**1.20**(1.17, 1.24)	**1.14**(1.10, 1.18)	**1.33**[§](1.28, 1.38)	**1.20**(1.16, 1.24)	**1.12**(1.08, 1.16)	**1.31**[§] (1.26, 1.37)	**1.10** (1.05, 1.14)	**1.18** (1.12, 1.22)
Delinquency	**1.13**(1.07, 1.19)	**1.52**(1.44, 1.61)	**1.63**[§](1.54, 1.73)	**1.21**(1.14, 1.28)	**1.44**(1.36, 1.52)	**1.68**[§] (1.57, 1.78)	**1.39** (1.30, 1.47)	**1.16** (1.10, 1.23)
Other								
Somatic	**1.25**(1.22, 1.29)	**1.08**(1.04, 1.12)	**1.31**[§](1.26, 1.36)	**1.23**(1.19, 1.27)	**1.10**(1.06, 1.15)	**1.30**[§] (1.25, 1.35)	**1.05** (1.02, 1.10)	**1.18** (1.12, 1.23)
Thought	**1.67**(1.51, 1.84)	**1.41**(1.26, 1.58)	**1.95**[§](1.75, 2.18)	**1.77**(1.59, 1.97)	**1.29**(1.14, 1.46)	**1.97**[§] (1.76, 2.21)	**1.11** (1.01, 1.23)	**1.52** (1.34, 1.74)
Attention	**1.22**(1.17, 1.28)	**1.12**(1.06, 1.17)	**1.35**[§](1.28, 1.42)	**1.26**(1.20, 1.32)	**1.11**(1.05, 1.17)	**1.40**[§] (1.32, 1.48)	**1.11** (1.04, 1.17)	**1.25** (1.18, 1.35)

[a] Regressions performed using No-Disorder group as reference; significant ORs (P<0.005) are in bold type

[b] Models adjusted for participant gender and age, plus maternal education, drinking, depression, anxiety and marital status as per Table 4; No Disorder group used as reference

[c] Fully adjusted regressions were repeated, using MHD as reference (CAMHD vs MHD) and using AUD as reference (CAMHD vs AUD), to allow comparison between ORs for comorbid and single disorder types

[§] Odds Ratio for the CAMHD group was significantly higher (*P*<0.05) than that for either single-disorder group as determined above

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Summary of Chapter 5

It was possible to detect indicators of potential comorbidity in groups as young as 10-14 years. Co-occurring drinking and depressive symptoms were found in nearly 6% of pre-adolescent school children. These levels were consistent with international reports. Low school commitment was more strongly linked to the dual condition than single conditions, as were family substance problems. In young adults, comorbidity was associated with more behavioural problems (notably aggression and delinquency) than were single disorders. Behaviour problems were also more severe for the comorbid group. It appears that indicators of adult comorbidity can be detected early, and that this comorbidity conveys additional burdens over single disorders.

Chapter 6: Indicators across the life course

Studies described in Chapter 5 suggested that comorbidity was associated with poorer social function than single disorders. However the behaviour problems exhibited in adulthood were not necessarily present at 14 years as indicators of later comorbidity. As such, examination of other factors and earlier developmental periods was warranted.

Perinatal factors associated with comorbid alcohol and mental health disorders

This chapter aimed to identify factors from very early childhood which may predict the onset of comorbidity. Barker's hypotheses regarding the foetal origin of disease made it important to examine perinatal factors, as pathways governing mental health conditions and alcohol use disorders may be determined pre-birth. Drinking, smoking and mental health of the mother during pregnancy were potentially influential during this period. Factors such as birth weight and early IQ may indicate disrupted foetal development, which may later manifest as comorbidity, and socio-economic factors may also be relevant.

As shown in Table 13, maternal binge drinking and smoking during pregnancy both predicted comorbidity in their offspring, but only maternal smoking predicted comorbidity more strongly than single conditions in the fully adjusted model. There was some evidence for a dose response to maternal smoking. Maternal depression, anxiety and mental distress did not appear to predict alcohol use disorders or comorbidity in the offspring.

Further investigation of the role of socio-economic disadvantage led to the development of paper 6.1 included here. In order to examine a number of domains commonly used as proxies for socio-economic standing, a scale was created to reflect socio-economic disadvantage from the family of origin, incorporating family income, maternal education, paternal education, maternal employment and paternal employment. The relationship between this very early disadvantage and comorbid alcohol use and mental health disorders was tested, and the impact of more proximal measures of socio-economic standing investigated.

Table 13: Associations between maternal characteristics during pregnancy and comorbidity at young adulthood

Bivariate associations

Factor	Category	MHD only		AUD only		Comorbid	
		OR	**(CI_{95})**	**OR**	**(CI_{95})**	**OR**	**(CI_{95})**
Drinking	Non-binge	0.99	(0.78, 1.25)	**1.46**	(1.09, 1.96)	1.32	(0.95, 1.83)
	Binge	**1.46**	1.01, 2.11)	**1.87**	(1.21, 2.91)	**2.33**	(1.47, 3.69)
Smoking	Any	**1.76**	(1.43, 2.16)	**1.50**	(1.18, 1.89)	**2.68***	(2.07, 3.47)
	1-9/day	**1.85**	(1.41, 2.43)	**1.51**	(1.10, 2.07)	**2.55**	(1.82, 3.56)
	10-19/day	**1.60**	(1.16, 2.21)	**1.71**	(1.20, 2.42)	**2.80***	(1.93, 4.05)
	20+/day	**1.98**	(1.37, 2.87)	0.96	(0.57, 1.60)	**2.90**	(1.87, 4.50)
Depression	Yes	0.98	(0.57, 1.69)	1.07	(0.59, 1.95)	1.16	(0.60, 2.23)
Anxiety	Yes	**1.51**	(1.10, 2.07)	1.18	(0.81, 1.73)	1.15	(0.75, 1.77)
Mental distress	Per point	**1.06**	(1.02, 1.11)	1.02	(0.97, 1.07)	**1.05**	(1.00, 1.11)
	Yes	**1.46**	(1.02, 2.09)	1.31	(0.86, 1.99)	**1.73**	(1.13, 2.65)

Fully adjusted associations [a]

		OR	**(CI_{95})**	**OR**	**(CI_{95})**	**OR**	**(CI_{95})**
Drinking	Non-binge	0.93	(0.73, 1.20)	**1.42**	(1.04, 1.94)	1.25	(0.88, 1.79)
	Binge	1.17	(0.79, 1.75)	**1.80**	(1.12, 2.88)	**1.68**	(1.01, 2.77)
Smoking	1-9/day	**1.66**	(1.24, 2.22)	1.31	(0.93, 1.85)	**2.28**	(1.58, 3.27)
	10-19/day	**1.49**	(1.06, 2.10)	**1.50**	(1.03, 2.19)	**2.50***	(1.68, 3.73)
	20+/day	**1.66**	(1.10, 2.50)	0.72	(0.40, 1.31)	**2.51**	(1.55, 4.07)
Depression	Yes	0.98	(0.57, 1.69)	1.07	(0.59, 1.95)	1.16	(0.60, 2.23)
Anxiety	Yes	**1.51**	(1.10, 2.07)	1.18	(0.81, 1.73)	1.15	(0.75, 1.77)
Mental distress	Per point	**1.04**	(1.00, 1.09)	0.99	(0.94, 1.04)	1.01	(0.95, 1.07)

Reference group for drinking is abstainers; reference group for smoking is non-smokers

[a] Model has also been adjusted for maternal age and socio-economic disadvantage

* $OR_{comorbid} > OR_{AUD}$ and OR_{MHD} ($P<0.05$)

6.1 Socio-economic disadvantage

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Title

Does early socio-economic disadvantage predict comorbid alcohol and mental health disorders?

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Running title

Socio-economic disadvantage and comorbidity

ABSTRACT

Background: Alcohol and mental health disorders are highly prevalent in the general population, with co-occurrence recognised as a major public health issue. Socio-economic factors are frequently associated with both disorders but their temporal association is unclear. This paper examines the association between prenatal socio-economic disadvantage and comorbid alcohol and mental health disorders at young adulthood.

Methods: An unselected cohort of women was enrolled during early pregnancy in the large longitudinal Mater-University of Queensland Study of Pregnancy (MUSP), at the Mater Misericordiae Public Hospital in Brisbane, Australia. The mothers and their offspring were followed over a twenty-one year period. Offspring from the MUSP birth cohort who provided full psychiatric information at age 21 and whose mothers provided socioeconomic information at baseline were included (n=2399). Participants were grouped into no-disorder, mental health disorder only, alcohol disorder only or comorbid alcohol and mental health disorders according to DSM-IV diagnoses at age 21 as assessed by the Composite International Diagnostic Interview. We used multivariate logistic regression analysis to compare associations of disorder group with single measures of prenatal socio-economic disadvantage including family income, parental education and employment, then created a cumulative scale of socioeconomic disadvantage.

Results: Greater socio-economic disadvantage was more strongly associated with comorbidity (OR 3.36; CI_{95} 1.37, 8.24) than with single disorders. This relationship was not fully accounted for by maternal mental health, smoking and drinking during pregnancy.

Conclusion: Multiple domains of socio-economic disadvantage in early life are associated with comorbid alcohol and mental health disorders.

Key words:

Alcohol, comorbid, longitudinal, mental health, socioeconomic

1. BACKGROUND

Alcohol and mental health disorders are highly prevalent in the general population (Merikangas and Kalaydjian, 2007), with adolescence and early adulthood the prime periods for emergence (Kessler et al., 2005; Teesson et al., 2009). The consequences of these disorders (King et al., 2000; Gore et al., 2011; Mojtabai, 2011; Whiteford et al., 2013), particularly when co-occurring, are increasingly recognised as a major public health issue and their global health and economic burden is high. Mental health and alcohol disorders contribute to 183.9 million Disability Adjusted Life Years annually, peaking in young adults (Whiteford et al., 2013), and treatment of comorbid mental health and alcohol disorders is both more complex (Tiet and Mausbach, 2007; Connolly et al., 2011) and more costly than single disorders (King et al., 2000), with worse projected outcomes (Bruce et al., 2005). As such, understanding how these joint conditions emerge is of great interest to researchers, policy makers and health professionals (Rush and Koegl, 2008; Swendsen et al., 2009; Cerda et al., 2010; Green et al., 2012).

Yet little is known about specific predictors of co-occurrence of these conditions. Beyond individual, familial and hereditary factors, the role of socioeconomic status (SES), long linked to general morbidity (Adler and Stewart, 2010), deserves increased research attention. Cross-sectionally, SES has been associated separately with alcohol disorders (Windle and Davies, 1999; Caldwell et al., 2008; Rush and Koegl, 2008; Swendsen et al., 2009; Adler and Stewart, 2010; Melotti et al., 2011; Young-Wolff et al., 2011; Green et al., 2012; Karriker-Jaffe, 2013) and with depression and anxiety (de Graaf et al., 2002; Gilman et al., 2003; Melchior et al., 2007; Cerda et al., 2010). A number of studies have linked socio-economic factors and comorbid alcohol and mental health disorders (Ross, 1995; Costello et al., 1997; Windle and Davies, 1999; Armstrong and Costello, 2002; de Graaf et al., 2002; Rush and Koegl, 2008; Cerda et al., 2010; Green et al., 2012; Mulia and Zemore, 2012; Pulkki-Raback et al., 2012), but whether these associations differs from the single disorders is unclear: the use of varying measures makes comparisons challenging (Cerda et al., 2010). Aspects such as low personal income (Ross, 1995; Pulkki-Raback et al., 2012) and lower family social support (Windle and Davies, 1999) have been cross-sectionally associated with comorbid alcohol and mental health problems in large national studies (Mulia and Zemore, 2012). Other studies however have

found this to hold only for Caucasian groups (Costello et al., 1997). Similarly, educational status has been implicated in some (Ross, 1995; Green et al., 2012) but not all (Rush and Koegl, 2008) findings.

It is unclear which aspects of SES-based disadvantage are more strongly associated with alcohol and mental health comorbidity. Studies comparing multiple measures of disadvantage have shown increased risk of depression (Eley et al., 2004) for some but not all SES measures used (McLaughlin et al., 2012), but results for comorbidity are again conflicting. Some comparisons have found that low income is more strongly associated than is education (Ross, 1995; Pulkki-Raback et al., 2012), while others suggest that lower education is more strongly associated with common mental disorders (Araya et al., 2003) or comorbid disorders (de Graaf et al., 2002). Generalisation of these seemingly inconsistent associations is complicated by heterogeneity of study designs (Ross, 1995; Costello et al., 1997; de Graaf et al., 2002; Araya et al., 2003; Mulia and Zemore, 2012) and diversity in sample characteristics (Costello et al., 1997; Rush and Koegl, 2008; Green et al., 2012). The cumulative effect of multiple dimensions of socioeconomic disadvantage has been argued to impact on health problems later in life (Turrell et al., 2003; Marmot, 2005; Chartier et al., 2010; Marie-Mitchell and O'Connor, 2013), but it is unknown whether cumulative disadvantage affects comorbid alcohol and mental health disorders. Some studies have investigated the impact of cumulative adversities on common mental health disorders by using composite measures which allow multiple factors to be considered simultaneously (Eley et al., 2004; Chartier et al., 2010; McLaughlin et al., 2012; Marie-Mitchell and O'Connor, 2013). However, where such composite measures include parental psychopathology, family conflict and health behaviours with socio-economic factors, as for the Adverse Childhood Events scale, it is not possible to distinguish between the impact of SES-based and behavioural factors on the outcome of interest (Marie-Mitchell and O'Connor, 2013). Our study is the first to use a cumulative measure of disadvantage based only on socio-economic factors to investigate its relationship with comorbidity, and considers the effects of parental mental health, drinking and smoking separately.

Another gap in the existing evidence is that most studies have measured SES and comorbidity in adulthood. However, adult SES may be the result of mental health and substance disorders developed during adolescence, which in turn can affect

completion of education, and reduce adult employment opportunities and income (Skapinakis et al., 2006; Lee et al., 2013). Some longitudinal studies suggest this may be the case (Costello et al., 1997; Windle and Davies, 1999; Green et al., 2012) as they have shown childhood SES measures to have stronger separate associations with mental disorders and alcohol problems (Laaksonen et al., 2007; Cohen et al., 2010; Green et al., 2012) than measures from later life. No studies have explored more distant SES and its impact on alcohol and mental health comorbidity, yet the fact that childhood measures are more strongly associated with each disorder type points to the possibility that distal socio-economic disadvantage may be an important factor in the development of alcohol and mental health comorbidity.

Taken together, this evidence suggests the importance of assessing multiple indicators of socio-economic disadvantage in predicting comorbid disorders, and looking at SES very early in life, ideally via a prospective design. This paper aims to examine the impact of a number of indicators of SES from the family of origin, both singly and cumulatively, on comorbid alcohol and mental health disorders in young adults. We use a birth cohort study, the Mater-University of Queensland Study of Pregnancy (MUSP), with detailed information about the parents at the time of pregnancy allowing temporality to be addressed.

2. METHODS

2.1 Study design and participants

The Mater-University of Queensland Study of Pregnancy (MUSP) is a birth cohort study of mothers and children. Mothers were enrolled at their first clinic visit during pregnancy to the Mater Misericordiae Public Hospital in Brisbane between 1981 and 1983, with 7223 eligible participants at baseline. The MUSP was approved by the Behavioural and Social Sciences Ethics Review Committee at the University of Queensland and has been extensively described elsewhere (Najman et al., 2005). Dyads were followed up at birth, 5 days and 6 months, then 5, 14 and 21 years after birth with 3778 members of the offspring cohort (52%) participating at age 21. At enrolment and follow ups, participants gave written, informed consent. Only offspring

for whom complete data on prenatal socio-economic factors and mental health and alcohol use at age 21 are available were included in the main analyses.

2.2 Measures

2.2.1Comorbid mental health and alcohol disorders

At the 21–year follow up, 2539 offspring participants (35% of baseline) were administered the mental health and substance use disorders modules of the Composite International Diagnostic Interview (CIDI). Responses were coded to yield DSM-IV disorder diagnoses for occurrence over the participant's lifetime, to avoid missing episodes occurring before the year preceding interview. The 'any alcohol use disorder' diagnosis included alcohol abuse and dependence (AUD), whereas 'any mental health disorder' (MHD) included all participants reporting an anxiety, affective, eating or psychotic disorder. Within each of these groups, the presence of multiple disorders was possible.

A four-category variable "Comorbidity Group" was created: No (DSM-IV) disorder; Mental health disorder only (MHD only, i.e. no alcohol disorder); Alcohol use disorder only (AUD only, i.e. no mental health disorder) or Comorbid (i.e. 'any alcohol use disorder' plus 'any mental health disorder'). Concurrence of disorders was examined using ages of onset of most recent episodes for the disorders comprising each individual's comorbid status. All 'Comorbid' participants were found to have episodes of alcohol use disorder and mental health disorder occurring within 12 months of each other, indicating temporal overlap.

2.2.2 Socio-economic measures

SES measures were investigated for association with comorbidity group according to previous findings (Swendsen et al., 2009; Najman et al., 2010; Australian Institute of Health & Welfare, 2012; Pulkki-Raback et al., 2012). Family income, parental employment and parental education were assessed at baseline and coded binomially for disadvantage as below.

Family income was recorded as less than $2600pa, <$5200pa, < $10,400pa, <$15,600pa, <$20,80pa, <$26000pa or >$26000pa. The 1982 minimum wage was $7857; unemployment benefits were $6427 (married) or $3856 (single with dependents) (Cameron, 1983). To account for the number of persons supported by the recorded family income, we conservatively coded un-partnered mothers as

disadvantaged if family income was < $5200 and married/de facto participants as disadvantaged if < $10,400.

Maternal pre-pregnancy employment was coded as disadvantaged if recorded as 'unemployed', or 'on benefits'. A small proportion of women who reported 'studying' (0.64%) were also classed as 'disadvantaged', as this was presumed to have limited their employment at that time. 'Home duties' was not coded as disadvantaged as this represented participation in home-based (although unpaid) work. Partner employment was coded as disadvantaged if 'unemployed', 'studying', 'on benefits', 'in prison' or 'no partner'.

Education completed by mother/father was recorded as <Year 10; <Year 12; post-high school qualification or university qualification, and coded as disadvantaged if less than Year 12. Mother's ethnicity was recorded at baseline as white, Asian or Aboriginal/Islander and examined categorically. Children's socio-economic disadvantage at time of CIDI diagnosis (21 years) was estimated using the level of education completed and coded as disadvantaged if less than Year 12. As many (37%) offspring were still studying at that time and 65% living with their parents, their income and employment were not considered measures that would accurately reflect SES-based disadvantage. Although strongly associated with socio-economic disadvantage, we did not separately consider family structure in this study, as this was incorporated in the individual measures of disadvantage described above, and so was highly correlated with these.

2.2.3 Covariates

Maternal age at pregnancy, smoking, drinking, anxiety and depression were included as covariates, as previous studies have shown these to be associated with both mental health and substance use problems in their offspring (Merikangas et al., 1998a; Alati et al., 2006; Saraceno et al., 2009). Although these items may impact on disorder development during adolescence, baseline measures were used to preclude any potential impact of child disorders. Maternal anxiety and depression were assessed using the Delusions-Symptoms-States Inventory (DSSI (Bedford and Foulds, 1977)). The DSSI contains anxiety and depression subscales; the depression subscale has been found to correlate strongly with other scales of depression, including the Beck's Depression Inventory (Najman et al., 2000), and achieved Cronbach's α values of 0.88 in the maternal sample; the anxiety subscale

reached 0.84. Anxiety and depression were recorded as cases if positive for at least four of the seven symptoms from that subscale (Bedford and Foulds, 1977). Maternal smoking (non-smoker/smoker) and binge drinking (never/more than occasionally drank > 5 glasses of alcohol) during pregnancy were self-reported.

Participants' adolescent drinking (Behrendt et al., 2008) and behaviour problems (Ferdinand et al., 2001) have been associated with later alcohol or mental health problems. We used participants' self-reported adolescent drinking (less than 3 drinks/at least 3 drinks per occasion) at age 14. Behavioural problems were also assessed at age 14 using the Achenbach Youth Self Report (Achenbach, 1997). We used the Total Problems scale, with those falling into the higher 10% of the scale scores defined as having behaviour problems, consistent with Achenbach's definition of caseness (Achenbach, 1997).

2.3 Statistical analyses

Each variable was examined individually and correlation analyses undertaken to determine the degree to which overlap may occur. Exploratory factor analysis was undertaken to examine potential variable groupings, using principal-components factoring and varimax rotation. Finally a cumulative scale was constructed where binomial scores were summed to generate a Socio-Economic Disadvantage Score ranging from 0 to 5. We fitted multinomial logistic regression models with Odds Ratios (OR) and 95% confidence intervals (CI_{95}) to produce point estimates for the relationships between comorbidity group and socio-economic disadvantage, with the No-Disorder group as reference. We initially used individual indicators of SES, then SES factors generated above and finally the composite disadvantage scale. To establish differences between single-disorder groups and the Comorbid group, we reversed the reference category to the Comorbid group and repeated the analyses. In Model 1, we adjusted for potential confounding by maternal age during pregnancy. Since most other influences would likely be on the causal pathway between distal SES and adult comorbidity, we investigated these as potential mediators. In models 2-5, we investigated the roles of maternal mental health, binge drinking and smoking during pregnancy. Factors excluded from the final model included maternal racial background, offspring age and gender, because they were not found to be associated with comorbidity (data not shown). In a supplementary analysis, we compared the impacts of smoking before and during pregnancy on the relationship

on the associations reported here. In a second supplementary analysis, we investigated the roles of participants' own drinking and behaviour problems at age 14 and their educational level at age 21 as potential mediators of the effect of distal socio-economic disadvantage.

Finally, we used multiple imputations to assess how loss to follow up may have affected our results. Starting from Missing at Random assumption (Sterne et al., 2009), we used the STATA procedure to multiply impute our missing data (Ware et al., 2012). We used multivariate regression analyses to determine whether our socio-economic variables were associated with attrition, then included these in the imputation process in order to account for the related missingness. Variables used for the imputation models included participant gender, maternal age, marital status, anxiety, depression, binge drinking and smoking at baseline, which had earlier been found to be associated with loss to follow up (Salom et al., in press), in addition to the prenatal socio-economic disadvantage score and participant education as described above. We used 10 cycles of regression to generate 10 data sets and repeated our final analysis using the imputed data, then repeated with 20 and 50 cycles. All analyses were undertaken using STATA 12.1 (StataCorp, USA).

3. RESULTS

In this sample, 49 % reported no (DSM-IV) disorders; 23% reported a mental health disorder only (i.e. no alcohol disorder); 16% reported an alcohol use disorder only and 12% reported experiencing both mental health and alcohol disorders within a 12 month period (Table 1). Participants in the MHD Only and Comorbid groups had similarly complex mental health disorders (7.3 and 7.5% respectively reported more than 3 diagnoses).

We found weak to moderate correlation between individual SES measures (Supplementary Table 1). Univariate multinomial regressions (Table 2) showed that low family income and maternal employment were associated with comorbidity but not with single disorder groups; low parental education appeared a risk for each disorder group and although effect sizes were largest for comorbidity, these were not distinct from single disorder groups. Paternal employment was not found to be associated with single or dual disorders, and we found no interaction between individual measures of SES.

Principal component analysis showed two factors with eigenvalues of 1.78 and 1.23 respectively. These accounted for 60.24% of the variance: the first loaded most heavily on family income, mother's employment and father's employment (scores 0-3). The second comprised maternal and paternal education (scores 0-2). Factor scores are standardised to a mean of 0 and standard deviation of 1, which allowed us to compare effect sizes in regression models of comorbidity group (Table 2). Disadvantage based on education (Factor 2) was more strongly associated with comorbidity (OR 1.33; CI_{95} 1.16, 1.52; continuous variable) than that based on economic factors (Factor 1: OR 1.15; CI_{95} 1.00, 1.33).

The composite Socio-Economic Disadvantage scale was associated with the Comorbid group, but not either single-disorder group (Table 2). A distinct dose response was seen; at the highest level of disadvantage, the odds of belonging to the Comorbid group were over three times those for single disorders (Figure 1). Maternal age at baseline was strongly but inversely related to socio-economic disadvantage; as mother's age increased, participants were less likely to be in the most disadvantaged group (OR 0.01; CI_{95} 0.003, 0.01). However there was no difference in the relationships between mother's age and single or comorbid disorders (Supplementary Table 2). Adjusting for maternal age reduced the magnitude of the relationship (Table 3) between socio-economic disadvantage and comorbid disorders but it remained stronger than with single disorder types.

Maternal smoking and binge-drinking in pregnancy, maternal depression and maternal anxiety at baseline were all related to increasing socio-economic disadvantage (Supplementary Table 2a). Separate inclusion of maternal mental health and maternal binge-drinking in pregnancy reduced the magnitude of the disadvantage/comorbidity relationship only slightly and did not remove the difference between comorbid and single disorder relationships (Table 4). Maternal smoking in pregnancy most strongly attenuated the likelihood of comorbidity at all levels of disadvantage, but the relationship of comorbidity with greatest disadvantage remained. Maternal mental health, tobacco and alcohol use at other time periods did not change substantively the associations shown in the main analysis (data not shown).

In supplementary analyses, the impact of mothers continuing to smoke during pregnancy was shown to be different to that of smoking before pregnancy

(Supplementary Table 3). Although both were associated with comorbidity, pre-pregnant smoking had no impact on its relationship with disadvantage, while smoking during pregnancy accounted for most (but not all) of the relationship. Mother's race was not significantly associated with single or dual disorders. Low education attainment by participants was related to increasing socio-economic disadvantage; their adolescent drinking and behaviour problems were not (Supplementary Table 2b). Adolescent drinking, behaviour problems and low education each attenuated the magnitude of the early socioeconomic disadvantage/comorbidity relationship but both the relationship and the differentiation of comorbidity from single disorder types remained (Supplementary Table 4). Attrition analysis showed that individually, loss to follow up was associated with male gender, lower maternal age, maternal unemployment, and partner unemployment and low education. Maternal anxiety and depression during pregnancy also predicted attrition, as did increasing cumulative socio-economic disadvantage score (Supplementary Table 5). Multiple imputation analysis showed very similar results to those from complete case analysis (Supplementary Table 6); sensitivity analyses using 20 and 50 cycles of imputation did not materially change point estimates (results available on request).

4. DISCUSSION

Our study shows for the first time that increasing levels of cumulative prenatal socio-economic disadvantage predict comorbid alcohol and mental health disorders in young adults, with odds ratios three times those for single constituent disorder types. This is not merely reflective of greater disorder *complexity* in the comorbid group; comorbid and mental health only groups had similar proportions of multiple mental health diagnoses. The effect of this gradient is distinct from more proximal SES measures, and appears only partially mediated by factors such as smoking, drinking and/or maternal mental health status during pregnancy. The impact of these factors measured at other time points was not substantively different. Comparison of component dimensions showed that the strongest contributors to the gradient of disadvantage were more likely to be education-based, demonstrating the importance of considering a range of indicators of socio-economic status.

We used multiple measures to assess socio-economic disadvantage derived from family of origin in order to account for the different social processes reflected (Turrell et al., 2003). We explored low family income because it restricts access to material possessions and non-subsidised health services, reduces nutrition and residential stability and so creates stress (Skapinakis et al., 2006; Adler and Stewart, 2010). We also investigated parent employment which may limit availability of basic needs and residential security, but also impact on social participation (Ahnquist et al., 2012) and mental well-being not attained when income is derived from benefits (Turrell et al., 2003). Further, parental education may strongly influence health literacy and the potential ability to understand and respond to health challenges, but also impact on personal aspirations, employment opportunities and family income (Australian Institute of Health & Welfare, 2012). Although our study showed some correlation between these measures, each contributed individually to comorbid alcohol and mental health disorders as has been shown for other conditions (Turrell et al., 2003; Chartier et al., 2010; Kawachi et al., 2010).

In line with some cross-sectional studies (de Graaf et al., 2002; Araya et al., 2003), the strongest component of the relationship of SES with comorbidity appears in this study to be education. Other studies found that income was more strongly linked to these outcomes (Ross, 1995; Pulkki-Raback et al., 2012). This may depend on differing education gradients between countries where studies were conducted. Where high school completion rates were very high (70%, e.g. Finland (Pulkki-Raback et al., 2012) and Canada (Ross, 1995)), education played a smaller role than where a steeper gradient was present. In our study, only 30% of the parent sample had completed high school, similar to Dutch (de Graaf et al., 2002) and Chilean (Araya et al., 2003) studies, where strong associations were found between education and comorbidity. As expected, participants' own education reduced the strength of the association between early socio-economic disadvantage and comorbidity (see Supplementary Table 4). However the association remained with statistical evidence of a difference from single disorder types, demonstrating the unique role of early disadvantage in the development of comorbidity, as opposed to the development of single disorders. Future studies are needed to confirm the robustness of our findings.

The accumulation of prenatal disadvantages showed the strongest association in our study. Those with disadvantage in most areas were at greater risk of developing comorbid disorders, indicating that eliminating disadvantage in one sphere only would be insufficient. For example, in countries where access to health services is not greatly limited by income, this suggests that not only access to material advantages (Bauman et al., 2006) is important, but that factors associated with parental education may affect the family's ability to cope with complex disorders or access the available support or treatment services. This highlights the necessity of considering multiple indicators of disadvantage to allow for contextual differences.

This impact of disadvantage specifically on comorbid disorders is not wholly mediated by parental behaviours, as has been suggested; it appears to also work independently of several factors associated with SES. Maternal anxiety and depression through pregnancy, although regarded as stressors affecting foetal development and later depression and substance use (Merikangas et al., 1998b; Rao, 2010), did not appear to mediate the relationship between disadvantage and comorbidity. Similarly, although persons of higher disadvantage are more likely to be born of mothers who continue to smoke or drink during pregnancy (Guerri et al., 2009; Hannigan et al., 2010), our analyses suggest that these covariates did not wholly account for the relationship with comorbidity. The supplementary analysis of maternal smoking appears to indicate an impact during pregnancy which is distinct from that of smoking beforehand. As to the influence of participants' own drinking and behaviour problems in adolescence, a supplementary analysis showed no substantive differences with the results reported here (Supplementary Table 4).

Our findings have several implications. From an epidemiological perspective, they highlight the importance of evaluating the role of socio-economic factors as main effects in the development of substance and mental health disorders, not merely as confounders. The factor comparisons demonstrate the usefulness of multiple measures in the assessment of SES, to allow for variations in population context. The cumulative impact of multiple disadvantages suggests that addressing a single factor (Marmot, 2005; Bauman et al., 2006) will not reduce the likelihood of comorbid disorders in the population. In addition to equalising financial access to medical care (Adler and Stewart, 2010), it may be important to provide other supports to families in order to improve uptake of available interventions. There are also important

clinical implications. It will be important for treatment professionals to be aware that those presenting for co-occurring alcohol and mental health disorders are likely to have a history of multiple socio-economic disadvantages. In the context of complex treatment plans required for comorbidity (Tiet and Mausbach, 2007; Connolly et al., 2011), clinicians should consider that as well as having limited financial resources with which to attend services, clients may come from lower education backgrounds. As such they will need additional support to understand the disorders and to assist with treatment uptake, plan compliance and management of recurring symptoms.

This paper has significant strengths. It draws on a large and representative community sample, with gradients of income, education and employment allowing comparison of a number of prenatal socioeconomic factors, and is the first of which we are aware to assess the impact of accumulating disadvantage on comorbid alcohol and mental health disorders. The use of longitudinal data from participants and families of origin allows temporality of associations to be addressed in a meaningful way, and eliminates confounding by the impact of early mental health and alcohol disorders on participants' own education, employment and income (Kawachi et al., 2010; Lee et al., 2013). We have shown that although correlated with adult disadvantage, prenatal SES differentiated between single and dual disorders.

The results should be seen in the context of some limitations. Firstly, the largely Caucasian population did not allow racial background to be sufficiently addressed as a socio-economic factor. Antenatal socio-economic variables were self-reported; it is possible that parental education was more reliably recorded than income or employment, which may have resulted in weaker associations involving income. It is worth noting that attrition over 21 years has resulted in our final sample comprising approximately one third of the original cohort, which may have introduced bias into our results. If the socio-economic risk factors and comorbid outcomes described here were less prevalent in those missing, our models would over-estimate the association between pre-natal socio-economic disadvantage and comorbid alcohol/mental health disorders at age 21 (Najman et al., 2005). Our analyses showed that attrition was associated with greater socio-economic disadvantage, such that disadvantage is likely to have been under-represented in our final sample. It is thus likely that the associations here are a conservative estimate of the impact of

socio-economic disadvantage on the development of comorbid alcohol and mental health disorders. Our imputation analysis produced virtually the same results as the complete case analysis, suggesting confidence in the robustness of our findings.

In conclusion, we found that accumulated prenatal socio-economic disadvantage was strongly associated with the development of comorbid alcohol and mental health disorders in young adults, not wholly mediated by maternal health behaviours, and the impact was greater than for single disorders alone.

Table 1: Participant characteristics at 21 year follow up

Factor	Stage	Category	N (%)
Participants	21 years	Completed CIDI	2539
Gender	21 years	Female	1299 (51.2%)
Age	21 years	Mean ±SD	20.6 years ± 0.86
Comorbidity group	21 years	No disorder	1237 (48.7%)
		MHD	592 (23.3%)
		AUD	406 (16.0%)
		Comorbid	305 (12.0%)
Own education	21 years	< Year 12	514 (20.5%)
Drinking at 14	14 years	Yes	155 (6.4%)
YSR Total problems	14 years	Highest 10% score	172 (8.5%)
Family income	pregnancy	Low	720 (29.8%)
Low maternal education	pregnancy	< Year 12	1791 (71.0%)
Low partner education	pregnancy	< Year 12	1693 (66.7%)
Maternal unemployment	pregnancy	Disadvantaged	312 (12.4%)
Partner unemployment	pregnancy	Disadvantaged	266 (10.6%)
Marital status	pregnancy	Un-partnered	248 (9.8%)
Maternal age	pregnancy	Mean age ±SD	25.0 years ±5.1
Maternal drinking	pregnancy	Yes	128 (5.1%)
Maternal smoking	pregnancy	Yes	914 (36.3%)
Maternal depression	pregnancy	Yes	90 (3.4%)
Maternal anxiety	pregnancy	Yes	247 (10.4%)

Table 2: Univariate models of comorbidity class in young adults, predicted by indicators of pre-natal socio-economic disadvantage (SED)

Disadvantage Measure	Category	MH only OR (CI_{95})	AUD only OR (CI_{95})	Comorbid OR (CI_{95})
Low family income	Yes	1.22 (0.98, 1.52)	0.99 (0.76, 1.28)	**1.32** (1.01, 1.75)
Low maternal education	Yes	**1.31** (1.06, 1.63)	**1.39** (1.08, 1.80)	**1.66** (1.24, 2.23)
Low partner education	Yes	**1.42** (1.15, 1.75)	**1.27** (1.00, 1.61)	**1.64** (1.24, 2.17)
Maternal unemployment	Yes	1.31 (0.98, 1.76)	1.02 (0.71, 1.46)	**1.56** (1.09, 2.22)
Partner unemployment	Yes	0.94 (0.68, 1.31)	1.09 (0.76, 1.57)	1.25 (0.85, 1.84)
SED Factor 1 (disadvantage from parental income & employment)	continuous	1.07 (0.96, 1.20)	1.00 (0.87, 1.14)	**1.15** (1.00, 1.33)
	0	Reference		
	1	1.25 (0.99, 1.60)	0.96 (0.72, 1.28)	1.19 (0.87, 1.63)
	2	1.28 (0.90, 1.80)	1.11 (0.74, 1.66)	**1.58** (1.05, 2.39)
	3	1.26 (0.87, 1.82)	1.30 (0.87, 1.95)	1.51 (0.97, 2.35)
SED Factor 2 (disadvantage from parental education)	continuous	**1.19** (1.08, 1.31)	**1.16** (1.03, 1.30)	**1.33** (1.16, 1.52)
	0	Reference		
	1	1.07 (0.79, 1.47)	1.18 (0.82, 1.68)	**1.65** (1.05, 2.59)
	2	**1.52** (1.15, 2.02)	**1.51** (1.09, 2.10)	**2.34** (1.55, 3.54)
SED scale (5-variable composite score)	0=low	Reference		
	1	1.26 (0.88, 1.81)	1.26 (0.84, 1.90)	1.69 (0.99, 2.87)
	2	**1.46** (1.04, 2.05)	1.41 (0.96, 2.07)	**2.12** (1.29, 3.48)
	3	**1.89** (1.29, 2.77)	1.54 (0.99, 2.39)	**3.02** (1.79, 5.17)
	4	**1.92** (1.02, 3.07)	1.58 (0.91, 2.73)	**2.36** (1.22, 4.59)
	5=high	**1.15** (0.48, 2.73)	0.99 (0.35, 2.78)	**3.97#** (1.65, 9.55)

# denotes that $OR_{(comorbid)}$ is significantly greater (P <0.025) than either $OR_{(MH)}$ or $OR_{(AUD)}$

Figure 1: Association of increasing socio-economic disadvantage with comorbid alcohol and mental health disorders, adjusted for maternal age during pregnancy

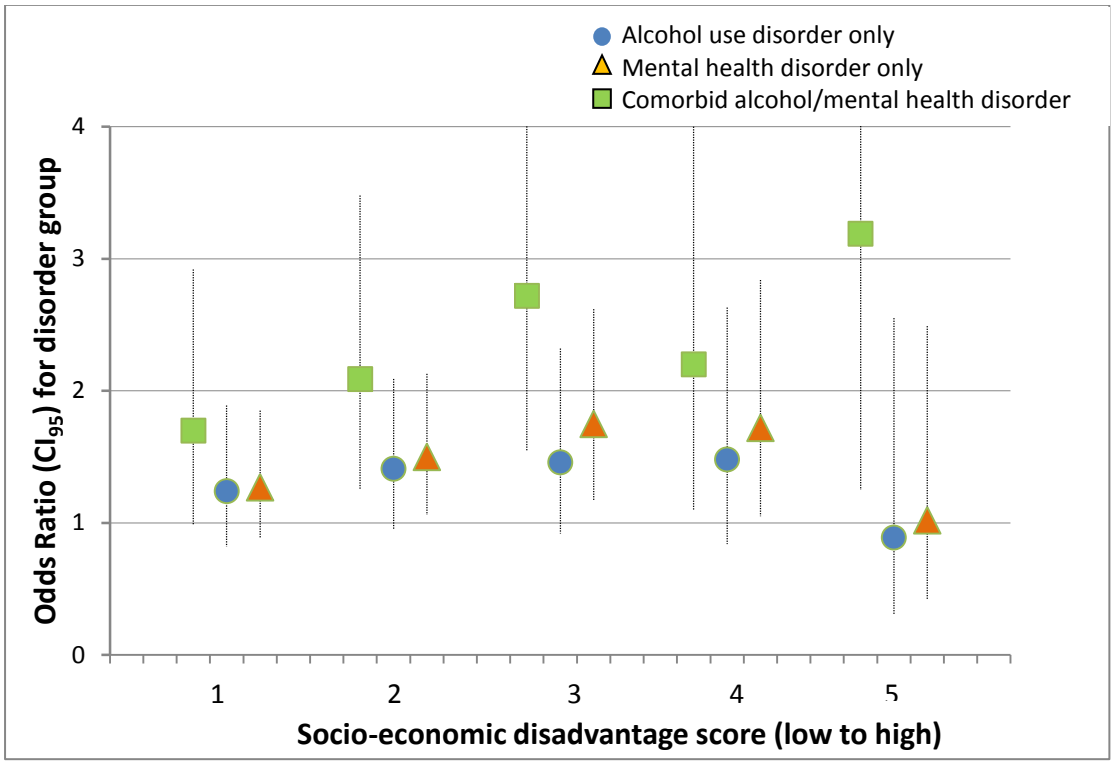

Table 3: Multinomial model of comorbidity group at age 21, with socio-economic disadvantage as predictor

Socio-economic disadvantage score	Comorbidity group	Unadjusted OR (CI_{95})	Model 1: Maternal age OR (CI_{95})	Model 2: Maternal age, marital status OR (CI_{95})
0		Reference		
1	MH only	1.26 (0.88, 1.81)	1.23 (0.86, 1.78)	1.23 (0.86, 1.78)
	AUD only	1.26 (0.84, 1.90)	1.22 (0.81, 1.84)	1.22 (0.81, 1.84)
	Comorbid	1.69 (0.99, 2.87)	1.64 (0.97, 2.79)	1.64 (0.97, 2.79)
2	MH only	**1.46** (1.04, 2.05)	**1.42** (1.01, 2.00)	**1.42** (1.01, 2.00)
	AUD only	1.41 (0.96, 2.07)	1.37 (0.93, 2.01)	1.37 (0.93, 2.01)
	Comorbid	**2.12** (1.29, 3.48)	**2.06** (1.25, 3.40)	**2.06** (1.25, 3.40)
3	MH only	**1.89** (1.29, 2.77)	**1.78** (1.21, 2.62)	**1.77** (1.20, 2.61)
	AUD only	1.54 (0.99, 2.39)	**1.42** (0.90, 2.22)	1.38 (0.88, 2.17)
	Comorbid	**3.02** (1.79, 5.17)	**2.82** (1.64, 4.86)	**2.76 (**1.60, 4.77)
4	MH only	**1.92** (1.02, 3.07)	**1.73** (1.07, 2.81)	**1.69** (1.02, 2.80)
	AUD only	1.58 (0.91, 2.73)	1.37 (0.78, 2.41)	1.25 (0.69, 2.23)
	Comorbid	**2.36** (1.22, 4.59)	**2.10** (1.07, 4.13)	1.94 (0.96, 3.92)
5	MH only	1.15 (0.48, 2.73)	1.00 (0.41, 2.40)	0.96 (0.39, 2.37)
	AUD only	0.99 (0.35, 2.78)	0.82 (0.29, 2.32)	0.71 (0.24, 2.10)
	Comorbid	**3.97#** (1.65, 9.55)	**3.36#** (1.37, 8.24)	**2.98#** (1.17, 7.63)

# indicates that $OR_{(comorbid)}$ is significantly higher than either $OR_{(MH)}$ or $OR_{(AUD)}$ (P <0.05)
Model 1: adjusted for mother's age at baseline
Model 2: adjusted for mother's age, marital status at baseline (reference is 'partnered')

Table 4: Examining maternal factors as potential mediators: Multinomial models of comorbidity group at age 21, with socio-economic disadvantage as predictor

Socio-economic disadvantage (score)	**Co-morbidity group**	**Model 2: Maternal age/MH** OR (CI_{95})	**Model 3: Maternal age/drinking** OR (CI_{95})	**Model 4: Maternal age/smoking** OR (CI_{95})	**Model 5: Maternal age/ MH/smoke/drink** OR (CI65)
0		Reference			
1	MH only	1.27 (0.88, 1.85)	1.24 (0.86, 1.79)	1.21 (0.84, 1.75)	1.24 (0.86, 1.81)
	AUD only	1.24 (0.82, 1.89)	1.25 (0.82, 1.89)	1.21 (0.80, 1.82)	1.26 (0.82, 1.92)
	Comorbid	1.70 (0.99, 2.92)	1.61 (0.94, 2.74)	1.58 (0.93, 2.70)	1.59 (0.92, 2.75)
2	MH only	**1.50** (1.06, 2.13)	**1.44** (1.02, 2.03)	1.33 (0.94, 1.87)	1.41 (0.99, 2.01)
	AUD only	1.41 (0.95, 2.09)	1.38 (0.94, 2.04)	1.31 (0.89, 1.93)	1.38 (0.92, 2.06)
	Comorbid	**2.09** (1.25, 3.48)	**1.97** (1.20, 3.26)	**1.78** (1.08, 2.96)	**1.77** (1.05, 2.97)
3	MH only	**1.75** (1.17, 2.62)	**1.80** (1.22, 2.65)	**1.62** (1.10, 2.40)	**1.61** (1.07, 2.41)
	AUD only	1.46 (0.92, 2.32)	1.43 (0.91, 2.25)	1.33 (0.85, 2.09)	1.42 (0.89, 2.26)
	Comorbid	**2.72** (1.55, 4.76)	**2.71** (1.57, 4.67)	**2.36** (1.36, 4.09)	**2.23** (1.26, 3.94)
4	MH only	**1.72** (1.05, 2.84)	**1.75** (1.08, 2.84)	1.48 (0.91, 2.42)	1.52 (0.92, 2.53)
	AUD only	1.48 (0.84, 2.63)	1.39 (0.79, 2.45)	1.24 (0.70, 2.19)	1.41 (0.79, 2.53)
	Comorbid	**2.20** (1.10, 4.37)	1.94 (0.98, 3.84)	1.50 (0.75, 3.00)	1.60 (0.79, 3.24)
5	MH only	1.02 (0.42, 2.49)	0.86 (0.34, 2.15)	0.71 (0.28, 1.79)	0.75 (0.29, 1.90)
	AUD only	0.89 (0.31, 2.55)	0.80 (0.28, 2.28)	0.71 (0.25, 2.03)	0.80 (0.28, 2.32)
	Comorbid	**3.19#** (1.25, 8.12)	**3.10#** (1.26, 7.63)	2.34**¥** (0.94, 5.81)	2.22 (0.86, 5.75)

Model 2: mother's age plus mother's anxiety & depression during pregnancy
Model 3: mother's age plus maternal binge drinking (>5 drinks/session) during pregnancy
Model 4: maternal age plus smoking during pregnancy
Model 5: maternal age, depression, anxiety, smoking and drinking in pregnancy

# indicates that $OR_{(comorbid)}$ is significantly higher than either $OR_{(MH)}$ or $OR_{(AUD)}$ (P <0.05)
¥ indicates that $OR_{(comorbid)}$ is significantly higher than either $OR_{(MH)}$ or $OR_{(AUD)}$ (P <0.08)

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Childhood

Early childhood indictors of comorbidity

Although some prenatal factors appeared to be strongly associated with comorbidity at young adulthood, and previous studies have suggested that gestational disturbance may manifest as low birth weight or restricted IQ, Table 14 below shows that those childhood measures do not appear to be related to comorbidity at young adulthood in this study. As a result, this avenue was not further pursued.

Table 14: Bivariate associations between early childhood indicators and comorbidity at 21 years

Factor	Category	MHD only		AUD only		Comorbid	
		OR	**CI_{95}**	**OR**	**CI_{95}**	**OR**	**CI_{95}**
Birth weight [a]	1 (lowest)	1.32	(0.96, 1.82)	1.24	(0.86, 1.77)	1.21	(0.80, 1.83)
	2	**1.44**	(1.05, 1.98)	1.24	(0.87, 1.79)	**1.56**	(1.05, 2.33)
	3	**1.50**	(1.10, 2.04)	1.35	(0.95, 1.91)	1.39	(0.93, 2.07)
	4	1.24	(0.91, 1.70)	1.16	(0.82, 1.65)	1.30	(0.87, 1.93)
	5 (highest)	Reference					
IQ [b]	Below	0.79	(0.54, 1.16)	0.70	(0.44, 1.09)	0.86	(0.54, 1.37)
	Normal	Reference					
	Above	1.10	(0.79, 1.53)	0.95	(0.65, 1.40)	0.61	(0.37, 1.01)
	Per unit	1.00	(0.99, 1.01)	1.00	(0.99, 1.01)	0.99	(0.98,1.00)
	Mean score	100.9	(99.7, 102.2)	101.4	(100.0, 102.8)	99.8	(98.2, 101.5)

[a] Birth weight was adjusted for gestational age and gender to yield a z-score. This was then categorised into quintiles.
[b] IQ was measured at 5 year using the Peabody test

The literature suggests that maternal mental health, smoking drinking and stress during childhood may influence the development of mental health disorders in their children, and that parenting practices may impact this development. However, findings in this cohort suggested that only maternal anxiety in early childhood was influential.

Table 15 below shows that maternal anxiety at five years appeared to predict comorbidity, but not alcohol or mental health disorders at 21 years. This relationship remained significantly different (OR 1.76, CI_{95} 1.24, 2.49; $P<0.05$ for difference) after adjustment for gender, socio-economic disadvantage and maternal smoking in pregnancy. No other maternal factors differentiated comorbidity from single disorders. In contrast, parenting behaviours did not appear to be related to comorbidity group at young adulthood (Table 16).

Table 15: Bivariate associations of maternal factors in early childhood with comorbidity at 21 years

Maternal variable	category	MHD only	AUD only	Comorbid
		OR (CI$_{95}$)	**OR (CI$_{95}$)**	**OR (CI$_{95}$)**
Depression	Yes	0.91 (0.56, 1.48)	0.42 (0.20, 0.88)	1.38 (0.81, 2.35)
Anxiety	Yes	1.18 (0.88, 1.58)	1.10 (0.78, 1.55)	**1.83*** (1.31, 2.56)
Stress level	High	1.06 (0.76, 1.47)	0.75 (0.50, 1.14)	1.14 (0.76, 1.71)
Stressful life events	High	**1.38** (1.10, 1.72)	1.01 (0.77, 1.33)	**1.46** (1.10, 1.93)
Smoking	Any	**1.5**8 (1.27, 1.96)	**1.48** (1.15, 1.90)	**1.92** (1.46, 2.52)
Drinking	Any	0.83 (0.64, 1.07)	1.16 (0.85, 1.60)	1.40 (0.96, 2.04)
	Binge	1.10 (0.70, 1.72	**2.39** (1.49, 3.84)	**2.28** (1.30, 3.99)

Maternal variables were self-reported at 5 years
* $OR_{comorbid} > OR_{AUD}$ and OR_{MHD} ($P<0.05$)

Table 16: Bivariate associations of parenting in early childhood with comorbidity at 21 years

Parenting behaviour	Use	MHD only	AUD only	Comorbid
		OR (CI$_{95}$)	**OR (CI$_{95}$)**	**OR (CI$_{95}$)**
Control	High	1.10 (0.79, 1.54)	0.83 (0.55, 1.26)	0.64 (0.38, 1.06)
Child autonomy	High	0.84 (0.62, 1.13)	**0.65** (0.45, 0.95)	1.19 (0.84, 1.70)
Physical punishment	High	1.24 (0.84, 1.83)	0.99 (0.62, 1.58)	1.04 (0.61, 1.78)
Reasoning	High	1.16 (0.73, 1.85)	0.79 (0.43, 1.44)	1.20 (0.66, 2.18)
Consequences	High	1.14 (0.74, 1.75)	1.41 (0.90, 2.21)	0.80 (0.43, 1.47)

Parenting behaviours were self-reported by the mother at 5 years

Adolescence

The literature on single disorders suggests that familial aggregation of disorders is common. Both heritability of substance and mental health disorders and behavioural modelling or social learning have been proposed. Intellectual ability to cope with adversity has also been proposed as important in the development of disorders.

In analyses following on from those at 5 years, IQ scores at 14 years measured with the Raven matrices were linked to comorbidity, such that each point higher on the Raven score was associated with a 2% reduction in the odds of comorbidity. However no such associations were found when using the Wide Ranging Achievement Test (WRAT) to measure IQ (Table 17).

Table 17: Associations between IQ measures at 14 years and comorbidity at 21 years

IQ measure		MHD only	AUD only	Comorbid
		OR (CI$_{95}$)	**OR (CI$_{95}$)**	**OR (CI$_{95}$)**
Raven	Mean Score	0.98 (0.97, 1.00)	0.98 (0.96, 1.01)	**0.98** (0.96, 0.99)
	Low	1.53 (0.98, 2.39)	0.78 (0.46, 1.34)	1.39 (0.82, 2.35)
	High	0.84 (0.61, 1.16)	**0.61** (0.41, 0.90)	0.76 (0.50, 1.17)
WRAT	Mean Score	1.00 (0.97, 1.02)	0.99 (0.96, 1.01)	0.99 (0.96, 1.01)
	Low	**1.69** (1.11, 2.58)	1.18 (0.73, 1.89)	0.98 (0.56, 1.72)
	High	1.13 (0.79, 1.61)	0.81 (0.52, 1.27)	0.61 (0.35, 1.06)

Models adjusted for gender and socio-economic disadvantage

In the following study, the family environment during adolescence was considered as this is widely held to be a period of heightened developmental sensitivity. We were able to examine contributions to comorbidity from domains found to be influential in other studies. This work is described in paper 6.2.

6.2 Family factors and comorbidity

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Supplementary materials published online in support of this paper appear in Appendix 6 of this thesis.

Title

Familial factors associated with development of alcohol and mental health comorbidity

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Abstract

Background and aim: Co-occurring mental health and alcohol problems appear to be associated with greater health burdens than either single disorder. This study compares familial and individual contributions to development of comorbid alcohol/mental problems and tests whether these differ from single disorders.

Design: Women (n=6703) were recruited during pregnancy to the longitudinal Mater-University of Queensland Study of Pregnancy (MUSP). Mother/offspring dyads were followed over 21 years.

Setting: Mater-Misericordiae Public Hospital, Brisbane, Australia.

Participants: Primary offspring from the MUSP with full psychiatric information at 21 years and maternal information at 14 (n=1755).

Measurements: Structured interviews at 21 yielded a four-category outcome using mental health and alcohol modules of the Composite International Diagnostic Interview [no disorder, alcohol only, mental health only, and comorbid alcohol/mental health]. Multinomial logistic regression models were adjusted for gender, maternal mental health and substance use, family environment and adolescent behaviour.

Findings: Maternal smoking (OR=1.56; CI_{95}=1.09-2.22 vs no-disorder) and low mother-offspring warmth (OR=3.19; CI_{95}=1.99-5.13) were associated with mental health/alcohol comorbidity in young adults, as were adolescent drinking (OR=2.22; CI_{95}=1.25-3.96), smoking (OR=2.24; CI_{95}=1.33-3.77) and attention/thought problems (OR=2.04; CI_{95}=1.18-3.52). Some differences were seen from single disorders. In a sub-sample with paternal data, fathers' drinking problems (OR=2.41; CI_{95}=1.10-5.29) were more strongly associated with offspring mental health/alcohol comorbidity than both single disorders ($p<0.05$).

Conclusions: Maternal smoking and low mother-child warmth appear to be related to alcohol, mental health and comorbid disorders at age 21, possibly via constituent alcohol and mental health disorders. Adolescent drinking and attention/thought problems appear to be associated with comorbid disorders but not with individual alcohol and mental health disorders.

Keywords:

Comorbid; family factors; mental health problems; longitudinal; alcohol problems

Introduction

Disorders of alcohol and mental health contribute to 183.9 million Disability Adjusted Life Years annually (1). Health and economic burdens associated with co-occurrence of these conditions are very high (1-4), involving complex and costly treatment (2, 5, 6), and poor projected outcomes (7). Understanding how these joint conditions emerge is therefore of great interest to researchers, health practitioners and policy makers involved in ameliorating the development of comorbid disorders in the population (8-10).

Parental history of anxiety, depression and alcohol disorders is typically associated with mental health or alcohol disorders in offspring (11-15). However the extent to which parental mental health problems predict co-occurrence is unclear. Family histories of mental health or alcohol problems were linked to dual substance use/mental health diagnoses in a clinical sample (16). In a community sample (10), those associations appeared specific to comorbidity with alcohol (10). Other studies (13, 17, 18) have suggested that familial transmission of comorbidity may depend on disorder subtypes, but not all reports agree this familial transmission is specific to in the development of comorbidity with alcohol disorders. Findings from the Netherlands Study of Depression and Anxiety (19) suggest that alcohol dependence comorbid with anxiety or depression was more likely in adults with a family history of these disorders. Nurnberger's review of family studies (20) and Nolen-Hoeksema's study of women (21) suggest maternal alcohol problems and depression as important risk factors, but a study of the offspring of twin fathers found (18) that only maternal depression, not her alcohol use, was associated with offspring comorbidity. There are also non-findings where no associations with parental mental health were detected (22, 23).

These inconclusive findings may be in part due to study features such as cross sectional design (19, 21, 24), different measures evaluating parental disorders (10, 21), retrospective offspring report of parent disorders (16, 19, 22), or findings from specialised cohorts (10, 11, 16, 18, 24-26). There are also additional limitations and methodological problems specific to this topic. Firstly, not all of the above studies were able to account for factors such as family structure, child behaviour and parent-child closeness. These have been shown to be important. Findings on the aetiology

of single disorders suggest associations of adolescent behaviours with either disorder (27, 28) as well as early onset of licit substance (tobacco and/or alcohol) use, particularly alcohol disorders (29). A study of the Seattle Social Development Project found family conflict during adolescence preceded comorbid mental health and licit substance use at young adulthood (30). None of these studies have investigated behaviours as precursors to comorbid conditions. There is also no evidence of associations with other family environment factors such as parental communication, mother-offspring warmth and family conflict, which have been found to be important for the development of single disorders (31-33), although potentially gender-related (32, 34).

Another main limitation of existing studies is the use of lifetime diagnoses to define comorbidity. Using this method, some participants classified as comorbid may have no temporal overlap between the alcohol and mental health disorders comprising their comorbid status (10, 17-19, 22, 24, 35). This may make it difficult to identify factors specific to development of comorbidity, as opposed to individual disorders which may be episodic and not co-occur over a lifetime.

In this paper, we used a large population based cohort study to assess the contributions of maternal and paternal substance use and mental health problems to young adults' comorbid alcohol/mental health disorders. We hypothesized that factors influencing comorbidity would be different to those for single disorder types. Importantly, we addressed existing limitations by confirming co-occurrence of alcohol and mental health disorders reported by our participants. Additionally, in accounting for family environment and child behaviour factors through prospective measures, we provided a more detailed understanding of the impact of parents on the development of comorbid alcohol and mental health disorders in young adults.

Methods

Sample

The Mater-University of Queensland Study of Pregnancy (MUSP) is a linked birth cohort study of mothers and children. Mothers (n=6703) were enrolled at their first clinic visit during pregnancy to the Mater Misericordiae Public Hospital in Brisbane between 1981 and 1983. The MUSP was approved by the Behavioural and Social

Sciences Ethics Review Committee at the University of Queensland and has been extensively described elsewhere (36). Dyads were followed up at birth, 5 days and 6 months, then 5, 14 and 21 years. At follow ups, participants gave written, informed consent. Only primary offspring for whom complete data on mental health and alcohol use at age 21 are available, and whose mothers provided information at age 14, were included in the main analyses (n=1755). Subsequent children born to these mothers during recruitment (n=520) were excluded from this analysis to obviate confounding by sibling effects.

Measures:

Outcome: Comorbid mental health and alcohol disorders

At 21 years, 2342 eligible offspring were administered the mental health and substance use modules of the Composite International Diagnostic Interview (CIDI (37)). Responses were coded to yield lifetime DSM-IV diagnoses. The 'any alcohol use disorder' diagnosis included alcohol abuse and dependence, whereas 'any mental health disorder' included all participants reporting an anxiety, affective, eating or psychotic disorder. Within each of these groups, the presence of multiple disorders was possible. In supplementary analyses, we excluded those with other substance disorders (n=336) as previous work suggests that precursors of alcohol/mental health comorbidity are distinct from those for illicit substance/mental health comorbidity (18).

A four-category variable "Comorbidity Group" was created: No (DSM-IV) disorder; mental health disorder but no alcohol disorder (MHD); alcohol use disorder but no mental health disorder (AUD) or Comorbid ('any alcohol use disorder' plus 'any mental health disorder'). Comorbid participants were also required to have episodes of alcohol disorder and mental health disorder within a 12-month period, to indicate temporal overlap. This was confirmed for each individual by testing whether onset of the most recent episodes of alcohol and mental health disorders fell within 12 months of each other. This allowed us to include co-occurring episodes prior to the last-12-month diagnoses used by other studies which sought to confirm co-occurrence (38).

Potential predictors:

Maternal mental health and substance use

Maternal mental health and substance use were assessed at 14 years. Depression and anxiety were assessed using the Delusions-Symptoms-States Inventory (DSSI (39)), which contains anxiety and depression subscales. The depression subscale has been found to correlate strongly with other depression scales, including Beck's Depression Inventory (40) (depression α=0.88; anxiety α=0.84). Anxiety and depression are typically recorded as cases where at least four of seven symptoms from that subscale are endorsed (39). A combined DSSI score summing all symptoms endorsed has been used to indicate mental distress (41). We dichotomised this score as positive for the highest 10% of scores (α=0.90).

Mothers reported how often they drank alcohol and how many drinks they consumed per occasion. These were combined to generate three categories: non-drinkers, regular drinkers (more than a few times/month) who did not binge (never >5 drinks/session) and drinkers who did binge (>5 drinks/session). Any self-reported maternal daily smoking was coded as positive.

Family environment during adolescence

The Parker Bonding instrument was used at 21 years to record offspring perception of maternal warmth and involvement during childhood ((42); α=0.88). As parental warmth is a defining component of authoritative parenting, protective of substance use (33), we used that subscale in our analyses; the lowest 10% of scores were coded as low warmth (42). Open family communication was reported by mothers at 14 years using Barnes and Olson's Open Family Communication scale ((43); α=0.853). This is a 10-item composite with higher scores indicating worse communication. The highest 10% were coded as poor communication as described (43). In single items, mothers reported on cohabitation with the child's father at 14 years and any experience of violence within their relationship during the past seven years; both were dichotomised (yes/no).

Maternal education status

Maternal education level was self-reported at baseline and coded as low if less than Year 12 (high school).

Adolescent behaviour

Adolescent behaviour was assessed at 14 years using Achenbach's Youth Self Report (44, 45). We used internalising and externalising behaviour scales and a combined attention and/or thought subscale. For each, the highest 10% were coded as having behaviour problems, consistent with Achenbach's definition of 'caseness' (46). At 14, participants reported how often they consumed alcohol, and how many drinks per occasion. Youth drinking was dichotomised (positive if drinking at least "a few times a year" and more than "1 or 2 glasses per occasion"). Any adolescent smoking in the previous week was self-reported at 14 and dichotomised as (no smoking/smoking).

Maternal reports of fathers' mental health and substance use

At 14 years, mothers reported on smoking by the child's natural father (smoker/non-smoker). In a subsample of participants, mothers were asked "Has [he] ever had an alcohol problem?" 'Paternal alcohol problems' was coded positive if this item was endorsed. She also reported whether he had ever had severe depression, difficulties concentrating when a child, overactivity when a child, a schizophrenic episode or panic attacks. 'Any paternal mental health problems' was coded positive if any item was endorsed.

Statistical Analysis

We determined the distribution of comorbidity groups at child age 21 across each factor and examined univariable relationships using multinomial logistic regressions, initially using No Disorder as reference. Multivariable regression models were constructed, comprising maternal education, mental health, alcohol and tobacco use, family environment, participant gender and adolescent behaviour. We tested for gender interactions with each measure. Additionally, using a restricted cohort (n=787), we assessed the impact of fathers' mental health and substance use. As many parents were separated at 14 years, we stratified this analysis to see if paternal influences were different when living with the child.

To compare the comorbid group with single disorder groups, we repeated these analyses, using each group in turn as reference. Lastly, in order to assess

confounding by non-alcohol substance disorders, we repeated the main analyses, excluding participants with other substance disorders.

Finally, we assessed how attrition may have affected our results, using a multivariable regression model of attrition with baseline predictors (maternal age, marital status, anxiety, depression, drinking and smoking and participant gender). Starting from a Missing at Random assumption (47), we used the STATA procedure to multiply impute our missing data. Imputation models used baseline factors above, in addition to variables used in regression models. We imputed missing data from both predictors and outcomes; this has been suggested as appropriate if a stable imputation model can be achieved which is not determined solely by analytical factors (48). We used 20 cycles of imputation and repeated our final analysis using imputed datasets. Sensitivity analysis used 50 cycles, with and without imputation of the outcome variable. As the paternal-information subsample was not randomly selected, we used inverse probability weightings to account for the reduced cohort and compared weighted results to the complete case analyses. All analyses were undertaken using STATA 12.1 (StataCorp, USA).

Results:

Twelve percent of the cohort (n=279) was assessed as having lifetime comorbid alcohol and mental health disorders (AUD+MHD) at age 21, with temporal overlap confirmed in a 12-month period. Mental health disorders only (MHD) were found in 23% (n=548), and alcohol disorders only (AUD) in 16% (n=381); 48% (n=1134) had none of these DSM-IV disorders (Supplementary Table 1). Those with AUD only were more likely to be male; MHD-only participants were more likely to be female, but comorbidity did not vary with gender.

Compared to No-Disorder, maternal smoking appeared associated with all three disorder groups (Table 1), maternal mental distress was related to comorbidity and MHD, and maternal binge drinking was associated with comorbidity and AUD. Paternal smoking was only linked to comorbidity, and paternal drinking to comorbidity and MHD; paternal mental problems were not associated with any group.

In the fully-adjusted model, maternal mental distress, poor communication, relationship violence, and adolescent externalising were no longer associated with any disorder group, compared to no-disorder, and maternal drinking was only associated with AUD (Supplementary Table 2). Direct comparisons between disorder groups (Table 2) showed that maternal smoking predicted comorbidity, but not more so than AUD or MHD alone. Low maternal warmth was more strongly related to comorbidity than to AUD, but not more than MHD. Adolescent smoking and attention and/or thought behaviour problems were strong predictors of comorbidity, but did not differentiate it from either single disorder. Adolescent drinking was also strongly linked to comorbidity, more so than to MHD, but not differently to AUD. Males were more likely to develop AUD and females, MHD, but gender did not predict comorbidity and all gender interactions were non-significant. Exclusion of participants with non-alcohol substance disorders produced no substantive change in these relationships (data on request).

Analysis of the restricted sample with paternal information (Table 3) showed that only paternal alcohol problems were associated with comorbidity (not single disorders); this was more pronounced when fathers lived with children.

Attrition was significant. Those lost by age 21 were more likely to be male, with younger mothers who were un-partnered at pregnancy and reported anxiety, depression and smoking at baseline (Supplementary Table 3). Although missing data reduced the complete case analysis for our mother-environment-child model to 1755 of the 2342 who were administered the CIDI at age 21, from the baseline cohort of 6703, multiple imputation produced results not materially different to those from the final model (Supplementary Table 4). Sensitivity analyses using data from 50 cycles of imputation produced very similar results as did imputation of predictors but not outcome (data on request). Similarly, inverse probability weighting of the paternal model gave results congruent with the complete case analysis (data on request)

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Discussion

This is the first study to examine development of alcohol and mental health comorbidity in a non-selected population of young adults, considering a range of familial and individual domains, using robust diagnostic measures and confirming disorder co-occurrence. In this community sample a sizeable proportion of young adults (12%) reported co-occurring alcohol and mental health disorders consistent with DSM-IV clinical diagnoses (37). This is consistent with reports of AUD in 31% of US young adults (49) and 26-37% of those with AUD also reporting MHD (50).

This study extends findings from three other important studies on the development of comorbidity (18, 21, 51). The Nolen-Hoeksema study of women (21) investigated maternal and paternal influences, however this was a cross-sectional design in a gender-specific cohort with less rigorous measures of disorder in parents and offspring, and no information on family environment or child behaviour. The Seattle Social Development Project (30) looked at detailed family factors, but did not examine parent issues or child thought/attention disorders. The study of offspring of twin fathers (18) also failed to examine offspring licit substance use or behavioural problems, or confirm co-occurrence of offspring disorders. Ours is the first study which uses a longitudinal design, confirms co-occurrence, and assesses parental influences, family environment, and adolescent behaviour, early alcohol and tobacco use on comorbidity.

In our final model, neither maternal drinking nor mental health problems predicted comorbidity. These findings support evidence from some studies (10, 18), but not others where parental alcohol use was found to be associated with comorbid alcohol and depression problems (19, 21, 22). This discrepancy may reflect different study designs (19, 21), or reduced capacity to account for family environment or offspring behavioural problems (21, 22). Others have suggested that parental history is non-specific in its association with offspring psychopathology (52), or is associated with disorder *severity* in offspring (53). In this study, maternal drinking was specific, but linked only to offspring drinking disorders, not comorbidity. If the association was with disorder severity, we would have expected this association to have been stronger for the comorbid group, which was not the case in our study.

Of family environment factors, only low mother-child warmth strongly predicted comorbidity, although not more than mental health disorders. In contrast, items suggesting family conflict (parent separation, poor communication and relationship violence) were not associated with comorbidity. This is consistent with Raudino's work showing closeness with parents was inversely related to later depression (54), but contrary to work done by Herrenkohl (30), where family conflict during adolescence predicted comorbid mental health and licit substance use at young adulthood. It is possible that our measures did not adequately capture family conflict, but our study is the first to account for mother-offspring warmth, which may have influenced results. Similarly, we report the contributions of adolescent behaviour, alcohol and tobacco use, which are not presented in the Herrenkohl study. Our study found that thought and/or attention problems in adolescence were strongly predictive of young adult comorbidity. While these behaviour symptoms have been linked with later heavy drinking (27, 55), this is the first study to associate them with the development of comorbid alcohol/mental health problems. The non-distinction between comorbid and single disorder types is consistent with arguments that the thought problems scale describes odd ideas or behaviours or a lack of reality grounding which may indicate later mental health issues (27). Similarly, it has been suggested that adolescent attention problems may transition into an 'irresponsible' syndrome in young adulthood (56), which may be consistent with alcohol abuse (57), but would include comorbidity. More work is however needed to better understand the link we found with comorbid problems and possible mechanisms behind the association.

Consistent with existing work on the aetiology of alcohol disorders, associations with externalising behaviours were not seen after adjustment for other important individual factors (27). In contrast, early tobacco and alcohol use remained linked with comorbidity. These factors may be markers, rather than predictors, of comorbidity as suggested in the evidence reporting early transition to alcohol disorders (29). Exclusion of non-alcohol substance disorders from the sample confirms these relate specifically to alcohol/mental health comorbidity. Further research should investigate the roles of early licit drug use and adolescent behaviour, including links with maternal warmth, as these relationships maybe bi-directional (58, 59).

Unlike maternal drinking, in the sub-sample with paternal data, fathers' alcohol problems were strongly predictive of comorbidity. This effect was not seen where parents were separated, and may suggest paternal modelling of drinking behaviour rather than heritability. Although these associations are limited by being drawn from a restricted sub-sample of our cohort, our study adds to the existing evidence by reporting separately on each parental influence, rather than looking selectively at one parent or non-specifically at 'any family history' of drinking or mental health problems (10, 16, 19). Consensus is lacking between the two studies which accounted for maternal and paternal contributions. In one, fathers' alcohol problems were not associated with comorbidity (18); whereas in the other, fathers' drinking was linked to comorbidity, though less strongly than mothers'. Both these studies had limitations as the first used a selective high-risk sample and the second did not adjust for parental mental health or family environment (21). Because of the reduced sample in our analyses, our findings of a strong influence of paternal drinking problems on development of comorbidity should be seen as preliminary. Future studies with the capacity to explore both parental influences should replicate our preliminary findings and ascertain whether they are robust or due to chance.

Strengths and limitations

A major strength of this study is its use of a large, population based cohort. We used validated measures of maternal mental health, relationship bonding and adolescent behaviour to examine associations with DSM-IV criteria for mental health and alcohol disorders in young adults. The associations reported are robust and account for a range of family environment and behavioural factors, and we compare the relative contributions of paternal and maternal alcohol disorders, mental distress and smoking. Additionally, most factors considered were directly assessed at 14 years, providing longitudinal information not biased through indirect report or recall. We acknowledge however that maternal warmth was assessed at age 21 by retrospective young-adult report and so may have been subject to recall bias. Similarly, maternal report of fathers' factors may have introduced some bias.

Our study has some limitations. Although we assessed parental contributions to offspring comorbidity in light of numerous family environment and behavioural factors, we were not able to account for peer and sibling influences or genetic contribution (60). Additionally, over the 21-year course of the study, we have

experienced considerable attrition, which may have introduced bias into our results. However, analysis of the multiply-imputed dataset to adjust for attrition gave results not substantially different from the complete case analysis. This gives us some confidence that our findings may not be biased. Lastly, our information on the fathers' mental health and substance problems is for a restricted sub-sample only, although an inverse probability analysis conducted for this sub-sample was congruent with the complete case analysis.

Despite these limitations, we have confidence in reporting that in a population based cohort, maternal smoking and low mother-child warmth appear involved with the development of comorbidity in young adults, possibly via the constituent alcohol and mental health disorders. Adolescent behaviour and drinking appear to be early markers of this comorbidity. Future research should confirm these findings as the cohort ages and comorbidity develops further.

Table 1: Univariate relationships between hypothesised correlates at child age 14 and young adult comorbidity class

Predictors	category	AUD+MHD	AUD only	MHD only
Maternal factors [a]		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Mental distress	Yes	**1.81** (1.25, 2.63)	1.24 (0.86, 1.80)	**1.42** (1.04, 1.96)
Drinking	Any	1.06 (0.74, 1.52)	**1.48** (1.05, 2.09)	0.86 (0.66, 1.12)
	Binge	**2.34** (1.44, 3.81)	**1.98** (1.21, 3.25)	1.14 (0.75, 1.72)
Smoking	Any	**2.19** (1.67, 2.87)*	**1.46** (1.13, 1.88)	**1.51** (1.21, 1.89)
Family environment [b]				
Maternal warmth	Low	**2.68** (1.84, 3.92)	1.07 (0.69, 1.67)	**2.15** (1.56, 2.97)
Communication	Poor	**2.01** (1.29, 3.12)	**1.71** (1.12, 2.60)	**1.53** (1.04, 2.24)
Parents separated	Yes	**1.77** (1.34, 2.32)	**1.35** (1.05, 1.74)	**1.55** (1.24, 1.93)
Relationship violence	Any	**1.60** (1.10, 2.32)	1.15 (0.80, 1.67)	**1.43** (1.06, 1.95)
Adolescent behaviour [c]				
Internalising	Yes	**2.26** (1.55, 3.28)	1.04 (0.68, 1.59)	**2.80** (2.08, 3.77)
Externalising	Yes	**3.59** (2.32, 5.56)*	**2.51** (1.62, 3.87)	**2.29** (1.53, 3.42)
Attention/Thought	Yes	**3.05** (2.10, 4.43)	**1.67** (1.13, 2.47)	**2.58** (1.88, 3.55)
Drinking	≥3/occasion	**3.67** (2.37, 5.68)*	**2.22** (1.41, 3.49)	1.34 (0.85, 2.12)
Smoking	Any	**4.37** (2.98, 6.40)*	**2.79** (1.90, 4.09)	**2.35** (1.65, 3.36)
Demographic factors [d]				
Gender	Female	0.98 (0.76, 1.25)*	**0.24** (0.18, 0.31)	**2.95** (2.37, 3.66)
Maternal education	Low	**1.66** (1.24, 2.23)	**1.39** (1.08, 1.80)	**1.31** (1.06, 1.63)
Paternal factors [e]				
MH problems	Ever	1.07 (0.46, 2.49)	1.11 (0.55, 2.23)	0.85 (0.44, 1.64)
Alcohol problems	Ever	**2.58** (1.74, 2.83)*	0.97 (0.63, 1.50)	**1.50** (1.06, 2.10)
Smoking	Any	**2.08** (1.57, 2.75)*	1.13 (0.87, 1.47)	1.18 (0.93, 1.48)

Models are unadjusted, using the No Disorder group used as reference

**OR (comorbid) is significantly different to MHD only or AUD only (p<0.05)*

[a] *Maternal factors were self-reported at 14 year follow-up*

[b] *Family environment factors were assessed via maternal report at 14 years, except for Maternal warmth, assessed by offspring report at 21 years*

[c] *Adolescent behaviour factors were self-reported at 14 years*

[d] *Maternal education was recorded at baseline*

[e] *Paternal factors were reported by mother at 14 years*

Table 2: Multinomial logistic regression model of young adult comorbidity class, by maternal factors, family environment and adolescent behaviour

		AUD+MHD *vs* **no disorder**	**AUD+MHD** *vs* **AUD only**	**AUD+MHD** *vs* **MHD only**
Maternal factors [a]		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Mental distress	Yes	1.08 (0.66, 1.79)	1.22 (0.66, 2.26)	1.21 (0.70, 2.09)
Drinking	Drink	1.19 (0.75, 1.90)	0.65 (0.36, 1.16)	1.52 (0.92, 2.50)
	Binge	1.36 (0.70, 2.63)	0.56 (0.25, 1.25)	1.82 (0.90, 3.68)
Smoking	Yes	**1.56** (1.09, 2.22)	1.28 (0.84, 1.96)	1.14 (0.77, 1.67)
Family environment [b]				
Maternal warmth	Low	**3.19** (1.99, 5.13)	**3.01*****(1.62, 5.60)	1.37 (0.85, 2.21)
Communication	Poor	1.15 (0.63, 2.08)	0.83 (0.42, 1.63)	0.96 (0.51, 1.80)
Parents separated	Yes	1.28 (0.89, 1.85)	1.02 (0.66, 1.57)	0.92 (0.62, 1.36)
Relationship violence	Ever	0.79 (0.47, 1.34)	0.89 (0.48, 1.67)	0.77 (0.44, 1.33)
Adolescent behaviour [c]				
Internalising	Yes	1.12 (0.66, 1.90)	1.21 (0.62, 2.34)	**0.56***(0.33, 0.96)
Externalising	Yes	1.42 (0.79, 2.59)	1.02 (0.52, 2.03)	1.13 (0.60, 2.11)
Attention/Thought	Yes	**2.04** (1.18, 3.52)	1.40 (0.73, 2.70)	1.52 (0.86, 2.68)
Drinking	Yes	**2.22** (1.25, 3.96)	1.63 (0.82, 3.26)	**3.11*****(1.62, 5.99)
Smoking	Yes	**2.24** (1.33, 3.77)	1.29 (0.70, 2.38)	1.38 (0.80, 2.37)
Demographics [d]				
Gender	Female	1.07 (0.77, 1.42)	**4.30*****(2.83, 6.54)	**0.36*****(0.25, 0.52)
Maternal education	Low	1.41 (0.97, 2.05)	1.24 (0.80, 1.93)	1.28 (0.85, 1.93)

Models are fully adjusted for all factors, reference groups as shown
*Difference vs alternative reference group is significant * P<0.05; **P<0.01; ***P<0.005*
[a] *Maternal factors were self-reported at 14 year follow-up*
[b] *Family environment factors were assessed via maternal report at 14 years, except for Maternal warmth, assessed by offspring report at 21 years*
[c] *Adolescent behaviour factors were self-reported at 14 years*
[d] *Maternal education was recorded at baseline*
[e] *Paternal factors were reported by mother at 14 years*

Table 3: Multinomial logistic regression models of comorbid alcohol and mental health disorders in young adults, showing the impact of father issues

		MODEL 1:	MODEL 2:	
		All participants *(n=797)*	**If father present** *(n=688)*	**If father separated** *(n=99)*
Maternal factors [a]		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Mental distress	Yes	1.27 (0.53, 3.09)	1.60 (0.58, 4.41)	0.65 (0.02, 19.61)
Drinking	Drink	0.79 (0.40, 1.56)	0.61 (0.30, 1.24)	n/a
	Binge	0.78 (0.26, 2.32)	0.63 (0.18, 2.16)	n/a
Smoking	Yes	1.33 (0.71, 2.51)	1.63 (0.83, 3.19)	0.14 (0.01, 2.48)
Family environment [b]				
Maternal warmth	Low	1.09 (0.43, 2.74)	0.83 (0.26, 2.63)	2.06 (0.14, 30.84)
Communication	Poor	1.36 (0.52, 3.52)	0.86 (0.25, 2.91)	10.09 (0.26, 385.4)
Parents separated	Yes	1.00 (0.46, 2.17)	*Not included*	*Not included*
Relationship violence	Ever	0.98 (0.34, 2.83)	0.60 (0.13, 2.73)	0.99 (0.12, 7.91)
Adolescent behaviour [c]				
Internalising	Yes	1.59 (0.70, 3.65)	1.38 (0.54, 3.50)	27.94 (1.74, 449)
Externalising	Yes	0.91 (0.33, 2.49)	0.44 (0.13, 1.48)	12.80 (0.56, 2.91)
Attention/Thought	Yes	1.86 (0.73, 4.75)	**3.11** (1.13, 8.56)	n/a
Drinking	Yes	**3.73** (1.49, 9.33)	**5.69** (2.04, 15.90)*	0.44 (0.01, 28.2)
Smoking	Yes	**2.62** (1.11, 6.21)	2.56 (0.98, 6.69)	11.25 (0.43, 296)
Paternal factors [e]				
Mental health	Yes	0.84 (0.28, 2.55)	0.87 (0.24, 3.13)	0.22 (0.00, 12.24)
Alcohol problems	Yes	**2.41** (1.10, 5.29)**	**3.17** (1.24, 8.11)	1.03 (0.15, 8.07)
Smoking	Yes	1.37 (0.77, 2.44)	1.46 (0.78, 2.73)	1.88 (0.23, 15.39)

Model 1: Model includes all participants for whom paternal information was available and is adjusted for gender and maternal education. No-disorder group was used as reference; odds ratios shown are for the comorbid group only.

Model 2: as per Model 1; then stratified by parental separation

n/a indicates cell size was too small to provide an odds ratio

*** indicates that the odds ratio for the comorbid group is greater than for either MHD only or AUD only group ($p<0.05$); * indicates $p<0.10$*

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Young adulthood

Chapter 5 reported that comorbid young adults experience significant behaviour problems, including aggression and delinquent behaviours. This is in keeping with evidence indicating that substance and mental health disorders are associated with aggressive behaviour towards others. In addition to individual traits, which in our previous papers were strongly associated with comorbidity, factors outside the individual may be linked to such behaviour. The “normalisation” of violence through neighbourhood exposure and witnessing parental relationship violence may play a role, as may traumas such as childhood sexual assault. The following study investigated whether those with substance use and mental health disorders, in addition to perpetrating violence, were more likely to be vulnerable to experience of relationship violence and specifically intimate partner violence. The multiple forms of intimate partner violence were compared and potential gender differences investigated. This work is described in paper 6.3.

6.3 Vulnerability to intimate partner violence

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Title:

Substance use and mental health disorders are linked to different forms of intimate partner violence victimisation

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Abstract:

Background: Substance and mental health disorders convey significant health burden and impair interpersonal relationships. We tested associations between comorbid substance and mental health disorders and different forms of intimate partner violence (IPV) experienced by young adults.

Method: Mothers (n=6703) were recruited during pregnancy to the longitudinal Mater-University of Queensland Study of Pregnancy. Mother/offspring dyads were followed up from birth to 21 years. Offspring with complete psychiatric data at 21 years who reported having had an intimate partnership were included (n=1781). Participants' experiences of psychological, physical and severe combined IPV were assessed at 21 years using a summarised form of the Composite Abuse Scale. We used the Composite International Diagnostic Interview to obtain lifetime diagnoses of mental health and substance disorders. Multivariable logistic regression models of each IPV form were adjusted for individual, family and neighbourhood factors during adolescence, and for other forms of IPV.

Results: We have shown specific links between different forms of IPV experienced and individual substance and mental health disorders. Mental health disorders were related to all three forms of IPV, while alcohol disorders were linked to psychological IPV (OR_{AUD}=1.86; 1.21-2.86) and illicit substance disorders to physical IPV (OR_{SUD}=2.07; 1.25-3.43). The co-occurrence of related disorders was strongly linked to psychological and physical IPV.

Conclusions: Intimate partner violence was experienced by both men and women. Substance and mental health disorders were associated with specific forms of IPV victimisation, suggesting that screening IPV clients and mental health/substance disorder patients for the converse problems may be important for intervention planning.

Keywords

Intimate partner violence; alcohol; mental health; comorbid; domestic violence; relationships

1. Introduction

Intimate partner violence (IPV) is an issue of global concern, with prevalence estimates ranging between 10% and 75% depending on the country surveyed (Garcia-Moreno et al., 2006; Feder et al., 2013; Fulu et al., 2013). The World Health Organisation defines IPV as "behaviour by an intimate partner that causes physical, sexual or psychological harm" (Feder et al., 2013). Although most victims have experienced more than one type of IPV (Hegarty et al., 2004; Thompson et al., 2006; Krebs et al., 2011), the majority of evidence on victimisation to date describes physical IPV. Some studies however suggest that different factors may be associated with victims' experience of each form of harm (Hegarty et al., 2004; Jonas et al., 2014). For example, being a victim of physical IPV has been associated with alcohol disorders (Fergusson et al., 2013), illicit substance use (Smith et al., 2012), mood (la Flair et al., 2012) and anxiety disorders (Schonbrun et al., 2013). As to psychological IPV, there is initial evidence that common mental disorders may be associated with higher prevalence of this form of violence (Coker et al., 2000; Hegarty et al., 2005; Thompson et al., 2006). Little is known about how these disorders link to sexual IPV victimisation (Krebs et al., 2011; Devries et al., 2014).

Identification of different forms of IPV may be important. Firstly, treatment for psychological IPV differs from that for physical or sexual forms. Secondly, identification of and intervention for psychological IPV may help prevent progression to other forms of IPV in the relationship (Krebs et al., 2011).

The associations with mental health and substance use disorders are also useful to consider. Although the World Health Organisation no longer recommends universal screening for IPV, it endorses enquiry via conditions which may contribute to or be worsened by IPV (Feder et al., 2013). In general it appears that common mental health disorders, including alcohol and illicit substance use, may play an important role in becoming a victim of IPV. This is additionally concerning given that substance use and mental health disorders contribute substantially to the global disease burden (Whiteford et al., 2013) and are frequently comorbid with each other (Merikangas and Kalaydjian, 2007; Teesson et al., 2009). These comorbidities present additional challenges. Treatment approaches are more complex (Tiet and Mausbach, 2007; Connolly et al., 2011) and more costly (King et al., 2000), societal participation is impaired (King et al., 2000) and behavioural problems are more severe (Salom et al., 2014). These factors may also affect therapy for IPV.

Although existing literature on IPV victimisation is substantial, there are a number of shortcomings. Firstly, few studies include all three types of intimate partner violence (Coker et al., 2000; Hegarty et al., 2004; Thompson et al., 2006; Krebs et al., 2011) and none of these has examined links between IPV forms and different types of mental health disorders, meaning the links with comorbidities could not be assessed (McPherson et al., 2007; Boden et al., 2012; Fergusson et al., 2013; Schonbrun et al., 2013; Jonas et al., 2014). Secondly, gender differences need further investigation. The existing literature is heavily weighted towards female victimisation (Coker et al., 2000; Stith et al., 2004; Krebs et al., 2011; Devries et al., 2014) and many studies are drawn from treatment samples (McPherson et al., 2007; Engstrom et al., 2008). A number of national studies have however shown that men are victims, and of each type of IPV (Smith et al., 2012; Jonas et al., 2014; Kraanen et al., 2014). Factors involved in male victimisation may differ from those for women. For example, depression in men has been linked to their experience of psychological IPV, while in women depression appears related to physical partner violence (Renner et al., 2014); hence it is important to consider gender differences.

Many studies were cross-sectional and therefore unable to assess the role of contributing factors, since retrospective reports of these factors may be subject to recall bias (Coker et al., 2000; Vest et al., 2002; Hegarty et al., 2005; Thompson et al., 2006; Kraanen et al., 2014; Selic et al., 2014). A few longitudinal studies have emerged with mixed results. Depression has been linked (Johnson et al., 2014; Longmore et al., 2014) and not linked (Halpern et al., 2009; Fergusson et al., 2013) with physical IPV. Similarly, findings for alcohol have been positive (Fergusson et al., 2013) and negative (Johnson et al., 2014), with another line of research suggesting that observed links between these disorders and IPV experience may be explained by other factors (Boden et al., 2012). These studies have considered only physical IPV, or have included sexual IPV in their assessment, not measuring psychological IPV.

In this study, we examine the associations between alcohol, illicit substance and mental health disorders and different forms of intimate partner violence. We hypothesize that co-occurring disorders may be more strongly linked to IPV victimisation than single disorders, and that these relationships may be gender patterned, as are substance and mental health disorders. We adjust for participants' own violent behaviour (Coker et al., 2000; Longmore et al., 2014), experience of childhood sexual abuse (Stith et al., 2004; Renner et al., 2014), observation of parental IPV (Bonomi et al., 2014), living in a neighbourhood

where violence is normalised (Selic et al., 2014), and socio-economic factors such as low education (Boden et al., 2013), unemployment (Smith et al., 2012) and restricted income (Coker et al., 2000; Garcia-Moreno et al., 2006; Thompson et al., 2006; Krebs et al., 2011) which have all been related to intimate partner violence victimization.

We add to the existing literature on IPV in a number of ways. Our study is a large population-based sample comprising both men and women for whom we have measures consistent with clinical diagnoses of alcohol, illicit substance and mental health disorders. Our data also comprise prospectively-collected measures from individuals and their family of origin to assess adolescent and early life factors which may contribute to victimisation or confound the relationships with these disorders. Lastly, we have measures of psychological, physical and sexual IPV; these were assessed early in adulthood, so that most experience of IPV will have been recent, thus reducing the potential for recall bias. In summary, we are able evaluate the relationships of alcohol, illicit substance and mental health disorders with different types of IPV victimization, singly and in combination.

2. Method

2.1 Sample

The Mater-University of Queensland Study of Pregnancy (MUSP) comprises a linked pre-birth cohort of mothers and children. Mothers (n=7223) were enrolled at their first antenatal clinic visit to the Mater Misericordiae Public Hospital in Brisbane between 1981 and 1983. The MUSP was approved by the Human Ethics Review Committee at the University of Queensland and has been extensively described (Hegarty et al., 1999; Najman et al., 2014). Dyads were followed over 21 years, with participants giving written, informed consent at each stage. For this study, we included in the analyses only offspring for whom complete mental health and substance data at 21 years, and maternal and self-reports at 14 years were available, and who reported ever having an intimate relationship. The sample (n=1781) was 51% female with a mean age of 20.6 years: other demographics are shown in Supplementary Table 1.

2.2 Measures

Outcome

Intimate partner violence victimization was measured at 21 years using a modified Composite Abuse Scale (Hegarty et al., 1999; Hegarty et al., 2005). This scale had been developed to extend the Conflict Tactics Scale (Straus et al., 1996) by incorporating measures of psychological violence such as humiliation, control and social isolation, and delineating between psychological, physical and sexual violence (Hegarty et al., 2005). The scale comprised 20 items which assessed frequency of ever having experienced psychological IPV (12 items included blame for the partner's violence, insults and separation from friends and family; α=0.92), physical IPV (5 items; α=0.93) and severe combined IPV (3 items included rape, forced sex with others and assault with a weapon; α=0.75). Psychological, physical and severe combined IPV were recorded separately and dichotomised such that for physical and severe combined IPV, endorsement of any item was positive (Krebs et al., 2011; Okuda et al., 2011; Boden et al., 2012). For psychological IPV, endorsement of two items was required (Krebs et al., 2011). In addition, frequency scores for each item within the sub-scales were summed to generate a severity score for each IPV form.

Predictors

Alcohol, illicit substance and mental health disorders

At 21 years, 2226 eligible offspring were administered the mental health and substance use modules of the Composite International Diagnostic Interview (CIDI). Responses were coded to yield lifetime diagnoses using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Association, 2000) (DSM-IV). The 'any alcohol use disorder' and 'any illicit substance use disorder' diagnoses included abuse and dependence, and 'any mental health disorder' included all participants reporting an anxiety, affective, eating or psychotic disorder. Within each group, the presence of multiple disorders was possible. An eight-category variable "Disorder Group" was created: No (DSM-IV) disorder; mental health disorder but no substance disorder (MHD); alcohol use disorder but no mental health or illicit substance disorder (AUD); or illicit substance use disorder other than alcohol, with no mental health disorder (SUD). Comorbid AUD/MHD, AUD/SUD, SUD/MHD and AUD/SUD/MHD comprised the other categories.

Covariates

Measures at birth

Child gender and maternal age were recorded at birth. Maternal education was self-reported at first antenatal clinic visit, and dichotomised (at least Year 12/ less than Year 12) to approximate socio-economic disadvantage.

Measures in adolescence

We assessed aggressive behaviour at 14 years using Achenbach's Youth Self Report (YSR; α=0.87) and dichotomised responses such that scores in the top 10% constituted 'aggression problems' according to Achenbach's case-ness definition (Achenbach, 1997; 2005).

Neighbourhood problems (Bonomi et al., 2014) were reported by mothers at 14 years. Vandalism, burglary, car theft, drug abuse, street violence, unemployment, driving offences, alcohol abuse and school truancy in the residential area were recorded as being no problem, moderate or a major problem. These items were summed to give a 'neighbourhood problems' score; the highest 10% were categorised as 'problematic' (α=0.93). Mothers reported at 14 years whether they had "experienced violence in a relationship with a partner" during the previous 7 years. This was dichotomised (no violence/violence) (Bauer et al., 2013).

At 21 years, participants reported whether they had left home before age 17 (when most Queensland children complete Year 12) and whether they had experienced sexual assault before the age of 16 (Engstrom et al., 2008). Both were dichotomised (no/yes).

In sensitivity analyses, we considered participants' adolescent drinking and internalising behaviour problems as early markers of developing alcohol and mental health disorders (Salom et al., 2015). Drinking was self-reported at age 14 and dichotomised such that drinking at least "a few times a year" and more than "1 or 2 glasses per occasion" was classed as regular. We used the internalising scale of Achenbach's YSR and categorised scores such that the highest 10% constituted internalising problems (Achenbach, 1997; 2005) (α=0.87).

Measures at adulthood

Participant age was recorded at 21 years; education level was self-reported and dichotomised (at least Year 12/less than Year 12). Cohabitation with a partner (Longmore et al., 2014) (no/yes) and the number of children at home were also self-reported at 21 (Vest et al., 2002). We also examined the impact of paid work (at least part-time,

dichotomised), self-reported at age 21, as employment has been shown to provide a measure of protective independence (Boden et al., 2012; Selic et al., 2014).

2.3 Statistical Analysis

Prevalence and severity of each type of IPV victimization were determined across the DSM-IV substance/mental health disorder groups. These IPV forms were not mutually exclusive. For each form of IPV, the bivariate relationship with DSM-IV disorder group was modelled using logistic regression. Each of these models was then adjusted for gender, age, education, cohabitation, number of children in care, leaving home early, childhood sexual assault, adolescent aggression, residential area problems, parental relationship violence, mother's education and mother's age at childbirth as described above.

To then account for participants having experienced multiple forms of IPV (Devries et al., 2014), we adjusted each multivariable model above for the other forms of IPV (i.e. the psychological IPV model was adjusted for physical IPV and for severe combined IPV, etc.). A multinomial model using a five-category outcome (no IPV, psychological only, physical only, severe combined only, and multiple IPV types) proved unstable due to the small numbers who experienced only severe combined abuse.

In sensitivity analyses, we adjusted the models for participants' drinking and internalising problems at 14 years. In order to compare single disorders to combined disorders, we repeated the regression analyses above, using each combined disorder group in turn as reference. We also assessed interactions between disorder groups and gender.

Attrition

Finally, we assessed how attrition may have affected our results, using a multivariable regression model of loss to follow-up with baseline predictors (maternal age, marital status, anxiety, depression, drinking and smoking and participant gender). We used inverse probability weighting with robust estimates for standard errors to account for those lost to follow-up from the 7223 original cohort members, according to recommendations (Hogan et al., 2004; Ware et al., 2012). We fitted baseline predictors in a logistic regression model (response vs nonresponse as outcome) to determine weights for each individual using the inverse probability of response. We then repeated the multivariable analyses including the weighting adjustments, and compared weighted results to the complete case analyses. All analyses were undertaken using STATA 12.1 (StataCorp, USA).

3. Results:

Nearly 41% (n=1324) of young adults reported ever experiencing psychological violence from an intimate partner (Table 1); of these, 44% were male. Physical IPV was reported by 39.7% (n=1293) of respondents (49% of whom were male) and severe combined abuse by 6.6% (n=215; 32% male). There was considerable overlap between abuse types: 24.5% of participants (n=792) reported experiencing two types of IPV and 5% (n=167) reported all three (Figure1).

Bivariate analyses suggested that experiences of psychological or physical IPV were more likely in those with alcohol, mental health and illicit substance disorders, but that severe combined IPV was associated only with mental health disorders (Table 2). Psychological and physical IPV severity scores were higher in those with all three disorder types, but severe combined IPV scores were only higher for those with MHD. Most covariates were linked to at least one DSM-IV disorder group (Supplementary Table 2) and so were included in multivariable models as potential confounders. This initial adjustment accounted for a relatively small proportion of the relationships between disorder type and IPV type (Table 3A). Further adjusting the models for other forms of intimate partner violence reduced the strength of relationships between substance or mental health disorders and IPV (Table 3B). In the final models, once other types of IPV were accounted for, psychological IPV was associated with alcohol but not illicit substance disorders. Physical IPV was associated with illicit substance but not alcohol disorders. Severe combined abuse was not associated with either substance disorder, but all three forms of IPV were linked to mental health disorders (Supplementary Table 3).

For psychological and physical forms of IPV, the presence of both mental and substance (including alcohol) disorders increased the likelihood of experiencing IPV ($P<0.05$). The addition of further substance disorders did not significantly strengthen the association. For severe combined abuse, the presence of substance in addition to mental health disorders did not significantly increase the association. Interactions between gender and disorder type were not significant.

Likelihood ratio tests indicated that for each model, the strongest contributing factor was experience of another form of IPV. For psychological IPV, $\chi^2_{Phys}=322.6$, $P<0.0001$; for physical IPV, $\chi^2_{emot}=325$, $P<0.0001$; for SCA, $\chi^2_{phys}= 24.4$; $P<0.0001$). Of other factors, the disorder group was most influential (Psychological: $\chi^2=34.2$, $P<0.001$; Physical $\chi^2=40.6$,

P<0.001; Severe Combined χ^2=17.9, *P*<0.02). Early life factors that were independently significant in the models were different for each IPV form experienced. Females were more likely to report having experienced psychological IPV. Male gender was a risk for physical IPV while those who had been aggressive as adolescents were less likely to report experiencing physical IPV at adulthood. Childhood sexual abuse and leaving home early predicted severe combined abuse.

As missing data reduced our sample to 1655 of the 2342 administered the CIDI at age 21, (from a baseline cohort of 7223), we generated a weighted model using baseline factors associated with attrition (Supplementary Table 4). Relationships using weighted data were very similar to those reported above (Supplementary Table 5).

In sensitivity analyses, adjustment for adolescent drinking did not substantively change the relationships shown; it was not independently related to experience of any IPV type. Adjustment for adolescent internalising problems accounted for some of the relationship between MHD and severe combined abuse (OR_{SCA} 2.19; CI_{95} 1.09, 5.18) but not other forms. Internalising was independently associated with psychological (OR_{EMOT} 1.62; CI_{95} 1.13, 2.33) but not physical or severe combined IPV. Adjustment of the models for paid employment did not alter the results described above.

4. Discussion

In this paper we have examined the links between different comorbidities of substance use and mental health disorders and different forms of IPV victimisation. Our results indicate that once we accounted for other forms of IPV experienced, psychological IPV was experienced by those with individual and comorbid alcohol and mental health disorders, while physical IPV was related to individual and comorbid illicit substance and mental health disorders. Severe combined abuse appeared associated only with mental health disorders. These relationships were independent of gender and adolescent drinking, but were partially accounted for by adolescent internalising problems.

IPV victimisation rates described here are supported by other lifetime reports, where physical IPV prevalence ranged from 30-40% (Halpern et al., 2009; Krebs et al., 2011; Johnson et al., 2014), but higher than past-year prevalences (10-13%) reported in some longitudinal studies (Boden et al., 2012; Schonbrun et al., 2013). Variation between psychological IPV scales used may account for the broad range of lifetime prevalence estimates (6-60%) reported elsewhere (Coker et al., 2000; Krebs et al., 2011).

Our study adds to the evidence as we were able to account for other forms of IPV, as suggested by de Vries and colleagues (Devries et al., 2014). This is important, as approximately 70% of those who reported physical IPV also experienced psychological IPV, and 83% of those who experienced severe combined abuse also reported both physical and psychological forms. It has enabled us to suggest a possible explanation for the heterogeneity of relationships previously reported between different forms of IPV and individual substance or mental health disorders. The link we observed between physical IPV and all three disorder types when examining IPV forms separately is consistent with numerous earlier reports of physical IPV (la Flair et al., 2012; Smith et al., 2012; Fergusson et al., 2013; Longmore et al., 2014). However, once we adjusted for the presence of other IPV, our model showed that only mental health and illicit substance disorders were associated with the physical form. This finding is supported by results from a large UK study (Jonas et al., 2014) and is in line with interpretations from work by Boden *et al* (Boden et al., 2012) that the association found by others of alcohol use and physical IPV is explained by previously unmeasured factors. One potential interpretation is that having alcohol and mental disorders is related to being a victim of psychological IPV, with the presence of illicit substance disorders associated with a hypothetical escalation from

psychological to physical IPV. Further studies, able to address temporal ordering of IPV forms, are needed to explore this possibility.

A link between psychological IPV and mental health disorders is congruent with other reports (Hegarty et al., 2004; Jonas et al., 2014; Renner et al., 2014). The relationship we found to alcohol disorders is not supported by other evidence (Coker et al., 2000; Jonas et al., 2014), which may be due to differences in sample selection (one study being based on a clinical sample), and different definition of psychological IPV in other studies. A lack of association between severe combined abuse and any substance disorders in our study is only supported by one other report (Coker et al., 2000). The de Vries (Devries et al., 2014) meta-analysis which associated alcohol with sexual violence noted both considerable heterogeneity among the results analysed and the inability to account for other types of IPV.

In this study we have asked whether substance and mental disorders render a person vulnerable to IPV, but the associations apply equally in the reverse direction (i.e. IPV predicting disorder), which is consistent with suggestions proposed by others (Okuda et al., 2011; Devries et al., 2014). The inclusion of adolescent behaviours problems in our model provides some clues. Internalising at 14 accounted for some (but not all) of the link between young adult mental disorders and severe combined abuse, and was independently associated with psychological IPV, suggesting mental disorders may precede these forms. This was not the case for adolescent drinking. There have been suggestions that IPV results in increased depression and substance use (Beydoun et al., 2012; Young-Wolff et al., 2013); our results may be consistent with these. This might be explained by self-medication (Bolton et al., 2009) in response to distress caused by IPV. However in such case we would expect an association between substance disorders and severe combined abuse, which was not found.

It is also possible that experience of IPV and substance/mental health disorders emerge concurrently during late adolescence and early adulthood due to shared risk factors. Alcohol and other substance disorders may result in deficits in executive function or social perceptions, and these may reduce the ability to attend to social cues or process potentially provocative situations (Sher et al., 2005; Clements and Schumacher, 2010). Rather than being on the causal pathway to IPV, substance disorders may render the person less able to employ relationship coping strategies (Stuart et al., 2009) and avoid potentially violent situations. Similarly, behavioural under-control associated with

substance and mental disorders (Elbogen and Johnson, 2009; ten Have et al., 2014) may place the person at increased risk of IPV. This would appear to be separate from aggression. Despite the often reciprocal nature of IPV (Coker et al., 2002; Longmore et al., 2014), subjects' own aggression did not account for the relationship between IPV and substance or mental disorders. Future studies with capacity to test for factors which may mediate the relationship between mental health disorders and IPV are needed for this interpretation to be further explored.

In addition to clarifying previously-seen links between different IPV forms and single disorder types, ours is the first study to find robust associations between comorbid disorders and the different forms of IPV experienced. This appears to be a cumulative but specific effect, since the addition of an unrelated disorder was not associated with further increase in risk of each type of IPV. This cumulative finding is consistent with the more severe social impairment associated with comorbidity over single disorders (King et al., 2000; Kay-Lambkin et al., 2014; Salom et al., 2014).

We have also noted gender differences, but these were in the form of IPV experienced, not the associations between IPV and disorder type. Despite the focus on female victims of IPV in the literature, we found that physical IPV was experienced by similar proportions of females and males; this may reflect items endorsed, which ranged from being slapped to being kicked, hit or bitten. In contrast, psychological IPV and severe combined abuse were more commonly experienced by women. We did not however find a significant interaction between gender and disorder type, despite suggestions by one report of gender differences in the link between depression and IPV (Renner et al., 2014). That study however comprised only rural couples and examined depressive symptoms, rather than clinical diagnoses of depression.

These results have implications for screening and intervention. The World Health Organisation recommends (Feder et al., 2013) screening for IPV exposure when assessing conditions potentially caused or complicated by IPV. Substance use and mental health disorders constitute such conditions, and our results suggest it would be prudent to screen both male and female patients. Mental health services are particularly implicated as mental health disorders were associated with all IPV forms. When working with substance-using clients, results suggest those with alcohol use disorders (particularly when comorbid with MHD) should be screened for psychological IPV; other research indicates that monitoring for progression to other forms of IPV may be prudent (Krebs et

al., 2011). The presence of illicit substance use disorders may suggest that physical IPV is also a risk, again particularly if comorbid with MHD. Substance use disorders are less likely to suggest occurrence of sexual IPV; this is more a risk if other IPV forms are occurring. Similarly, practitioners supporting IPV victims should be encouraged to screen for substance and mental health disorders which may complicate their support options.

This study has considerable strengths. We used a large population-based sample comprising both men and women and clinically-derived measures of substance and mental disorders. Additionally, we were able to control for a broad range of individual and family factors associated with IPV. The cohort size allowed us to examine the experience of different forms of intimate partner violence, both individually and comparatively, the latter being a noted shortfall of the current literature (Devries et al., 2014).

These findings need to be considered in light of possible study limitations. Because of the cross sectional nature of our main analysis we are unable to assign temporal precedence to either the disorders or IPV, though our analyses suggest that early mental health problems (but not drinking) may increase the risk of experiencing intimate partner violence. Additionally, attrition in our sample was significant and may have introduced some bias to our results. The analyses of our weighted data were not materially different to the complete case analysis, giving us confidence in our findings.

Despite these reservations, this paper has shown specific links between different IPV forms and individual substance and mental health disorders: mental health disorders were related to all three forms of intimate partner violence, while alcohol disorders were linked to psychological IPV and illicit substance use disorders to physical IPV. Moreover, we have shown that co-occurrence of related disorders was more strongly linked to psychological and physical IPV. The high prevalence of intimate partner violence victimisation in both men and women warrants further investigation of these relationships using prospective studies.

Figure 1: Experience of multiple forms of Intimate Partner Violence by young adults

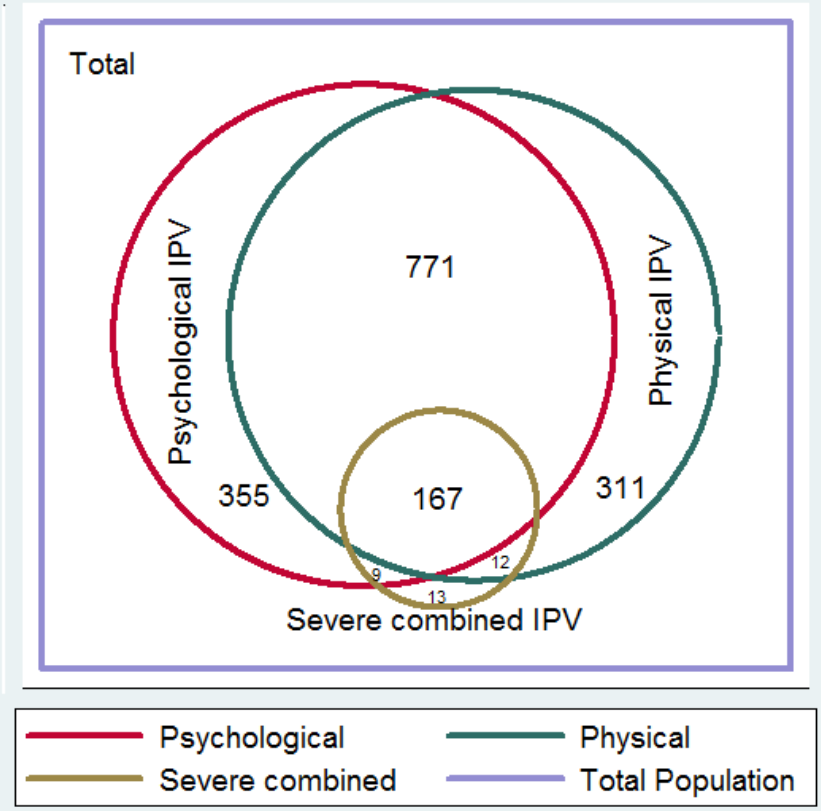

Table 1: Prevalence and severity of psychological, physical and severe combined Intimate Partner Violence (IPV) victimization across substance and mental health disorder types

	Measure	NIL	MHD	AUD	AUD/MHD	SUD	SUD/MHD	AUD/SUD	AUD/SUD/ MHD	
	N (%)	**926 (42%)**	**418 (19%)**	**196 (9%)**	**117 (5%)**	**118 (5%)**	**111 (5%)**	**173 (8%)**	**167 (7%)**	**Range**
Psychological IPV	**N=1324 (40.8%)**									
	Prevalence [a]	% (SE)	24.6 (1.4)	42.5 (2.4)	42.0 (3.6)	59.3 (2.6)	43.1 (4.6)	55.6 (4.8)	44.1 (3.9)	71.0 (3.6)	
	Severity [b]	Mean (SE)	25.7 (0.1)	28.8 (0.4)	27.2 (0.3)	30.1 (0.7)	27.3 (0.4)	31.7 (1.0)	27.4 (0.4)	32.9 (0.8)	24-84
Physical IPV	**N=1293 (39.7%)**									
	Prevalence [a]	% (SE)	24.5 (1.4)	38.3 (2.4)	42.4 (3.6)	47.4 (4.7)	47.4 (4.7)	56.9 (4.8)	50.0 (3.9)	75.2 (3.4)	
	Severity [b]	Mean (SE)	10.8 (0.1)	12.0 (0.2)	11.7 (0.2)	12.8 (0.4)	11.9 (0.3)	13.8 (0.5)	12.4 (0.3)	15.1 (0.4)	10-35
Severe Combined IPV	**N=215 (6.6%)**									
	Prevalence [a]	% (SE)	1.9 (0.6)	7.2 (1.2)	3.1 (1.3)	12.1 (3.2)	2.6 (1.5)	12.8 (3.2)	6.6 (1.9)	17.3 (2.9)	
	Severity [b]	Mean (SE)	6.0 (0.1)	6.1 (0.1)	6.0 (0.1)	6.2 (0.1)	6.0 (0.1)	6.2 (0.1)	6.2 (0.1)	6.3 (0.1)	6-21

[a] Prevalence of ever having experienced IPV
[b] Combined quantity/frequency score indicating severity of IPV

Table 2: Bivariate models of psychological, physical and severe combined IPV victimization in young adults

Each form of IPV is modelled separately.

Factor		Model 1: Psychological IPV OR (CI_{95})	Model 2: Physical IPV OR (CI_{95})	Model 3: Severe combined IPV OR (CI_{95})
Substance use and mental health disorders – 21 years				
No disorder		Reference	Reference	Reference
MHD only	Yes	**2.27** (1.77, 2.90)	**1.91** (1.49, 2.45)	**4.06** (2.21, 7.45)
AUD only	Yes	**2.23** (1.61, 3.09)	**2.27** (1.64, 3.14)	1.69 (0.66, 4.34)
SUD only	Yes	**2.33** (1.56, 3.46)	**2.78** (1.87, 4.12)	1.39 (0.40, 4.83)
AUD/MHD	Yes	**4.47** (2.99, 6.71)	**2.78** (1.87, 4.12)	**7.14** (3.42, 14.91)
SUD/MHD	Yes	**3.84** (2.55, 5.78)	**4.06** (2.70, 6.11)	**7.66** (3.66, 16.03)
AUD/SUD	Yes	**2.42** (1.71, 3.43)	**3.08** (2.19, 4.34)	**3.69** (1.70, 8.03)
AUD/MHD/SUD	Yes	**7.52** (5.18, 10.90)	**9.32** (6.32, 13.74)	**10.87** (5.79, 20.39)
Demographics – 21 years				
Gender	Female	1.02 (0.89, 1.17)	**0.72** (0.62, 0.83)	**1.80** (1.34, 2.43)
Age	Per 5 yrs	**2.14** (1.41, 3.23)	**1.65** (1.09, 2.49)	**2.27** (1.01, 5.12)
Education	<Year 12	**2.03** (1.71, 2.41)	**2.13** (1.80, 2.53)	**2.65** (1.98, 3.54)
Cohabitation	Yes	1.13 (0.96, 1.34)	**1.32** (1.12, 1.56)	0.93 (0.68, 1.27)
Children in care	0-3	**2.03** (1.69, 2.44)	**2.29** (1.90, 2.76)	**2.57** (2.08, 3.19)
Adolescent factors -14 years				
Residential area	Problems	1.26 (0.98, 1.63)	**1.34** (1.04, 1.73)	1.48 (0.94, 2.34)
Own aggression	YSR	**0.57** (0.45, 0.73)	**0.51** (0.39, 0.65)	**0.25** (0.11, 0.56)
Sexual assault <16	Yes	**2.63** (2.08, 3.33)	**2.48** (1.97, 3.13)	**5.55** (4.06, 7.59)
Left home <17	Yes	**3.55** (2.84, 4.55)	**3.97** (3.17, 4.98)	**5.44** (4.03, 7.33)
Parental relationship	Violent	**1.30** (1.04, 1.62)	**1.35** (1.08, 1.68)	1.08 (0.69, 1.68)
Maternal factors - birth				
Education	<Year 12	**1.24** (1.06, 1.46)	**1.43** (1.22, 1.67)	1.31 (0.95, 1.81)
Birth age	Per 5 yrs	**0.91** (0.84, 0.97)	**0.88** (0.82, 0.95)	**0.80** (0.69, 0.93)

Table 3: Multivariable logistic regression models of psychological, physical and severe combined IPV victimization in young adults

	Model 1: Psychological IPV	Model 2: Physical IPV	Model 3: Severe combined IPV
	OR (CI_{95})	**OR** (CI_{95})	**OR** (CI_{95})
A: Adjusted for covariates only			
No disorder	Reference	Reference	Reference
MHD only	**2.10** (1.59, 2.79)	**2.04** (1.51, 2.74)	**3.48** (1.62, 7.46)
AUD only	**2.10** (1.44, 3.06)	**1.70** (1.16, 2.50)	0.96 (0.20, 4.46)
SUD only	**2.31** (1.49, 3.60)	**2.59** (1.65, 4.06)	1.64 (0.43, 6.18)
AUD/MHD	**3.76*** (2.36, 6.00)	**2.40** (1.49, 3.87)	**7.12** (2.95, 17.21)
SUD/MHD	**2.74** (1.70, 4.42)	**3.66** (2.24, 5.97)	**5.14** (1.99, 13.29)
AUD/SUD	**1.84** (1.21, 2.78)	**1.79** (1.19, 2.69)	2.75 (0.98, 7.70)
AUD/SUD/MHD	**6.10*** (3.94, 9.45)	**7.44***(4.67, 11.83)	**7.25*** (3.22, 16.32)
B: Adjusted for other forms of abuse			
No disorder	Reference	Reference	Reference
MHD only	**1.66** (1.20, 2.30)	**1.56** (1.11, 2.20)	**2.68** (1.16, 6.15)
AUD only	**1.86** (1.21, 2.86)	1.32 (0.85, 2.04)	0.89 (0.18, 4.29)
SUD only	1.62 (0.98, 2.70)	**2.07** (1.25, 3.43)	1.00 (0.25, 4.02)
AUD/MHD	**3.09*** (1.81, 5.26)	1.23 (0.71, 2.16)	**4.84** (1.82, 12.82)
SUD/MHD	1.55 (0.89, 2.70)	**3.01*** (1.68, 5.38)	**2.66** (0.93, 7.62)
AUD/SUD	1.57 (0.98, 2.51)	1.37 (0.85, 2.20)	1.52 (0.45, 5.12)
AUD/SUD/MHD	**2.96** (1.79, 4.88)	**4.13** (2.43, 7.00)	**3.35** (1.42, 7.95)

Each form of IPV is modelled separately.

Models in Part A have been adjusted for gender, age, education, cohabitation, number of children in care, leaving home early, childhood sexual assault, adolescent aggression, residential area problems, parental relationship violence in adolescence, mother's education and mother's age at birth.

Models in Part B have been adjusted as above, plus other forms of IPV (e.g. the psychological IPV model was adjusted for physical and severe combined IPV).

* indicates that the OR for a combined disorder is greater than those for single disorders ($P<0.05$)

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Summary of Chapter 6

This body of work has identified factors across the life-course that were more strongly linked to comorbidity than to single disorders. Socio-economic disadvantage was predictive of comorbidity at young adulthood, with evidence for a gradient or dose response where greater disadvantage increased the risk of later comorbidity. Maternal smoking during pregnancy was also a risk, independent of pre-pregnant smoking and the socio-economic disadvantage with which that is often associated.

Other predictors included maternal anxiety in childhood, paternal drinking problems and low mother-child warmth. Although traumas such as parental relationship violence and separation were not associated with comorbidity after adjustment, childhood sexual assault constituted an additional risk. Drinking, smoking and attention/thought problems in the child during adolescence were strong indicators of later comorbidity.

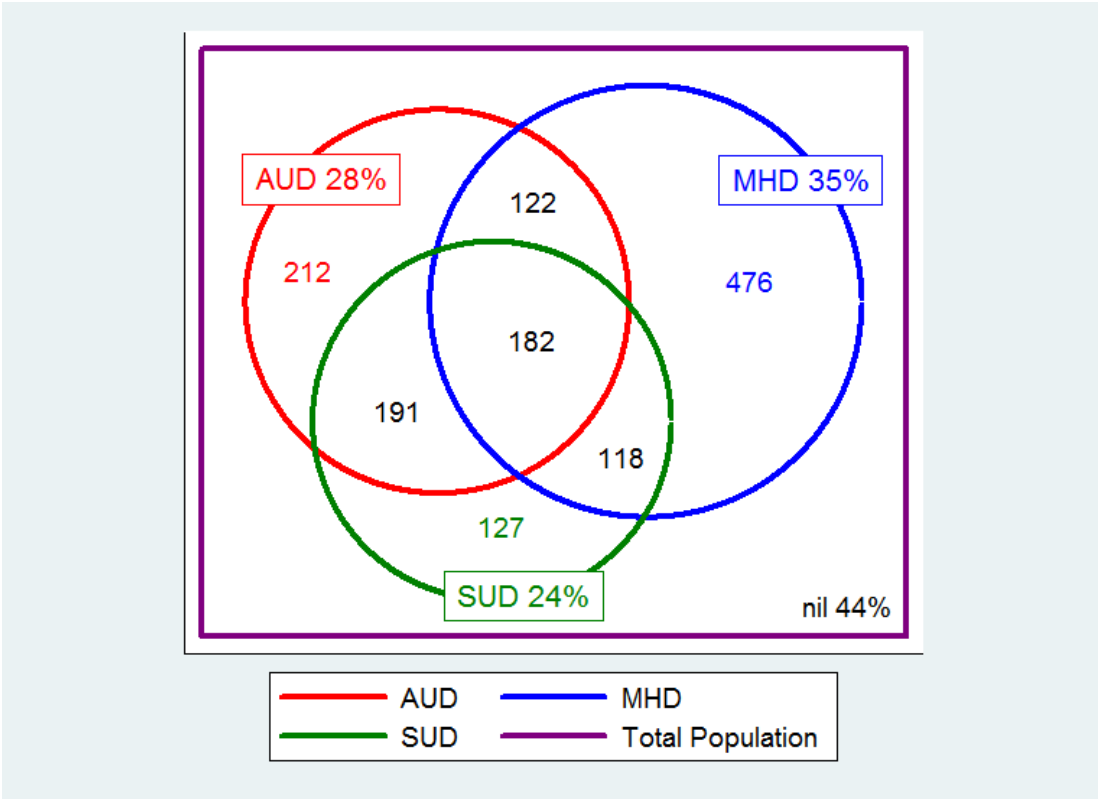
In young adulthood, those with comorbid disorders were more likely to exhibit problematic behaviour of their own, particularly aggression and delinquency, but also to be more vulnerable to the violent behaviour of others, particularly intimate partners.

Chapter 7: Other comorbidities

Preliminary studies (Chapter 4, Table 8) had indicated that those with comorbid alcohol and mental health disorders were also more likely to record illicit substance use disorders. In this section, the characteristics of young adults with illicit substance use disorders are compared to those with alcohol and mental health disorders, and the cross-over examined.

As can be seen in Figure 2, there is considerable overlap between those with mental health, substance and alcohol use disorders. Of those with alcohol use disorders, 43% also have a mental health disorder and 53% have an illicit substance use disorder.

Figure 2: Venn diagram of overlap between mental health, substance use and alcohol use disorders in MUSP young adults



In preliminary investigations, a 7-group variable was used to delineate the comorbidities. Each of these groups was exclusive (i.e. those in the AUD/MHD group had no SUD). As shown in Table 18 below, there are some consistencies between bivariate relationships for comorbid AUD/MHD and SUD/MHD, and some indication that tri-morbidity increases the strength of these relationships. Some differences are shown, but this modelling approach had limited utility in multivariable regressions due to the reductions in cell size and there was no ability to further delineate between types of substance abuse disorders. Hence, the Latent Class Modelling approach was adopted.

Table 18: Prevalence and bivariate relationships of multiple substance use and mental health disorder types

Modified version of Supplementary Table 2 from Intimate Partner Violence paper (Chapter 6)

		MHD	AUD	AUD/MHD	SUD	SUD/MHD	AUD/SUD	AUD/SUD/MHD
Prevalence	**N (%)**	926 (42%)	418 (19%)	196 (9%)	117 (5%)	118 (5%)	111 (5%)	173 (8%)
		OR (CI_{95})	**OR (CI_{95})**	**OR (CI_{95})**	**OR (CI_{95})**	**OR (CI_{95})**	**OR (CI_{95})**	**OR (CI_{95})**
Adult factors								
Gender	Female	**3.22** (2.45, 4.22)	**0.23** (0.16, 0.33)	**1.56** (1.04, 2.33)	**0.50** (0.34, 0.74)	**1.66** (1.15, 2.67)	**0.21** (0.12, 0.28)	**0.61** (0.44, 0.85)
Education	<Year 12	**1.74** (1.27, 2.37)	**2.16** (1.46, 3.19)	**2.53** (1.59, 4.01)	**3.06** (1.96, 4.76)	**3.88** (2.51, 6.00)	**3.84** (2.65, 5.58)	**3.99** (2.74, 5.80)
Adolescent factors								
Sexual abuse <16	Yes	**3.15** (2.12, 4.70)	0.59 (0.25, 1.39)	**4.64** (2.67, 8.06)	1.51 (0.72, 3.16)	**4.01** (2.25, 7.13)	1.65 (0.89, 3.07)	**5.98** (3.74, 9.55)
Left home early	Before 17	**2.96** (1.95, 4.49)	1.75 (0.94, 3.26)	**3.63** (1.98, 6.67)	**2.98** (1.59, 5.62)	**5.78** (3.35, 9.98)	**6.54** (4.12, 10.4)	**9.07** (5.81, 14.2)
Smoking	Any	**2.03** (1.32, 3.13)	**2.19** (1.21, 3.73)	**4.32** (2.50, 7.43)	**2.06** (1.06, 3.99)	**4.77** (2.71, 8.24)	**4.28** (2.62, 6.86)	**5.24** (3.30, 8.27)
Drinking	Regular	1.26 (0.72, 2.21)	**1.94** (1.03, 3.65)	**3.39** (1.75, 6.57)	**2.64** (1.31, 5.29)	**2.66** (1.29, 5.50)	**3.38** (1.92, 5.94)	**4.87** (2.90, 8.20)
Cannabis initiation age	Per year	1.01 (0.90, 1.13)	**0.85** (0.75, 0.96)	**0.83** (0.71, 0.97)	**0.76** (0.67, 0.87)	**0.78** (0.70, 0.92)	**0.65** (0.60, 0.75)	**0.62** (0.57, 0.69)
Internalising	YSR	**2.62** (1.94, 3.81)	0.89 (0.49, 1.61)	**2.11** (1.14, 3.50)	0.78 (0.37, 1.66)	**2.64** (1.55, 4.52)	1.18 (0.72, 2.19)	**2.10** (1.32, 3.43)
Externalising	YSR	**1.90** (1.14, 3.15)	**2.13** (1.14, 4.00)	**3.05** (1.54, 6.01)	**3.13** (1.60, 6.13)	**6.40** (3.59, 11.4)	**4.04** (2.03, 6.37)	**4.91** (2.91, 8.29)
Family of origin factors								
Socioeconomic disadvantage	Per point	**1.14** (1.03, 1.26)	**1.22** (1.04, 1.44)	**1.22** (1.02, 1.42)	0.96 (0.81, 1.14)	**1.24** (1.01, 1.47)	1.09 (0.94, 1.26)	**1.31** (1.14, 1.52)
Mother smoke	Any	**1.69** (1.35, 2.12)	**1.50** (1.10, 2.04)	**2.74** (1.87, 4.01)	**1.75** (1.20, 2.55)	**2.84** (1.98, 4.18)	**1.70** (1.24, 2.34)	**2.98** (2.16, 4.11)
Maternal mental distress	High	1.39 (0.90, 2.11)	1.18 (0.65, 2.11)	1.33 (0.66, 2.66)	1.17 (0.57, 2.42)	1.81 (0.97, 3.35)	1.55 (0.88, 2.72)	**2.01** (1.21, 3.34)
Maternal warmth	Low	**1.81** (1.21, 2.70)	1.07 (0.57, 1.99)	**2.99** (1.72, 5.17)	1.39 (0.78, 2.99)	**3.72** (2.19, 6.31)	0.92 (0.46, 1.83)	**2.46** (1.48, 4.08)

Adolescent factors recorded at 14 years, except age of cannabis initiation (recorded at 21 years)
Maternal factors recorded at baseline (during pregnancy) except maternal warmth (reported by child at 21 years)

Unlike earlier prospective studies which had used cannabis use as a proxy for illicit substance use disorders (171, 197), we included a range of illicit SUD, as well as alcohol use disorders, depression and anxiety in our analysis. From this, four latent classes were identified. These were: low-disorder; depression and anxiety/low substance use problems; alcohol/cannabis/low mental health problems; and poly-substance use/moderate mental health problems. Preliminary analyses indicated that the poly-substance/mental health problem group were truly users of multiple substances, with an average of five SUDs per member, whereas the AUD/MHD comorbid group from previous analyses had fewer (mean=1.7). Interestingly, the poly-substance group tended to have fewer mental health disorders (mean = 1.4) than the AUD/MHD comorbid group (mean = 1.8), and were more likely to be male. These groupings also differed somewhat from the analyses which included only cannabis disorders (171, 197), suggesting potential heterogeneity in the factors underlying illicit substance use disorders. Our previous papers had identified a range of individual and family factors as predicting comorbid mental health and alcohol use disorders. In this study, we were able to test whether the factors underlying comorbidity of illicit substance use and mental health disorders were different. This work is described in paper 7.1.

7.1 Comorbid poly-substance use and mental health disorders

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Title:

Predictors of comorbid poly-substance use and mental health disorders in young adults – a latent class analysis

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Abstract

Aim: Co-occurrence of mental health and substance-use disorders adds complexity to already-significant health burdens. This study tests whether mental health disorders group differently across substance use disorder types and compares associations of early factors with the development of differing comorbidities.

Design: Consecutive antenatal clinic attendees were recruited to the longitudinal Mater-University of Queensland Study of Pregnancy (MUSP). Mother/offspring dyads were followed over 21 years.

Setting: Mater-Misericordiae Public Hospital, Brisbane, Australia.

Participants: MUSP offspring with maternal baseline information (n=7223), offspring behaviour data at 14 (n=4815) and psychiatric diagnoses at 21 (n=2575).

Measurements: The Composite International Diagnostic Interview yielded lifetime diagnoses of mental health (MH) and substance use (SU) disorders for offspring, then latent class modelling predicted membership of poly-disorder groups. We fitted the resulting estimates in multinomial logistic regression models, adjusting for maternal smoking, drinking and mental health, adolescent drinking, smoking and behaviour and mother-child closeness.

Findings: Fit indices (BIC=12415; AIC=12234) from LCA supported a four-class solution: low-disorder (73.6%), MH/low-SU-disorder (10.6%), alcohol/cannabis/low-MH-disorder (12.2%), and poly-SU/moderate-MH-disorder (3.5%). Adolescent drinking predicted poly-SU/MH-disorders (OR 3.34; CI_{95}1.42-7.84), while externalising predicted membership of both SU-disorder groups ($OR_{alcohol/cannabis}$ 2.04, CI_{95}1.11-3.75; $OR_{poly\text{-}substance}$ 2.65, CI_{95}1.1-6.08). Maternal smoking during pregnancy predicted MH (OR 1.53, CI_{95}1.06-2.23) and alcohol/cannabis-use disorders (OR 1.73; CI_{95}1.22-2.45). Low maternal warmth predicted mental health disorders only (OR 2.21, CI_{95}1.32-3.71).

Conclusions: Mental health disorders are more likely in young adults with poly-substance-use disorders than those with alcohol/cannabis use disorders. Predictors of comorbid mental health/poly-substance use disorders differ from those for alcohol/cannabis use disorders, and are detectable during adolescence.

Introduction

Substance use disorders are frequent and commonly co-occur with mental health disorders such as depression and anxiety (1-4). Between them, mental health and substance use disorders contribute 184 million disability adjusted life years to the global burden of disease each year (5), with the majority of this being experienced by younger persons (6). This co-occurrence is also associated with poorer individual health outcomes (7-10). As a result the antecedents of this comorbidity are of great interest to recommend appropriate policies for prevention and treatment.

There has been considerable focus on the varying structures of this comorbidity (1, 11-16), and only larger studies have had the power to separately examine risk factors associated with licit and illicit substance use disorders (17-20). These have found anxiety and depression to be strongly associated with both alcohol and illicit substance use disorders, with family mental health disorders also important. Fewer still have examined patterns of use for specific illicit substances (21-23). Although cannabis use is common among adolescents and young adults, poly-substance use is also common, and distinct clusters of substance use types have been identified (24-27). Young people tend to cluster into groups who use predominantly alcohol, or cannabis, or multiple substances (27, 28). There is some evidence that these clusters may be differentially associated with mental health disorders, with suggestions that cannabis use disorder is more strongly associated with depression and anxiety than is alcohol use, while poly-substance use disorders are associated with aggression and psychoses (28-30).

There is an extensive literature on the factors which precede illicit drug use and disorders (as reviewed by Fergusson (31) and Blanco (32) and colleagues). Predictors include gender, parent behaviours and psychopathology, child temperament and exposure to early abuse, but some differences have been shown between the antecedents of use and disorder. Many of the predictors are also common to the development of alcohol and mental health disorders (33, 34), but less is known about the development of specific comorbidities of substance use and mental health disorders in the general population. Our research group reported recently that maternal smoking and low mother-child warmth were associated with development of alcohol/mental health disorder comorbidity in a population-based prospective cohort (35). Two other prospective studies included cannabis use disorders in their study of substance use groupings, and found paternal closeness

important for cannabis, but not alcohol/mental health disorder groups (29), and that high school completion did not differentiate between alcohol- and cannabis-use-disorder groups (30). No longitudinal studies however have examined the antecedents of other illicit substance use/mental health disorder comorbidity in non-clinical samples using prospectively-collected measures.

This paper aims to address the gaps in the existing evidence regarding the comorbidities of different classes of substance use disorder with mental health disorders, and the antecedents of these conditions. We examine clustering of alcohol, cannabis and other illicit substance use disorders with common mental health disorders in a longitudinal study of young adults. The prospective design of this study allows us to examine family and individual factors which may contribute to the development of each of these clusters. We use latent class analysis (LCA) to characterise the clustering of substance use disorders with mental health disorders (2, 16, 36) and multinomial regressions to identify early-life factors which may differentiate the development of clustered disorders. We test whether 1) mental health disorders are associated with the different classes of substance use disorders seen in young adults, and 2) compare the early-life factors associated with these disorder groupings.

Methods

Sample

The Mater-University of Queensland Study of Pregnancy (MUSP) is a birth cohort study of mothers and children. Mothers were enrolled at their first antenatal clinic visit to the Mater Misericordiae Public Hospital in Brisbane between 1981 and 1983, with 7223 eligible participants at baseline. Mother-child dyads were followed up at birth, 5 days and 6 months, then 5, 14 and 21 years after birth with 4815 members of the offspring cohort participating at age 14 and 3778 members (52%) participating at age 21. Only offspring for whom complete data on mental health and alcohol use disorders at age 21 were available (n=2539; 35%) were included in the main analyses. The MUSP was approved by the Human Ethics Review Committee at the University of Queensland and has been extensively described elsewhere (37, 38). At enrolment and follow ups, participants gave written, informed consent.

Outcome variables

At the 21–year follow up, 2575 offspring participants (36% of baseline) were administered the mental health and substance use disorders modules of the Composite International Diagnostic Interview (CIDI). Responses were coded to yield DSM-IV disorder diagnoses for occurrence over the participant's lifetime. From these, we generated seven binary DSM-IV diagnoses, combining substance abuse and/or dependence into single 'disorder' categories as per DSM-V: any anxiety disorder, any depressive disorder, alcohol use disorder (AUD), cannabis use disorder (CUD), stimulant (amphetamine or cocaine) use disorder, depressant (opiate or sedative) use disorder and hallucinogen (LSD) use disorder.

Early life factors

Participants' adolescent drinking (39), smoking, and behaviour problems (40) have been associated with later alcohol or mental health problems. We used participants' drinking (less than 3 drinks/at least 3 drinks per occasion, according to NHMRC guidelines (41)) and smoking (nil/any), self-reported at age 14. Behavioural problems were also assessed at 14 years using the Achenbach Youth Self Report (42). Consistent with Achenbach's definition of case-ness, we used the Internalising and Externalising Problems scales, with those falling into the highest 10% of each scale scores defined as having behaviour problems (42).

Early (during pregnancy) measures of maternal age, smoking, drinking, anxiety and depression were included as covariates, as previous studies have shown these to be associated with both mental health and substance use problems in their offspring (34, 43, 44). Mothers reported how often they drank alcohol and how many drinks they consumed per occasion. These were combined to generate three categories according to Australian National Health and Medical Research (NHMRC) Guidelines: non-drinkers, regular drinkers (more than a few times/month) who did not binge (never >4 drinks/session) and drinkers who did binge (>4 drinks/session). Any self-reported maternal daily smoking was coded as positive.

Depression and anxiety were assessed using the Delusions-Symptoms-States Inventory (DSSI (45)), which contains anxiety and depression subscales. The depression subscale has been found to correlate strongly with other depression scales, including Beck's Depression Inventory (46). Anxiety and depression are typically recorded as cases where at least four of seven symptoms from that subscale are endorsed (45) (depression α=0.88; anxiety α=0.84). A combined DSSI

score summing all symptoms endorsed (α=0.90) has been used to indicate mental distress (47).

Participants' perception of maternal warmth and involvement during childhood (48) were measured using the Parker Bonding instrument. As parental warmth is a defining component of authoritative parenting, which has been found to be protective of substance use (49), we used that subscale in our analyses (α=0.88). The Parker Bonding and DSSI scores were dichotomised for consistency with the YSR such that lowest 10% for warmth and highest 10% for distress, which constitute greater risk for single conditions, were positive.

Socio-economic disadvantage from the participants' family of origin was estimated using a scale incorporating levels of parent education, employment and family income (50). This was used as a continuous variable such that higher scores indicated greater disadvantage, previously associated with increased likelihood of comorbidity (50).

In sensitivity analyses, we also examined maternal use of cannabis prior to pregnancy (self-reported at baseline; nil/any) and offspring childhood sexual abuse (self-reported at 21 years; no/yes), both of which have been reported in the literature as associated with development of substance use disorders. Age of first use for cannabis by offspring (also associated with later substance use disorders) was self-reported by participants at 21 years during the main MUSP questionnaire. This was categorised as less than 15 years (consistent with measures of drinking at 14 years), 15-17 years, and 18-plus years.

We also assessed whether offspring risk-taking tendencies (as a measure of disinhibition, suggested to be related to poly-substance use disorders (51)) may be a component of an underlying trait associated with different classes of substance use disorder. Risk-taking/sensation seeking was assessed at 21 years using a scale comprising 16 items (α=0.82). In line with other factors, this was dichotomised such that the highest 10% of scores were coded as positive.

Analytical approach

Latent Class Analysis

We used latent class analysis (LCA) to categorise young adults by poly-substance use disorder, using the seven binary DSM-IV diagnoses as indicator variables in Mplus version 6. LCA is a technique used to identify unobserved heterogeneity in a

population, assigning individuals to empirically derived classes, with the optimal number of classes determine by a combination of the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC), the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (A-LMRT), and the bootstrap likelihood ratio test (BLRT) (52). After determining the 'best' fitting model which ranged from 2 to 5 classes (no more than 5 classes were tested as we included only 7 indicator variables), individuals' posterior probabilities (i.e., the probabilities of each individual belonging to each of the classes) were then exported to Stata version 12.1 for regression analysis in which the class variable was used as a multinomial outcome. To account for the uncertainty in the class membership we used 100 random draws of each participant's posterior probability to create 100 datasets, with the variability across these datasets reflecting the uncertainty (53).

Multinomial logistic regression

Bivariate associations were examined between latent class and maternal mental health, socio-economic disadvantage, alcohol and tobacco use, mother-child warmth, participant gender and adolescent smoking, drinking and behaviour problems. Multivariable regression models were constructed, using factors whose relationship was significant at bivariate level and the low-disorder class as reference. To compare the poly-substance class with other disorder classes, we repeated these analyses, using each class in turn as reference. In sensitivity analyses, we adjusted for childhood sexual abuse, maternal use of cannabis prior to pregnancy and offspring risk-taking, and examined the contribution of early onset of cannabis use.

Attrition Analysis

Finally, we assessed how attrition may have affected our results, using a multivariable regression model of loss to follow up with baseline predictors (maternal age, marital status, anxiety, depression, drinking and smoking and participant gender). We used inverse probability weighting with robust estimates for standard errors to account for those lost to follow-up from the 7223 original cohort members, according to recommendations (54, 55). We fitted baseline predictors in a logistic regression model (response vs nonresponse as outcome) to determine weights for each individual using the inverse probability of response. We then repeated the multivariable analyses including the weighting adjustments, and compared weighted results to the complete case analyses. Unless otherwise stated, all analyses were undertaken using STATA version 12.1 (StataCorp, USA).

Results

Results from the LCA suggested that a four-class solution was the best fit for the data (Table 1). Although the five-class solution presented the lowest AIC value, statistical significance for both likelihood ratio tests decreased markedly above four classes. These four classes of disorder are shown in Figure 1, with one class exhibiting high probabilities of alcohol use disorder (AUD), cannabis use disorder (CUD) and stimulant use disorder, in addition to moderate probabilities of all other psychiatric diagnoses (PSUD/MHD; n=91; 4% of sample). The three other classes consisted of a normative group (n=1888; 74% of sample) with low probabilities of all diagnoses, a class with high probabilities of alcohol and cannabis use disorders (AUD/CUD; n=314; 12%), and a class with high probabilities of affective and anxiety disorders (MHD; n=272; 11%).

Tobacco disorders, also diagnosed using the CIDI, were excluded from the latent class modelling as they distinguished people poorly between classes. Models including nicotine dependence resulted in unacceptably low entropy (approximately 0.70 for all classes) so these were omitted from this analysis. Bivariate associations showed that the poly-substance/mental health disorder group had the highest likelihood of tobacco disorders (OR 10.44; CI_{95} 6.56, 16.62 compared to the normative group), and twice that of the alcohol/cannabis and MHD groups (P<0.002).

In this fully adjusted model (Table 3), drinking at 14 years was associated only with the poly-substance group (OR 3.57; CI95 1.53, 8.34). Externalising behaviour problems at 14 years and male gender predicted membership of both the AUD/CUD group and the PSUD/MHD group. Female gender, low maternal warmth and internalising at 14 years predicted membership in the MHD group. Maternal smoking predicted both mental health problems and poly-substance use disorders. Childhood sexual abuse was an independent predictor of all three disorder groups but did not alter the relationships reported in the multivariate model. High offspring risk-taking tendencies predicted membership of both SUD classes ($OR_{AUD/CAN}$ 2.63, CI_{95} 1.68, 4.11; $OR_{PSUD/MHD}$ 3.19, CI_{95} 1.57, 6.49), and accounted for a proportion of the relationship between adolescent externalising and PSUD/MHD (OR 2.29, CI_{95} 0.94, 5.58) but did not substantively alter other relationships. Mother's use of cannabis was related at bivariate level to membership of the alcohol/cannabis (OR 1.67; CI_{95} 1.18, 2.35) and poly-substance groups (OR 1.88; CI_{95} 1.08, 3.27), but not in the

multivariate model. In a final sensitivity analysis, inclusion in the multivariate model of factors not reaching statistical significance at bivariate level (Supplementary Table 1) did not substantively alter the relationships shown in in Table 3.

Those included in the final analysis were less likely to be male, have mothers who smoked or experienced greater mental distress during pregnancy, or have come from families with greater socio-economic disadvantage (Supplementary Table 2). They were also more likely to have smoked or exhibited externalising behaviour problems at 14 years. However, after mutual adjustment, only maternal smoking was significantly related to exclusion from the final model. Results incorporating inverse probability weightings were substantively unchanged from the complete case analyses (Supplementary Table 3).

Discussion

This is the first paper to prospectively examine the early life factors related to the different combinations of mental health and substance use disorders in young adults. We showed that young adults with illicit substance use disorders segregated into two groups; one with alcohol and cannabis (but not other illicit substance) use disorders, and the other with multiple illicit substance use disorders. Mental health disorders were more likely in the latter, poly-substance group than in the alcohol/cannabis group, and adolescent drinking predicted membership of this most disordered group.

The latent classes we identified are somewhat similar to those seen in large population based studies, which identify a group using predominantly alcohol, a limited-range substance use group (predominantly alcohol/cannabis) and an extended-range poly-substance use group or groups (24). These studies tend to use measures of use, rather than disorder, and although several have found an association between psychological distress and poly-substance use (26, 56, 57), only one has shown that mental health *disorders* (anxiety and mood disorders) were associated with extensive poly-substance use (22). It may be as suggested by Connor (24) that our study was not large enough to separate ecstasy and stimulants from other illicit substances, or it may be that the consideration of mental health disorders suggests other delineating factors for the groups. The largest population based study (n=8538), which did include mental health disorders, found classes most similar to ours (22), suggesting that sample size was not an issue of concern.

The existing large population based studies, which have investigated latent classes of poly-substance use and mental health problems, are mostly cross-sectional with

no capacity to prospectively consider early life predictors, and seldom describe disorders. The present study is one of few to investigate life course predictors of these disorder-based classes. Two longitudinal studies have done similar work, but have included disorders of only cannabis use rather than other illicit substance use. Although both found a four-class solution, groupings differed from ours. Young adults in the Seattle Social Development Project (30) cohort formed classes where anxiety and depression grouped with cannabis use disorder in one class, but unlike our solution, found just anxiety linked to alcohol use disorders in another group. Young adults from the Offspring of Twins study (29) formed groups where anxiety and depression were most likely in those with moderate alcohol/cannabis probability, rather than the highest.

Although neither of these analyses included illicit substance disorders other than cannabis, which may have influenced the groupings, some of our findings regarding early predictive factors are consistent, with few predictors differentiating between the AUD/CUD and PSUD/MHD groups (29, 30, 58). Childhood sexual abuse predicted membership of both the alcohol/cannabis and the poly-substance groups, and adolescent internalising problems were not associated with either. Similarly, low mother-child closeness was unrelated in our analyses to either group (29). Although this factor has been observed to contribute to alcohol/mental health disorder comorbidity by some (35), our negative finding is congruent with an earlier study which used structural equation modelling of poly-substance use. In that study, Galaif and colleagues reported that parental support and bonding only reduced the likelihood of poly-substance use in adolescence, but not in adulthood (59), which is consistent with our findings based on a population of young adults.

In contrast to the Seattle sample, we found that adolescent externalising was associated with membership of both alcohol/cannabis and poly-substance groups, but our finding is supported by other reports of adolescent externalising being related to poly-substance use disorders in adulthood (31).

Our work, which extends previous studies by including other illicit substance use disorders, questions whether cannabis use disorders are representative of poly-substance use disorders. The association of mental health disorders with the poly-substance group, rather than the alcohol/cannabis group, suggests that young adults with cannabis use disorders are not a homogeneous group. We also found that drinking in adolescence distinguished the poly-substance group from the

alcohol/cannabis group. The relationship between early drinking and adult poly-substance use disorders was also reported by Fergusson and colleagues (31), but that study suggested that the impact of most childhood factors on poly-substance use disorders was mediated via cannabis use, in line with the concept of cannabis as a gateway drug (60). In a supplementary analysis, we examined the contribution of early (before 15 years) onset of cannabis use, finding that it was strongly associated with membership of the PSUD/MHD group (OR 66.7, CI_{95} 16.3, 272.2). This seems to support the findings of Fergusson and colleagues. However, the age of cannabis use onset was retrospectively reported in our study, and may have been biased by participants' recall of substance use status, therefore this result must be treated with caution.

Our study has a number of strengths. The large unselected cohort provides a representative sample of size comparable to several population based LCA studies, but with the advantage of substance use and mental health disorder diagnoses and prospective measures for potential early-life contributing factors. Our measures of mental health, substance and behavioural problems are robust and well characterised, and the use of latent class analysis allows us to examine the groupings of mental health and substance use disorders according to unobserved latent characteristics. However, it must be taken in the context of some limitations. Although we assessed the impact of maternal history of substance use and mental distress, information on paternal factors was not available and may have been influential. As with many longitudinal studies, our sample has been subject to considerable attrition, with only 35% of the original cohort included. Nonetheless, the results of our inverse probability weightings were not substantively changed from the complete case analyses, giving us confidence in this report.

Taken together these results suggest that the comorbidity of mental health with alcohol use disorders that we described in earlier reports (35) is different in its antecedents to that with illicit substance use disorders. Mental health disorders appear more likely among those with poly-substance use disorders than those with alcohol and cannabis use disorders, and the early use of alcohol and cannabis appear to contribute to the development of poly-substance use disorders. This is supported by recent work suggesting that different comorbidities of cannabis use disorders have differing genetic contributions, and that environmental influences are stronger for some combinations than others (61). Our work extends the literature in that we have been able to examine the grouping of mental health disorders with a

broad range of licit and illicit substance use disorders, finding that the cannabis use disorders considered in earlier longitudinal studies of this type are not homogeneous and confirming that early use of substances presents a risk for the development of poly-substance use disorders and associated mental health problems.

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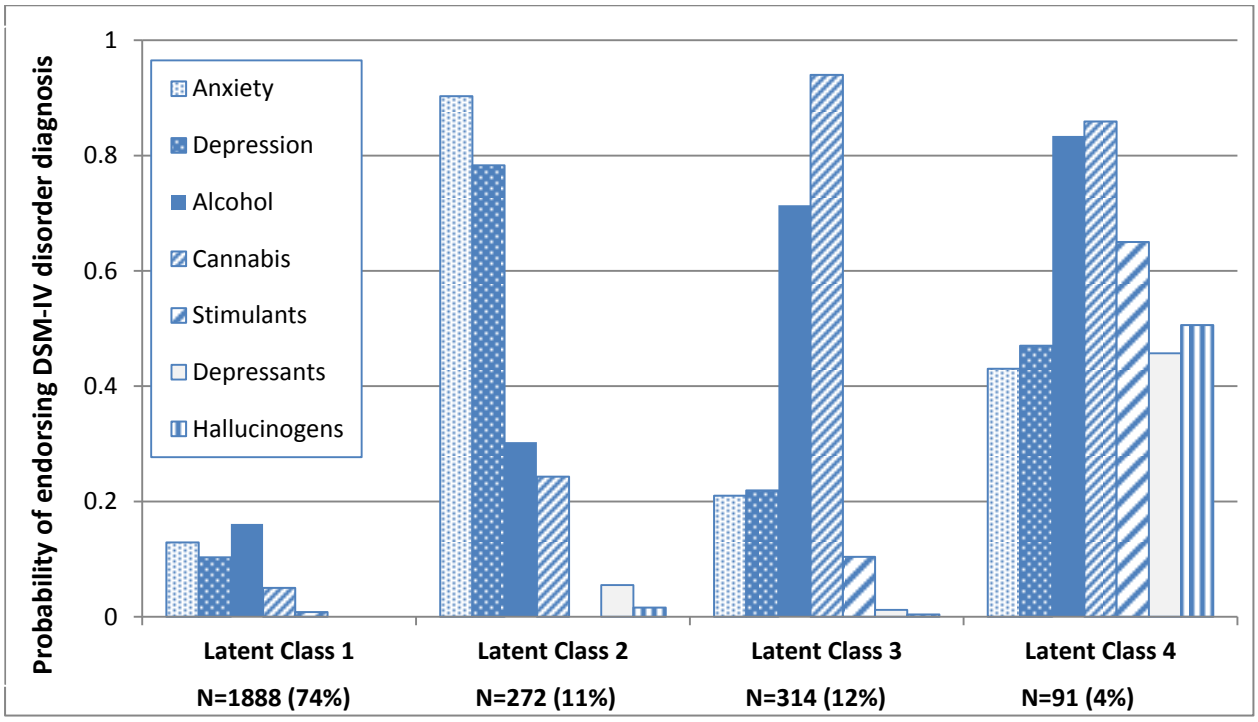
Table 1: Fit indices of Latent Class Analysis of seven lifetime DSM-IV psychiatric diagnoses [from 2 to 5 classes among the full-sample; *n* = 2565]

Solution	BIC	AIC	Entropy	A-LMRT	BLRT
2 class	12634	12546	0.77	<0.001	<0.001
3 class	12451	12316	0.77	<0.001	<0.001
4 class	**12415**	12234	0.79	<0.001	<0.001
5 class	12456	12228	0.85	0.014	0.030

Note: Bayesian Information Criterion (BIC); Akaike Information Criterion (AIC); Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (A-LMRT); Bootstrap Likelihood Ratio Test (BLRT).

Figure 1: Latent classes of substance use/mental health disorders in young adults



Latent Class 1: normative
Latent Class 2: **AUD/CAN** (alcohol and cannabis use disorders)
Latent Class 3: **MHD** (anxiety and depression)
Latent Class 4: **PSUD/MHD** (alcohol, cannabis and other illicit substance use disorders plus anxiety/depression)

Table 2: Distribution and bivariate relationships of early maternal and child factors with LCA class at young adulthood

	Latent Class 2 MHD		Latent Class 3 AUD/CAN		Latent Class 4 PSUD/ MHD	
	%	OR (CI_{95})	%	OR (CI_{95})	%	OR (CI_{95})
Maternal factors						
Socio-economic disadvantage [a]	-	**1.23** (1.08, 1.39)	-	**1.16** (1.03, 1.31)	-	1.10 (0.90, 1.33)
Smoking [a]	47	**1.83** (1.38, 2.42)	47	**1.70** (1.29, 2.24)	47	**1.71** (1.07, 2.72)
Drinking – mod. [a]	66	0.94 (0.67, 1.32)	69	1.24 (0.87, 1.76)	68	1.29 (0.72, 2.30)
Drinking - binge [a]	11	1.28 (0.77, 2.14)	13	1.59 (0.96, 2.64)	11	1.36 (0.57, 3.26)
Anxiety [a]	12	1.35 (0.85, 2.15)	9	1.06 (0.67, 1.68)	19	1.75 (0.94, 3.26)
Depression [a]	4	1.24 (0.58, 2.63)	5	1.59 (0.83, 3.07)	8	2.08 (0.77, 5.59)
Mental distress	11	1.59 (0.99, 2.55)	9	1.35 (0.83, 2.19)	15	**2.13** (1.10, 4.13)
Pre-pregnant cannabis use [a]	17	1.35 (0.92, 1.97)	22	**1.67** (1.18, 2.35)	21	**1.88** (1.08, 3.27)
Low warmth [b]	18	**2.27** (1.50, 3.45)	12	1.38 (0.86, 2.20)	16	1.86 (0.95, 3.63)
Child characteristics						
Gender (female)	79	**2.86** (2.03, 4.01)	29	**0.40** (0.29, 0.55)	34	**0.49** (0.31, 0.77)
Age	-	0.98 (0.95, 1.01)	-	0.99 (0.97, 1.02)	-	0.97 (0.93, 1.02)
Drinking [c]	10	**2.01** (1.19, 3.39)	11	**2.30** (1.39, 3.81)	19	**4.68** (2.47, 8.86)
Smoking [c]	16	**2.16** (1.39, 3.35)	18	**2.46** (1.64, 3.68)	24	**3.81** (2.16, 6.69)
Internalising [c]	29	**2.88** (2.00, 4.14)	12	1.08 (0.67, 1.75)	17	1.57 (0.81, 3.04)
Externalising [c]	12	**2.20** (1.31, 3.68)	17	**2.83** (1.78, 4.49)	19	**4.20** (2.25, 7.84)
Childhood sexual abuse [d]	29	**4.68** (3.20, 6.84)	9	**1.79** (1.11, 2.90)	29	**5.10** (2.93, 8.90)
Risk-taking [d]	9	1.14 (0.69, 1.88)	21	**2.69** (1.83, 3.95)	20	**3.42** (1.94, 6.05)

MHD = anxiety/depression; AUD/CAN = alcohol and cannabis use disorders only; PSUD/MHD = alcohol and illicit substance use disorders plus anxiety/depression

[a] Maternal factors measured in pregnancy

[b] Mother-child warmth during adolescence

[c] Offspring factors measured at 14 years

[d] Self-reported at 21 years

Table 3: Multinomial logistic regression models of LCA class at 21 years, as predicted by early maternal and child factors

	Latent class 2 MHD	Latent class 3 AUD/CAN	Latent class 4 PSUD/MHD
Factor	**OR (CI_{95})**	**OR (CI_{95})**	**OR (CI_{95})**
Gender (female)	**2.28** (1.50, 3.44)	**0.36** (0.25, 0.52)	**0.30** (0.16, 0.59)
Maternal smoking in pregnancy [a]	**1.51** (1.04, 2.18)	**1.76** (1.25, 2.48)	1.26 (0.68, 2.33)
Low mother-child warmth [b]	**1.85** (1.07, 3.19)	1.45 (0.81, 2.58)	1.73 (0.73, 4.07)
Child drinking at 14	1.65 (0.84, 3.21)	1.57 (0.83, 2.99)	**3.57** (1.53, 8.34)
Child smoking at 14	1.35 (0.74, 2.44)	1.68 (0.96, 2.94)	2.03 (0.90, 4.59)
Internalising at 14 [c]	**1.92** (1.22, 3.02)	0.94 (0.52, 1.70)	1.15 (0.49, 2.72)
Externalising at 14[c]	1.39 (0.71, 2.72)	**1.94** (1.07, 3.52)	**2.58** (1.10, 6.02)
Childhood sexual abuse[d]	**3.09** (1.87, 5.10)	**2.23** (1.22, 4.07)	**4.69** (2.06, 10.67)

MHD= mental health disorder (anxiety and/or depression); AUD/CAN = alcohol and cannabis use disorders only; PSUD/MHD = alcohol and illicit substance use disorders plus anxiety/depression

[a] Maternal smoking measured in pregnancy

[b] Mother-child warmth during adolescence

[c] Offspring behaviour problems measured at 14 years

[d] Self-reported at 21 years

Model is fully adjusted for all factors above, plus socio-economic disadvantage and maternal anxiety/depression in pregnancy.

Summary of Chapter 7

This study found some differences between the previously-identified predictors of alcohol/mental health comorbidity and illicit substance/mental health comorbidity. Adolescent drinking and externalising problems predicted both comorbidities. Early maternal smoking and low mother-child warmth were linked only to alcohol-based comorbidity, not to illicit substance use/mental health disorders. The age of cannabis initiation accounted for the association of childhood drinking with poly-substance use and was a strong predictor of poly-substance use disorders, but as discussed in the manuscript, there are some concerns regarding the validity of this measure. This paper demonstrated that illicit substance use disorders are associated with mental health disorders but are not homogeneous in these links, and that although many of those with comorbid alcohol use and mental health disorders may also have illicit substance disorders, the two comorbidities are not interchangeable.

Chapter 8: General discussion

Introduction

The prevalence of comorbid substance and mental health disorders, as noted extensively in clinical reports (65, 68, 273) and population based studies (22, 23, 39, 40, 42, 274), indicates this is an issue of clinical and public health relevance as it places a considerable burden on the well-being of individuals. The development of comorbidity has been studied in longitudinal frameworks (12, 143, 269, 275) but there have been few direct comparisons of comorbidity to single disorders (155, 197, 276, 277). Fewer still have used broadly representative cohorts (171). Such a comparison is useful in identifying factors specifically influencing the development of comorbidity, but it is also useful in the discussion of whether comorbidity should be considered a distinct entity, rather than an extension of its constituent mental health or alcohol use disorders. A thorough understanding of the inter-relationship between contributing factors, as developed here, is essential if considering targets for intervention. In addition, only a few studies have questioned whether the co-occurrence of mental health disorders with alcohol, the legal and most commonly-used substance, has different antecedents to that involving illicit substance use disorders (171, 197).

This research program aimed to answer three main questions:

1. What are the prevalence, types and onset of comorbidities of mental health and alcohol use disorders in young Australians?

2. Are there factors from different phases of the life cycle which predict the onset of comorbidity, which differentiate it from its constituent disorders, and which may present targets for intervention?

3. Are there risk factors across the life span which differentiate alcohol-based comorbidity from illicit substance use/mental health comorbidities?

Here we discuss the implications of these findings and suggest areas for future research.

Descriptive findings

At 21 years, we found that approximately 59% of the sample had experienced a DSM-IV disorder during their lifetime. Of these, half (28% of the sample) had experienced a lifetime alcohol use disorder, and a quarter (12% of the sample) recorded alcohol and

mental health disorders which co-occurred within a 12 month period, and so could be considered comorbid. Those with alcohol use disorders were one and a half times more likely to have a mental health disorder than those without, and the relationships of alcohol with anxiety-based and depressive disorders were similar, allowing us to combine the mental health disorders into a single group. The prevalence figures reported here are consistent with estimates from large population studies in the US (NESARC(88) and NCS(22)), the UK (Mental Health(6)), the Netherlands (NESDA(190)) and other European countries (40), as well as some prospective studies (278). The age of onset of this comorbidity in the MUSP cohort ranged from 15 to 22 years, indicating that late adolescence/early adulthood is indeed a sensitive time for its development (22, 279), but our analyses using the Healthy Neighbourhoods Study suggest that identification of at-risk individuals may take place even earlier.

How early can we detect comorbidity?

Indicators of developing co-occurring disorders may emerge well before late adolescence. National studies have reported comorbidity in 13-17 year olds (22) and prospective studies in the mid-teens (279), but we were able to detect co-occurring drinking and depressive symptoms in a sample of even younger, predominantly pre-teen, students. The prevalence of this co-occurrence in the Healthy Neighbourhoods group was about half that of disorder comorbidity in MUSP young adults, but the association between recent drinking and depressive symptoms was similar to that between AUD and depressive disorders in the MUSP. These ratios are also consistent with large population studies from Australia (280) and overseas (21, 274, 281).

In the MUSP 14-year-olds, a small group was identified with co-existing drinking and internalising problems. This condition predicted comorbidity in early adulthood, after accounting for adolescent smoking and maternal disorders, suggesting it may have been a ‘precursor’ group. Taken together, these results show that early symptoms of later co-occurring disorders may be detected during the pre-teen years.

Are some phases of life more important in the development of comorbidity?

Even prior to pregnancy, socio-economic disadvantage derived from the family of origin distinguished comorbidity from single disorders. Multiple domains of disadvantage were involved, with evidence of a dose response that was not seen for single disorders. This builds on other findings that both low income and poor educational backgrounds were

linked to comorbidity, but emphasises the importance of parental education over financial concerns in this group. Although this concurs with some reports (8, 190, 191), it contrasts with others (187, 188), suggesting that where there is greater inequality across a socio-economic indicator, disadvantage in that domain plays a more significant role. This also highlights the importance of considering multiple indicators when comparing populations. Additionally, this provides the first indication that accumulating socio-economic disadvantage increases the odds of the more complex condition.

During pregnancy, maternal health behaviours were important. Mothers' smoking predicted offspring comorbidity over single disorders, again with some evidence for a dose response relationship. The independence of this link from smoking at other time points suggest an impact specific to pregnancy. This is supported by other reports of in-pregnancy smoking being associated with childhood behaviour problems, learning difficulties and psychological disturbances, all related to comorbidity (282-284). With regard to maternal drinking in this period, any drinking predicted adult alcohol use disorders, but only binge drinking was linked to comorbidity. Together with the independence from SES, these relationships may point to some physiological disturbance of gestation. Certainly smoking in pregnancy has been linked to changes in DNA methylation and the resulting altered gene expression which has been implicated in children's depression (283). Methylation of stress-response genes in women who smoked and drank has also been linked to their own alcohol and mental health disorders (285). Interestingly, although these prenatal influences could be considered stressors on foetal development, child birth-weight and early IQ were not linked to comorbidity, suggesting that the *in utero* disturbances did not manifest via such measures.

In light of evidence from other reports for the heritability of individual and dual disorders (134, 144, 146, 286), our results were mixed. Our finding that maternal mental health was associated with offspring comorbidity only when present during childhood, and not in adolescence, may suggest the early relationship was due to the child learning anxious behaviour from the mother as seen in other studies (153), rather than inheriting the disorder. In contrast, maternal binge drinking before pregnancy was associated with increased odds of comorbidity, but this was not the case for such drinking at 5 and 14 years, suggesting a heritable trait rather than a learned behaviour. Conversely, paternal alcohol problems more strongly predicted comorbidity when the father and child cohabited, which points to a behaviour modelling effect rather than heritability.

We did not find that family practices had a strong influence on the development of comorbidity. This is inconsistent with existing evidence that parenting behaviours such as control, limit setting and physical punishment are linked to anxiety, depression and alcohol problems (193, 287-289). It is possible that our parenting measures were less robust than others such as those in observational studies, or that parenting behaviours have more impact at other time points (such as adolescence), at which these factors were not assessed in the MUSP.

In contrast, the strong link we report between low mother-offspring warmth during childhood and mental health/alcohol comorbidity in young adults is consistent with our findings from the Healthy Neighbourhoods sample, where family closeness was associated with lower odds of concurrent drinking/depressive symptoms. This may indicate that the quality of the relationship, rather than specific parenting practices, is important, as has been found in some studies (162, 171, 290).

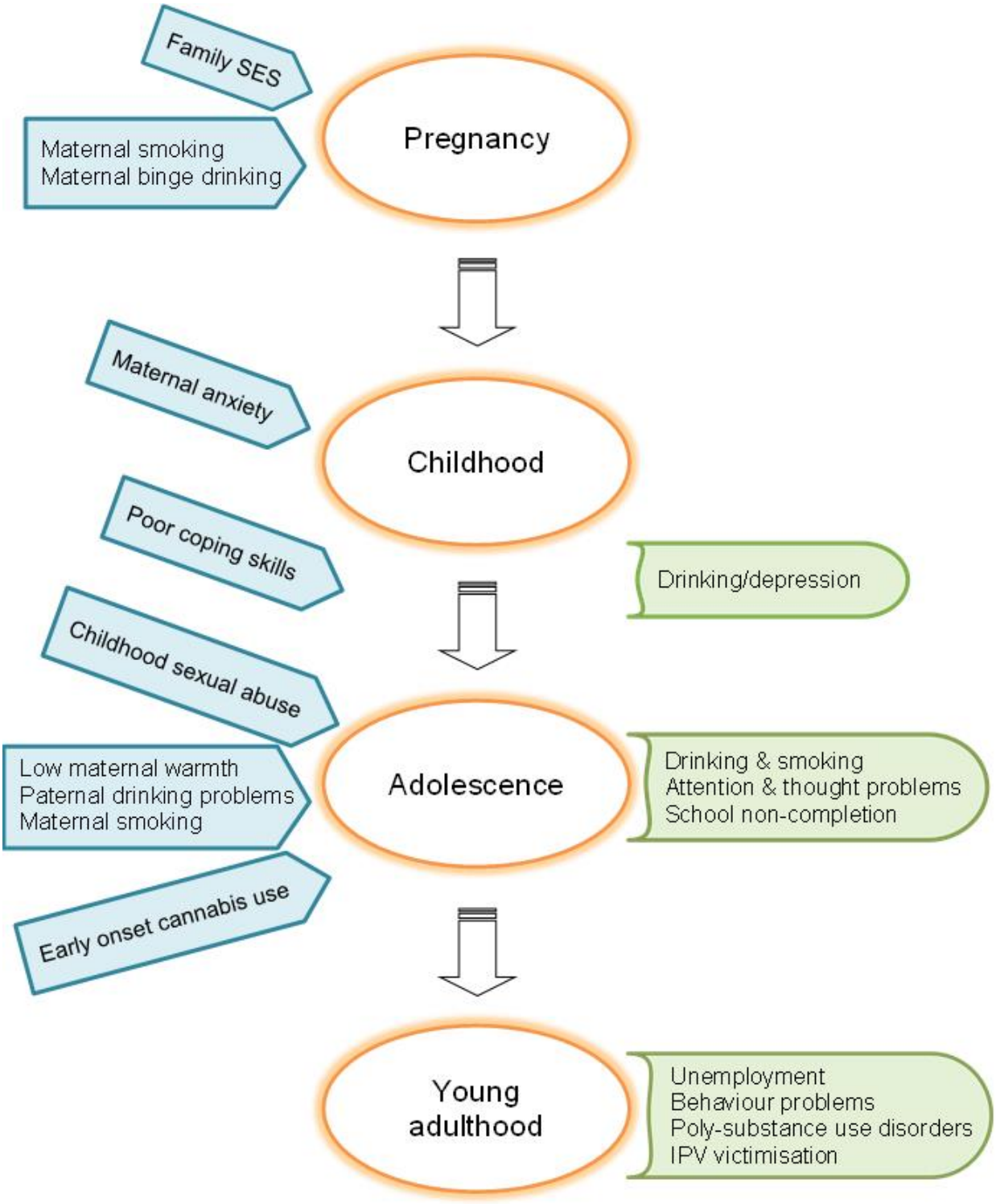
Our finding that good adaptive stress-coping skills were associated with much lower odds of combined drinking/depressive symptoms in pre-teens was cross-sectional and so causal directions may only be speculated upon, but certainly coping skills have been linked in other studies to greater resilience in young people (117, 185). This ability to cope with challenges has been linked to intelligence (291), although the link between IQ and depression has been shown to vary from childhood to adolescence (292). Although stronger adolescent problem-solving skills, as measured here by the Raven matrices, were linked to lower risk of comorbid disorders, our study did not provide strong evidence for the role of IQ in the development of comorbidity.

Adolescent behaviours are generally regarded as indicators of shared genetic risk, rather than causal factors, for later disorder (293). In the MUSP cohort, adolescents' own drinking, smoking and attention/thought problems were associated with comorbidity but not with single disorders. The work of Behrendt and colleagues suggests that this effect is not due to accelerated progress from alcohol use to disorder in the presence of early-onset mental health problems (10, 294, 295). However, there is evidence that heavy drinking during periods of high neural plasticity such as adolescence can cause permanent damage (296). This may suggest it is plausible for drinking during adolescence to have some impact on comorbid disorder development, in addition to being an early marker of developing problems.

In short, this research demonstrates that factors at different stages of development predict comorbidity in young adults. Pregnancy and adolescence appear to be stages of

increased vulnerability, and indicators of disorder begin to appear during early-mid adolescence. This information is summarised in Figure 3 below.

Figure 3: Summary of developmental influences on comorbidity at young adulthood



How does comorbidity differ from single disorders?

There have been suggestions that alcohol/mental health comorbidity is merely an expression of severity of mental health disorders, rather than a specific entity (297). If such was the case, we would expect the conditions associated with comorbidity to be more severe than mental health disorders, but that predictive factors would not differ. If comorbidity should be regarded as a separate class of disorder, there may be some common liabilities, but it should be possible to identify distinct underlying contributors (298).

Is it just severity?

As the CIDI is a hierarchical system, where questioning on a condition ceases if thresh-holds for initial conditions are not met (e.g. dysthymia prior to depression), it was not possible to use symptom count as a measure of severity. Using the mean number of diagnosed mental disorders, as suggested by Angst (15), there was little difference between the MHD only and comorbid groups, although more of the comorbid group had multiple (4+) disorders. In contrast, self-reported impairment due to alcohol use was greater in the comorbid group than the AUD only group, suggesting that mental health disorders may add a dimension of difficulty that impedes the individual's ability to cope with alcohol use disorders. The comorbid group was also more likely at young adulthood to be unemployed, to smoke and to have started smoking earlier, in line with findings from large national studies (88, 299). The increased likelihood and severity of behaviour problems in the comorbid group also suggest that the dual diagnosis condition is more debilitating. However, the associated behaviour problems also provide a point of difference: those reported by the comorbid group were specific, focussing on aggression and delinquency, rather than the internalising problems commonly associated with mental health disorders. This may argue for a distinction beyond severity.

Independent risk factors or shared underlying causes?

Certainly this research has confirmed that the conditions associated with comorbidity are more acute than those of the single disorders. In addition to behavioural problems, early-life factors associated with development also distinguish comorbidity from other mental health problems. The responses to increasing levels of socio-economic disadvantage and heavier smoking during pregnancy were not seen for single disorders; neither was the relationship with maternal anxiety in early childhood. Adolescent drinking and attention/thought disorders predicted only comorbidity, while higher Raven IQ scores

reduced its likelihood. Taken together, these would seem to suggest comorbidity may be distinct from the constituent disorders and not merely an issue of severity.

Multiple contributions

For other contributing factors, the links were merely *stronger* to comorbidity than to the single disorders. For example, maternal drinking pre-birth, and smoking and low warmth during adolescence were also linked to later mental health disorders in their offspring, but not to alcohol use disorders alone. These appeared to contribute to comorbidity via mental health disorders. These relationships are summarized in Table 19 below.

Table 19: Summary of life course factors contributing to comorbidity at young adulthood: specificity and potential pathways of contributions

Factor	Effect is specific to comorbidity	Effect is stronger for comorbidity	Factor acting via MHD	Factor acting via AUD
Prior to pregnancy				
Socio-economic disadvantage	Dose	✓	✓	-
Maternal binge drinking		✓	✓	-
During pregnancy				
Binge drinking		✓	✓	-
Smoking	Dose	✓	✓	✓
Early childhood				
Maternal anxiety	✓	-	-	-
Adolescence				
Maternal smoking		✓	✓	-
Low warmth		✓	✓	-
IQ (Raven)	✓	-	-	-
Paternal drinking	✓	-	-	-
Adolescent drinking	✓	-	-	-
Adolescent smoking		✓	✓	✓
Attention/thought problems	✓	-	-	-

Information from fully adjusted models

Smoking in pregnancy however was linked to both alcohol and mental health problems, suggesting contributions from both disorders. The dose response seen may result from such dual contributions and indicate an interaction of some type. The apparent independence of in-pregnancy smoking from that pre- and post-pregnancy may suggest a gestational impact. Smoking during pregnancy has been linked to methylation, and thus the modulation of expression, of genes which are related to both conditions (283), which

may explain its link to comorbidity. There is some support for this from genetic studies. The gene for the serotonin transporter monoamine oxidase A (MAO-A) has noted sensitivity to methylation (285), and variations in its activity have been linked to depression and alcohol use disorders. The MAO-A gene interacts with different alleles of the gene for alcohol dehydrogenase (responsible for metabolising alcohol) in those with comorbid mental health and alcohol use disorders (300, 301). A third candidate gene is CHRM2, for the muscarinic acetylcholine receptor, which slows the heart rate as part of the autonomic nervous system and reduces the response to stress. Variation in this gene has been linked to both substance and depressive disorders (302). Recent genome-wide association studies have linked variants of other genes with mental health disorders such as major depression and this area of research is rapidly expanding (154). The MUSP data available for this study did not permit this type of analysis, but this area may be of future interest, particularly if the involvement during pregnancy can be confirmed.

How does this comorbidity link to other conditions?

It is also possible that comorbidity contributes to other conditions via its constituent disorders. In the study of Intimate Partner Violence (IPV) victimisation, we found that experiences of emotional and physical forms of IPV were associated with different substance use disorders. Being a victim of emotional abuse was linked to the presence of alcohol use disorders, while physical abuse, often a progression from emotional abuse, was related to other substance use disorders after accounting for the emotional abuse. Vulnerability to all three forms of IPV was associated with mental health problems. The impact of comorbidity appeared very much to be the result of the separate contributions of alcohol, other substance or mental health disorders. Although experience of IPV is often reported as part of reciprocal behaviour and linked to the victim's own aggression (249, 303) (itself associated with comorbidity), our results were independent of this factor. These findings concurred with results from a recent UK study (304), but in accounting for the first time for the multiple forms of IPV experienced, our results challenge earlier links reported between alcohol use disorders and physical IPV victimisation (249, 305, 306).

Together, these findings indicate that those with comorbid disorders experience more problems across numerous dimensions than those with either alcohol use or mental health disorders alone. This is in line with both clinical (307) and population based findings by others (71), and serves to highlight the need for an improved understanding of comorbidity.

Is alcohol-based comorbidity different to that involving illicit substance use disorders?

In order to investigate alcohol as the most widely used, but legal, psychoactive substance, the majority of these analyses have focussed on alcohol, rather than substance use in general as in numerous other reports. However, as shown in preliminary studies here, many of the AUD group also have other substance use disorders. Our Latent Class Analysis (Chapter 7) separated those with alcohol use disorders into two distinct classes; those whose substance use problems were limited to alcohol and cannabis, and those who also used multiple illicit substances. Mental health disorders appeared even more likely in the case of poly-substance use (PSU) than for the alcohol/cannabis group. This may support our findings from in the Healthy Neighbourhoods study (Chapter 5, paper 1), where a group of children who used cannabis (1.1%) were more likely to report co-occurring drinking and depressive symptoms ($P<0.02$) than those who did not.

Although adolescent drinking and externalising predicted poly-substance based comorbidity as well as that based on alcohol, the strongest predictor of PSU was early initiation to cannabis use. Every year that cannabis initiation was delayed reduced the likelihood by 36%. This link was not seen for alcohol based comorbidity, and did not apply to early initiation of drinking or smoking for PSU. This may support the idea of cannabis, rather than alcohol or tobacco, as a 'gateway' drug for other illicit substance use (308) and is congruent with a recent review of the impacts of early cannabis use (309), but suggests that the relationship between mental health disorders and illicit substances may be different to that with alcohol.

In the MUSP cohort, some predictors of the latent classes differed from those for alcohol/mental health comorbidity. Maternal smoking in pregnancy and low maternal warmth in childhood were not significant predictors of PSU-based comorbidity. This is consistent with earlier work by Todorov and colleagues showing that psychiatric comorbidities with licit and illicit substances grouped differently in a latent class analysis and had different antecedents (310). Interestingly, a recent analysis of longitudinal data from the NESARC showed that development of cannabis disorders was mediated more by proximal factors (such as early cannabis use) than the earlier factors (such as maternal smoking) implicated in the development of alcohol use disorders (311). In addition to the (male) gender bias for PSU, these reports highlight the differences between alcohol comorbid with mental health and illicit substance use disorders comorbid with mental health problems, and reinforce the need for these disorder combinations to be examined separately as has been done in this study.

Implications

For early identification and prevention

This study has a number of implications for early intervention. Firstly, it is possible to identify markers appearing in early adolescence that are linked to later comorbidity. Adolescent drinking, smoking and attention/thought problems all predicted comorbidity. Currently these behaviours are seen as marking the emergence of single conditions, but this research suggests they should also be considered as possible markers when screening for co-occurring disorders. If this screening can be done in the pre-teen years rather than mid-adolescence, interventions may be able to take place prior to full disorders becoming established.

Other factors predicting comorbidity, e.g. maternal smoking in pregnancy and paternal drinking problems, offer targets for family-based prevention programs, as do those which seek to strengthen children's coping skills and parent-child closeness. Existing programs which address these issues could thus be applied to reducing comorbidity. Socio-economic disadvantage provides a greater challenge, due to the involvement of multiple domains. Reducing financial barriers to treatment, for example, would be insufficient; strategies to reduce disparities in employment and education levels of parents would also be necessary. However when clients present with either alcohol use or mental health disorders, and high socio-economic disadvantage is noted, screening for comorbid conditions should be recommended.

For treatment and contingency management

Treatment strategies for comorbidity are changing. Early efforts focussed on identifying a primary disorder for initial treatment in the expectation that improvement in the secondary disorder would be seen. However, modelling by Glantz and colleagues (24) suggests that despite the interrelationship between mental health & substance use disorders, treating one (e.g. the mental health disorder) is not a cost effective way of preventing the other. This would suggest that more benefit may be gained by addressing early symptoms common to both disorder types. Although some success has been noted with pharmaceutical treatment of the mental health component (312), recent reports (29, 85, 86) suggest that addressing both issues concurrently in treatment can successfully improve each condition.

Considerations for treatment providers include the aggressive behaviour associated with comorbidity, and the likelihood that those seeking treatment will come from more

disadvantaged backgrounds, and have experienced trauma such as intimate partner violence. Each of these will add complexity to treatment planning, but being aware of the specific social and individual profiles of these clients may be helpful for service providers.

Encouraging affected young people into treatment should be pursued, as studies suggest that the prevalence of comorbid disorders increases over early adulthood, rising to one in five by age 30 rather than resolving (278). Such engagement has additional benefits, reducing the likelihood of subsequent arrest, including for violent or substance related crimes (313). This may prove challenging, although some reports suggest that those with co-occurring disorders are more likely to seek help (314). Additionally, those with substance use disorders are unlikely to access mental health services (280), which may limit recognition of their accompanying mental health disorders at the presenting agency. However, successes reported with outpatient (313) or even computer-based therapies (86) may offer modalities that are more attractive to younger clients than traditional in-patient settings and more broadly effective than pharmacotherapies alone (312, 315).

Strengths and limitations

A major strength of this study is its use of the large, population based MUSP cohort. This sample is larger than some of the well-developed longitudinal cohorts (e.g. the Christchurch and Dunedin studies (316, 317)) and provides information at later stages of development than several very large birth cohorts (e.g. the ALSPAC (258)). The unselected sample allows generalisation of our findings to a broader population than those from specialised cohorts or clinical groups. Follow-ups at ages critical to disorder development (prenatal, childhood, adolescence and young adulthood) have allowed identification of comorbidity at early stages, assessment of the sensitivity of different developmental phases to contributing factors, and have reduced reliance on recall. The breadth of information gathered in the MUSP has allowed the studies to account for a wide range of family, individual and environmental influences. Even after attrition, the size of the sample has allowed direct comparison of more domains of influence in the regression models than has been possible in other studies.

Additionally, the measures of mental health and substance use disorders are well-validated, being based on the DSM-IV, although our disorder classes reflects the newer DSM-V in that distinctions between abuse and dependence are not maintained. The measures of most contributing factors are either based on widely-used instruments (e.g.

the YASR for behaviour, the DSSI for maternal mental health, the Parker Bonding scale for mother-child warmth), or have been constructed using validated guidelines (e.g. the use of NHMRC drinking guidelines to construct the maternal regular drinking/binge drinking measures from quantity/frequency information and the extension of the widely-used Conflict Tactics Scale to differentiate between forms of IPV). Some measures were limited; information on paternal health behaviours was reported by the mothers, and was only collected on a sub-sample of the cohort, both of which may have introduced some bias. The measures of parenting at 5 years achieved only moderate reliability (Crohnbach's α ranged from 0.48-0.82), and were not available at 14 years.

As with any study, there are also limitations. Over the 21-year course of the MUSP, the sample has been subject to considerable attrition, and the limited application of the CIDI at 21 years resulted in only 36% of the original cohort being included in final analyses here. This may have introduced bias into the results, as those who were lost tended to have more health and socio-economic disadvantages, both of which are linked to the disorder outcomes. On the other hand, it is also possible that this type of attrition resulted in an underestimation of the associations found. Despite this, analyses which accounted for attrition via multiple imputations or inverse probability weighting confirmed the results of complete case analyses, giving confidence in these findings.

A second limitation was the large time interval between the adolescent and young adult follow-ups. Later adolescence is a period of great sensitivity for the development of disorders but also for education, relationship initiation, employment and other significant life events. Although some of this information was collected, time frames were not always distinguishable, so that some analyses were effectively cross-sectional. Thirdly, although it has been possible to assess the contribution of multiple domains to the development of disorders, it has not been possible to account for peer or sibling influences. Both of these have been shown to be important in the development of substance use disorders (161), and although some siblings were included in the MUSP cohort, the study does not contain information on all siblings, so these data were not usable. There may also be other residual confounding for which we have not been able to account.

Lastly, as previously noted, it has not been possible to assess genetic contributions to the disorders. Although the MUSP contains measures of maternal use of alcohol and cannabis, these are not disorder diagnoses, and without this and paternal information, heritability cannot be determined. Similarly, follow ups to young adulthood did not include an opportunity to collect biological samples, precluding any molecular analyses.

Complex concepts

In addition to conventional limitations, it is important to recognise that several key concepts considered in this thesis are complex constructs without universal definitions to guide analysis and thus present inherent challenges. Comorbidity, intimate partner violence and socio-economic disadvantage are all subject to underlying assumptions and contextual variation.

The concept of comorbidity, discussed extensively in the Introduction, is complex. The DSM-IV presents disorders separately, with no defined categories of comorbidity, and symptoms may be shared between diagnostic disorders such as depression and anxiety. Thus, it can be difficult to make a case for homologous comorbidity (i.e. multiple diagnoses within a diagnostic spectrum) as a separate entity, whereas heterologous comorbidity (i.e. diagnoses across spectra such as depression and substance use) may be more distinct. For this reason, we did not consider co-occurrence of multiple mental health disorders, but specifically focussed on co-occurrence of conditions from different spectra, and ensured temporal overlap.

Heterologous comorbidity may reflect either etiologically independent conditions or a manifestation of shared underlying factors. The significant overlap between mental health, alcohol and illicit substance disorders shown in Figure 2 (page 72) may suggest the latter. However the use of Latent Class Analysis as described in Chapter 7 allowed us to further examine this idea, finding differences between the predictors of multi-morbidity and those for mental health disorders alone that may support the former suggestion.

Adding an additional dimension, the literature reports that mental health disorders are often comorbid with physical disorders (31, 318), again complicating the care required for each condition, but those discussions are beyond the scope of this thesis.

Socio-economic constructs are similarly heterogeneous and vary broadly across the literature, as discussed in paper 6.1 (page 64). Factors are defined according to local and temporal norms, with the impact of disadvantage (characterised as falling ‘below the norm’) manifesting differently between populations. In constructing a multi-component scale, we were able to examine the cumulative nature of disadvantage as it related to mental health and substance use disorders. By using factor analysis, we were able to examine potentially ‘competing’ contributions by a number of correlated dimensions of this disadvantage. This was particularly useful in that it acknowledged that a single factor did not consistently define socio-economic disadvantage, and that consideration of multiple

indicators was needed to allow for contextual differences. This highlighted the need for multiple strategies to address disadvantage as a risk factor.

Intimate Partner Violence is an issue currently receiving increased attention in Australia. Much of the public attention focusses on physical aspects of IPV. As discussed in paper 6.3 (page 70), this reflects the majority of literature, including previous Global Burden of Disease studies (319). However, psychological or emotional abuse and controlling behaviours are increasingly recognised as part of IPV (320) and so inclusion of these aspects in our examination was vital and provided a significant contribution to the literature. Cultural understandings of IPV also vary considerably, with under-reporting likely among cultures with gender-inequitable social norms or acceptance of spousal dominance (320). This makes international comparisons challenging (321). Given the culturally homogeneous nature of the MUSP cohort, we were not able to consider the role of these differences. However, the issue of victim gender is important across cultural barriers. As noted in paper 6.3, most reports of IPV focus on female victims, further limiting public understanding of this issue. By analysing the high levels of male IPV victimisation found in a non-selected population, this paper provides an important perspective and contributes further to the IPV debate.

Commentary on analytical choices

A number of specific analytical choices were made for the analyses described in this thesis. Technical details of the analyses are discussed in Chapter 3, with further description and commentary in each of the papers for which methods were used. However some overall comments are made here.

In the majority of these analyses, the outcome of interest was a variable with four non-overlapping categories. Standard diagnostic definitions from the DSM-IV were used to construct four conditions: Mental Health Disorder, Alcohol Use Disorder, Comorbid Alcohol/Mental Health Disorder or neither. These categories were not ordinal, as we were unable to assign comparative severities (as discussed on page 82), and so logistic regression was indicated. This approach did not require dependent variables to be statistically independent of each other, nor did it assume normal distributions for predictor variables. This was essential when modelling familial factors which may be highly correlated and whose distribution may be skewed.

It would have been possible to undertake a series of individual logistic regressions, comparing the comorbid group with each other category in turn. However by using the

comorbid group as a reference category in multinomial analyses, it was possible to evaluate differences both from the null category and the single disorders, generating category-specific odds ratios with no loss of sensitivity or increase in the scale of errors (256). For paper 5.1 (page 59), the outcome (co-occurrence of drinking and depressive symptoms in very young adolescents) also fitted these criteria. For analyses where the outcomes of interest did overlap (e.g. paper 6.3 on intimate partner violence, page 70), the tandem comparison approach was necessary, with the regression analysis for each form of violence being adjusted for the presence of other forms. As a result, it was not possible to directly compare factors predicting each form of violence within a single model.

We used latent class analysis to answer a different question (paper 7.1, page 75). The outcome of interest was not initially defined; we asked whether common mental health disorders were more likely in the presence of specific substance use disorders. With no a priori assumptions as to these associations, it was appropriate to model the groupings using a latent rather than observed variable. The use of latent class modelling and subsequent multinomial logistic regression analyses allowed pooling of information that would not have been possible from individual regressions.

Directions for future research

In summary, comorbidity of alcohol use and mental health disorders is a debilitating condition that often arises early in life and has characteristics which distinguish it both from its constituent disorders and from comorbidities involving illicit substance use disorders. The evidence from this study has strongly confirmed that those with comorbid disorders experience behaviour problems, multi-morbid mental health challenges, impairment and relationship vulnerabilities that exceed the issues faced by those with either alcohol or mental health problems alone. For the first time, these studies consider the influence on comorbidity of parental substance use and mental health, family characteristics and individual behaviours in a single model. We have identified predictors which are specific to this comorbidity and others which are more strongly linked to comorbid conditions than single disorders. These emerge by adolescence and so provide targets for early intervention.

In future work, the impact of family management needs to be assessed using more sensitive instruments, or at a more sensitive time point. Our measures did not show associations with any disorder, which does not concur with reports showing that positive

parenting strategies can ameliorate the impact of early-emerging disorders. As mentioned previously, the impact at adolescence needs greater research attention.

Good adaptive coping skills were linked to lower likelihood of co-occurring symptoms in this research. This may suggest that improving coping skills could reduce development into comorbid disorders, but longitudinal data is required for this. If the link is confirmed, trials of coping-skill based interventions for comorbidity should be considered. Additionally, early drinking may be more than an indicator of developing disorder. The effect of alcohol in adolescence, a period of significant neuroplasticity, may play a physiologically causal role in comorbidity (296), and should be further investigated.

It will also be important to assess the further development of comorbidity as this cohort ages, to examine the pathways of natural recovery *vs* escalating disorders, and to consider the factors which influence this trajectory. Data currently being finalised from the MUSP 30-year follow-up will allow this to be done.

Investigation using a more recent cohort may also be enlightening. Cultural comparisons indicate that drinking is not just an issue in Australia but also in developing nations (37). A similarly-recruited cohort in this decade is likely to be more culturally diverse than that from the 1980s and thus allow assessment of cultural contributions. Patterns of smoking and drinking during pregnancy have also changed since this cohort was recruited; current cultural norms suggest that both have considerably declined (34). The prevalences of smoking and drinking in younger women in general have been slowly decreasing over the last decade (34), but analyses of the MUSP dyads have shown that women whose mothers drank were likely to drink much more than their mothers, although they smoked less (322, 323). The gender balance of disorders may also have changed, with reductions in the male dominance of substance use having been noted, along with considerable increase in the drinking of young women (324).

Finally, the contributions of genetics to these conditions, both in conferring vulnerability and contributing to gene x environment effects, need to be established. Recent developments in molecular approaches show promise for this issue. Genome wide association studies (GWAS) can be used to link novel DNA variations (polymorphisms) to cases of substance use or mental health disorders, opening up new areas of investigation (154). This field has expanded hugely in the wake of large consortia which pool case data and DNA screening results. Candidate gene association studies (CGAS) narrow this approach, examining polymorphisms in genes for which *a priori* links to a disorder have

been identified (325), as does exome sequencing, which analyses only the coding sequences within the genome and may be used to identify causal gene variants.

However powerful, these approaches do not provide mechanistic information, or indicate which factors may impact on *expression* of the genes of interest. Methylation studies identify structural modification of the DNA, rather than mutations. Such modifications have been linked to specific environmental contexts and so may provide physical evidence of gene-environment interaction. High-throughput complementary DNA (cDNA) sequencing examines transcription of DNA, identifying genes which are differentially expressed under specific conditions (326). These latter methods can thus suggest functional links between gene alterations and the predicting or resulting conditions.

No single technique is sufficient to provide a complete picture. Results from GWAS to date indicate a large number of associations with relatively small effect sizes (327) and suggest complex interactions between polymorphic regions, or at least an accumulation of effects from multiple variants (328). This then requires huge sample sizes to accommodate the multilevel modelling necessary for understanding these relationships. Additionally, symptom cross-over between disorders may lessen the strength of associations between individual variation and specific disorder (329), and the polygenic nature of many disorders requires isolation of multiple variants to disclose a large enough effect (330).

Despite such limitations, robust examples of the contributions by genetic studies to our understanding of substance and mental health disorders do exist. Variations in genes coding for alcohol metabolism enzymes impact on the amount of alcohol that can be consumed before toxicity is experienced, increasing likelihood of abuse and dependence (328). Alterations in serotonin and dopamine transporters or receptors alter the function of the brain's reward centres, associated with pleasure seeking via substance use. Polymorphisms in opioid or NMDA receptors may be used to predict an individual's response to treatment with pharmacotherapies such as naltrexone or acamprosate (331) and in glucocorticoid receptors to behavioural interventions for mental health problems (332).

Although molecular analyses may suggest mechanistic information or predict individual responses to therapy, epidemiological methods such as those used in this thesis are useful at to identify population level factors presenting a risk for comorbidity or potential for intervention. It is the nexus of behavioural, environmental and genetic information that will be increasingly important. As discussed earlier, participant smoking has been linked to

functional changes in stress-response genes due to methylation, which have been linked to subsequent substance disorders (285). Other recent studies demonstrate the contribution of interactions between epidemiological data (e.g. childhood adversity, anxiety diagnoses) and genetic data (e.g. polymorphisms in alcohol metabolism or stress-response genes) to studies of complex conditions (301, 333). DNA samples collected as part of the MUSP 30-year follow-up may permit both genome wide association studies and methylation analyses in future investigations, both of which may yield information as to the mechanisms behind the associations provided here through observational epidemiology.

Conclusion

This study provides a detailed understanding of the complex interplay between factors involved in the early development of comorbid alcohol use and mental health disorders. Using a cohort that can be considered representative of the general population, it has shown that such disorders are common, and present wide-ranging health and social challenges at a younger age than previously thought. These challenges are similar to those due to single disorders, but this study provides further evidence that impacts are more pronounced and felt in multiple domains. A number of behaviours have been identified which may be used to screen early in adolescence for signs of comorbidity, and to distinguish this condition from single disorders. Our results also highlight the necessity to recognise the heterogeneity of relationships between substance use and mental health disorders in comorbidity.

The early-life predictive factors identified here provide opportunities for the design of interventions. Initiatives to reduce the prevalence of maternal smoking during pregnancy fall within the scope of current government health promotion activity. Similarly, strategies such as bolstering youth coping skills and providing support for improvement of parent-child relationships are currently in use and would require little adaptation for use to reduce comorbidity. Addressing the cumulative nature of socio-economic disadvantage that has contributed strongly in this study requires multiple and complex interventions, but the benefits of investment in such strategies would encompass social and justice-related improvements, as well as those of health. With an improved understanding of the aetiology of comorbid alcohol and mental health disorders comes the opportunity to address the burdens with which it is associated.

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Appendices

Appendix 1: Ethics Approval

School of Population Health

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To Ms Caroline Salom

From Lisa Fitzgerald

Date 27 October, 2011

Re Ethics Approval CS271011

CC Associate Professor Rosa Alati

Professor Jake Najman

Dear Caroline,

Thank you for your application for ethics approval for your project:

'Development and features of comorbid mental illness and alcohol misuse in offspring from the MUSP longitudinal study'

The School of Population Health Research Ethics Committee has reviewed the materials submitted and ethics approval has been given.

Yours faithfully

Lisa Fitzgerald

Lecturer in Population Health Social Sciences

Chair, SPH Research Ethics Committee

Appendix 2: Characterisation of variables used in this thesis

This appendix contains further detail on the cohorts and the variables used in this thesis. Information is arranged in the order in which the variables appear in the thesis.

Table 20: Non-disorder substance use in MUSP offspring

Stage		Tobacco	Alcohol	Cannabis
		N (%)	N (%)	N (%)
14 years	Missing	2069	2066	-
	No	4552 (88%)	4787 (93%)	-
	Yes	602 (12%)	366 (7%)	-
21 years	Missing	3457	3457	3469
	No	2276 (60%)	2276 (60%)	3289 (88%)
	Yes (regular)	1490 (40%)	856 (23%)	465 (12%)
	Binge	-	634 (17%)	
	Age started	15.45	15.88	15.81

Table 21: Marital status of MUSP mothers

Stage	Status	N (%)
FCV	Missing	0
	Partnered	6292 (87%)
	Not partnered	931 (13%)
5 years	Missing	2045
	Partnered	4551 (88%)
	Not partnered	627 (12%)
14 years	Missing	2084
	Partnered	4184 (81%)
	Not partnered	955 (19%)
	Not with child's father	3497 (68%)
	Living with child's father	1658 (32%)

Table 22: Parenting behaviours at 5 years

	Maternal control	Physical punishment	Reasoning with child	Consequential parenting
	N (%)	N (%)	N (%)	N (%)
Missing	2083	4044	4017	3147
High	560 (11%)	424 (13%)	273 (9%)	377 (9%)
Not high	4490 (89%)	2755 (87%)	2931 (91%)	3699 (91%)
	α=0.64	α=0.61	α=0.82	α=0.73

Table 23: Mother-child relationship during adolescence

	Maternal warmth	Open communication
	N (%)	N (%)
Missing	3598	2131
Low/poor	364 (10%)	414 (10%)
Not low/poor	3261 (90%)	4678 (90%)
	α=0.88	α=0.85

Table 24: Family environment to 14 years

	Violence in mother's relationship	Problems in residential area
	N (%)	N (%)
Missing	2106	3561
Present	641 (13%)	362 (10%)
Not present	4476 (87%)	3300 (90%)
	-	α=0.93

Table 25: Maternal substance use and mental health

Stage		Smoking	Drinking
		N (%)	N (%)
Pre-pregnancy	Missing	59	43
	No	3611 (50%)	3786 (53%)
	Yes (regular)	3553 (50%)	2599 (36%)
	Binge	-	795 (11%)
FCV	Missing	162	43
	No	4350 (61%)	1809 (25%)
	Yes (regular)	2812 (39%)	4557 (63%)
	Binge	-	814 (11%)
5 years	Missing	2022	2013
	No	3255 (63%)	1177 (23%)
	Yes (regular)	1946 (37%)	3580 (69%)
	Binge	-	453 (9%)
14 years	Missing	2051	2051
	No	3570 (69%)	940 (18%)
	Yes (regular)	1602 (31%)	3713 (72%)
	Binge	-	519 (10%)

Table 26: Maternal mental health

Stage		Depression	Anxiety	Mental distress
		N (%)	N (%)	N (%)
FCV	Missing	289	275	289
	No	6534 (94%)	6038 (87%)	6257 (90%)
	Yes	400 (6%)	910 (13%)	677 (10%)
5 years	Missing	1998	1998	1998
	No	4883 (93%)	4735 (84%)	4653 (89%)
	Yes	342 (7%)	850 (16%)	572 (11%)
14 years	Missing	2058	2058	2058
	No	4733 (92%)	4196 (81%)	4496 (87%)
	Yes	432 (8%)	969 (19%)	669 (13%)
		α=0.88	α=0.84	α=0.90

Table 27: Father's substance use and mental health as reported by mother

	Smoking	Drinking problem	Mental health problem
Missing	3757	3546	4669
No	2356 (68%)	3062 (83%)	2731 (93%)
Yes	1110 (32%)	615 (17%)	183 (7%)

Table 28: Socio-economic factors from family of origin

	Family income	Maternal employment	Paternal employment	Maternal education	Paternal education
Missing	474	56	106	53	0
Disadvantaged	2308 (34%)	1201 (17%)	1126 (16%)	5229 (73%)	5033 (70%)
Not disadvantaged	4441 (66%)	5966 (83%)	5991 (84%)	1941 (27%)	2190 (30%)

Table 29: Socio-economic disadvantage from family of origin

Score	0	1	2	3	4	5
N	693	1452	2480	1154	641	256
%	10%	22%	37%	17%	10%	4%

Table 30: Characteristics in early childhood

	Mean (SE)	Missing
Mother's age at birth (years)	25.44 (± 0.06)	0
Birth weight (grams)	3386 (± 6)	1
IQ (Peabody; age 5)	99.43 (± 0.22)	3224
IQ (Raven: age 14)	42.1 (±0.12)	3430
IQ (WRAT: age 14)	42.3 (± 0.1)	3436

Table 31: Characteristics of youth, reported at 21 years

	Education <Year 12	Cohabiting w/ partner	≥1 child in care	Left home before 17	Childhood sexual abuse
Missing	3463	3456	3456	3465	3542
No	2974 (79%)	2773 (74%)	3429 (91%)	3330 (89%)	3332 (91%)
Yes	786 (21%)	994 (26%)	338 (9%)	428 (11%)	349 (9%)

Table 32: Behavioural problems at 14 years (Achenbach's Youth Self Report)

Subscale	Range	Mean score (SE)	Missing	% problem	α
Internalising	0-49	13.9 (0.10)	2486	11%	0.87
Anxious/depressed	0-48	43.0 (0.06)	2363	14%	0.84
Withdrawn	0-13	3.5 (0.03)	2186	10%	0.62
Externalising	0-51	13.0 (0.10)	2408	9%	0.87
Aggressive	0-36	9.4 (0.08)	2327	8%	0.84
Delinquent	0-21	3.6 (0.04)	2222	9%	0.71
Somatic	0-18	4.5 (0.04)	2157	9%	0.70
Thought	0-14	3.2 (0.03)	2193	9%	0.81
Attention	0-18	5.2 (0.04)	2222	9%	0.73
Total problems	0-195	169.1 (12.30)	2864	10%	0.85

Table 33: Behavioural problems at young adulthood (Achenbach Young Adult Self Report)

Subscale	Range	Mean score (SE)	Missing	% problem	α
Internalising	0-45	10.8 (0.10)	3558	4%	0.91
Anxious/depressed	0-34	8.2 (0.10)	3539	10%	0.91
Withdrawn	0-13	2.6 (0.04)	3516	7%	0.72
Externalising	0-41	9.5 (0.10)	3574	5%	0.87
Aggressive	0-21	4.3 (0.06)	3541	9%	0.81
Delinquent	0-16	2.4 (0.04)	3522	7%	0.72
Intrusive	0-13	2.8 (0.04)	3515	8%	0.72
Somatic	0-24	4.6 (0.06)	3524	8%	0.81
Thought	0-9	0.8 (0.02)	3509	8%	0.62
Attention	0-13	3.3 (0.04)	3516	7%	0.70
Total problems	0-119	28.9 (0.30)	3702	5%	0.96

Appendix 3: Supplementary material published online in support of paper 5.1

Title

Individual, school-related and family characteristics distinguish co-occurrence of drinking and depressive symptoms in very young adolescents

Authors

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Running title:

Co-occurrence of pre-disorder drinking/depression in pre-teens

This material supplements but does not replace the content of the paper published in *Drug and Alcohol Review*

Table 34: Attributable Risk of co-occurring drinking/depressive symptoms in 10-14 year old students by factor

Factor	Attributable Risk (AR) %
5+ school moves	6.2
Academic achievement (low)	7.1
School commitment (low)	6.9
Family conflict (present)	8.7
Family substance problem (present)	9.8
Family closeness (low)	7.1
Adaptive stress coping skills (low)	**10.5**
Gender (female)	0.0
School level (secondary)	3.6
School sector	0.9

Table 35: Prevalence and gender balance of drinking and depressive symptoms across Australian students, comparing measures of drinking and depressive symptoms

	Symptoms consistent with depression *(SMFQ cut-off of 11)*		**Some depressive symptoms** *(SMFQ cut-off of 8)*	
	Recently drank (30 days)	**Ever drank** (lifetime)	**Recently drank** (30 days)	**Ever drank** (lifetime)
	% (CI_{95})	**% (CI_{95})**	**% (CI_{95})**	**% (CI_{95})**
Null group	**68.6 (67.6, 69.6)**	**51.1 (50.0, 52.2)**	**57.5 (56.5, 58.6)**	**46.3 (45.2, 47.4)**
Males	66.8 (65.3, 68.3)	45.5 (43.9, 47.0)	55.6 (54.0, 57.2)	41.7 (40.2, 43.3)
Females	68.5 (67.1, 69.9)	53.7 (52.2, 55.2)	57.1 (55.5, 58.6)	47.5 (46.0, 49.1)
Depression only	**14.6 (13.8, 15.3)**	**10.4 (9.8, 11.1)**	**23.0 (22.1, 23.9)**	**22.8 (21.9, 23.7)**
Males	12.0 (11.0, 13.1)	8.6 (7.7, 9.5)	20.2 (18.9, 21.4)	29.6 (28.2, 31.7)
Females	17.7 (16.6, 18.9)	12.7 (11.7, 13.7)	26.9 (25.5, 28.2)	17.7 (16.6, 18.9)
Drinking only	**11.1 (10.5, 11.8)**	**28.6 (27.6, 29.6)**	**11.1 (10.5, 11.8)**	**15.9 (15.1, 16.7)**
Males	15.3 (14.2, 16.4)	36.6 (35.1, 38.2)	15.3 (14.2, 16.4)	13.3 (12.3, 14.4)
Females	7.9 (7.1, 8.7)	22.7 (21.5, 24.0)	7.9 (7.1, 8.7)	19.2 (18.0, 20.3)
Both symptoms	**5.7 (5.2, 6.2)**	**9.8 (9.2, 10.5)**	**8.3 (7.7, 8.9)**	**15.0 (14.2, 15.8)**
Males	5.9 (5.1, 6.6)	9.3 (8.4, 10.1)	9.0 (8.1, 9.9)	15.3 (14.2, 16.4)
Females	5.8 (5.1, 6.6)	10.9 (9.9, 11.8)	8.2 (7.4, 9.0)	15.6 (14.5, 16.7)

Table 36: Multinomial logistic regression models of co-occurring drinking/depressive symptoms in young Australian students, by measure of drinking

		Recent drinking model		Ever drank model	
Factor		**OR**	**CI_{95}**	**OR**	**CI_{95}**
School moves	1-2	1.28	0.98, 1.66	**1.41**	1.07, 1.85
	3-4	**1.41**	1.03, 1.92	**1.56**	1.13, 2.15
	5+	**1.91**	1.25, 2.91	**2.50****	1.65, 3.79
Low academic achievement		**1.57**	1.22, 2.03	**1.46**	1.12, 1.89
Low school commitment		**2.86*****	2.25, 3.65	**3.27****	2.55, 4.19
Family conflict	Present	**3.29**	2.64, 4.10	**3.24**	2.59, 4.07
Family substance problem	Present	**2.51****	1.85, 3.40	**3.20*****	2.37, 4.32
Family closeness	Good	**0.61**	0.48, 0.78	**0.53**	0.41, 0.68
Adaptive stress coping skills	Good	**0.18****	0.14, 0.23	**0.17****	0.13, 0.21
Gender	Female	1.07	0.86, 1.33	1.13**	0.91, 1.42
SES		0.96	0.92, 1.00	0.97	0.93, 1.02

For clarity of comparison, only the values for the co-occurring drinking/depressive group (compared to the Norm group) are shown here.

Recent drinking model: drinking/depressive = SMFQ score ≥11 (last 2 weeks) plus last month alcohol consumption. Ever drank model: drinking/depressive = SMFQ score ≥11 (last 2 weeks) plus any lifetime alcohol consumption.

Figures in **bold** indicate that the OR for drinking/depressive is significantly different to the Norm group ($P<0.05$).

Asterisks (**) indicate that the OR for drinking/depressive was significantly different to both depressive alone and for drinking alone (*$P<0.05$ for both; ** $P<0.01$; ***$P<0.005$ for both)'

Differences between the drinking/depressive group and drinking-only or depressive-only groups were evaluated by repeating the regression each group in turn as reference.

Table 37: Multinomial logistic regression models of co-occurring drinking/depressive symptoms in young Australian students, by measure of depressive symptoms

		High symptoms model: SMFQ cut-off of 11		Lower symptoms model: SMFQ cut-off of 8	
Factor		**OR**	**CI_{95}**	**OR**	**CI_{95}**
School moves	1-2	1.28	0.98, 1.66	1.10	0.88, 1.38
	3-4	**1.41**	1.03, 1.92	1.30	0.99, 1.71
	5+	**1.91**	1.25, 2.91	1.38	0.93, 2.03
Low academic achievement		**1.57**	1.22, 2.03	**1.66**	1.32, 2.09
Low school commitment		**2.86*****	2.25, 3.65	**3.25*****	2.64, 4.00
Family conflict	Present	**3.29**	2.64, 4.10	**3.65***	3.01, 4.43
Family substance problem	Present	**2.51***	1.85, 3.40	**2.86***	2.14, 3.81
Family closeness	Good	**0.61**	0.48, 0.78	**0.56**	0.45, 0.70
Adaptive stress coping skills	Good	**0.18***	0.14, 0.23	**0.20*****	0.16, 0.24
Gender	Female	1.07	0.86, 1.33	1.03	0.85, 1.25
SES		0.96	0.92, 1.00	0.99	0.95, 1.02

For clarity of comparison, only the values for the co-occurring drinking/depressive group (compared to the "norms" group) are shown here.

High symptoms model: drinking/depressive = SMFQ score ≥11 (last 2 weeks) plus last month alcohol consumption.

Lower symptoms model: drinking/depressive = SMFQ score ≥8 (last 2 weeks) plus last month alcohol consumption.

Figures in **bold** indicate that the OR for drinking/depressive was significantly different to the norm group ($P<0.05$).

Asterisks (*) indicate that the OR for drinking/depressive was significantly different to both depressive alone and for drinking alone (*$P<0.05$ for both; ** $P<0.01$; ***$P<0.005$ for both)

Differences between the drinking/depressive group and drinking-only or depressive-only groups were evaluated by repeating the regression each group in turn as reference.

Appendix 4: Supplementary material published on line in support of paper 5.2

Title

Do young people with comorbid mental and alcohol disorders experience worse behavioural problems?

Authors

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Behaviour in comorbid alcohol/mental health

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Table 38: Cases of each YASR subscale in young adults, by comorbidity category*

Disorder Type:	No disorder	MHD only	AUD only	CAMHD	
No of participants	1237 (48.7%)	592 (23.3%)	405 (16.0%)	305 (12.0%)	
YASR subscale	**Cases (%)**	**Cases (%)**	**Cases (%)**	**Cases (%)**	***P*-value†**
Internalizing					
Anxiety/depression	36 (3%)	122 (21%)	10 (3%)	51 (17%)	Ns
Withdrawn	47 (4%)	63 (11%)	14 (4%)	30 (10%)	Ns
Externalizing					
Intrusive	67 (6%)	55 (9%)	32 (8%)	**46 (16%)**	0.01
Aggression	41 (3%)	73 (13%)	37 (10%)	**78 (27%)**	<0.001
Delinquency	23 (2%)	26 (5%)	63 (16%)	**71 (24%)**	0.01
Other					
Somatic	26 (2%)	71 (12%)	22 (6%)	**60 (20%)**	0.002
Thought	36 (3%)	75 (13%)	26 (7%)	**65 (22%)**	0.001
Attention	33 (3%)	55 (9%)	21 (5%)	38 (13%)	Ns

* Participants scoring in the top 10% of each subscale were classified as cases.

† Multinomial regression analysis of the number of cases of each YASR subscale by comorbidity class, adjusted for covariates as before, indicates the likelihood that the CAMHD group has more cases of that subscale than other disorder types.

Ns = non-significant

Table 39: Association of comorbidity class with number of YASR dimensions at case level per individual

No of YASR subscales at case level [a] per participant	**No disorder**		**MHD only**		**AUD only**		**CAMHD**	
	n	(%)	n	(%)	n	(%)	n	(%)
0	1,032	(83.43)	350	(59.12)	284	(70.12)	134	(43.93)
1	149	(12.05)	116	(19.59)	60	(14.81)	65	(21.31)
2	31	(2.51)	48	(8.11)	34	(8.4)	37	(12.13)
3	14	(1.13)	31	(5.24)	18	(4.44)	24	(7.87)
4+	11	(0.88)	47	(9.95)	9	(2.22)	45	(12.75)
Total participants	1,237		592		405		305	

Multinomial regression model [b] of comorbidity class, by number of case-level subscales per individual

	No disorder	**MHD only**	**AUD only**	**CAMHD**
	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
unadjusted	1.00	**1.93** (1.72, 2.15)	**1.55** (1.36, 1.76)	**2.31**** (2.05, 2.60)
adjusted	1.00	**1.96** (1.75, 2.21)	**1.46** (1.27, 1.67)	**2.27**** (2.01, 2.57)

[a] Participants scoring in the top 10% of each subscale were classified as cases. The number of subscales reaching case level for each participant was then recorded.

[b] This model uses the number of YASR dimensions at case level per individual as a continuous variable. Model is adjusted for participant age and gender plus maternal education, drinking, depression, anxiety and marital status, and uses the No Disorder category as reference.

**Individuals with comorbid alcohol and mental health disorders (CAMHD) have significantly more dimensions of the YASR achieving case level than those with MHD only or AUD only ($p<0.01$).

Table 40: Multinomial logistic regression models of comorbidity category at age 21, with YASR dimensions as predictors, showing the effect of multiple imputation on models

YASR Dimension	Disorder groups compared to No-Disorder group: adjusted models [a]			CAMHD group compared to single-disorder groups [b]	
	MHD only OR (CI_{95})	**AUD only** OR (CI_{95})	**CAMHD** OR (CI_{95})	**CAMHD vs MHD** OR (CI_{95})	**CAMHD vs AUD** OR (CI_{95})
Internalizing					
Anxiety / depression	1.15 (1.13, 1.18)	1.01(0.98, 1.03)	1.16 (1.13, 1.18)	1.00 (0.98, 1.03)	**1.15 (**1.12,1.18)
imputed	*1.16 (1.13, 1.18)*	*1.01 (0.98, 1.04)*	*1.16 (1.14, 1.18)*	*1.00 (0.98, 1.03)*	***1.15** (1.11, 1.18)*
Withdrawn	1.26 (1.20, 1.32)	0.99 (0.94, 1.05)	1.25 (1.18, 1.33)	0.99 (0.94, 1.05)	**1.26 (**1.17, 1.35)
imputed	*1.30 (1.22, 1.38)*	*1.00 (0.92, 1.09)*	*1.26 (1.20, 1.33)*	*0.97 (0.90, 1.05)*	***1.26 (**1.17, 1.36)*
Externalizing					
Intrusive	1.15 (1.10, 1.21)	1.09 (1.04, 1.15)	1.23 (1.17, 1.30)	**1.07 (**1.01, 1.14)	**1.13 (**1.06, 1.21)
imputed	*1.16 (1.09, 1.23)*	*1.09 (1.01, 1.19)*	*1.22 (1.13, 1.32)*	*1.06 (0.98, 1.14)*	***1.12 (**1.04, 1.20)*
Aggression	1.20 (1.16, 1.24)	1.12 (1.08, 1.16)	1.31 (1.26, 1.37)	**1.10 (**1.06, 1.14)	**1.17 (**1.12, 1.23)
imputed	*1.21 (1.17, 1.26)*	*1.11 (1.06, 1.16)*	*1.32 (1.26, 1.38)*	***1.09 (**1.05, 1.13)*	***1.19 (**1.14, 1.25)*
Delinquency	1.21 (1.14, 1.28)	1.44 (1.36, 1.52)	1.68 (1.57, 1.78)	**1.38 (**1.30, 1.47)	**1.17 (**1.10, 1.24)
imputed	*1.20 (1.14, 1.27)*	*1.42 (1.33, 1.51)*	*1.65 (1.55, 1.76)*	***1.37 (**1.29, 1.45)*	***1.16 (**1.10, 1.23)*
Other					
Somatic	1.23 (1.19, 1.27)	1.10 (1.06, 1.15)	1.30 (1.25, 1.35)	**1.06 (**1.02, 1.10)	**1.18 (**1.13, 1.23)
imputed	*1.25 (1.21, 1.29)*	*1.10 (1.05, 1.16)*	*1.31 (1.27, 1.35)*	***1.05 (**1.01, 1.08)*	***1.19 (**1.13, 1.25)*
Thought	1.77 (1.59, 1.97)	1.29 (1.14, 1.46)	1.97 (1.76, 2.21)	**1.11 (**1.01, 1.23)	**1.53 (**1.34, 1.73)
imputed	*1.75 (1.56, 1.97)*	*1.27 (1.17, 1.37)*	*1.96 (1.77, 2.16)*	***1.12 (**1.23, 1.02)*	***1.55 (**1.75, 1.36)*
Attention	1.26 (1.20, 1.32)	1.11 (1.05, 1.17)	1.40 (1.32, 1.48)	**1.11** (1.05, 1.18)	**1.26 (**1.18, 1.34)
imputed	*1.29 (1.22, 1.35)*	*1.10 (1.03, 1.18)*	*1.37 (1.29, 1.44)*	*1.06 (0.99, 1.14)*	***1.24 (**1.16, 1.32)*

Legend for Table 40:

[a] Regressions performed using No-Disorder group as reference; models are adjusted for participant gender and age, plus maternal education, drinking, depression, anxiety and marital status. Significant ORs (P<0.05) are in bold type

[b] Regressions performed using either MHD or AUD as reference group; models are adjusted for participant gender and age, plus maternal education, drinking, depression, anxiety and marital status. Significant ORs (P<0.05) are in bold type

Table 41; Multinomial logistic regression models of comorbidity category at age 21, with YASR dimensions as predictors, showing the effect of adjusting for illicit substance use disorders

	Mutually adjusted models [a]			Adjusted for illicit substance use disorders [b]		
YASR Dimension	**MHD only** OR (CI_{95})	**AUD only** OR (CI_{95})	**CAMHD** OR (CI_{95})	**MHD only** OR (CI_{95})	**AUD only** OR (CI_{95})	**CAMHD** OR (CI_{95})
Internalizing						
Anxiety / depression	**1.15** (1.13, 1.18)	1.01 (0.98, 1.03)	**1.16** (1.13, 1.18)	**1.15** (1.13, 1.17)	0.99 (0.96, 1.02)	**1.14** (1.11, 1.16)
Withdrawn	**1.26** (1.20, 1.32)	0.99 (0.94, 1.05)	**1.25** (1.18, 1.33)	**1.26** (1.20, 1.32)	0.96 (0.90, 1.02)	**1.20** (1.13, 1.28)
Externalizing						
Intrusive	**1.15** (1.10, 1.21)	**1.09** (1.04, 1.15)	**1.23** (1.17, 1.30)	**1.15** (1.09, 1.20)	**1.08** (1.02, 1.14)	**1.22** (1.15, 1.29)
Aggression	**1.20** (1.16, 1.24)	**1.12** (1.08, 1.16)	**1.31** (1.26, 1.37)	**1.19** (1.15, 1.23)	**1.08** (1.04, 1.13)	**1.26** (1.21, 1.31)
Delinquency	**1.21** (1.14, 1.28)	**1.44** (1.36, 1.52)	**1.68** (1.57, 1.78)	**1.16** (1.09, 1.24)	**1.32** (1.23, 1.40)	**1.48** (1.38, 1.59)
Other						
Somatic	**1.23** (1.19, 1.27)	**1.10** (1.06, 1.15)	**1.30** (1.25, 1.35)	**1.21** (1.17, 1.26)	**1.06** (1.02, 1.11)	**1.24** (1.19, 1.29)
Thought	**1.77** (1.59, 1.97)	**1.29** (1.14, 1.46)	**1.97** (1.76, 2.21)	**1.69** (1.51, 1.88)	1.12 (0.97, 1.28)	**1.67** (1.47, 1.89)
Attention	**1.26** (1.20, 1.32)	**1.11** (1.05, 1.17)	**1.40** (1.32, 1.48)	**1.24** (1.18, 1.30)	**1.05** (1.00, 1.12)	**1.31** (1.23, 1.40)

Odds ratios are comparison with the No-Disorder group. Significant ORs ($P<0.05$) are in bold type

[a] Models are adjusted for participant gender and age, plus maternal education, drinking, depression, anxiety and marital status.

[b] Models are further adjusted for illicit substance use disorders.

Appendix 5: Supplementary material published online in support of paper 6.1

Title

Does early socio-economic disadvantage predict comorbid alcohol and mental health disorders?

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This material supplements but does not replace the content of the peer-reviewed paper published in *Drug and Alcohol Dependence*.

Table 42: Correlation between Socio-Economic Disadvantage variables

	Family income	Maternal education	Partner education	Maternal employment	Partner employment
Family income	1	0.095***	0.115***	0.308***	0.400***
Maternal education	0.095***	1	0.309***	0.067***	0.030*
Partner education	0.115***	0.309***	1	0..081***	0.096***
Maternal employment	0.308***	0.067***	0.081***	1	0.337***
Partner employment	0.400***	0.030*	0.096***	0.337***	1
Marital status	0.257***	0.059***	0.098***	0.596***	0.304***

Figures below the diagonal are Pearson's correlation coefficients
Figures above the diagonal are Spearman's rho correlation coefficients
*denotes *P*<0.05; *** denotes *P*<0.001

Table 43: Univariate relationships of maternal factors with socio-economic disadvantage (SED) and with comorbidity group at age 21

SED SCORE	Comorbid alcohol/MH disorder OR (CI_{95})	Maternal age at pregnancy OR (CI_{95})	Maternal anxiety OR (CI_{95})	Maternal depression OR (CI_{95})	Maternal smoking in pregnancy OR (CI_{95})	Maternal bingeing in pregnancy OR (CI_{95})	Mother un-partnered at pregnancy OR (CI_{95})
0	**Reference**						
1	1.69 (0.99, 2.87)	**0.27** (0.17, 0.41)	**1.39** (0.99, 1.96)	1.62 (0.89, 2.97)	**1.50** (1.22, 1.86)	1.84 (0.91, 3.71)	1.36 (0.78, 2.38)
2	**2.12** (1.29, 3.48)	**0.18** (0.12, 0.27)	**1.62** (1.18, 2.23)	**2.07** (1.18, 3.65)	**2.17** (1.78, 2.64)	**2.65** (1.37, 5.12)	1.57 (0.93, 2.64)
3	**3.02** (1.79, 5.17)	**0.05** (0.03, 0.08)	**2.39** (1.71, 3.34)	**3.23** (1.81, 5.78)	**2.72** (2.19, 3.36)	**3.15** (1.59, 6.25)	**7.16** (4.31, 11.89)
4	**2.36** (1.22, 4.59)	**0.01** (0.01, 0.02)	**3.52** (2.48, 5.00)	**6.81** (3.81, 12.16)	**4.20** (3.31, 5.33)	**3.45** (1.68, 7.10)	**26.9** (16.2, 44.7)
5	**3.97** (1.65, 9.55)	**0.01** (0.00, 0.01)	**4.80** (3.19, 7.21)	**9.19** (4.90, 17.23)	**5.99** (4.38, 8.18)	**6.73** (3.16, 14.35)	**68.5** (39.8, 118.1)
COMORBIDITY GROUP							
No disorder	**Reference**						
MHD only	**-**	**0.49** (0.30, 0.80)	**1.51** (1.10, 2.07)	0.98 (0.57, 1.69)	**1.76** (1.43, 2.16)	**1.92** (1.13, 3.26)	1.31 (0.94, 1.83)
AUD only	**-**	**0.54** (0.31, 0.96)	1.18 (0.81, 1.73)	1.07 (0.59, 1.95)	**1.50** (1.18, 1.89)	1.44 (0.76, 2.75)	1.37 (0.94, 1.99)
Comorbid	**-**	**0.39** (0.21, 0.74)	1.15 (0.75, 1.77)	1.16 (0.60, 2.23)	**2.68** (2.07, 3.47)	**2.11** (1.12, 3.98)	**1.75** (1.19, 2.57)

Table 44: Univariate relationships of participant factors with socio-economic disadvantage (SED) and with comorbidity group at age 21

SED SCORE	Comorbid alcohol/MH disorder OR (CI_{95})	Own drinking at age 14 OR (CI_{95})	Own behaviour problems at age14 OR (CI_{95})	Own low education at age 21 OR (CI_{95})
0	**Reference**			
1	1.69 (0.99, 2.87)	0.72 (0.47, 1.08)	**0.63** (0.44, 0.90)	**2.91** (1.90, 4.47)
2	**2.12** (1.29, 3.48)	0.94 (0.65, 1.36)	0.83 (0.61, 1.14)	**4.41** (2.93, 6.64)
3	**3.02** (1.79, 5.17)	1.29 (0.86, 1.93)	**0.54** (0.37, 0.81)	**5.43** (3.53, 8.35)
4	**2.36** (1.22, 4.59)	1.27 (0.78, 2.06)	**0.56** (0.34, 0.93)	**5.54** (3.43, 8.96)
5	**3.97** (1.65, 9.55)	1.56 (0.81, 3.01)	0.43 (0.18, 1.03)	**9.80** (5.26, 18.3)
COMORBIDITY GROUP				
No disorder	**Reference**			
MHD only	**-**	1.34 (0.85, 2.12)	**0.44** (0.29, 0.69)	**1.84** (1.43, 2.36)
AUD only	**-**	**2.22** (1.41, 3.49)	**0.50** (0.30, 0.82)	**2.44** (1.86, 3.20)
Comorbid	**-**	**3.67** (2.37, 5.68)	**0.33** (0.17, 0.65)	**2.88** (2.15, 3.86)

Table 45: Differences between the impact of smoking during pregnancy and before pregnancy on the association of comorbidity with socio-economic disadvantage

Socio-economic disadvantage score	Comorbidity group	Model 1: Unadjusted OR (CI_{95})	Model 2: Smoking before pregnancy OR (CI_{95})	Model 3: Smoking during pregnancy OR (CI_{95})
0		Reference		
1	MH only	1.26 (0.88, 1.81)	1.24 (0.82, 1.88)	1.23 (0.64, 2.35)
	AUD only	1.26 (0.84, 1.90)	1.25 (0.78, 2.02)	0.78 (0.41, 1.50)
	Comorbid	1.69 (0.99, 2.87)	1.91 (0.96, 3.78)	1.42 (0.64, 3.16)
2	MH only	**1.46** (1.04, 2.05)	1.30 (0.87, 1.94)	1.52 (0.83, 2.76)
	AUD only	1.41 (0.96, 2.07)	1.47 (0.93, 2.31)	0.91 (0.50, 1.66)
	Comorbid	**2.12** (1.29, 3.48)	**2.13** (1.11, 4.12)	1.53 (0.72, 3.23)
3	MH only	**1.89** (1.29, 2.77)	1.57 (0.98, 2.51)	**2.21** (1.16, 4.18)
	AUD only	1.54 (0.99, 2.39)	1.21 (0.69, 2.11)	1.26 (0.66, 2.41)
	Comorbid	**3.02** (1.79, 5.17)	**3.02** (1.47, 6.21)	2.04 (0.92, 4.52)
4	MH only	**1.92** (1.02, 3.07)	1.21 (0.61, 2.40)	1.96 (0.97, 4.00)
	AUD only	1.58 (0.91, 2.73)	1.42 (0.68, 2.98)	1.18 (0.56, 2.47)
	Comorbid	**2.36** (1.22, 4.59)	0.60 (0.13, 2.82)	1.71 (0.70, 4.15)
5	MH only	1.15 (0.48, 2.73)	0.92 (0.18, 4.58)	0.83 (0.28, 2.44)
	AUD only	0.99 (0.35, 2.78)	1.85 (0.45, 7.60)	0.40 (0.10, 1.51)
	Comorbid	**3.97#** (1.65, 9.55)	3.45 (0.64, 18.43)	1.86 (0.62, 5.54)

Model 1: unadjusted
Model 2: adjusted for maternal smoking before pregnancy only (excluding smoking during pregnancy)
Model 3: adjusted for maternal smoking during pregnancy only (excluding smoking before pregnancy)
# indicates that $OR_{(comorbid)}$ is significantly higher than either OR or $OR_{(AUD)}$ (P <0.05)

Table 46: Examining participant factors as potential mediators: Multinomial models of comorbidity group at age 21, with socio- economic disadvantage as predictor

Socio-economic disadvantage	Comorbidity group	Model 2a. Mat age, own behavior prob	Model 3a. Mat age, own drinking@14	Model 4a. Mat age, own education	Model 5a. Mat age, all own factors
		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})	OR (CI65)
0		Reference			
1	MH only	1.17 (0.79, 1.74)	1.27 (0.87, 1.84)	1.19 (0.83, 1.71)	1.14 (0.76, 1.70)
	AUD only	1.43 (0.89, 2.30)	1.31 (0.86, 2.00)	1.11 (0.74, 1.69)	1.34 (0.83, 2.16)
	Comorbid	1.90 (1.05, 3.46)	**1.78** (1.03, 3.07)	1.49 (0.87, 2.55)	1.82 (0.99, 3.33)
2	MH only	1.33 (0.91, 1.92)	**1.48** (1.05, 2.10)	1.34 (0.95, 1.89)	1.23 (0.84, 1.78)
	AUD only	1.49 (0.95, 2.34)	**1.48** (1.00, 2.21)	1.20 (0.81, 1.77)	1.30 (0.83, 2.05)
	Comorbid	**2.11** (1.19, 3.73)	**2.15** (1.29, 3.60)	**1.80** (1.09, 2.98)	**1.83** (1.03, 3.27)
3	MH only	**1.82** (1.20, 2.28)	**1.91** (1.28, 2.83)	**1.65** (1.11, 2.44)	**1.71** (1.11, 2.61)
	AUD only	1.51 (0.90, 2.54)	1.49 (0.94, 2.37)	1.21 (0.76, 1.90)	1.31 (0.78, 2.23)
	Comorbid	**3.00** (1.62, 5.57)	**2.87** (1.64, 5.02)	**2.44** (1.41, 4.22)	**2.57** (1.37, 4.82)
4	MH only	**1.79** (1.05, 3.07)	1.63 (0.98, 2.71)	1.61 (0.99, 2.61)	1.64 (0.95, 2.82)
	AUD only	1.54 (0.80, 2.95)	1.41 (0.78, 2.54)	1.15 (0.65, 2.05)	1.38 (0.71, 2.67)
	Comorbid	**2.35** (1.09, 5.10)	**2.05** (1.00, 4.17)	1.79 (0.90, 3.55)	2.08 (0.95, 4.57)
5	MH only	1.06 (0.41, 2.74)	0.94 (0.38, 2.37)	0.87 (0.36, 2.10)	0.90 (0.35, 2.36)
	AUD only	0.89 (0.28, 2.88)	0.71 (0.23, 2.22)	0.65 (0.23, 1.86)	0.69 (0.21, 2.27)
	Comorbid	**3.16**[¥](1.11, 8.94)	**3.20**[#](1.26, 8.14)	2.33[¥](0.91, 5.92)	1.97 (0.65, 6.01)

Model 2a: adjusted for maternal age at pregnancy, participants' behaviour problems (YSR total problems) at age 14
Model 3a: adjusted for maternal age at pregnancy, participants' drinking at age 14
Model 4a: adjusted for maternal age at pregnancy, participants' own low education level by age 21
Model 5a: adjusted for maternal age at pregnancy, own drinking at 14, own behaviour problems at 14 and low education level
[#] indicates that $OR_{(comorbid)}$ is significantly higher than either OR or $OR_{(AUD)}$ (P <0.05); [¥] indicates that $OR_{(comorbid)}$ is significantly higher than either OR or $OR_{(AUD)}$ (P <0.08)

Table 47: Comparing complete case analyses (n=2388) and multiply imputed (n= 7223) models of comorbidity group at age 21

Socio-economic disadvantage score	**Co-morbidity group**	**Model 1: Unadjusted** OR (CI_{95})	***Model 1 Imputed*** OR (CI_{95})	**Model 2: Maternal age** OR (CI_{95})	***Model 2 Imputed*** OR (CI_{95})	**Model 4: Maternal age/smoking** OR (CI_{95})	***Model 4 Imputed*** OR (CI_{95})
0		Reference					
	MH only	1.26 (0.88, 1.81)	*1.24 (0.82, 1.86)*	1.27 (0.88, 1.85)	*1.20 (0.80, 1.82)*	1.21 (0.84, 1.75)	*1.17 (0.78, 1.78)*
1	AUD only	1.26 (0.84, 1.90)	*1.12 (0.61, 2.04)*	1.24 (0.82, 1.89)	*1.08 (0.59, 1.99)*	1.21 (0.80, 1.82)	*1.06 (0.58, 1.94)*
	Comorbid	1.69 (0.99, 2.87)	***1.87** (1.02, 3.40)*	1.70 (0.99, 2.92)	***1.81** (1.01, 3.26)*	1.58 (0.93, 2.70)	*1.72 (0.95, 3.11)*
	MH only	**1.46** (1.04, 2.05)	*1.43 (0.98, 2.10)*	**1.50** (1.06, 2.13)	*1.38 (0.94, 2.02)*	1.33 (0.94, 1.87)	*1.30 (0.89, 1.91)*
2	AUD only	1.41 (0.96, 2.07)	*1.28 (0.81, 2.00)*	1.41 (0.95, 2.09)	*1.22 (0.77, 1.95)*	1.31 (0.89, 1.93)	*1.17 (0.75, 1.85)*
	Comorbid	**2.12** (1.29, 3.48)	***2.21** (1.25, 3.91)*	**2.09** (1.25, 3.48)	***2.13** (1.20, 3.76)*	**1.78** (1.08, 2.96)	***1.88** (1.06, 3.34)*
	MH only	**1.89** (1.29, 2.77)	***1.95** (1.38, 2.76)*	**1.75** (1.17, 2.62)	***1.83** (1.29, 2.59)*	**1.62** (1.10, 2.40)	***1.70** (1.20, 2.41)*
3	AUD only	1.54 (0.99, 2.39)	*1.32 (0.79, 2.20)*	1.46 (0.92, 2.32)	*1.22 (0.72, 2.07)*	1.33 (0.85, 2.09)	*1.16 (0.69, 1.93)*
	Comorbid	**3.02** (1.79, 5.17)	***3.43** (1.86, 6.63)*	**2.72** (1.55, 4.76)	***3.21** (1.77, 5.81)*	**2.36** (1.36, 4.09)	***2.74** (1.49, 5.05)*
	MH only	**1.92** (1.02, 3.07)	***1.80** (1.19, 2.72)*	**1.72** (1.05, 2.84)	***1.63** (1.04, 2.57)*	1.48 (0.91, 2.42)	*1.45 (0.91, 2.29)*
4	AUD only	1.58 (0.91, 2.73)	*1.31 (0.77, 2.21)*	1.48 (0.84, 2.63)	*1.17 (0.67, 2.04)*	1.24 (0.70, 2.19)	*1.07 (0.62, 1.84)*
	Comorbid	**2.36** (1.22, 4.59)	***2.68** (1.41, 5.09)*	**2.20** (1.10, 4.37)	***2.42** (1.27, 4.63)*	1.50 (0.75, 3.00)	***1.90** (1.01, 3.61)*
	MH only	1.15 (0.48, 2.73)	*1.02 (0.32, 3.28)*	1.02 (0.42, 2.49)	*0.90 (0.27, 3.04)*	0.71 (0.28, 1.79)	*0.77 (0.24, 2.53)*
5	AUD only	0.99 (0.35, 2.78)	*0.87 (0.36, 2.10)*	0.89 (0.31, 2.55)	*0.76 (0.32, 1.83)*	0.71 (0.25, 2.03)	*0.68 (0.30, 1.56)*
	Comorbid	**3.97#** (1.65, 9.55)	***3.83**# (1.71, 8.49)*	**3.19#** (1.25, 8.12)	***3.40**# (1.41, 8.16)*	2.34 (0.94, 5.81)	***2.49**# (1.03, 6.01)*

# indicates that $OR_{(comorbid)}$ is significantly greater than either OR or $OR_{(AUD)}$ (P <0.05)

Table 48 Multinomial logistic regression models of comorbidity group at age 21, by socio-economic disadvantage, showing the effect of adjusting for offspring illicit substance use disorders

Socio-economic disadvantage score	Co-morbidity group	Age/smoking [a] OR (CI_{95})	plus SUD [b] OR (CI_{95})
0	Reference		
1	MH only	1.21 (0.84, 1.75)	1.28 (0.88, 1.86)
	AUD only	1.21 (0.80, 1.82)	1.38 (0.88, 2.15)
	Comorbid	1.58 (0.93, 2.70)	**1.80** (1.01, 3.20)
2	MH only	1.33 (0.94, 1.87)	**1.43** (1.00, 2.04)
	AUD only	1.31 (0.89, 1.93)	1.46 (0.96, 2.23)
	Comorbid	**1.78** (1.08, 2.96)	**1.94** (1.12, 3.34)
3	MH only	**1.62** (1.10, 2.40)	**1.63** (1.08, 2.45)
	AUD only	1.33 (0.85, 2.09)	1.45 (0.88, 2.37)
	Comorbid	**2.36** (1.36, 4.09)	**2.23** (1.22, 4.08)
4	MH only	1.48 (0.91, 2.42)	1.56 (0.94, 2.59)
	AUD only	1.24 (0.70, 2.19)	1.42 (0.77, 2.64)
	Comorbid	1.50 (0.75, 3.00)	1.60 (0.75,3.40)
5	MH only	0.71 (0.28, 1.79)	0.73 (0.29, 1.87)
	AUD only	0.71 (0.25, 2.03)	0.76 (0.25, 2.32)
	Comorbid	2.34 (0.94, 5.81)	2.13 (0.76, 6.00)

[a] Model adjusted for maternal age and smoking during pregnancy

[b] Model adjusted for maternal age and smoking during pregnancy, plus SUD in offspring

Appendix 6: Supplementary material published online in support of paper 6.2

Title

Familial factors associated with development of alcohol and mental health comorbidity

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Running title:

Familial factors and comorbid alcohol/mental health

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Table 49: Alcohol and mental health disorders at age 21

			AUD+ MHD	AUD only	MHD only	No Disorder
Predictors		N (%)	% (SE)	% (SE)	% (SE)	% (SE)
Prevalence	**% (SE)**		11.9 (0.6)	16.3 (0.7)	23.4 (0.8)	48.4 (1.0)
	N	2342	279	381	548	1134
Maternal factors [a]						
Mental distress	Yes	617 (9%)	16.9 (2.3)	16.1 (2.3)	26.6 (2.7)	40.4 (3.0)
Drinking	Any	3426 (72%)	11.3 (0.7)	16.5 (0.9)	22.4 (1.0)	49.8 (1.2)
	Binge	488 (10%)	19.7 (2.7)	17.5 (2.5)	23.3 (2.8)	39.5 (3.3)
Smoking	Any	1482 (31%)	16.9 (1.4)	17.0 (1.4)	25.6 (1.7)	40.4 (1.9)
Family environment [b]						
Maternal warmth	Low	332 (10%)	20.3 (2.6)	11.6 (2.1)	33.2 (3.0)	34.9 (3.1)
Communication	Poor	382 (10%)	17.3 (2.8)	19.5 (2.9)	25.9 (3.2)	37.3 (3.6)
Parents separated	Yes	1541(32%)	15.1 (1.3)	16.5 (1.4)	26.6 (1.7)	41.7 (1.9)
Family violence	Any	631 (13%)	15.5 (2.2)	15.2 (2.1)	27.2 (2.7)	42.0 (2.9)
Adolescent behaviour [c]						
Internalising	Yes	496 (11%)	16.8 (2.2)	10.8 (1.8)	38.5 (2.8)	33.9 (2.8)
Externalising	Yes	400 (9%)	22.0 (3.1)	21.4 (3.0)	28.6 (3.4)	28.0 (3.3)
Attention/Thought	Yes	495 (11%)	19.8 (2.4)	15.7 (2.2)	33.6 (2.9)	31.0 (2.8)
Drinking	Yes	341 (7%)	25.8 (3.6)	21.9 (3.3)	20.0 (3.2)	32.3 (3.8)
Smoking	Any	557 (12%)	23.9 (2.7)	21.8 (2.7)	27.6 (2.9)	26.7 (2.8)
Demographic factors [d]						
Gender	Female	3225 (48%)	11.7 (0.9)	6.1 (0.7)	34.2 (1.3)	48.0 (1.4)
Maternal education	Low	4845 (73%)	13.1 (0.8)	16.6 (0.9)	24.0 (1.0)	46.3 (1.2)
Paternal factors [e]						
MH problems	Ever	166 (7%)	10.6 (3.8)	16.7 (4.6)	19.7 (4.9)	53.0 (6.2)
Alcohol problems	Ever	551 (16%)	19.2 (2.5)	12.2 (2.1)	26.5 (2.8)	42.0 (3.2)
Smoking	Any	1424 (35%)	16.6 (1.4)	15.4 (1.4)	22.5 (1.6)	45.4 (1.9)

[a] *Maternal factors were self-reported at 14 year follow-up*
[b] *Family environment factors were assessed via maternal report at 14 years, except for Maternal warmth, assessed by offspring report at 21 years*
[c] *Adolescent behaviour factors were self-reported at 14 years*
[d] *Maternal education was recorded at baseline*
[e] *Paternal factors were reported by mother at 14 years*

Table 50: Multinomial logistic regression model of young adult comorbidity class, by maternal factors, family environment and adolescent behaviour

		AUD+MHD	AUD only	MHD only
Maternal factors		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Mental distress	Yes	1.18 (0.73, 1.90)	1.06 (0.66, 1.69)	0.87 (0.58, 1.31)
Drinking	Drink	1.04 (0.68, 1.59)	**1.69** (1.10, 2.57)	0.79 (0.58, 1.08)
	Binge	1.23 (0.66, 2.28)	**2.11** (1.15, 3.87)	0.74 (0.44, 1.22)
Smoking	Yes	**1.57** (1.12, 2.20)	1.22 (0.88, 1.68)	**1.34** (1.01, 1.76)
Family environment				
Maternal warmth	Low	**2.98** (1.89, 4.70)	1.13 (0.65, 1.94)	**2.31** (1.55, 3.44)
Communication	Poor	1.27 (0.74, 2.19)	1.28 (0.77, 2.14)	1.19 (0.74, 1.89)
Parents separated	Yes	1.23 (0.87, 1.75)	1.25 (0.90, 1.73)	**1.32** (1.01, 1.75)
Relationship violence	Ever	0.80 (0.49, 1.33)	0.89 (0.55, 1.44)	1.05 (0.72, 1.55)
Adolescent behaviour				
Internalising	Yes	1.20 (0.73, 1.97)	0.95 (0.55, 1.63)	**2.01** (1.38, 2.93)
Externalising	Yes	1.43 (0.81, 2.54)	1.35 (0.76, 2.41)	1.30 (0.77, 2.18)
Attention/Thought	Yes	**2.09** (1.24, 3.51)	1.53 (0.89, 2.61)	1.37 (0.88, 2.14)
Drinking	Yes	**2.00** (1.15, 3.47)	1.49 (0.83, 2.69)	0.70 (0.39, 1.26)
Smoking	Yes	**2.37** (1.44, 3.90)	1.67 (0.98, 2.85)	**1.60** (1.01, 2.53)
Demographics				
Gender	Female	1.04 (0.77, 1.42)$^{++}$	**0.25** (0.18, 0.35)	**2.90** (2.24, 3.76)
Maternal education	Low	1.27 (0.89, 1.80)	1.16 (0.85, 1.57)	1.10 (0.85, 1.43)

Model is fully adjusted for all factors, with the No Disorder group as reference.
$^{++}$ OR (comorbid) is significantly different to both MHD only and AUD only ($p<0.05$)

Table 51: Multivariable attrition analysis showing the likelihood of being lost to follow up (LFU) at age 21 according to baseline factors

Covariate	Category	Odds of being LFU	
		Unadjusted	Adjusted
		OR (CI_{95})	OR (CI_{95})
Participant gender	Female	**0.83** (0.75, 0.91)	**0.82** (0.74, 0.91)
Maternal age at FCV[$]		**0.98** (0.97, 0.98)	**0.98** (0.97, 0.99)
Mother's marital status at FCV[$]	No partner	**1.58** (1.35 1.84)	**1.34** (1.13, 1.58)
Mother's education at FCV[$]	< Year 12	**1.16** (1.04, 1.29)	1.08 (0.97, 1.21)
Maternal binge in pregnancy	Yes	**1.30** (1.05, 1.61)	1.01 (0.86, 1.18)
Maternal smoking in pregnancy	Yes	**1.22** (1.10, 1.34)	**1.14** (1.02, 1.27)
Mother depressed at FCV[$]	Depressed	**1.52** (1.17, 1.99)	**1.50** (1.15, 1.96)
Mother anxious at FCV[$]	Anxious	**1.29** (1.08, 1.53)	**1.30** (1.09, 1.54)

[$] FCV = First clinic visit in pregnancy (baseline)

Multivariable model is adjusted for all factors listed. All factors were used for the multiple imputation model.

Table 52: Effect of multiple imputation on model

		Complete cases (n=1755)			Multiply imputed (n=6703)		
		vs No Disorder	*vs* AUD	*vs* MHD	*vs* No Disorder	*vs* AUD	*vs* MHD
Maternal cluster		OR (CI_{95})	Differences		OR (CI_{95})	Differences	
Mental distress	Yes	1.08 (0.66, 1.79)			1.26 (0.80, 1.98)		
Drinking	Drink	1.19 (0.75, 1.90)			1.09 (0.76, 1.56)		
	Binge	1.36 (0.70, 2.63)			1.58 (0.91, 2.72)		
Smoking	Yes	**1.56** (1.09, 2.22)			**1.47** (1.08, 2.01)		
Family environment cluster							
Maternal warmth	Low	**3.19** (1.99, 5.13)	***		**2.26** (1.57, 3.27)	***	
Communication	Poor	1.15 (0.63, 2.08)			1.28 (0.74, 2.20)		
Parents separated	Yes	1.28 (0.89, 1.85)			1.32 (0.90, 1.93)		
Family violence	Ever	0.79 (0.47, 1.34)			0.92 (0.58, 1.48)		
Adolescent behaviour cluster							
Internalising	Yes	1.12 (0.66, 1.90)		*	1.03 (0.62, 1.73)		*
Externalising	Yes	1.42 (0.79, 2.59)			1.44 (0.81, 2.56)		
Attention/Thought	Yes	**2.04** (1.18, 3.52)			**2.03** (1.29, 3.21)		
Drinking	Yes	**2.22** (1.25, 3.96)		***	**1.96** (1.15, 3.74)		***
Smoking	Yes	**2.24** (1.33, 3.77)			**2.18** (1.42, 3.34)		
Demographics							
Gender	Female	1.07 (0.77, 1.42)	***	***	0.94 (0.68, 1.29)	***	***
Maternal ed	Low	1.41 (0.97, 2.05)			**1.48** (1.13, 1.93)		

*Difference vs alternative reference group is significant * P<0.05; **P<0.01; ***P<0.005*
Models are fully adjusted for all factors, with the reference group as shown.
For ease of model comparison, only ORs for comorbid alcohol/mental health group are shown.

Table 53: Multinomial logistic regression model of young adult comorbidity class, after exclusion of individuals with non-alcohol substance use disorders

		AUD+MHD *vs* **no disorder**	**AUD+MHD** *vs* **AUD only**	**AUD+MHD** *vs* **MHD only**
Maternal factors [a]		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Mental distress	Yes	1.33 (0.73, 2.42)	1.63 (0.77, 3.46)	1.53 (0.80, 2.91)
Drinking	Drink	0.95 (0.55, 1.64)	0.57 (0.29, 1.13)	1.39 (0.78, 2.47)
	Binge	0.89 (0.39, 2.05)	**0.36***(0.13, 0.95)	1.41 (0.59, 3.37)
Smoking	Yes	**1.58** (1.02, 2.46)	1.35 (0.80, 2.27)	1.11 (0.69, 1.77)
Family environment [b]				
Maternal warmth	Low	**3.92** (2.25, 6.83)	**4.27*****(1.98, 9.20)	**1.77*** (1.01, 3.11)
Communication	Poor	1.11 (0.53, 2.34)	0.73 (0.32, 1.71)	0.84 (0.39, 1.81)
Parents separated	Yes	1.31 (0.83, 2.06)	1.03 (0.61, 1.76)	0.93 (0.58, 1.50)
Relationship violence	Ever	0.62 (0.31, 1.22)	0.78 (0.35, 1.76)	0.66 (0.33, 1.34)
Adolescent behaviour [c]				
Internalising	Yes	1.25 (0.67, 2.33)	1.48 (0.65, 3.32)	0.71 (0.38, 1.34)
Externalising	Yes	1.49 (0.71, 3.10)	0.99 (0.42, 2.34)	1.24 (0.57, 2.68)
Attention/Thought	Yes	**2.28** (1.17, 4.44)	1.97 (0.85, 4.52)	1.47 (0.74, 2.94)
Drinking	Yes	**2.06** (1.05, 4.24)	1.64 (0.68, 3.96)	**2.80****(1.25, 6.28)
Smoking	Yes	**2.34** (1.23, 4.33)	1.34 (0.62, 2.88)	1.66 (0.85, 3.24)
Demographics [d]				
Gender	Female	1.33 (0.89, 1.99)	**5.57*****(3.34, 9.29)	**0.41*****(0.26, 0.65)
Maternal education	Low	1.41 (0.73, 1.80)	0.94 (0.55, 1.60)	1.05 (0.65, 1.71)

Models are fully adjusted for all factors, reference groups as shown
*Difference vs alternative reference group is significant * P<0.05; **P<0.01; ***P<0.005*
[a] *Maternal factors were self-reported at 14 year follow-up*
[b] *Family environment factors were assessed via maternal report at 14 years, except for Maternal warmth, assessed by offspring report at 21 years*
[c] *Adolescent behaviour factors were self-reported at 14 years*
[d] *Maternal education was recorded at baseline*
[e] *Paternal factors were reported by mother at 14 years*

Appendix 7: Supplementary material published online in support of paper 6.3

Title:

Substance use and mental health disorders are linked to different forms of intimate partner violence victimisation

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Running title:

Intimate partner abuse and alcohol/mental disorders

This material supplements but does not replace the content of the paper published in *Drug and Alcohol Dependence*

Table 54: Prevalence of Psychological, Physical and Severe Combined intimate partner violence victimisation in young adults

			Form of IPV experienced		
			Psychological	**Physical**	**Severe combined**
		N (%)	**% (SE)**	**% (SE)**	**% (SE)**
Overall			**40.8 (0.9)**	**39.7 (0.9)**	**6.6 (0.4)**
Demographic factors					
Gender	Female	3315 (51%)	41.1 (1.2)	36.1 (1.1)	8.1 (0.6)
Own ed	<Year 12	708 (21%)	54.6 (1.9)	54.3 (1.9)	12.2 (1.3)
Cohabitation	Yes	990 (30%)	44.9 (1.6)	45.1 (1.6)	7.1 (0.8)
Own age	Mean (SE)	20.6 (0.1%)	20.7 (2.4)	20.7 (0.02)	20.7(0.06)
Children in care	Mean	0.1 (0.4%)	0.20 (.01)	0.21 (.01)	0.39 (.05)
Family factors					
Residential area	Problems	456 (10%)	45.7 (3.1)	45.8 (3.1)	8.8 (1.8)
Teen aggression	YSR	2601 (38%)	29.3 (2.4)	25.9 (2.3)	1.7 (0.7)
Sexual assault <16	Yes	337 (10%)	61.7 (2.7)	59.2 (2.7)	21.6 (2.3)
Left home <17	Yes	407 (12%)	67.7 (2.4)	68.7 (2.3)	20.8 (2.0)
Parents' relationship	Violence	641 (14%)	45.9 (2.6)	45.4 (2.6)	6.5 (1.3)
Mother's ed	<Year 12	4920 (73%)	42.4 (1.0)	42.1 (1.0)	75.4 (2.4)
Mother age @birth	Mean (SE)	25.3 (0.6%)	25.5 (0.14)	25.4 (0.14)	24.8 (0.35)

Table 55: Univariate relationships between potential confounders and disorder type

		MHD	AUD	AUD/MHD	SUD	SUD/MHD	AUD/SUD	AUD/SUD/MHD
		OR (CI_{95})	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Adult factors								
Gender	Female	**3.22** (2.45, 4.22)	**0.23** (0.16, 0.33)	**1.56** (1.04, 2.33)	**0.50** (0.34, 0.74)	**1.76** (1.15, 2.67)	**0.18** (0.12, 0.28)	**0.61** (0.44, 0.85)
Age	Per 5yr	1.59 (0.78, 3.23)	**3.77** (1.45, 9.81)	2.21 (0.68, 7.21)	**7.22** (2.18, 23.8)	1.57 (0.47, 5.23)	**3.87** (1.41, 10.6)	**5.20** (1.87, 14.48)
Education	<Year 12	**1.74** (1.27, 2.37)	**2.16** (1.46, 3.19)	**2.53** (1.59, 4.01)	**3.06** (1.96, 4.76)	**3.88** (2.51, 6.00)	**3.84** (2.65, 5.58)	**3.99** (2.74, 5.80)
Cohabitation	Yes	1.02 (0.77, 1.35)	0.92 (0.64, 1.32)	0.92 (0.58, 1.44)	0.89 (0.57, 1.40)	1.19 (0.74, 1.92)	0.81 (0.55, 1.19)	**0.65** (0.43, 0.96)
# children in care	0-3	**1.54** (1.15, 2.07)	0.77 (0.44, 1.34)	**1.78** (1.17, 2.71)	1.08 (0.62, 1.89)	**2.09** (1.41, 3.09)	1.38 (0.92, 2.10)	**1.78** (1.23, 2.57)
Adolescent factors								
Residential area	Problems	0.91 (0.58, 1.42)	0.79 (0.42, 1.50)	1.34 (0.70, 2.57)	0.78 (0.35, 1.73)	1.77 (0.96, 3.27)	0.88 (0.45, 1.70)	1.43 (0.82, 2.47)
Teen aggression	YSR	**0.56** (0.38, 0.84)	0.99 (0.62, 1.56)	**0.40** (0.18, 0.89)	0.51 (0.25, 1.03)	**0.25** (0.09, 0.69)	**0.53** (0.29, 0.97)	**0.28** (0.13, 0.61)
Sexual assault <16	Yes	**3.15** (2.12, 4.70)	0.59 (0.25, 1.39)	**4.64** (2.67, 8.06)	1.51 (0.72, 3.16)	**4.01** (2.25, 7.13)	1.65 (0.89, 3.07)	**5.98** (3.74, 9.55)
Left home <17	Yes	**2.77** (1.81, 4.24)	1.25 (0.63, 2.47)	**3.23** (1.75, 5.94)	**2.74** (1.45, 5.19)	**4.99** (2.86, 8.72)	**5.51** (3.41, 8.89)	**7.46** (4.70, 11.85)
Drinking	Regular	1.26 (0.72, 2.21)	1.62 (0.83, 3.17)	**3.21** (1.65, 6.27)	**2.33** (1.12, 4.83)	**2.58** (1.24, 5.37)	**2.80** (1.53, 5.12)	**4.43** (2.57, 7.61)
Cannabis use	Regular	1.16 (0.55, 2.43)	**2.81** (1.36, 5.82)	**2.72** (1.13, 6.56)	**22.89** (12.9, 40.7)	**16.44** (9.0, 29.9)	**36.30**(21.4, 61.6)	**30.82** (18.1, 52.5)
Internalising	YSR	**2.72** (1.94, 3.81)	0.89 (0.49, 1.61)	**2.00** (1.14, 3.50)	0.78 (0.37, 1.66)	**2.64** (1.55, 4.52)	1.25 (0.72, 2.19)	**2.12** (1.32, 3.43)
Family of origin factors								
Parents' relationship	Violence	1.21 (0.83, 1.74)	0.87 (0.50, 1.49)	1.32 (0.74, 2.38)	1.22 (0.67, 2.23)	**2.49** (1.49, 4.16)	1.46 (0.89, 2.38)	**1.84** (1.16, 2.92)
Mother's education	<Year 12	**1.33** (1.02, 1.72)	**1.48** (1.03, 2.11)	1.48 (0.94, 2.31)	0.96 (0.64, 1.45)	1.39 (0.89, 2.18)	1.29 (0.90, 1.86)	**1.66** (1.12, 2.45)
Mother birth age	per 5yr	**0.88** (0.78, 0.99)	0.90 (0.77, 1.05)	**0.79** (0.65, 0.97)	1.10 (0.91, 1.31)	0.84 (0.69, 1.03)	0.91 (0.77, 1.06)	**0.83** (0.70, 0.98)

Table 56 Logistic regression models of psychological, physical and severe combined IPV victimization in young adults

		1. Unadjusted	2. Adjusted for covariates	3. Adjusted for other forms of IPV
		OR (CI_{95})	**OR (CI_{95})**	**OR (CI_{95})**
Psychological IPV				
No disorder		1.00	1.00	1.00
MHD only	Yes	**2.27** (1.77, 2.90)	**2.10** (1.59, 2.79)	**1.66** (1.20, 2.30)
AUD only	Yes	**2.23** (1.61, 3.09)	**2.10** (1.44, 3.06)	**1.86** (1.21, 2.86)
SUD only	Yes	**2.33** (1.56, 3.46)	**2.31** (1.49, 3.60)	1.62 (0.98, 2.70)
AUD/MHD	Yes	**4.47** (2.99, 6.71)	**3.76*** (2.36, 6.00)	**3.09*** (1.81, 5.26)
SUD/MHD	Yes	**3.84** (2.55, 5.78)	**2.74** (1.70, 4.42)	1.55 (0.89, 2.70)
AUD/SUD	Yes	**2.42** (1.71, 3.43)	**1.84** (1.21, 2.78)	1.57 (0.98, 2.51)
AUD/MHD/SUD	Yes	**7.52** (5.18, 10.90)	**6.10*** (3.94, 9.45)	**2.96** (1.79, 4.88)
Physical IPV				
No disorder		1.00	1.00	1.00
MHD only	Yes	**1.91** (1.49, 2.45)	**2.04** (1.51, 2.74)	**1.56** (1.11, 2.20)
AUD only	Yes	**2.27** (1.64, 3.14)	**1.70** (1.16, 2.50)	1.32 (0.85, 2.04)
SUD only	Yes	**2.78** (1.87, 4.12)	**2.59** (1.65, 4.06)	**2.07** (1.25, 3.43)
AUD/MHD	Yes	**2.78** (1.87, 4.12)	**2.40** (1.49, 3.87)	1.23 (0.71, 2.16)
SUD/MHD	Yes	**4.06** (2.70, 6.11)	**3.66** (2.24, 5.97)	**3.01*** (1.68, 5.38)
AUD/SUD	Yes	**3.08** (2.19, 4.34)	**1.79** (1.19, 2.69)	1.37 (0.85, 2.20)
AUD/MHD/SUD	Yes	**9.32** (6.32, 13.74)	**7.44***(4.67, 11.83)	**4.13** (2.43, 7.00)
Severe Combined IPV				
No disorder		1.00	1.00	1.00
MHD only	Yes	**4.06** (2.21, 7.45)	**3.48** (1.62, 7.46)	**2.68** (1.16, 6.15)
AUD only	Yes	1.69 (0.66, 4.34)	0.96 (0.20, 4.46)	0.89 (0.18, 4.29)
SUD only	Yes	1.39 (0.40, 4.83)	1.64 (0.43, 6.18)	1.00 (0.25, 4.02)
AUD/MHD	Yes	**7.14** (3.42, 14.91)	**7.12** (2.95, 17.21)	**4.84** (1.82, 12.82)
SUD/MHD	Yes	**7.66** (3.66, 16.03)	**5.14** (1.99, 13.29)	**2.66** (0.93, 7.62)
AUD/SUD	Yes	**3.69** (1.70, 8.03)	2.75 (0.98, 7.70)	1.52 (0.45, 5.12)
AUD/MHD/SUD	Yes	**10.87** (5.79, 20.39)	**7.25*** (3.22, 16.32)	**3.35** (1.42, 7.95)

2. Covariates include gender, age, education, cohabitation, number of children in care, leaving home early, childhood sexual assault, adolescent aggression, residential area problems, parental relationship violence in adolescence, mother's education and mother's age at birth.

3. Models have been adjusted for covariates as above, plus other forms of IPV (e.g. the psychological IPV model was adjusted for physical and severe combined IPV).

* indicates that the OR for a combined disorder is greater than those for single disorders ($P<0.05$)

Table 57: Multivariable logistic regression analysis of attrition showing the likelihood of being lost to follow up (LFU) at 21 years according to baseline factors

Covariate	Category	Odds of being LFU	
		Unadjusted OR (CI_{95})	**Adjusted** OR (CI_{95})
Participant gender	Female	**0.83** (0.75, 0.91)	**0.82** (0.74, 0.91)
Maternal age at FCV[$]		**0.98** (0.97, 0.98)	**0.98** (0.97, 0.99)
Mother's marital status at FCV[$]	No partner	**1.58** (1.35 1.84)	**1.34** (1.13, 1.58)
Mother's education at FCV[$]	< Year 12	**1.16** (1.04, 1.29)	1.08 (0.97, 1.21)
Maternal binge in pregnancy	Yes	**1.30** (1.05, 1.61)	1.01 (0.86, 1.18)
Maternal smoking in pregnancy	Yes	**1.22** (1.10, 1.34)	**1.14** (1.02, 1.27)
Mother depressed at FCV[$]	Depressed	**1.52** (1.17, 1.99)	**1.50** (1.15, 1.96)
Mother anxious at FCV[$]	Anxious	**1.29** (1.08, 1.53)	**1.30** (1.09, 1.54)

[$] FCV = First antenatal clinic visit (baseline)

Multivariable model is adjusted for all factors listed above. All factors were used for the inverse probability weighting model.

Table 58 Allowing for attrition: effect of inverse probability weighting on models of Psychological, Physical and Severe Combined intimate partner violence

	Model 1: Psychological IPV	Model 2: Physical IPV	Model 3: Severe combined IPV
	OR (CI_{95})	**OR (CI_{95})**	**OR (CI_{95})**
Complete case analyses; n=1655			
MHD only	**1.66** (1.20, 2.30)	**1.56** (1.11, 2.20)	**2.68** (1.16, 6.15)
AUD only	**1.86** (1.21, 2.86)	1.32 (0.85, 2.04)	0.89 (0.18, 4.29)
SUD only	1.62 (0.98, 2.70)	**2.07** (1.25, 3.43)	1.00 (0.25, 4.02)
AUD/MHD	**3.09** (1.81, 5.26)	1.23 (0.71, 2.16)	**4.84** (1.82, 12.82)
SUD/MHD	1.55 (0.89, 2.70)	**3.01** (1.68, 5.38)	**2.66** (0.93, 7.62)
AUD/SUD	1.57 (0.98, 2.51)	1.37 (0.85, 2.20)	1.52 (0.45, 5.12)
AUD/SUD/MHD	**2.96** (1.79, 4.88)	**4.13** (2.43, 7.00)	**3.35** (1.42, 7.95)
Inverse Probability Weighting data analyses; n=1683			
MHD only	**1.79** (1.29, 2.48	**1.45** (1.00, 1.99)	**2.91** (1.16, 7.34)
AUD only	**1.69** (1.06, 2.69)	1.29 (0.82, 2.05)	0.45 (0.06, 3.72)
SUD only	1.53 (0.88, 2.67)	**2.18** (1.27, 3.74)	1.05 (0.27, 4.16)
AUD/MHD	**2.74** (1.52, 4.95)	1.37 (076, 2.48)	**6.38** (2.28, 17.86)
SUD/MHD	1.75 (0.98, 3.10)	**2.49** (1.34, 4.61)	**4.54** (1.41, 14.61)
AUD/SUD	1.60 (0.96, 2.66)	1.31 (0.79, 2.16)	1.57 (0.44, 5.65)
AUD/SUD/MHD	**2.79** (1.63, 4.76)	**3.90** (2.24, 6.79)	**2.87** (1.19, 6.93)

All models have been adjusted for gender, age, education, cohabitation, number of children in care, leaving home early, prior sexual assault, adolescent aggression, residential area problems, mother's relationship violence, mother's education and mother's age at birth, and for other forms of IPV

Appendix 8: Supplementary material published online in support of paper 7.1

Title:

Predictors of poly-substance use and mental health disorders in young adults – a latent class analysis

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Running title:

Latent classes of poly-substance use in young adults

This material supplements but does not replace the content of the peer-reviewed paper published in *Addiction*

Table 59: Multinomial logistic regression models of LCA class at 21 years as predicted by early maternal and child factors

	Latent class 2 MHD	Latent class 3 AUD/CAN	Latent class 4 PSUD/MHD
Factor	**OR (CI_{95})**	**OR (CI_{95})**	**OR (CI_{95})**
Gender (female)	**2.29** (1.51, 3.46)	**0.36** (0.25, 0.52)	**0.30** (0.15, 0.59)
Socio-economic disadvantage [a]	1.09 (0.93, 1.27)	1.04 (0.90, 1.20)	0.96 (0.75, 1.24)
Maternal smoking in pregnancy [a]	**1.52** (1.05, 2.22)	**1.72** (1.22, 2.43)	1.23 (0.66, 2.30)
Maternal drinking - mod [a]	1.06 (0.68, 1.65)	1.13 (0.74, 1.74)	1.28 (0.58, 2.82)
Maternal drinking - binge [a]	0.91 (0.44, 1.86)	1.28 (0.68, 2.42)	1.42 (0.46, 4.42)
Maternal mental distress [a]	1.29 (0.68, 2.46)	0.97 (0.51, 1.86)	1.22 (0.43, 3.47)
Low mother-child warmth [b]	**1.86** (1.08, 3.22)	1.49 (0.84, 2.64)	1.88 (0.79, 4.49)
Child drinking at 14	1.58 (0.80, 3.11)	1.64 (0.87, 3.07)	**3.51** (1.50, 8.24)
Child smoking at 14	1.22 (0.66, 2.25)	1.66 (0.95, 2.89)	1.98 (0.85, 4.64)
Internalising at 14 [c]	**1.93** (1.22, 3.02)	0.96 (0.53, 1.72)	1.00 (0.41, 2.45)
Externalising at 14[c]	1.32 (0.65, 2.68)	**1.94** (1.07, 3.52)	**2.56** (1.09, 6.00)
Childhood sexual abuse[d]	**3.10** (1.87, 5.12)	**2.21** (1.21, 4.04)	**4.60** (2.02, 10.49)

MHD= mental health disorder (anxiety and/or depression); AUD/CAN = alcohol and cannabis use disorders only; PSUD/MHD = alcohol and illicit substance use disorders plus anxiety/depression

[a] Measured in pregnancy; drinking (mod) = less than 5 drinks/occasion; drinking (binge) = ≥5 drinks/occasion

[b] Mother-child warmth during adolescence

[c] Offspring behaviour problems measured at 14 years

[d] Self-reported at 21 years

Model is fully adjusted for all factors above

Table 60: Regression models of loss to follow up (LFU) by young adulthood, according to early maternal and child factors

	LFU unadjusted	LFU Fully adjusted
Factor	**OR (CI_{95})**	**OR (CI_{95})**
Gender (female)	**0.83** (0.75, 0.91)	1.15 (0.97, 1.36)
Socio-economic disadvantage [a]	**1.20** (1.16, 1.26)	1.01 (0.94, 1.09)
Maternal smoking in pregnancy [a]	**1.22** (1.10, 1.34)	**0.81** (0.67, 0.97)
Maternal drinking - mod [a]	**0.74** (0.65, 0.83)	0.86 (0.71, 1.05)
Maternal drinking - binge [a]	0.99 (0.82, 1.18)	0.99 (0.72, 1.37)
Maternal mental distress [a]	**1.59** (1.34, 1.88)	1.16 (0.85, 1.59)
Low mother-child warmth [b]	**1.05** (0.84, 1.32)	0.88 (0.66, 1.18)
Child drinking at 14	1.22 (0.98, 1.51)	1.08 (0.76, 1.54)
Child smoking at 14	**1.34** (1.13, 1.60)	1.31 (0.97, 1.76)
Internalising at 14 [c]	**0.75** (0.63, 0.90)	0.81 (0.62, 1.05)
Externalising at 14[c]	**1.24** (1.01, 1.51)	0.97 (0.69, 1.36)
Childhood sexual abuse[d]	1.08 (0.86, 1.36)	1.09 (0.81, 1.46)
High risk-taking[d]	1.06 (0.85, 1.34)	1.10 (0.84, 1.43)

[a] Measured in pregnancy; drinking (mod) = less than 5 drinks/occasion; drinking (binge) = ≥5 drinks/occasion

[b] Mother-child warmth during adolescence

[c] Offspring behaviour problems measured at 14 years

[d] Self-reported at 21 years

Table 61: Impact of Inverse Probability Weighting on model of latent class membership

Complete case analysis

	MHD	AUD/CAN	PSUD/MHD
Factor	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Gender (female)	**2.53** (1.70, 3.76)	**0.40** (0.28, 0.58)	**0.43** (0.24, 0.77)
Maternal smoking [a]	**1.54** (1.06, 2.23)	**1.73** (1.22, 2.45)	1.26 (0.68, 2.33)
Low warmth [b]	**2.21** (1.32, 3.71)	1.45 (0.81, 2.58)	1.73 (0.73, 4.07)
Drinking [c]	1.65 (0.84, 3.21)	1.57 (0.83, 2.99)	**3.49** (1.53, 7.98)
Smoking [c]	1.35 (0.74, 2.44)	1.68 (0.96, 2.94)	2.03 (0.90, 4.59)
Internalising [c]	**2.14** (1.38, 3.30)	0.94 (0.52, 1.70)	1.15 (0.49, 2.72)
Externalising [c]	1.39 (0.71, 2.72)	**1.91** (1.05, 3.46)	**2.25** (1.01, 5.10)

With Inverse Probability Weighting of results

	MHD	AUD/CAN	PSUD/MHD
Factor	OR (CI_{95})	OR (CI_{95})	OR (CI_{95})
Gender (female)	**2.57** (1.72, 3.85)	**0.40** (0.28, 0.58)	**0.43** (0.24, 0.79)
Maternal smoking [a]	**1.50** (1.04, 2.18)	**1.74** (1.24, 2.45)	1.21 (0.66, 2.24)
Low warmth [b]	**2.15** (1.28, 3.59)	1.48 (0.83, 2.65)	1.63 (0.70, 3.83)
Drinking [c]	1.52 (0.77, 2.98)	1.57 (0.82, 3.00)	**3.41** (1.36, 8.55)
Smoking [c]	1.45 (0.80, 2.61)	1.65 (0.94, 2.90)	1.91 (0.82, 4.44)
Internalising [c]	**2.13** (1.38, 3.30)	1.01 (0.57, 1.80)	1.25 (0.54, 2.88)
Externalising [c]	1.15 (0.56, 2.36)	**1.99** (1.10, 3.58)	2.00 (0.85, 4.71)

MHD= mental health disorder (anxiety and/or depression); AUD/CAN = alcohol and cannabis use disorders; PSUD/MHD = alcohol and illicit substance use disorders plus anxiety/depression

[a] Maternal factors measured at first clinic visit in pregnancy; [b] mother-child warmth during adolescence;

[c] Offspring factors measured at 14 years

Models are fully adjusted for all factors above, plus socio-economic disadvantage and maternal anxiety/depression in pregnancy.

Appendix 9: Text of Salom et al (additional publication)

LETTER TOTHE EDITOR

Evidence that community-based prevention reduces adolescent alcohol use: A commentary on Gilligan *et al*.

Drug and Alcohol Review (2012) DOI: 10.1111/j.1465-3362.2012.00463.x

Sir—Gilligan and colleagues [1] conclude there is little evidence for methodologically rigorous interventions to guide community-level and other system-level approaches to alcohol harm reduction. Gilligan *et al*. adopt a novel and potentially informative research design to advance our understanding of the gaps in this research, and provide recommendations to improve system-level approaches to alcohol intervention. Experts were initially identified through a search of addiction journals from 2005 to 2008. This targeted selection represents about 24% of relevant addiction journals (in 2012), most notably excluding many former Excellence in Research Australia 'A' and 'B' ranked titles. We also contend many evidence-based community-level prevention approaches that impact on alcohol are published in non-addiction journals. In this commentary, we briefly review examples of studies that may have not been captured in this search strategy. These examples show an excellent source of information on evidence-based, methodologically rigorous, community-level approaches that have a demonstrated impact on alcohol use.

Two of these approaches are focused on building partnerships with communities that address identified local problems. The first is Communities That Care (CTC). Based on over three decades of empirical data [2,3] CTC provides a means of initially identifying and quantifying community-level risk and protective profiles potentially related to a range of adolescent problems (including but not limited to alcohol use). Community-based coalitions are established, community readiness developed and the delivery of well documented evidence-based strategies that match identified deficits across community profiles is applied. A US trial of the system, involving 24 communities (n = 4407) using matched random assignment to either CTC or no program followed up over several years, showed substantial reductions in alcohol use initiation, with gains maintained 5 years post

implementation [3]. Studies also indicate that the process of community engagement (consultation, coalition formation and local prevention planning) is effective, sustainable [4] and, in the case of CTC, has a benefit–cost ratio for delinquency of $4.40 for every dollar invested [5].

The second example is PROSPER (PROmoting School–community–university Partnerships to Enhance Resilience) [6], a system designed to build sustainable partnerships to promote diffusion of evidence-based interventions. The PROSPER framework has been shown to enhance family/youth protective factors and reduce substance abuse relative to comparable communities [7,8]. It has excellent fidelity, with effects maintained up to six consecutive years [9]. PROSPER also results in significant increases in expert knowledge in the delivery and evaluation of evidence-based interventions [10].The positive findings for CTC and PROSPER are consistent with more modest long-term effects of other coalition-based community programs on alcohol use and misuse [11]. In sum, we believe that studies over the last two decades provide good evidence that community level prevention strategies are effective, and there is good support for the processes that contribute to these effects.

We agree with almost all the points that Gilligan *et al*. make about how to improve system-level approaches to alcohol intervention (see p. 661) [1]. However, many of the recommendations appear to be more general ones that apply to the broad research field (e.g. publication bias, the importance of researcher training for intervention research, routine collection of relevant data, the need for funding to build capacity, the need for journals to consider alternative designs to randomised controlled trials and the value of pilot research). Gilligan and co-authors argue that gold standard measures are elusive and have questionable reliability. We believe that psychometrically valid and reliable measures are available that are specifically designed as a focus for epidemiological assessment and intervention, based on a broad spectrum of community risk and protective factors. The above studies, together with several studies conducted in Australia, provide considerable evidence that well-established instruments are available that have good reliability, cross-sectional and longitudinal predictive validity and interventional utility [12–15].

The above empirical trials point to a range of more specific ways in which alcohol-related community-level intervention research can be improved. The available evidence indicates that the development of community coalitions is central to the delivery of sustainable interventions [10]. Additionally, two-way transfer of knowledge is a key element of the CTC/PROSPER systems: researchers provide skills training in evidence

based interventions, and communities provide specific local knowledge to facilitate tailoring of interventions to local communities. Feedback of data-based community risk and protective profiles is a key way of building partnerships and showing the responsiveness of external organisations to local conditions. For researchers in the area of community-level alcohol intervention, there are also important gains to be made by examining empirical support for other problems related to alcohol misuse. The above community-based interventions target known risk factors for alcohol use and misuse (e.g. delinquency, family problems, school engagement), so improvements in non-alcohol-related risks are likely to have positive implications for alcohol use and misuse. By virtue of their broad focus, such research often appears in journals outside the substance abuse area.

In sum, Gilligan *et al*. state that community-level research 'should be derived from methodologically rigorous intervention research' (p. 659) [1]. We think that there exists solid evidence for the effectiveness of particular types of community-level alcohol intervention. Furthermore, available studies show key processes that are important for the success of these approaches. Building researcher skills in these areas will be an important strategy for increasing evidence-based community-level intervention research. In Australia, coalition-driven community interventions for adolescent alcohol abuse are emerging. Consistent with Gilligan *et al*., we believe that investment in this next generation of prevention science is needed, but we arrive at this conclusion primarily on trial-based evidence of efficacy and cost-effectiveness.

Key words: adolescent, alcohol, coalition, community, prevention.

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Appendix 10: Abstract of Quek et al (additional publication)

Title

An evaluation of the *Choices* Schoolies program in North Queensland

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Introduction and Aims:

'Schoolies' is a celebration of the end of school for young people finishing Year 12. Many young people attend with expectations to drink and engage in other risky behaviours. Although Schoolies organisers are implementing safety response strategies, there is little information on pre-Schoolies interventions as a harm minimisation strategy. 'Choices' is written, directed and performed each year by Conservatorium of Music students and incorporates contemporary pop culture with safety messages to encourage students to make better choices during Schoolies. This paper presents fi ndings from an exploratory study investigating the effectiveness of the Choices program at reducing risky behaviours in Year 12 students during Schoolies.

Method:

In study 1, Year 12 students were invited to complete pre- and post-Choices questionnaires assessing knowledge of safe celebration, alcohol expectancies, intention to attend Schoolies and satisfaction with the program. In study 2, young people were randomly approached during Schoolies at Whitsunday to complete a brief survey assessing alcohol use, drug use and other risk taking behaviours.

Results:

Preliminary findings suggest that Choices increased student knowledge on safe celebration but did not change their alcohol expectancies. In the Schoolies survey, young people who attended Choices reported engaging in less risk taking behaviours than peers who had not attended Choices.

Conclusion:

The implications for the further development of preventative measures such as the Choices program for the management of risky alcohol consumption in young people are discussed.