Using linked data to assess maternal mental and behavioural disorders in pregnancy

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Using linked data to assess maternal mental and behavioural disorders in pregnancy.

A thesis in fulfilment of the requirements for the degree of Doctor of Philosophy

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National Drug & Alcohol Research Centre

Declarations

Thesis Title and Abstract | Declarations | Inclusion of Publications Statement | Corrected Thesis and Responses

Thesis Title

USING LINKED POPULATION DATA TO ASSESS MATERNAL MENTAL AND BEHAVIOURAL DISORDERS IN PREGNANCY

Thesis Abstract

Chapter 1 - Introduction. This overview defines mental and behavioural disorders (MBD) and examines current knowledge about MBD in pregnancy. Maternal MBD in pr egnancy are often overlooked. Most studies focused on a single class of MBD. This thesis used linked birth and inpatient data from NSW to assess MBD prevalence and n eonatal outcomes for maternal MBD in NSW maternities between 2002 and 2006.

Chapter 2 – Methods. Describes data linkage, MBD definitions and preliminary data processing.

Chapter 3 – Admissions for MBD in pregnancy. The study compared MBD admissions in pregnancy with MBD admissions pre-pregnancy. Overall, admissions for MBD were lower in early pregnancy (RR 0.71) and higher in late pregnancy (RR 1.91). Drug disorder admissions were more than 3-fold higher in late pregnancy. Schizophrenia admissions increased from early pregnancy and alcohol admissions remained lower throughout pregnancy. Baseline MBD admissions rates were higher for multiparous th an primiparous maternities.

Chapter 4 – Admissions with MBD in pregnancy. MBD prevalence in pregnancy was 2.4% overall, 1.4% for drug/alcohol disorders (DA) and 1.2% mental disorders (M D). Pregnancy DA prevalence was the same, psychotic disorder prevalence was half, affective disorder a third and anxiety a tenth that for comparable disorders in women of reproductive age. Coexisting MBD ranged from 23.6% for anxiety to 91.5% for sedative disorders. Smokers and residents in outer regional or more remote locations we re identified as maternity populations at high risk of MBD.

Chapter 5 – Neonatal outcomes. Effects of MBD on perinatal mortality, preterm birth, small size at birth, neonatal morbidity, and admission to neonatal intensive care wer e assessed. Adverse outcomes were on average 3- 4-fold higher for MBD relative to no MBD. Effects were universally attenuated by adjustment for smoking and co-existi ng MBD. Independent effects of opiate and cannabis disorders remained for most adverse neonatal outcomes, but not for schizophrenia or bipolar disorder.

Chapter 6 – Discussion and conclusions. This thesis demonstrates the value of linked population data; has added to the evidence for pregnancy as risk for MBD; provid ed the first comprehensive prevalence estimates of MBD in NSW maternities; provided evidence to support findings elsewhere of an independent association of alcohol, c annabis, or opiate disorder, but not for schizophrenia or bipolar disorder with poor neonatal outcomes.

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Abstract

Chapter 1 - Introduction. This provides an overview of mental and behavioural disorders (MBD) definitions and current knowledge about MBD in pregnancy. Maternal MBD in pregnancy are often overlooked. Most studies of MBD in pregnancy focused on a single class of MBD. This thesis used linked data from NSW Perinatal Data Collection and the NSW Admitted Patient Data Collection to assess diagnosed MBD in NSW maternities between 2002 and 2006.

Chapter 2 – Methods. Describes data linkage, MBD definitions and preliminary data processing.

Chapter 3 – Admissions for MBD in pregnancy. A study to compare rates of MBD admissions in pregnancy relative to MBD admissions in a baseline period. Overall, admissions for MBD were lower in early pregnancy (RR 0.71) and higher in late pregnancy (RR 1.91). Drug disorder admissions were more than 3-fold higher in late pregnancy. Schizophrenia admissions increased from early pregnancy and alcohol admissions remained lower throughout pregnancy. Baseline MBD admissions rates were higher for multiparous than primiparous maternities.

Chapter 4 – Admissions with MBD in pregnancy. MBD prevalence in pregnancy was 2.4% overall, 1.4% for drug/alcohol disorders (DA) and 1.2% mental disorders (MD). Pregnancy DA prevalence was the same, psychotic disorder prevalence was half, affective disorder a third and anxiety a tenth that of comparable disorders in women of reproductive age. Coexisting MBD ranged from 23.6% for anxiety to 91.5% for sedative disorders. Smokers and residents in outer regional or more remote locations were identified as maternity populations at high risk of MBD.

Chapter 5 – Neonatal outcomes. Assessed relative risks of individual classes of MBD on perinatal mortality, preterm birth, small size at birth, neonatal morbidity, and admission to neonatal intensive care (NICU). Adverse outcomes were on average 3- 4-fold higher for MBD relative to no MBD. Effects were universally attenuated by adjustment for smoking and co-existing MBD. Independent effects of opiate and cannabis disorders remained for most adverse neonatal outcomes, but not for schizophrenia or bipolar disorder.

Chapter 6 – Discussion and conclusions. This thesis demonstrates the value of linked population data; has added to the evidence for pregnancy as risk for MBD; provided the first comprehensive prevalence estimates of MBD in pregnancy for all maternities in NSW, including both high and low prevalence MBD; provided evidence to support findings elsewhere of an independent association of alcohol, cannabis, or opiate disorder with poor neonatal outcomes, but not for schizophrenia or bipolar disorder.

Table of Contents

List of Tables and Figures

Tables

Appendix tables

Figures

List of abreviations

Abbreviation	Description
AIHW	Australian Institute of Health and Welfare
ACS	Australian Coding Standards
APDC	Admitted Patient Data Collection
CHeReL	Centre for Health Records Linkage
EDC	Estimated date of conception
DA	Drug/alcohol disorder
GA	Gestational age
ICD10	International classification of death and disease, 10th revision
ICD10-AM	International classification of death and disease, 10th revision, Australian modification
IHPA	Independent Hospital Pricing Authority
MBD	Mental or behavioural disorder
MD	Mental disorder
N	Number
NDSHS	National Drug Strategy Household Survey
NHS	National Health Survey
NICU	Neonatal intensive care unit
NSMHW	National Survey of Mental Health and Wellbeing
NSW	New South Wales
PAF	Population attributable fraction
PDC	Perinatal Data Collection
SAS	Statistical Analysis System
w	Weight applied to PDC records, derived from sampling fractions
WHO	World Health Organisation

List of Symbols

Symbol	Description
%	Per cent
‰	Per thousand

Glossary

Term	Description
Additional diagnosis	ICD10-AM codes in an inpatient episode record for diseases, disorders or conditions that coexist with the principal diagnosis.
Admission	see Inpatient episode
Baby	A person who has recently been born. For the purpose of this thesis, a baby can be live born or stillborn. The medical term for an unborn baby of 7 or more weeks of gestational age is a fetus.
Birth	An event defined as the complete separation of the mother and her baby at the end of pregnancy that occurs to a baby. A live birth is so defined if the baby shows signs of life after separation from the mother. Multiple-birth maternities are associated with two or more births.
Birthing / birthed	The act of giving birth. This term is used in preference the term 'Delivery'.
Conception	Defined physiologically as the implantation of the fertilised egg into the woman's uterus. Medical records do not capture the date of conception, but this can be estimated from the gestational age and date of birth.
Epidemiology	Defined as the study of disease in populations that are defined in time, place and person.
Fetus	The medical term for an unborn baby of 7 or more weeks of gestational age.
Gestational age	Duration of pregnancy at a specified time, for example at registration for antenatal care. The international convention is to report gestational age in completed weeks from the first day of the mothers last menstrual period (WHO ICD10). For consistency, other methods of estimating gestational age use the same notional starting point. The most accurate estimate of gestational age is from ultrasound in early pregnancy.

ICD10-AM code	A 4- or 5- digit code given to a disease, disorder, or condition in accordance with the International Classification of Disease and Death 10th revision. Between 2002 and 2006 the NSW Admitted Patient Data Collection used ICD10-AM versions 3 and 4.
Inpatient episode	The basic administrative unit of health care in a hospital. In this thesis the term admission is used synonymously with the term inpatient episode.
Maternity	An event defined as the complete separation of the mother and her baby at the end of pregnancy that occurs to a mother. The term 'Maternity' has the same meaning as the term 'Confinement'. Most maternities are associated with a single birth. Multiple-birth maternities are associated with two or more births.
Mental and behavioural disorder	Mental and behavioural disorder diagnostic groups are defined by the presence of one or more ICD10 diagnoses listed in Chapter V: Mental health disorders. Drug/alcohol disorder definitions also included additional ICD10 diagnoses listed in Table 2.1.
Mother	A female person who has given birth.
Neonatal	The first 28 days of life. Counted as days 0-27. The first day of life, or day of birth, is counted as day zero.
Perinatal death	A stillbirth or neonatal death.
Pregnancy	Physiological process of reproduction. Pregnancy is not a disease, but pregnant women are subject to complication from disease. Pregnancy is defined in time as the period from conception to birth if the person is the baby or birthing if the person is the mother.
Principal diagnosis	First listed ICD10-AM code in an inpatient episode record that is considered at the end the episode to be the main reason for inpatient care.
Stillbirth	A birth after which the baby that shows no signs of life at birth if the pregnancy has continued for at least 20 weeks, or if gestation is not known, the baby weighs 400g or more.

Chapter 1. Introduction

Mental and behavioural disorders (MBD) impact on the health of women of all ages. In Australia, MBD were responsible for 22% of the non-fatal burden of disease among Australian women in 2015 (Australian Institute of Health and Welfare (AIHW) 2019). Anxiety disorders contributed the largest number of years lived with a disability in women aged 15-44 years and four other mental or behavioural disorders (depression, bipolar disorder, eating disorders and either alcohol use disorder or drug use disorder) ranked in the top 10 conditions resulting in disability in these age groups (Australian Institute of Health and Welfare (AIHW) 2019). While there is good information about MBD in the general population, information about MBD in pregnancy is patchy.

Pregnancy and the first postnatal year together make up the period defined for assessment of perinatal mental health (Austin, Highet et al. 2017). MBD have been recognised as common complications of the perinatal period (Howard, Molyneaux et al. 2014). Perinatal MBD are clinically equivalent to the disorders in non-pregnant women (Brockington 1996). What distinguishes perinatal MBD is their timing in relation to pregnancy and childbirth. There is evidence that in some women recent childbirth triggers the onset of mental disorders and for those with established disorders the risk of relapse is increased (Munk-Olsen, Laursen et al. 2006, Jones, Chandra et al. 2014). The bulk of literature on perinatal MBD focuses on the postnatal period, during which MBD peak in onset, severity, and fatality. Less evidence has been produced about MBD in the pregnancy period (Astbury, Cabral de Mello et al. 2009).

The importance of MBD in pregnancy stems from their potential for harm to the mother and to the baby(s) to whom she gives birth. MBD have been recognised as one of the leading causes of maternal death (Austin, Kildea et al. 2007, Paschetta, Berrisford et al. 2014). The presence of maternal MBD has been reported to adversely impact the well-being of the newborn (Ross, Graham et al. 2014, Stein, Pearson et al. 2014, Vigod, Kurdyak et al. 2014, Rusner, Berg et al. 2016) and increase the risk of developmental and psychological disturbances in childhood and adolescence (Stein, Pearson et al. 2014). However, there is some evidence that early interventions to treat new mothers with MBD, address social adversity and provide parenting support has the potential to improve the outcomes for these children (Stein, Pearson et al. 2014).

This chapter begins with an overview of MBD definition, and the classification system used to record MBD survey and administrative collections. Next, information about MBD from national surveys and routine population-based data collections, and their capacity to report on MBD in pregnancy, are discussed. This is followed by an overview of current knowledge of MBD in pregnancy from observational studies. Finally, the gaps in current knowledge about MDB in pregnancy are listed and the capacity of linked administrative data to address these deficits is considered.

1.1 What are mental and behavioural disorders?

MBD are disorders of that affect a person's emotional and/or cognitive functioning. Most people will be affected by MBD at some time in their lives, though not all will seek or receive help. Stigma surrounding MBD are profound (Corrigan 2011). For many MBD the peak onset is in adolescence and early adulthood (Kessler, Amminger et al. 2007, Oscar 2016). Thus, MBD are present at time when they disrupt the education of affected individuals, their establishment in the workforce and the formation of partnerships and parenting. MBD impose a heavy socio-economic burden on society through direct costs of health and social support as well as indirect costs from the loss of skills and the loss of productivity (Neil, Carr et al. 2013, Lee, Chatterton et al. 2017). Poor mental health is intricately linked with social inequality (Marmot 2014). This relationship is complex and dynamic. The chance of current or lifetime mental disorder is substantial across all social strata, but increases as social equity decreases (Marmot 2014). At the same time, mental disorder is a potent individual risk factor for poverty, socially and financially, thus leading to even further inequality (Marmot 2014).

Definition of MBD

The World Health Organisation (WHO) defines mental or behavioural disorder (MBD) as "*a clinically recognizable set of symptoms or behaviours associated in most cases with distress and with interference with personal functions. Social deviance or conflict alone, without personal dysfunction, should not be included in mental disorder as defined here.*" (World Health Organisation (WHO) 1992, International Advisory Group for the Revision of ICD Mental and Behavioural Disorders 2011). ICD10 definition and classification of mental and behavioural disorders are broadly similar, but not identical to those to the Diagnostic Statistical Manual 5th

revision (DSM5) , which is used in clinical data collections predominantly but not exclusively in the USA (American Psychiatric Association 2021).

Diagnostic criteria for individual MBD are set out in '*The ICD10 Classification of Mental and Behavioural Disorders - Clinical Descriptions and Diagnostic Guidelines*' (World Health Organisation (WHO) 1992). These guidelines represent an international clinical consensus on the balance of symptoms for individual MBD disorders and aid clinical, educational, and administrative uses of ICD10 classification of MBD. Clinical guidelines have increased diagnostic agreement among clinicians working in different localities, and improved the quality of statistical reporting of MBD from WHO member countries (Jablensky 1999), which include Australia. The Australian and New Zealand College of Psychiatrists recognises and promotes the use of clinical guidelines in health services settings to ensure diagnostic consistency (Royal Australian and New Zealand College of Psychiatrists 2016).

Despite their limitations, ICD10 definitions of MBD are widely accepted as the best available means to conceptualise and communicate clinical information globally by those caring for patients with MBD (Kendell and Jablensky 2003). However, symptom-based definitions of mental disorders used by ICD10 have been criticised because of their poor relationship with disease process and aetiology (Regier, Kaelber et al. 1998, Bolton 2009, Goldberg 2010, Maj 2015, Craddock 2018). The ICD10 classification of MBD pre-dates late 20th and early 21st century advances in genetics and neuroscience. Alternative systems for classifying MBD have been developed, including Research domain criteria (ReCoDe) (Cuthbert 2014) and the Hierarchical Taxonomy Of Psychopathology (HiTOP) (Kotov, F. Krueger et al. 2017). Both apply dimensional frameworks that conceptualise an individual's mental health in terms of where they sit on the spectrum of a series of psychopathological continuums. As relationships between the structure and functioning of the brain and the mind are elucidated, it is likely that symptom-based classifications of mental disorders will be replaced with classifications informed by genetics, neurophysiology, biological sciences and behavioural sciences (Hyman 2007, Stein 2014, Maj 2015, Schildkrout 2016). For now, ICD10 remains the mainstay of clinical definition and categorisation of mental disorders in clinical settings and administrative data collections (Jablensky 2009, Maj 2015, Reed, First et al. 2019).

1.2 ICD10 classification of MBD

The *International Classification of Diseases, Injuries, and Causes of Death*, generally shortened to the International Classification of Diseases (ICD) is used to classify morbidity and mortality and monitor health issues to a common standard within and between countries (International Advisory Group for the Revision of ICD Mental and Behavioural Disorders 2011). The 10th revision (ICD10) is currently used in Australia and elsewhere (World Health Organization (WHO) 2006). The 11th revision (ICD11) was released in June 2018 to enable member countries to prepare for implementation (World Health Organization (WHO) 2019). This process is anticipated to take several years and at the time of writing there is no plan in Australia to replace ICD10.

Mental and behavioural disorders are listed in Chapter 5. The main groups are set out in Figure 1.1. MBD were separated into drug/alcohol disorders (ICD10 F10-F19) and mental disorders (ICD10 F00-F09, F20-F99). This reflects the divide between health services that care for individuals with these two categories of MBD that extends into public health practice. In Australia, drug and alcohol treatment services (AODTS) provide specialist care for individuals with drug or alcohol addiction (Australian Institute of Health and Welfare (AIHW) 2018), whereas mental health and psychiatric services provide specialist care for individuals with mental disorders (Australian Institute of Health and Welfare (AIHW) 2019).

Figure 1.1 lists the range of substances with psychotropic properties that can be coded in ICD10. Harms associated with drug or alcohol disorders include intoxication, addiction, psychosis, amnesia and, when stopped, withdrawal syndromes, which are included as fourth digit codes. Nicotine, in the form of tobacco, and alcohol are legally available to adults with minimal restrictions. Tobacco and alcohol companies have invested heavily in distancing their products from drugs in the minds of consumers and health professionals. Drugs can be legal or illegal. Legal drugs are largely, but not exclusively pharmaceutical products, which are controlled by statute and clinical practice regulations. Illegal drugs are forbidden by law, with penalties for their manufacture, distribution, and possession. Pharmaceutical drugs can be misused or illegally obtained, for example, illegal opiates in the form of heroin have been largely replaced by pharmaceutical opiates that can be used legally if prescribed by a doctor. Stimulants are another group of drugs that can be obtained on prescription or illegally. The 10 classes represented by the first 2-digits in ICD10 are a common framework for classifying MBD into

clinically relevant groups, but other groupings using ICD10 3- and 4-digit disorder codes are common in the mental health literature, particularly those concerned with perinatal mental health.

Drug/alcohol disorders (F10-F19)

Code	*Description*
F10–F19	Disorders due to psychoactive substance use
F10	*Alcohol*
F11	*Opiates*
F12	*Cannabis*
F13	*Cocaine*
F14	*Stimulants*
F15	*Sedative-hypnotics*
F16	*Solvents*
F17	*Hallucinogens*
F18	*Tobacco*
F19	*Polydrug (includes unspecified substance)*

Mental disorders (F00-F09, F20-F99)

Code	*Description*
F00–F09	Organic, including symptomatic, mental disorders
F20–F29	Schizophrenia, schizotypal and delusional disorders
F30–F39	Mood [affective] disorders
F40–F48	Neurotic, stress-related and somatoform disorders
F50–F59	Behavioural syndromes associated with physiological disturbances and physical factors
F60–F69	Disorders of adult personality and behaviour
F70–F79	Mental retardation
F80–F89	Disorders of psychological development usually occurring in childhood
F90–F98	Disorders with onset in childhood & adolescence
F99	Unspecified mental disorder

Figure 1.1 ICD10 Chapter V - Mental and behavioural disorders

Australian modifications to ICD10

Member countries can tailor ICD classifications to their own needs. The ICD10 Australian modification (ICD10-AM) was introduced in 1998 to align the classification with Australian clinical practice (Independent Hospital Pricing Authority (IPHA) 2019). ICD10-AM is mandated

for clinical coding in all public and private hospitals across Australia (Independent Hospital Pricing Authority (IHPA) 2019). New codes can be added for country-specific conditions or a 5th digit can be added to an existing ICD10 4-digit codes to expand the information about a condition (Independent Hospital Pricing Authority (IPHA) 2019). A new version of ICD10-AM is produced every 2 years to keep the classification relevant to current practice.

Australian Coding Standards (ACS) incorporate ICD10 regulations modified for Australian circumstances for use alongside ICD-10-AM (Independent Hospital Pricing Authority (IPHA) 2019). Australian coding standards are updated every 2 years in line with ICD10-AM. In Australian hospitals a trained clinical coder will review the documentation in the medical record and assign the relevant ICD10-AM codes to the hospital inpatient episode record. Australian Coding Standards allow clinical coders to work to a common standard, but the quality of record keeping between hospitals may vary. In this thesis ICD10 refers to the parent WHO classification and applies equally to ICD10-AM. Reference to ICD10-AM is specific to Australia.

ICD10 morbidity coding

ICD10 defines the main condition for use in single-condition reporting as "*the condition, diagnosed at the end of the episode of health care, primarily responsible for the patient's need for treatment or investigation. If there is more than one such condition, the one held most responsible for the greatest use of resources should be selecte*d" (World Health Organisation (WHO) 2016). ICD10 advises that all conditions that contributed to the episode of care should be listed. These are defined as conditions "*that coexist [with the main condition] or develop during the episode of care and affect the management of the patient. Conditions that have no bearing on the current episode should not be recorded*" (World Health Organisation (WHO) 2016). The WHO definitions form the basis of the definitions of the principal diagnosis and additional diagnosis used in Australian health data collections (Australian Institute of Health and Welfare (AIHW) 2015).

ICD10 coding of pregnancy-related morbidity and mortality

Revisions that led to ICD10 were undertaken in the 1980s and completed in 1989 (World Health Assembly 1990). This coincided with international outcry about the 100-fold disparity in maternal mortality between high- and low-income countries (Rosenfield and Maine 1985,

Zureick-Brown, Newby et al. 2013) and renewed interest in identifying causes of maternal mortality and morbidity. Non-obstetric causes of maternal death had been recognised as a component of maternal mortality in ICD9. ICD10 expanded the range of non-obstetric disorders relevant to pregnancy that could be identified in morbidity data by introducing 2 new codes ('O98' for infectious diseases and 'O99' for non-infectious diseases) that flag that the next listed ICD10 code as a pregnancy complication (World Health Organisation (WHO) 2019). The fourth digit for these flags points to the ICD10 chapter(s) in which the complicating condition is classified. In Figure 1.2, ACS 0505 refers to the use of the flag for MBD complicating pregnancy.

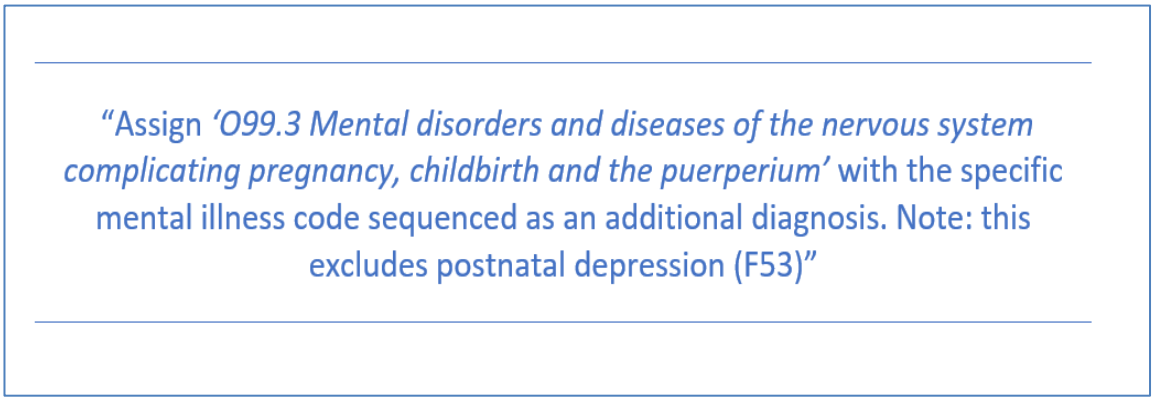


Figure 1.2 Australian coding standard 0505: Mental illness complicating pregnancy.

Practical aspects of ICD coding and coding practice

Clinical coding is the process by which morbidity information is transferred from the medical record into the electronic record for an inpatient episode. Medical coders are trained professionals who apply ACS criteria. Generally, diagnoses included in an inpatient episode are limited to those that meet the criteria for the main reason for inpatient care (ACS 0001) or for an additional diagnosis (ACS 0002). The latter are restricted to conditions that initiate or change treatment, initiate a diagnostic procedure, or increases monitoring. During pregnancy care, however, a third rule applies that includes "*diagnoses for conditions that complicated the pregnancy, were aggravated by pregnancy…even if they did not meet the criteria for an additional diagnosis*" (ACS 1512).

Clinicians are responsible for the completeness and accuracy of the clinical record (Independent Hospitals Pricing Authority (IPHA) 2020). In many hospitals this task falls to junior medical staff, with consultant supervision. Diagnostic skills, team working, the quality of supervision and record keeping all contribute to the accuracy of the clinical record. The discharge summary, or

equivalent, produced by the clinician at the end of each episode of inpatient care is used by clinical coders assign ICD10-AM codes that form morbidity data for each inpatient episode.

Clinical coders are required to verify that each diagnosis in the discharge summary has been documented in the medical record. Discrepancies must be discussed with clinicians, who make any nescessary revisions. If no discrepancies are found or those identified have been resolved, coding can be completed. Corrections to the discharge summary not completed in a timely manner can contribute to errors in hospital morbidity data.

MBD in hospital inpatient morbidity data from antenatal and maternity admission include all clinically recognised MBD. ICD10 O989/O99 flags differentiate disorders that complicated the pregnancy without necessarily increasing the complexity of care provided.

1.3 National population surveys of MBD

There are four Australian national surveys that are primarily used to identify MBD: i) National Surveys of Mental Health and Wellbeing (NSMHW) carried out in 1997 and 2007 that assessed respondents using a diagnostic interview designed for use by lay interviewers; ii) surveys of people living with psychosis carried out in 1997-98 and 2010 obtained information about attendees of mainstream mental health services; iii) National health surveys carried out every 3 years collected self-report of mental health ; and iv) National Drug Strategy Household Surveys carried out every 3 years collected self-reported information about substance use. NSMHW, surveys of people living with psychosis and NHS surveys report by sex and age, which allows analysis of MBD in women of reproductive age, but none of these surveys asked women about pregnancy or breastfeeding.

Since 2001, NDSHS have asked female respondents about pregnancy or breastfeeding in the previous 12 months (Callinan and Ferris 2014). Surveys in 2001 to 2007 asked “at any time in the last 12 months when you were pregnant or breastfeeding, did you use any of the following” with two sets of tick boxes for each substance, one set for pregnancy and the other for breastfeeding (Callinan and Ferris 2014). In 2010 there were three sets of tick boxes: before knowledge of pregnancy; after knowledge of pregnancy; and breastfeeding. Since 2013, tick boxes for substance use have been included in 3 separate questions: before pregnancy was recognised; after pregnancy was recognised; and while breastfeeding (Callinan and Ferris 2014). These NDSHS findings have been instrumental in demonstrating lower drug and alcohol use among

pregnant women than among women in the general population. Moreover, 2013 and 2016 surveys demonstrated decreases in tobacco use, alcohol use and illicit drug use once pregnancy was recognised (Australian Institute of Health and Welfare (AIHW) 2014, Australian Institute of Health and Welfare (AIHW) 2017).

1.4 MBD from patient data collections

Australian health data collections collate information from jurisdictional data collections. National Minimum Datasets (NMDS) provide standards for consistent data collection in each Australian state and territory, allowing collation of jurisdictional collections for national reporting (Australian Institute of Health and Welfare (AIHW) 2020). The Admitted Patient Care NMDS and the Perinatal NMDS define the minimum data required from jurisdictional collections respectively for an episode of inpatient care and a birth. Jurisdictional collections can include additional information to support local policy and decision-making.

MBD in admitted patient data collections

ICD10-AM coded data forms the basis of morbidity information in inpatient data collections from all Australian states and territories (Australian Institute of Health and Welfare (AIHW) 2015). MBD can be present as a principal diagnosis or an additional diagnosis. Each hospital employs trained coders who are responsible for transferring clinical information in the hospital record to data in the hospital administration records at the conclusion of each episode of care. These data are used primarily for the management hospital activity and allocation of funds for inpatient services (Australian Institute of Health and Welfare (AIHW) 2018). Diagnostic data are needed for case-mix calculations that account for the complexity of cases (patients) treated in different hospitals. More complex cases attract more funding. It is in the interests of hospitals to ensure the diagnostic data are accurate and complete. These data also contribute to assessments disease burden in the Australian population (Australian Institute of Health and Welfare (AIHW) 2019).

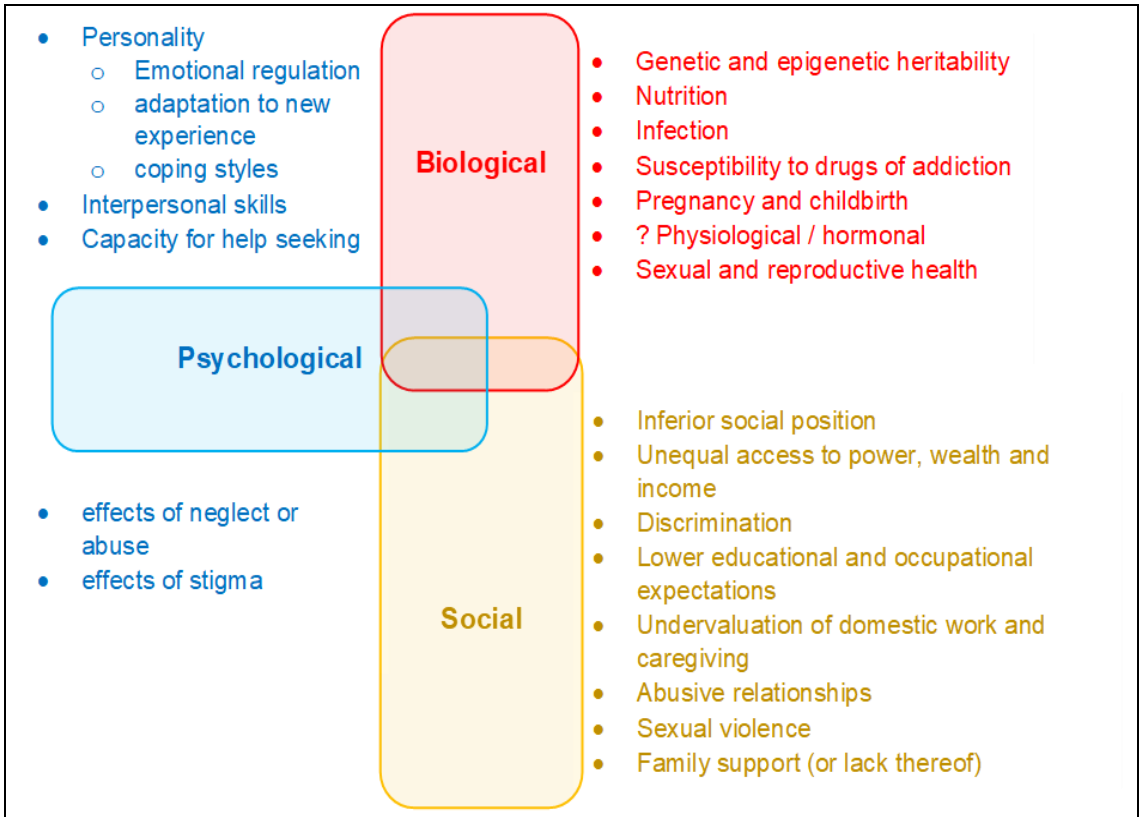
MBD in Perinatal Data Collections (PDC)

PDCs in each state and territory obtain information about all births in their geographical catchment. Information about MBD are not at present mandated for the Perinatal NMDS, but information about tobacco use (smoking) in pregnancy has been available from the NSW PDC

since 1998 and standardised data have been collected across Australia since 2010 (Laws PJ, Grayson N et al. 2006, Li, Zeki et al. 2012). These data are used for national surveillance, to inform policy and monitor effects of interventions aimed at reducing smoking in pregnancy (Australian Institute of Health and Welfare (AIHW) National Perinatal Epidemiology and Statistics Unit and AIHW 2013). Smoking prevalence in the NSW PDC has fallen progressively from 17.1% in 2001 to 8.4% of maternities in 2016 (Centre for Epidemiology and Research. NSW Department of Health 2002, Centre for Epidemiology and Research. NSW Department of Health 2017) . Among smokers, the proportion who smoked heavily (more than 10 cigarettes per day) fell from 47% in 2001 to 13.0% in 2016 (Centre for Epidemiology and Research. NSW Department of Health 2002, Centre for Epidemiology and Research. NSW Department of Health 2017). These trends in NSW data are also observed in national data.

1.5 Determinants of mental and behavioural disorders in women

As summarised in Figure 1.3, a review organised the determinants of MBD in women these into three domains: biological, psychological and social determinants (Fisher, Herrman et al. 2014). Some determinants are specific to women, such as pregnancy and childbirth, some are more common in women than in men, such as social inferiority and sexual violence, and some apply equally to both sexes, such as genetic and epigenetic heritability. A key message from Figure 1.3 is that the determinants of mental and behavioural disorders in women are multifactorial. Furthermore, interaction between factors may also be important (Fisher, Herrman et al. 2014).



Sourced from: Determinants of Mental Disorders in Women (Fisher, Herrman et al. 2014)

Figure 1.3: Determinants of mental and behavioural disorders in women

Biological determinants

Genetic predisposition to mental disorder varies between individual disorders. Genes associated with psychiatric disorders are fundamental to brain development (Oscar 2016). An estimated 60-80% of schizophrenia, 59% of bipolar disorder and 32% of major depressive disorders have been attributed to heredity (Fisher, Herrman et al. 2014).

Epigenetic mechanisms are now thought to contribute to heritability of schizophrenia and major depressive disorders (Gluckman, Hanson et al. 2005, Van Den Bergh 2011, Hoffmann, Sportelli et al. 2017). Epigenetic mechanisms, such as DNA methylation, alter gene expression in response to environmental stimuli (Hoffmann, Sportelli et al. 2017, Yan, Zhao et al. 2018) and is one aspect of prenatal programming (Van Lieshout and Krzeczkowski 2016).

Prenatal infection and nutrition have been associated with increased schizophrenia risk (McGrath and Susser 2009).

Babies conceived during the height of the Dutch famine during World War II had a two-fold increased risk of developing congenital anomalies of the central nervous system, schizophrenia, and schizophrenia-spectrum personality disorders (Neugebauer, Hoek et al. 1999, Kuh and Ben-Shlomo 2004, McGrath and Susser 2009). Similar findings with respect to schizophrenia have been described in rural residents exposed to the Chinese famine of 1959-1961 (He, Chen et al. 2018). In a famine calories, proteins, and micronutrients are deficient. Calorie- and/or protein-type malnutritions are found among the world's poorest but are uncommon in high income countries such as Australia, where over-nutrition predominates. Micronutrient malnutrition can be present in apparently well-nourished or over-nourished populations. Preliminary evidence suggests maternal folate and vitamin D insufficiencies may play a role in the development of schizophrenia in their offspring (McGrath and Susser 2009).

Maternal infections in pregnancy, particularly first trimester infections, have also been associated with schizophrenia in the offspring. Evidence from studies of banked tissues support earlier ecological studies that associated schizophrenia with prenatal exposure to influenza, rubella and toxoplasmosis (McGrath and Susser 2009). It is notable that these infections have also been associated with structural anomalies of the central nervous system (Hutto 2006, Luteijn, Brown et al. 2014, Hijikata, Okahashi et al. 2020).

The quality of parental care has been shown to affect the epigenetic status of several genes, including those associated with psychotic disorders (Pishva, Kenis et al. 2014). These genes are involved in hypothalamic–pituitary–adrenal (HPA) axis function and hippocampus-related learning and memory processes. Animal studies have shown the quality of maternal care was associated with epigenetic alterations (Pishva, Kenis et al. 2014). A key study in rats demonstrated differences in postnatal care by the mother led to epigenetic changes in the promoter region of the glucocorticoid receptor in the hippocampus that could be averted by cross-fostering or administration of a histone acetylation inhibitor (Weaver, Cervoni et al. 2004). Altered receptor genes changed synaptic plasticity and long-term potentiation, which are recognised as contributors to the pathogenesis of schizophrenia (Pishva, Kenis et al. 2014). Epigenetic changes in glutamate (an amino acid and excitatory neurotransmitter) receptors, have been observed in DNA from peripheral blood of patients with schizophrenia (Weaver, Cervoni et al. 2004, Kordi-Tamandani, Dahmardeh et al. 2013, Pishva, Kenis et al. 2014). Similar epigenetic changes could explain the blunted HPA responses observed in trauma-exposed children.

Other biological factors implicated in the aetiology of MBD, include sexual and reproductive health. However, the notion that physiological and hormonal changes associated with puberty, the menstrual cycle, pregnancy, and menopause render women intrinsically vulnerable to poor mental health has been challenged (Patel 2004) and this view is supported by systematic reviews that found no relationship between sex hormone changes and either depression or anxiety (Astbury and Cabral 2000, Piccinelli and Wilkinson 2000). Pathology of the reproductive system, including but not limited to unwanted pregnancy, sexually transmitted infections, infertility, pelvic inflammatory disease and endometriosis, can be mentally as well as physically debilitating (Fisher, Herrman et al. 2014).

Pregnancy and childbirth are listed as biological risk factors for MBD in Figure 1.3, but many of the social and psychological determinants listed may be accentuated when a woman is pregnant and or has recently given birth. For example, pregnancy and recent childbirth can be associated with increased social restrictions, limit employment capacity with the consequences of reductions in autonomy and income. Partner violence may be exacerbated at this time. The evidence for pregnancy and childbirth as risk factors for MBD is considered more fully in Section 1.6.

Psychological determinants

Psychological functioning can contribute to resilience as well as susceptibility to mental disorders. Women have been reported to have higher rates of anxiety and depression throughout the life-course (Patel 2004). Theories explaining the greater vulnerability of women to mood disorders postulated a greater propensity to catastrophise, personalise and worry excessively have been criticised for not considering the entrenched social norms that confine women to inferior positions in society and limit their opportunities (Fisher, Herrman et al. 2014). Gender-based stereotypes have been demonstrated to influence diagnostic and therapeutic decision making by mental health professionals (Fisher, Herrman et al. 2014). Broverman's study of 79 clinically trained psychologists found high levels of agreement between clinicians on the characteristics of a mentally healthy adults, which aligned with the characteristics of mentally healthy males, but those of healthy female subjects differed, irrespective of clinician gender and paralleled prevailing sex-role stereotypes (Broverman, Broverman et al. 1970). Healthy women were characterised as more submissive, less independent, less adventurous, more easily influenced, less aggressive, less competitive, more excitable, more emotional, more

concerned with appearance, less objective, and disliking math and science more than healthy men (Broverman, Broverman et al. 1970). Gender stereotypes have also been identified in definitions of personality disorders, depression and anxiety disorders (Ali, Caplan et al. 2010).

Psychological functioning can be adversely affected by emotional and physical violence to which women are more prone than men (García-Moreno, Jansen et al. 2005, Fisher, Herrman et al. 2014). Gender-based violence has been recognised as a global public health problem (Krug, Dahlberg et al. 2002, Fisher, Herrman et al. 2014). Sexual violence against women during childhood and adolescence is common. For example, one third of a randomly selected cohort of women living in areas covered by 4 electoral roles in New Zealand reported at least on one instance of unwanted sexual experience before the age of 16 (Anderson, Martin et al. 1993).

Social determinants

Hypotheses about the social causes of MBD bring into play factors that limit women's roles, denigrate their contribution to society and increase their exposure to physical and emotional violence (Fisher, Herrman et al. 2014). The association between economic difficulties and an increased risk for anxiety and depression (Marmot 2014), higher levels of vulnerability to social risk factors and lower levels of protective factors that result from the place of women in society increase the risk of mental disorder (Patel 2004, Fisher, Herrman et al. 2014). However, in some circumstances, gender-specific social expectations influence the progress towards mental disorders in men and women (Fisher, Herrman et al. 2014). For example, women pre-disposed to mental disorders may be protected by lower educational and occupational expectations that are not extended to men (Fisher, Herrman et al. 2014).

1.6 Pregnancy and birth as determinants of MBD

Seminal studies

Three studies have been fundamental in shaping our understanding of the effect of pregnancy and birth as a determinant of MBD.

1. ***Paffenbarger: Hamiliton County,Ohio (USA)***

Mental disturbance following childbirth had been described in medical texts from the late 1700s (Trede, Baldessarini et al. 2009) but the first epidemiological study of perinatal mental disorders was carried out by Ralph Paffenbarger (Paffenbarger Jr 1964). He systematically reviewed the

medical records for women aged 15 to 44 who were admitted to a psychiatric hospital in Hamilton County, Ohio between 1940 and 1958 and cross-referenced maternity hospital records to identify 314 women admitted for MBD during pregnancy or within 6 months of giving birth. Two mothers of the same race who gave birth immediately before and after each case mother were selected as controls. Of the 314 women who were cases, 72 (22.9%) were admitted during pregnancy and 242 (77.1%) were admitted postnatally.

The frequency of hospital admissions was similar across the pregnancy period, but the frequency of postnatal mental disorder admissions rose sharply in the first month after childbirth then fell progressively over the postnatal year. Over two thirds (68%) of admissions in the postnatal year were in the first postnatal month. In 1957-1958 the prevalence of postnatal mental disorder was 19 per 10,000 births, nearly 4 times the prevalence of antenatal mental disorder (5 per 10,000 births).

2. Kendell: Edinburgh (Scotland)

Kendell linked psychiatric admission records with 54,087 birth records between 1972 and 1979 for women resident in the city of Edinburgh (Kendell, Chalmers et al. 1987). This provided a large geographically defined cohort with information about obstetric and demographic risk. Psychiatric admissions in each 30-day period in the 2 years before and 2 years after birth were tabulated.

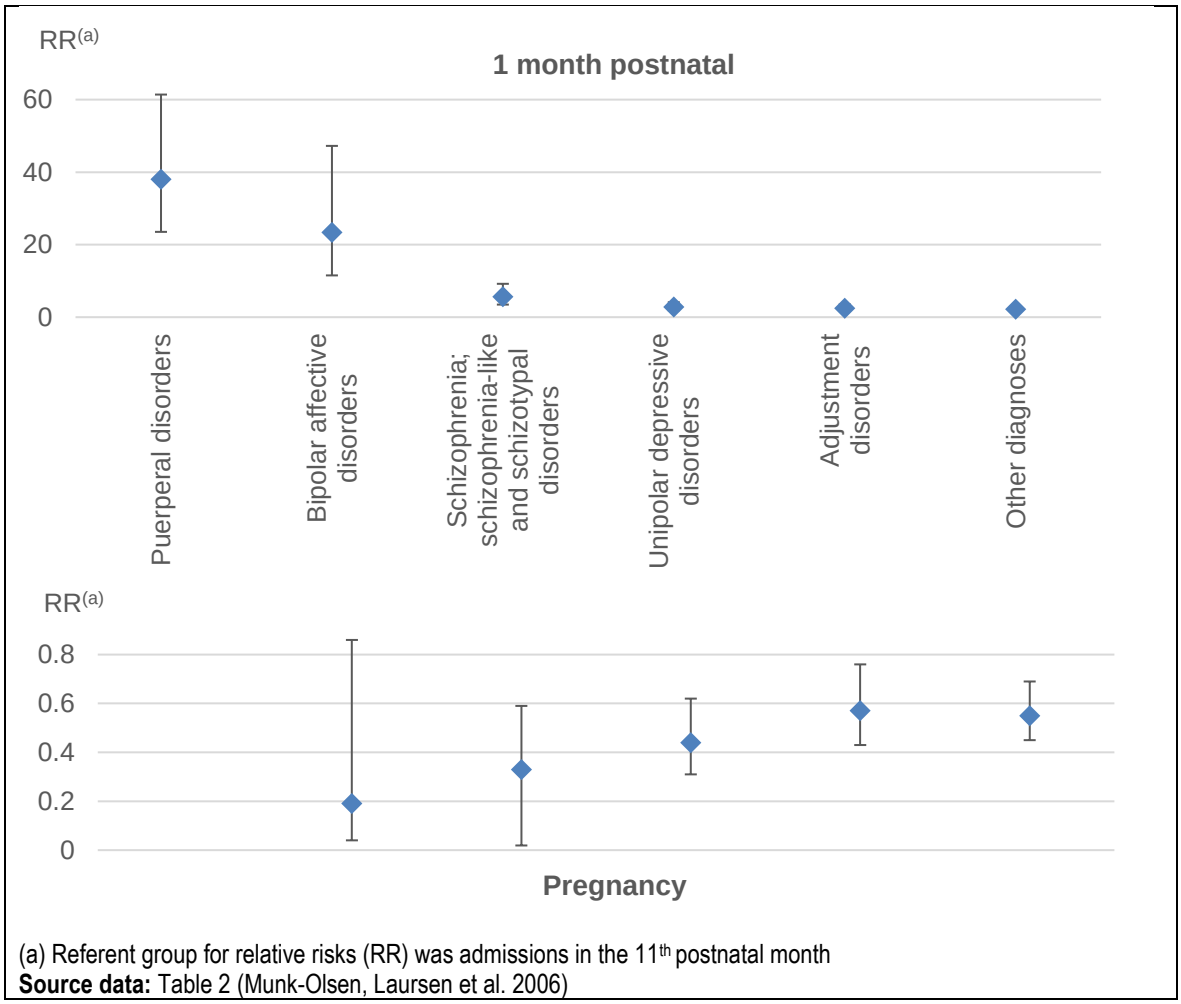
Admissions were lowest (5 per month) in the first months of pregnancy, increased as pregnancy progressed, peaked at 68 admissions per month in the first month after birthing and fell thereafter. At the end of 2 years, MBD admission rates remained significantly higher than in the months before pregnancy. Using admissions in first 15 months as the baseline, he estimated 74% of admissions for any mental disorder and 92% of admissions for psychosis within 90 days of childbirth were directly attributable to childbirth. Among primiparous mothers, 83% of postnatal mental disorders were attributable to childbirth. However, from the 4th postnatal month, risk of postnatal admission was greater for multiparous women.

3. Munk-Olsen: Denmark

Twenty years later, Munk-Olsen (Munk-Olsen, Laursen et al. 2006) examined disorder-specific incidence of perinatal admission in primiparous (first time) mothers. She used national population linked records system to follow over 2 million women born in Denmark from the age of 15 years find the first lifetime hospital admission for specific classes of MBD, in the perinatal

period for women who became mothers for the first time. Between 1973 and 2005, 630,373 women had a first baby.

Incidence of any MBD in the perinatal period was lowest during pregnancy (0.7 per 1,000 person years) and peaked at 9.45 per 1,000 person-years at 10-19 postnatal days, after which MBD incidence fell progressively to 1.25 per 1,000 person years in the 12th month after childbirth. Incidence of MBD among women who did not give birth was 2.07 per 1,000 person-years. The effects (relative rates, using incidence at 12 months postnatal as the baseline) were highest for all classes of disorder in the first months after childbirth. Effects during pregnancy for each of these disorders were protective (relative rates less than unity). These results have been depicted in Figure 1.4.



(a) Referent group for relative risks (RR) was admissions in the 11th postnatal month
Source data: Table 2 (Munk-Olsen, Laursen et al. 2006)

Figure 1.4 Effect of pregnancy and time since birthing on first-ever hospital admission for specified mental disorders in primiparous Danish mothers.

Australian study

Xu compared hospital admission rates for mental disorders before, during and after a pregnancy ending in a birth in NSW between 2003 and 2009 for first-time mothers (Xu, Sullivan et al. 2016). In line with the foregoing studies, rates of first hospital admissions for mental disorders in the period and all hospital admissions for MBD were lowest during pregnancy and admissions rose sharply immediately after birthing. At the end of the postnatal year, admission rates for mental disorders were higher than prenatal admission rates.

This study, by contrast to earlier studies, included drug/alcohol disorders as a class of MBD. Admission rates for drug/alcohol disorders were 2.73 admissions/1000PY (95%CI 2.50–2.96) in the baseline year before pregnancy, lowest in pregnancy with 0.74 admissions/1000PY (95%CI 0.61–0.87), and 1.43 admissions/1000PY (95%CI 1.26–1.60) in first postnatal year (Xu, Sullivan et al. 2016). In contrast to mental disorders, admissions for drug/alcohol disorders were lower at the end of the postnatal year than in the baseline year.

Is pregnancy protective against MBD?

The three seminal studies and the later Australian study described above have consistently demonstrated lower rates of admission for MBD in pregnancy than in the periods before or after Furthermore, in all four studies, the peak onset of MBD in the period immediately after giving birth. This has contributed to the notion that pregnancy protects against the onset of MBD (Astbury, Cabral de Mello et al. 2009).

However, closer examination of admissions for MBD during pregnancy from these studies reveals inconsistencies: Munk-Olsen's study presented admissions in pregnancy as a single time period (Munk-Olsen, Laursen et al. 2006) compared with postnatal, but not antenatal admission rates; in Paffenbarger's study admission rates did not change substantially during pregnancy study (Paffenbarger Jr 1964); admissions for MBD increased as pregnancy advanced in Kendell's study (Kendell, Chalmers et al. 1987), whereas admission rates for MBD fell progressively over the course of the pregnancy in Xu's study (Xu, Sullivan et al. 2016).

1.7 Prevalence of MBD in pregnancy

Surveys of MBD in pregnant women

Two maternity population surveys measured point prevalence of mental and behavioural disorders in the second trimester of pregnancy. In 2001-2002, Andersson surveyed 1,795 women (74% of all maternities) resident in a defined geographical area in the north of Sweden when they attended one of the three hospitals providing maternity services in (Andersson, Sundström-Poromaa et al. 2003). Borri used trained clinicians to assess 1,066 urban women (49% of resident women who gave birth) attending a large university hospital in Italy between 2004 and 2006 for ultrasound scan in the second trimester of pregnancy (Borri, Mauri et al. 2008).

The prevalence of mental disorders reported from these two studies is summarised in Table 1.1. Major depressive disorder (MDD) prevalence was similar in both studies, but the prevalence of other disorders differed. Bipolar disorder was uncommon in both these populations of pregnant women. Substance use disorders, schizophrenias and psychotic were not assessed by the survey instrument used in Andersson's study (Andersson, Sundström-Poromaa et al. 2003).Borri's team found no cases of schizophrenia or psychosis (Borri, Mauri et al. 2008). The largest difference was in the prevalence of anxiety disorders. The range of individual anxiety disorders identified by the survey instruments used by each study were different, and so were not comparable.

Table 1.1 Mental and behavioural disorders from population surveys of pregnant women

Study		Mental health assessment	Mental disorders				
			ANX	DEP	MDD	BD	SU
	N		*%*	*%*	*%*	*%*	*%*
Andersson (Andersson, Sundström-Poromaa et al. 2003) **2000-2001** **Nth Sweden**	1,795	PRIME-MD: DSM4-based survey	6.6	11.6	3.3	‡0.1	…
Borri (Borri, Mauri et al. 2008) **2004-2007** **Pisa, Italy**	1,066	SCID4-I: semi-structured interview	21.7	7.9	3.0	0.6	0.2

Abbreviations: ANX anxiety; DEP any depression; MDD major depressive disorder; BD bipolar disorder; DSM4 Diagnostic and Statistical Manual of Mental Disorders version 4; SCID-I Structured Clinical Interview for DSM4 Axis I Disorders; … not included; ‡ based on one case.

The range of individual anxiety disorders identified by the survey instruments used by each study varied. The Swedish study used PRIME-MD, a DSM-IV-based survey designed for use by lay interviewers, which did not assess psychotic disorders (Andersson, Sundström-Poromaa et al. 2003). The Italian study used a semi-structured interview for major DSM-IV Axis I diagnoses that was administered by trained mental health professionals (Borri, Mauri et al. 2008).

These two relatively small, intensive studies of MBD in pregnancy provide a comprehensive measure of MBD in their respective populations. The prevalence estimates from these two studies relate directly to the areas where the studies were undertaken and cannot not be generalised without caution. Prevalence estimates for individual disorders have been included with estimates from observational studies of MBD in pregnancy.

A widely quoted study from the USA reported that the prevalence of perinatal MBD was similar among 1,524 pregnant or recently pregnant (last 12 months) women and 13,025 non-pregnant women. This large, nationally representative sample of women from a household survey in the USA, conducted between 2001 and 2002, compared the prevalence of different types of MBD using DSM criteria (Vesga-López, Blanco et al. 2008). Results were not reported separately for pregnant women and were therefore not included in Table 1.1.

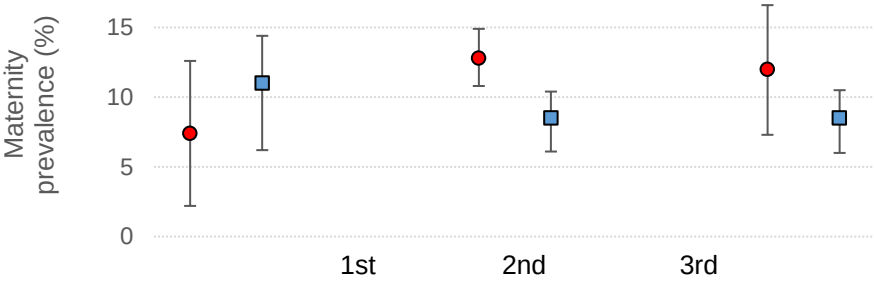
MBD prevalence from observational studies

Depression prevalence

Two systematic reviews have independently estimated the prevalence of depression across the trimesters of pregnancy, using aggregated results from studies conducted in high-income countries. Bennet included 21 studies of women aged 18 or over from general obstetric services or population surveys published between 1989 and 2003 (Bennett, Einarson et al. 2004). Gavin included 26 studies of various designs including cross-sectional, cohort studies and randomised trials of treatment efficacy that estimated a general population prevalence of depression conducted between 1980 and 2004 (Gavin, Gaynes et al. 2005). Their main findings are compared in Figure 1.5.

There was no statistically significant difference in the prevalence of depression at different stages of pregnancy from either study. One group showed a tendency to lower prevalence in later pregnancy (Gavin, Gaynes et al. 2005), and the other group showed a tendency to higher prevalence of depression in later pregnancy (Bennett, Einarson et al. 2004). Second and third

trimester prevalence estimates obtained by Gavin (Gavin, Gaynes et al. 2005) and colleagues were lower than those obtained by Bennett and colleagues (Bennett, Einarson et al. 2004).



	Bennett (Bennett, Einarson et al. 2004)		Gavin (Gavin, Gaynes et al. 2005)	
Trimester	**S**	**Prevalence (95%CI)**	**S**	**Prevalence (95%CI)**
1st	5	7.4 (2.2,12.6)	2	11.0 (7.6, 15.8)
2nd	10	12.8 (10.7, 14.8)	4	8.5 (6.6, 10.9)
3rd	14	12.0 (7.4, 16.7)	5	8.5 (6.5, 11.0)

Abbreviation: S: number of studies used in the meta-analysis

Figure 1.5 Prevalence of depression in 1st, 2nd, and 3rd trimester of pregnancy from systematic reviews

Differences in depression prevalence in Figure 1.5 from these meta-analyses may reflect the definitions of depression applied by each group. Bennett's group used a more restrictive definition of depression diagnosed by clinical interview from either the Beck Depression Inventory or the Edinburgh Postnatal Depression Scale (Bennett, Einarson et al. 2004) Gavin's group additionally included studies with self-reported assessments of depression using 1 of 12 different validated survey instruments and also required that depression could be distinguished from bipolar disorder and psychosis (Gavin, Gaynes et al. 2005). Both sets of reviewers noted substantial variation in the levels of depression reported by the included studies, which is reflected in the wide confidence intervals around the prevalence estimates.

Anxiety disorder prevalence

Anxiety disorders in pregnancy have received less attention than depression (Breitkopf, Primeau et al. 2006, Coleman, Morgan et al. 2006, Fairbrother, Janssen et al. 2016), despite being the most prevalent group of mental disorders among women of reproductive age. The prevalence of anxiety disorders in pregnancy from two systematic reviews (Ross and McLean 2006, Goodman, Chenausky et al. 2014) are presented in Table 1.2. The ranges of prevalence reported

for different types of anxiety disorder from each review were broadly similar, despite differences in the timing and numbers of studies available to each review.

Table 1.2 Prevalence of anxiety disorders in pregnancy from systematic reviews and a population study

	Systematic reviews				Population-based study
Disorder	**Ross and McLean, 2006 (Ross and McLean 2006) [a]**		**Goodman et al, 2014 (Goodman, Chenausky et al. 2014) [b]**		**Fairbrother et al, 2016 (Fairbrother, Janssen et al. 2016)**
No.S		*Prevalence range [c]*	*No.S*	*Prevalence range [c]*	*Prevalence (95%CI)*
Generalised anxiety disorder	1	8.5	7	0.4 – 8.5	2.6 (0.8. 4.4)
Obsessive compulsive disorder	2	0.2 – 1.2	6	0.2 – 3.4	2.9 (1.0, 4.8)
Panic disorder	3	1.4 – 2.0	7	0.2 – 0.4	1.6 (0.1, 3.0)
Post-traumatic stress disorder	4	0.0 – 8.1	7	0.7 – 7.9	‡
Specific phobia	nr		5	3.6 – 19.0	7.4 (4.5, 10.3)
Social phobia	nr		6	0.4 – 4.1	4.8 (2.4, 7.2)
Agoraphobia	nr		3	0.4 – 17.2	‡
Any anxiety disorder	nr		7	4.4 – 24.0	15.8 (11.7, 19.9)

(a) Results for studies in pregnancy.
(b) Results for studies in high-income countries.
(c) Confidence limits for prevalence from included studies were not reported in either review

Abbreviations: No.S: number of studies included in the review of each disorder; nr: not reported; ‡ imprecise estimate

prevalence results were not pooled so the number of studies included in the review and the range of reported prevalences in studies of individual disorders were presented in Table 1.2. Ross and McLean included all English language reports with original data for anxiety in the perinatal period (Ross and McLean 2006). Goodman, et al included reports of 1 or more anxiety disorders in pregnancy in studies that used DSM or ICD criteria in diagnostic interviews (Goodman, Chenausky et al. 2014), but Table 1.2 only included results for the studies in high income countries.

Table 1.2 also includes prevalence estimates of anxiety disorders in pregnancy from a recent population-based Canadian study (Fairbrother, Janssen et al. 2016).

Drug/alcohol disorder prevalence

Estimates of the prevalence of maternal drug and alcohol disorders (per 1,000 maternities or births) from Australian population-based study are presented in Table 1.3. All these studies obtained data about drug disorder directly or indirectly from hospital records. To be counted as

a disorder, drug or alcohol use needs to have been recognised as harmful or consistent with addiction by a clinician and the diagnosis recorded in the medical record.

The earliest of these studies reported prevalence of drug and alcohol use (recorded as yes or no) for all maternities in South Australia between 1998 and 2002 and reviewed a 20% sample of records to extract information about the frequency of use and classes of drug used (Kennare, Heard et al. 2005). In NSW, Burns obtained information about drug disorder diagnoses (Burns, Mattick et al. 2006) and alcohol disorder diagnoses (Burns, Mattick et al. 2006) from hospital inpatient records with an obstetric diagnosis linked with PDC data. This data linkage was carried out before NSW instituted a dedicated health records linkage facility. This linkage design missed non-obstetric admissions during pregnancy for these women, which would be more likely in early pregnancy before pregnancy was recognised or antenatal care initiated.

Table 1.3 Prevalence of drug and alcohol use in pregnancy from population studies

	Population	Alcohol	Cannabis	Opiate	Stimulant	Any drug
		Prevalence /1000 maternities/births				
O'Leary (O' Leary, Halliday et al. 2013)	WA 1985-2006	2.1				
Burns (Burns, Mattick et al. 2006)	NSW 1998-2002	0.8				
Burns (Burns, Mattick et al. 2006)	NSW 1998-2002		5.2	4.7	1.3	
Abdel-Latif (Abdel-Latif, Oei et al. 2013)	ACT&NSW 2004		9.2	6.5	3.4	14.0
O'Donnell (O'Donnell, Anderson et al. 2013)	WA 1990-2005					5.8
Kennare (Kennare, Heard et al. 2005)	SA 1998-2002					7.9

Abbreviations: ACT Australian Capital Territory; NSW New South Wales; SA South Australia; WA Western Australia,

A NSW and ACT state-wide audit of maternal substance use sought information from heads of midwifery in district and tertiary public hospitals providing maternity about care for births with maternal substance use in 2004 (Abdel-Latif, Oei et al. 2013). The medical records were reviewed by researchers to obtain details of illicit drug use and mental health disorders in these mothers. The authors restricted the audit to public hospitals, where prevalence of substance was higher (Burns, Mattick et al. 2006).

O'Leary (O'Leary, Halliday et al. 2013), obtained birth records linked with Hospital Morbidity Data System, the Mental Health Outpatients data set and the Perth-based Drug and Alcohol

Treatment Services. This was a more extensive linkage than that in NSW (Burns, Mattick et al. 2006, Burns, Mattick et al. 2006), which only used the Admitted Patient Data Collection for information about drug or alcohol disorders.

O'Donnell and colleagues (O'Donnell, Anderson et al. 2013) linked births by mother with administrative data from inpatient and outpatient mental health services: WA Hospital Morbidity Data Collection, and the WA Mental Health Information System.

Serious mental disorder prevalence

Serious mental disorder generally refers to schizophrenia, bipolar disorder, and other psychotic disorders. These disorders are also referred to as low prevalence disorders because they are substantially less common in the general population than anxiety, depression, and drug/alcohol disorders. The lack of information about prevalence of serious mental disorders in pregnancy has been highlighted (Jones, Chandra et al. 2014). Observational studies of serious mental disorder as a risk factor for adverse neonatal outcomes, discussed below, did not, as a rule, report prevalence. Nor were they designed to do so.

Borderline personality disorder, also known as emotionally unstable personality disorder, is considered a serious mental disorder in the perinatal period (Department of Health 2018). There have been no measures of the prevalence of borderline personality disorder in pregnancy in Australia, but 2.7% (95%CI 1.4 to 4.0) of Australian women older than 25 years have been estimated to have the disorder (Quirk, Berk et al. 2017).

1.8 Neonatal outcomes of MBD in pregnancy

MBD in pregnancy is associated with increased mortality and morbidity of babies. Perinatal mortality includes stillbirth, or the birth of a dead baby, and death in the neonatal period, defined as the first 28 days after birth. Preterm birth and small size at birth, measured either as low birthweight or small size for gestational age, underly a wide variety of neonatal morbidities. Preterm birth is a birth at less than 37 weeks gestational age. Low birthweight is weight at birth less than 2,500 grams. Small size for gestational age is a birthweight below the 10^{th} centile of the standard weight for the gestation at which the birth occurred.

Neonatal outcomes following maternal depresssion

The effect of depression in pregnancy on preterm birth and birthweight has been assessed by two meta-analyses. Grigoriadis and colleagues combined the results of 15 studies to report pooled effect of preterm birth (OR 1.37, 95%CI 1.04 - 1.81) with moderate heterogeneity found among the individual study results (Grigoriadis, Vonderporten et al. 2013). Pooled results did not show significant effects on mean gestational age (9 studies), mean birthweight (11 studies) or low birthweight (7 studies) (Grigoriadis, Vonderporten et al. 2013). Grote's study(Grote, Bridge et al. 2010) likewise showed depression increased risks of preterm birth (20 studies: pooled RR 1.13, 95%CI 1.06-1.21). Grote also found an association between depression in pregnancy and low birthweight (11 studies: pooled RR 1.18, 1.07-1.30), but no effect on small size for gestational age (12 studies: pooled RR 1.03, 95%CI 0.99-1.08).

These meta-analyses, carried out within three years of each other used different inclusion criteria and quality measures that substantially altered the mix of studies used to pool effects. Grotte screened 682 citations, retrieved 57 articles, and included 29 studies, whereas Grigoriadis reviewed 3,074 abstracts, retrieved 735 articles, and included 30 studies. Both selected prospective longitudinal studies with antenatal assessment of depression. Grigoriadis excluded studies from non-English language publications, studied published before 1980, and studies of adolescents and included studies with any measure of depression. Grote included non-English language studies that assessed depression with a screening questionnaire or structured psychiatric interview but excluded studies that did not separate unipolar and bipolar depression. Only 14 studies were common to both. Grote included 3 studies from low- and middle-income countries where low birthweight is more prevalent. Both meta-analyses noted different study methodologies with respect to tools used to measure depression, the selection of controls, study exclusions and range of confounders. Included studies also varied in their capacity to adjust for maternal smoking, drug, and alcohol use. Despite these limitations, these two independent meta-analyses found modest pooled effects of depression in pregnancy on preterm birth (Grote, Bridge et al. 2010, Grigoriadis, Vonderporten et al. 2013), and marginally positive or no effect of depression on low birthweight (Grote, Bridge et al. 2010).

Neonatal outcomes following maternal anxiety disorder

The evidence for effects of maternal anxiety on neonatal outcomes comes from a single study that pooled results from 15 cohort studies carried out in USA, England, Canada, Germany,

France, Sweden, Norway, China, and Bangladesh. Anxiety was associated with preterm birth (12 studies, pooled RR 1.5 95%CI 1.33-1.70) and with low birthweight (6 studies, pooled RR1.76, 95%CI 1,32-2.33) (Ding, Wu et al. 2014). Most of the 15 included studies were small, ranging in size from 66 to 510 participants with anxiety. There were 10 different tools used to assess anxiety, which differ in their, methods of assessment, time frame and construct of anxiety. Self-administered screening tests such as the Self Rating Anxiety Scale and the Hospital Anxiety and Depression rating Scale measure the present or recent past, whereas the State-Trait Anxiety Inventory measures how the subject generally feels (Kellner and Uhlenhuth 1991). By contrast tests based on diagnostic interviews by lay interviewers (PRIME-MD: Primary Care Evaluation of Mental Disorders) or mental health professional interviews (DSM-IV) were diagnostic tools. Eleven studies assessed anxiety once, 8 in the second trimester. Eight studies reported unadjusted relative risks, and among the remaining 7, only 5 adjusted for smoking. and none for comorbid drug use or depression.

Neonatal outcomes following maternal drug or alcohol disorders

Increased perinatal mortality, low birthweight, small size for gestational age preterm birth and admission for neonatal care have been widely reported in babies whose mothers had used alcohol or drugs during pregnancy. A large Australian population-based study of births between 1998 and 2002 reported preterm birth was twice as common among mothers with an alcohol disorder (15.5% vs 6.0%) and small size for gestational age was three times higher (30.1% vs 9.7%) than in mothers without an alcohol disorder (Burns, Mattick et al. 2006). Ater adjusting for maternal smoking, concurrent drug disorder and other confounders, the association between maternal alcohol disorder and preterm birth was no longer significant, but the odds of small size for gestational age was increased by a factor of 1.8 (95%CI 1.4, 2.3) (Burns, Mattick et al. 2006) In the same population, compared with mothers without a disorder, the odds of small size for gestational age was doubled among mothers with an opioid disorder (aOR 1.9, 95%CI 1.7, 2.1) or maternal cannabis disorder (aOR 2.0, 95%CI 1.7, 2.2) and the odds of preterm birth was increased three-fold for mothers with an opioid disorder (aOR 3.0, 95%CI), two-fold among mothers with a cannabis disorder (aOR 2.2, 95%CI 1.9, 2.5) and marginally among mothers with a stimulant disorder (aOR 1.5, 95%CI 1.1, 2.0) after adjustment for maternal smoking, concurrent substance disorder and sociodemographic confounders (Burns, Mattick et al. 2006). Allowing for variations due to different methods for identifying maternal substance use, these effects are broadly similar to those reported from other studies (Patra, Bakker et al. 2011, Ross, Graham et

al. 2014, Srikartika and O'Leary 2015, Gunn, Rosales et al. 2016, Cohen, Osorio et al. 2017, Metz, Allshouse et al. 2017).

Neonatal outcomes following maternal serious mental disorders

The evidence is inconsistent for increased risk of adverse perinatal and neonatal outcomes among births to women with schizophrenia and bipolar disorder. Published studies used data linkage to identify mothers with a diagnosis of bipolar disorder of schizophrenia in a geographically defined population. Table 1.4 compares the effects of bipolar disorder and Table 1.5 compares the effects of schizophrenia on preterm birth and small size for gestational age.

Table 1.4: Effects of maternal bipolar disorder on preterm birth (PTB) and small size for gestational age (SGA) from published research

Study	PTB effect (95%CI)	SGA effect (95%CI)
Mei-Dan (Mei-Dan, Ray et al. 2015) **Canada, 2002-2011**	**aOR 1.95 (1.68-2.26)**	aOR 1.15 (0.92-1.43)
	Adjusted for: maternal age, parity, infant sex, obesity, alcohol/drug disorder, diabetes, hypertension, thromboembolism, gestational diabetes, hypertension and preeclampsia/eclampsia	
Lee (Lee and Lin 2010) **Taiwan, 2001-2003**	**aOR 2.08 (1.53–2.83)**	**aOR 1.47 (1.14–1.91)**
	Adjusted: maternal age, education level, marital status, and gestational hypertension, and infant's gender and parity, family income, parental age difference, and paternal education	
Boden (Boden, Lundgren et al. 2012) **Sweden, 2005-2009**	**Rx aOR: 1.50 (1.01-2.24)** **noRx aOR: 1.48 (1.08-2.03)**	Rx aOR: 0.93 (0.46-1.88) noRx aOR: 1.41 (0.88-2.24)
	Adjusted: maternal age, cohabitation, smoking, maternal height, alcohol/drug disorder.	
Jablensky (Jablensky, Morgan et al. 2005) **WA 1980-1992**	aOR 1.06 (0.82–1.36)	aOR 1.11 (0.86–1.44)
	Adjusted: maternal age, maternal marital status, plurality, Aboriginality, and sex	

Abbreviations: aOR adjusted odds ratio; Rx treated; noRx not treated; 95%CI 95% confidence interval

In Table 1.4, bipolar disorder doubled the risk of preterm birth in Canada(Mei-Dan, Ray et al. 2015), and Taiwan (Lee and Lin 2010). Neither of these studies differentiated between women with treated or untreated disorders. In Sweden the risk of preterm birth was increased by 50% in mothers with bipolar disorder whether they used treatment or not (Boden, Lundgren et al. 2012). No effect of bipolar disorder on preterm birth was found in Australia (Jablensky, Morgan et al. 2005). Small size for gestational age was increased by 47% among mothers with bipolar disorder in Taiwan (Lee and Lin 2010), but no effect of bipolar disorder on small size for gestational age was reported from the other studies.

Effects of maternal schizophrenia on preterm birth and small size for gestational age are presented in Table 1.5. In 4 of the 5 studies, preterm birth was between 20% higher (Nilsson, Hultman et al. 2008) and 75% higher (Vigod, Kurdyak et al. 2014) compared to births without maternal mental disorder. Small size for gestational age at birth was increased by schizophrenia in 4 of the 5 studies. Effect sizes ranged from 34% higher (Bennedsen, Mortensen et al. 1999) to 52% higher (Lee and Lin 2010) than for non-schizophrenic mothers.

Table 1.5: Effect of maternal schizophrenia on preterm birth (PTB) and small size for gestational age (SGA) from published research

Study	PTB effect (95%CI)	SGA effect (95%CI)
Vigod (Vigod, Kurdyak et al. 2014) **Canada 2002-2011**	**aOR 1.75 (1.46–2.08)** *Adjusted for: maternal age, parity, income, community size, PP diabetes mellitus, PP hypertension, PP thromboembolic disease and infant sex.*	**aOR 1.49 (1.19–1.86)**
Lee (Lee and Lin 2010) **Taiwan, 2001-2003**	**aOR 1.33 (0.99–1.79)** *Adjusted for: maternal age, education, marital status, gestational hypertension, infant sex, parity, family income, parental age difference, paternal education*	**aOR 1.52 (1.23–1.87)**
Jablensky (Jablensky, Morgan et al. 2005) **WA 1980-1992**	aOR 1.14 (0.79–1.63) *Adjusted for: maternal age, marital status, plural birth, infant sex, Aboriginality*	**aOR 1.38 (1.00–1.90)**
Bennedsen (Bennedsen, Mortensen et al. 1999) **Denmark 1973-1993**	**aRR 1.34 (1.08–1.66)** *Adjusted for: maternal age, parity, certainty LMP, baby sex, birth year*	**aRR 1.34 (1.17–1.53)**
Nilsson (Nilsson, Hultman et al. 2008) **Sweden 1983-2002**	**aOR 1.2 (1.0–1.4)** *Adjusted for: schizophrenia in spouse, maternal age, parity, maternal and paternal education, cohabitation status and maternal smoking*	aOR 0.9 (0.7–1.2)

Abbreviations: aOR adjusted odds ratio; aRR adjusted relative risk; 95%CI 95% confidence interval: PP pre-pregnancy

None of these studies distinguished different forms of schizophrenia such as those with positive symptoms (previously termed type 1) and negative symptoms (previous termed type 2). Diagnostic follow-up periods, that is the time during which diagnoses could contribute to MBD ascertainment, varied. Longer periods would be expected to increase the number of women identified but at the expense of including women whose disorder is quiescent or well managed. Only one study adjusted for maternal smoking (Nilsson, Hultman et al. 2008) and none for maternal drug or alcohol disorders or co-existing MBD.

Mechanisms of MBD effects on neonatal outcomes

Evidence from observational studies suggests maternal MBD are associated with preterm birth and small size for gestational age. Evidence of causal relationship is strengthened by the existence of at least 4 biologically plausible mechanisms: i) catecholamine and hypothalamic-pituitary axis activation by stress; ii) bacterial infection initiation of labour; iii) nutrition; iv) pharmacological actions of psychotropic drugs.

Maternal stress during pregnancy is commonplace for women with MBD, particularly those with limited social support or financially insecurity. Acute stress elevates catecholamines that constrict blood flow to the uterus, thus decreasing fetal nutrient and oxygen supplies and stressing the fetus (Ross and McLean 2006, Littleton, Breitkopf et al. 2007). Chronic stress activates the maternal hypothalamic-pituitary axis to elevate plasma cortisol, which can cross the placenta or increase placental corticotrophin release hormone that stimulates the fetal cortisol production. Cortisol is a catabolic (promoting tissue breakdown) steroid and elevated fetal cortisol retards fetal growth. Furthermore, increased production of placental corticotrophin release hormone in late pregnancy has been suggested as a fetal signal for the onset of labour (Bennett 2018).

Bacterial infections can stimulate uterine inflammation capable of triggering preterm labour because the onset of labour is mediated by local tissue hormones that promote inflammation (Bennett 2018). Several MBD such as drug/alcohol disorders, bipolar disorder and schizophrenia are associated with risky and unsafe sexual behaviours or with sexual exploitation that can increase the risk of genital tract infection (Huestis and Choo 2002, Fisher, Herrman et al. 2014).

MBD can also act though nutritional pathways to increase the risk of maternal anaemia, insulin resistance and maternal hypertension, which in turn impact on fetal wellbeing through abnormal placental growth, development and function (Wu, Imhoff-Kunsch et al. 2012). Malnutrition-induced IUGR and preterm birth can also arise through maternal endocrine disorders, disturbances in normal metabolic processes, impaired maternal immunity, or activation of preterm birth (Wu, Imhoff-Kunsch et al. 2012).

The potential for direct harm to the fetus from psychotropic drugs, including alcohol, nicotine, medications used to treat mental disorders and illicit drugs, stems from the ease with which they cross the placenta (Ross, Graham et al. 2014). Once in the fetal circulation they can directly

affect neuroendocrine mechanisms governing fetal growth and development (Ross, Graham et al. 2014). From the fetal circulation they can enter the amniotic fluid, which from mid-pregnancy is swallowed by the fetus, increasing their duration of action (Pollard 2007). Key mechanisms by which individual substances act on preterm birth and fetal growth restriction vary. Alcohol, as well as being a neurotoxin and teratogen, stimulates catecholamine release and can damage the placenta (Pollard 2007, Scott-Goodwin, Puerto et al. 2016). Cannabis smoking decreases oxygen availability by increasing carboxyhaemoglobin over and above levels included by tobacco smoking (Richardson, Hester et al. 2016). The placenta limits endogenous and exogenous cannabis transfer from the mother to the fetus, but overstimulation of placental endocannabinoid receptors inhibits cytotrophoblast proliferation (Scott-Goodwin, Puerto et al. 2016). In early pregnancy this can reduce placental growth and ultimately fetal growth. Cocaine increases maternal and uterine contractility (Ross, Graham et al. 2014, Darke, Lappin et al. 2019). Fetal dependence can develop that result in neonatal withdrawal syndromes. The best known is neonatal abstinence syndrome in babies born to mothers with opiate disorders but withdrawal syndromes (Finnegan 1994, Darke, Lappin et al. 2019), but can occur with other substances such as cocaine, cannabis, and amphetamines (Wells 2019). Opiate withdrawal increases muscular activity. Antenatal withdrawal increases energy and oxygen consumption in the mother and the fetus (Finnegan 1994). Increased maternal oxygen use deprives the fetus and increases fetal stress, contributing to growth restriction and preterm birth.

1.9 Gaps in the literature and how this thesis will address them

There are at least three key knowledge gaps in relation to MBD in pregnancy that this thesis seeks to address. First, the evidence for the widely held view that pregnancy is protective for MBD is limited and conflicting. This has been examined in Section 1.6 under the heading "*Is pregnancy protective against MBD*?". Second, information on the prevalence of classes of MBD in pregnancy is patchy: prevalence in pregnancy of drug/alcohol disorders have been measured in Australia, and prevalence of common MBD, such as anxiety and depression, have been assessed in several high-income countries worldwide. There is no information, however, about the prevalence in pregnancy of serious MBD, such as schizophrenia and bipolar disorder. Comprehensive information about MBD in pregnancy is lacking in Australia and elsewhere. Third, neonatal outcomes have been studied in Australia for drug disorders and alcohol disorders, but information about neonatal outcomes for mental disorders in Australia is lacking. To date. studies world-wide have been limited by their inability to account for the effects of co-existing MBD and maternal smoking in pregnancy.

This thesis aims to generate new knowledge to address these gaps. NSW is the most populous Australian state with about 90,000 births annually, representing one third of maternities in Australia and has instituted health data linkage to provide population-based data for researchers. A dataset of maternities linked with inpatient MBD episodes in NSW between 2000 and 2006 had been prepared for an earlier study in which maternal MBD had been included as a secondary explanatory variable (Walker, Hilder et al. 2014). The decision to use these data was pragmatic. This maternity population was large enough to examine the main classes of MBD from admissions during pregnancy. The study period shortly predates the Australian surveys of common mental disorders in 2007 (Slade, Johnston et al. 2009) and psychotic mental disorders in 2010 (Morgan, Waterreus et al. 2011). These datasets are the current gold standard for population prevalence of depression, anxiety, drug/alcohol disorders and psychotic disorders (National Mental Health Strategy 2018) and are used to contextualise and contrast maternity prevalence of these disorders. This cohort provides a baseline against which results from analyses of a future iteration of linked maternities/inpatient MBD episodes can be compared.

Specifically, this thesis comprises the following chapters:

Chapter 2 describes the data and analytic methods used to prepare the data for the three in this thesis.

Chapter 3 examines whether pregnancy is protective for MBD in this maternity population. The study measures 2-monthly rates of admission for MBD, defined as admissions with a principal diagnosis of MBD, across pregnancy and for the periods before and after pregnancy. These are the first Australian results for all mothers, not just first-time mothers.

Chapter 4 presents data on the prevalence of a comprehensive range of classes of MBD in pregnancy. Specifically, this chapter considers the pregnancy prevalence of MBD overall and individual classes of MBD, the extent of MBD comorbidity and groups at high risk for MBD within the NSW population.

Chapter 5 examines the effects and impacts of maternal MBD on neonatal outcomes: perinatal mortality, preterm birth, small size for gestational age, neonatal morbidity and admission for neonatal care. Linked data used for this thesis extended the range and improved the quality of neonatal outcomes. This is the first study to simultaneously assess the association of all classes of MBD on baby outcomes and report their potential burden on adverse neonatal outcomes.

Chapter 6 discusses the implications of the findings from these studies for research, policy and practice.

Chapter 2. Methods common to all studies

This chapter describes the linked data and the analytic methods to prepare the data used in the chapters that follow.

2.1 Data linkage

Principles of health data linkage in NSW

Linkage of health data in NSW is carried out by the Centre for Health Record Linkage (CHeReL). The CHeReL was established in 2006 to undertake probabilistic matching of person-identifying data in a secured environment, in accordance with the best practice protocol for data linkage (Kelman, Bass et al. 2002). A central tenet of the best practice protocol is the separation of source data, data linkage and research data: only the linkage facility was provided with the person-identifying data for records to be included in the project by the data custodians of each state-wide data source; when the linkage was completed the person-identifying data returned to the relevant data custodian included an anonymised person identifier specific to the project; the data extracts prepared by data custodians for researchers included anonymised person identifiers in place of person identifying data. This preserves the privacy of the data subject while allowing the use of person-identifying data for linkage.

A feature of the CHeReL is the master linkage key, which links records by person from all contributing data sources. From the outset, NSW vital registrations (birth and death registration), NSW Perinatal Data Collection and the NSW Admitted Patient Data Collection have contributed data to the CHeReL master linkage key. The number of data sources that contribute data has expanded over time. The current list of contributors to the master linkage key is available from the CHeReL website (Centre for Health Record Linkage 2013). When linked records in the master linkage key are updated, all the person identifying information from each data source is used to find the best matches between records from each source.

Linked data identified from the master linkage key has important implications for matching baby records. Birth notifications to the PDC include hospital medical record numbers, but not baby names. Baby names may not be given by parents until the birth is registered, which can be 6 or more weeks after birth. Babies admitted to different hospitals in their first weeks of life may have different names. The master linkage key collates identifying information from all data

sources to identify persons across each data collection. Accurate record linkage for babies from multiple births (twins, triplets, and higher order multiple births) is more difficult than for singleton babies because they usually share date of birth and maternally derived data such as residential address.

Linkage design

The Perinatal Data Collection was nominated as the primary data set for linkage. Records from all other data sources were linked with these records. There were seven steps in this process.

Step one: Source data custodians notify the CHeReL with a file of patient identifiers for records to be linked for the study: all mothers aged 18 years or over who gave birth between 2000 and 2006; and 2 sets of selected APDC records: (1) women aged 18-44 whose hospital episode included a diagnosis of MBD; and (2) neonates (aged 0 to 27 days).

Step two: Maternal PDC records were linked by mother with selected APDC records. A project-specific unique person number for each mother (mother-PPN) was added to linked records from each data source.

Step three: A random 10% sample of PDC mothers with no linked APDC records were selected as control mothers. Randomised selection was obtained using the Statistical Analysis System (SAS) RANUNI function. This function assigned a random number between 0 and 1 to the set of PDC mothers and samples a fraction. A mother-PPN was added to selected records.

Step four: The PDC study records with mother-PPNs were returned to PDC data custodian.

Step five: The PDC data custodian added the baby identifier to each study PDC record and returned the PDC these to CHeReL.

Step six: A second linkage of PDC and neonatal APDC records by baby was performed and a baby-PPN was added to each linked record from each source.

Step seven: The study records with baby-PPNs were returned to data custodians to prepare the study data to be sent to researchers as outlined above. The PDC data custodian included 2 pseudonymised unique person identifiers: one for the mother; and one for the baby.

The linkage design was developed by this author in consultation with NSW Health data custodians. This was the first data linkage by the CHeReL across the perinatal period for both mothers and their babies.

The data linkage schematic depicted in Figure 2.1. summarises the 2-stage linkage design. The description above refers only to linkage of data used in this thesis, namely APDC and PDC records. However, Figure 2.1 recognises that PDC mother records were also linked with data sources used in the overarching study (Walker, Hilder et al. 2014) that were not relevant to the studies in this thesis. Mothers whose PDC records linked with data from these other sources, but not with APDC records were retained in the data to avoid distortion of the sampling and maintain a direct relationship with the number of maternities in source population. The contribution of these maternities to the final study data has been noted Table 2.2. Nodata from these sources were used in this thesis.

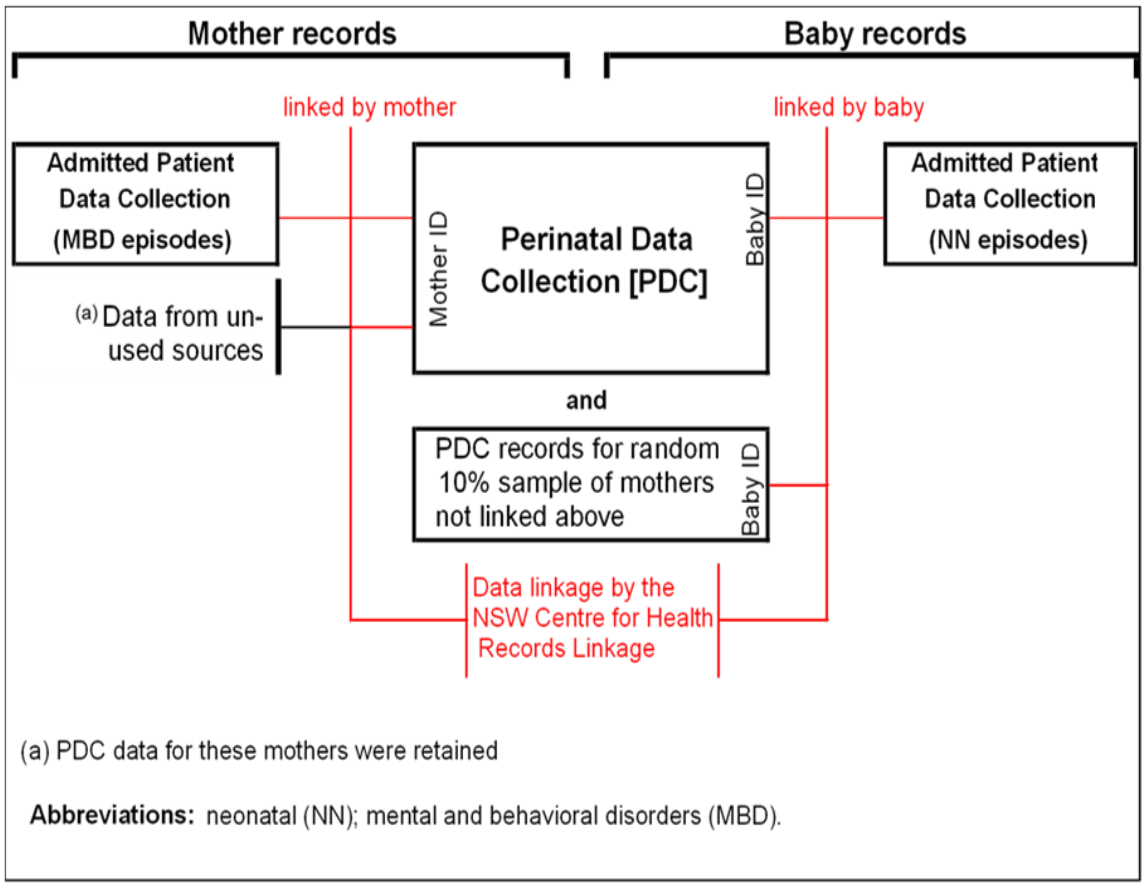


Figure 2.1 Data linkage design schematic

Ethical considerations

Custodians of health data collections have a duty to protect the privacy of data subjects (NSW Government 1998, NSW Government 2002). Some of the linked data sources in the overarching study were considered particularly sensitive. Therefore, measures to reduce the chance of spontaneous recognition of an individual were negotiated with the data custodians. Dates for all events in all data requests were replaced with the age in days of the data subject. Year of birthing from the PDC record was provided to enable study results to be related to results for annual cohorts of maternities from the *NSW Mothers and babies* report series. The set of unlinked maternity records was limited to a random sample rather than the whole population. These restrictions did not compromise the main analyses but did limit some aspects of quality control.

Ethics approval for the data linkage and the use of the linked data for this thesis was obtained from each appropriate ethics committee: the NSW Population & Health Services Research Ethics Committee [CI NSW Study Reference number: 2008/10/103] the Justice Health Human Research & Ethics Committee [Reference number GEN119/06], NSW Correctional Services Ethics Committee [Reference number: 07/876], and the Aboriginal Health Ethics Committee [Reference number: 674/08].

2.2 Data sources used in the linkage

NSW Perinatal Data Collection (PDC)

This state-wide surveillance system collects details of all live births and stillbirths of at least 400g birthweight or at least 20 weeks gestation that take place in NSW (Centre for Epidemiology and Research. NSW Department of Health 2006). Notification of the details of each birth to the state health authority by the birth attendant is a statutory requirement (NSW Department of Health 2009). Data are collected soon after birth using information from antenatal and birth records. Each PDC record relates to one baby and contains maternal socio-demographic information and clinical information about the pregnancy, birth, newborn condition at birth and newborn admission.

PDC records selected for linkage

PDC records for women aged 18-44 who gave birth between 1st January 2000 and 31st December 2006 were selected as the base cohort.

NSW Admitted Patient Data Collection (APDC)

Information about services for patients admitted to public and private hospitals, public multi-purpose health services, and private day procedure centres in NSW are collected to audit activity in public hospitals. They are used nationally to assess hospital performance against the National Health Performance Framework (Australian Institute of Health and Welfare (AIHW) 2007) and the basis for activity based funding (Independant Hospitals Pricing Authority (IPHA)). Each record relates to an episode of care that includes demographic details collected on admission to hospital; information about procedures, diagnoses and discharge details is added at completion of the episode. From July 2000, the APDC included patient names as mandatory fields for NSW public hospitals, and as voluntary fields for private hospitals (Centre for Health Record Linkage 2013).

Up to 55 diagnoses are coded to ICD10-AM for each hospital episode. The first-listed diagnosis is the principal diagnosis, defined as "the diagnosis established, after study, to be chiefly responsible for occasioning an episode of admitted patient care"(National Centre for Classification in Health 2003, Health Data Standards Committee 2008). Additional diagnoses code for conditions "either coexisting with the principal diagnosis or arising during the episode of admitted patient care" (National Centre for Classification in Health 2003, Health Data Standards Committee 2008).

APDC-MBD Women's episodes selected for linkage

APDC episodes for women aged 18-44 that commenced between 1st July 2000 and 31st December 2006 and included one or more mental and behaviour disorder MBD diagnoses (F10-F99, T40, T42, T43, F10-F19, E24.4, G31.2, G62.1, G72.1, I426, K29.2, K70, K86.0, O35.4, R78.0, T51, X45, X60-X84, Y10-Y19, Y87.0Y15, Y57.3, Y90, Y91, Z50.2, Z71.4, Z72.1, Z72.2, Z91.5) or a flag for admission to a psychiatric ward were selected for linkage by mother. The list of MBD was intentionally broad.

The data obtained for the study comprised maternal age (in days) at the start and end, the principal diagnosis and all additional diagnoses for each episode.

APDC-NN Neonatal episodes selected for linkage

APDC episodes for children aged 0-27 days that commenced between 1st July 2000 and 31st January 2007 and a diagnosed perinatal condition (ICD10 Chapter 16) were selected for linkage. The request for episodes to the end of January ensured all study babies were follow to the end

of the neonatal period. Selection of episodes with a perinatal diagnosis excluded inpatient episodes for well babies. Stillborn babies are not admitted to hospital in NSW.

2.3 Preparing the linked data for research

The linked data provided to researchers comprised all maternities for mothers whose PDC record(s) linked with data from at least one of the other data sources noted above and all maternities for a random 10% sample of mothers with no linked records who gave birth in NSW between July 2000 and December 2006 (the comparison group). Linked population data, even those linked to the highest standards by a dedicated authority, are not research ready. Additional processing to validate and prepare the data for epidemiological analysis was needed.

Weighting

Weighting related the numbers of mothers from the sampled data to the source population. The weight (w), derived as the inverse sampling fraction applied to the mother, was added to each of her PDC records. All mothers with linked data from any source were selected for the study. This is a sampling fraction of 1 and these mothers were assigned a weight of 1. The 10% random sample of mothers with no linked records were assigned a weight of 10. Failure to include mothers linked with non-APDC data sources in the study population would result in a small, but systematic bias in population-based estimates.

Class of MBD

The framework in Table 2.1 sets out the ICD10-AM codes that defined classes of MBD used in this thesis. The main classes comprised drug/alcohol disorder and mental disorder. The framework of individual classes of MBD was developed for studies of perinatal mental health (Xu, Austin et al. 2012, Xu, Hilder et al. 2012). Individual mental disorder classes were combined to align with classes of MBD reported from national surveys.

The separation of depression with psychotic features from depression facilitates comparison with Australian population surveys of psychotic disorders, which included (Australian Bureau of Statistics 2008, Morgan, Waterreus et al. 2011) (Morgan, Waterreus et al. 2011). The schema was refined by the author to expand drug/alcohol use diagnoses in line with those other studies of substance use in pregnancy (Burns, Mattick et al. 2006, Burns, Mattick et al. 2006, O'Leary, Halliday et al. 2013). The author flagged codes that specify postnatal disorders: ‘F53’ diagnoses

and 'F32' diagnoses with a 5th digit indicating postnatal onset. These codes were removed from algorithms that selected episodes in pregnancy.

Tobacco use disorders (F17) were excluded from the conditions that comprised drug/alcohol use in Table 2.2. ICD10 tobacco use disorders were rarely recorded in APDC records. Smoking recorded using ICD10 behavioural or lifestyle factors had not been requested. Information about smoking in the PDC was used. See Table A2.1 for more detail.

Table 2.1 Definition of mental and behavioural disorders (MBD) used in this thesis.

Class of MBD		ICD10-AM diagnostic codes	
		ICD10 Chapter 5	Other ICD10 chapters
Mental disorders	**Psychotic disorders**		
	Schizophrenia	F20.0–F22.9, F24.0–F24.9, F25.0–F25.9, F28.0–F28.9, F29.0–F29.9	
	Psychosis	F23.0–F23.9, F32.3 (a), F33.3, F39.0–F39.9, F53.1(a)	
	Affective disorders		
	Bipolar disorder	F30.0, F30.2, F30.8, F30.9, F31.0–F31.6, F31.8–F31.9, F34.0, F38.0	
	Depression	F32.0–F32.2(a), F32.4–32.9(a), F33.0–F33.2, F33.4–33.9 F34.1, F38.1–F38.9, F53.0(a)	
	Anxiety disorders		
	Anxiety	F40.0–F42.9	
	Adjustment	F43.0–F43.9	
	Not included in surveys		
	Personality disorder	F60.0–F69.9, F60.31	
	Other mental disorders	F00.0–F09.9, F26.0–F27.9, F30.1, F31.7, F34.2–37.9, F44.0–F49.9, F50.0–F52.9, F53.2–F53.9(a), F54.0–F59.9, F70.0–F99.9	
Drug/alcohol disorders	Alcohol	F10.0–F10.9	O35.4, R78.0, T51.0–T51.9, X65.0–X65.9, Y15.0–Y15.9, Y57.3, Y90.0–Y91.9, Z50.2, Z71.4, Z72.1
	Opiates	F11.0–F11.9	T40.0–T40.4
	Cannabis	F12.0–F12.9	T40.7
	Stimulants	F15.0–F15.9, F14.0–F14.9	T43.6, T40.5
	Sedatives	F13.0–F13.9	T42.3, T42.4
	Polydrug	F19.0–F19.9	
	Other drug	F16.0–F16.9, F18.0–F18.9	O35.5, T40.6, T40.8, T40.9, T42.0–T42.2, T42.6–T43.5, T43.0–T43.9, Z72.2

(a) ICD-10AM F53 codes and F32 codes with '1' as the 5th digit specify postnatal onset were omitted from algorithms that assigned diagnostic groups in pregnancy.

Abbreviation: ICD10-AM: International Classification of Diseases 10th revision, Australian modification

Quality control

Validation of linked maternities

About 60% of study mothers contributed more than one maternity to study. Quality control carried out previously by the author found 178 (0.27%) of the 66,477 original study mothers had implausible or inconsistent data across their linked PDC records. This included for duplications (same baby with two different mothers), mothers with an excessive number of maternities (up to 15 in 6 and a half years); inconsistent changes between maternities in maternal age and year of birthing; and overlapping pregnancy periods (Hilder, Walker et al. 2016). It was not possible to distinguish between transcription error in one or both records and data linkage error. Therefore, these mothers and all their maternities were excluded from the study data.

Excluded diagnoses

Some diagnoses specified to select APDC records for linkage (listed in Section 2.1) were not required because they were outside the study definitions of MBD diagnostic groups in Table 2.1. These included diagnoses for self-harm (X60-X84, Y10-Y19, Y87.0, Z91.5) and Complications of alcohol use (G31.2, G62.1, G72.1, I426, K29.2, K70, K86.0).

Diagnoses fom admissions to a psychiatric ward

In addition to the list of specified MBD diagnoses, APDC inpatient episodes selected for linkage included those flagged as admissions to a psychiatric ward (see 'Maternal APDC records selected for linkage' above). In total, 522 inpatient episodes for 465 mothers lacked at least one of the specified diagnoses. Diagnoses in these episodes were examined to check for conditions inadvertently omitted from the specification. External causes (trauma or poisoning) accounted for the majority (91.1%) of this group. The most common individual diagnosis was 'T39.1: *poisoning or adverse effects of 4-aminophenol derivative*s', which are metabolites of acetaminophen (paracetamol) on 149 (27.0%) of the unassigned inpatient episodes. Open wounds of the forearm and hand not associated with a fracture or contusion (S61.7, S61.88 and S61.9) accounted for 8.0% of episodes in this group. Poisoning may have occurred by accident or intent. Likewise, forearm injuries could have been accidental or resulted from injecting. In the absence of a diagnosis indicating intentional self-harm or drug use, these and other diagnoses did not warrant any change to the definitions of mental and behavioural disorder diagnostic groups (see Table 2.1) used in this thesis.

Between 2002 and 2006, 291 mothers lacked a MBD diagnosis specified for linkage. The linkage status for these mothers and all their maternities was revised, the population weight originally assigned was retained, and they were included with control mothers. These are included in in Figure 2.2 below as "Unspecified diagnoses".

Inpatient episodes with inconsistent birthing episodes

Apart from the small number of planned home births (less than 1%) mothers gave birth in a hospital or birth centre. This generates an inpatient episode record the with an ICD10-AM diagnoses 'Z37: *Outcome of delivery*' that records birth multiplicity and vital status of the baby(s). Birthing episodes for a given mother that did not contain a PDC date of birthing between the episode start and end dates from any of the linked maternity records were considered inconsistent.

Inconsistent interval between pregnancy and inpatient episode start date

The duration of the intervals (a) between the start of the linkage period and the estimated date of conception and (b) between the date of birthing and the end of the linkage period in whole years cannot exceed the number of years between the year of birthing and the start or end of study period.

The CHeReL undertakes a clerical review when the linkage is complete to assess the accuracy of matching. For this linkage 0.30% of matches had been assessed by the CHeReL as incorrect. The overall error rate did not exceed the 0.30% CHeReL estimated linkage error rate. Validation found slightly higher error rates were found among study mothers with a linked MBD record (0.37%).

Handling of invalid APDC:PDC linked records

The quality control processes described above identified some PDC:APDC linked records that were no longer required and some problematic PDC:APDC linked records that arose either because of inaccuracies in one or both records or because the two records were erroneously linked and belonged to two different people. It was not possible to distinguish between these two reasons for the inconsistency. The PDC portion of these linked records were retained as the veracity of their motherhood was not in question, but their APDC portion of the linked record was not used. Retaining these mothers was important for preserving the integrity of the population sample. Figure 2.2 summarises these changes. At the beginning of the quality control process there were 27,404 mothers with one or more linked APDC records and 38,895 mothers

with no linked APDC records. At the end of the quality control processes, mothers who no longer had at least one valid linked APDC record were reassigned and treated as control mothers. However, they retained the sample weight originally assigned. The final study data comprised 54,894 maternities for 39,942 mothers with no linked APDC record, and 37,483 maternities for 26,357 mothers with a valid linked APDC record that were taken forward as linked PDC:APDC records.

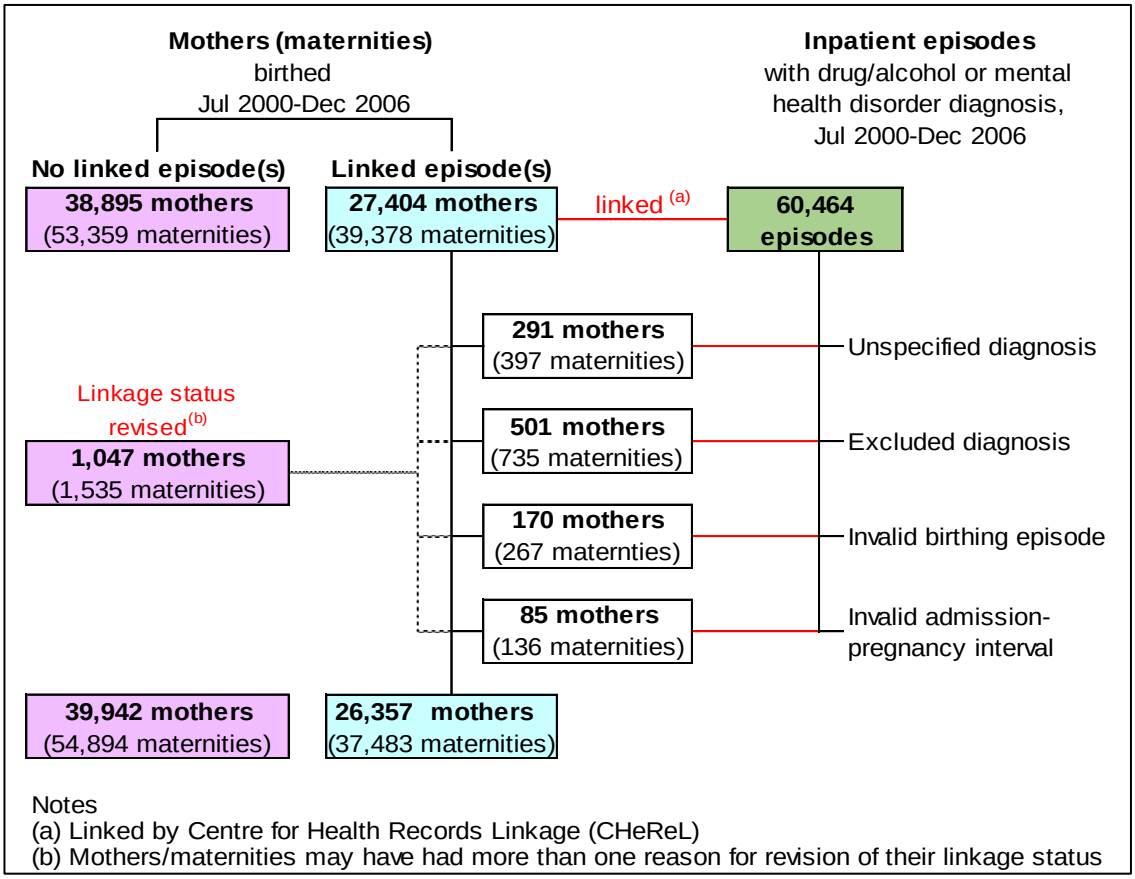


Figure 2.2: Maternities and mothers with linked inpatient episode records

Assigning maternal MBD status

Figure 2.3 is a simple view of the processes used to generate the linked maternity file and relates to a hypothetical mother with three maternities. All maternities were linked with data from inpatient episodes that commence during the diagnostic follow-up period (see below), which for the purpose of Figure 2.3 is the pregnancy period, that is , from the estimated date of conception to the date of birthing, inclusive. Only maternities 2 and 3 were identifies as having MBD in pregnancy, but maternity 1 was not. Episode 'D' did not commence in the pregnancy period, and MBD data from this episode did not contribute to the linked data for maternity 3.

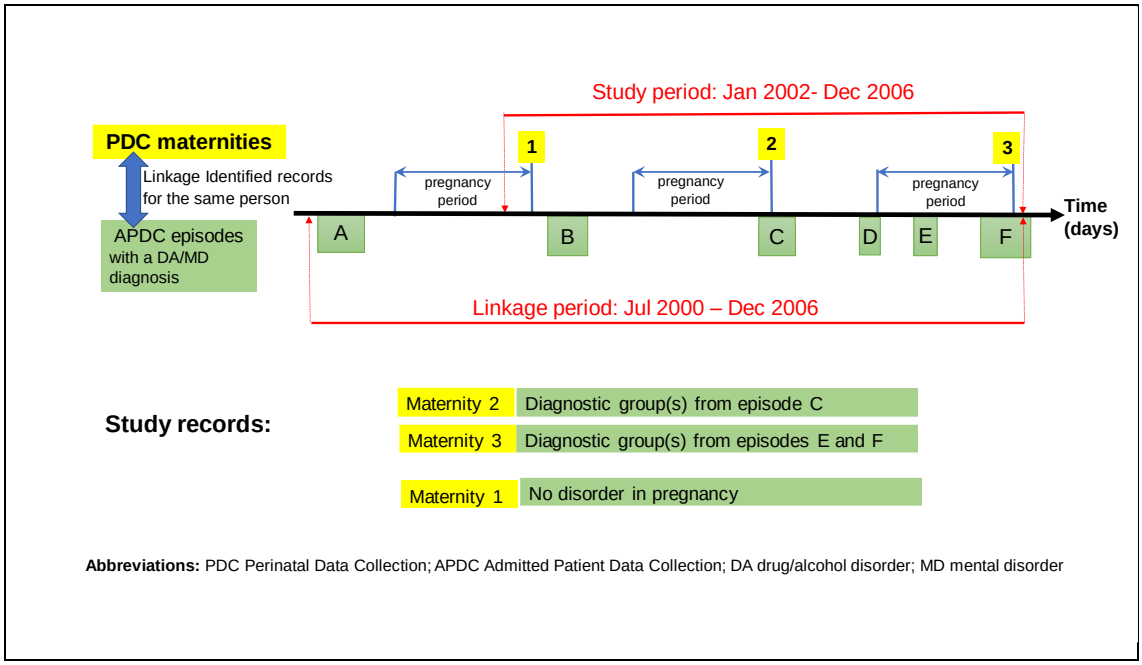


Figure 2.3 Example to demonstrate selection and selection of data from of linked APDC:PDC records to study records for one mother

Diagnostic-follow-up period

The diagnostic follow-up period defines the period during which linked APDC records contributed MBD diagnoses. In Figure 2.3 and for analyses Chapters 4 and 5, the diagnostic follow-up period is the pregnancy period. In Chapter 3, the diagnostic follow-up period included APDC episodes that commenced in pregnancy and in the 6 months before conception in addition to the pregnancy period. Episode 'A' and episode 'D' in Figure 2.3 contributed MBD diagnoses in the pre-pregnancy periods if they commenced within the specified time frame.

The diagnostic follow-up period in other studies that identify maternal MBD from hospital admissions varies. Studies have used pregnancy (Burns, Mattick et al. 2006, Burns, Mattick et al. 2006) or varying periods that include pregnancy and up to 5 years prior to pregnancy (Lee and Lin 2010, Lin, Chen et al. 2010, O' Leary, Halliday et al. 2013, Vigod, Kurdyak et al. 2014, Mei-Dan, Ray et al. 2015).

Adding class(es) of MBD to the maternity record

Data from inpatient episodes that commenced in the diagnostic period were combined into a single record. Individual classes of MBD had been assigned using the definitions in Table 2.1. Episodes for a given maternity were sequenced chronologically and the sequence number added as a suffix to each data item from the inpatient record. For example, a maternity temporally

associated with 20 admissions would have 20 non-missing items for the age at the start of episode (start-age1 start-age2… start-age20), 20 items for alcohol disorder (alcohol-1, alcohol-2 … alcohol-20), and so forth. Each class of MBD was identified as a disorder from a principal diagnosis of a disorder from an additional diagnosis.

Appendix Tables A2.1and A2.2 list the counts of each ICD10-AM code in the 15,210 episodes that commenced during pregnancy. The final inpatient episode data included did not include episodes exclusively with MBDs specific to the postnatal period.

Neonatal follow-up

PDC notifications completed at or soon after birth may miss information on later admissions for neonatal care. Outcomes of neonatal were incomplete among babies transferred to regional or tertiary centers with neonatal facilities or readmitted after discharge from the birth hospital. Information about neonatal mortality and morbidity were added to the study data by linking the PDC and neonatal APDC episodes by baby (see Figure 1.1).

There were up to 6 neonatal episodes per baby. Records for each baby were concatenated. Neonatal morbidity was defined by the presence of a linked neonatal admission that included an "ICD10-AM Chapter 16 *Certain perinatal conditions*" diagnosis. Death of a baby in hospital is recorded in the inpatient episode record as a method of separation. The number of hours spent in neonatal intensive care unit NICU was recorded for each admission. Admission to NICU was defined by one or more hours spent in NICU in any neonatal episode. Linked neonatal admission data added a further 54 neonatal deaths to the 265 identified in the PDC. This represented 16.9% of the total (319) neonatal deaths.

PDC variables used in studies

Maternal ages were grouped in 5-year bands except for the youngest ages (18-19 years) and the oldest ages (40 years or older). **Country of birth** was grouped as 'Australia' and all other countries as 'Elsewhere'.

Information from the two smoking variables in the PDC: maternal smoking (yes/no); and the number (N) of cigarettes smoked in the second half of pregnancy were combined as a single variable for **maternal smoking**. Smokers with missing information on the number of cigarettes

smoked per day and those that reported zero cigarettes per day in the second half of pregnancy were included with smokers of 1-10 cigarettes per day in the combined variable.

Mothers who identified as Torres Strait Islanders were included with **Aboriginal mothers.**

Maternal parity of 4 or more were grouped.

Birth multiplicity presented singletons and grouped twin, triplet and higher order multiple births.

Maternal hypertension and **Maternal diabetes** were collected for the PDC as pre-existing disease and gestational disease were combined as a single variable. Maternities with both pre-existing and gestational disease were assigned to pre-existing disease.

Area-based measures of **remoteness** and socio-economic status were derived by NSW Health from PDC data from the postcode of usual residence. **Socio-economic status** was measured using the Index for Areas (SEIFA) Index of Relative Social Disadvantage (IRSD). This is a composite measure produced by the Australian Bureau of Statistics from census data for home ownership, car ownership and so forth. Areas were ranked and divided into 5 equal population groups (Australian Bureau of Statistics (ABS)). The 5 standard **remoteness** areas derived from the PDC postcode of usual residence and the Australian Statistical Geography Standard (ASGS) (Australian Bureau of Statistics (ABS)) were re-grouped to combine ASGS “Outer regional”, “Remote” and “Very remote” into a single category: “More remote”.

Data processing

All data manipulations and tabulations of final study data were carried out by the author using SAS version 9.2 (Cary Institute). Statistical analyses were obtained from SAS for multivariable adjusted estimates of relative risk. The 95%CI for simple proportions and crude relative risks were calculated using standard formulae (Armitage 2002) in spreadsheets devised by the author. Tables and figures were produced from SAS outputs using Microsoft Excel.

2.4 Final study data

Table 2.2 presents the numbers of MBD exposed maternities by year of birthing. Maternities from July 2000 to December 2001 were included in Table 2.2 for completeness but did not contribute to study cohorts because not all these maternities had been followed throughout the

pregnancy period. All study babies were followed to the end of the neonatal period for hospital diagnosed morbidity. Population weights (w) were used to produce the population estimates of the annual numbers of maternities in Table 2.2. The final rows in Table 2.2 compare these with actual numbers from PDC. The weighted number of maternities to mothers aged 18 to 44 years in the final study data in between 2002 and 2006 is very closely approximate the actual number of maternities for women aged 18 to 44 years in the NSWS maternity population.

Table 2.2 Final study data

	w[a]	2000-2001	Year of birthing 2002	2003	2004	2005	2006	Total	2002-2006
			Number of maternities						
Linked APDC records									
during pregnancy	1	n/a	1,835	1,818	2,231	2,504	1,974		**10,362**
not during pregnancy	1	n/a	3,923	4,039	3,849	3,960	3,687		**19,458**
Total	1	7,663	5,758	5,857	6,080	6,464	5,661	37,483	**29,820**
No linked APDC record									
Other linked record [b]	1	447	349	323	309	302	300	2,030	**1,583**
APDC link not valid	1	344	278	226	235	241	211	1,535	**1,191**
No linked record	10	11,826	7,706	7,640	7,676	8,120	8,361	51,329	**39,503**
Total study maternities		**20,640**	**14,091**	**14,046**	**14,300**	**15,127**	**14,533**	**92,737**	**72,097**
Estimated NSW maternities [c]		**n/a**	**83,445**	**82,806**	**83,384**	**88,207**	**89,782**		**427,624**
Mother aged 20-44									
Estimated NSW maternities			80708	80512	80875	85619	87327		**415,041**
Actual NSW maternities [d]			80759	81523	80741	85539	87623		**416,185**
%difference [e]			**-0.1**	**-1.2**	**0.2**	**0.1**	**-0.3**		**-0.3**

(a) Weight (w) is applied to each maternity to derive population-based estimates.
(b) 'Other linked record' refers to PDC records linked to data sources not used in this thesis (see Figure 2.1). Exclusion of these records would distort the population sample and could bias population-based estimates.
(c) Maternities estimated by applying study weight (w).
(d) Values from NSW Mothers and Babies tables by maternal age.
(e) Percentage difference was calculated with actual number of NSW maternities as the reference

Chapter 3. Admissions for MBD in pregnancy

The first study in this thesis examines rates of admissions for MBD in pregnancy and uses admissions in the 6 months prior to pregnancy as the baseline. This adds to the small number of studies of this topic and contributes to the resolution of conflicting findings from existing studies.

3.1 Background

There have been three key international longitudinal studies of admission for mental and behavioural disorders (MBD) before, during and after pregnancy, (Paffenbarger Jr 1964, Kendell, Chalmers et al. 1987, Munk-Olsen, Laursen et al. 2006, Xu, Sullivan et al. 2016) and one recent Australian-specific study (Xu, Sullivan et al. 2016). All four studies found rates of MBD-related hospital admissions were lower during pregnancy than in the periods preceding or following pregnancy and rates of MBD-related hospital admissions were highest in the immediate postnatal period. This has contributed to the widespread view of pregnancy as a period of general psychological wellbeing (World Health Organization 2009).

However, closer inspection of these studies revealed different directions in the trend of admission rates over the course of pregnancy. One study was not informative as pregnancy was treated as a single interval (Munk-Olsen, Laursen et al. 2006). A small, statistically insignificant decrease from 27 admissions in the first trimester (first third) of pregnancy to 21 admissions in the third trimester (last third) of pregnancy was seen in the report of admissions to psychiatric hospitals in Hamilton county, Ohio between 1940 and 1958 (Paffenbarger Jr 1964). In Edinburgh in the 1960s, admissions for MBD increased from 5 per month at 7-8 months before birth to 8 per month at 1-2 months before birth, where months were counted as 30-day periods (Kendell, Chalmers et al. 1987). In a study of admissions for MBD among primiparous mothers in NSW between 2002 and 2010, rates of admission halved from 10 to 5 per 1,000 person-years across the pregnancy period (Xu, Sullivan et al. 2016). Among the two informative studies, one study showed admissions to a psychiatric hospital increased over the course of the pregnancy, and the other showed rates of admission to hospital for MBD decreased as pregnancy advanced.

Methodological differences do not explain these contradictory findings. The two studies of interest were carried out more than 50 years apart in different countries. Over time, maternity populations in high-income countries have become older and most of the management of MBD

has been moved out of hospitals and into the community. There are also differences between these two studies. The earlier study considered mental disorders among all mothers whereas the more recent study was concerned with first time mothers and included drug and alcohol disorders with her MBD (Xu, Sullivan et al. 2016). Rising and falling rates of admission during pregnancy have different implications for the understanding of the potential for pregnancy to impact on MBD and could have implications for the development of appropriate policy responses and screening options for women during pregnancy.

3.2 Aims

The purpose of this study was to examine the temporal associations of admission for MBD among maternities in NSW between 2002 and 2006. There were two specific aims. First, to determine rates of admission for MBD in 2-monthly intervals across the period from 6 months before conception to birthing, stratified by maternal parity. Second, to examine rates of admission by specific classes of MBD: depression, anxiety and adjustment combined, schizophrenia, bipolar disorder, alcohol disorder and drug disorder.

3.3 Methods

Definitions

Maternity, like birth, was defined as the complete separation of the mother and her baby(s) at the end of pregnancy (World Health Organisation (WHO) 2003). Maternity occurs to the mother, whereas birth occurs to the baby. 'Maternity' is used in preference to the term 'Confinement' (Australian Bureau of Statistics 2005, Centre for Epidemiology and Research. NSW Department of Health 2007).

The **pregnancy period** was defined as the period from the estimated date of conception to the date of birthing, inclusive. Date of conception was estimated from the gestational age at birth and the date of birthing. The date of birthing and pregnancy duration (gestational age at birth) are included in the Perinatal Data Collection (PDC) record. A **month** was defined as 365.25/12 or 30.4 days.

A **primiparous** mother gave birth for the first time. A **multiparou**s mother had given birth at least once previously. Maternal parity recorded in NSW PDC (birth records) was used to define each maternity as primiparous or multiparous.

An **admission** was an episode of inpatient care as represented by one APDC record. The main reason for inpatient care was the **principal diagnosis**, which is assigned at the end of the episode after consideration of the circumstances of the admission (World Health Organisation (WHO) 2003, Australian Institute of Health and Welfare (AIHW) 2015). In NSW hospital inpatient data this was the first-listed diagnosis. Up to 54 **secondary diagnoses** can be included in the admission record for coexisting conditions or complications.

Mental or behavioural disorders (MBD) were defined as disorders in the WHO International Classification of Causes of Disease and Death 10th revision Chapter V (World Health Organisation (WHO) 2016). These have been categorised into diagnostic groups in Table 2.1 in Chapter 2 of the thesis.

Data for this analysis

The data used for this study were maternity records from the NSW Perinatal Data Collection (PDC) for women aged 18 or over between 2000 and 2006 that were linked by mother with selected hospital inpatient records from the NSW Admitted Patient Data Collection (APDC). Selected hospital inpatient records were for women aged 18-44 whose inpatient morbidity data included one or more MBD diagnoses. A random 10% sample of PDC mothers with no diagnosis of MBD in their inpatient records were included as control mothers.

The study sample comprised PDC records for all births between 2002 and 2006 to study mothers. Chapter 2 details the source datasets, population sampling, data linkage, population weights, ascertainment of MBD in pregnancy, and periods of diagnostic follow-up. Weighted maternities used in all analyses generate population-based estimates that represent all maternities in NSW between 2002 and 2006.

Analysis

The number of admissions in each interval with MBD as the principal diagnosis formed the numerator. If a woman was admitted more than once for MBD in a single interval, each admission was counted separately in the numerator for that interval. The denominator was the number of person-years contributed to the interval by all maternities in NSW between 2002 and 2006. All maternities contributed 1 month of person-time to each 1-month interval in the pre-pregnancy period and in the first 5 month of pregnancy. As pregnancy progressed, completed maternities were censored and did not contribute person-time to subsequent intervals.

Maternities were weighted to produce estimates related to the source population (see Chapter 2 for details of weighting). MBD admissions rates were measured in 2-month intervals before and after conception. Total person-time in each period was used as the denominator to calculate admission rates and expressed per 1,000 person-years. Admission rates in each interval were treated as a proportion to calculate 95%CI using the standard formula (Armitage 2002).

The analysis applied to all MBD and individual classes of MBD: alcohol disorder; all classes of drug disorder combined; depression; anxiety and adjustment disorders; schizophrenia; and bipolar disorder. These classes accounted for over 95% of all MBD principal diagnoses in the study period.

The non-specific principal diagnosis 'ICD10 099.3: *MBD complicating pregnancy, childbirth or the puerperium*' was replaced by the specific class of MBD that occasioned the episode of inpatient care. This was obtained from the specific MBD secondary diagnosis recorded in accordance with ICD10-AM coding rules (World Health Organisation (WHO) 2003). Where 2 or more MBD secondary diagnoses were present, the first listed diagnosis was selected. An 'ICD10 Chapter V: *Mental and behavioural disorders'* diagnosis was available for all but 14 such admissions. All 14 of these admissions included a diagnosis from another ICD10 chapter used to define MBD in Table 2.1.

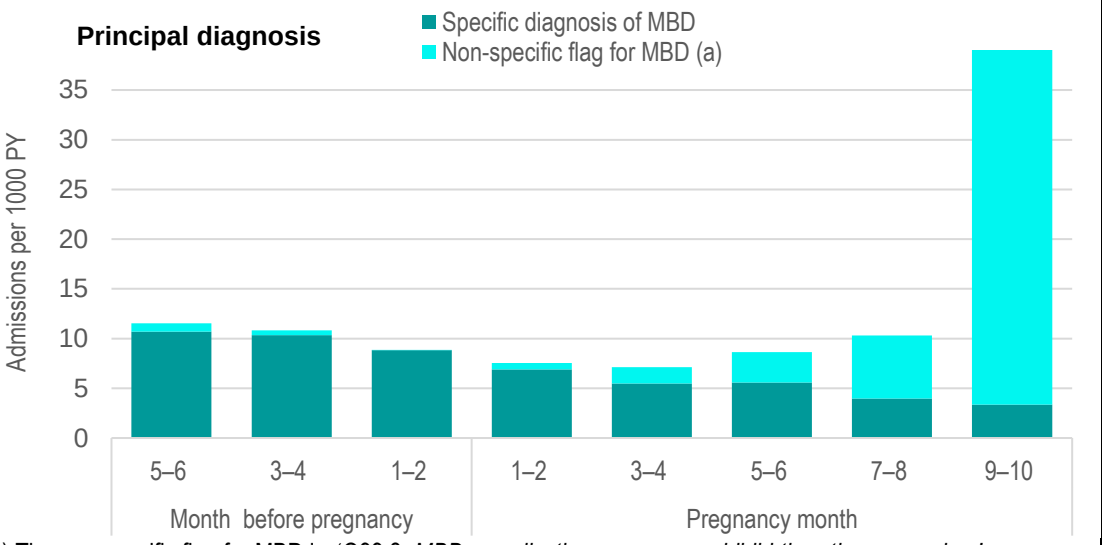
The effects of early pregnancy (months 1 to 5 post-conception) and late pregnancy (months 6 to 10 post-conception) on admission for MBD were measured as the rate of admissions for MBD in the respective interval relative to the admission rate for the disorder in the 6 months before conception. The 95%CI were calculated using the standard formula (Armitage 2002).

3.4 Results

Between 2002 and 2006 there were 427,624 maternities in NSW, of which 176,398 (41.3%) were to primiparous mothers and 251,226 (58.7%) were to multiparous mothers. These maternities were linked by mother with 5,996 admissions for MBD in the period from 6 months before conception to birthing. Of these, 3,760 admissions for MBD commenced during pregnancy (pregnancy admissions) and 2,236 admissions for MBD commenced in the 6 months prior to conception (pre-pregnancy admissions).

Trends in admission for MBD

Figure 3.1 shows the trend in 2-monthly admission rates for all MBD across the period from 6 months before pregnancy to birthing for all maternities in NSW between 2002 and 2006. Overall admission rates for MBD trended downwards across the pre-pregnancy period and in early pregnancy from 11.5 (95%CI 10.8, 12.3) admissions per 1,000 person years at 5-6 months before pregnancy to a nadir of 7.1 (95%CI 6.5, 7.8) admission per 1,000 person years in months 3 and 4 of pregnancy. Thereafter admission rates rose and peaked at 39.1 (95%CI 37.1, 41.2) admissions per 1,000 person years in months 9 and 10 of pregnancy.



(a) The non-specific flag for MBD is 'O99.3: *MBD complicating pregnancy, childbirth or the puerperium'*
Source data: Table A3.1

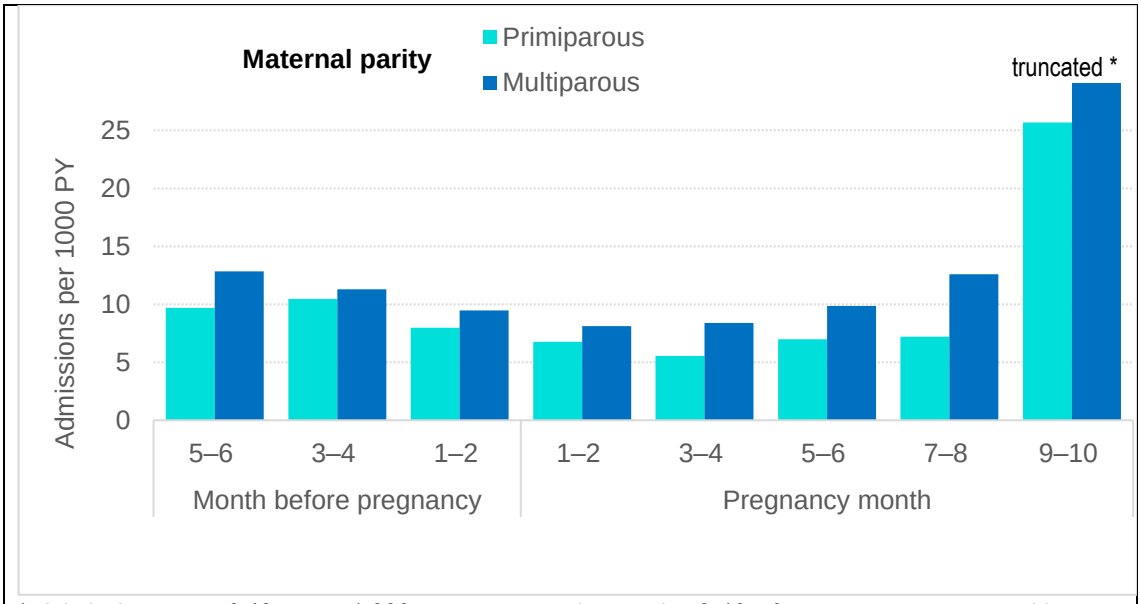
Figure 3.1: Admissions for MBD in 2-monthly intervals from 6 months before conception to birthing by diagnostic type, maternities in NSW 2002-2006.

Admissions by form of the MBD principal diagnosis

Overall, 2,168 (36.1%) of the 5,996 admissions for MBD identified MBD as a complication of pregnancy by listing '099.3: *MBD complicating pregnancy, childbirth or the puerperium'* as the principal diagnosis (lighter colour bars in Figure 3.1). These comprised 2,052 (55.1%) of the 3,760 pregnancy admissions and 97 (4.4%) of the 2,236 pre-pregnancy admissions. Maternities with a pre-pregnancy 'O99.3' diagnosis were to multiparous mothers and related to the previous maternity. In Figure 3.1, few admissions listed 'O99.3' as the principal diagnosis in pre-pregnancy and early pregnancy intervals, buts the frequency increased as pregnancy advanced to 91.4% of admissions at 9-10 months after conception. The specific diagnosis available for each of these admissions was used to assign the relevant MBD principal diagnosis group.

MBD admissions by maternal parity

Figure 3.2 compares admission rates for MBD in primiparous and multiparous maternities. Admission rates for both groups were U-shaped, like those for all maternities, but admission rates among multiparous maternities exceed those among primiparous maternities. The average admission rate for MBD in the 6 months before pregnancy for multiparous maternities was higher at 11.2 (95%CI 10.6, 11.8) per 1,000 person years than for primiparous maternities at 6.6 (95%CI 8.8, 10.0) admissions /1,000 person years. MBD admission rates peaked at 9-10 months post-conception reaching 18.4 (95%CI 23.6, 28.9) /1000 person years for primiparous maternities and 49.7 /1000 person years for multiparous maternities. The bar representing admission rates for multiparous maternities at 8-9 months was truncated in Figure 3.2.



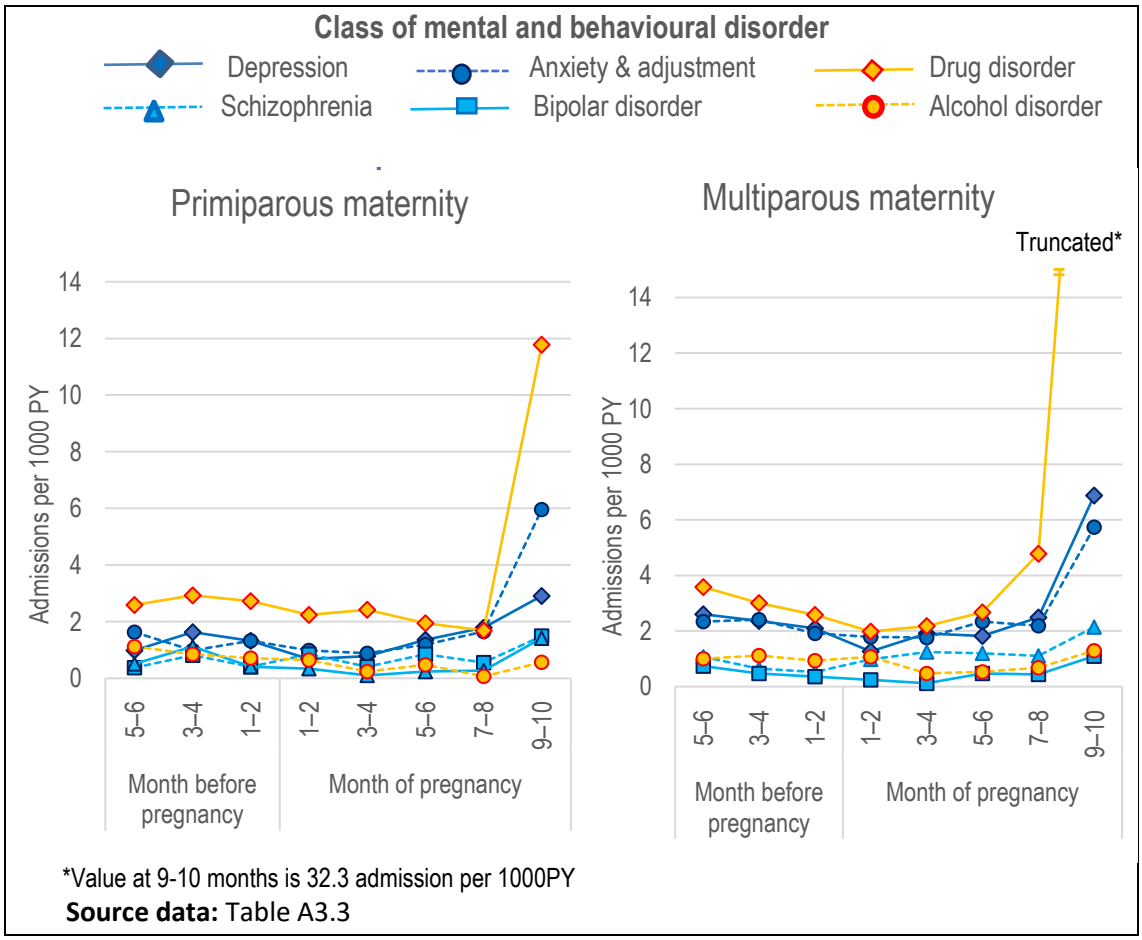
* Admission rate of 49.7 per 1,000 person years in months 9-10 of pregnancy among multiparous maternities was not displayed.
Source data: Table A3.2

Figure 3.2: Admissions for MBD in 2-monthly intervals by maternal parity, maternities in NSW 2002-2006.

Admissions by class of MBD

Figure 3.3 depicts admission rates for six classes of MBD: depression, anxiety and adjustment disorder combined, schizophrenia, bipolar disorder, alcohol disorder and drug disorder separately among primiparous and multiparous maternities. These 6 classes of MBD account for 5,379 (89.5%) of the 5,996 admissions for MBD that commenced from 6 months before conception to birthing for study maternities. Admission rates for depression, anxiety and

adjustment combined and drug disorders followed similar trends to that demonstrated above for all MBD and baseline (pre-pregnancy) admission rates were higher for multiparous maternities. For example, rates of admission for depression averaged 1.3 (95%CI 1.1, 1.6) per 1000PY among primiparous maternities and 2.4 (95%CI 2.3, 3.5) per 1000PY among multiparous maternities. The results for schizophrenia admissions by maternal parity are better appreciated from the source data Table A3.3, which reports the bi-monthly admission rates and their 95%CI. In both primiparous and multiparous mothers, admissions for schizophrenia were slightly higher in months 1 and 2 of pregnancy than in the baseline period, increased over the course of the pregnancy, and peaked in months 9 and 10. There was a small, but statistically borderline increase in the baseline admission rates for schizophrenia from 0.5 (95%CI 0.4, 0.7) per 1000PY in primiparous mothers to 0.7 (95%CI 0.6 ,0.9) per 1000PY in multiparous mothers. Admission rates for multiparous mothers were higher and more unstable than those for primiparous mothers as pregnancy progressed.



*Value at 9-10 months is 32.3 admission per 1000PY

Source data: Table A3.3

Figure 3.3: Admissions for selected classes of MBD in 2-monthly intervals by maternal parity, maternities in NSW 2002-2006.

Averaged baseline rates pre-pregnancy, early pregnancy, and late pregnancy for all MBD, and for 6 classes of MBD are presented in Table 3.1 stratified by maternal parity. The effect of early and late pregnancy on admission rates for MBD in Table 3.1 were calculated as the admission rate in the relevant interval relative to the admission rate in the pre-pregnancy interval (RR). Overall, early pregnancy was associated with a 29% lower risk of admission for MBD (RR 0.71, 95%CI 0.69, 0.76) while the late pregnancy was associated with a 91% higher risk of admission for MBD (RR1.91, 95%CI 1.85, 2.03) relative to admissions for MBD in the pre-pregnancy period.

Table 3.1 presents the effects of early and late pregnancy on admission for individual classes of MBD. Among all study maternities, depression, anxiety, and adjustment disorders combined, and drug disorder, were associated with lower rates of admission in early pregnancy (relative rates (RR) respectively, 0.63, 0.62 and 0.75) and higher rates of admission in late pregnancy (RR respectively 1.51, 1.31 and 2.52) relative to admissions for these disorders in the pre-pregnancy period. Relative rates of admissions for schizophrenia were higher both in early pregnancy (RR1.40, 95%CI 1.24, 1.76) and late pregnancy (RR 1.80, 95%CI 1.59, 2.35) than pre-pregnancy. Bipolar disorder admission rates were lower in early pregnancy (RR0.36, 95%CI 0.30, 0.52), but admission rates in late pregnancy were not significantly different from baseline or pre-pregnancy rates (RR 1.03, 95%CI 0.89, 1.35). Alcohol disorders were associated with lower rates of admission both in early pregnancy (RR 0.66, 95%CI 0.58, 0.83) and late pregnancy (RR 0.57, 95%CI 0.49, 0.74) than in the baseline period.

Table 3.1: Rates and relative rates of admission for MBD in the 6 months before pregnancy (referent group), early pregnancy and late pregnancy, maternities in NSW 2002-2006

		Admissions for [a]:											
Interval (b)		**Depression**		**Anxiety & Adjustment**		**Schizophrenia**		**Bipolar disorder**		**Alcohol disorder**		**Drug disorder**		**MBD**	
	PY	*N*	r‰ *(95%CI)*	*N*	r‰ *(95%CI)*	*N*	r‰ *(95%CI)*	*N*	r‰ *(95%CI)*	*N*	r‰ *(95%CI)*	*N*	r‰ *(95%CI)*	*N*	r‰ *(95%CI)*
Before pregnancy	213,812	*412*	**1.9** (1.7, 2.1)	*395*	**1.8** (1.7, 2)	*141*	**0.7** (0.6, 0.8)	126	**0.6** (0.5, 0.7)	207	**1.0** (0.8, 1.1)	626	**2.9** (2.7, 3.2)	*2,236*	**10.5** (10, 10.9)
Early pregnancy	178,177	*176*	**1.2** (1.1, 1.4)	*204*	**1.1** (1, 1.3)	*130*	**0.9** (0.8, 1.1)	*28*	**0.2** (0.1, 0.3)	*91*	**0.6** (0.5, 0.8)	*311*	**1.3** (1.1, 1.4)	*1,054*	**7.5** (7.1, 7.9)
Late pregnancy	140,162	*334*	**2.9** (2.6, 3.2)	*338*	**2.4** (2.2, 2.7)	*126*	**1.2** (1, 1.4)	*68*	**0.6** (0.5, 0.7)	*64*	**0.5** (0.4, 0.7)	*1,034*	**7.4** (6.9, 7.8)	*2,089*	**17.4** (16.7, 18)
			RR		**RR**		**RR**		**RR**		**RR**		**RR**		**RR**
Before pregnancy			**[ref]**		**[ref]**		**[ref]**		**[ref]**		**[ref]**		**[ref]**		**[ref]**
Early pregnancy			**0.63** (0.58, 0.74)		**0.62** (0.57, 0.73)		**1.40** (1.24, 1.76)		**0.36** (0.3, 0.52)		**0.66** (0.58, 0.83)		**0.43** (0.4, 0.5)		**0.71** (0.69, 0.76)
Late pregnancy			**1.51** (1.41, 1.74)		**1.31** (1.21, 1.51)		**1.80** (1.59, 2.25)		**1.03** (0.89, 1.35)		**0.57** (0.49, 0.74)		**2.52** (2.39, 2.78)		**1.66** (1.61, 1.76)

(a) Admissions for MBD listed MBD as the main reason for admission.
(b) Early pregnancy interval was defined as pregnancy months 1 to 5. Late pregnancy period was defined as pregnancy months 6 to 10.
Abbreviations: PY person years; N number of admissions; r‰ rate of admissions per 1,000 person-years; CI confidence limits; RR relative rate

3.5 Comment on the results

Key findings

This study determined rates of admission for MBD in 2-monthly intervals across the period from 6 months before conception to birthing for maternities in NSW between 2002 and 2006. The 6 months prior to pregnancy were used as the baseline for comparisons of admission rates during pregnancy. Early pregnancy (1-4 months after conception) was associated with lower rates of admission for MBD and late pregnancy (7-10 months after conception) with higher rates of admission for MBD. These effects were evident both in primiparous maternities (first time mothers) and multiparous maternities (for mothers who have previously given birth) and applied to admissions for all MBD, depression, anxiety and adjustment disorders combined and drug disorders. Admissions for schizophrenia overall were increased across pregnancy relative to 6 pre-pregnancy months, but the pattern of admissions. Early pregnancy was associated with lower rates of admission for bipolar disorder and alcohol disorder, but in late pregnancy rates of admission for alcohol remained lower, while admissions for bipolar disorder rose to pre-pregnancy rates.

Increased admissions for MBD as pregnancy progressed is consistent with the recognised increase in psychological and emotional strains as pregnancy advances (Brockington 1996, Buist, Gotman et al. 2011). It is possible that some of the increase in admissions for MBD in later pregnancy occurred because pregnant women were more able to discuss psychological symptoms later in pregnancy as trust developed with their maternity carers (Austin, Highet et al. 2017). Opportunities to detect MBD later in pregnancy are also afforded by the increased frequency of antenatal visits scheduled in later pregnancy (Department of Health 2018). Increasing rates of admission for MBD in this study is consistent with Kendell's observations in Edinburgh over 40 years ago (Kendell, Chalmers et al. 1987).

The spike in admissions for maternal drug disorders in late pregnancy should not be interpreted as a higher onset of addictive or harmful behaviours at this time. It is possible that these behaviours were present but unrecognised earlier in the pregnancy or did not warrant antenatal admission. Fetal growth restriction is routinely screened for in later pregnancy, often as an impatient, and is clinically easier to detect as pregnancy advances. Furthermore, it is standard practice to consider maternal drug or alcohol use when investigating fetal growth restriction in antenatal admissions. In late pregnancy maternal drug disorders may manifest as clinically

detectable fetal growth restriction. This suggests a reversed direction of the association, that is detection of fetal growth restriction identifies mothers with drug/alcohol disorders, maybe the more likely as an explanation for the spike in admissions among in mothers who attended early for antenatal care. The subset of mothers with a drug/alcohol disorder who have delayed or did not their presentation for antenatal care discussed in the limitation section below. Higher rates of admission were observed for other MBD in late pregnancy. It is also possible that women with severe mental disorders who are distressed by the pregnancy could be admitted for induction of labour or caesarean birth once the pregnancy has reached term.

Strengths and limitations

This is the first Australian study to compare admission rates for MBD in pregnancy with those in the months prior to pregnancy for all mothers. The focus on primiparous mothers has been important for establishing the relationship between pregnancy with the onset of mental and behavioural disorders in women (Munk-Olsen, Laursen et al. 2006). Although this study uses the same metrics, this study is not seeking to determine incidence of disease per se. This requires longer diagnostic follow-up periods that start in early adolescence (Munk-Olsen, Laursen et al. 2006). Nor did this study distinguish between incident and recurrent episodes of MBD. These have little meaning in an observational period as short at 5 years. Rather, all admissions for MBD have been used to compare rates in pre-pregnancy and pregnancy periods for a defined cohort of maternities. Person-time was used to adjust for variations in pregnancy duration, which can vary from 20 weeks to over 40 weeks. Admission rates reflect the need of individuals within this population for specialist services for MBD immediately before and during pregnancy. This applies equally to primiparous and multiparous maternities.

The use of admissions for MBD as a proxy for a recent and severe episode of MBD has strengths as well as limitations. Its strength lies in the standardisation that flows from strong adherence to professional standards applied to the use of inpatient services in Australia. Admissions for MBD are overseen by a consultant psychiatrist who has undergone training and accreditation from the Australian and New Zealand College of Psychiatrists. Australian perinatal mental health initiatives have improved the awareness of MBD among maternity carers, the need for multidisciplinary care and access to health services for mothers with mental illness (Buist, Austin et al. 2008). In large populations, individual differences in practice and access to services average out.

The 6 months before conception, when women were not pregnant, has been used as the benchmark for admission rates in this population. Women who are planning a pregnancy may be more motivated to comply with treatment and make lifestyle changes that improve their mental health as well as their physical health. This may explain the downward trend in admission rates evident across the pre-pregnancy period. Only women who succeeded in becoming pregnant and whose pregnancies continued to at least 20 weeks gestation are included in these data. The effects of unwanted pregnancy and pregnancy loss before 20 weeks gestational age cannot be examined.

The downward trends in the pre-pregnancy period continued in early pregnancy. As pregnancy progressed admissions for MBD rose. A key driver of this finding were admissions for MBD complicating pregnancy, indicated by 'O99.3: *MBD complicating pregnancy, childbirth or the puerperium'* coded as the principal diagnosis. If MBD principal diagnoses were restricted to those in ICD10 'Chapter 5: *Mental and behavioural* disorders' admission rates fell progressively as pregnancy advanced, mirroring the findings from another NSW study (Xu, Sullivan et al. 2016). T function of an 'O99' diagnosis is to qualify a non-obstetric diagnosis as a condition that complicated pregnancy, was aggravated by pregnancy or was the main reason for obstetric care (World Health Organisation (WHO) 2016). Admissions with 'O99.3' as the principal diagnosis MBD are thus equally valid as a diagnosis from ICD10 Chapter 5 to indicate MBD as the main reason for the admission. Adherence to ICD10-AM coding rules ensures that the specific disorder can be retrieved, if required.

A limitation of these data is the upward bias of gestational age assessment in women who present for antenatal care after 20 weeks gestation. Ultrasound estimates of gestational age are not reliable in these circumstances. In these circumstances gestational age is estimated from LMP, which is biased towards over-estimation of gestational age (Kramer, McLean et al. 1988). This applies disproportionately to mothers with drug/alcohol disorders, shifts the gestational age distributions to the right, over-estimates gestations at the upper extreme and contributes disproportionally to the spike in admissions at 9th and 10th months of pregnancy. Mothers who have experienced previous removal of a child may be over-represented in mothers who accessed antenatal care later or not at all. This is consistent with the larger spike among multiparous than among primiparous mothers. Babies of these mothers are likely to be at increased risk of adverse health outcomes**.**

Rates of hospital admission in each interval can be affected both by differences in the prevalence of these disorders and differences in the diagnostics thresholds for admission. For example, women diagnosed with schizophrenia are more likely to be admitted to hospital for initial diagnosis and management of exacerbations of their disorder than are women with an anxiety disorder. However, high-prevalence disorders such as anxiety may generate more admissions overall than low-prevalence disorders such as schizophrenia which may result in increased numbers of admissions per person. In other words, increased admission rates may indicate a larger number of women with the disorder admitted once, or a smaller number of women admitted on multiple occasions. The current study design allows comparisons of admission rates over the course of the pregnancy for all MBD and for each class of MBD, but not admission rates between individual classes of MBD. Prevalence of MBD in pregnancy will be examined in the next chapter.

3.6 Summary and next step

When applied to all NSW maternities between 2002 and 2006 and all data for MBD as the main reason for admission to hospital were utilised, admissions for MBD fell in early pregnancy but increased as pregnancy advanced. By late pregnancy rates of admissions for MBD exceeded the admission rates in the 6-month period before pregnancy. This pattern was the same for primiparous and multiparous maternities, but admission rates for multiparous mothers started from a higher baseline. In this population, pregnancy does not appear to protect against MBD admission. Admission rates reflect the number of admissions per person as well as the disorder prevalence The next step is to determine the prevalence in pregnancy of MBD from hospital morbidity data.

Chapter 4. Admissions for MBD in pregnancy

Chapter 3 considered trends in admission rates during pregnancy or the 6 months prior, where MBD was identified as the main reason for the episode of care. This ignored admissions during pregnancy where MBD was listed as an additional diagnosis. As explained in Chapter 1 ICD10 morbidity data from inpatient episodes includes clinically relevant conditions co-existing with pregnancy. This chapter uses information from admissions that commenced during pregnancy with any mention of MBD morbidity or as a clinically recognised disorder to identify mothers with MBD in pregnancy and measure the prevalence of MBD in pregnancy.

4.1 Background

MBD prevalence in women of reproductive age in the general popualtion

Prevalence of MBD from national surveys in Australia (Australian Bureau of Statistics 2008, Morgan, Waterreus et al. 2011) remain the gold standard estimates of the prevalence of MBD in the general population (COAG Health Council 2017). Among Australian women in the reproductive age-groups, the most prevalent class of mental and behavioural disorder (MBD) was anxiety disorder (12-month prevalence 21.2%-21.7%), followed by depression (12-month prevalence 13.5%-14.9%), while substance disorder (12-month prevalence 2.6%-9.8%) was the least prevalent class of MBD (Australian Bureau of Statistics 2008, Slade, Johnston et al. 2009). Reproductive age is defined in females as 15 to 44 years (World Health Organization (WHO) 2006). Psychotic disorder 12-month prevalence was substantially lower. In the 2010 survey, the 12-month prevalence of psychotic disorder ranged from 2.3 per 1,000 women aged 16-24 to 3.9 per 1,000 women aged 35-44 years (Morgan, Waterreus et al. 2011).

The 2007 National Survey of Mental Health and Wellbeing (NSMHW) obtains information about MBD from all participants using a standard screening tool. Not all participants identified in the survey as having a form of MBD would recognise themselves as having a disorder. In 2007, less than half (40.7%) of the women who met the criteria for a MBD at some time and were symptomatic in the past 12 months had used mental health services in this period (Slade, Johnston et al. 2009). The National Survey of People Living with Psychosis selected participants from users of mental health services (Morgan, Waterreus et al. 2011).

MBD prevalence in pregnancy

MBD have similar clinical features and course in the perinatal period to those among non-pregnant women (Brockington 1996). MBD in contemporaneous survey samples of pregnant and non-pregnant women in other high-income countries found no substantial differences in prevalence between these two populations (O'Hara, Zekoski et al. 1990, Breitkopf, Primeau et al. 2006, Vesga-López, Blanco et al. 2008, Uguz, Gezginc et al. 2010, Biaggi, Conroy et al. 2016). However, these studies did not report MBD in pregnancy separately from MBD in the postnatal period and none obtained data for psychotic disorders.

Two small population-based surveys of pregnant women in Sweden and Italy reported point prevalence of major depressive disorder in pregnancy as 3%, but varied point prevalence for other classes of MBD (Andersson, Sundström-Poromaa et al. 2003, Borri, Mauri et al. 2008). Definitions of MBD and survey instruments differed and neither study was large enough to reliably estimate the point prevalence of bipolar disorder or schizophrenia. In Western Australia, a population-based data linkage study found 2.7% of births in 2005 with a mother with MBD in inpatient or outpatient records in the 12 months prior to the birth year (O'Donnell, Anderson et al. 2013). The most common classes of MBD were substance-related disorders (29.8% of all MBD), depression (24.7%) and adjustment and stress disorders (20.6%) (O'Donnell, Anderson et al. 2013).

Most studies of MBD in pregnancy focused on a single class of disorder. Prevalence of maternal depression in pregnancy has been the subject of two systematic reviews, neither of which showed any trend in depression prevalence across the three pregnancy trimesters and pooled estimates that ranged between 7.4% and 12.8% (Bennett, Einarson et al. 2004, Gavin, Gaynes et al. 2005). A systematic review of prevalence of anxiety in pregnancy found estimates ranged between 4.4% and 24% (Goodman, Chenausky et al. 2014). The prevalence of drug disorder in pregnancy from 3 population-based studies in South Australia (Kennare, Heard et al. 2005), Western Australia (O'Donnell, Anderson et al. 2013) and New South Wales (Abdel-Latif, Oei et al. 2013) were estimated respectively as 0.8%, 0.6% and 1.4%. A population-based data linkage study in New South Wales between 1998 and 2002 estimated pregnancy prevalence of opiate disorder (0.47%), cannabis (0.52%), stimulant disorder (0.13%) (Burns, Mattick et al. 2006) and alcohol disorder (0.08%) (Burns, Mattick et al. 2006). In Western Australian the prevalence of

alcohol disorder in pregnancy was 0.09% among non-Aboriginal mothers and 2.3% among Aboriginal mothers (O'Leary, Halliday et al. 2013).

Reports of prevalence of schizophrenia, psychosis, and bipolar disorder) are sparse (Jones, Chandra et al. 2014). Studies of schizophrenia, psychosis, and bipolar disorder in pregnancy were designed to compare maternal and/or neonatal outcomes rather than determine prevalence (Bennedsen, Mortensen et al. 1999, Jablensky, Morgan et al. 2005, Nilsson, Hultman et al. 2008, Lee and Lin 2010, Lin, Chen et al. 2010, Boden, Lundgren et al. 2012, Vigod, Kurdyak et al. 2014, Mei-Dan, Ray et al. 2015).

MBD comorbidity

Comorbidity between individual MBD is common (Jane-Llopis and Matytsina 2006). A quarter (25.4%) of Australian women who met the criteria for anxiety disorder, affective disorder or substance use disorder in the 12 months prior to the 2007 National Survey of Mental Health and Wellbeing (NSMHW) were found to have two or more classes of these mental disorder (Teesson, Slade et al. 2009).

Two Australian studies assessed MBD comorbidity in pregnancy. A NSW audit reviewed the medical records of mothers with a drug disorder and determined that 45% met DSM-IV criteria for one or more mental disorders (Oei, Abdel-Latif et al. 2009). The most common mental disorders present as comorbid conditions in mothers with a drug disorder were depression (79.8%), anxiety (19.6%), schizophrenia (7.8%), bipolar disorder (3.8%), psychosis (3.3%) and personality disorder (3.0%) (Oei, Abdel-Latif et al. 2009). A study from 3 Victorian hospitals reported 56.1% of mothers with a mental disorder used alcohol, illicit drugs, smoked or refused to disclose substance use, compared with 17.4% of mothers without mental disorder (Zhao, McCauley et al. 2017).

In summary

Prevalence of MBD in Australia has been established by large population-based national surveys. By contrast, the introductory chapter to this thesis highlighted that Australian information about MBD during pregnancy is patchy. Australian estimates of drug and alcohol disorder prevalence in pregnancy are available, but information on the prevalence of other classes of MBD in pregnancy is lacking. There is a growing literature on the prevalence in pregnancy of depression and anxiety. However, information about the pregnancy prevalence of bipolar disorder,

schizophrenia, and psychosis in limited, as is information about MBD comorbidity in pregnancy. To begin to address that knowledge gap, information about all MBD from linked hospital admissions during pregnancy has been used to determine pregnancy prevalence of MBD.

4.2 Aims

There are four specific aims of this study. First, to determine the prevalence of MBD in pregnancy overall and for individual classes of MBD from linked birth and hospital admission records for maternities in NSW between 2002 and 2006. Second, to compare the pregnancy prevalence of MBD with prevalence of comparable disorders among women of reproductive age in the general population. Third, to determine the extent of MBD comorbidity for individual classes of MBD. Fourth, identify MBD high prevalence population sub-groups.

4.3 Methods

Definitions

Maternal MBD were defined by the presence of a MBD diagnosis (principal or additional diagnosis) from a linked inpatient episode that commenced in pregnancy. Maternal MBD were categorised into 6 classes of drug/alcohol disorder (alcohol, cannabis, opiate, stimulant, sedative, and other drug disorders) and 8 classes of mental disorder (depression, anxiety, adjustment disorder, bipolar disorder, schizophrenia, psychosis, personality disorder, and other mental disorders). Two 'catch-all' categories 'Other drug disorders' and 'Other mental disorders' accounted for the contribution of less commonly encountered disorders. Definitions for each class of disorder used in all studies in this thesis have been set out in Chapter 2, Table 2.1.

MBD categories for comparison with MBD from national 2007 NSMHW combined maternal depression and maternal bipolar disorder as "Affective disorders"; maternal anxiety and maternal adjustment disorders as "Anxiety disorders"; and used drug/alcohol disorders as "Substance use disorders". Maternal schizophrenia and psychosis were combined as "Psychotic disorders" for comparison of prevalence with the 2010 national survey of people living with psychosis (Morgan, Waterreus et al. 2011).

Data for this analysis

The data used for this study were maternity records from the NSW Perinatal Data Collection (PDC) for women aged 18 or over between 2000 and 2006 that were linked by mother with

selected hospital inpatient records from the NSW Admitted Patient Data Collection (APDC). Selected hospital inpatient records were for women aged 18-44 whose inpatient morbidity data included one or more MBD diagnoses. A random 10% sample of PDC mothers with no diagnosis of MBD in their inpatient records were included as control mothers.

The study sample comprised PDC records for all births between 2002 and 2006 to study mothers. Chapter 2 details the source datasets, population sampling, data linkage, population weights, ascertainment of MBD in pregnancy, and periods of diagnostic follow-up. Weighted maternities used in all analyses generate population-based estimates that represent all maternities in NSW between 2002 and 2006.

Analysis

Pregnancy prevalence of MBD was calculated as the proportion of maternities with a maternal MBD listed as the main reason for hospital admission or as a coexisting condition. The 95% confidence intervals (α=0.05) were calculated using the binomial method unless events were rare (<1 per 1,000), when the Poisson method was used (Armitage 2002). Confidence intervals that include zero indicate imprecise prevalence estimates.

MBD prevalence among women of reproductive age from national surveys.

The 12-month prevalence of anxiety, affective and substance disorders among data for women of reproductive age in the general population was calculated from the number of women in reproductive age groups (16 to 44 years) with each disorder in the 12 months prior from Table 3 of the 2007 NSMHW (Australian Bureau of Statistics 2008). A subset (40.7%) of women with a stated disorder used mental health services in the 12 months prior to the survey (Table 12 NSMHW (Australian Bureau of Statistics 2008). This group would be reasonably expected to have an MBD diagnosis included in their health records when admitted to hospital during pregnancy. The 12-month prevalence of psychotic disorders among women of reproductive age were calculated from numbers in Table 2-2 of the 2010 survey of people living with psychosis, all of whom had used mental health services (Morgan, Waterreus et al. 2011). Each woman with a 12-month mental disorder contributed one person-year of disorder.

Comparing MBD maternity prevalence from inpatient morbidity data and from national survey data

Pregnancy has an average duration of 9 months, but this duration varies considerably. Valid gestations in the NSW PDC range from less than 20 weeks (5 months) to 44 weeks (10 months)

(Centre for Epidemiology and Research. NSW Department of Health 2006). Prevalence of disorders expressed per unit of person-time rather than by person takes these differences in duration into account and facilitates comparison between MBD maternity prevalence from inpatient morbidity and prevalence from general population surveys. Whereas each woman from national surveys contributes one person year, each maternity contributes a fraction of one person year calculated from the duration of the pregnancy.

MBD comorbidity

MBD comorbidity for each maternity was assessed by assigning a unique value in an exponential series (1,2,4,8,16 etc) to each class of MBD present during pregnancy. The sum value for each maternity was used to count the number of individual classes of MBD present and the diagnostic clusters. Maternities with each class of MBD were identified as having of no additional MBD comorbidity, a comorbid drug/alcohol disorder, a comorbid mental disorder or comorbidity with both main classes of MBD.

MBD prevalence by maternal sociodemographic and obstetric characteristics

Maternal sociodemographic and obstetric characteristics collected for the PDC have been described in Chapter 2. The number and percentage of maternities stratified by maternal and pregnancy characteristics for each of the two main classes of MBD, drug/alcohol disorder and mental disorder, and maternities with neither disorder. Distributions of each characteristic among maternities with a drug/alcohol disorders and mental disorders were each compared with maternities with neither disorder. Differences between the two distributions were assessed using a chi-square test (alpha=0.05) that assessed the chance that the characteristic was similarly distributed in two population subsets. A probability less than 0.001 indicates an extremely small chance that the two population are similar. Pregnancy prevalence of drug/alcohol disorder and mental disorder were calculated for each stratum of the sociodemographic and obstetric characteristics and used to identify high-prevalence sub-populations.

Prevalence of drug/alcohol disorders and mental disorders were determined for maternities stratified by maternal sociodemographic and obstetric characteristics obtained from the NSW PDC. Relative prevalence (RPr) was calculated after nominating a referent category for each characteristic.

4.4 Results

The weighted five-year cohort of maternities occurring in NSW between 2002 and 2006 consisted of 427,624 maternities that were followed throughout pregnancy for inpatient admission with a diagnosis MBD. In total, 10,362 (2.42%, 95%CI: 2.38, 2.47) maternities had one or more ICD-10 MBD diagnoses in pregnancy, 5,055 maternities (1.2%, 95%CI: 1.1, 1.2) had a drug/alcohol disorder diagnosis and 6,147 maternities (1.4%: 95%CI, 1.4, 1.5) had a mental disorder diagnosis.

Examination of the 14,638 MBD admissions that contributed a diagnosis of MBD to study maternities found a quarter (N= 3,760, 25.7%) of these admissions identified MBD as the principal diagnosis and three quarters (N=10,858, 84.3%) identified MBD as a secondary diagnosis. Among the latter, 10,047 (92.4%) listed a disorder from 'ICD10-AM Chapter XV: *Pregnancy, Childbirth and the Puerperium*' as the main reason for admission. In only 831 (7.6%) of episodes with MBD as a secondary diagnosis was the main reason for admission listed as a disorder in another ICD10-AM chapter.

Prevalence of MBD overall and individual classes of MBD

The prevalence of individual disorders within these broad groups is shown in Table 4.1. Cannabis disorder was present in 46.9% and opiate disorder in 38.8% of maternities with maternal drug/alcohol disorder. Depression was present in 49.3% and anxiety in 31.2% of maternities with a mental disorder.

Two categories were included for completeness. "Other drug disorders" accounted for 8.0% of maternities with a drug/alcohol disorder and comprised hallucinogen disorders (ICD10 F16), solvent disorders (ICD10 F18) and diagnoses from other ICD10 chapters that did not specify the class of drug. "Other mental disorders" accounted for 10.4% of maternities with a mental disorder in Table 4.1. Intellectual disability (ICD10 F70-F72) followed by behavioural disorders (ICD10 F90-F98) and then eating disorders (ICD10 F750) were the most common classes of MBD among maternities with "Other mental disorders".

Table 4.1: Prevalence of individual classes of mental and behavioural disorders in pregnancy, weighted maternities in NSW 2004-2006

Disorder class	Maternities with MBD			Pregnancy prevalence			
		wi class	all MBD				
	N	(%)	(%)	Pr%	(95%CI)	Pr‰	(95%CI)
Drug/alcohol disorder	**5,055**	**(100.0)**	(48.8)	**1.2**	**(1.1, 1.2)**		
Cannabis	2,371	(46.9)				**5.5**	**(5.3, 5.8)**
Opiate	1,960	(38.8)				**4.6**	**(4.4, 4.8)**
Alcohol	726	(14.4)				**1.7**	**(1.6, 1.8)**
Stimulant	667	(13.2)				**1.6**	**(1.4, 1.7)**
Polydrug	251	(5.0)				**0.6**	**(0.5, 0.7)**
Sedatives	188	(3.7)				**0.4**	**(0.4, 0.5)**
Other drug disorders	403	(8.0)				**0.9**	**(0.9, 1.0)**
Mental disorder	**6,147**	**(100.0)**	(59.3)	**1.4**	**(1.4, 1.5)**		
Depression	3,031	(49.3)				**7.1**	**(6.8, 7.3)**
Anxiety	1,918	(31.2)				**4.5**	**(4.3, 4.7)**
Adjustment	533	(8.7)				**1.3**	**(1.1, 1.4)**
Schizophrenia	431	(7.0)				**1.0**	**(0.9, 1.1)**
Bipolar	392	(6.4)				**0.9**	**(0.8, 1.0)**
Personality	312	(5.1)				**0.7**	**(0.6, 0.8)**
Psychosis	108	(1.8)				**0.3**	**(0.2, 0.3)**
Other mental disorders	639	(10.4)				**1.5**	**(1.4, 1.6)**
Affective disorders	3,385		(32.7)	0.8	**(0.8, 0.9)**		
Anxiety disorders	2,388		(23.0)	0.6	**(0.6, 0.7)**		
Psychotic disorders	482		(4.7)	0.1	**(0.1, 0.1)**		
MBD [(a)]	**10,362**		**(100.0)**	**2.4**	**(2.4, 2.5)**		

(a) A maternity can have more than one1 MBD. The number of maternities with MBD is not the sum of numbers of maternities with individual classes of MBD

Abbreviation: wi within; MBD mental or behavioural disorder; Pr% prevalence per 100 maternities; Pr‰ prevalence per 1,000 maternities.

MBD in pregnancy compared with MBD in women of reproductive age

Table 4.2 presents the 12-month prevalence of anxiety disorders (21.4%), affective disorders (8.5%), substance use disorders (5.0%), and psychotic disorders (0.3%) among Australian women of reproductive age. Prevalence of substance, affective and anxiety disorders were adjusted to reflect the 40.7% of women who had used mental health services in the previous year (Australian Bureau of Statistics 2008) and expressed per 1,000 person years. Pregnancy prevalence (17.2 per 1,000 person years) of drug/alcohol disorder was similar to substance disorder prevalence among women of reproductive age who had used mental health services in the past year (20.3 per 1,000 person years). However, pregnancy prevalence of psychotic

disorders was nearly half (1.6 vs 3.3 per 1,000 person years), affective disorders nearly one third (11.4 vs 34.4 per 1,000 person years), and anxiety disorders less than one tenth (6.5 vs 87.0 per 1,000 person years) the prevalence among comparable women of reproductive age.

Table 4.2: Prevalence of MBD in women of reproductive age who used mental health services from national surveys compared with pregnancy prevalence of MBD.

	NSMHW 2007[a]	Living with Psychosis 2010 [b]	12-month disorder and used mental health services[c]		Maternity population	
	12m Pr%	*12m Pr%*	*12m Pr%*	***/1000 PY***	*Pr%*	***/1000 PY***
Substance disorders	5.0		2.0	**20.3**	1.2	**17.2**
Affective disorders	8.5		3.5	**34.4**	0.8	**11.4**
Anxiety disorders	21.4		8.7	**87.0**	0.6	**6.5**
Psychotic disorders		0.3	0.3	**3.3**	0.1	**1.6**

(a) Secondary analysis - 2007 NSMHW Table 3 (Australian Bureau of Statistics 2008).

(b) Secondary analysis - Table 2-2 Living with Psychosis 2010 (Morgan, Waterreus et al. 2011).

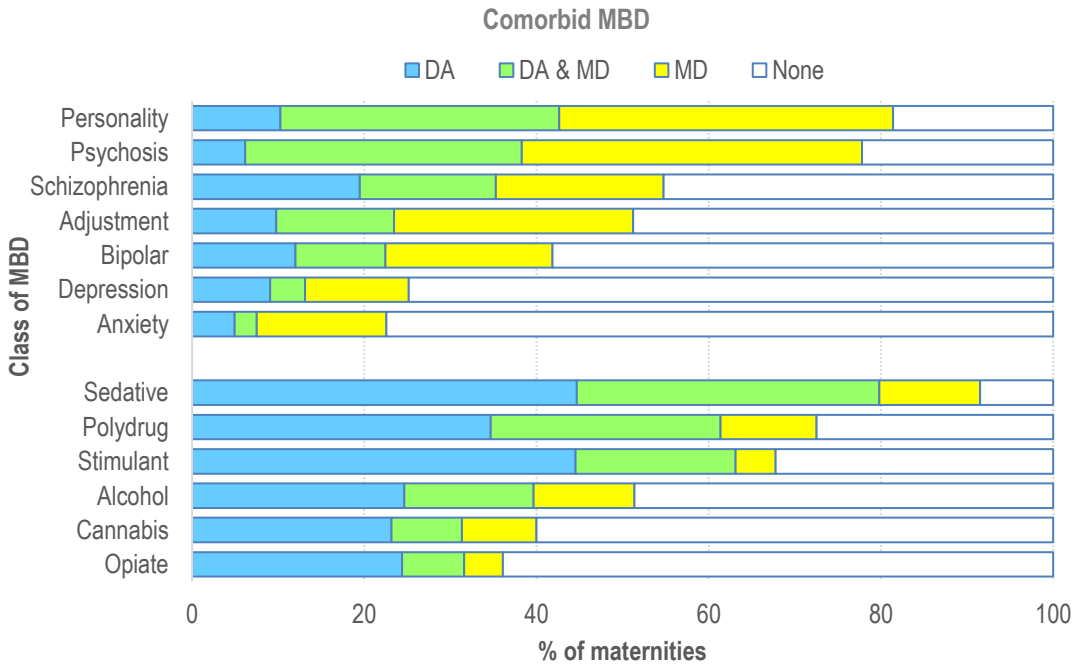
(c) 40.7% of females with a 12-month disorder used mental health services NSMHW (Australian Bureau of Statistics 2008).

Abbreviations: NSMHW National Survey of Mental Health and Wellbeing; 12m Pr% 12-month prevalence expressed as a percentage; Preg Pr% pregnancy prevalence /1000 PY: per 1,000 person years

Comorbidity between classes of MBD in pregnancy

Two or more individual classes of MBD were present for 2,102 (20.3%) of the 10,362 maternities with MBD to a maximum of 7 classes of MBD. In 840 (40.0%) of the 2,102 maternities with MBD comorbidity, both drug/alcohol and mental disorders were present. The remaining 60% of maternities had either 2 or more co-existing classes of mental disorder or of drug/alcohol disorder. MBD comorbidity was more common in maternities with a drug/alcohol disorder (30.6%) than among maternities with a mental disorder (22.6%).

Figure 4.1 depicts the proportion of maternities with a comorbid drug/alcohol disorder, mental disorder or both, by class of MBD. The lowest level of MBD comorbidity was for anxiety disorders (22.6%), followed by depression (25.2%) and opiate disorder (36.1%). Highest levels of MBD comorbidity was for sedatives (91.5%), followed by personality disorder (81.4%) and psychosis (77.8%).



Abbreviations: DA inpatient drug/alcohol use disorder; MD mental disorder
Source data: Table A4.1

Figure 4.1: Proportion of maternities with comorbid MBD by MDB diagnostic group, maternities in NSW 2002-2006

High-MBD prevalence maternity populations

Table 4.3 and Table 4.4 present respectively the sociodemographic and obstetric correlates for the two main classes of MBD, drug/alcohol disorders and mental disorders. Compared to maternities without MBD, maternities with a drug/alcohol disorder were younger, with more mothers aged 18-19 years (6.3% vs 2.9%) and fewer mothers aged 40+ years (2.0% vs 3.3%); more likely to be Australian-born (92.1% vs 71.0%); less likely to reside in major cities (58.6% vs 64.4%); and more likely to reside in areas of social disadvantage (7.0% vs 19.7%); more likely to smoke (80.9% vs 13.5%); and more likely to identify as Aboriginal or Torres Strait Islander (15.3% vs 2.5%).

Maternities with a mental disorder compared with maternities without MBD had more of the youngest mothers aged 18-19 years (4.0% vs 2.9%), but also more of the oldest mothers age 40+ years (4.2% vs 3.3%); were more likely to be to Australian-born (83.8% vs 71.0%), less likely to reside in major cities (61.9% vs 64.4%), less likely to reside in areas of least social disadvantage (13.6% vs 19.7%) and more likely to have identified as Aboriginal or Torres Strait Islander (5.0% vs 2.5%).

From Tables 4.3 and 4.4. the prevalence drug/alcohol disorders among maternities for mothers who smoked more than 10 cigarettes per day were 34.9 (95%CI 33.5, 37.6) times higher and 20.2 (19.4, 21.9) higher among maternities with a mother who smoked 10 or fewer cigarettes than among maternities with a non-smoking mother. There was a 12-fold (95%CI 11.3, 13.5) increased prevalence among mothers not registered for antenatal care and an 11-fold (95%CI 10.8, 12.4) increased prevalence among mothers who lived in outer regional or more remote areas compared with residents of major cities. Prevalence of drug/alcohol disorders were 6.6 (95%CI 6.4, 7.1) time higher among Aboriginal mothers than among non-Indigenous mothers. The prevalence of mental disorders among mothers was 10.2 (95%CI 9.7, 11.1) higher among mothers who lived in outer regional or more remote areas compared with residents of major cities, but more modest increased prevalence of 2- to 4-fold for population subgroups defined by other sociodemographic or obstetric risk factors including smoking and late registration for antenatal care.

Table 4.3: Prevalence and relative prevalence of main classes of MBD stratified by sociodemographic characteristic, NSW maternities 2002-2006

	No MBD	Drug/alcohol disorder			Mental disorder		
	N (↓%)	*N (%)*	Pr%	***RPr (95%CI)***	*N (%)*	Pr%	***RPr (95%CI)***
All maternities	417,262 (100)	5,055 (100)	1.2		6,147 (100)	1.4	
Maternal age (years)							
18 – 19	12,024 (2.9)	319 (6.3) †	2.5	**4.2 (3.9, 4.7)**	243 (4) †	1.9	**1.6 (1.5, 1.8)**
20 – 24	62,253 (14.3)	1,191 (23.6)	1.9	**3.1 (3.0, 3.4)**	1,210 (19.7)	1.9	**1.6 (1.6, 1.7)**
25 – 29	118,838 (27.8)	1,253 (24.8)	1.1	**1.7 (1.7, 1.9)**	1,634 (26.6)	1.4	**1.2 (1.1, 1.2)**
30 – 34	147,511 (34.7)	896 (17.7)	0.6	**[ref]**	1,763 (28.7)	1.2	**[ref]**
35 – 39	72,359 (17.0)	456 (9)	0.6	**1.0 (1.0, 1.2)**	1,037 (16.9)	1.4	**1.2 (1.2, 1.3)**
40+	14,077 (3.3)	100 (2)	0.7	**1.2 (1.0, 1.4)**	260 (4.2)	1.8	**1.5 (1.4, 1.8)**
Country of birth							
Australia	305,435 (71)	4,611 (91.2) †	1.5	**[ref]**	5,152 (83.8) †	1.7	**[ref]**
Elsewhere	122,189 (29)	444 (8.8)	0.4	**0.2 (0.2, 0.3)**	995 (16.2)	0.8	**0.5 (0.5, 0.5)**
Area of residence							
Major cities	268,571 (64.4)	2,960 (58.6) †	1.1	**[ref]**	3,807 (61.9) †	1.4	**[ref]**
Inner regional	145,012 (26.3)	1,583 (31.3)	1.1	**1.0 (1.0, 1.1)**	1,757 (28.6)	1.2	**0.9 (0.8, 0.9)**
More remote	3,828 (8.4)	468 (9.3)	12.2	**11.4 (10.8, 12.4)**	541 (8.8)	14.1	**10.2 (9.7, 11.1)**
Missing data	3,951 (0.9)	44 (0.9)			42 (0.7)		
Disadvantage quintile							
Q1 (least)	82,055 (19.7)	354 (7) †	0.4	**[ref]**	838 (13.6) †	1.0	**[ref]**
Q2	92,515 (21.7)	734 (14.5)	0.8	**1.9 (1.7, 2.1)**	1,152 (18.7)	1.2	**1.2 (1.2, 1.4)**
Q3	72,959 (16.9)	1,022 (20.2)	1.4	**3.3 (3.1, 3.7)**	1,610 (26.2)	2.2	**2.2 (2.1, 2.4)**
Q4	78,215 (18.2)	923 (18.3)	1.2	**2.8 (2.6, 3.1)**	1355 (22)	1.7	**1.7 (1.6, 1.9)**
Q5 (most)	96,796 (22.6)	1,197 (23.7)	1.2	**2.9 (2.7, 3.3)**	1,150 (18.7)	1.2	**1.2 (1.1, 1.3)**
Missing data	(0.9)	44 (0.9)			42 (0.7)		
Aboriginal							
Yes	1,1353 (2.5)	774 (15.3) †	6.8	**6.6 (6.4, 7.1)**	307 (5.0) †	2.7	**1.9 (1.8, 2.2)**
No	415,584 (97.3)	4,278 (84.6)	1.0	**[ref]**	5,837 (95.0)	1.4	**[ref]**
Missing data	(0.2)	3 (0.1)			3 (0.0)		
Maternal smoking							
Non-smoker	363,831 (85.1)	950 (18.8)	0.3	**[ref]**	4,035 (65.6)	1.1	**[ref]**
1–10 /day	31,625 (7.4)	1,670 (33.0)	5.3	**20.2 (19.4, 21.9)**	985 (16.0)	3.1	**2.8 (2.7, 3)**
>10 /day	26,585 (6.2)	2,421 (47.9)	9.1	**34.9 (33.5, 37.6)**	1,106 (18.0)	4.2	**3.8 (3.6, 4)**
Missing data	1,781 (0.4)	14 (0.3)			21 (0.3)		

Abbreviations: Pr% prevalence expressed as a percentage; RPr relative prevalence; [ref] reference group; CI confidence interval

Symbol: † Chi-squared test for homogeneity p<0.001

Table 4.4: Prevalence and relative prevalence of MBD stratified by obstetric characteristics, NSW maternities 2002-2006

	No MBD	Drug/alcohol disorder			Mental disorder		
	N (%)	*N (%)*	Pr%	***RPr (95%CI)***	*N (%)*	Pr%	***RPr (95%CI)***
All maternities	417,262 (100)	5055 (100)	1.2		6147 (100)	1.4	
Maternal parity							
0	172,657 (41.4)	1,506 (29.8) †	0.9	**[ref]**	2,512 (40.9) †	1.4	**[ref]**
1	14,1829 (34.0)	1,317 (26.1)	0.9	**1.1 (1, 1.1)**	1,760 (28.6)	1.2	**0.9 (0.8, 0.9)**
2	63,730 (15.3)	1,001 (19.8)	1.5	**1.8 (1.7, 1.9)**	961 (15.6)	1.5	**1.0 (1.0, 1.1)**
3	23,234 (5.6)	568 (11.2)	2.3	**2.7 (2.6, 3)**	501 (8.2)	2.1	**1.5 (1.4, 1.6)**
4+	15,071 (3.6)	659 (13.0)	4.1	**4.8 (4.6, 5.3)**	410 (6.7)	2.6	**1.8 (1.7, 2.0)**
Missing data	741 (0.2)	4 (0.1)			3 (0.0)		
Birth multiplicity							
Singleton	410,467 (98.4)	4,973 (98.4)	1.2	**[ref]**	6,032 (98.1)	1.4	**[ref]**
Multiple	6,795 (1.6)	82 (1.6)	1.2	**1.2 (1, 1.4)**	115 (1.9)	1.7	**1.2 (1, 1.4)**
Gestation at ANC registration							
< 14 weeks	276,115 (66.2)	1,897 (37.5) †	0.7	**[ref]**	3,604 (58.6) †	1.3	**[ref]**
14 –19 weeks	97,001 (23.2)	1,348 (26.7)	3.1	**4.7 (4.5, 5)**	1,595 (25.9)	3.7	**2.9 (2.8, 3.1)**
20+ weeks	40,805 (9.8)	1,511 (29.9)	1.5	**2.2 (2.2, 2.4)**	847 (13.8)	0.8	**0.7 (0.6, 0.7)**
Not registered	3,341 (0.8)	299 (5.9)	8.1	**12.0 (11.3, 13.5)**	101 (1.6)	2.7	**2.1 (1.9, 2.6)**
Diabetes							
None	395,727 (94.8)	4,945 (97.8) †	1.2	**[ref]**	5,777 (94.0) †	1.4	**[ref]**
Gestational	18,890 (4.5)	82 (1.6)	0.4	**0.3 (0.3, 0.4)**	306 (5.0)	1.6	**1.1 (1.0, 1.3)**
Pre-existing	26,45 (0.6)	28 (0.6)	1.0	**0.8 (0.7, 1.2)**	64 (1.0)	2.3	**1.6 (1.4, 2.1)**
Hypertension							
None	359,022 (86.0)	4,596 (90.9) †	1.2	**[ref]**	5,300 (86.2) *	1.4	**[ref]**
Gestational	19,437 (4.7)	174 (3.4)	0.9	**0.7 (0.6, 0.8)**	416 (6.8)	2.1	**1.4 (1.4, 1.6)**
Pre-existing	4,429 (1.1)	35 (0.7)	0.8	**0.6 (0.5, 0.9)**	87 (1.4)	1.9	**1.3 (1.2, 1.6)**
Missing data	212 (0.1)	250 (4.9)			344 (5.6)		

Abbreviations: DA drug/alcohol; MD mental disorder; Pr% prevalence expressed as a percentage. RPr relative prevalence; [ref] reference group; CI confidence interval

Symbol: † Chi-squared test for homogeneity p<0.001; * chi-square test for homogeneity p<0.01

4.5 Comment on results

Key findings

In NSW between 2002 and 2006, 2.4% of maternities had a diagnosis of MBD in pregnancy from hospital inpatient morbidity data. Pregnancy prevalence of drug/alcohol disorders was 1.2% and of mental disorders was 1.4%. The most prevalent individual classes of drug/alcohol disorder

were cannabis disorder present in 5.5 per 1,000 maternities and opiate disorder present in 4.6 per 1,000 maternities. A diagnosis of depression was present in 7.1 per 1,000 maternities, anxiety in 4.5 per 1,000 maternities, schizophrenia in 1.0 per 1,000 maternities, bipolar disorder in 0.9. per 1,000 maternities and personality disorder in 0.7 per 1,000 maternities.

Among women of reproductive age in the Australian population surveyed in 2007, the prevalence of substance disorder that occasioned the use of mental health services was 20.3 per 1,000 person years, similar to the pregnancy prevalence of substance use disorders in the maternity population of 17.2 per 1,000 person years. Psychotic disorder prevalence in pregnancy was nearly half, affective disorder prevalence nearly one third, and anxiety disorder prevalence less than one tenth the prevalence of comparable disorders among women of reproductive age.

Overall, one in five maternities with MBD had at least one other comorbid MBD. The rate of MBD comorbidity ranged from 23.6% for anxiety to 91.5% for sedative disorders.

Prevalence of drug/alcohol disorders among maternities for mothers who smoked 10 or more cigarettes per day were 35 times higher and maternities for smokers of less than 10 cigarettes per day were 20 times higher than prevalence among maternities for non-smokers. Drug/alcohol disorders were 11 times more prevalent among maternities for mothers who failed to register for antenatal care than among maternities for mothers who registered for antenatal care in the first trimester. Maternities for mothers who resided in outer regional or more remote areas had more than 10-fold increased prevalence of both drug/alcohol disorders and mental disorders relative to maternities for mothers who resided in major cities.

Strengths and limitations

A strength of this thesis is that MBD prevalence was determined for NSW maternities over a five-year period, which provides a large population for study. Sampled data were weighted to return population-based estimates of prevalence in the whole population and in population sub-groups. This a fundamental requirement for prevalence studies (Boyle 1998). This population was large enough to obtain robust estimates of both low prevalence and high prevalence MBD in pregnancy.

A further strength of this thesis was the comprehensive information for MBD in pregnancy available from inpatient morbidity in hospitals across NSW. This is a highly valid and standardised measure of MBD. Nevertheless, this measure of MBD is subject to diagnostic

variability between clinicians, between-hospital differences in access to MBD expertise in multidisciplinary teams, and the quality of hospital record keeping and coding. Mental disorders in the perinatal period often go undetected (Austin, Middleton et al. 2013). Less than half (45.9%) of the women in a survey of recent mothers in two Australian states reported being asked about depression, anxiety or other worries during antenatal visits (Yelland and Brown 2014). Poor mental health knowledge and skills among maternity carers (McCauley, Elsom et al. 2011) may contribute to under-recognition of these disorders during pregnancy care. The stigma associated with these disorders may also be a factor in under-reporting (Corrigan 2011). Recently updated national pregnancy care guidelines recommend training to improve the understanding of mental disorders among health professionals caring for pregnant women and universal screening for anxiety and depression (Department of Health 2018).

The use of linked hospital morbidity data to identify maternities with MBD is advantageous because of the near universal coverage of the maternity population. Over 99% of women in NSW gave birth in hospital or birth centre (Centre for Epidemiology and Research. NSW Department of Health 2007). During the birthing admission, information to document the birth from the mother's records of antenatal care is incorporated into the hospital records, including information about any disorders that affected the management or outcomes for the mother and/or her baby(s). Accurate record keeping can be onerous and the quality of record keeping can vary. Electronic systems for maternity records keeping were introduced to improve record keeping and reduce the administrative load by generating summaries, referrals and the mandatory notifications required after each birth. During the years covered by this study over two thirds of notifications to the PDC were received from electronic hospital information systems (Centre for Epidemiology and Research. NSW Department of Health 2002) and by 2016 all of notifications to the PDC from hospitals were electronic (Centre for Epidemiology and Research. NSW Department of Health 2017).

Three quarters of maternal MBD were from inpatient episodes where MBD was included as a secondary diagnosis. However, in the absence of information about admissions for non-pregnancy related disorders other than MBD it is not possible to determine whether mothers with MBD are more or less likely than mothers without MBD to have a physical disorder such as asthma, heart disease or kidney disease.

The choice to restrict the general population comparator to women of reproductive age with MBD who also used mental health services as was critical. This assumes women who have not used mental health services would be less likely to report MBD or have MBD recorded in referrals when they attend hospital for reasons unrelated to their mental health. This assumption warrants further investigation that was outside the scope of this thesis.

The use of published data restricted the availability of the information on service use by women with MBD. More granular information about service use by disorder was only reported for men and women combined. Among persons with a substance use disorder alone 11.1% also used mental health services compared with 21.2% of persons with anxiety disorder alone and 44.8% for persons with an affective disorder alone (Australian Bureau of Statistics 2008). Better comparison data for women from the NSMHW 2007 would take service use by type of MBD into account.

Personality disorders were not included in the range of MBD assessed by the NSMHW (Australian Bureau of Statistics 2008). Disordered personality traits are not uncommon. A UK study that screened for any type of disorder personality trait estimated 16% of women in an urban maternity population were affected (Crowley, Molyneaux et al. 2019) . In Sweden the prevalence of disordered personality traits was 6.4% among primiparous mothers (Börjesson, Ruppert et al. 2005). If a conservative prevalence estimate of 7.5% applied, there would be about 315,000 mothers with disordered personality, a 100-fold more than the 312 mothers in the study population. More detailed examination of these maternities is needed. Caution needs to be applied to any results related to personality disordered maternities as this might be a biased study population. A further limitation of morbidity data from inpatient collections is the lack of information about disease onset and duration if the disorder is listed as coexisting with the main reason for admission. This means that it is not possible to use these data to inform on the timing MBD. In 2007 condition onset data items related to each ICD10 diagnosis were introduced to the NSW Admitted Patient Data Collection to distinguish conditions present before admission and conditions arising during the admission. For this study, the presence of any MBD diagnosis during an admission in the pregnancy period points to the disorder present at some time in the pregnancy.

4.6 Summary and next step

The previous chapter considered the frequency of hospital admissions for MBD before and during pregnancy. This chapter presents data on the variety of all MBD documented in hospital admissions during pregnancy for NSW maternities between 2002 and 2006. Pregnancy prevalence for specific classes of MBD ranged from 0.1% for psychotic disorders to 1.2% for drug/alcohol disorders. Two or more classes of MBD were present in 20.3% of maternities. The question arises about the extent to which these disorders are associated with poor neonatal outcomes, which is the focus of Chapter 5.

Chapter 5. Neonatal outcomes of MBD in pregnancy

The previous chapter measured the prevalence of MBD in pregnancy from hospital morbidity data and demonstrated a substantial level of MBD comorbidity. In this chapter, the comprehensive information on MBD for all maternities will be used to assess observed levels of perinatal mortality and neonatal morbidity for individual classes of MBD and the independent effects of these disorders on adverse newborn and neonatal outcomes. Effects measured as relative risks in this study indicate the strength of the association between the maternal MBD and the newborn or neonatal outcome but cannot be interpreted as causal. The impact, or burden, of MBD on newborn and neonatal outcomes contributes to public health consideration of the need for intervention at a population level.

5.1 Background

Neonatal outcomes in mothers with MBD

MBD present during pregnancy in mothers as described in chapters 3 and 4 can have consequences for the survival and health of the newborn baby. Drugs, alcohol,l and some medications used to treat MBD may cause direct harm to the fetus. The same properties which allow substances, or their metabolites, to cross into the brain allow them to cross the placenta (Ross, Graham et al. 2014). In the fetal circulation they may affect growth and development. Some substances, such as opioids or medications used regularly by the mother during pregnancy, may induce dependence in the fetus and withdrawal syndromes in the baby after birth (Buist 2014, Ross, Graham et al. 2014, Huizink 2015, Darke, Lappin et al. 2019, McQuire, Daniel et al. 2019). Harm to fetal health from MBD can also be caused indirectly through nutritional deficiencies, anaemia, poor sleep, maternal hypoxaemia, reduced uterine blood flow, reduced placental function, increased uterine contractility, changes to the hypothalamic-pituitary-adrenal function, and increased susceptibility and exposure to infection (Littleton, Breitkopf et al. 2007, Grote, Bridge et al. 2010, Goodman, Chenausky et al. 2014, Ross, Graham et al. 2014, Jarde, Morais et al. 2016, Darke, Lappin et al. 2019, McQuire, Daniel et al. 2019).

Current knowledge of the effects of MBD on neonatal outcomes have come from studies focused on a single class or a related group of disorders. Increased perinatal mortality, low

birthweight, small size for gestational age preterm birth and admission for neonatal care have been consistently reported from studies of maternal drug use disorders (Burns, Mattick et al. 2006, Burns, Mattick et al. 2006, Ross, Graham et al. 2014, Cohen, Osorio et al. 2017, Metz, Allshouse et al. 2017) and alcohol use disorders (Burns, Mattick et al. 2006, Patra, Bakker et al. 2011, Srikartika and O'Leary 2015). Less consistent findings of increased preterm birth, small size for gestational age or admission for neonatal care have been reported from studies of mental disorders in pregnancy (Grote, Bridge et al. 2010, Lin, Chen et al. 2010, Ban, Tata et al. 2012, Boden, Lundgren et al. 2012, Grigoriadis, Vonderporten et al. 2013, Jones, Chandra et al. 2014, Vigod, Kurdyak et al. 2014, Mei-Dan, Ray et al. 2015, Rusner, Berg et al. 2016). Reviews of neonatal outcomes associated with depression and anxiety note differential use of adjustment, with unadjusted estimates from up to half of the included studies, but did not comment on variation in factors used (Grote, Bridge et al. 2010, Grigoriadis, Vonderporten et al. 2013, Goodman, Chenausky et al. 2014). Many studies of perinatal outcomes of serious mental disorder did not account either for smoking (Jablensky, Morgan et al. 2005, Lee and Lin 2010, Lin, Chen et al. 2010, Mei-Dan, Ray et al. 2015), or for drug/alcohol disorders (Jablensky, Morgan et al. 2005, Lee and Lin 2010, Lin, Chen et al. 2010) that may act as confounders or effect modifiers.

Maternal smoking in pregnancy

Maternal smoking has been recognised for over a century as a threat to optimal fetal and early childhood growth and development (Abel 1980). Smoking is now accepted as cause of lower birthweight, by virtue of consistently strong, dose-dependent associations; elucidation of mechanisms of by which nicotine and carbon monoxide in cigarette smoke act to restrict fetal growth; and reduced low birthweight in intervention trials of smoking reduction in pregnancy (Abel 1980, Lumley 1987). There is evidence of increased perinatal morality among births to smoking mothers, but the effects of maternal smoking on preterm birth are conflicting (Newnham 1991).

In Australia, smoking reduction in pregnancy has been recognised as a public health priority (Laws PJ, Grayson N et al. 2006). As a consequence, maternal smoking continues to be monitored as a core quality indicator of maternity care (Australian Institute of Health and Welfare (AIHW) 2018) and antenatal smoking cessation interventions have been established (Coleman, Chamberlain et al. 2015, Chamberlain, O'Mara-Eves et al. 2017)

5.2 Aim

This study has two specific aims. First, to measure the observed and independent effects of individual classes of MBD in pregnancy on perinatal mortality, preterm birth, small size for gestational age, neonatal morbidity, and admission to NICU, for maternities in NSW between 2002 and 2006. Second, to quantify the burden of classes of MBD in pregnancy on these adverse neonatal outcomes and contrast these with the burden of maternal smoking.

5.3 Methods

Defintions

Maternity MBD was defined by the presence of an MBD diagnosis, except MBD exclusive to the postnatal period, in a linked admission that commenced during the pregnancy period. ICD10-AM definitions were detailed in Chapter 2, Table 2.1 for classes of mental disorder, including depression, anxiety, schizophrenia, bipolar disorder, personality disorder, alcohol disorder, cannabis disorder, opiate disorder, and stimulant disorder.

Perinatal and neonatal outcomes

Perinatal deaths are defined as stillbirths and deaths of live-born babies in the neonatal period. Stillbirth data were obtained from the PDC record. Neonatal death data was obtained from the PDC (265 neonatal deaths) and a further 54 neonatal deaths from linked neonatal admissions, yielding a total of 319 neonatal deaths. Information about gestational age at birth and birthweight were obtained from the PDC record. **Preterm birth** was defined as gestational age at birth less than 37 weeks. **Small size for gestational age (SGA)** was defined as a birthweight below the 10th centile of Intergrowth-21st (IG21st) newborn weight standards for births at or after 37 or more completed weeks gestational age (Villar, Ismail et al. 2014) and IG21st fetal weight standards for births before 37 completed weeks gestational age. **Neonatal morbidity** was defined by the presence an "ICD10-AM Chapter XVI: *Conditions originating in the perinatal period"* diagnosis in a linked neonatal admission. **Admission to NICU** was defined by one or more hours spent in NICU in any neonatal admission. The number of hours in neonatal intensive care unit NICU was summed across all admissions for each neonate.

Data for this analysis

The data used for this study were maternity records from the NSW Perinatal Data Collection (PDC) for women aged 18 or over between 2000 and 2006 that were linked by mother with selected hospital inpatient records from the NSW Admitted Patient Data Collection (APDC). Selected hospital inpatient records were for women aged 18-44 whose inpatient morbidity data included one or more MBD diagnoses. A random 10% sample of PDC mothers with no diagnosis of MBD in their inpatient records were included as control mothers.

The study sample comprised PDC records for all births between 2002 and 2006 to study mothers. These PDC records were further linked by baby with hospitalisations for persons aged 0 to 27 days on admission. Chapter 2 details the source datasets, population sampling, data linkage, population weights, ascertainment of MBD in pregnancy, and periods of diagnostic follow-up. Weighted maternities used in all analyses generate population-based estimates that represent all maternities in NSW between 2002 and 2006.

Analysis

Exposures were specific classes of maternal MBD: depression, anxiety, adjustment disorder bipolar disorder, schizophrenia, personality disorder, alcohol disorder, opiate disorder, cannabis disorder and stimulant disorder. Results for neonatal effects of “Sedative disorder”, “Polydrug disorder”, “Other drug disorder” and “Other mental disorder” were not “reported because of their small numbers, potential for generating unstable estimates that are difficult to interpret. Apart from “Sedative disorder”, these classes of MBD lack specificity. “Other drug” and “Other mental disorders” combine several classes of MBD, while polydrug disorder is used to classify disorders due to the abuse of multiple drug types as well as unknown drug type (World Health Organisation (WHO) 2016). Neonatal outcomes comprised perinatal mortality, preterm birth, small size for gestational age at birth, the diagnosis of neonatal disorder from ICD10 Chapter 16 *Conditions arising in the perinatal period* and admission to a neonatal intensive care unit (NICU).

The effects of maternity exposure to individual classes of MBD were measured as relative risks (RR), with the risk in the group without the disorder as the reference. Crude risks and RR and their 95%CI were calculated using standard formulas (Armitage 2002). Adjusted RRs (aRRs) were obtained from exponential transformation of the coefficients for each covariate in generalized estimating equations (GEE) modelling the logarithm of risk. Classes of MBD with statistically significant crude RR were entered as covariates in linear models that also included covariates for confounding factors and effect modifiers. Stepwise adjustments of RR of preterm birth and

small size at birth associated with individual classes of MBD were undertaken using 5 models of increasing complexity: (1) no adjustment (crude RR); (2) adjusted for confounders – maternal age, parity, socioeconomic status, diabetes and hypertension; (3) adjusted for confounders and smoking in pregnancy; (4) adjusted for confounders, maternal smoking and comorbid drug/alcohol disorder; and (5) adjusted for confounders, maternal smoking and any comorbid MBD. increasing complexity Statistically significant decline in RR due to increased model complexity are indicated by no overlap in 95%CIs. GEEs use an iterative process that converge towards the maximum likelihood estimates of standard errors. Failure to converge is more likely for models applied to smaller numbers of outcome events and/or containing larger numbers of covariates. Models specified a binomial distribution in the first instance and a Poisson distribution if non-convergence occurred. Repeated subject measurements were used to improve robustness of standard error estimates in Poisson models (Zou 2004). Use of the unique mother identifier as the repeated subject in GEE models had the added advantage of adjusting for repeated maternities for the same mother. Weights derived from the sampling fractions for each maternity/birth described in Chapter2 were applied to all models to yield effects related to the population from which the data were sourced.

Confounding factors

Factors from Chapter 4 that were shown to be correlated with MBD in pregnancy and known to be assoicated with adverse perinatal outcomes were included as model cofactors: maternal age, parity, socioeconomic status, maternal diabetes and hypertension were included in models as sociodemographic and obstetric confounders. These factors derive from the Perinatal Data Collection and have been described in Chapter 2.

Potential impact

Impact is a public health measure of disease burden that combines the effect and the prevalence of an exposure, MBD in this study, in the population. Impact is measured by the population attributable fraction (PAF). The intuitively simplest formulation of the PAF is the attributable risk (risk difference between those exposed and those not exposed) multiplied by the prevalence of the exposure in the population (Armitage 2002). For example, perinatal mortality attributable to MBD can be calculated as the risk among those with MBD minus the risk among those without MBD. This subtracts the perinatal mortality due to other causes. The attributable risk of perinatal mortality multiplied by the prevalence of MBD yields the PAF, or proportion of perinatal mortality that would be prevented if MBD were eliminated from the population (Armitage

2002). Two assumptions need to be met for the PAF to be valid. First is that there is no residual confounding and the second is that the effect is causal. In this study multivariable regression was used to adjust for confounders. An alternative formula for PAF uses the adjusted relative risk (aRR) and the number of factor-affected cases (pd) to calculate PAF using the formula: $pd\left(\frac{aRR-1}{aRR}\right)$ (Rockhill, Newman et al. 1998). Effects from a single observational study cannot be interpreted as causal (Schünemann, Hill et al. 2011). The measure of potential impact generated for this study is therefore an indicative measure. It has been calculated in this study to provide a public health perspective to consequences of MBD for the baby.

5.4 Results

The study data comprised 72,097 maternities, 10,362 of which were to mothers with a linked MBD in pregnancy. When weighted to be representative of maternities in NSW between 2002 and 2006 the results related to 427,624 maternities.

Association between MBD and neontal outcomes

Perinatal mortality

In the weighted study population perinatal mortality was 8.5 per 1,000 maternities. In Table 6.2, alcohol disorder, cannabis disorder, opiate disorder, stimulant disorder, sedative disorder, bipolar disorder, adjustment disorder and personality disorder were each associated with increased perinatal mortality relative to those without the disorder. After adjustment for coexisting MBD, smoking and other confounding factors only alcohol disorders (RR 2.34, 95%CI 1.35 to 4.04) and opiate disorders (RR1.81, 95%CI 1.22 to 2.70) had a statistically significant association with perinatal mortality. These relative risks for perinatal mortality were greater than the relative risks for smoking (RR1.35, 95%CI 1.02 to 1.79). Adjusted effects were lower than their respective crude effects. For example, the crude relative risk of alcohol disorder on perinatal mortality was 3.25 (95%CI 2.09 to 5.06), whereas the adjusted relative risk was lower at 2.34 (95%CI 1.35, 4.04).

Table 5.1: Perinatal deaths, crude and adjusted relative risks and population attributable risks associated with maternal MBD, weighted maternities NSW 2002-2006

		Perinatal death		Crude RR (a)				Adjusted RR (a,b)			PAF
		N	‰	RR	lcl	ucl		aRR	lcl	ucl	(%)
All maternities		3,636	8.5								
Maternal MBD in pregnancy	Alcohol	20	27.5	**3.25**	2.09	5.06	†	**2.34**	1.35	4.04	0.31
	Cannabis	44	18.6	**2.20**	1.61	2.99	†	ns			
	Opiates	41	20.9	**2.48**	1.80	3.40	†	**1.81**	1.22	2.70	0.51
	Stimulants	16	24.0	**2.83**	1.73	4.64	†	ns			
	Schizophrenia	5	11.6	1.46	0.66	3.26					
	Bipolar	8	20.4	**2.40**	1.20	4.80	†	ns			
	Depression	32	10.6	1.24	0.87	1.78					
	Anxiety	15	7.8	0.92	0.55	1.54					
	Personality	9	28.8	**3.40**	1.78	6.50	†	ns			
	Mother smoked	733	11.8	**1.49**	1.19	1.87	†	**1.35**	1.02	1.79	5.25

(a) Referent group for calculating relative risks are maternities without the disorder.

(b) Adjusted for coexisting maternal mental and behavioral disorders, smoking, maternal age, maternal socioeconomic status maternal parity, maternal diabetes, maternal hypertension.

Abbreviations: N number of affected maternities; RR relative risk aRR adjusted relative risk; lcl lower 95% confidence limit; ucl upper 95% confidence limit; PAF(%) population attributable fraction expressed as a percentage; ‰ per 1,000 maternities; † significant effect – RR 95%CI does not cross 1. ns statistically non-significant result.

Preterm birth

Preterm birth accounted for 6.3% of maternities in this cohort. In Table 6.2, relative risks of preterm birth were significant for all classes of MBD on, and ranged from 1.74 (95%CI 1.52, 1.99) for maternities to mothers with anxiety disorder to 3.99 (95%CI 3.65, 4.36) for maternities to mothers with opiate disorder.

After adjustment for coexisting MBD, smoking and other confounding factors only alcohol disorders (1.29, 95%CI 1.05 to 1.59), cannabis disorder (2.11, 95%CI 1.88 to 2.36), opiate disorders (2.42, 95%CI 2.15 to 2.71), depression (1.27, 95%CI) and anxiety (1.26, 95%CI 1.07 to 1.47) had significant risks of preterm birth relative to maternities for mothers with no MBD.

Cannabis disorders (RR 2.11, 95%CI 1.88 to 2.36) and opiate disorders (RR 2.42, 95%CI 2.15, 2.71) were more strongly associated with preterm birth than smoking (1.50, 95%CI 1.36 to 1.65).

Table 5.2 Preterm births, crude and adjusted relative risks and population attributable risks associated with maternal MBD, weighted maternities NSW 2002-2006

		Preterm birth		Crude RR [(a)]				Adjusted RR [(a,b)]			PAF
		N	%	RR	lcl	ucl		aRR	lcl	ucl	(%)
All maternities		26,888	6.3								
Maternal disorder in pregnancy	Alcohol	128	17.6	**2.81**	2.39	3.31	†	**1.29**	1.05	1.59	0.11
	Cannabis	534	22.5	**3.63**	3.34	3.96	†	**2.11**	1.88	2.36	1.04
	Opiates	485	24.7	**3.99**	3.65	4.36	†	**2.42**	2.15	2.71	1.06
	Stimulants	165	24.7	**3.95**	3.45	4.53	†	ns			
	Schizophrenia	61	14.2	**2.25**	1.80	2.81	†	ns			
	Bipolar	56	14.3	**2.27**	1.78	2.91	†	ns			
	Depression	385	12.7	**2.03**	1.84	2.25	†	**1.43**	1.27	1.61	0.43
	Anxiety	209	10.9	**1.74**	1.52	1.99	†	**1.26**	1.07	1.47	0.16
	Personality	46	14.7	**2.35**	1.78	3.10	†	ns			
Mother smoked		5,831	9.4	**1.63**	1.51	1.77	†	**1.50**	1.36	1.65	7.22

(a) Referent group for calculating relative risks are maternities without the disorder.

(b) Adjusted for coexisting maternal mental and behavioral disorders and smoking, maternal age, maternal socioeconomic status maternal parity, maternal diabetes, maternal hypertension.

Abbreviations: N number of affected maternities; RR relative risk aRR adjusted relative risk; lcl lower 95% confidence limit; ucl upper 95% confidence limit; PAF(%) population attributable fraction expressed as a percentage; † significant effect – RR 95%CI does not cross 1. ns statistically non-significant result.

Small size for gestational age

Overall, 4.7% of maternities in the weighted maternity population gave birth to a baby who was small for gestational age. SGA was associated with all classes of maternal MBD, with relative risks ranging from 1.39 (95%CI 1.21, 1.60) for maternities to mothers with an anxiety disorder to 4.61 (95%CI 3.99, 5.34) for maternities to mothers with alcohol disorder.

After adjustment for coexisting MBD, smoking and other confounding factors only alcohol disorders (aRR2.20, 95%CI 1.89 to 2.57), cannabis disorder (aRR 2.00, 95%CI 1.80 to 2.23) and opiate disorders (aRR 1.74, 95%CI 1.54 to 1.97) were significantly associated with SGA. By contrast, smoking after adjustment, smoking increased the risk of SGA by a factor of 2.36 (95%CI 2.15, 2.60).

Table 5.3 Small size for gestational age, crude and adjusted relative risks and population attributable risks associated with maternal MBD, weighted maternities NSW 2002-2006

		SGA		Crude RR [(a)]				Adjusted RR [(a,b)]			PAF
		N	%	**RR**	lcl	ucl		**aRR**	lcl	ucl	%
All maternities		20,166	4.7								
Maternal disorder in pregnancy	Alcohol	157	21.6	**4.61**	3.99	5.34	†	**2.20**	1.89	2.57	0.43
	Cannabis	443	18.7	**4.03**	3.66	4.43	†	**2.00**	1.80	2.23	1.10
	Opiates	323	16.5	**3.54**	3.17	3.95	†	**1.74**	1.54	1.97	0.68
	Stimulants	89	13.3	**2.84**	2.32	3.47	†	ns			
	Schizophrenia	58	13.5	**2.82**	2.24	3.55	†	ns			
	Bipolar	35	8.9	**1.89**	1.38	2.61	†	ns			
	Depression	198	6.5	**1.39**	1.21	1.60	†	ns			
	Anxiety	142	7.4	**1.57**	1.34	1.85	†	ns			
	Personality	32	10.3	**2.18**	1.57	3.02	†	ns			
Mother smoked		5,923	9.6	**2.45**	2.26	2.67	†	**2.36**	2.15	2.60	16.93

(a) Referent group for calculating relative risks are maternities without the disorder.

(b) Adjusted for coexisting maternal mental and behavioral disorders and smoking, maternal age, maternal socio-economic status maternal parity, maternal diabetes, maternal hypertension.

Abbreviations: N number of affected maternities; RR relative risk aRR adjusted relative risk; lcl lower 95% confidence limit; ucl upper 95% confidence limit; PAF(%) population attributable fraction expressed as a percentage; † statistically significant effect; ns statistically non-significant result.

Neonatal morbidity

Overall, 30.8% of maternities in the weighed maternity population were diagnosed in the neonatal period with some form of neonatal morbidity. Table 6.5 shows the crude and adjusted relative risks of neonatal morbidity for each class of MBD in pregnancy. Crude relative risks were higher among maternities with the specified classes of MBD in pregnancy than in maternities without the specified class. Crude relative risks ranging from 1.41 (95%CI 1.34, 1.49) for maternities to mothers with anxiety disorder to 2.67 (95%CI 2.61, 2.74) among maternities to mothers with opiate disorder.

Table 5.4 Neonatal morbidity, crude and adjusted relative risks and population attributable risks associated with maternal MBD, weighted maternities NSW 2002-2006

		NN morbidity		Crude RR [(a)]				Adjusted RR [(a,b)]			PAF
		N	%	**RR**	lcl	ucl		**aRR**	lcl	ucl	%
All maternities		131,507	30.8								
Maternal disorder in pregnancy	Alcohol	379	52.2	**1.70**	1.58	1.82	†	**1.30**	1.18	1.42	0.07
	Cannabis	1,283	54.1	**1.77**	1.70	1.84	†	**1.51**	1.43	1.59	0.33
	Opiates	1,600	81.6	**2.67**	2.61	2.74	†	**2.62**	2.51	2.73	0.75
	Stimulants	415	62.2	**2.03**	1.91	2.15	†	**1.32**	1.21	1.43	0.08
	Schizophrenia	217	50.3	**1.58**	1.44	1.73	†	**1.22**	1.08	1.37	0.03
	Bipolar	185	47.2	**1.54**	1.38	1.71	†	ns			
	Depression	1,348	44.5	**1.45**	1.39	1.51	†	**1.27**	1.21	1.33	0.22
	Anxiety	833	43.4	**1.41**	1.34	1.49	†	**1.29**	1.22	1.37	0.14
	Personality	137	43.9	**1.43**	1.26	1.62	†	**0.75**	0.64	0.87	-0.04
Mother smoked		18,789	30.3	**0.98**	0.95	1.02					

(a) Referent group for calculating relative risks are maternities without the disorder.

(b) Adjusted for coexisting maternal mental and behavioral disorders, smoking, maternal age, maternal socioeconomic status maternal parity, maternal diabetes, maternal hypertension.

Abbreviations: N number of affected maternities; RR relative risk aRR adjusted relative risk; lcl lower 95% confidence limit; ucl upper 95% confidence limit; PAF(%) population attributable fraction expressed as a percentage; † significant effect – RR 95%CI does not cross 1. ns statistically non-significant result.

After adjustment for coexisting MBD, smoking and other confounding factors, a significant effect on neonatal morbidity was evident for all classes of MBD except bipolar disorder. Unlike other classes of MBD, which were associated with attenuated, but increased risk of neonatal morbidity, personality disorder was associated with lower neonatal morbidity (aRR 0.75, 95%CI 0.64 to 0.87). The largest independent effects of MBD on neonatal morbidity were observed for maternities to mothers with an opiate disorder (aRR 2.62, 95%CI 2.51 to 2.73) followed by

maternities to mothers with a cannabis disorder (aRR 1.51, 95%CI 1.43 to 1.59). Smoking had no effect on neonatal morbidity in Table 5.4.

Admission to a neonatal intensive care unit

Overall, 3.5% of maternities in the weighted maternity population were admitted as neonates to a NICU. Table 6.6 also presents the crude and adjusted relative risks of NICU admission by class of MBD in pregnancy. Crude relative risks of NICU admission were increased for babies born to mothers with all classes of MBD in pregnancy and ranged from 1.48 (95%CI 1.10 to 1.41) among maternities to mothers with depression to 6.77 (95%CI 6.14 to 7.46) among maternities to mothers with opiate disorder and 6.77 (95%CI 5.39 to 8.51) among maternities to mothers with a polydrug disorder.

Table 5.5 Admissions to NICU, crude and adjusted relative risks and population attributable risks associated with maternal MBD, weighted maternities NSW 2002-2006

		NICU		Crude RR [a]				Adjusted RR [a,b]			PAF
		N	%	**RR**	lcl	ucl		**aRR**	lcl	ucl	%
All maternities		14,894	3.5								
Maternal disorder in pregnancy	Alcohol	72	9.9	**2.86**	2.29	3.57	†	**1.49**	1.17	1.89	0.16
	Cannabis	195	8.2	**2.38**	2.06	2.74	†	**1.29**	1.10	1.51	0.29
	Opiates	450	23.0	**6.77**	6.14	7.46	†	**5.23**	4.61	5.94	2.44
	Stimulants	75	11.2	**3.24**	2.61	4.03	†	ns			
	Schizophrenia	40	9.3	**2.57**	1.91	3.45	†	ns			
	Bipolar	23	5.9	**1.69**	1.13	2.51	†	ns			
	Depression	156	5.1	**1.48**	1.26	1.74	†	ns			
	Anxiety	99	5.2	**1.49**	1.22	1.81	†	**1.29**	0.99	1.48	0.12
	Personality	28	9.0	**2.58**	1.79	3.72	†	ns			
Mother smoked		2,859	4.6	**1.40**	1.26	1.56	†	**1.24**	1.10	1.41	3.75

(a) Referent group for calculating relative risks are maternities without the disorder.

(b) Adjusted for coexisting maternal mental and behavioral disorders, smoking, maternal age, maternal socioeconomic status maternal parity, maternal diabetes, maternal hypertension.

Abbreviations: N number of affected maternities; RR relative risk aRR adjusted relative risk; lcl lower 95% confidence limit; ucl upper 95% confidence limit; PAF(%) population attributable fraction expressed as a percentage; † significant effect – RR 95%CI does not cross 1. ns statistically non-significant result.

The largest independent associations of MBD with neonatal morbidity were observed for maternities with maternal opiate disorder (aRR 5.23, 95%CI 4.61 to 5.94. Modest associations with admission to NICU were evident for maternal alcohol disorder (aRR 1.49, 95%CI 1.17 to

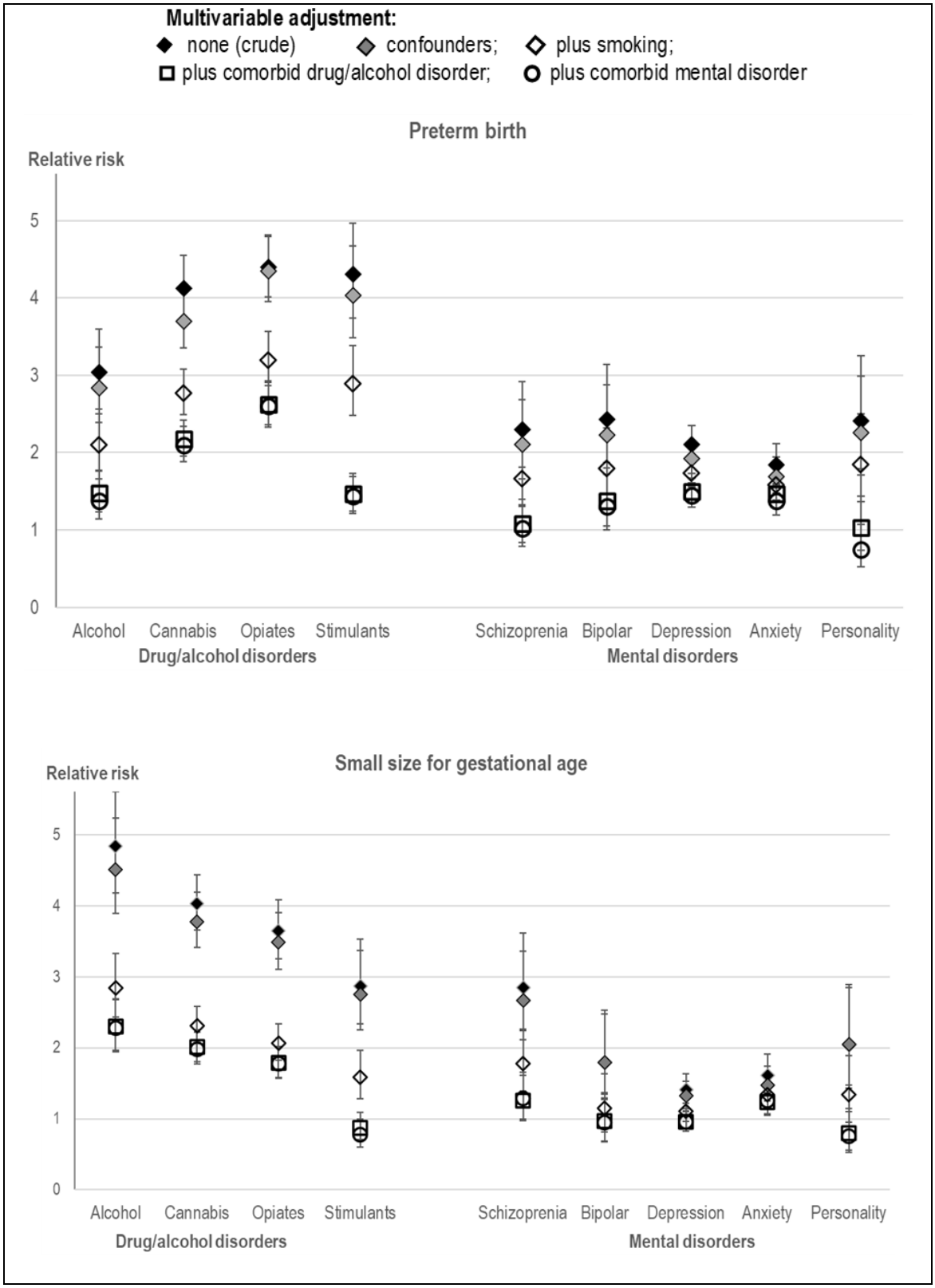
1.89), anxiety (aRR 1.29, 95%CI 0.99 to 1.48) and cannabis disorder (aRR 1.29, 95%CI 1.10 to 1.51).

Stepwise adjustment for confounders and mediators

Figure 5.1 shows RRs and RR95%CIs for 9 classes of MBD on preterm birth and small size for gestational age by model complexity. The least complex model was the unadjusted model that produced the crude RR. The subsequent categories of complexity reflect the progressive addition of covariates to the model: sociodemographic and obstetric confounding factors; maternal smoking in pregnancy; comorbid maternal drug/alcohol disorders; and finally, comorbid mental disorder.

There was relatively little change to RRs of either outcome after adjustment for sociodemographic and obstetric factors (model1 vs model2). Substantial attenuation of RRs for both outcomes were evident when maternal smoking was added to the models (model2 vs model3), Further attenuation was evident when comorbid drug disorders were added as covariates to the models. These falls in RR were significant for drug disorders. Addition of comorbid mental disorders to the models made little difference to the RR for any class of MBD except personality disorders.

Figure 5.1: Stepwise multivariable adjustment of effects of MBD on preterm birth and small size for gestational age, weighted maternities NSW 2002-2006



Impact of MBD on neonatal outcomes

The final column in Tables 5.1 to 5.5 presents the PAF for specific classes of MBD with independent effects in fully adjusted models. Maternal MBD accounted respectively for 0.31+0.51=0.81% perinatal deaths, 0.11+1.04+1.06+0.43+0.16=2.90% preterm birth, 0.43+1.10+0.68=2.21% small size for gestational age., By contrast, maternal MBD had substantially larger impacts on neonatal outcomes, and accounted for 5.25% of perinatal death, 7.22% of preterm birth and 16.93% of small size for gestational age.

5.5 Comment on results

Key findings

MBD increased the risk of adverse neonatal outcomes

The presence of MBD increased the crude risks of adverse neonatal outcomes between 2- and 7-fold compared with no MBD. Adjustment for confounders and effect modifiers attenuated the strength of the associations between classes of MBD and adverse neonatal outcomes, in some cases nullifying the effect. For two key outcomes, preterm birth and small size at birth, adjustment for maternal smoking and coexisting drug/alcohol disorder contributed the largest reductions in effect. For two key outcomes, preterm birth and small size at birth, stepwise adjustment for confounding and mediating factors point to maternal smoking and coexisting drug/alcohol disorder as main contributors to the reductions in effect.

Drug/alcohol disorders

Opiate disorders were associated with increased relative risks for all adverse neonatal outcomes considered. For most outcomes, opiate disorder was associated with the largest effects. The exceptions were perinatal mortality and small size for gestational age where associations were stronger for maternal alcohol disorders. Crude RR of perinatal mortality were doubled by maternal cannabis disorder, but there was no independent association, suggesting the increased perinatal mortality associated with maternal cannabis disorder was mediated by coexisting maternal smoking and comorbid MBD.

The contribution of maternal alcohol, opiate and cannabis disorders to adverse neonatal outcomes are not in dispute and these results align with those reported previously (Burns, Mattick et al. 2006, Burns, Mattick et al. 2006). Admission to NICU and preterm birth for were

not associated in this study with maternal stimulant disorder in contradiction to previous findings (Burns, Mattick et al. 2006). Stimulants drugs include cocaine methamphetamines, MDMA (ecstasy), amphetamines. The contributions of drug type to stimulant disorders varies over time. The setting of this study precedes the availability of cheap, addictive forms methamphetamine commonly known as 'crystal meth' which comprised an increasing proportion of methamphetamine use from 2010 onwards (Australian Institute of Health and Welfare (AIHW) 2017).

Mental disorders

Crude risks of perinatal mortality and morbidity were increased among mother with mental disorders relative to those without these disorders. Crude RRs were generally higher for drug/alcohol disorders than for mental disorders. Adjustment for confounders and effect modifiers lowered the RRs. With few exceptions, mental disorders did not have an independent effect of adverse neonatal outcomes. After adjustment for confounders and effect mediators a modest increased risk of admission for a condition arising in the perinatal period persisted for all mental disorders except bipolar disorder. Independent effects of mental disorder on preterm birth remained for mothers with depression and anxiety and there was borderline increased risk of admission to neonatal intensive care among mothers with anxiety disorder.

Maternal schizophrenia and maternal bipolar disorders were crudely associated with increased risks of adverse outcome, but these conditions did not contribute independently to the risks of either preterm birth or small size for gestational age. This contrasts with associations of these disorders with preterm birth and low birthweight reported in other studies (Jablensky, Morgan et al. 2005, Lee and Lin 2010, Vigod, Kurdyak et al. 2014, Mei-Dan, Ray et al. 2015). These differences are likely to have arisen because earlier studies did not control for both maternal smoking and drug/alcohol use.

Information about outcomes of personality disorders in pregnancy is sparse (Howard, Molyneaux et al. 2014). In this study maternal personality disorder was crudely associated with increased risks of preterm birth and small size for gestational age. This is consistent with findings of poorer neonatal outcomes in an earlier study of women with borderline personality disorder(Blankley, Galbally et al. 2015). Blankley et al did not adjusted for confounders, maternal smoking and comorbid MBD in pregnancy. In this study independent associations between personality disorders and neonatal outcomes were no longer apparent after adjustment for

confounders and effect mediators. The level of attenuation of effects of personality disorders on neonatal morbidity was extreme enough to change the direction of effect from a risk factor (RR greater than 1) to a protective factor (RR less than 1). Under-ascertainment of maternal personality disorders in Chapter 4 together and possible bias in the diagnosis of personality disorder suggests that this finding could be an artifact.

Contribution of maternal smoking and coexisting drug/alcohol disorders

Stepwise adjustment RRs of preterm birth and small size for gestational age demonstrated the largest fall in RR occurred when maternal smoking in pregnancy was added to the models and the next largest followed the addition of comorbid drug/alcohol disorders as covariates to the models. The declines were more substantial and statistically significant for MBD classes of drug disorder than for MBD classes of mental disorder.

The results from the stepwise adjustment of the effects of MBD on preterm birth and small size at birth in this study point to maternal smoking in pregnancy and the presence of comorbid drug/alcohol disorders as significant effect modifiers for most classes of MBD. Interventions to minimise drug and alcohol abuse in pregnancy in mothers with mental disorders could reduce the risks of preterm birth and small size at birth to levels comparable to those for mothers without these disorders. These results should be reassuring to NSW mothers with mental disorders and those responsible for their care in pregnancy. Confirmation of these findings is needed before these disorders can be ruled out as a cause of poor newborn and neonatal outcomes.

Impact of MBD on perinatal outcomes

The burden of maternal MBD was determined and contrasted with smoking burden to give a public health perspective to these results. The 2.44% of admissions to NICU related to maternal opiate disorder is not trivial. Strong associations in the context of low disorder prevalence result in a small population impact. This is demonstrated by the 7% burden of maternal smoking on preterm birth compared with 1% for maternal opiate disorder and cannabis disorder, despite weaker the independent association with preterm birth for maternal smoking (aRR 1.50) compared with those for cannabis disorder (aRR 2.1) and opiate disorder (aRR 2.4). The impact of MBD on neonatal outcomes has rarely been assessed. One study in Western Australia found the impact of alcohol disorders at any time from 1 year before to 1 year after pregnancy on stillbirths among Indigenous mothers (PAF 7.9%) to be higher than for non-Indigenous mothers

(PAF 0.8%) (O'Leary, Halliday et al. 2013). Among non-Indigenous mothers the impact of alcohol disorder during pregnancy on stillbirth was 0.1% (O'Leary, Halliday et al. 2013). This broadly similar to the impact of alcohol disorder in pregnancy on perinatal mortality (PAF 0.3%) in the current study, allowing for the fact that stillbirths comprise 4 out of 5 perinatal deaths.

Interpreting results

Crude relative risks represent those observed in the population, whereas adjusted relative risks represent independent effects. When comparing these results with those from other studies, or comparing population subsets, the RR values may reflect different distributions of maternal characteristics. Some characteristics, such as maternal age confound the relationship between MBD and neonatal outcomes, whereas others contribute directly to the effect MBD has on the health of the neonate.

Comorbid drug/alcohol disorders and to a lesser extent, comorbid mental disorders are better understood as effect modifiers than as confounders of the relationship between maternal MBD disorders and neonatal outcomes. Confounders and effect modifiers are associated both with the exposure and the outcome, but effect modifiers, also known as intermediate variables, are on the causal pathway, whereas confounders are not. Smoking, like alcohol or drug abuse, is likely to be intermediate in the relationship between maternal MBD and adverse neonatal outcomes.

For neonatal service providers, the extent to which effects of MBD are mediated by co-existing MBD or smoking, or due to confounding effects of other maternity characteristics is immaterial. In this context the important statistic is the number of affected individuals who will need neonatal services. For epidemiologists, it is the independent effects of specific classes of MBD that inform our understanding of the mechanisms by which MBD act. For public health practitioners, the presence of a modifiable mediating factor that explains a sizable portion of the effect of an exposure that cannot easily be altered is important because they point to areas for targeted intervention. In this study for example, preventing preterm birth or small size in the babies of mothers with a drug or alcohol disorder, schizophrenia or bipolar disorder could potentially be achieved with interventions to reduce maternal smoking or comorbid drug disorder. Additional analysis to assess the relationships between confounders and mediators (Richiardi, Bellocco et al. 2013, VanderWeele and Tchetgen Tchetgen 2014) is needed to determine potential gains from a targeted intervention. This was beyond the scope of this study.

Strengths and limitations

A strength of this study was the comprehensive view of MBD for a large maternity population. Information about maternal MBD was obtained from inpatient morbidity data, which for pregnancy-related admissions include all recognised clinically relevant MBD. Conditions considered to be clinically relevant can vary between clinicians and over time. MBD are more likely be recognised for women with the most florid or severe forms of the disorder. The increasing importance of MBD in pregnancy is reflected in the weight given to these conditions in national guidelines for pregnancy management (Intergovernmental Committee on Drugs 2006, Department of Health 2018)If, over time, less severe forms of disorder are included in hospital morbidity data, the magnitude of the associations between MBD from hospital morbidity data and neonatal outcomes could be reduced.

The current study did not separately consider neonatal outcomes in maternities MBD and co-existing physical disorders. Chapter 4 reported less than 1 in 10 (7.6%) admissions with MBD as a secondary diagnosis were for non-pregnancy related conditions, that is for physical disorders. Furthermore, the study design did not allow identification of maternities with a physical disorder in the absence of MBD.

Alcohol is the most widely used substance used by women of reproductive age in the general population. It is also the most difficult to characterise. Poor recognition of maternal alcohol disorder in pregnancy has been demonstrated by other researchers (O' Leary, Halliday et al. 2013). The resulting under ascertainment of maternal alcohol disorder status would bias effects towards null. The effects of maternal alcohol disorder are likely to be underestimated.

Linked neonatal admission data used in this improved the quality of outcome data and identified babies who became unwell or were admitted to neonatal intensive care throughout the neonatal period. PDC neonatal outcomes are limited to those in the birth hospital and miss information about babies transferred to another hospital. For example, linked neonatal admission data in this study added a further 54 neonatal deaths to the 265 identified in PDC data, increasing neonatal deaths by 20%.

This series of 312 maternities with maternal personality disorder represents the largest Australian series to report perinatal and neonatal outcomes for this group of disorders. The level of attenuation of effects of personality disorders on neonatal morbidity was extreme enough to

change the direction of effect from a risk factor (RR greater than 1) to a protective factor (RR less than 1). However, this may be a biased study population subset. Ascertainment of personality disorder defined by a diagnosis in inpatient episodes was estimated to be in the order of 1% in Chapter 4. It is likely that many women with limited access to mental health services would have been less likely to receive a diagnosis of personality disorder. In a biased population, this "protective effect" could be an artifact.

The small sizes of maternity populations with maternal schizophrenia, bipolar disorder and personality disorder contribute to the wide confidence limits in the analysis of RR and the stepwise analysis. However, in contrast to maternity personality disorder, maternal schizophrenia and bipolar disorders were found in Chapter 4 to be credibly smaller than in the general population of women of reproductive age. Larger population aggregates are needed to overcome this limitation.

The choice of relative risks rather than odds ratios to measure the effects of drug/alcohol use, mental disorder and smoking provided less biased comparisons, particularly for relatively common conditions. This property has been the subject of statistical review (Knol, Le Cessie et al. 2012). Reporting relative risks aligns with the current best practice (Barger 2018, Norton, Dowd et al. 2018).

A limitation of the data used for this analysis was the absence of information about level of neonatal care from the data items requested for the over-arching study. Level of neonatal care can be used as a proxy for severity of neonatal morbidity and would have provided a more complete picture.

5.6 Summary and next step

This chapter showed that although there are deleterious consequences of all classes of maternal MBD for the survival and wellbeing of the baby at birth and in the first 28 days, a substantial portion of preterm birth and small size for gestational age these could be explained by maternal smoking and drug disorders acting as intermediate factors. Schizophrenia, bipolar disorder, and personality disorder were not independently associated with the poor neonatal outcomes considered. Maternal MBD were more strongly associated with adverse neonatal outcomes were generally stronger than those for smoking. However, the public health consequences, measured by the proportion of each neonatal outcome that pregnancy that could be subtracted

if maternal exposure was eliminated, were lower for MBD than for smoking. The implications of the findings of this chapter, along with the findings from chapters 3 and 4, are discussed in Chapter 6.

Chapter 6. Discussion and conclusions

The topic of MBD in pregnancy was introduced in Chapter 1, and three important gaps in current knowledge were identified. Three studies were carried out using linked population data for maternities in NSW in the 5-years between 2002 and 2006. Chapter 2 described the linked population data used in each of these studies. Each study addressed one of the gaps in current knowledge of MBD in pregnancy identified in Chapter 1. This chapter summarizes the key findings from each of the results chapters, discusses their implications, suggests further research that could improve knowledge about MBD in pregnancy and the conclusions from this thesis.

6.1 Key findings

Chapter 3: This study assessed trends in of rates of admission for MBD in pregnancy compared with baseline admission rates in the 6 months before pregnancy. This addressed the relative paucity and inconsistencies in information about trends in rates of admissions for MBD in pregnancy.

- MBD admission rates were 29% lower in early pregnancy and 91% higher in late pregnancy.
- Trends in admissions for depression, anxiety and adjustment disorders combined and bipolar disorder, followed the same pattern as all MBD. Admission rates for bipolar disorder were 67% below baseline rates in early pregnancy and no different to baseline rates in late pregnancy. Rates of admission for schizophrenia increased by 38% in early pregnancy and were 83% higher than baseline in late pregnancy. Admissions for a drug disorder fell 25% below the baseline rate in early pregnancy and increased over 3-fold in late pregnancy, while admissions for alcohol disorder fell in early pregnancy and remained consistently low.
- Trends in rates of admission for MBD overall and for individual classes of MBD followed the same patterns in primiparous and multiparous maternities, but baseline admission rates for multiparous maternities were higher for depression and anxiety and adjustment disorders combined.

These trends in admission rates support the findings of an earlier study in Edinburgh (Kendell, Chalmers et al. 1987). Higher baseline admissions anxiety and depression in multiparous

mothers are consistent with findings that admission rates for these disorders in first-time mothers remained elevated for up to 2 years after the birth (Xu, Austin et al. 2012).

Chapter 4: Prevalence of MBD from linked hospital admissions with a diagnosis of MBD that commenced during pregnancy addressed the lack of comprehensive information about maternity prevalence of MBD in Australia and the limited information world-wide about prevalence of schizophrenia and bipolar disorder.

- Maternity prevalence was 2.4% for MBD overall; 1.2% for drug/alcohol disorders; 0.8% for affective disorders; 0.6% for anxiety disorders; and 0.1% for psychotic disorders. A diagnosis in pregnancy of schizophrenia was present in 1.0 per 1,000 maternities, bipolar disorder in 0.9 per 1,000 maternities and personality disorder was present in 0.7 per 1,000 maternities.
- Maternity prevalence (per 1,000 person-years) of drug/alcohol disorders was similar, of psychotic disorders was halved, of affective disorders was a third and of anxiety disorders a tenth of the estimated 12-month prevalence (per 1000 persons years) of comparable disorders in women of reproductive age from national surveys.
- Pregnancies for one in five (20.3%) of maternities were complicated by more than one class of MBD to a maximum of 7 classes of MBD.
- Prevalence of a drug/alcohol disorder was 34-fold higher among maternities for mothers who smoked 10 or more cigarettes per day and 20-fold higher maternities for mothers who smoked less than 10 cigarettes per day than among maternities for non-smoking mothers. Maternities for mothers who resided in outer regional or more remote areas were 11-fold higher prevalence of a drug/alcohol disorder and 10-fold higher prevalence of mental disorder than maternities for mothers who resided in metropolitan areas.

This study provides the estimates of the prevalence MBD in pregnancy in a five-year period. This improves estimates from previous Australian studies that examined trends in maternities with a history of MBD and 12-month prevalence of MBD over a period of more than 20-years (O'Donnell, Anderson et al. 2013) or reported on estimates for first-time mothers (Xu, Sullivan et al. 2016). Demonstration of substantial MBD comorbidity informed the need to adjust for co-existing MBD when assessing independent effects of disorders on neonatal outcomes. Targeted interventions in population sub-groups with high relative prevalence of MBD are more cost-effective than interventions in the whole maternity population.

Chapter 5: This study assessed effects and impacts of classes of MBD on perinatal mortality, preterm birth, small size for gestational age, neonatal morbidity and admission to NICU in singleton maternities. This study was able to account for coexisting mental disorders, maternal smoking, addressing the failure of previous studies to account for the effects of these factors.

- Crude rates of perinatal mortality and neonatal morbidity for all classes of MBD were 2- to 7-fold higher than rates in maternities without MBD. These Effects for all disorders were attenuated by multivariable adjustment.
    - Crude rates of perinatal mortality and neonatal morbidity for all classes of MBD were 2- to 7-fold higher than rates in maternities without MBD. These Effects for all disorders were attenuated by multivariable adjustment.
    - After adjustment, neonatal morbidity was increased in maternities with most classes of MBD, but for other adverse neonatal outcomes drug/alcohol disorders were more important predictors of adverse neonatal outcome than mental disorders. Alcohol and opiate disorders were independently associated with all adverse neonatal outcomes considered, and cannabis disorders with all adverse neonatal outcomes except perinatal mortality. Depression and anxiety increased rates of preterm birth and anxiety increased rates of admission to NICU.
    - Comorbid drug/alcohol disorders substantially attenuated the strength of the association of all classes of drug/alcohol disorder, schizophrenia, bipolar disorder and personality disorder with preterm birth and small size for gestational age over and above reductions after adjustment for confounders and maternal smoking.
    - The burden of opiate disorder on adverse neonatal outcomes was higher than for other drugs or alcohol and most evident among admission to NICU. In the study population, 2.4% of NICU admission would have been prevented if maternal opiate disorder could be eliminated, compared with reductions of 0.2% and 0.3% respectively for elimination of maternal alcohol disorder and cannabis disorders. By contrast eliminating maternal smoking would reduce NICU admission by 3.4%. The impacts of MBD on other neonatal outcomes were modest in comparison with impacts of smoking.

This study is consistent with reported increased preterm birth associated with depression (Grote, Bridge et al. 2010, Grigoriadis, Vonderporten et al. 2013), adds to the evidence for anxiety disorder as a risk factor for preterm birth but does not support anxiety disorder as a

risk factor for small size for gestational age. Schizophrenia and bipolar disorder were not independently associated with adverse neonatal outcomes despite observed crude increased risk. This does not support findings of modest effects in earlier studies, none of which adjusted both for maternal smoking and co-existing alcohol/drug disorders (Bennedsen, Mortensen et al. 1999, Jablensky, Morgan et al. 2005, Nilsson, Hultman et al. 2008, Boden, Lundgren et al. 2012, Vigod, Kurdyak et al. 2014, Mei-Dan, Ray et al. 2015).

6.2 Implications of study findings

Pregnancy as a determinant of MBD

The perception of pregnancy as protective against MBD and accounts of perinatal mental disorders that give relatively little, if any, attention to disorders in pregnancy, and direct attention instead to MBD in the postnatal period (Jones 2008, O'Hara and Wisner 2014, Paschetta, Berrisford et al. 2014) need to be challenged. The study in Chapter 3 indicates that while early pregnancy may have been protective, later pregnancy was associated with increased admission for all classes of MBD. Later pregnancy as a promoter of MBD aligns with increasing physical discomfort, social constraints and pregnancy complications as pregnancy advances (Brockington 1996). Anxiety about birthing is now more commonly encountered (Ross and McLean 2006) and can be present in first time mothers because of their inexperience or in mothers in a subsequent pregnancy who experienced fetal loss or a traumatic birth (Goodman, Chenausky et al. 2014). For such women it is important to ensure their access to models of antenatal care that ensure flexible access to one or a small team of maternity carers to promote the development of trusted relationships.

Surveillance of MBD in pregnancy

Australian guidelines for the care of pregnant women (Department of Health 2018) provide evidence-based recommendations for optimal maternity care and the woman-centred approach to the provision of maternity care (COAG Health Council 2019). These emphasize the importance of recognizing women with MBD and instituting appropriate care. A woman-centered approach recognizes that maternity care needs to be individualized, incorporating the values of safety, respect, choice, and access to services. Maternity and MBD policies and practice guidelines need to be supported by robust surveillance (Department of Health 2011) that monitors the detection, service provision and outcomes for mothers with MBD.

The need for information about drug use, alcohol use and mental disorder in pregnancy in the national perinatal data has been the subject of several workshops and the collection of these data continues to be a priority for national perinatal data development (Australian Institute of Health and Welfare (AIHW) 2017). A binary (yes/no) data item to indicate a person is experiencing or has previously experienced a mental health condition has recently been added to the dataset for jurisdictional supply of data on a voluntary basis for the National Perinatal Data Collection (Australian Institute of Health and Welfare (AIHW) 2020). There has been little progress in developing more detailed data items for surveillance of MBD in pregnancy.

Depression and anxiety disorders

The study in Chapter 4 included estimates of the relative prevalence of MBD among women of reproductive age and women who give birth. High prevalence MBD such as anxiety and affective disorders were poorly represented when using linked hospital admission data for ascertainment of MBD. These disorders are usually managed in the community. Alternative methods for surveillance of these disorders in pregnancy are available. Antenatal screening using the Edinburgh Depression Score is recommended for all pregnant women (Department of Health 2018) and has been suggested as the basis for surveillance and interventions to prevent postnatal harm to the mother and baby (Khanlari, Barnett Am et al. 2019).

Drug and alcohol disorders

By contrast, the prevalence of drug/alcohol disorders from inpatient morbidity data in this maternity population was similar to the estimated 12month prevalence of drug/alcohol disorder that occasioned treatment among women of reproductive age from a national survey (Australian Bureau of Statistics 2008).

Serious mental disorders

Maternity prevalence of psychotic disorders in the NSW was about half that found among women of reproductive age in the general population. Reduced fertility of women with schizophrenia has been reported from the UK (Howard, Kumar et al. 2002). Women with schizophrenia may have lower fertility because of side-effects of some medications, because their relationships are less stable, or by choice (Howard 2005).

Borderline personality disorder is recognised as serious mental disorder in pregnancy alongside schizophrenia, psychosis and bipolar disorder (Department of Health 2018). The largest published Australian series followed 42 women (Blankley, Galbally et al. 2015). available, the

use of maternity-linked hospital morbidity data has been demonstrated in this thesis to be feasible, captures the high rates of MBD comorbidity identified in surveys (Blankley, Galbally et al. 2015, Crowley, Molyneaux et al. 2019) and can be linked with neonatal outcomes.

Linked birth and hospital morbidity data provide a reasonable representation of the maternity prevalence of psychotic disorders and substance disorders. Such data are needed for health services planning for maternity care, postnatal parenting support, and the need for additional psychological and social interventions in the early years for women with these disorders.

Consequences of preterm birth and fetal growth restriction

In Chapter 5, between 1 in 4 and 1 in 5 babies of mothers with alcohol or drug disorder were born preterm, and between 1 in 5 and 1 in 7 babies were born small for gestational age. These levels of morbidity are not trivial. Preterm birth and small size have long- and short-term implications for the health of the newborn. In the short term these babies require increased clinical monitoring and are more likely to require neonatal care, which is resource intensive and expensive. In 2006 annual recurrent costs were estimated as $1,195 per day for a special care nursery (SCN) cot and $2,466 per day for a neonatal intensive care unit (NICU) cot (Queensland Health 2006). Babies born preterm or small for their gestational age are less likely to have breastfeeding established and maintained, and have long-term physical health conditions, especially respiratory conditions and developmental delays (McMillen, Adams et al. 2001, Behrman and Butler 2007). In high income countries parental bonding with sick babies who need intensive care is not necessarily diminished and may be enhanced (Beckwith and Cohen 1978, Hoffenkamp, Tooten et al. 2012). However, in high income countries, women who are disadvantaged financially and have symptoms of depression were more likely to demonstrate poorer maternal attachments with their babies (Alhusen, Gross et al. 2012). Interactions between of maternal mental disorders and preterm birth or small size at birth on longer-term poor outcomes may be relevant to follow-up studies such as the Mercy Pregnancy and Emotional Well-being Study (MPEWS), which aims investigate early developmental mechanisms and modifiers for maternal, fetal and child emotional well-being (Galbally, Ijzendoorn et al. 2017) and future follow-up studies of babies born to mothers with drug disorders.

In the long term, preterm birth and small size at birth increase the individual's risk of cardiovascular disease, renal disease and metabolic syndrome in adulthood (Barker, Osmond et al. 1989, Barker, Osmond et al. 1993, Gluckman, Hanson et al. 2005). Cognitive and

neurodevelopmental delays also have life-long consequences and become evident in childhood. Cognitive and neurodevelopmental scores at 9 to 10 years were more strongly associated with small size than preterm birth, a finding consistent with better outcomes for earlier birthing of babies diagnoses with reduced fetal growth (Fattal-Valevski, Toledano-Alhadef et al. 2009). Existing evidence that schizophrenia and bipolar disorder increase the risk of preterm birth and small size for gestational age was examined in Chapter 1 and found to be mixed. The evidence-base was small and few of the studies were able to account for the effects of smoking and comorbid maternal alcohol/drug use. The study in Chapter 5 adjusted for smoking, comorbid MBD factors and other factors, after which neither schizophrenia nor bipolar disorder to be independently associated with any of the adverse neonatal outcomes considered. Furthermore, a substantial portion of the effect of schizophrenia and bipolar disorder appeared to be explained by smoking and comorbid alcohol/drug disorder. The presence of a modifiable risk factor in the context of a chronic disorder is important. If confirmed, interventions to reduce smoking and drug/alcohol disorders prenatally in women with schizophrenia and bipolar disorder could improve the health of their babies and will be reassuring for those who avoided smoking and were free from alcohol and drug disorder in pregnancy.

Increasing community tolerance of cannabis

While of opiate and stimulant use continue to be viewed as problematic, community tolerance for cannabis use has increased, with greater support for legalisation legalising cannabis use and lower support for penalties applied to the sale and supply of cannabis (Australian Institute of Health and Welfare (AIHW) 2017). The study in Chapter 4 found cannabis disorder to be the most prevalent maternal drug disorder in NSW maternities between 2002 and 2006 and in this population cannabis disorder in pregnancy doubled the risks of preterm birth and small size for gestational age after accounting for maternal smoking, alcohol disorders, and other drug disorders (Chapter 5). The findings from this study add to evidence from other studies (Gunn, Rosales et al. 2016, Metz, Allshouse et al. 2017) that cannabis disorder in pregnancy is a threat to the health and wellbeing of the neonate. The Generation R study suggested that cannabis use increased the risk of fetal growth restriction over and above that of tobacco (El Marroun, Tiemeier et al. 2009). Unlike tobacco, which primarily affects late fetal growth, cannabis use in early pregnancy was associated with fetal growth restriction detectable by 20 weeks gestation (El Marroun, Tiemeier et al. 2009). The authors concluded that to prevent the potential harmful

effects of intrauterine cannabis exposure, women should quit using cannabis before conception (El Marroun, Tiemeier et al. 2009).

6.3 Methodological considerations

Data from linked birth and hospital admission data

In Australia, greater accountability in health care expenditure has driven the expansion of administrative health data collections (Sax 1990). Despite the obvious limitations of using data that were not designed for research and the potential for varied quality of information capture between service providers, the value of these data is offset by their size, accessibility, the use of standardized systems for diagnostic and other coding, large numbers, defined geographic coverage and relatively complete capture of health system contacts (De Coster, Quan et al. 2006). In NSW, the quality of inpatient data, including morbidity data, is monitored (Activity Based Funding Taskforce 2016). This increases the confidence that information obtained from hospital morbidity data is reliable. When applied to the study of MBD, hospital morbidity data have the advantage of standardized clinical definitions. Data linkage is a method particularly suited to studies in the perinatal period because of the extent and diversity in potential exposures that can impact on maternal and newborn health, the range of maternal and infant outcomes many of which extend across the life-course, and the relatively low cost of extending follow-up (Zylbersztejn, Gilbert et al. 2019). The availability of a dedicated record linkage authority in NSW has relieved researchers of the onerous task of record linkage, but not the need to understand the structure and quality of the source data collections, the methods used in data linkage and their implications for the quality of the linked data (Benchimol, Smeeth et al. 2015).

Chapter 2 in this thesis described the data linkage and preparation of the linked data used in each of the studies. The need for transparency and reproducibility of research methods has been highlighted in a recent survey in the journal *Nature* (Baker 2016). This reported more than 70% of researchers were unable to reproduce another scientist's experiments, and more than half were unable to reproduce their own experiments (Baker 2016). Successful replication of research findings relies on the availability of detailed accounts of the methods. Publication of details of record linkage and the method used to prepare linked data in peer-reviewed journals provides for expert and independent oversight and at the very least should be provided as a supplement to reports of the main study findings. Guidelines for reporting data linkage have

been developed to assist researchers (Benchimol, Smeeth et al. 2015, Gilbert, Lafferty et al. 2018).

Ascertainment of maternal MBD from inpatient morbidity data

A strength of using diagnostic data from inpatient data collections to assess prevalence of MBD in Australia is their availability for almost all mothers. In 2004 for example, only 0.1% of NSW mothers planned a home birth (Centre for Epidemiology and Research. NSW Department of Health 2005). Remaining maternities were planned to occur in a hospital or birth centre where an inpatient episode record would be generated. ICD10 coding standards ensure that clinically recognised MBD, including MBD managed wholly in the community, are included in hospital morbidity data for antenatal and maternity admissions.

The extent of clinical recognition of MBD in pregnancy is directly related to the clinical importance attached to these disorders by obstetricians, midwives and other clinicians involved in pregnancy care. Maternal drug/alcohol disorders have been of concern for decades (Intergovernmental Committee on Drugs 2006). Attention paid to mental disorders in national evidence-based guidelines for the care of pregnant women has increased (Department of Health 2011, Department of Health 2018). Studies that informed *beyondblue* clinical practice guidelines were carried out in the early 2000s (Buist, Austin et al. 2008). Spikes in depression and anxiety in hospital morbidity from pregnancy-related admissions in 2003 and 2004 in NSW have been attributed to the increased attention to MBD resulting from these studies (Xu, Austin et al. 2012). Future trends in prevalence of MBD in maternity populations are likely to reflect the increased clinical recognition of mental disorders.

Medical record keeping in maternity settings have benefited from the use of maternity information systems. These electronic record systems were designed to support the complex information needs of clinicians and clinical teams providing maternity care (Craswell, Moxham et al. 2013). These have eased the administrative burden of mandatory birth notifications and improved the quality of referrals (Hawley, Hepworth et al. 2017). During the years covered by studies in this thesis, over two thirds of notifications to the NSW PDC were received from a maternity information system (Centre for Epidemiology and Research. NSW Department of Health 2002). By 2016 all of notifications to the PDC from hospitals were from 1 of 6 maternity information systems (Centre for Epidemiology and Research. NSW Department of Health 2017).

Maternity information systems improve the chance that MBD identified during antenatal care is available to clinicians attending the birth and that it will be included in hospital morbidity data.

A limitation of MBD ascertainment from hospital morbidity data is that not all individuals with MBD will be recognised, and that the disorders that are recognised will be biased towards established and more severe forms of disorder. This means that 'true' prevalence of maternal MBD will be higher, although less severe forms of MBD may have smaller effects on neonatal outcomes. MBD misclassification is not random. Errors in MBD in hospital morbidity data are more likely to be omissions rather than erroneous reporting of MBD, which will under-estimate the 'true' effects on neonatal outcomes described in Chapter 5.

Measuring prevalence

Prevalence studies need either whole population data or sampled data that can be related back to the whole population. Excluding study participants can alter the relationship between the sampled and the source populations. In this study only mothers whose linked maternity records cast doubt about whether they were for the same person were excluded. Mothers with linked hospital admission records that did not meet study definitions for MBD and those whose maternity record appeared to have been incorrectly linked with a hospital admission record for a different person were retained for the study. Although data from their linked hospital admission records were not used, they were counted as mothers. It is possible that in some cases the data used to validate the linkage contained errors due to faulty transcription in one or both records. This could mean that some maternities with MBD in pregnancy were misclassified as non-MBD. This biases prevalence estimates downwards and may bias neonatal outcomes in either direction. These biases may be amplified in MBD sub-groups. Invalid linkage for 255 (0.9%) of all mothers with a linked MBD admission suggests that the effects of any bias would have been small.

Measuring effect and impact

The study in Chapter 5 considered the consequences of maternal MBD in pregnancy for the baby in terms of their effect and potential impact on the main neonatal mortality and morbidity of babies in their first 28 days. Relative risk assessed the strength of the association between the maternal MBD and baby outcomes. The findings of this study alone cannot be used to determine whether a particular class of MBD could be considered or eliminated as a cause of these adverse outcomes. Evidence for causation requires findings to be replicated elsewhere, using different

methods, preferably experimental rather than observational (Schünemann, Hill et al. 2011). Other criteria can contribute to the evidence of causation, such as a dose-response or biological gradient and demonstration of biological mechanisms (Schünemann, Hill et al. 2011). Once MBD are established or eliminated as a cause of mortality or morbidity in the first 28 days this information can be used in clinical settings in counselling or to inform maternity policy.

Measuring impact moves consideration of risk beyond the individual to risk in the population. There are many competing calls on the public purse. Impact can be used by public health practitioners to prioritize the need for interventions. Even if we could assume, for example, that maternal cannabis disorder caused babies to be small for gestational age the 1.1% impact in 2002-2006 was much lower than the 16.9% impact of maternal smoking. Smoking prevalence in the NSW maternity population has been falling and is now half seen in the study period. In more contemporaneous maternity populations, the impact from drug disorders may be different and the balance may be more favorable towards interventions to reduce maternal drug and alcohol use.

National and international comparisons

Within Australia, differences in MBD prevalence between jurisdictions are relatively small. The 2017-18 National Health Survey found that MBD defined as alcohol and drug problems, mood (affective) disorders, anxiety related disorders, organic mental disorders and other mental and behavioural conditions affected 20.0% of Australians overall but ranged from 15.9% in the Northern Territory to 22.7% in Queensland (Australian Bureau of Statistics 2018). Likewise maternity services within each state or territory have some points of difference but are broadly similar across Australia. As such, estimates from linked maternity and inpatient MBD morbidity data that are collected using national standards for a populous state, such as NSW, will be a reasonable, if not exact representation of maternity MBD across Australia.

However, for international comparisons of MBD prevalence and to a lesser extent, the neonatal effects of MBD, it is important to include sufficient information to contextualize the data such as descriptions of mental health service systems, identification of the criteria that may affect thresholds for admission for MBD and the characteristics of the constituent populations.

6.4 Future research

Four areas for future research would improve the quality and utility of the linked data. First, to update and extend this study nationally; second to pilot extended neonatal outcomes in NSW to include congenital anomaly; third to extend surveillance of the neonate into childhood; and fourth to use linked data to assess time to next pregnancy.

- **Update and extend the study nationally.**
  The current study uses linked birth and hospital admission data from NSW. Standardized birth and hospital admission data are collected Australia-wide and data linkage facilities are available to all states and territories. This would provide contemporaneous nation-wide information on MBD in pregnancy and contribute to monitoring national maternity guidelines related to serious mental disorders.
- **Extend neonatal outcomes to include congenital anomaly.**
  Adding data about congenital anomalies would provide more complete information about neonatal outcomes. These relatively rare conditions can have lifelong consequences for the infant and questions about their association with drug/alcohol disorders and medications used to treat mental disorders are unresolved. NSW maintains a register of congenital conditions that retains person identifying data for 5 years.
- **Extending surveillance into early childhood.**
  The effects of preterm birth and fetal growth restrictions have lifelong implications for the infant's health and wellbeing (Longo et al. 2013; Markopoulou et al. 2019). Health effects are mediated by epigenetic programming. This alters the expression of genes in response to the environment. Most epigenetic programming occurs in the first 1000 days which includes pregnancy and extends to the age of 2 years (Barker 2012; Linnér and Almgren 2020; Moore et al. 2017). Early childhood exposures, including but not limited to breastfeeding and weaning practices, nutrition, security of parental attachments, household mobility and the strength of family and community supports available for vulnerable parents can also exert epigenetic changes. Adequate capture of such data at a population level is the main challenge for studies that extend surveillance into early childhood. Some neurodevelopmental outcomes are captured at a population level in the Australian Early Development Census carried out on a triennial basis from

2012 when children start school and national testing of children in schools from the age of 7 years.

- **Time to next pregnancy**

  Maternal drug disorder during pregnancy was associated with increased neonatal morbidity. Maternities with a drug disorder were to younger mothers of higher parity, consistent with higher fertility in this group. Retrospective assessment of the time to next maternity characterised by the presence or absence of maternal drug disorder will inform the potential for interventions such as improved uptake of effective postnatal contraception and prevent repeated maternity with maternal drug disorder.

6.6 Conclusions

This thesis demonstrated the use of linked birth and hospital admission data in NSW to improve knowledge about MBD in pregnancy. These studies, using linked population data for maternities in NSW, Australia have added to the evidence base for pregnancy as a risk for MBD overall, and for anxiety and depression disorders in particular; provided the first comprehensive set of prevalence estimates of MBD in pregnancy for all maternities in NSW, including estimates for both high prevalence and low prevalence MBD; provided evidence to support findings elsewhere of an independent association of alcohol, cannabis or opiate disorder and of no independent association of schizophrenia or bipolar disorder with increased mortality and morbidity in the first 28 days. Updating and extending these data nationally could make an important interim contribution to national surveillance of MBD in pregnancy, particularly drug disorders and serious mental disorders such as schizophrenia and bipolar disorder. In turn, improved surveillance creates the opportunity to improve the understanding of MBD contribution to the health outcomes of newborns in their first 28 days.

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Appendix A: Supplementary tables

Table A2.1: Frequency of drug/alcohol diagnoses from linked episodes that commenced in pregnancy, maternities in NSW 2002-2006

		Alcohol F10	Opiates F11	Can-nabis F12	Stimu-lants F14, F15	Sed-atives F13	Poly-drug F19	Other F16, F18	Tob-acco F17
Chapter V: MBD									
4th digit				*Number of episodes with the diagnosis*					
0	Acute intoxication	137	2	6	1	2	2	0	0
1	Harmful use	265	175	1712	67	438	91	8	46
2	Dependence	284	2995	1172	128	428	205	6	111
3,4	Withdrawal state	26	87	40	9	10	21	0	6
5-9	Other/unspecified	4	10	74	1	41	10	2	2
Total		**716**	**3269**	**3004**	**206**	**919**	**329**	**16**	**165**
Other Chapters									
XV	Pregnancy	4	…	…	…		…	214	…
XIX	Poisoning	19	41	1	10	60	…	68	…
XX	External causes	18	…	…	…	…	…		
XXI	Health status	200	…	…	…	…	…	197	6071
Total		**241**	**41**	**1**	**10**	**60**	**…**	**479**	**6071**
Any chapter		**957**	**3,310**	**3,005**	**216**	**979**	**329**	**495**	**6236**
Chapter V: MBD in pregnancy									
4th digit				*Per cent of episodes with the diagnosis*					
0	Acute intoxication	14.6	0.1	0.2	0.5	0.2	0.6	…	…
1	Harmful use	28.2	5.3	57.0	31.0	44.7	27.7	1.6	0.7
2	Dependence	30.2	90.5	39.0	59.3	43.7	62.3	1.2	1.8
3,4	Withdrawal state	2.8	2.6	1.3	4.2	1.0	6.4	…	0.1
5-9	Other / unspecified	0.4	0.3	2.5	0.5	4.2	3.0	0.4	0.0
Total		**76.3**	**98.8**	**100.0**	**95.4**	**93.9**	**100.0**	**3.2**	**2.6**
Other Chapters		**25.2**	**1.2**	**0.0**	**4.6**	**6.1**	**0**	**96.8**	**97.4**
Any chapter		**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Table A2.2: Diagnoses in pregnancy MBD episodes, maternities in NSW 2002-2006

ICD10-AM		Episodes		
Code	Description	N	%	%
F32.90	Depressive episode, unspecified - specified as not postnatal onset	2,723	65.9	17.9
F53.0	Postnatal depression	379	9.2	2.5
F32.9	Depressive episode, unspecified	203	4.9	1.3
F32.91	Depressive episode, unspecified - arising in the postnatal period	202	4.9	1.3
F32.20	Severe depressive episode without psychotic symptoms - specified as not postnatal onset	185	4.5	1.2
F32.2	Severe depressive episode without psychotic symptoms	44	1.1	0.3
F33.9	Recurrent depressive disorder, unspecified	113	2.7	0.7
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms	103	2.5	0.7
F34.1	Dysthymia	61	1.5	0.4
F32.21	Severe depressive episode without psychotic symptoms - arising in the postnatal period	22	0.5	0.1
F32.10	Moderate depressive episode – specified as not postnatal onset	20	0.5	0.1
F38.8	Other specified mood [affective] disorders	19	0.5	0.1
F32.80	Other depressive episode -specified as not postnatal onset	17	0.4	0.1
F32.00	Mild depressive episode - specified as not postnatal onset	13	0.3	0.1
F33.1	Recurrent depressive disorder, current episode moderate	9	0.2	0.1
F33.0	Recurrent depressive disorder, current episode mild	8	0.2	0.1
F33.8	Other recurrent depressive disorders	4	0.1	0.0
F32.81 F32.0 F32.11	Other depressive episode - arising in the postnatal period Mild depressive episode Moderate depressive episode - arising in the postnatal period	8	0.2	0.1
Depression		**4,133**	**100.0**	**27.2**
F41.9	Anxiety disorder, unspecified	1131	50.8	7.4
F41.0	Panic disorder	408	18.3	2.7
F41.2	Mixed anxiety and depressive disorder	388	17.4	2.6
F41.1	Generalised anxiety disorder	86	3.9	0.6
F42.9	Obsessive-compulsive disorder, unspecified	73	3.3	0.5
F41.8	Other specified anxiety disorders	39	1.8	0.3
F40.8	Other phobic anxiety disorders	25	1.1	0.2
F40.01	Agoraphobia with panic disorder	23	1.0	0.2
F40.00	Agoraphobia without mention of panic disorder	21	0.9	0.1
F40.2	Specific (isolated) phobias	21	0.9	0.1
F42.0	Predominantly obsessional thoughts or ruminations	8	0.4	0.1
F41.3 F40.1 F42.2 F42.8	Other mixed anxiety disorders Social phobias Mixed obsessional thoughts and acts Other obsessive-compulsive disorders	5	0.2	0.0
Anxiety		**2228**	**100.0**	**14.7**
F43.2	Adjustment disorders	358	60.8	2.4
F43.0	Acute stress reaction	118	20.0	0.8
F43.1	Post-traumatic stress disorder	87	14.8	0.6
F43.9	Reaction to severe stress, unspecified	26	4.4	0.2

F43.8	Other reactions to severe stress			
Adjustment		**589**	**100.0**	**3.9**

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ICD10-AM				**Episodes**
Code	**Description**	**N**	**%**	**%**
F20.9	Schizophrenia, unspecified	429	52.6	2.8
F20.0	Paranoid schizophrenia	104	12.8	0.7
F20.5	Residual schizophrenia	75	9.2	0.5
F25.9	Schizoaffective disorder, unspecified	63	7.73	0.4
F29	Unspecified nonorganic psychosis	57	6.99	0.4
F22.0	Delusional disorder	27	3.31	0.2
F20.8	Other schizophrenia	20	2.45	0.1
F25.2	Schizoaffective disorder, mixed type	12	1.47	0.1
F25.1	Schizoaffective disorder, depressive type	7	0.86	0.0
F25.8	Other schizoaffective disorders	7	0.86	0.0
F25.0	Schizoaffective disorder, manic type			
F28	Other nonorganic psychotic disorders			
F20.1	Hebephrenic schizophrenia	14	1.72	0.1
F20.2	Catatonic schizophrenia			
F21	Schizotypal disorder			
Schizophrenia		**815**	**100**	**5.4**

F32.30	Severe depressive episode with psychotic symptoms -specified as not postnatal onset	27	21.4	0.2
F53.1	Puerperal psychosis	24	19.0	0.2
F23.9	Acute and transient psychotic disorder, unspecified	25	19.8	0.2
F39	Unspecified mood [affective] disorder -Affective psychosis NOS	14	11.1	0.1
F23.90	Acute and transient psychotic disorder, unspecified - without mention of acute stress	13	10.3	0.1
F23.2	Acute schizophrenia-like psychotic disorder	6	4.8	0.0
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms	6	4.8	0.0
F23.0	Acute polymorphic psychotic disorder without symptoms of schizophrenia			
F32.31	Severe depressive episode with psychotic symptoms -arising in the postnatal period			
F23.20	Acute schizophrenia-like psychotic disorder - without mention of acute stress			
F23.30	Other acute predominantly delusional psychotic disorders - without mention of acute stress	11	8.7	0.1
F23.80	Other acute and transient psychotic disorders - without mention of acute stress			
F23.91	Acute and transient psychotic disorder, unspecified - with mention of acute stress			
F32.3	Severe depressive episode with psychotic symptoms			
Psychosis		**126**	**100.0**	**0.8**

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ICD10-AM Code	Description	N	Episodes %	%
F31.9	Bipolar affective disorder, unspecified	464	78.8	3.1
F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms	20	3.4	0.1
F31.8	Other bipolar affective disorders	18	3.1	0.1
F31.3	Bipolar affective disorder, current episode mild or moderate depression	15	2.5	0.1
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms	14	2.4	0.1
F30.0	Hypomania	11	1.9	0.1
F31.0	Bipolar affective disorder, current episode hypomanic	11	1.9	0.1
F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms	10	1.7	0.1
F30.9	Manic episode, unspecified	8	1.4	0.1
F31.6	Bipolar affective disorder, current episode mixed	7	1.2	0.0
F30.8	Other manic episodes			
F30.2	Mania with psychotic symptoms			
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms	11	1.9	0.1
F34.0	Cyclothymia			
F38.0	Other single mood [affective] disorders - mixed affective episode			
Bipolar		**589**	**100.0**	**3.9**
F60.31	Emotionally unstable personality disorder - borderline type	324	62.0	2.1
F60.9	Personality disorder, unspecified	101	19.3	0.7
F60.2	Dissocial personality disorder	22	4.2	0.1
F60.7	Dependent personality disorder	15	2.9	0.1
F60.8	Other specific personality disorders	15	2.9	0.1
F60.30	Emotionally unstable personality disorder - impulsive	7	1.3	0.0
F69	Unspecified disorder of adult personality and behaviour	7	1.3	0.0
F61	Mixed and other personality disorders	6	1.1	0.0
F60.5	Anankastic personality disorder			
F68.8	Other enduring personality changes			
F60.6	Anxious [avoidant] personality disorder			
F63.8	Other habit and impulse disorders			
F60.0	Paranoid personality disorder	26	5.0	0.2
F60.4	Histrionic personality disorder			
F63.9	Habit and impulse disorder, unspecified			
F62.8	Other enduring personality changes			
F63.3	Trichotillomania			
F68.1	Intentional production or feigning of symptoms or disabilities			
Personality disorders		**523**	**100.0**	**3.4**

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ICD10-AM			Episodes	
Code	**Description**	**N**	**N**	**%**
F53.8,9 F	Other, Not specified mental and behavioural disorders associated with the puerperium	216	28.2	1.4
F70-F72	Mild, moderate or severe intellectual disability	140	18.3	0.9
F90-F98	Behavioural disorders	90	11.8	0.6
F50	Eating disorders	84	11.0	0.6
F80-F84	Psycho-developmental disorders	75	9.8	0.5
F44-F48	Neuroses	60	7.8	0.4
F00-F09	Organic disorders	32	4.2	0.2
F51	Nonorganic sleep disorders	22	2.9	0.1
F31.7	Bipolar affective disorder, currently in remission	16	2.1	0.1
F55	Abuse of non-dependence-producing substances	13	1.7	0.1
F33.4	Recurrent depressive disorder, currently in remission	8	1.0	0.1
F34.9	Persistent mood [affective] disorders			
F52.5	Nonorganic vaginismus			
F30.1	Mania without psychotic symptoms	9	1.2	0.1
F54	Psychological or behavioural factors associated with disorders or diseases classified elsewhere			
Other mental health disorders		**765**	**100.0**	**5.0**
Any mental or behavioural disorder				**100.0**

Supplementary tables for Chapter 3

Table A3.1 Admissions for MBD in 2-monthly intervals from 6 months before conception to birthing by diagnosis type, maternities in NSW 2002-2006.

Month	Person-time	Specific MBD			Non-specific MBD			All MBD			
	PY	*N*	*(%)*	*rate (a)*	*N*	*(%)*	*rate (a)*	*N*	*(%)*	*rate (a)*	*(95%CI)*
Pre-pregnancy											
4–5	71,271	762	(92.7)	**10.7**	61	(7.3)	**0.9**	823	(100)	**11.5**	(10.8, 12.3)
2–3	71,271	746	(95.6)	**10.5**	35	(4.4)	**0.5**	781	(100)	**11.0**	(10.1, 11.6)
0–1	71,271	629	(99.5)	**8.8**	3	(0.5)	**0.0**	632	(100)	**8.9**	(8.2, 9.6)
0-5	**213,812**	**2137**	**(95.6)**	**10.0**	**99**	**(4.4)**	**0.5**	**2236**	**(100)**	**10.5**	(10, 10.8)
During pregnancy											
0–1	71,271	492	(91.3)	**6.9**	47	(8.7)	**0.7**	539	(100)	**7.6**	(6.9, 8.2)
2–3	71,271	395	(76.6)	**5.5**	120	(23.4)	**1.7**	515	(100)	**7.2**	(6.5, 7.8)
4–5	71,171	400	(64.7)	**5.6**	217	(35.3)	**3.0**	617	(100)	**8.7**	(8, 9.3)
6–7	70,469	283	(38.4)	**4.0**	448	(61.6)	**6.4**	731	(100)	**10.4**	(9.6, 11.1)
8–9	34,157	121	(8.6)	**3.5**	1237	(91.4)	**36.2**	1358	(100)	**39.8**	(37.1, 41.2)
0-9	318,339	1691	(44.9)	**5.3**	2069	(55.1)	**6.5**	3760	(100)	**11.8**	(11.3, 12.1)

(a) rate per 1,000 person years

A3.2 Admissions for MBD in 2-monthly intervals from 6 months before conception to birthing by maternal parity, maternities in NSW 2002-2006

	Primiparous maternities				Multiparous maternities				All maternities			
Interval (months)	**Person-years**	**Admissions**			**Person-years**	**Admissions**			**Person-years**	**Admissions**		
	PY	N	rate(a)	(95%CI)	PY	N	rate(a)	(95%CI)	PY	N	rate (a)	(95%CI)
Before conception												
5–6 months	29,400	285	9.7	(8.6, 10.8)	41,871	538	12.8	(11.8, 13.9)	71,271	823	11.5	(10.8, 12.3)
3–4 months	29,400	308	10.5	(9.3, 11.6)	41,871	473	11.3	(10.3, 12.3)	71,271	781	11.0	(10.1, 11.6)
1–2 months	29,400	235	8.0	(7, 9)	41,871	397	9.5	(8.6, 10.4)	71,271	632	8.9	(8.2, 9.6)
Total	**88,199**	**828**	**9.4**	**(8.8, 10)**	**125,613**	**1,408**	**11.2**	**(10.6, 11.8)**	**213,812**	**2,236**	**10.5**	**(10, 10.8)**
After conception												
1–2 months	29,400	199	6.8	(5.8, 7.7)	41,871	340	8.1	(7.3, 9)	71,271	539	7.6	(6.9, 8.2)
3–4 months	29,400	163	5.5	(4.7, 6.4)	41,871	352	8.4	(7.5, 9.3)	71,271	515	7.2	(6.5, 7.8)
5–6 months	29,351	205	7.0	(6, 7.9)	41,820	412	9.9	(8.9, 10.8)	71,171	617	8.7	(8, 9.3)
7–8 months	29,013	209	7.2	(6.2, 8.2)	41,456	522	12.6	(11.5, 13.7)	70,469	731	10.4	(9.6, 11.1)
9–10 months	14,097	362	25.7	(23.1, 28.3)	20,060	996	49.7	(46.6, 52.7)	34,157	1358	39.8	(37.1, 41.2)
Total	**131,261**	**1,138**	**8.7**	**(8.2, 9.2)**	**187,078**	**2,622**	**14.0**	**(13.5, 14.5)**	**318,339**	**3,760**	**11.8**	**(11.3, 12.1)**

A3.3a Admission rates (per 1000 person years) for selected classes of mental and behavioural disorders in 2-monthly intervals from 6 months before conception to birthing, primiparous maternities in NSW 2002-2006

	Class of MBD																					
Month	Depression				Anxiety & Adjustment				Schizophrenia				Bipolar				Alcohol disorder				Drug disorder			
	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl
Before conception																								
5 and 6	29	**1.0**	0.6	1.3	48	**1.6**	1.2	2.1	11	**0.4**	0.2	0.6	15	**0.5**	0.3	0.8	33	**1.1**	0.7	1.5	76	**2.6**	2.0	3.2
3 and 4	48	**1.6**	1.2	2.1	29	**1.0**	0.6	1.3	24	**0.8**	0.5	1.1	33	**1.1**	0.7	1.5	25	**0.9**	0.5	1.2	86	**2.9**	2.3	3.5
1 and 2	39	**1.3**	0.9	1.7	39	**1.3**	0.9	1.7	12	**0.4**	0.2	0.6	12	**0.4**	0.2	0.6	21	**0.7**	0.4	1.0	80	**2.7**	2.1	3.3
1 to 6	116	**1.3**	1.1	1.6	116	**1.3**	1.1	1.6	47	**0.5**	0.4	0.7	60	**0.7**	0.5	0.9	79	**0.9**	0.7	1.1	242	**2.7**	2.4	3.1
After conception																								
1 and 2	20	**0.7**	0.4	1.0	29	**1.0**	0.6	1.3	25	**0.9**	0.5	1.2	10	**0.3**	0.1	0.6	19	**0.6**	0.4	0.9	66	**2.2**	1.7	2.8
3 and 4	24	**0.8**	0.5	1.1	26	**0.9**	0.5	1.2	12	**0.4**	0.2	0.6	3	**0.1**	0.0	0.2	7	**0.2**	0.1	0.4	71	**2.4**	1.9	3.0
5 and 6	40	**1.4**	0.9	1.8	35	**1.2**	0.8	1.6	25	**0.9**	0.5	1.2	7	**0.2**	0.1	0.4	14	**0.5**	0.2	0.7	57	**1.9**	1.4	2.4
7 and 8	51	**1.8**	1.3	2.2	48	**1.7**	1.2	2.1	16	**0.6**	0.3	0.8	8	**0.3**	0.1	0.5	2	**0.1**	0.0	0.2	49	**1.7**	1.2	2.2
9 and 10	38	**2.7**	1.8	3.6	84	**6.0**	4.7	7.2	21	**1.5**	0.9	2.1	20	**1.4**	0.8	2.0	8	**0.6**	0.2	1.0	166	**11.8**	10.0	13.6
1 to 10	173	**1.3**	1.1	1.5	222	**1.7**	1.5	1.9	99	**0.8**	0.6	0.9	48	**0.4**	0.3	0.5	50	**0.4**	0.3	0.5	409	**3.1**	2.8	3.4

A3.3b Admission rates (per 1000 person years) for selected classes of mental and behavioural disorders in 2-monthly intervals from 6 months before conception to birthing, multiparous maternities in NSW 2002-2006

	Class of MBD																							
Months	Depression				Anxiety & Adjustment				Schizophrenia				Bipolar				Alcohol disorder				Drug disorder			
	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl	N	rate	lcl	ucl
Before conception																								
5 and 6	109	**2.6**	2.1	3.1	98	**2.3**	1.9	2.8	45	**1.1**	0.8	1.4	31	**0.7**	0.5	1.0	42	**1.0**	0.7	1.3	170	**4.1**	3.5	4.7
3 and 4	99	**2.4**	1.9	2.8	101	**2.4**	1.9	2.9	27	**0.6**	0.4	0.9	20	**0.5**	0.3	0.7	47	**1.1**	0.8	1.4	173	**4.1**	3.5	4.7
1 and 2	88	**2.1**	1.7	2.5	80	**1.9**	1.5	2.3	22	**0.5**	0.3	0.7	15	**0.4**	0.2	0.5	39	**0.9**	0.6	1.2	147	**3.5**	2.9	4.1
1 to 6	296	**2.4**	2.1	2.6	279	**2.2**	2.0	2.5	94	**0.7**	0.6	0.9	66	**0.5**	0.4	0.7	128	**1.0**	0.8	1.2	384	**3.1**	2.8	**3.4**
After conception																								
1 and 2	60	**1.4**	1.1	1.8	75	**1.8**	1.4	2.2	41	**1.0**	0.7	1.3	10	**0.2**	0.1	0.4	45	**1.1**	0.8	1.4	128	**3.1**	2.5	3.6
3 and 4	86	**2.1**	1.6	2.5	74	**1.8**	1.4	2.2	52	**1.2**	0.9	1.6	5	**0.1**	0.0	0.2	20	**0.5**	0.3	0.7	111	**2.7**	2.2	3.1
5 and 6	82	**2.0**	1.5	2.4	98	**2.3**	1.9	2.8	50	**1.2**	0.9	1.5	20	**0.5**	0.3	0.7	22	**0.5**	0.3	0.7	134	**3.2**	2.7	3.7
7 and 8	108	**2.6**	2.1	3.1	91	**2.2**	1.7	2.6	46	**1.1**	0.8	1.4	18	**0.4**	0.2	0.6	28	**0.7**	0.4	0.9	226	**5.5**	4.7	6.2
9 and 10	122	**6.1**	5.0	7.2	115	**5.7**	4.7	6.8	43	**2.1**	1.5	2.8	22	**1.1**	0.6	1.6	26	**1.3**	0.8	1.8	647	**32.3**	29.8	34.7
1 to 10	458	**2.4**	2.2	2.7	453	**2.4**	2.2	2.6	232	**1.2**	1.1	1.4	75	**0.4**	0.3	0.5	141	**0.8**	0.6	0.9	1,246	**6.7**	6.3	**7**.0

Supplementary tables for Chapter 4

Table A4.1: Comorbidity by MBD diagnostic group, maternities in NSW 2002-2006

		Comorbid diagnosis				
Diagnostic group (N)	**None**	**DA**	**MD**	**DA&MD**	**Any**	**Total**
			% of maternities			
Alcohol (726)	48.6	24.7	11.7	15.0	51.4	100.0
Cannabis (2,371)	60.0	23.2	8.6	8.2	40.0	100.0
Opiate (1,960)	63.9	24.4	4.5	7.2	36.1	100.0
Stimulant (667)	32.2	44.5	4.6	18.6	67.8	100.0
Sedative (188)	8.5	44.7	11.7	35.1	91.5	100.0
Polydrug (251)	27.5	34.7	11.2	26.7	72.5	100.0
Other drug (403)	5.7	55.6	16.4	22.3	94.3	100.0
Schizophrenia (431)	45.2	19.5	19.5	15.8	54.8	100.0
Psychosis (81)	22.2	6.2	39.5	32.1	77.8	100.0
Bipolar (392)	58.2	12.0	19.4	10.5	41.8	100.0
Depression (3,031)	75.1	9.0	12.2	3.8	24.9	100.0
Anxiety (1,918)	77.4	5.0	15.1	2.6	22.6	100.0
Adjustment (533)	48.8	9.8	27.8	13.7	51.2	100.0
Personality (312)	18.6	10.3	38.8	32.4	81.4	100.0
Other MD (424)	56.8	9.7	25.0	8.5	43.2	100.0
			Prevalence among maternities (‰)			
Alcohol	0.83	0.42	0.20	0.25	0.9	1.70
Cannabis	3.33	1.28	0.48	0.45	2.2	5.54
Opiate	2.93	1.12	0.21	0.33	1.7	4.58
Stimulant	0.50	0.69	0.07	0.29	1.1	1.56
Sedative	0.04	0.20	0.05	0.15	0.4	0.44
Polydrug	0.16	0.20	0.07	0.16	0.4	0.59
Other drug	0.05	0.52	0.15	0.21	0.9	0.94
Schizophrenia	0.46	0.20	0.20	0.16	0.6	1.01
Psychosis	0.04	0.01	0.07	0.06	0.1	0.19
Bipolar	0.53	0.11	0.18	0.10	0.4	0.92
Depression	5.30	0.64	0.85	0.29	1.78	7.09
Anxiety	3.47	0.22	0.68	0.11	1.0	4.49
Adjustment	0.61	0.12	0.35	0.17	0.6	1.25
Personality	0.14	0.07	0.28	0.24	0.6	0.73
Other MD	0.56	0.10	0.25	0.08	0.4	0.99

Abbreviations: DA drug/alcohol disorder alone; MD mental disorder alone; DA&MD both disorders;