Explaining risk for suicide-related behaviour in adolescent offspring of mothers with depression

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Declarations and statements

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This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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Papers resulting from work within the current thesis

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Additional related papers to which I have contributed

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Abbreviations

ADHD – Attention Deficit Hyperactivity Disorder

ALSPAC –Avon Longitudinal Study of Parents and Children

CFI - Comparative Fit Index

CI – Confidence Interval

DAWBA – Development and Well-Being Assessment

DBD – Disruptive Behaviour Disorder

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

EPDS – Edinburgh Postnatal Depression Scale

FIML – Full Information Maximum Likelihood

FMI – Fraction of Missing Information

GAD – Generalised Anxiety Disorder

GWAS – Genome Wide Association Study

ICD-10 – International Classification of Diseases, Tenth Revision

LCGA – Latent Class Growth Analysis

LMR-LRT – Lo, Mendell & Rubin Likelihood Ratio Test

MAR – Missing At Random

MICE – Multivariate Imputation by Chained Equations

MDD – Major Depressive Disorder

OADP – Oregon Adolescent Depression Project

ODD – Oppositional Defiant Disorder

OR – Odds Ratio

PAR – Population Attributable Risk

RCT – Randomised Controlled Trial

RMSEA – Root-Mean Square Error of Approximation

SEM – Structural Equation Modelling

SSABIC – Sample Size Adjusted Bayesian Information Criterion

WLSMV –Weighted Least Squares Means and Variance Adjusted estimation

YAM – Youth Aware of Mental health programme

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Summary

Background: There is evidence to suggest that maternal depression is associated with suicide-related behaviour in offspring; however pathways contributing to risk remain unclear. The aim of this thesis was to investigate mechanisms of the association between maternal depression and offspring suicidal ideation and attempt in a general population sample.

Methods: Data were utilised from a population-based birth cohort, the Avon Longitudinal Study of Parents and Children. Maternal depression symptoms were assessed on 10 occasions from pregnancy to child age 11 years. Offspring suicide-related behaviour was assessed at age 16 years. Latent class growth analysis was used to derive trajectories of maternal depression symptoms. Pathways mediating risk between maternal depression and offspring suicide-related behaviour were then examined using structural equation modelling.

Results: Five distinct classes of maternal depression symptoms were identified (minimal, mild, increasing, sub-threshold, chronic-severe). Compared to offspring of mothers with *minimal* symptoms, the greatest risk of suicidal ideation was found for offspring of mothers with *chronic-severe* symptoms [OR 3.04 (95% CI 2.19, 4.21)], with evidence for smaller increases in risk for offspring of mothers with *sub-threshold, increasing* and *mild* symptoms. The pattern of findings was similar when examining risk for offspring suicide attempt. The majority of the association between maternal *chronic-severe* depression and offspring suicidal ideation was explained through maternal suicide attempt and offspring psychopathology. However, there was also evidence for indirect effects via both the parent-child relationship and peer victimisation.

Conclusion: Findings from this thesis highlight that risk for suicide-related behaviour should be considered in offspring of mothers with sustained depression symptoms, even when symptoms are below clinical levels. Suicide prevention efforts in offspring of depressed mothers should be targeted at offspring with psychopathology and offspring whose mothers have made a suicide attempt. Interventions aimed at improving the parent-child relationship, or reducing peer victimisation may also be beneficial.

Chapter 1: Introduction

Suicide is the second leading cause of death among adolescents and young adults worldwide, and prevention of youth suicide is a major public health priority (National Action Alliance for Suicide Prevention, 2014; World Health Organization, 2014). Given that suicidal ideation and behaviour often precede suicide (Beck, Brown, Steer, Dahlsgaard, & Grisham, 1999; Brown, Beck, Steer, & Grisham, 2000; Prinstein et al., 2008), understanding risk factors for suicide-related behaviour is important for suicide prevention strategies (Lewinsohn, Rohde, & Seeley, 1996). For the purposes of this thesis the term 'suicide-related behaviour' encompasses suicidal ideation, suicide plans and attempts but does not include self-harm without suicidal intent. The offspring of mothers with depression are known to be at increased risk for suicide-related behaviour, however the mechanisms remain unclear. Therefore, this thesis examines potential mechanisms of the association between maternal depression and subsequent offspring suicide-related behaviour using a general population sample. The introductory chapter will first provide a definition of suicide-related behaviour and outline important considerations when assessing suicide-related behaviour in adolescents. The epidemiology and developmental course of adolescent suicide-related behaviour will be described next, including a brief summary of existing literature and recommendations for treatment and prevention. The second part of the introductory chapter will focus on intergenerational transmission. Recent literature investigating the transmission of suicide-related behaviour from mothers to offspring will first be reviewed, followed by a more detailed discussion of key studies that have examined the association between maternal depression and offspring suicide-related behaviour. The focus of this thesis is on the impact of maternal rather than paternal depression partly due to the quality of data available, but also because, in general, evidence from previous literature is stronger for the association between maternal depression and offspring suicide-related behaviour compared to paternal depression. In the final section, possible casual and non-causal explanations for the association between maternal depression and offspring suicide-related behaviour will be considered. The chapter will end with specific aims and rationale for the present thesis.

1.1: Suicide-related behaviour in adolescence

1.1.1: Definition and assessment

There is a difficulty in conceptualising suicidal ideation and behaviour, and research in this area suffers from the problem of inconsistent nomenclature. Suicide-related ideation can range from thoughts of death to persistent preoccupation with killing oneself and studies have used a wide range of measures including both categorical and dimensional definitions. In addition, multiple terms are used to refer to the same behaviour. This can lead to problems such as limited comparability of findings across studies; therefore the use of standardised terms and clear operational definitions are important (Posner, Oquendo, Gould, Stanley, & Davies, 2007). A

standardised nomenclature has been described by Silverman and colleagues (2007). Silverman and colleagues refer to suicide-related thoughts and behaviours as consisting of ideations (i.e. suicidal thoughts), communications (i.e. suicide threats and plans) and behaviours (i.e. suicide attempt and suicide). Each of the criteria is defined on the basis of the presence or absence of suicidal intent (with presence of suicidal intent meaning the aim, purpose or goal of the behaviour is to die). Suicidal behaviours are also defined by the presence or absence of injury. Therefore a suicide attempt is defined as "a self-inflicted, potentially injurious behaviour with a non-fatal outcome for which there is evidence (either explicit or implicit) of intent to die" (Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007). Definitions for all suicide-related terminology used throughout this thesis are given in Table 1.1, with the main terms used in analyses highlighted in bold.

Table 1.1 – Definitions for suicide-related terminology used throughout this thesis

Term	Definition
Suicide-related ideation	Thoughts of death with or without suicidal intent
Suicidal ideation	**Thoughts specifically about killing oneself by whatever means or wishing to be dead**
Suicide plan	A proposed method for acting on suicidal thoughts that will lead to a potentially self-injurious outcome
Suicide attempt	**Self-inflicted, potentially injurious behaviour with a non-fatal outcome including some intention to die at the time of the attempt**
Suicide	Self-inflicted death with suicidal intent
Suicidal behaviour	Suicide attempt or suicide
Suicide-related behaviour	Suicidal ideation, suicide plan or suicide attempt
Self-harm	Self-inflicted, potentially injurious behaviour (with or without suicidal intent)

Lack of comparability across studies, especially regarding the prevalence of suicide-related behaviour is also likely due to different approaches toward the assessment of suicide-related behaviour in adolescents (Burless & De Leo, 2001; Klimes-Dougan, 1998). Differences may depend on the reporter (i.e. self-report or parent-report), the measure used (i.e. interview or questionnaire measure), the question wording and amount of retrospection required (i.e. lifetime or past year) and the type of sample (i.e. community, clinical or accident and emergency admission). Evidence relating to each of these will be discussed briefly below.

Although the importance of multiple informants has been highlighted (Klimes-Dougan, 1998), clinical, high-risk and community studies have all shown that using parent-reports to assess suicide-related behaviour in offspring may miss children at risk and therefore the child-report is considered to be the single most important source of information (Breton, Tousignant, Bergeron, & Berthiaume, 2002; Hammerton, Zammit, Potter, Thapar, & Collishaw, 2014; Klaus, Mobilio, & King, 2009; Klimes-Dougan, 1998; Prinstein, Nock, Spirito, & Grapentine, 2001). Additionally, agreement across different measures (such as self-report questionnaire, psychiatric interview and clinician interview) has been found to be low (Bjärehed, Pettersson, Wangby-Lundh, & Lundh, 2012; Breton et al., 2002; Ougrin & Boege, 2013; Prinstein et al., 2001), supporting the use of multiple measurement approaches. When this is not possible, it has been found that adolescents are more likely to disclose suicide-related behaviour with the anonymity of self-report questionnaire rather than in face-to-face interview (Breton et al., 2002; Klimes-Dougan, 1998; Prinstein et al., 2001). However, it is important to note that it is unclear which method of assessment is more accurate, for example, although adolescents may report more openly when a questionnaire measure is used rather than an interview, they may also be more likely to misinterpret the questions (Safer, 1997; Velting, Rathus, & Asnis, 1998). It is important for studies to clearly define what is meant by suicidal ideation and suicide attempt, and include questions on the level of severity and degree of suicidal intent (Burless & De Leo, 2001; Silverman et al., 2007), especially in terms of distinguishing self-harm with and without suicidal intent (Burless & De Leo, 2001; Mars, Heron, Crane, Hawton, Kidger, et al., 2014). In a recent study using the same community sample that is utilised in this thesis (the Avon Longitudinal Study of Parents and Children; ALSPAC), risk factors were examined for adolescent self-harm with and without suicidal intent. The study found that the prevalence of self-harm without suicide intent was higher (11.9%) than for self-harm with suicidal intent (6.8%), and both common and unique risk factors were identified showing the importance of accurately assessing whether or not suicidal intent is present (Mars, Heron, Crane, Hawton, Kidger, et al., 2014).

Studies have also shown more accurate reporting of suicide-related behaviour in adolescents when shorter time spans were used, thereby decreasing the amount of retrospection required. For example, a prospective, longitudinal study of offspring of depressed and well mothers found that lifetime reports underestimated the prevalence of suicide-related behaviour compared to repeated assessment every three years, especially in younger children (Klimes-Dougan, 1998). In addition, it has been recommended that the time span used be made clear and kept consistent across studies to allow comparison of findings, therefore either lifetime or 1-year prevalence should be used (Burless & De Leo, 2001). Finally, the sample utilised to assess suicide-related behaviour will likely impact on the prevalence reported. It has been found that 50% to 80% of suicide attempters do not present to medical health care services (Burless & De Leo, 2001), and

a third of young people with suicidal ideation or self-harm and a psychiatric disorder do not present to specialist services, even when their parents are known to services (Potter et al., 2012). Additionally, only one in eight adolescents who self-harm present to hospitals, meaning that self-harm is mostly hidden at the community level (Hawton, Rodham, Evans, & Weatherall, 2002). Another study using the ALSPAC sample also found that only a third of adolescents that reported self-harming with a desire to die had subsequently sought medical help (Kidger, Heron, Lewis, Evans, & Gunnell, 2012). It is likely that prevalence of suicide-related behaviour based on samples of hospitalised adolescents will not only be underestimated, but will also provide a biased sample given that medically treated cases are non-random (Goldman-Mellor et al., 2013). Therefore, it is essential to investigate suicide-related behaviour in community samples. The accurate assessment of suicide-related behaviour in adolescents is crucial, both clinically and in research studies, in order to identify risk factors for suicide-related behaviour and correctly identify those most at risk for targeted prevention and intervention.

1.1.2: Relationship between suicidal thoughts, attempts and suicide

Previous studies have reported evidence for treating suicide-related behaviour on a continuum, with passive thoughts of death and suicide being extremes on a spectrum of risk (Brent et al., 1988; Lewinsohn et al., 1996). This evidence comes, in part, from studies showing a greater burden of the same risk factors in those that have made a suicide attempt compared to those that report suicidal ideation (Fergusson & Lynskey, 1995), and in those that have died by suicide compared to those that have made an attempt (Brent et al., 1988). Other studies provide support for the dimensional model of suicide-related behaviour by reporting strong associations between suicidal ideation, suicide attempt and suicide. Previous self-harm has been shown to be one of the strongest risk factors for adolescent suicide, both in prospective samples (Hawton & Harriss, 2007; Kotila & Lonnqvist, 1989) and case-control autopsy studies (Brent, Baugher, Bridge, Chen, & Chiappetta, 1999; Shaffer et al., 1996) with studies showing a 10-60 fold increase in suicide risk compared with the general population (Bridge, Goldstein, & Brent, 2006). Additionally, a recent meta-analysis found that hospital attendance for self-harm increased risk for suicide in the next 5 years by 3.9% (equating to approximately 1 in 25 self-harm patients dying by suicide in the 5 years after hospital presentation) (Carroll, Metcalfe, & Gunnell, 2014). It was also found that the risk was greater for males, older patients and those using methods other than self-poisoning (Carroll et al., 2014). Studies that have focused specifically on young people have also highlighted the importance of male gender and self-harm method in increasing suicide risk. In a study examining self-harm hospital presentations in children and adolescents in the UK, the risk of later suicide was greater for those who presented with self-cutting compared to self-poisoning. Suicide risk was also associated with male gender, history of psychiatric treatment and history of self-harm (Hawton et al., 2012). Results were similar in a recent population-based cohort study using multiple linked health-care databases in Canada to

specifically examine the suicide risk associated with non-fatal self-poisoning in adolescence (Finkelstein et al., 2015). This study found that non-fatal self-poisoning in adolescence was associated with a 30-fold increased risk of suicide one year later; additionally most suicides occurred several years after the first hospital visit for self-poisoning (Finkelstein et al., 2015). Again, factors associated with suicide after self-poisoning were male gender, recurrent self-poisoning and psychiatric care in the previous year (Finkelstein et al., 2015).

Studies have also reported strong associations between suicidal ideation and future suicide attempt. A recent national survey of adolescents in the United States (US) found that approximately one third of adolescents with suicidal ideation went on to make an attempt, with the vast majority (86%) of these attempts occurring within one year of the onset of suicidal ideation (Nock et al., 2013). Additionally, in a prospective, community sample of adolescents (Reinherz, Tanner, Berger, Beardslee, & Fitzmaurice, 2006), it was found that those who reported thoughts about killing themselves at age 15 years were nearly 12 times more likely to have made a suicide attempt by age 30 years. Prospective studies of adult psychiatric outpatients have also shown strong associations between suicidal ideation and suicide (Beck et al., 1999; Brown et al., 2000). Several factors have been shown to strengthen the association between ideation and attempt in adolescents including the severity, frequency and pervasiveness of the ideation (Kessler, Borges, & Walters, 1999; Miranda, Ortin, Scott, & Shaffer, 2014) and the combination of suicidal ideation and self-harm without suicidal intent (Scott, Pilkonis, Hipwell, Keenan, & Stepp, 2014). This evidence indicates that the early detection and prevention of suicidal ideation in adolescents is important for suicide prevention strategies.

However, not all people with suicidal ideation attempt suicide and most attempters do not die by suicide. Different risk factors may predict ideation, escalation from ideation to attempt, and escalation from attempts to suicide, despite strong links between these aspects of suicide-related behaviour. Therefore, not differentiating between different types of suicidal behaviour could be problematic as preventative methods may be different for different subtypes of suicide-related behaviour (Bursztein & Apter, 2009). In addition, for milder forms of ideation without suicidal intent, such as thoughts of death or life not being worth living, the level of risk for the development of more serious forms of suicide-related behaviour is unclear. Some studies that have investigated items relating to these milder forms of suicide-related ideation, found higher rates of each item in adolescents that had made a suicide attempt than in those that reported self-harm without suicidal intent or no self-harm (Kidger et al., 2012; Larsson & Sund, 2008; Roberts, Roberts, & Chen, 1998). For example, using the same sample as this thesis, Kidger and colleagues (2012) found that adolescents who had self-harmed with a desire to die were more likely to report that they felt life was not worth living and they wished they were dead, compared to adolescents that reported self-harm without suicidal intent and those that did not report self-harm. However, it is important to note that in these studies the direction of effects is

not clear and it could be that adolescents that have made a suicide attempt are more likely to experience suicide-related ideation following the attempt than those who reported self-harm without suicidal intent or have not self-harmed. Other studies have shown the predictive validity of scales of suicide-related ideation in adolescents, predicting both clinically validated suicidal ideation (Hammerton et al., 2014) and suicide attempt (Huth-Bocks, Kerr, Ivey, Kramer, & King, 2007; Larzelere, Smith, Batenhorst, & Kelly, 1996; Shaffer et al., 2004). Additionally, in a sample of adult psychiatric outpatients, it was found that passive thoughts of wanting to be dead increased risk for later suicide (Brown, Steer, Henriques, & Beck, 2005). However, others believe that these milder suicidal thoughts are, in part, normative behaviour, with many adolescents experiencing some form of suicide-related ideation which would be unlikely to turn into something more serious (Dhossche, Ferdinand, Van Der Ende, Hofstra, & Verhulst, 2002; Marcenko, Fishman, & Friedman, 1999).

1.1.3: Epidemiology and developmental course

In the United Kingdom (UK) in 2012, suicide rates in 15-29 year olds were 9.1 and 2.5 per 100,000 in males and females respectively (World Health Organization, 2014) although this is likely to be an underestimate, given problems with misclassification of suicide in young people (Hawton, Saunders, & O'Connor, 2012). The most common suicide methods used worldwide are self-poisoning with pesticides, hanging and jumping (Gunnell, Eddleston, Phillips, & Konradsen, 2007; World Health Organization, 2014). In the US, firearms is one of the most common suicide methods; whereas in the UK, self-poisoning, often using paracetamol, is a common method (Bridge, Goldstein, & Brent, 2006; Hawton et al., 2012; World Health Organization, 2014). Recent trends have shown increases in more novel methods of suicide, such as increases in helium inhalation as a method of suicide in England and Wales (Gunnell et al., 2015); however, these methods currently only account for a small proportion of total suicides (Gunnell et al., 2015).

In a recent report by the Centers for Disease Control and Prevention, it was shown that in the US, there are 25 suicide attempts for every suicide (Crosby, Ortega, & Melanson, 2011). In community studies of adolescents and young adults across the US, Europe and New Zealand, the lifetime prevalence of suicide attempt has been found to range from 1% to 11% (Carli et al., 2014; Evans, Hawton, Rodham, & Deeks, 2005; Fergusson, Horwood, Ridder, & Beautrais, 2005; Goldman-Mellor et al., 2013; Kokkevi, Rotsika, Arapaki, & Richardson, 2012; McLoughlin, Gould, & Malone, 2015; Nock et al., 2013; Plener, Libal, Keller, Fegert, & Muehlenkamp, 2009) and the lifetime prevalence for suicidal ideation ranges from 10% to 40% (Bridge et al., 2006; Evans et al., 2005; Fergusson et al., 2005; Kidger et al., 2012; McLoughlin et al., 2015; Nock et al., 2013; Plener et al., 2009). Table 1.2 shows the prevalence reported for both suicidal ideation and suicide attempt in recent key community studies across Europe, the US and New Zealand. As mentioned previously, community studies are essential when

estimating the prevalence of suicide-related behaviour due to the large numbers of adolescents not seeking services (Burless & De Leo, 2001; Hawton et al., 2012; Kidger et al., 2012; Lahti, Harju, Hakko, Riala, & Räsänen, 2014; Potter et al., 2012).

Table 1.2 – Prevalence of lifetime self-reported suicidal ideation and suicide attempt in adolescents and young adults in key community studies

Study	Sample size	Age range	Question	Country	Rate
(Fergusson et al., 2005)	1,265	18 years	Suicidal ideation: Has ever thought of killing self Suicide attempt: Has made an attempt to kill self	New Zealand	Suicidal ideation (but no suicide attempt): 17.2% Suicide attempt: 5.4%
(Plener et al., 2009)	665	14-17 years	Suicidal ideation: Has ever talked or thought about committing suicide Suicide attempt: Has ever attempted suicide	Germany	Suicidal ideation: 36.4% Suicide attempt: 6.5%
(Kokkevi et al., 2012)	45,806	15-16 years	Self-harm thoughts: Has ever thought of harming self Suicide attempt: Has ever attempted suicide	17 European countries	Self-harm thoughts (median): 30.8% Suicide attempt (median): 10.5%
(Kidger et al., 2012)	4,810	16-17 years	Suicidal ideation: Has ever thought of killing self Suicide attempt: Ever seriously wanted to kill self during self-harm act	UK	Suicidal ideation: 15.8% Suicide attempt: 5.7%
(Nock et al., 2013)	6,483	13-18 years	Suicidal ideation: Has seriously thought about committing suicide Suicide attempt: Has attempted suicide	US	Suicidal ideation: 12.1% Suicide attempt: 4.1%
(Goldman-Mellor et al., 2013)	1,037	24 years	Suicide attempt: Reports of cutting or stabbing oneself, overdosing on pills, taking poison, attempting to gas oneself, attempting to hang or strangle oneself, attempting to shoot oneself, attempting to drown, jumping from a high place, crashing a car or motorcycle on purpose, burning oneself, or other method, accompanied by self-reported intent to die	New Zealand	Suicide attempt: 8.8%
(Carli et al., 2014)	5,350	15 years	Suicide attempt: Lifetime history of suicide attempt	11 European countries	Suicide attempt: 3.9%

An increase in prevalence is seen in the transition from childhood to adolescence for suicidal ideation and suicide attempt (Andrus et al., 1991; Fergusson & Lynskey, 1995; Gould, Greenberg, Velting, & Shaffer, 2003; Hawton et al., 2007; Lewinsohn et al., 1996; Nock et al., 2013; Perry et al., 2012), highlighting that adolescence is a particularly important time for suicide prevention strategies. Suicide before the age of 15 is extremely rare (Bertolote & Fleischmann, 2002; Klomek, Krispin, & Apter, 2009). Figure 1.1 shows the lifetime rates of suicide-related ideation (including thoughts of death, wishing to be dead, suicidal ideation or suicide plan) for young people in the Oregon Adolescent Depression Project (OADP), a representative sample of 1,709 high school students aged 14-18 years who completed a diagnostic interview containing questions about suicide-related ideation (Lewinsohn et al., 1996).

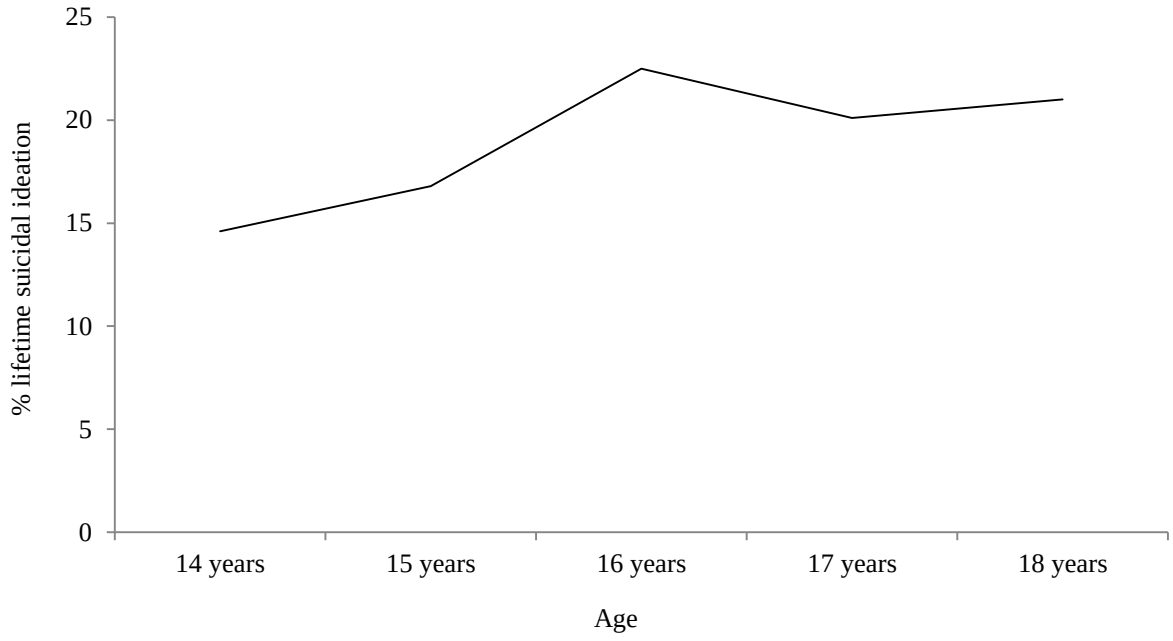


Figure 1.1 - Percentage of high school students in the Oregon Adolescent Depression Project (OADP) aged 14-18 years that reported lifetime suicide-related ideation; percentages taken from Lewinsohn et al., 1996

There are a number of factors that likely contribute to the peak in suicide-related behaviour in adolescence, including the increase in psychopathology from childhood to adolescence (Brent et al., 1999; Costello, Copeland, & Angold, 2011; Shaffer et al., 1996), paralleled by less support and more autonomy from parents (Brent et al., 1999; Bridge et al., 2006). It may be that the increase in suicide-related behaviour is more closely related to pubertal stage rather than chronological age, with puberty reflecting a time of neurodevelopmental vulnerability (Hawton et al., 2012). Suicide-related behaviour is also thought to be more common in adolescents than adults (Hawton et al., 2007; Kessler et al., 1999; Lewinsohn et al., 1996; Moran et al., 2012; Nock, Hwang, Sampson, & Kessler, 2011; Perry et al., 2012); however, the decline in suicide

attempts by young adulthood does not seem to be accounted for by a parallel decrease in depression (Lewinsohn, Rohde, Seeley, & Baldwin, 2001). This is in contrast to the pattern for suicide. Despite suicide being one of the leading causes of death in young people, suicide rates do not peak in adolescence; rather, in the UK, highest rates are found in middle-aged men (World Health Organization, 2014).

The increase in suicide-related behaviour from childhood to adolescence is more pronounced in females (Garrison, Addy, Jackson, McKeown, & Waller, 1991; Hawton et al., 2003; Hawton et al., 2007; Lewinsohn et al., 2001; Lewinsohn et al., 1996; Nolen-Hoeksema & Girgus, 1994) with rates of suicide attempt being 2-3 times higher for female compared to male adolescents (Lewinsohn et al., 1996). The higher rate of female suicide-related behaviour could be due to a higher prevalence of depression in females. However, it has been found that when depression level is controlled, adolescent females are still at greater risk of suicidal ideation implying that female gender increases risk for suicidal ideation independently from depression (Allison, Roeger, Martin, & Keeves, 2001). Conversely, the pattern of gender differences is reversed for suicide with higher rates in males compared to females (Gunnell & Lewis, 2005; Lahti et al., 2014; Park, 2015; Wasserman, Cheng, & Jiang, 2005). This pattern is seen across North America, Western Europe, Australia and New Zealand with rates being up to five times higher in adolescent males compared to females (Gunnell & Lewis, 2005; Lahti et al., 2014; Park, 2015; Wasserman et al., 2005). It is likely that there are several factors contributing to this gender disparity including psychopathological factors (for example, males tend to show greater aggression and are more likely to have comorbid mood and alcohol disorders increasing risk for suicide), gender-related method preferences (for example, more violent methods being used by males), gender differences in help-seeking (with males often less likely to ask for help) and the gender dependent variation in reporting of suicide (with a possible underreporting of suicide in females due to differences in methods used and cultural factors) (Brent et al., 1999; Gould et al., 2003; Gunnell & Lewis, 2005; Lahti et al., 2014; Lewinsohn et al., 2001; McLoughlin et al., 2015; Park, 2015; Schrijvers, Bollen, & Sabbe, 2012; Shaffer et al., 1996).

Both community and clinical samples have shown a high risk for repetition of suicide attempts (Beghi & Rosenbaum, 2010; Borges et al., 2006; Goldman-Mellor et al., 2013; Goldston et al., 2015; Lahti et al., 2014; Lewinsohn et al., 2001; Mars, Heron, Crane, Hawton, Lewis, et al., 2014; Winsper, Lereya, Zanarini, & Wolke, 2012). Recurrence of suicide attempt has been shown to be stronger in female compared to male adolescents (Lahti et al., 2014; Lewinsohn et al., 2001). In a recent sample of 180 adolescents followed up after psychiatric hospitalisation, Goldston and colleagues (2015) found evidence for escalation of recurrent suicide attempts, with decreasing time between attempts and increasing suicidal intent. The risk of negative outcomes in adulthood following adolescent suicide-related behaviour is also well established (Fergusson et al., 2005; Goldman-Mellor et al., 2013; Herba, Ferdinand, van der Ende, &

Verhulst, 2007; Mars, Heron, Crane, Hawton, Lewis, et al., 2014; Reinherz et al., 2006). Prospective, longitudinal community samples have shown negative consequences in adulthood of both childhood (Herba et al., 2007) and adolescent suicidal ideation (Reinherz et al., 2006) including psychiatric disorder, suicide-related behaviour, poorer functioning and lower socio-economic status. Additionally, a recent study using the ALSPAC sample found that adolescents who self-harmed with and without suicidal intent were at increased risk of future self-harm, psychiatric disorder and substance misuse in early adulthood (Mars, Heron, Crane, Hawton, Lewis, et al., 2014). In another prospective study using a birth cohort from New Zealand, self-reported suicide attempt by age 24 years was associated with mental and physical health problems, recurrent suicide attempts, more violence and self-reported loneliness in adulthood (Goldman-Mellor et al., 2013). These associations were not accounted for by earlier psychiatric disorder or social class. These studies, and evidence cited in Section 1.1.2 reporting strong associations between suicidal ideation, suicide attempt and later suicide, again highlight the importance of identifying at-risk adolescents early and reducing the risk of making a first attempt, not only for the individual but also to prevent costly health and social problems in later life (Goldston et al., 2015). Current evidence for the treatment and prevention of adolescent suicide-related behaviour is discussed next.

1.1.4: Treatment and prevention

Few interventions currently exist for adolescent suicide-related behaviour and the majority of existing randomised controlled trials (RCTs) lack power to detect effects as outcomes are uncommon, especially for suicide attempt and suicide (Asarnow & Miranda, 2014; Brent et al., 2013; Hawton et al., 2012; Ougrin, Tranah, Stahl, Moran, & Asarnow, 2015; Robinson, Hetrick, & Martin, 2011). In addition, inconsistent terminology is often used making it difficult to draw comparisons across studies. A recent meta-analysis of 19 RCTs reporting effects of therapeutic interventions on reducing self-harm with and without suicidal intent in adolescents found effects of dialectic behaviour therapy, cognitive-behavioural therapy and mentalisation-based therapy on self-harm when considered broadly. However, there was no evidence that any of the interventions specifically reduced suicide attempts (Ougrin et al., 2015). These findings could be due to low power when examining suicide attempts separately or could reflect important differences in treatment response for self-harm with and without suicidal intent (Ougrin et al., 2015). However, there is some evidence for effectiveness of therapeutic interventions in reducing suicide attempts in adults (Bateman & Fonagy, 2009; Brown, Henriques, Xie, Hollander, & Beck, 2005; Linehan et al., 2006) indicating that failure to find effects in adolescents could be due to lack of power. Another review of RCTs aiming to reduce suicidal ideation or the recurrence of suicide attempts or self-harm in adolescents (Brent et al., 2013) found that successful interventions tended to have a focus on family interactions (such as attachment based family therapy; (Diamond et al., 2010)). It is important to note, however, that

the majority of RCTs typically use clinical samples, meaning that results may differ for adolescents not seeking treatment.

There is evidence that public health interventions that restrict access to, and lethality of, means for suicide, such as limiting access to firearms and pesticides, changing packaging regulations for medication such as paracetamol and detoxification of gas supplies, are important for reducing suicide rates in both adolescents and adults (Collishaw, 2015; Gunnell, Murray, & Hawton, 2000; Gunnell, Middleton, & Frankel, 2000; Gunnell, Eddleston, Phillips, & Konradsen, 2007; Hawton et al., 2012; Mann, Haas, Mehlum, & Phillips, 2005; Miller, Barber, White, & Azrael, 2013; Sarchiapone, Mandelli, Iosue, Andrisano, & Roy, 2011; World Health Organization, 2014). Additionally, some success has come from universal suicide prevention intervention in schools including screening for suicide risk, gatekeeper training (i.e. educating adults working closely with school children to identify those at high risk for suicide and refer them to a mental health professional if necessary) and whole school programmes (Asarnow & Miranda, 2014; Aseltine, James, Schilling, & Glanovsky, 2007; Cusimano & Sameem, 2011; Hawton et al., 2012; Robinson et al., 2013; Wasserman et al., 2015; Wilcox et al., 2008; Wyman, 2014). A recent multicentre cluster-randomised controlled trial, the Saving and Empowering Young Lives in Europe (SEYLE) study, found that the Youth Aware of Mental Health Programme (YAM), which aims to build pupils' skills in self-identification and coping, was associated with a reduction in risk of both suicide attempt and severe suicidal ideation at 1 year follow-up (Wasserman et al., 2015). Within the YAM group, 0.75% reported suicidal ideation, compared to 1.37% of the control group. The pattern of findings was similar for suicide attempt. Although this study is one of the largest of its kind, the absolute reduction of risk for YAM on suicidal ideation and attempts combined was only 1%, highlighting the difficulty in preventing adolescent suicide-related behaviour (Brent & Brown, 2015). Additionally, those with a history of suicide attempt at baseline were excluded from the trial, therefore it is unclear whether the programme would have similar effects amongst those at high risk (Brent & Brown, 2015). There has also been a recent increase in computerised cognitive behavioural interventions specifically aimed at reducing suicidal thoughts, and these have shown some success in adults (van Spijker, van Straten, & Kerkhof, 2015). Given that there are multiple pathways to suicide, the recent report by the World Health Organisation (2014) highlighted the importance of multicomponent interventions for suicide-related behaviour.

1.1.5: Summary

Suicide-related behaviour is common in adolescence and can have severe and long lasting consequences into adulthood including increased risk of suicide. Therefore the early detection and prevention of adolescent suicide-related behaviour is a public health priority. Given that a large proportion of adolescents with suicide-related behaviour do not access services,

identifying those most at risk in community samples is essential. Identifying key risk factors for adolescent suicide-related behaviour will highlight those most at risk to target for early intervention and prevention. The next section will discuss literature examining the impact of both maternal suicidal behaviour and maternal depression on offspring suicide-related behaviour.

1.2: Patterns of intergenerational transmission

1.2.1: Maternal suicidal behaviour

There is strong evidence from family, twin and adoption studies for the familial transmission of both suicide attempt and suicide (Brent & Mann, 2005; Brent & Melhem, 2008; Brent et al., 2014; Petersen, Sørensen, Andersen, Mortensen, & Hawton, 2013; Petersen, Sørensen, Kragh Andersen, Bo Mortensen, & Hawton, 2014; von Borczyskowski, Lindblad, Vinnerljung, Reintjes, & Hjern, 2011). A recent meta-analysis of 14 studies reported nearly a 4-fold greater risk of suicide attempt in offspring of parents that had made a suicide attempt compared with the offspring of parents that had not made a suicide attempt (Geulayov, Gunnell, Holmen, & Metcalfe, 2012). It is thought that both suicide attempt and suicide form part of the clinical phenotype that is transmitted (Brent, Bridge, Johnson, & Connolly, 1996; Brent & Melhem, 2008); however there is less evidence for the familial transmission of suicidal ideation especially after adjusting for psychiatric disorder (Brent et al., 1996; Brent & Melhem, 2008; Lieb, Bronisch, Hofler, Schreier, & Wittchen, 2005; Zalsman, Levy, & Shoval, 2008).

Both twin and adoption studies provide support for a strong role of genetic factors in explaining the familial transmission of both suicide attempt (Petersen et al., 2014) and suicide (Petersen et al., 2013; Tidemalm et al., 2011; von Borczyskowski et al., 2011) with heritability estimates in adults ranging from 30% to 60% for attempts (Fu et al., 2002; Statham et al., 1998; Voracek & Loibl, 2007). The genetic component likely includes liability to impulsive aggression which is the tendency to react with aggression when frustrated (Brent et al., 1996; Brent & Melhem, 2008; Brent & Mann, 2006). There is also some evidence for an environmental component though findings have been more mixed (Petersen et al., 2013, 2014; Tidemalm et al., 2011; von Borczyskowski et al., 2011; Wilcox, Kuramoto, Brent, & Runeson, 2012). Tidemalm and colleagues (2011) used Swedish population registers to examine family clustering of suicide and found higher suicide risk in the siblings of family members that had died by suicide compared to the offspring. This finding provided some support for a shared environmental influence given that both pairs have 50% genetic similarity, but siblings have more shared environment than parent-offspring pairs. More recently, two adoption studies using Danish population registers did not find increased suicide risk in adoptive siblings of adoptees that died by suicide (Petersen et al., 2013) or attempted suicide (Petersen et al., 2014) indicating no influence of the shared environment, however, these findings could be due to a lack of power due to small numbers

when examining suicide attempt and suicide. Additionally, given evidence for an increased risk of suicide in adoptees and a decreased risk in twins compared to the general population, caution is required when generalising findings from twin and adoption studies to the general population (Petersen et al., 2013; Voracek & Loibl, 2007). Possible mechanisms that might explain familial transmission of suicidal behaviour via the shared environment include the transmission of an adverse rearing environment or childhood maltreatment (Brent & Mann, 2005; Brent & Melhem, 2008) and imitation (Brent & Melhem, 2008; Geulayov et al., 2012), however evidence suggests that the intergenerational transmission of suicidal behaviour is unlikely to be explained by imitation alone (Brent & Mann, 2005; Brent & Melhem, 2008; Burke et al., 2010; Statham et al., 1998).

There is also evidence that intergenerational risk for suicidal behaviour is inherited distinctly from psychiatric disorder (Brent et al., 1996; Brent & Mann, 2005; Christiansen, Goldney, Beautrai, & Agerbo, 2011; Kuramoto et al., 2010; Mittendorfer-Rutz, Rasmussen, & Wasserman, 2008; Petersen et al., 2014; Tidemalm et al., 2011). However, the same meta-analysis described earlier (Geulayov et al., 2012), found that adjustment for both the transmission of psychiatric disorder from parent to offspring and socio-demographic factors reduced the association between parent and offspring suicide attempt by approximately 40%, indicating that some part of the association is explained by the transmission of psychiatric disorder. Additionally, given that the majority of studies that have examined the independent effects of parental suicide attempt and psychiatric disorder have used Scandinavian population registers, only hospitalisation for psychiatric disorder has been examined and the impact of untreated or less severe disorders in parents and offspring is unclear (Geulayov et al., 2012). Few studies have examined the familial transmission of suicidal behaviour in community samples (Geulayov et al., 2012; Geulayov, Metcalfe, Heron, Kidger, & Gunnell, 2014; Lieb et al., 2005). Community samples are important because they can avoid problems from selection bias present in studies utilising population registers. For example, using population registers will exclude the large proportion of individuals that do not seek treatment for suicidal behaviour and psychiatric disorder. In a recent study utilising the ALSPAC sample (Geulayov et al., 2014), maternal suicide attempt from pregnancy to child age 11 years was associated with a 3-fold increased risk of both later suicidal ideation and suicide attempt in adolescent offspring after adjusting for maternal depression symptoms in pregnancy. This is one of the few studies to use a large, prospective, representative sample to show the risk to offspring associated with earlier suicide attempt in a parent. Another recent study, also using the ALSPAC sample, provided evidence for the specificity of the intergenerational transmission of suicide attempt by showing that maternal suicide attempt was a specific risk factor for offspring suicide attempt but not for offspring self-harm without suicidal intent (Mars, Heron, Crane, Hawton, Kidger, et al., 2014). These results support findings from an earlier, smaller, prospective community sample of

adolescents and young adults that found maternal suicide attempt was associated with both suicidal ideation and suicide attempt in offspring after adjusting for maternal psychiatric disorder (Lieb et al., 2005).

Overall, there is strong evidence for the intergenerational transmission of suicidal behaviour with findings from a number of different study designs concluding that there is likely both a genetic and environmental component to this. Previous studies, mainly using population registers, have also provided evidence that the familial transmission of suicidal behaviour is, at least in part, distinct to the transmission of psychiatric disorder; however, the specific impact of parental depression on offspring suicide-related behaviour has received less attention. Given that parental depression is more prevalent in the general population compared with parental suicidal behaviour, and that most parents with depression will never make a suicide attempt, findings from these studies may have greater implications for public health. The key studies in this area will be discussed next.

1.2.2: Maternal depression

Adult Major Depressive Disorder (MDD) is common, especially in women of a child-bearing age, with past year prevalence estimates for this group of approximately 10% (Ertel, Rich-Edwards, & Koenen, 2011). Symptoms of MDD from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013) are listed in Appendix 1. Depression is often recurrent and is a leading cause of disability worldwide (Murray & Lopez, 2013). Therefore many offspring will be exposed to maternal depression during their childhood. Evidence suggests that these offspring will be at increased risk for suicidal ideation (Garber, Little, Hilsman, & Weaver, 1998), suicide attempt (Lewinsohn, Olino, & Klein, 2005; Mittendorfer-Rutz et al., 2008) and suicide (von Borczyskowski, Lindblad, Vinnerljung, & Hjern, 2010).

A review conducted in 1997 concluded that there was strong evidence that parental psychopathology was a correlate of offspring suicide-related behaviour, but that most of the literature to date had used cross-sectional samples and therefore could not establish temporal precedence (Wagner, 1997). Since then the number of longitudinal studies has increased with a wide range of study designs being utilised (including Scandinavian population registers, high-risk samples and community samples) to further examine the association between parental psychiatric disorder, or specifically depression, and offspring suicide-related behaviour. The key longitudinal studies have been summarised in Table 1.3 and will be discussed in more detail below.

Table 1.3 – Key studies that have examined the association between parental psychiatric disorder and offspring suicide-related behaviour

Study	Study name/ description	Sample size	Age range of offspring	Follow-up time period	Parental psychiatric disorder	Outcome	Risk for offspring
Scandinavian population registers							
(Webb, Pickles, Appleby, Mortensen, & Abel, 2007)	Population-based cohort study of entire Danish population	570,312 participants were eligible at age 16 years	1-25 years	Birth (1973-1997) until 1999	Records of parental psychiatric disorders resulting in admission to hospital	Offspring suicide	2- to 3-fold higher risk of suicide for offspring of parents that had previously been hospitalised for psychiatric illness; 6-fold higher risk for offspring with both parents admitted
(Stenager & Qin, 2008)	Nested case-control study using data from Danish longitudinal registers	4,142 suicide victims and 82,840 matched controls	9-45 years	1969 until 1997	As above	Offspring suicide	Parental psychiatric history was a risk factor for offspring suicide, especially for female offspring. This association remained when adjusting for offspring psychiatric disorder, but only when the mother had been hospitalised within the past few years. Parental affective disorders did not have an additional effect over other disorders
(Mittendorfer-Rutz et al., 2008)	Nested case-control study through linkage of Swedish registers	14,440 cases and 144,400 matched controls	10-31 years	Birth (1968-1980) until 1999	Psychiatric disorders in parents recorded in inpatient care register before suicide attempt in index subject	Offspring suicide attempt	Affective disorder in the father and mother showed independent associations with offspring suicide attempt; associations slightly attenuated when adjusting for parental suicidal behaviour and offspring hospitalisation for psychopathology
(von Borczyskowski et al., 2010)	Cohort study using Swedish registry data	2,471,496 adult offspring	19-57 years	1987 until 2001	At least 1 parent with a psychotic or affective disorder based on inpatient admission data when the offspring were adults	Offspring suicide	Parental psychotic or affective disorder was a risk factor for offspring suicide; association was stronger for female offspring compared to male

Study	Study name/ description	Sample size	Age range of offspring	Follow-up time period	Parental psychiatric disorder	Outcome	Risk for offspring
(von Borczyskowski et al., 2011)	Cohort study using Swedish registry data	27,600 adult adoptees and 2,443,896 non adoptees	18+ years	1987 until 2001	At least 1 biological parent with a discharge from hospital or underlying or contributing cause of death a diagnosis of psychotic or mood disorder	Offspring suicide	Suicide and indicators of severe psychiatric disorder in biological parents had a similar effect on offspring suicide in the adopted and non-adopted offspring
(Mittendorfer-Rutz, Rasmussen, & Lange, 2012)	Nested case-control study through linkage of Swedish registers	15,193 cases and 151,930 matched controls	15-31 years	Birth (1973-1983) until 2006	Psychiatric disorders in parents recorded in inpatient care register and diagnosis specific disability pension	Offspring suicide attempt	Short term exposure (within 2 years) to maternal inpatient care had significantly stronger effect on suicide attempt risk in women compared to men; adolescence was the most critical period for the impact of exposure to parental hospitalisation for a psychiatric disorder
(Niederkrotenthaler, Floderus, Alexanderson, Rasmussen, & Mittendorfer-Rutz, 2012)	Case-control study through linkage of Swedish registers	17,159 suicide attempters, 1,407 suicide victims and up to 10 randomly selected controls per case	10-31 years	Birth (1973-1983) until 2006	Parental diagnosis specific disability pension and inpatient care due to mental illness	Offspring suicide attempt and suicide	Offspring exposed to parental markers of morbidity were at increased risk for suicide and suicide attempt; effects remained after adjusting for covariates and parental suicide attempt
(Wilcox et al., 2012)	Retrospective cohort study using Swedish registers to identify adoptees with biological parent with psychiatric hospitalisation or suicidal behaviour	8,391 adoptees	Not provided	1973 until 2003	Parental hospitalisation for psychiatric disorders	Offspring suicide and hospitalisation for suicide attempt	Exposure to hospitalisation of an adoptive mother because of a psychiatric disorder amplified adoptees' risk of suicide attempt hospitalisation among those adoptees at high genetic risk of suicide or suicide attempt

Study	Study name/ description	Sample size	Age range of offspring	Follow-up time period	Parental psychiatric disorder	Outcome	Risk for offspring
High-risk							
(Melhem et al., 2007)	Prospective study of offspring of parents with a mood disorder recruited from psychiatric institutes in Pittsburgh and New York	365 offspring of 203 parents	Mean age 20 years	Up to 6 years	Parents diagnosed with mood disorder	Offspring new onset suicidal attempt or ideation resulting in emergency referral or major change in treatment	Precursors of early onset suicidal behaviour in offspring of parents with mood disorders included mood disorder, impulsive aggression and parental history of suicide attempt, sexual abuse and self-reported depression
(Cox et al., 2012)	As above	352 offspring of 212 parents	Mean age 18 years	Up to 8 years	As above	Offspring NSSI and suicide attempt	Younger age, suicidal ideation and depression at time point prior to NSSI predicted NSSI at follow-up in multivariate analysis. NSSI predicted future suicide attempt over and above history of suicide attempt, along with offspring aggression
(Brent et al., 2014)	As above	701 offspring of 334 parents	Mean age 17.7 years	Mean of 5.6 years	As above	Offspring suicide attempt	Offspring mood disorder, offspring history of suicide attempt and parental suicide attempt were independently associated with suicide attempt in offspring of parents with mood disorders

NSSI - Non-Suicidal Self-Injury

Study	Study name/ description	Sample size	Age range of offspring	Follow-up time period	Parental psychiatric disorder	Outcome	Risk for offspring
Community							
(Garber et al., 1998)	Prospective community study of offspring of mothers with and without a history of mood disorder	240 offspring	Mean age 12 years	1 year	Parents diagnosed with DSM-III-R history of mood disorder	Offspring suicidal symptoms on a scale of 0-10	Maternal depression history predicted offspring suicide symptoms at follow-up, even after controlling for offspring suicide symptoms at baseline
(Lewinsohn et al., 2005)	Oregon Adolescent Depression Project (OADP) - representative sample of high school students	1,709 offspring	Mean age 17 years	Up to age 24 years	Parents assessed at follow-up interview for lifetime diagnoses of MDD before baseline interview	Offspring suicide attempt	Paternal MDD was associated with offspring lifetime suicide attempt assessed in adolescence. The association remained after controlling for comorbidity in parent and psychopathology in offspring. Maternal MDD was associated with offspring lifetime suicide attempt in adolescence only when offspring was living with mother
(Klimes-Dougan, Lee, Ronsaville, & Martinez, 2008)	Prospective community study of offspring of mothers with MDD, bipolar and no psychiatric diagnosis	192 offspring of 98 parents	Younger siblings: age 3 years; older siblings: approximately 3 years older	11 years	Parents diagnosed with MDD or bipolar disorder	Offspring suicide-related behaviour (ideation, plans or attempts) and suicide plan/attempt	Offspring of depressed/bipolar mothers were more likely to report suicide-related behaviour than offspring of well mothers, but developmental trajectories differed for offspring of depressed and bipolar mothers in that offspring of depressed mothers showed more persistence of suicide-related behaviour than offspring of bipolar mothers

DSM-III-R - Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised; MDD – Major Depressive Disorder

Study	Study name/ description	Sample size	Age range of offspring	Follow-up time period	Parental psychiatric disorder	Outcome	Risk for offspring
(Kerr, Owen, & Capaldi, 2008)	Oregon Youth Study – sample of boys recruited on the basis of community risk for delinquency	206 boys	9 years	20 years	Mean parental depression symptoms score over 3 assessments (child age 9, 10 & 11) measured using CES-D in mother and father	Offspring suicidal ideation	Parental depression symptoms were associated with increased probability of suicidal ideation occurrence and recurrence; child depression symptoms did not fully account for this effect
(Wilcox et al., 2010)	College students from a large mid-Atlantic University	1,253 college students	18+ years	4 years	Maternal and paternal history of depression assessed with college student using a family tree questionnaire	Annual assessment of suicidal ideation and suicidal plans or attempts assessed at year 4	Presence of maternal depression was found to be higher in one-time ideators, persistent ideators and plan/ attempters as compared to non-ideators; paternal depression was associated with persistent ideation

CES-D – Centre for Epidemiologic Studies Depression Scale

The effects of parental hospitalisation for psychiatric disorder on offspring suicide risk are well-established from studies utilising Scandinavian population registers (Mittendorfer-Rutz et al., 2012, 2008; Niederkrotenthaler et al., 2012; Qin, Agerbo, & Mortensen, 2002, 2003; Stenager & Qin, 2008; von Borczyskowski et al., 2010, 2011; Webb et al., 2007; Wilcox et al., 2012). The impact of maternal hospitalisation for an affective disorder on offspring suicide attempt has been examined using a nested case-control design through linkage of Swedish registers (Mittendorfer-Rutz et al., 2012, 2008). Maternal hospitalisation for an affective disorder was associated with a nearly 2-fold increased risk of suicide attempt in offspring after adjusting for maternal suicidal behaviour (Mittendorfer-Rutz et al., 2008). These findings were later extended by showing that adolescence was the most critical period for the impact of exposure to parental hospitalisation for a psychiatric disorder (Mittendorfer-Rutz et al., 2012). As noted previously, other studies using Scandinavian population registers have supported the finding that parental hospitalisation for psychiatric disorder and parental suicidal behaviour exert independent effects on offspring suicide attempt (Niederkrotenthaler et al., 2012) and suicide (Niederkrotenthaler et al., 2012; Qin et al., 2002, 2003; von Borczyskowski et al., 2010).

However, parental suicide attempt may be an important factor in explaining increased suicide risk among offspring of parents with depression. Evidence for this comes from a series of high-risk studies of offspring of parents with a DSM-IV mood disorder recruited from clinics across Pittsburgh and New York (Brent et al., 2002, 2003, 2004, 2014; Burke et al., 2010; Cox et al., 2012; Mann et al., 2005; Melhem et al., 2007). The majority of these studies have been cross-sectional, however the most recent (Brent et al., 2014) examined risk for offspring suicide attempt across a period of nearly 6 years. This study found that, among offspring of parents (mostly mothers) with a mood disorder, parental suicide attempt was associated with nearly 5-fold increased odds of offspring suicide attempt after accounting for offspring history of mood disorder and history of suicide attempt. This finding also indicates that the familial transmission of suicide attempt is separate to the familial transmission of mood disorder (Brent et al., 2014).

Previous studies utilising high-risk samples and investigating risk to offspring from parental hospitalisation for a psychiatric disorder have advanced the understanding of the familial transmission of both mood disorders and suicidal behaviour. However, results from these studies may not be generalisable to the wider population (Mittendorfer-Rutz et al., 2012). Mothers hospitalised for psychiatric disorder represent the severe end of the spectrum of psychopathology, and so it is unclear whether findings are being driven by the severity of disorder in mothers that have been hospitalised or family disruption associated with the separation due to hospitalisation. Additionally, in the high-risk studies, parents were recruited from inpatient units, meaning that results may be relevant only for those with a clinically severe mood disorder and who seek, and have access to, health care. Therefore it is important to

additionally examine the impact of maternal depression on offspring suicide risk using community samples.

Evidence from existing longitudinal population studies suggests that maternal depressive disorder is associated with an increased risk of suicidal ideation in offspring (Garber et al., 1998; Kerr et al., 2008; Klimes-Dougan et al., 1999, 2008; Wilcox et al., 2010) compared to the general population. Using a sample of 240 young adolescents and their mothers (the majority of whom had a history of a mood disorder), Garber and colleagues found evidence for an association between maternal history of mood disorder and later offspring suicidal symptoms. A more recent study that assessed suicidal ideation repeatedly over a four year period in a sample of college students also found evidence that maternal history of depressive disorder, assessed retrospectively with the student, was associated with persistent suicidal ideation in offspring (Wilcox et al., 2010). There was also evidence that maternal history of depression was associated with offspring making a suicide plan or attempt during college (Wilcox et al., 2010). The few studies using longitudinal, community samples to specifically examine the association between maternal depressive disorder and offspring suicide attempt in adolescence, have shown mixed findings (Klimes-Dougan et al., 1999, 2008; Lewinsohn et al., 2005; Rohde, Lewinsohn, Klein, & Seeley, 2005). Two previous studies utilised the OADP; a longitudinal, representative sample of young adults and their parents (Lewinsohn et al., 2005; Rohde et al., 2005). Lewinsohn and colleagues (2005) found that maternal history of lifetime MDD was associated with offspring suicide attempt but only when the offspring lived with their mother, whereas Rohde and colleagues (2005) found that, in a subsample of offspring with MDD, maternal MDD was not associated with offspring suicide attempt, but was associated with offspring suicidal ideation. However, the lack of association with offspring suicide attempt could be a result of low power when examining a rare outcome in a small sample. Finally, a recent, large, cross-sectional study utilised data collected during interview across 21 nationally representative samples around the world to examine the association between specific parental disorders and offspring suicide-related behaviour (Gureje et al., 2011). This study assessed parental psychiatric disorders retrospectively with adult offspring and found that parental depression was associated with offspring suicidal ideation, but not suicide attempt, after adjusting for other co-morbid disorders and suicide in the parent; whereas, parental antisocial and anxiety disorders predicted both offspring suicidal ideation and suicide attempt among ideators (Gureje et al., 2011).

Although these studies add to the literature by utilising representative population samples that minimise selection bias, with a longitudinal design to establish temporal precedence, there are also a number of limitations to consider. First, few studies prospectively assessed maternal depression directly with the mother. Maternal history of depressive disorder has often been assessed, at least in part, retrospectively with the offspring (Gureje et al., 2011; Lewinsohn et

al., 2005; Rohde et al., 2005; Wilcox et al., 2010). This could result not only in recall bias and shared-rater bias but also inaccurate assessment as it is likely that many offspring will not be aware of depression in a parent (Eyre et al., 2014), or awareness may be associated with offspring depression. Second, despite the longitudinal nature of studies, the possibility of reverse causation has rarely been considered. Few studies examined findings after excluding offspring with earlier suicide-related behaviour, or adjusting for earlier suicide-related behaviour in analyses (Garber et al., 1998). Third, the small sample sizes used often limit power, especially to examine risk for rarer outcomes such as offspring suicide attempt. Fourth, studies focused more often on suicide-related behaviour in young adults (Gureje et al., 2011; Lewinsohn et al., 2005; Rohde et al., 2005; Wilcox et al., 2010) therefore it is not clear if results generalise to adolescents and finally, maternal suicide attempt was rarely assessed meaning the impact of maternal suicide attempt on the association between maternal depression and offspring suicide-related behaviour in the general population is still unclear.

Additionally, given that the majority of previous literature utilising community samples have examined links between a lifetime diagnosis of maternal depression and offspring suicide-related behaviour (Garber et al., 1998; Gureje et al., 2011; Klimes-Dougan et al., 1999, 2008; Lewinsohn et al., 2005; Rohde et al., 2005; Wilcox et al., 2010), heterogeneity in the course, timing and severity of depression that might influence risk for offspring suicide-related behaviour is typically not taken into account (Nandi, Beard, & Galea, 2009). Given that depression can be episodic or persistent, focusing on a single time point could give a misleading impression of the level and duration of maternal depression symptoms that offspring are exposed to. Longitudinal studies with repeated assessments of maternal depression symptoms will enable some aspects of this heterogeneity to be captured by identifying patterns of maternal depression over time. This allows severity as well as stability or change in maternal depression symptoms over time to be considered. Several studies have demonstrated the added value of using longitudinal trajectories of maternal depression symptoms to predict offspring psychopathology compared to an assessment at a single point in time or predefined measures of severity and chronicity (Cents et al., 2013; Nandi et al., 2009) but these have thus far not considered offspring risk of suicidal ideation or attempt. Furthermore, although risk to offspring due to chronic and severe maternal depression symptoms is well-established (Stein et al., 2014), less is known about the impact of sub-threshold levels of maternal depression, especially on risk for offspring suicide-related behaviour. This is important to consider given that a greater number of offspring will be exposed to lower levels of maternal depression symptoms and these offspring may be less likely to be known to services as mothers may have never been diagnosed with clinical depression.

1.2.3: Summary

Recently, some important studies have begun to examine the impact of both maternal suicide attempt and maternal depression on later offspring suicide risk in community samples. However, more research is needed to examine the impact of variation in the course of maternal depression in the general population on risk for offspring suicide-related behaviour in adolescence. Identifying which offspring are most at risk is essential to inform targeted prevention programs. After identifying offspring at risk, an important next step is establishing potentially modifiable mechanisms to explain the intergenerational transmission of risk. Currently, the pathways involved in the transmission of risk for suicide-related behaviour from depressed mothers to offspring are poorly understood. In order for targeted prevention for suicide-related behaviour to be effective, a good understanding of the mechanisms underlying the intergenerational transmission of risk is needed; therefore establishing why offspring of depressed mothers are at increased suicide risk compared to offspring of non-depressed mothers is a crucial question.

1.3: Possible explanations for the association between maternal depression and offspring suicide-related behaviour

Despite increasing interest in this area, the reasons for an association between maternal depression and offspring suicide-related behaviour remain unclear. The association could be confounded by socio-demographic risk factors, such as parental socio-economic status, education level or marital status, that are known associates of maternal depression (Skipstein, Janson, Stoolmiller, & Mathiesen, 2010) and are also related to offspring suicide risk (Johnson et al., 2002; Page et al., 2014). Alternatively shared genetic risk may confound the association with gene-variants associated with maternal depression being transmitted and also increasing risk of offspring suicide-related behaviour either directly or via the impact on offspring psychiatric disorder (Kendler, 2010). It is also possible that the association is causal, with maternal depression leading to offspring suicide-related behaviour via offspring depression or other mechanisms. Identifying potentially modifiable mechanisms of risk is an essential first step to establishing whether targeting specific risk factors in offspring of mothers with depression is likely to lead to a reduction in suicide-related behaviour. Potential explanations are discussed in more detail below.

1.3.1: Possible non-causal explanations

In addition to simultaneously testing competing mechanisms, it is also important to examine alternative explanations for associations observed by adjusting for potential confounders, minimising bias and considering the possibility of reverse causation to identify potential modifiable intervention targets.

Given that much of the evidence to date has come from Scandinavian population registers (Mittendorfer-Rutz et al., 2012, 2008; Niederkrotenthaler et al., 2012; Qin et al., 2002, 2003; Stenager & Qin, 2008; von Borczyskowski et al., 2010, 2011; Webb et al., 2007), the possibility of selection bias needs to be considered. As discussed earlier, using population registers will exclude the large proportion of individuals that do not seek treatment for suicide-related behaviour and psychiatric disorder. This referral bias can be avoided by examining risk for suicide-related behaviour in community samples. However, in the existing community studies, other types of bias may be present. Shared-rater bias may be present when maternal depression and offspring suicide-related behaviour are assessed using the same rater i.e. with the offspring (Gureje et al., 2011; Lewinsohn et al., 2005; Rohde et al., 2005; Wilcox et al., 2010). To reduce biases associated with shared-rater effects, a cross-rater approach needs to be used, i.e. mothers report on their own depression symptoms and offspring report on their own suicide-related behaviour. Additionally, few studies have assessed maternal depression prospectively. Retrospective assessment is subject to recall bias, especially when examining a life-time history of maternal depressive disorder. Finally, bias can also arise through selective attrition in longitudinal studies when the impact of missing data is not considered (Garber et al., 1998; Wilcox et al., 2010).

It is also possible that reverse causation may account for associations observed, at least in part, with earlier offspring suicide-related behaviour impacting on the course of maternal depression. Longitudinal studies examining risk to offspring across long time periods enable the temporal ordering of effects to be examined; however, few studies have excluded those offspring with previous suicide-related behaviour from analyses. Finally, the association between maternal depression and offspring suicide-related behaviour could be confounded by certain socio-demographic risk factors. Lower socio-economic status, maternal lack of education and being single are all known associates of maternal depression symptoms (Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Cents et al., 2013; Nandi et al., 2009; Skipstein et al., 2010) and there is some evidence that these factors are also related to offspring suicide risk (Chen et al., 2013; Evans, Hawton, & Rodham, 2004; Johnson et al., 2002; Page et al., 2014). Additionally, the association could be explained by familial background risk. A family history of depression and past episodes of depression or other psychiatric disorders in the mother are likely to impact on both recurrent depression in the mother and increased suicide risk in the offspring (Burcusa & Iacono, 2007; Cents et al., 2013; Gureje et al., 2011; Mars et al., 2012; Mittendorfer-Rutz et al., 2008; Qin et al., 2002; Santana et al., 2015; Stenager & Qin, 2008; von Borczyskowski et al., 2010). These potential confounding factors are important to consider in analyses. If the association between maternal depression and offspring suicide-related behaviour is explained by these measures of background risk, interventions aimed at treating the mother's

depression are unlikely to reduce adolescent suicide risk. The possibility of genetic confounding is discussed in more detail later.

Studies of adult twins have shown evidence for a genetic influence on suicide-related behaviour with heritability estimates of 30% to 50% for ideation (Fu et al., 2002; Linker, Gillespie, Maes, Eaves, & Silberg, 2012; Statham et al., 1998; Voracek & Loibl, 2007) and 30% to 60% for attempts (Fu et al., 2002; Statham et al., 1998; Voracek & Loibl, 2007). However, it is likely that the heritability of *adolescent* suicidal ideation is much lower than this with the few studies of adolescent twins finding either no genetic contribution to suicidal ideation (Linker et al., 2012), or a slightly higher concordance among monozygotic than dizygotic twins showing evidence of some genetic component to suicidal ideation (Cho, Guo, Iritani, & Hallfors, 2006) and suicide attempt (Cho et al., 2006; Glowinski et al., 2001). The increase in heritability with age is also seen for other psychiatric disorders, such as depression (Rice, Harold, & Thapar, 2002) as the role of the family and shared environment decreases rapidly in the transition from adolescence to adulthood.

Despite evidence from twin samples for a genetic influence on suicide-related behaviour in adults, there has been limited success identifying specific genes that contribute to vulnerability. Although the serotonergic system has been implicated, Genome-Wide Association Studies (GWAS) on suicidal ideation and suicide attempt have generally failed to identify specific genetic variants (Mullins et al., 2014; Sokolowski, Wasserman, & Wasserman, 2014; Turecki, 2001; Zalsman, 2012). More recently however, Mullins and colleagues (2014) utilised a different approach to examine common genetic variants for psychiatric disorders and suicidal phenotypes across four cohorts of adult patients with mood disorders (Mullins et al., 2014). A genetic risk profile score analysis was used to address problems of low power in previous GWAS that may have resulted in the limited success in identifying specific genetic variants for a complex phenotype such as suicide-related behaviour (Mullins et al., 2014). Genetic risk profile score analysis is a data reduction technique by which the multivariable information from even moderately associated alleles on a GWAS chip are collapsed into a single risk score. It was found that a genetic risk profile score for MDD was associated with treatment resistant suicidal ideation and with suicide attempt but only when all datasets were combined. The genetic risk profile score for suicide attempt was not associated with suicidal ideation; however these analyses were likely to have been underpowered (Mullins et al., 2014). Even so, these findings provide preliminary evidence that the genetic aetiology of suicidal ideation and suicide attempt is distinct with pleitropy between liability to suicidal ideation and depression, at least in adults with a mood disorder (Mullins et al., 2014). To date, no studies have examined common genetic variants for psychiatric disorders and suicidal phenotypes in adolescents using a genetic risk profile score approach.

Evidence that the association between parental hospitalisation for psychiatric disorder and offspring suicidal behaviour is, in part, explained by genetic confounding, comes from adoption studies using Scandinavian registry data (von Borczyskowski et al., 2011; Wender et al., 1986; Wilcox et al., 2012). Two of these studies found little evidence for an environmental influence on suicide (von Borczyskowski et al., 2011; Wender et al., 1986); however, the most recent of these adoption studies provided evidence for the importance of both genetic and environmental risk in a retrospective cohort study using Swedish registry data (Wilcox et al., 2012). An interaction was found between suicidal behaviour in the biological parent and hospitalisation for psychiatric disorder in the adoptive mother while the adoptee was younger than 18 years, on offspring risk for suicide attempt. When examining these risks separately, neither were associated with offspring suicide attempt suggesting that risk is likely to be greatest when both genetic risk and environmental risk are present (Wilcox et al., 2012). However, across these adoption studies, offspring of adoptive parents that were not hospitalised for a psychiatric disorder (controls) may still have been exposed to a psychiatric disorder that did not result in hospitalisation which could have resulted in an underestimation of true environmental effects (Wender et al., 1986). Therefore, the findings may not generalise to offspring of parents with less severe psychiatric disorders, or less severe outcomes in offspring such as suicidal ideation. There are also a number of limitations to adoption designs that are important to consider – there may be selection bias due to adoptive parents being screened prior to adoption resulting in a more advantaged subgroup compared to the general population. Additionally, in these studies, the age of the child at adoption and their situation before adoption were unknown meaning that the early postnatal environment could have confounded effects (von Borczyskowski et al., 2011; Wilcox et al., 2012).

In summary, there are convergent findings from a number of different study designs showing a genetic contribution to suicide risk in adults with evidence for polygenic inheritance (Mullins et al., 2014; Turecki, 2001). It is likely that suicidal ideation co-segregates with psychiatric disorder whereas vulnerability to act on suicidal thoughts may have a partially distinct genetic aetiology (Mann, Waternaux, Haas, & Malone, 1999). One possible genetically influenced mechanism involves reduced serotonergic activity which may be associated with impulsive-aggressive traits. These traits, in turn, might increase risk of acting on suicidal thoughts (Turecki, 2001). Currently, evidence from adolescents is sparser but also indicates the importance of both genetic and environmental factors in explaining the association between parental psychiatric disorder and offspring suicide risk. Less is known about the environmental impact of parental depression on offspring suicidal ideation in the general population. Given the strong overlap between depression and suicide-related behaviour that is likely due to both genetic and environmental effects common to both, a key explanation for the association between maternal depression and adolescent suicide-related behaviour is that offspring suicide-related behaviour follows on from the intergenerational transmission of depression. Evidence relating to this mechanism will be discussed next.

1.3.2: Possible causal explanations

As discussed, there is increasing evidence from large, longitudinal studies showing an association between maternal depression and offspring suicide-related behaviour across a range of different study designs including representative population samples and Scandinavian registry data, and there is some evidence that the association is, in part, environmentally mediated. If the association is casual, there are a number of potential mediators that might contribute to explaining the association. The impact of maternal suicidal behaviour was discussed earlier (section 1.2.1); briefly, mothers with depression are at high risk for making a suicide attempt (Brent et al., 2002) and there is strong evidence from community studies (Geulayov et al., 2014), high-risk samples (Brent et al., 2014) and Scandinavian registry data (Mittendorfer-Rutz et al., 2008) for the association between maternal suicide attempt with offspring suicidal ideation and behaviour. There is also evidence that the familial transmission of suicidal behaviour is, at least in part, distinct from the transmission of psychiatric disorder. Apart from the familial transmission of suicidal behaviour, maternal depression may also be linked to adolescent suicidal ideation through a number of other mechanisms. First, evidence relating to offspring psychopathology will be considered, followed by a discussion of literature relating to the family environment and peer victimisation as possible mechanisms.

There is long-standing evidence for the importance of psychiatric disorder in suicide risk with a disorder being present in 90% of adolescent suicide victims (Brent et al., 1988, 1993; McLoughlin et al., 2015; Shaffer et al., 1996) and over 80% of community cases of suicide attempt (Gould et al., 1998; Nock et al., 2013; Reinherz et al., 1995). The strongest evidence from population samples of adolescents is for the association between depression and suicide-related behaviour (Brent, 1995; Evans et al., 2004; Gould et al., 1998; Nock et al., 2013; Reinherz et al., 1995; Roberts & Chen, 1995) with depressive disorder posing approximately a 4-fold increased risk of later suicidal ideation and suicide attempt after adjusting for the presence of other disorders (Nock et al., 2013). Additionally, there is strong evidence for the familial transmission of depression with offspring of parents with a depressive disorder showing 2 to 4 fold greater risk of depression compared to offspring of non-depressed parents (Beardslee et al., 1988; Goodman et al., 2011; Halligan, Murray, Martins, & Cooper, 2007; Kendler, Davis, & Kessler, 1997; Lieb, Isensee, Höfler, Pfister, & Wittchen, 2002; Low et al., 2012; Merikangas, Risch, & Weissman, 1994; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Weissman et al., 2006). There is also evidence that the transmission of depression is due in part to environmental processes independent of inherited effects (Lewis, Rice, Harold, Collishaw, & Thapar, 2011; Silberg, Maes, & Eaves, 2010; Tully, Iacono, & McGue, 2008). Therefore, offspring depression is one of the most commonly assessed mechanisms for the association between maternal depression and offspring suicide-related behaviour. However, longitudinal studies examining the influence of maternal depression on offspring suicidal ideation have

found that adjustment for offspring depression symptoms does not fully account for risk effects (Kerr et al., 2008; Wilcox et al., 2010). Additionally, although suicidal ideation is a symptom in the diagnostic criteria for depressive disorder, studies have found that only half of depressed adolescents report suicidal ideation, and that suicidal ideation can occur in the absence of depression (King et al., 2001; Lewinsohn et al., 1996). Therefore, a diagnosis of depression is not sufficient as a causal explanation for suicidal ideation. Furthermore, there is some evidence that adolescents with depression and with suicide-related behaviour show different responses to treatment, with results from a meta-analysis showing that the average effect size for a change in suicide-related behaviour was only half the average effect size for a change in depression symptoms following psychotherapy (Weisz, McCarty, & Valeri, 2006). This highlights the importance of identifying risk factors for suicide-related behaviour other than a depression diagnosis.

Offspring of mothers with depression are at increased risk for a range of mental health problems in addition to depression (including anxiety, disruptive behaviour disorders, Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse) (Goodman et al., 2011; Low et al., 2012), and there is some evidence that each of these disorders is associated with both suicidal ideation and suicide attempt in adolescence (Boden, Fergusson, & Horwood, 2007; Evans et al., 2004; Gould et al., 1998; Nock et al., 2013; Verona & Javdani, 2011). Studies have consistently shown that depressive disorder is associated with suicide-related behaviour when taking account of other psychopathology (Gould et al., 1998; Nock et al., 2013), however findings as to whether the effects of other disorders are independent of depression and each other have been inconsistent. A recent national survey of US adolescents (Nock et al., 2013) found no independent effect of Generalised Anxiety Disorder (GAD) assessed retrospectively on suicide-related behaviour in adolescents. However, a prospective, longitudinal sample of adolescents (Boden et al., 2007), found that GAD was associated with later suicide-related behaviour after adjusting for the presence of other psychopathology. Findings for substance abuse have also been inconsistent with some studies showing an association with suicidal ideation (Nock et al., 2013) and others only with suicide attempt (Gould et al., 1998; Verona & Javdani, 2011). ADHD has generally been combined with disruptive behaviour disorders (Gould et al., 1998; Verona & Javdani, 2011) meaning it is difficult to draw conclusions about the independent effects; however, the national survey of US adolescents (Nock et al., 2013) examined the disorders separately and found an independent effect of Oppositional Defiant Disorder (ODD) on later suicidal ideation but that ADHD was only associated with the transition from ideation to attempt (Nock et al., 2013). Previous studies, however, have not fully taken account of the co-occurrence of offspring psychopathology by examining the effects of each disorder whilst adjusting for covariance between them. Given evidence that disorders tend to co-occur in adolescents (Caron & Rutter, 1991) and that high levels of comorbidity are associated with

suicide (Cavanagh, Carson, Sharpe, & Lawrie, 2003), taking account of this co-occurrence is important to examine the independent effects of specific aspects of offspring psychopathology.

A case-control autopsy study of adolescent suicide victims and demographically matched living controls was one of the first studies to show that a family history of depression increased risk for suicide after taking account of depression, conduct disorder and substance abuse in the suicide victim (Brent et al., 1994). A more recent longitudinal case-control study using Swedish inpatient care registers found that the association between maternal affective disorder and offspring suicide attempt was attenuated, although still present, when adjusted for whether offspring had been hospitalised due to a psychiatric disorder (Mittendorfer-Rutz et al., 2008). A cross-sectional study found a similar pattern of results when examining suicidal ideation and suicide attempt in adult offspring of parents with depression with adjustment for the presence of lifetime offspring psychiatric disorder (Gureje et al., 2011). However, more research is needed to examine the relative or differential importance of specific types of offspring psychopathology in explaining the association between maternal depression and subsequent offspring suicidal ideation and suicide attempt in adolescence. This is important given that offspring of mothers with depression show a broad range of psychopathology. Additionally, it is an essential first step to establishing whether treating specific symptoms in offspring of depressed mothers is likely to lead to a reduction in suicide-related behaviour.

Evidence discussed so far has highlighted the importance of considering both maternal suicidal behaviour and offspring psychiatric disorder as potential explanations of the association between maternal depression and offspring suicide-related behaviour (Brent et al., 2014; Gureje et al., 2011; Mittendorfer-Rutz et al., 2012, 2008). However, evidence suggests that the association is not entirely explained by these mechanisms (Gureje et al., 2011; Mittendorfer-Rutz et al., 2012, 2008), suggesting that additional mediators are important to consider. However, research investigating other mediating pathways that might explain suicide-related behaviour in offspring of depressed mothers is lacking.

Research on risk factors for adolescent suicidal ideation suggests additional possible risk pathways. A number of studies have highlighted the importance of the quality of the parent-child relationship in explaining risk for adolescent suicidal ideation (Boeninger, 2013; Fergusson & Lynskey, 1995a; King & Merchant, 2008), especially lack of support or availability of family members (Bridge et al., 2006; Connor & Rueter, 2006; Thompson, Mazza, Herting, Randell, & Eggert, 2005). The majority of these studies have shown that difficulties in the parent-child relationship predict adolescent suicidal ideation independently of the adolescent's own psychopathology (Boeninger, 2013; Connor & Rueter, 2006; Thompson et al., 2005). In a rural sample of adolescents, Connor & Rueter (2006) found a direct effect of observed maternal warmth, support and communication on subsequent offspring suicidal

ideation not mediated by offspring emotional distress. Using the same rural sample of adolescents, Boeninger and colleagues (2013) extended these findings by demonstrating that nurturant-involved parenting decreased risk of suicidal ideation over time after taking account of adolescents' prior suicide-related behaviour and internalising symptoms. Additionally, in a cross-sectional sample of potential high school drop-outs, Thompson and colleagues (2005) found a direct effect of lack of family support on suicide-related behaviour and an indirect effect through depression, anxiety and hopelessness. Furthermore, two cohort studies of depressed adolescents found that adolescent-rated poor family functioning was associated with later suicide attempt (Asarnow et al., 2011; Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011). Previous literature has also shown that maternal depression can lead to disruptions in the parent-child relationship (Keenan-Miller, Hammen, & Brennan, 2010; Lovejoy, Graczyk, O'Hare, & Neuman, 2000), and that these disruptions may be one pathway through which maternal depression increases risk for offspring psychiatric disorder (Goodman & Gotlib, 1999). However, only one study has tested whether the association between maternal depression and offspring suicidal ideation is explained, at least in part, by aspects of the family environment. Using a sample of 240 young adolescents and their mothers (the majority of whom had a history of a mood disorder), it was found that mother and child perceptions of the family environment at baseline fully mediated the association between maternal history of mood disorder and offspring suicidal symptoms one year later when also adjusting for offspring suicidal symptoms at baseline (Garber et al., 1998). In contrast to previous studies, neither maternal history of suicide attempt nor offspring depression symptoms at baseline were associated with offspring suicidal symptoms at follow-up; therefore these measures were not included in the analyses. Additionally, in this study maternal history of depression and suicide attempt were assessed retrospectively which may have resulted in recall bias and follow-up was only over a period of one year meaning that long term effects of the family environment on offspring suicidal ideation could not be evaluated.

Another well-established risk factor for adolescent suicidal ideation is peer victimisation (Brunstein Klomek, Sourander, & Gould, 2010; McLoughlin et al., 2015; van Geel, Vedder, & Tanilon, 2014). A number of longitudinal studies have focused on the detrimental effects of peer victimisation on later suicide-related behaviour in childhood or adolescence and found that peer victimisation was directly associated with suicidal ideation (Kaminski & Fang, 2009; Turner, Finkelhor, Shattuck, & Hamby, 2012; Winsper et al., 2012), self-harm (Fisher et al., 2012; Lereya et al., 2013) and suicide attempt (Kaminski & Fang, 2009) after accounting for depression symptoms and other psychopathology. Additionally, prospective longitudinal studies have recently shown that frequent peer victimisation in childhood is associated with both suicidal ideation (Takizawa, Maughan, & Arseneault, 2014) and suicide (Geoffroy, Gunnell, & Power, 2014) up to midlife, approximately 40 years after the assessment of bullying, showing

the strength of this relationship. However, a recent review highlighted that more longitudinal studies are needed to examine mechanisms of the association between peer victimisation and suicide-related behaviour (Hong, Kral, & Sterzing, 2014). Additionally, the association between maternal depression and peer victimisation is less clear. Some studies have shown that maternal depression is associated with maladaptive interpersonal cognitions and skills in the child (Hammen & Brennan, 2001) and increased risk of peer victimisation (Lereya & Wolke, 2012). It is likely that these associations are due, in part, to maladaptive interactions between mother and child (Hammen & Brennan, 2001; Lereya & Wolke, 2012). The impact of maladaptive parenting on later problems with peers is well-established (Elam et al., 2014; Johnson et al., 2002; Lereya et al., 2013; Whelan, Kretschmer, & Barker, 2014) with children learning poor social skills through negative interactions with the parent (social learning theory; (Putallaz & Heflin, 1990)). One recent study (Tsypes & Gibb, 2015) examined peer victimisation as a mediator of the association between maternal MDD in the child's lifetime and the onset of offspring suicidal ideation using a small, prospective sample of children aged 8 to 14 years. A direct effect of maternal MDD on offspring suicidal ideation and an indirect effect via both relational and overt victimisation were found among girls but not boys. Findings were the same when excluding those children with a lifetime history of MDD, however, the impact of maternal suicide attempt or the family environment were not considered.

In summary, there is evidence from a number of recent, longitudinal studies that both peer victimisation and problems in the parent-child relationship are associated with later adolescent suicidal ideation, and it is likely that these associations are not fully accounted for by psychopathology in the adolescent. Given that there are a number of potential pathways involved in the aetiology of adolescent suicidal ideation, testing competing mechanisms within the same model is critical. No studies have examined how both peer victimisation and the parent-child relationship simultaneously contribute to explaining the association between maternal depression and adolescent suicidal ideation. Additionally, it is not known whether these mechanisms will be important in explaining risk from both clinical and sub-threshold levels of maternal depression.

1.3.3: Summary

The association between maternal depression and offspring suicide-related behaviour is likely to be, in part, environmentally mediated. Evidence suggests that suicidal behaviour in the mother and psychopathology in the offspring are important mechanisms to consider, however, studies have shown that these factors do not completely explain the association, indicating other mechanisms should also be examined. The quality of the parent-child relationship is likely to play a role, with studies showing that maternal depression can impact on family relationships, and that a negative parent-child relationship is associated with adolescent suicidal ideation,

independently from the adolescent's own psychopathology. There is also strong evidence for an association between peer victimisation and later negative outcomes into adulthood including suicidal ideation; however it is currently less clear whether the effects of maternal depression spread outside of the family and impact on peer relationships. Peer victimisation and the parent-child relationship are important mechanisms to consider given that they are potentially modifiable and amenable to intervention (Brent et al., 2013; Hawton et al., 2012; Smith, Ananiadou, & Cowie, 2003). It is important to simultaneously test for competing mechanisms, adjust for potential confounders and consider the possibility of reverse causation to enable potential modifiable mechanisms to be identified. This has rarely been done in studies examining the association between maternal depression and offspring suicide-related behaviour in population samples.

1.4: Chapter summary

Suicidal ideation is common in adolescence and can have severe and long-lasting consequences into adulthood. Additionally, a prior suicide attempt is one of the most salient risk factors for later suicide. Therefore the early detection and prevention of suicide-related behaviour is a public health priority. Maternal depression is common, especially in women of child-bearing age, and it is well-established that offspring of mothers with depression are at increased risk for suicide-related behaviour. Therefore these offspring are a priority for preventive interventions. However, potential mechanisms explaining risk still remain unclear.

Existing studies have recently advanced the literature by showing a robust association between maternal depression and later suicidal ideation and attempt and by demonstrating that this association is likely to be, at least in part, environmentally mediated. Studies have also provided evidence that maternal suicidal behaviour and offspring psychopathology are important and distinct mechanisms, but together do not completely explain the association between maternal depression and offspring suicide-related behaviour. Finally, family relationships and peer victimisation have been identified as important risk factors for adolescent suicidal ideation across a number of prospective, longitudinal studies. However, it is unclear whether these factors explain the association between maternal depression and offspring suicidal ideation. There are also some existing limitations that still need to be addressed. These limitations are summarised below along with recommendations for how they can be overcome.

First, although there is evidence that more chronic and severe symptoms of maternal depression have a greater impact on offspring development (Stein et al., 2014) highlighting the importance of testing mechanisms for this group, it is not known whether risk mechanisms underlying links with offspring suicide-related behaviour vary by maternal depression severity. There is considerable heterogeneity in the severity and course of adult depression, and this has not been considered previously either in studies examining the association with offspring suicide-related

behaviour or in research investigating potential mechanisms. It is important to establish whether risk for adolescent suicide-related behaviour is confined to families where the parent is affected by severe clinical depression, or extends to adolescents of mothers who suffer from milder but sustained sub-threshold levels of depression. Sub-threshold levels of depression symptoms are more common than clinical depression in the general population, and these mothers are less likely to be in contact with services, highlighting the importance of recognising whether the offspring of mothers with sub-threshold symptoms are also at increased suicide risk. Previous studies of risk mechanisms have focused on mothers with a lifetime diagnosis of depression (Garber et al., 1998; Gureje et al., 2011). Therefore, more research is needed to establish if mechanisms underlying the link between maternal depression and offspring suicide-related behaviour in unselected population cohorts vary according to maternal depression symptom severity. To address this gap in the literature prospective, longitudinal designs are needed with repeated assessments of maternal depression symptoms. This will allow the heterogeneity in the course of maternal depression to be examined and by using group-based trajectory modelling, groups of mothers with differing levels of depression symptoms over time can be identified. This will allow examination of the risk effect of sub-threshold maternal depression and whether potential mechanisms vary by maternal depression course and severity.

Second, many important findings to date have come from studies utilising Scandinavian population registers. Although these studies have many advantages, it is important to examine whether results generalise to the wider population. Community samples are also important so as not to exclude adolescents with suicide-related behaviour that do not present to specialist services. Therefore, large, population-based samples are needed that examine risk for both adolescent suicidal ideation and suicide attempt.

Third, testing alternative explanations for associations observed is essential but not always done. Although residual confounding can never be eliminated in observational studies, adjusting for potential measured confounders is important to examine whether the association between maternal depression and offspring suicide-related behaviour is better explained by shared adversity between mother and child such as low socio-economic status or background familial risk. Additionally, it is also important to consider whether the association is explained by earlier suicide-related behaviour in the offspring impacting on the course of maternal depression, and this is rarely taken into account. To address these gaps, studies are needed that collect information on a wide variety socio-demographic and familial background risk measures before the assessment of maternal depression and that include repeated assessments of suicide-related behaviour in offspring.

Fourth, very few studies have examined mediators across a long developmental time span, covering the course of childhood and adolescence; an important consideration given that early

intervention is a recognised priority in suicide prevention (National Action Alliance for Suicide Prevention, 2014). Given that a number of different inter-related pathways are likely involved in the aetiology of adolescent suicidal ideation, testing competing mechanisms together is especially important.

1.5: Aims and rationale for the present thesis

The present thesis aims to address the current gaps in the literature by investigating potential mechanisms of the association between maternal depression symptom course over the first eleven years of their child's life and later adolescent suicidal ideation and suicide attempt in a large, population-based birth cohort. The specific aims of this thesis are as follows:

The first aim is to identify trajectories of maternal depression symptoms from pregnancy to child age 11 years and then to examine the association between maternal depression symptom course and adolescent suicidal ideation and suicide attempt at age 16 years. Analyses will examine whether any associations found are explained by a number of background socio-demographic and familial confounders assessed in pregnancy and test for the possibility of reverse causation by excluding offspring with earlier suicidal ideation from analyses. Finally, analyses will also investigate whether associations observed are explained through maternal suicide attempt or a diagnosis of depression in the offspring.

The second aim is to examine how much of the association between maternal depression symptom course and adolescent suicidal ideation and suicide attempt is explained through proximal offspring psychopathology at age 15 years including symptoms of MDD, GAD, Disruptive Behaviour Disorder (DBD), ADHD and alcohol abuse.

The third aim is to examine the role of additional hypothesised mediators that might contribute to explaining the association between differing levels of maternal depression across childhood and offspring suicidal ideation in adolescence. These mediators were assessed across childhood and adolescence and include maternal suicide attempt across the first eleven years of their child's life, the parent-child relationship and peer victimisation in middle childhood and offspring psychiatric disorder in adolescence (see Figure 1.2 for the theoretical model displaying all hypothesised pathways).

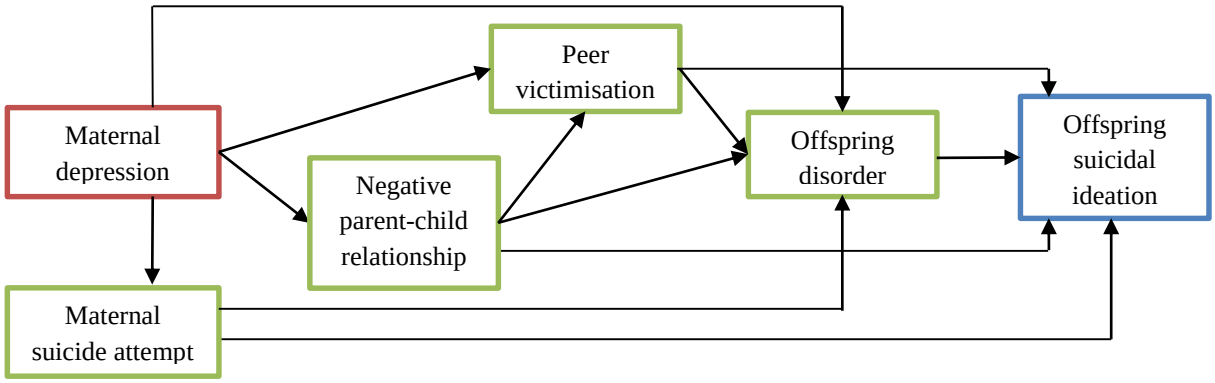


Figure 1.2 - Theoretical model displaying all hypothesised pathways from maternal depression to offspring suicidal ideation; red represents the exposure, green represents the mediators and blue represents the outcome

To address these aims data were utilised from ALSPAC, a UK birth cohort followed prospectively throughout childhood and adolescence via questionnaire and clinic assessments. The ALSPAC sample has a number of strengths that allow the current aims to be addressed. First, the longitudinal design and prospectively assessed measures allow for the temporal precedence of measures to be examined. Data are utilised across a period of 16 years and repeated measures of maternal depression are available across the whole of childhood. This means that the heterogeneity in maternal depression symptom course across childhood can be examined, and using prospectively assessed measures of depression also reduces recall bias. Adolescent suicide-related behaviour is assessed 5 years after the assessment of the exposure, maternal depression symptom course. Additionally, similar measures of offspring suicide-related behaviour are available at age 11 years meaning that these offspring can be excluded from secondary analyses to address the possibility of reverse causation. Second, given that ALSPAC is a large, population-based sample, this means that there is enough power to examine rarer outcomes in the general population such as the presence of a suicide attempt in both mother and offspring and these measures will not be subject to treatment bias. Third, a large number of socio-demographic and familial background risk variables are assessed in pregnancy meaning that a wide range of potential confounders can be accounted for. Finally, maternal self-reports were available for depression symptoms and offspring self-reports for suicide-related behaviour meaning that shared-rated bias will be reduced when examining initial associations.

Chapter 2: Methodology

This thesis analyses data from a large UK birth cohort; the 'Avon Longitudinal Study of Parents and Children' (ALSPAC). This chapter describes the sample used including details about recruitment and retention, summarises the procedure for collecting data and the ethical approval and describes the main measures and analytical techniques used across all subsequent chapters. Details regarding specific measures and procedures used in individual analyses will be described in the relevant results chapter. I had no role in the recruitment of families or the collection of data; however I derived all measures used in subsequent analyses.

2.1: Sample

The ALSPAC cohort was set up to examine genetic and environmental determinants of maternal and child health and development (Boyd et al., 2013). The ALSPAC study area, the former county of Avon, UK, comprises of rural areas, leafy suburbs, deprived inner city areas and moderate sized towns with a total population of one million (Golding, Pembrey, & Jones, 2001). The core enrolled sample consisted of 14,541 pregnant women who had an expected date of delivery between 1st April 1991 and 31st December 1992. There were 14,062 live births and all resulting children from these pregnancies were considered to be eligible. The sample is broadly representative of the UK population, however, mothers enrolled in ALSPAC were more likely to live in owner-occupied accommodation and have a car, more likely to be married and less likely to be non-white (Fraser et al., 2013). Additionally, children enrolled in ALSPAC had a higher educational attainment at age 16 years compared to the national average, and were less likely to be eligible for free school meals (Boyd et al., 2013).

2.2: Recruitment and retention

2.2.1: Recruitment

The recruitment procedure for ALSPAC was opportunistic. Contact was made with eligible women as early in pregnancy as possible by recruitment staff visiting community locations, promotion by routine antenatal and maternity health services and through local and national coverage in the media (Boyd et al., 2013). Pregnant women were given an 'expression of interest' card which they could return to request more information or decline participation in the study. This card contained sufficient details to enable ALSPAC staff to determine eligibility such as the mother's address and expected date of delivery (Golding et al., 2001). A study information booklet explaining reasons for carrying out the study and information on participation and confidentiality was then sent to eligible women that had requested further information, followed by an initial questionnaire (Golding et al., 2001). A flow chart of the ALSPAC enrolment campaign is shown in Figure 2.1.

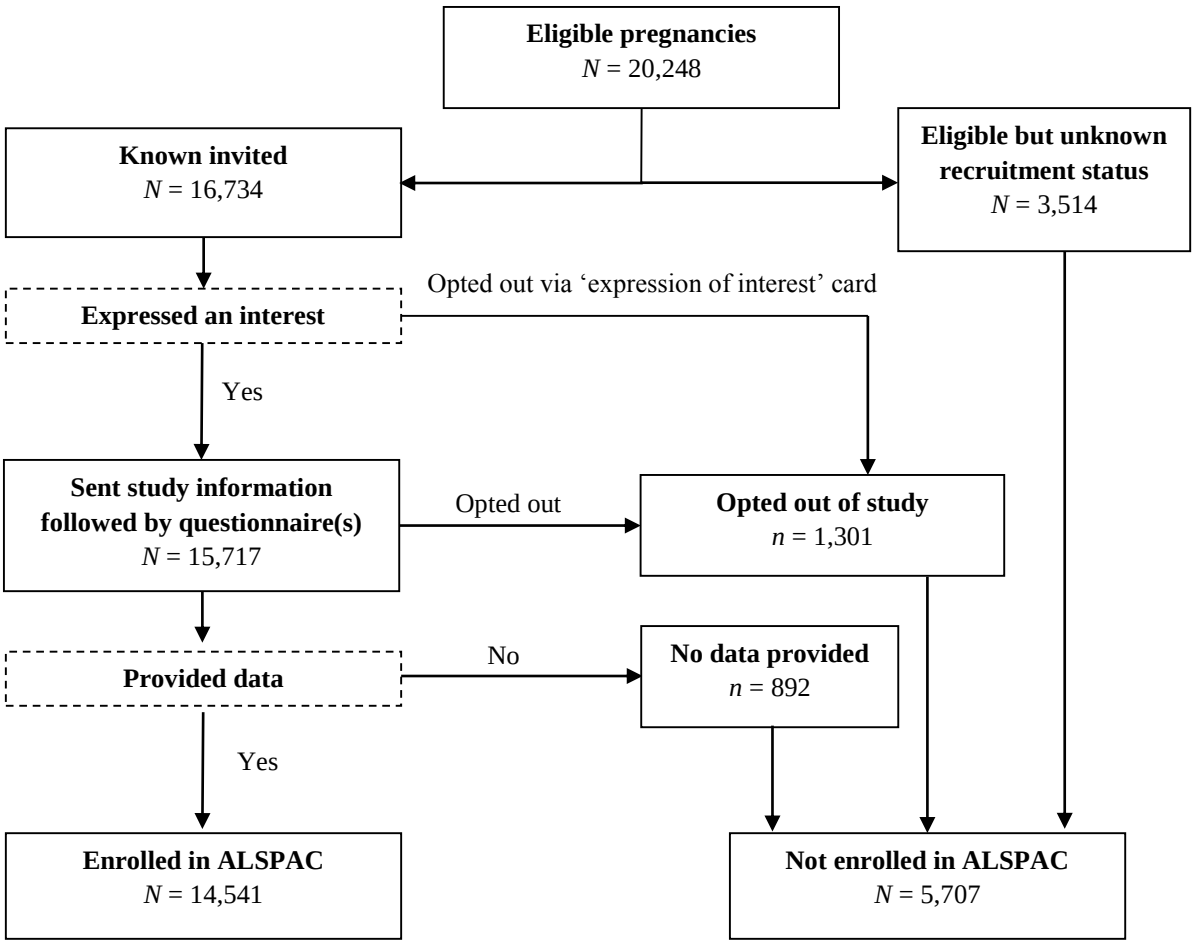


Figure 2.1 - Flow chart of recruitment in the 'Avon Longitudinal Study of Parents and Children' (ALSPAC) sample; adapted from Boyd et al., 2013

When children were aged 7 years, a second attempt was made to recruit eligible children where families had not responded initially however, these families were not included in any analyses for this thesis given that data were not collected prior to child age 7 years.

2.2.2: Retention

Loss to follow-up in ALSPAC was due to either permanent attrition reducing the proportion of the sample that were contactable for follow-up at each subsequent time point, or fluctuations in response, with participants exhibiting different patterns of questionnaire response, decreasing the sample that consistently responds (Boyd et al., 2013). For example, some mothers will complete every other questionnaire, whilst others will not respond for several occasions, and then will complete a questionnaire (Fraser et al., 2013). Eighty-two percent of mothers initially enrolled were still engaged with the study by child age 18 years (Fraser et al., 2013). A number of steps are taken to encourage ongoing participation in the study. Parents are sent newsletters updating them on the studies progress and findings and the study is highlighted in the media whenever possible. Additionally, all children are sent birthday cards and have been invited to join a club to keep them interested in the study (Golding et al., 2001). However, the amount of

missing data when examining specific measures throughout adolescence is much more substantial, especially when analyses require using data across multiple time points throughout childhood and adolescence. The amount and treatment of missing data in this thesis is described in more detail below.

The starting sample included mothers who had information on depression symptoms from at least five time points since birth of child to child age 11 years (N = 10,559). This was done to ensure that some data were available for each mother across the whole time period. Those mothers excluded from the starting sample (n = 3058) differed from those included on a number of demographic characteristics. Mothers were younger [OR 0.89 (95% CI 0.88, 0.90)] and had increased parity [OR 1.17 (95% CI 1.12, 1.22)]. They were also more likely to smoke in pregnancy [OR 2.31 (95% CI 2.11, 2.54)], come from a lower social class [OR 1.95 (95% CI 1.74, 2.18)] and be single [OR 2.62 (95% CI 2.38, 2.87)]. Given that these families had very little data across childhood and adolescence, they were excluded from all further analyses. Of the starting sample, 4,588 offspring had complete data on suicide-related behaviour at age 16 years (43%; 1904 males and 2684 females; mean age: 16.7 years, standard deviation: 0.2 years). Figure 2.2 gives further detail on retention. Those missing information on the outcome differed from the starting sample (N = 10,559) on a number of demographic characteristics. Mothers were younger [OR 0.93 (95% CI 0.93, 0.94)] and had increased parity [OR 1.20 (95% CI 1.15, 1.25)]. They were also more likely to smoke in pregnancy [OR 1.86 (95% CI 1.69, 2.05)], come from a lower social class [OR 1.86 (95% CI 1.72, 2.02)], be single [OR 1.61 (95% CI 1.46, 1.78)] and have a higher number of depression symptoms in pregnancy [OR 1.04 (95% CI 1.03, 1.05)]. Offspring were more likely to be male [OR 0.48 (95% CI 0.45, 0.52)].

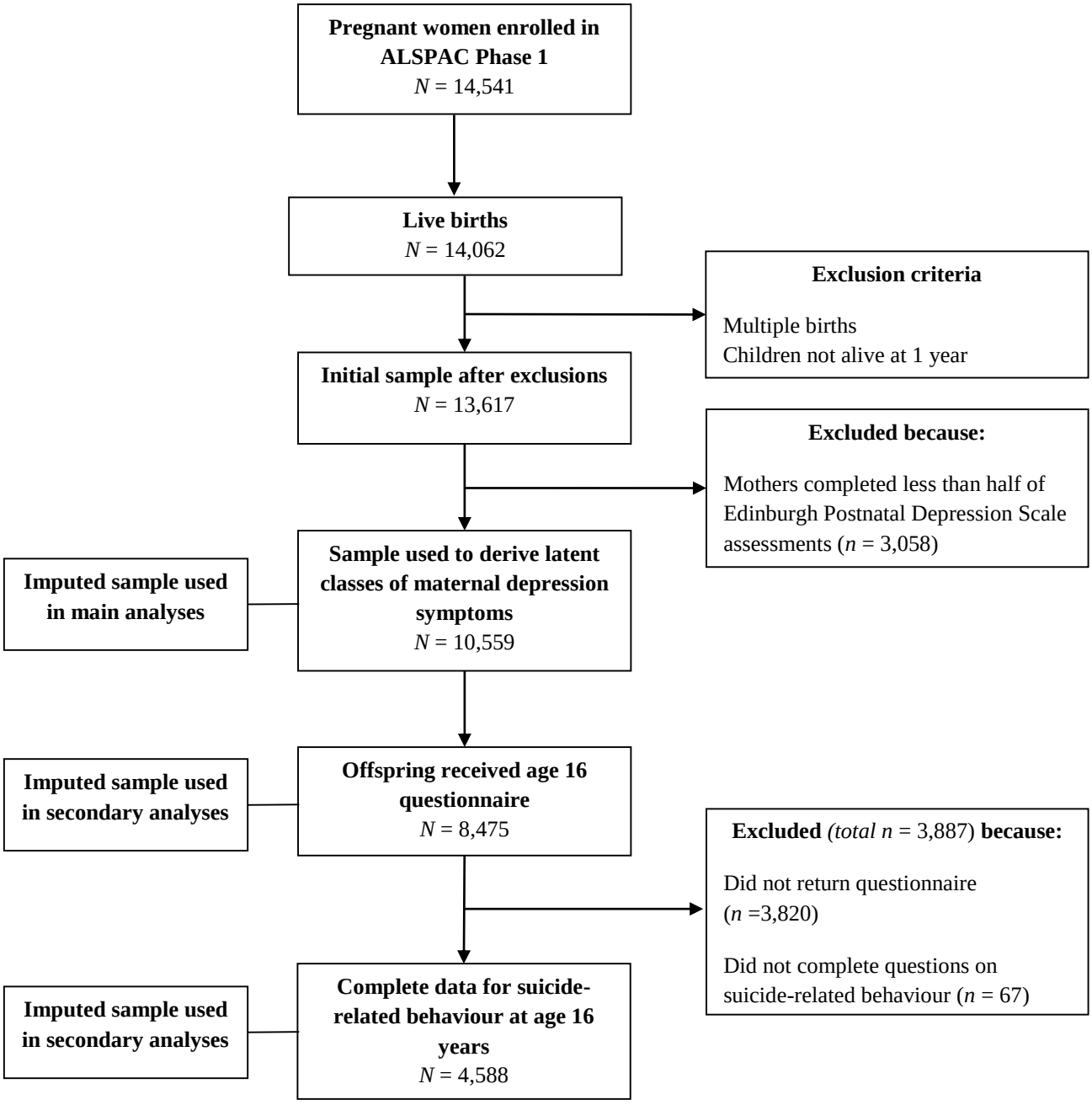


Figure 2.2 - Flow chart of retention in the 'Avon Longitudinal Study of Parents and Children' (ALSPAC) sample

The complete case sample across all measures utilised in subsequent analyses differs across each results chapter (Chapter 3: *N* = 3,735; Chapter 4: *N* = 2,445*;* Chapter 5: *N* = 2,599). Missing data for offspring suicide-related behaviour and psychopathology, maternal suicide attempt, the parent-child relationship, peer victimisation and other covariates were imputed using Multivariate Imputation by Chained Equations (MICE) (Van Buuren & Oudshoom, 2000) which assumes data are Missing At Random (MAR) i.e. given the observed data included in the imputation model, the missingness mechanism does not depend on the unobserved data (White, Royston, & Wood, 2011). As the ALSPAC sample has substantial information on socio-

demographic variables that predict missingness, missing information can be assumed to be dependent on observed data. These variables were included in the imputation model to make the assumption of MAR as plausible as possible. The imputation model also included other measures that have been found to be closely associated with offspring suicide-related behaviour and psychiatric disorder (including measures of offspring suicidal ideation, self-harm, psychiatric disorder and symptoms at multiple time points and measures of substance abuse), and the parent-child relationship and peer victimisation (including earlier measures of parenting and victimisation) and all other variables included in the analyses. Using binary and multinomial logistic and linear regression models as appropriate, 80 imputed datasets were derived, each with 10 cycles of regression switching. Predictive mean matching was used when continuous variables were not normally distributed. All analyses were then run on imputed datasets by combining estimates using Rubin's rules (White et al., 2011). It has been recommended that the number of imputed datasets exceeds 100*the maximum Fraction of Missing Information (FMI) value. FMI values were found to be no larger than 0.7, therefore imputing 80 datasets is adequate (White et al., 2011). All variables with missing data used in analyses were imputed up to the maximum sample size of 10,559 (i.e. those with data on the latent classes of maternal depression symptoms). Missing data were imputed with a fully conditional specification using the MICE (White et al., 2011) algorithm in STATA 13 (StataCorp, 2013).

The imputed sample of 10,559 is used for all analyses hereafter; however, sensitivity checks were performed by repeating analyses using alternative approaches to dealing with missing data. Main results tables within each chapter show results using four alternative approaches (1. full imputation, *N* = 10,559; 2. imputation for those sent questionnaires at age 16 years, *N* = 8,475; 3. imputation for those with complete outcome data, *N* = 4,588; 4. complete case analysis, *N* varies across chapters).

Table 2.1 shows demographics for those with complete data on suicide-related behaviour at age 16 years (*N* = 4,588) and each of the further imputed samples (*N* = 8,475; *N* = 10,559) in comparison to the original ALSPAC cohort that met inclusion criteria for this study (singletons and offspring alive at 1 year; *N* = 13,617). As shown in Table 2.1, the imputation procedure has corrected for biases present from selective attrition with the fully imputed sample being more representative of the original ALSPAC cohort than the sample with complete data on offspring suicide-related behaviour.

Table 2.1 - Demographics of the three imputed samples and the original cohort that met inclusion criteria

Sample demographics assessed during pregnancy[1]	Imputed sample [a] (*N* = 4,588)	Imputed sample [b] (*N* = 8,475)	Imputed sample [c] (*N* = 10,559)	Initial cohort [d] (*N* ≤ 13,617)
Female offspring (%)	58.5	50.5	48.4	48.4
Smoked in pregnancy (%)	16.6	20.7	22.5	25.8
Housing tenure (% rented)	14.5	19.1	21.5	26.7
Marital status (% single)	17.0	19.8	21.5	23.5
Maternal education (% < O-level)	18.4	24.2	26.6	26.7
Maternal depression (mean EPDS score at 32 weeks gestation)	6.36	6.77	6.90	7.05

[a] Sample with imputed data for mediators and confounders in those that had complete outcome data; [b] Sample with imputed data for mediators, confounders and outcome in those offspring that were sent the questionnaire at age 16 years; [c] Sample with imputed data for mediators, confounders and outcome in those that had complete exposure data (for those that have information on latent classes of maternal depression symptoms; main sample used throughout this thesis); [d] Original ALSPAC cohort that met inclusion criteria for this study

[1] Additional missing data on demographics: smoked in pregnancy missing for 792/13,617; housing tenure missing for 914/13,617; marital status missing for 858/13,617; maternal education missing for 1515 /13,617; maternal depression (Edinburgh Postnatal Depression Scale; EPDS) missing for 1895/13,617

2.3: Procedure

Parents and children have been followed up regularly since recruitment via questionnaire and clinic assessments. Data collection is ongoing, with data from offspring aged 24 years currently being collected. However, this thesis utilised data from pregnancy up to child age 16 years collected via both mother and child-rated questionnaire measures and clinic assessments.

For questionnaires sent to the mother during pregnancy, a reminder letter was sent if the questionnaire had not been returned within 7 days, with a second reminder letter being sent 10 days later. If the questionnaire had not been returned within a month, an ALSPAC team member phoned or visited the mother to encourage or help with the completion of the questionnaire (Golding et al., 2001). The delivery date was used to determine the dates of all subsequent questionnaires to mothers and children annually (Golding et al., 2001). All children in the study were invited to attend focus clinics from the age of 7 years. These focus clinics involved children and parents attending half day sessions annually. Interviews at focus clinics were conducted by trained psychology graduates.

Written, informed consent was obtained from all mothers who entered the ALSPAC study and ethical approval for the study was obtained from the ALSPAC Ethics and Law committee (IRB00003312) and the Local Research Ethics Committees. The ethics committee specifically approved the questionnaires and the clinic testing protocols including the methods of gaining consent.

Given that ALSPAC is a longitudinal study with many contact points with participants, consent was implied for self-completion questionnaire data when postal questionnaires were returned. All questionnaires to participants were logged when sent, reminded and returned, as were requests not to send further questionnaires. For data collected at the focus clinics, verbal consent was obtained from the parents or guardians on behalf of the children and verbal assent was obtained from the children before all measures. Verbal consent was used due to the large number of assessments at each half day clinic. Additionally, many assessments were repeat measures from earlier clinics and it was considered burdensome to ask participants to supply written consent for every measure. It was ensured that all participants were clear what was involved with each assessment and were informed that they could withdraw at any time. All written consent forms are filed securely and logged electronically (Hall, Maw, Midgley, Golding, & Steer, 2014).

The UK MRC and the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core funding support for ALSPAC. Further details on the sample characteristics and methodology have been described previously (Boyd et al., 2013; Fraser et al., 2013) and detailed information about ALSPAC can be found on the study website

(http://www.bristol.ac.uk/alspac). For information on all available ALSPAC data see the fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary).

2.4: Measures

Figure 2.3 shows a timeline of data collection for the main measures used in this thesis. Measures used were mainly from self-report questionnaires; however, information on offspring psychiatric disorders at age 15 years was collected using semi-structured interview at the focus clinic. Specific details on the main measures used across subsequent chapters (maternal depression symptoms, maternal suicide attempt, offspring psychiatric disorder and suicide-related behaviour) are given below. For further details on additional measures used in specific analyses, see relevant results chapters (Chapters 3, 4 and 5).

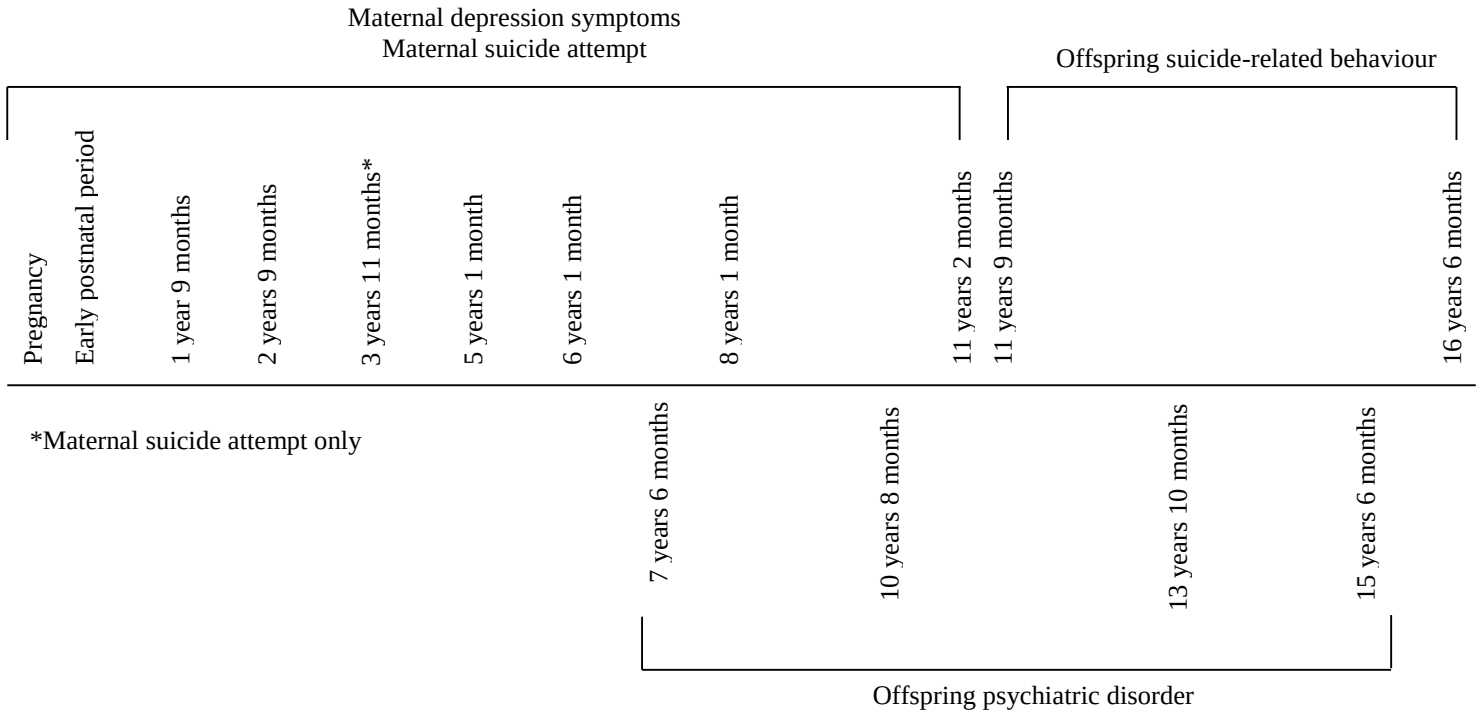


Figure 2.3 – Timeline of data collection in ALSPAC for main measures used in this thesis

2.4.1: Maternal depression symptom trajectories

Maternal depression symptoms were assessed at 10 time points (18 weeks gestation, 32 weeks gestation, 8 weeks postnatal, 8 months postnatal, 1 year 9 months, 2 years 9 months, 5 years 1 month, 6 years 1 month, 8 years 1 month and 11 years 2 months) using the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987). The EPDS is a self-report questionnaire used to assess symptoms of depression over the past week. It was devised for use in the postnatal period but it has been validated for use during pregnancy and in early parenthood using standardised psychiatric interviews (Eberhard-Gran, Eskild, Tambs, Opjordsmoen, & Samuelsen, 2001; Thorpe, 1993). It includes 10 items, each rated on a 4-point scale (0-3). Examples of questions include: *I have felt sad or miserable; I have been so unhappy that I have had difficulty sleeping; I have blamed myself unnecessarily when things went wrong*. The full list of items in the EPDS is provided in Appendix 2. Occasional missing data were imputed using hot deck imputation, substituting values from randomly drawn subjects closely matched on remaining items. This imputation method was used when less than four items on the questionnaire were missing. Symptom totals were calculated at each time point. Mothers' scores on the EPDS at each time point correlated moderately over time (r = .41 - .64) and internal consistencies at each time point were high (α = .85 - .89). A cut-off at 13 has been used to predict a clinical diagnosis of depression with a specificity of 95.7% and a sensitivity of 81.1% (Murray & Carothers, 1990).

2.4.2: Maternal suicide attempt

Maternal suicide attempt was assessed at 10 time points (from pregnancy to child age 11 years) using a self-report life events questionnaire (Brown & Harris, 1978) in which the mother was asked if she had attempted suicide since the previous assessment (beginning in pregnancy). All available time points were combined to create a binary 'yes/no' variable. Findings were robust to sensitivity analyses that examined alternative approaches to combining maternal suicide attempt across the 10 time points (i.e. only including mothers that had completed a minimum of seven assessments).

2.4.3: Offspring suicide-related behaviour

Suicide-related behaviour at age 16 years was assessed via a self-report postal questionnaire (Kidger et al., 2012). Relevant sections of the questionnaire are provided in Appendix 3. Participants were classified as having a lifetime history of suicidal ideation if they responded positively to either of the following questions: *Have you ever found yourself wishing you were dead and away from it all?*; *Have you ever thought of killing yourself, even if you would not really do it?* Due to mixed evidence regarding the importance of identifying risk factors for milder forms of suicide-related ideation, especially wishing to be dead (Brown, Steer, et al.,

2005; Kidger et al., 2012), for the purpose of this thesis, these two questions were combined to create a broad measure of suicidal ideation. After each question, participants were asked when the last time was that they felt this way. The analyses in the present thesis focus on children who reported suicidal ideation in the previous year (78% of those who reported lifetime suicidal ideation by age 16 years) partly to preserve the time ordering of events, but also due to evidence of more accurate reporting of suicidal ideation when shorter time spans are used (Klimes-Dougan, 1998). Sensitivity checks were performed by repeating all analyses using only the question: 'have you thought of killing yourself even if you would not really do it' as a more specific and severe measure of suicidal ideation. History of suicidal ideation at age 11 years was assessed using the childhood interview for borderline personality disorder (CI-BPD) (Zanarini, Horwood, Waylen, & Wolke, 2004) with the question: *Have you thought about killing yourself?* This time point was solely used in later analyses to exclude those who had already experienced suicidal ideation by age 11 years to rule out the possibility of reverse causation (offspring suicidal ideation before age 11 years influencing maternal depression).

Although the focus of this thesis is on adolescent suicidal ideation, secondary analyses investigated specific associations with lifetime history of suicide attempt by age 16 years. Suicide attempt was assessed using the same self-report questionnaire at age 16 years; however, only information on lifetime suicide attempt was available. Following the criteria set out by Silverman and colleagues (2007), suicide attempt was defined on the basis of suicidal intent but not injury. Therefore, participants were classified as having made a suicide attempt if they responded positively to the following question: *On any of the occasions when you have hurt yourself on purpose, have you ever seriously wanted to kill yourself?* Participants were also included if they reported '*I wanted to die'* as a reason to explain why they hurt themselves on purpose on the most recent occasion. Given the limitations of assessing suicidal intent using self-report (including bias, inaccuracy and ambivalence about dying), it has been recommended that behaviours are classified as suicidal when there is any evidence for suicidal intent (Nock, 2010). The procedure used in this thesis to classify suicide attempt is also in keeping with other studies using the ALSPAC cohort (Mars, Heron, Crane, Hawton, Kidger, et al., 2014; Mars, Heron, Crane, Hawton, Lewis, et al., 2014). Suicidal ideation and suicide attempt were examined as separate outcomes (as opposed to on an ordinal scale) for a number of reasons. First, as the focus of this thesis was on offspring suicidal ideation, the main reason that suicide attempt was included as a secondary outcome was to examine the clinical relevance of the main findings by examining risk for a more severe and clinically relevant sub-group (i.e. those that made a suicide attempt). Second, the outcomes were examined separately to allow examination of whether mechanisms differed for offspring suicidal ideation and suicide attempt. Further detail and validation of the measures of suicidal ideation and suicide attempt used in this thesis are provided in Chapter 3, section 3.4.3.

2.4.4: Offspring psychiatric disorder and symptoms

Offspring psychopathology was assessed using the Development and Well-Being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) parent (age 7, 10, 13 and 15 years) and child (age 15 years) versions. The DAWBA is a semi-structured interview consisting of open and closed questions about child mental health symptoms and their impact. When symptoms are identified by the structured questions, open-ended questions and additional prompts are used by interviewers to encourage the participant to describe the symptoms in more detail in their own words (Goodman et al., 2000). MDD over the previous month was generated at every time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV (American Psychiatric Association, 1994) or ICD-10 (World Health Organization, 1993) diagnosis of depression and generates diagnoses (see www.DAWBA.com for more information). Additionally, at age 15 years, parent versions of the DAWBA were used to assess symptoms of DBD (ODD over the past 6 months or conduct disorder over the past year) and symptoms of ADHD over the past 6 months. Child versions of the DAWBA at age 15 years were used to assess symptoms of MDD over the past month and symptoms of GAD over the past 6 months. Different time spans are used across the DAWBA sections to follow DSM-IV criteria. Each DAWBA section consisted of 20-25 questions that followed the diagnostic criteria operationalised in the DSM-IV or ICD-10. Continuous symptom scores were derived from the sum of all symptom items within the relevant section of the DAWBA. Symptom counts were derived following the procedure outlined in a recent study using this dataset (Davies et al., 2015). Additionally, at age 15 years, 'any disorder' (including DSM-IV or ICD-10 depressive disorders, anxiety disorders, DBD, ADHD and eating disorders) was derived using the same computerised algorithm described above. A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part of the ALSPAC data collection process (Goodman, Heiervang, Collishaw, & Goodman, 2011). Previous studies using the DAWBA have shown excellent discrimination in rates of diagnosed disorder between clinic and community samples, with high agreement between case note and DAWBA diagnoses in the clinic sample (Goodman et al., 2000).

2.4.5: Potential confounders

Potential socio-demographic and familial confounding factors assessed in pregnancy were chosen based on evidence from previous literature (Burcusa & Iacono, 2007; Campbell et al., 2007; Cents et al., 2013; Chen et al., 2013; Evans et al., 2004; Johnson et al., 2002; Mars et al., 2012; Matijasevich et al., 2015; Nandi et al., 2009; Skipstein et al., 2010). Maternal questionnaires completed during pregnancy were used to assess housing tenure (owned vs. rented), marital status (married vs. single), maternal level of education (below O-level, O-level or above O-level; O-level, or ordinary level, is an academic qualification taken at the end of

compulsory schooling which is now defunct in the UK and has been replaced with GCSE examinations), self-reported psychiatric disorder before pregnancy (yes/no; including drug addiction, alcoholism, schizophrenia, anorexia nervosa, severe depression or any other psychiatric disorder), maternal family history of depression (neither, one or both parents) and smoking in pregnancy (smoked tobacco in either the first three months or the last two weeks of pregnancy).

2.5: Statistical analyses

The two main statistical techniques used throughout this thesis, Latent Class Growth Analysis (LCGA) and Structural Equation Modelling (SEM), are described in detail below. Specific analytical techniques used in additional analyses are described in the relevant results chapter.

2.5.1: Latent Class Growth Analysis

LCGA is a type of analysis that combines both person-centred and variable-centred approaches (Nagin, 2005). In variable-centred analyses, the focus is on the relationship between variables, whereas the focus of person-centred analyses is on the relationship among individuals (Jung & Wickrama, 2008; Muthén & Muthén, 2000). LCGA is used when it is hypothesised that there are latent (unmeasured) subgroups in the population and the technique will cluster individuals into groups based on repeated continuous or categorical measures. LCGA includes both continuous and categorical latent variables, with the categorical latent variable used to create groups of individuals based on individual response patterns who are homogeneous within their group but heterogeneous across groups (Jung & Wickrama, 2008; Muthén & Muthén, 2000).

In this thesis, LCGA was used to identify qualitatively distinct patterns of depression symptoms in mothers over time from 18 weeks gestation to child age 11 years using the EPDS (as a continuous scale). Therefore, homogenous groups of mothers were identified based on specific growth parameters including each mother's initial level and rate of change in depression symptoms. Each mother was given a probability of belonging to each class and these probabilities were then used to assign each mother to their most likely class. In contrast to Growth Mixture Modeling (GMM), LCGA assumes no within class variance on the growth factors (the intercept and slope) and these are set to be zero. Given that our focus was to identify distinct groups of mothers rather than to examine within-group variability, we used the LCGA approach which helps with the clearer identification of classes and involves less computational burden than allowing the within class variance to be freely estimated (Jung & Wickrama, 2008). Figure 2.4 provides a path diagram for the LCGA model used in this thesis.

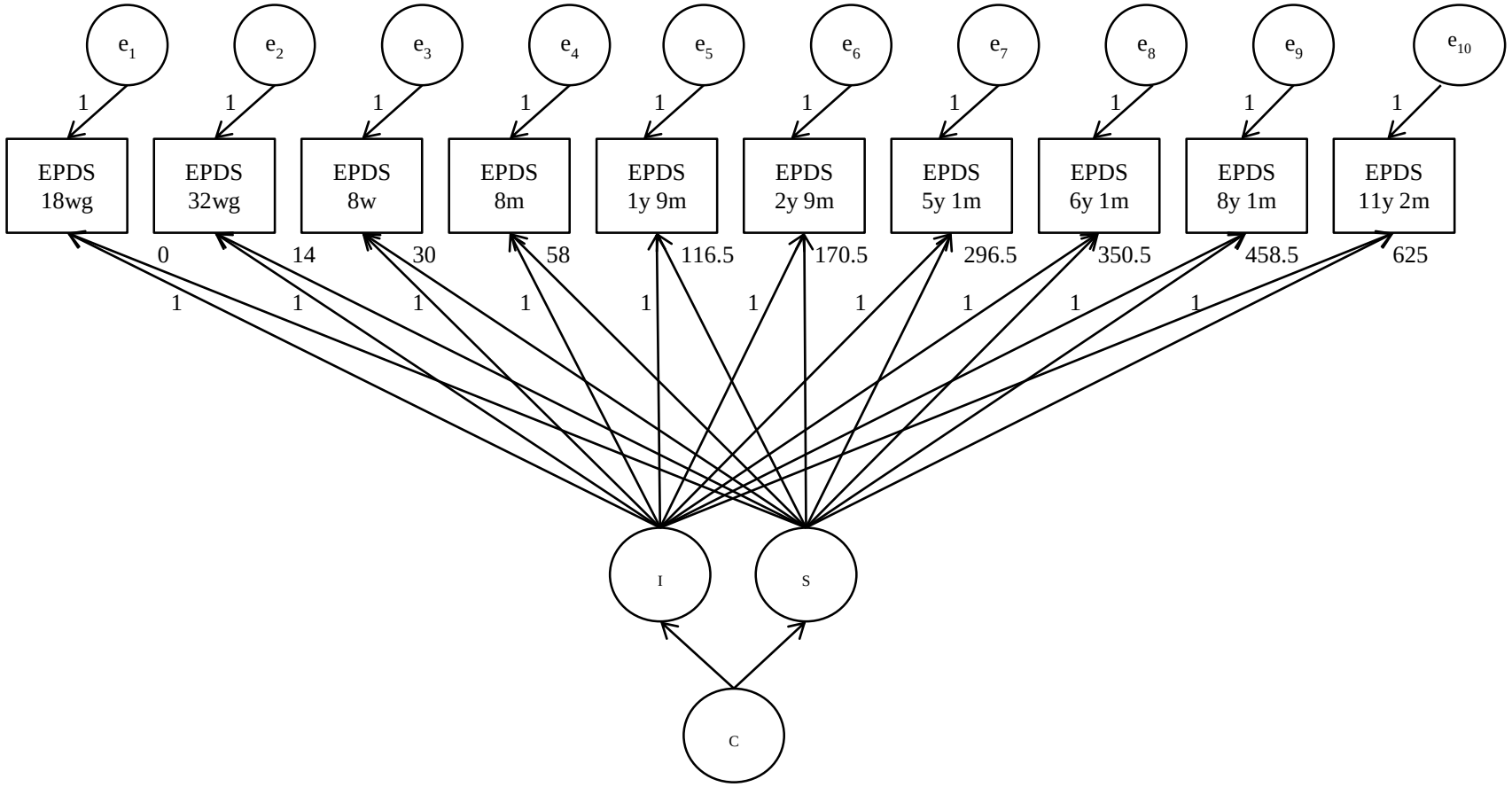


Figure 2.4 – Path diagram for Latent Class Growth Analysis (LCGA) model; I=intercept; S=slope; C=class; e=residual variance

The starting sample for these analyses included mothers who had information on depression symptoms from at least five time points since birth of child to age 11 years (N = 10,559). Given that list-wise deletion of families can increase sample bias (White et al., 2011), methods were taken to incorporate as much data as possible and for the derivation of latent classes, missing data was handled using Full Information Maximum Likelihood (FIML) estimation (Enders, 2010).

From previous literature (Barker, 2013; Campbell et al., 2007; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009; Mars et al., 2015; Skipstein et al., 2010) we expected to find between three and six classes of maternal depression symptoms; therefore, a series of models were fitted and theoretical and statistical steps were taken to decide which model provided the best fit to the data. These included a number of fit statistics (including the Sample Size Adjusted Bayesian Information Criterion (SSABIC), Lo, Mendell & Rubin Likelihood Ratio Test (LMR-LRT) and entropy values). Using the maximum probability rule, individuals were then assigned to the class for which they had the highest probability of membership. This approach is justified when the posterior probability scores for each trajectory group are high (above at least 0.7) indicating that there is clear separation of classes (Nagin, 2005). These analyses were conducted using M*plus* version 7 (Muthén & Muthén, 1998-2012). Further detail on the derivation and validation of the latent classes of maternal depression symptoms is provided in Chapter 3.

2.5.2: Structural Equation Modelling and mediation analyses

SEM is a general term that has been used to describe a large number of statistical models used to evaluate the validity of substantive theories with empirical data (Lei & Wu, 2007). It is a general approach to multivariate modelling and takes a confirmatory (hypothesis testing) approach. The goal is to determine whether a hypothesised theoretical model is consistent with the data collected to reflect this theory. Path analysis is a type of SEM where there is only a single measure of each theoretical variable and there are prior hypotheses regarding causal relationships among the variables (Kline, 2005). It allows the relationship between several related variables to be examined simultaneously.

Mediation analyses examine whether the association between an exposure and an outcome is explained through a hypothesised third variable (Preacher & Hayes, 2008). It is an expectation about how one variable changes another, which in turn, changes the outcome. Using the product of coefficients strategy (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002), the indirect effect can be calculated from the product of coefficients from exposure to mediator and from mediator to outcome. However, the distribution of the product of coefficients is rarely normally distributed leading to low power to detect an indirect effect. Therefore, bootstrapping is

recommended as a method to calculate the indirect effect (MacKinnon, 2004). As bootstrapping is a non-parametric test, it does not rely on the assumptions of normality that are often not met when calculating indirect effects (MacKinnon, 2004). Bootstrapping is a resampling procedure where many different data sets are created. Each time an individual case is randomly selected with replacement and put in a new data file with as many cases as the original data file. Each new data file will be slightly different from the original data file. For each new data file the indirect effect is calculated and stored. The indirect effect is then calculated as the mean of the indirect effects from all generated data sets. In this thesis, where multiple imputation was used, it was not possible to calculate bias-corrected bootstrapped confidence intervals around indirect effects, therefore 95% confidence intervals were calculated using the standard error. Indirect effects from exposure to outcome are free of the scale of measurement of the potential mediator (Hayes, 2009). Therefore indirect effects to the same outcome and from the same exposure can be directly compared. Using SEM allows indirect effects to be compared by putting equality constraints on the products of paths and examining change in model fit (Hayes, 2009). SEM also offers further advantages for conducting mediation analyses such as greater flexibility in model specification and estimation options and being able to easily conduct more complicated mediation models with multiple mediators (Preacher & Hayes, 2004, 2008).

In Chapters 4 and 5, a number of multiple mediation models were run using SEM to assess effects of the maternal depression classes on offspring suicide-related behaviour via potential mediators. Figure 2.5 provides a path diagram for a mediation model used in Chapter 4.

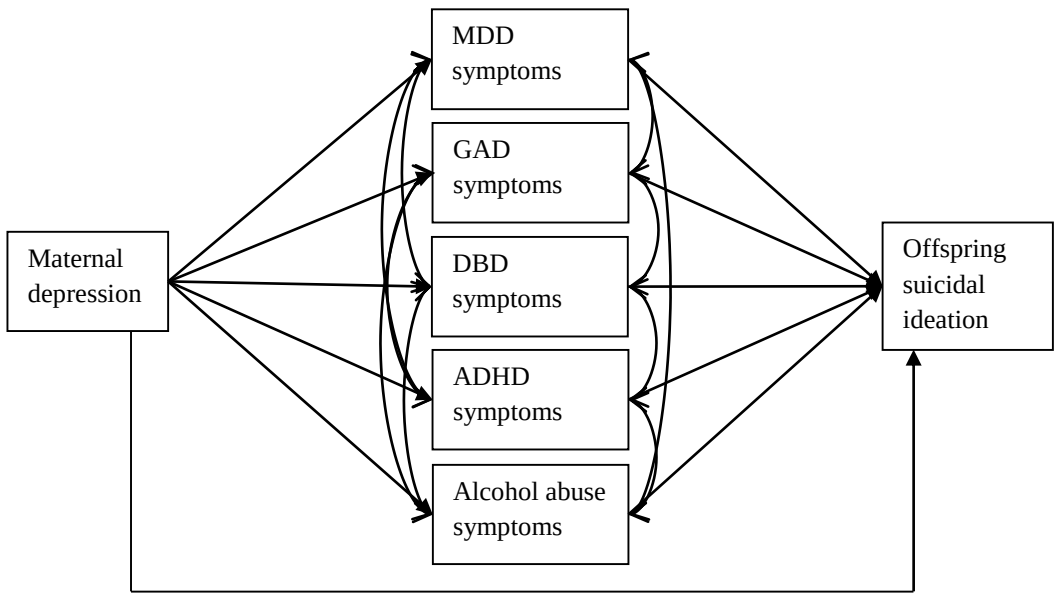


Figure 2.5 - Structural model examining the direct effect of maternal depression on offspring suicidal ideation, and the indirect effects through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse

A weighted least squares estimator (WLSMV) was used due to its robustness in analysing both continuous and categorical measures in SEM (Muthén & Muthén, 1998-2012). Results from path analyses with a continuous outcome are presented as linear regression coefficients and results with a categorical outcome (including indirect effects) are presented as probit regression coefficients (referred to throughout this thesis as B). Probit coefficients refer to the strength of the association between an exposure and probability of group membership. Therefore the coefficient represents the difference that a 1-unit change in the exposure variable makes in the cumulative normal probability of the outcome variable. Indirect effects were calculated using a non-parametric bootstrapping approach with 500 replications. To examine if the indirect effects within the same model differ in strength, post-hoc Wald Chi square tests were used to test the assumption of equality between constrained indirect effects. The final models were also rerun without using bootstrapping in order to calculate model fit statistics (the Root-Mean Square Error of Approximation (RMSEA) and the Comparative Fit Index (CFI)). RMSEA values below .05 (Browne & Cudeck, 1992) and CFI values above .90 (Hu, Bentler, & Kano, 1992) indicate close fit. These analyses were also conducted using M*plus* version 7 (Muthén & Muthén, 1998-2012).

Chapter 3: Derivation of maternal depression symptom trajectories and association with subsequent offspring suicide-related behaviour

The work presented in this chapter has been published: Hammerton, G., Mahedy, L., Mars, B., Harold, G. T., Thapar, A., Zammit, S., & Collishaw, S. (2015). Association between maternal depression symptoms across the first eleven years of their child's life and subsequent offspring suicidal ideation. *PLoS One, 10*(7), e0131885.

The published article has been edited for this chapter in order to include additional results (including additional descriptive information on offspring suicide-related behaviour and results previously available as supplementary materials) and to reduce the amount of repetition across Chapter 2 and section 3.3 in this chapter. However, there is some repetition of content in section 3.2 and the thesis introduction (Chapter 1).

Please see http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0131885 for the full published article.

3.1: Summary

Depression is common, especially in women of child-bearing age, and there is robust evidence that maternal depression is associated with mental health problems in offspring. Suicidal behaviour is a growing concern amongst young people and those exposed to maternal depression are likely to be especially at high risk. The aim of this chapter was to utilise a large, prospective population cohort to examine the relationship between depression symptom trajectories in mothers over the first eleven years of their child's life and subsequent adolescent suicidal ideation and suicide attempt. An additional aim was to test if associations were explained by maternal suicide attempt and offspring depressive disorder. Data were utilised from ALSPAC. Maternal depression symptoms were assessed repeatedly from pregnancy to child age 11 years. Offspring suicide-related behaviour was assessed at age 16 years. Using multiple imputation, data for 10,559 families were analysed. Using LCGA, five distinct classes of maternal depression symptoms were identified (minimal, mild, increasing, sub-threshold, chronic-severe). The prevalence of past year suicidal ideation at age 16 years was 15% (95% CI 14, 17%). Compared to offspring of mothers with *minimal* symptoms, the greatest risk of later suicidal ideation was found for offspring of mothers with *chronic-severe* symptoms [OR 3.04 (95% CI 2.19, 4.21)], with evidence for smaller increases in risk of suicidal ideation in offspring of mothers with *sub-threshold*, *increasing* and *mild* symptoms. These associations were not fully accounted for by maternal suicide attempt or a depression diagnosis in offspring. Twenty-six percent of non-depressed offspring of mothers with *chronic-severe* depression symptoms reported suicidal ideation. Associations were similar when examining risk for offspring suicide

attempt. Therefore, risk for suicide-related behaviour should be considered in young people whose mothers have a history of sustained high levels of depression symptoms, even when the offspring themselves do not have a diagnosis of depression.

3.2: Chapter introduction

Evidence from existing community studies suggests that maternal depressive disorder is associated with an increased risk of later suicidal ideation in offspring (Garber et al., 1998; Wilcox et al., 2010). Using a sample of 240 young adolescents and their mothers (the majority of whom had a history of a mood disorder), Garber and colleagues (1998) found evidence for an association between maternal history of mood disorder and offspring suicidal symptoms one year later (d' = 0.13), when adjusting for offspring baseline suicidal symptoms. A more recent study that assessed suicidal ideation repeatedly over a four year period in a sample of college students also found evidence that maternal history of depressive disorder, assessed retrospectively with the student, was associated with persistent suicidal ideation in offspring (Wilcox et al., 2010). There was also evidence of an association between maternal history of depression and offspring making a suicide plan or attempt during college (Wilcox et al., 2010).

The majority of previous literature has examined links between a lifetime diagnosis of maternal depression and offspring suicidal ideation (Garber et al., 1998; Wilcox et al., 2010). Heterogeneity in the course, timing and severity of depression that might influence risk for offspring suicidal ideation is typically not taken into account (Nandi et al., 2009). Given that depression can be episodic or persistent, focusing only on a single time point or on presence or not of a lifetime diagnosis could give a misleading impression of the level and duration of maternal depression symptoms that offspring are exposed to. Prospective longitudinal studies enable some aspects of this heterogeneity to be captured by identifying patterns of maternal depression symptoms over time. This allows severity as well as stability or change in maternal depression symptoms over time to be considered. Several studies have demonstrated the added value of using longitudinal trajectories of maternal depression symptoms to predict offspring psychopathology over an assessment at a single point in time or predefined measures of severity and chronicity (Cents et al., 2013; Nandi et al., 2009), but these have thus far not considered offspring risk of suicidal ideation or attempt.

The reasons for an association between maternal depression and offspring suicide-related behaviour also remain unclear. The association could be confounded by socio-demographic risk factors that are known correlates of maternal depression (Skipstein et al., 2010) and are also related to offspring risk of suicide-related behaviour (Johnson et al., 2002; Page et al., 2014). Alternatively, shared genetic risk factors may confound the association. It is also possible that

the association between maternal depression and offspring suicide-related behaviour reflects causal processes. It is possible, for example, that maternal depression leads to offspring suicide-related behaviour either due to exposure to maternal suicide attempt or by increasing risk for offspring depression (Brent et al., 1994; Bridge et al., 2006; Gureje et al., 2011; Mittendorfer-Rutz et al., 2008). At present, however, evidence is inconclusive and although depression itself is familial, previous studies have found that the association between maternal depression and offspring suicide-related behaviour is not fully explained by offspring depression (Gureje et al., 2011; Wilcox et al., 2010). More information from unselected population cohorts is needed to better understand the degree to which risk for suicide-related behaviour reflects confounding by correlated socio-demographic adversity and shared familial risk, or the role of maternal suicide attempt or offspring depressive disorder.

The present chapter examines the association between maternal depression symptom course over the first eleven years of their child's life and subsequent offspring suicidal ideation and attempt at age 16 years in a large, population-based birth cohort. The primary hypothesis is that variation in maternal depression symptom course from pregnancy to child age 11 years will be associated with subsequent offspring suicidal ideation at age 16 years over and above potential socio-demographic and familial confounders, with greatest risk for offspring of mothers with severe and chronic depression symptoms. However, it is also expected that sub-threshold maternal depression symptoms that persist over time will be associated with increased risk of offspring suicidal ideation. The secondary hypothesis is that the associations observed will be attenuated, but not completely explained through maternal suicide attempt or a diagnosis of depression in the offspring. Analyses will also examine whether findings are similar when examining risk for offspring lifetime suicide attempt.

3.3: Chapter methods

3.3.1: Sample

Data were utilised from a large UK birth cohort study; ALSPAC. Further detail on the sample is given in Chapter 2 (section 2.1).

3.3.2: Measures

<u>Maternal depression symptom trajectories</u>

Maternal depression symptoms were assessed at 10 time points (18 weeks gestation, 32 weeks gestation, 8 weeks postnatal, 8 months postnatal, 1 year 9 months, 2 years 9 months, 5 years 1 month, 6 years 1 month, 8 years 1 month and 11 years 2 months) using the EPDS. Further detail is given in Chapter 2 (section 2.4.1).

Maternal suicide attempt

Maternal suicide attempt was assessed at 10 time points (from pregnancy to child age 11 years) using a self-report life events questionnaire in which the mother was asked if she had attempted suicide since the previous assessment (beginning in pregnancy). All available time points were combined to create a binary 'yes/no' variable. Further detail is given in Chapter 2 (section 2.4.2).

Mothers known to services

For the purposes of validation, a measure of whether mothers were known to services due to their depression was derived. Mothers were considered to be known to services if they reported either seeing the doctor for their depression or taking medication for depression. Both questions were assessed at seven time points (from birth of child to child age 9 years) using a self-report questionnaire in which the mother was asked if she had seen the doctor or 'taken pills for depression' since the last assessment. Two binary 'yes/no' variables were then created by combining all available time points from birth of child to child age 3 years and then by combining all available time points from child age 3 years to 9 years. A measure of both 'early' and 'late' service use was derived in order to validate a trajectory of maternal depression showing increasing levels of symptoms over time. Again, findings were robust to sensitivity analyses that examined alternative approaches to combining time points.

Offspring suicide-related behaviour

Suicide-related behaviour at age 16 years was assessed via a self-report postal questionnaire (Kidger et al., 2012). Further detail is given in Chapter 2 (section 2.4.3).

Offspring Major Depressive Disorder (MDD)

Offspring diagnosis of depression was assessed using the DAWBA parent (age 7, 10 and 13 years) and child (age 15 years) versions. Diagnoses of MDD over the previous month were generated at each time point using a well-defined computerised algorithm that predicts the likelihood of a clinical rater assigning each child a DSM-IV or ICD-10 diagnosis of depression and generates diagnoses. A senior clinical psychiatrist reviewed the diagnoses and the DAWBA responses as part of the ALSPAC data collection process (Goodman et al., 2011). The presence of a diagnosis of MDD at any assessment was then calculated.

Potential confounders

Maternal questionnaires completed during pregnancy were used to assess housing tenure (owned vs. rented), marital status (married vs. single), maternal level of education (below O-

level, O-level or above O-level), self-reported psychiatric disorder before pregnancy (yes/no; including drug addiction, alcoholism, schizophrenia, anorexia nervosa, severe depression or any other psychiatric disorder), maternal family history of depression (neither, one or both parents) and smoking in pregnancy (smoked tobacco in either the first three months or the last two weeks of pregnancy).

3.3.3: Statistical analyses

Given that list-wise deletion of families can increase sample bias (White et al., 2011), methods were taken to incorporate as much data as possible and for the derivation of latent classes, missing data was handled using FIML estimation (Enders, 2010). The starting sample for these analyses included mothers who had information on depression symptoms from at least five time points since birth of child to age 11 years (N = 10,559). This was done to ensure that some data were available for each mother across the whole time period. Of the starting sample, 8,475 offspring were sent the questionnaire at age 16 years and of these 4,588 provided complete data on suicide-related behaviour (43% of starting sample; 1,904 males and 2,684 females; mean age: 16.7 years, standard deviation: 0.2 years). Finally, 3,735 offspring also had complete data on other covariates of interest. Missing data for offspring suicide-related behaviour and depressive disorder, maternal suicide attempt and other covariates were imputed using MICE (Van Buuren & Oudshoom, 2000). Further detail on the imputation procedure is given in Chapter 2 (section 2.2.2). Main results are presented for three different imputation approaches (1. full imputation, N = 10,559; 2. imputation for those sent questionnaires at 16, N = 8,475; 3. complete case analysis, N = 3,735). Analyses in this chapter were not presented for the imputed sample with complete data on offspring suicide-related behaviour (N = 4,588) due to this sample size being very close to the size of the complete case sample in these analyses.

LCGA (Nagin, 2005) was used to identify qualitatively distinct patterns of depression symptoms in mothers over time from 18 weeks gestation to child age 11 years using the EPDS. Further detail on LCGA is provided in Chapter 2 (section 2.5.1). The Population Attributable Risk (PAR) was calculated for offspring suicidal ideation based on exposure to any level of depression in the mother (i.e. mother part of *mild, increasing, sub-threshold or chronic-severe* class). Confidence intervals for PAR were estimated by hand from the upper and lower confidence interval of the relative risk between maternal depression and offspring suicidal ideation due to imputed data being used. Next, to examine if variation in maternal depression symptom course was associated with subsequent offspring suicidal ideation, a logistic regression analysis was performed with maternal depression class as the exposure variable (treated as a class membership categorical variable) and past year offspring suicidal ideation at age 16 years as the outcome (model 1). In model 2, potential socio-demographic and familial

confounders were adjusted for. Next maternal suicide attempt was included in analyses to examine if the association between maternal depression class and offspring suicidal ideation is explained through maternal suicide attempt (model 3). In model 4, offspring MDD was additionally included to examine if any association found is explained through offspring depression diagnosis. Next, analyses were rerun after excluding offspring who reported suicidal ideation prior to age 11 years to rule out the possibility of reverse causation (offspring suicidal ideation before age 11 years influencing maternal depression). Lastly, a parallel set of logistic regression analyses were performed between classes of maternal depression symptoms (with *minimal* class as the reference group) and offspring lifetime suicide attempt by age 16 years. Analyses were conducted using Stata version 13 (StataCorp, 2013) and M*plus* version 7 (Muthén & Muthén, 1998-2012).

3.4: Results

3.4.1: Latent classes of maternal depression symptoms

Based on fit statistics, size of latent classes and parsimony, a five class model represented the best fit to the data. Model fit statistics (SSABIC (entropy)) from 3 to 6 classes were: 505553 (0.86), 503123 (0.82), 501995 (0.80), 501003 (0.77), respectively. Lower SSABIC values reflect superior fit of a given model; however, a non-significant LMR-LRT for the 6 class model suggested that the 6 class solution did not significantly improve model fit over the 5 class solution, whereas a significant LMR-LRT for the 5 class model indicated that the 5 class model did improve model fit over the 4 class solution. The estimated posterior probability scores for each trajectory group for the five class model are presented in Table 3.1. Probabilities can range from 0 to 1 with 1 representing perfect classification. Ideally, individuals' probability of membership will approach 1 for one class with small probabilities for all other classes, indicating clear separation of classes. Average posterior probabilities for most likely latent class membership for the five class model ranged from .78 to .92 indicating relatively unambiguous classification. Findings from previous literature suggested that there could be a non-linear growth pattern to the data (Campbell et al., 2007; Cents et al., 2013); therefore a quadratic growth model was also fitted. However, as the five identified classes showed the same profile, we chose to keep the more parsimonious model (including the linear growth parameter).

Table 3.1 - Average posterior probability scores for most likely latent class membership (row) by latent class (column) for the five class model; bold represents average posterior class probability for trajectory membership

Most likely latent class membership	Latent class				
	Minimal	Mild	Increasing	Sub-threshold	Chronic-severe
Minimal	**.919**	.075	.007	.000	.000
Mild	.083	**.814**	.058	.046	.000
Increasing	.015	.140	**.784**	.061	.000
Sub-threshold	.000	.071	.035	**.867**	.027
Chronic-severe	.000	.000	.001	.074	**.925**

Five classes of maternal depression symptoms were identified, four showing stable levels of symptoms over time but differing in level of severity and one showing increasing symptoms. Figure 3.1 shows both the model fitted linear growth trajectories for each class and the observed pseudo-class trajectories for the five identified classes of maternal depression symptoms. Approximately 5% of the sample was identified as belonging to a class with high stable symptoms that were consistently above the clinical cut-off of 13 on the EPDS (*chronic-severe* class; average predicted probability of class membership: 0.93). Nearly 18% belonged to a class with sub-threshold symptoms over time, with symptom levels that were consistently just below the clinical cut-off on the EPDS and decreased very slightly over time (*sub-threshold* class; predicted probability: 0.87). Just under 6% belonged to a class with increasing symptoms over time, with symptom levels that rose to the clinical cut-off by the last time point (*increasing* class; predicted probability: 0.78). Just over 30% of the sample belonged to a class with stable mild symptoms over time (*mild* class; predicted probability: 0.81). Lastly, 40% of the sample belonged to a class with very low levels of depression symptoms over time (*minimal* class; predicted probability: 0.92). In all further analyses the *minimal* class is treated as the reference group unless otherwise stated.

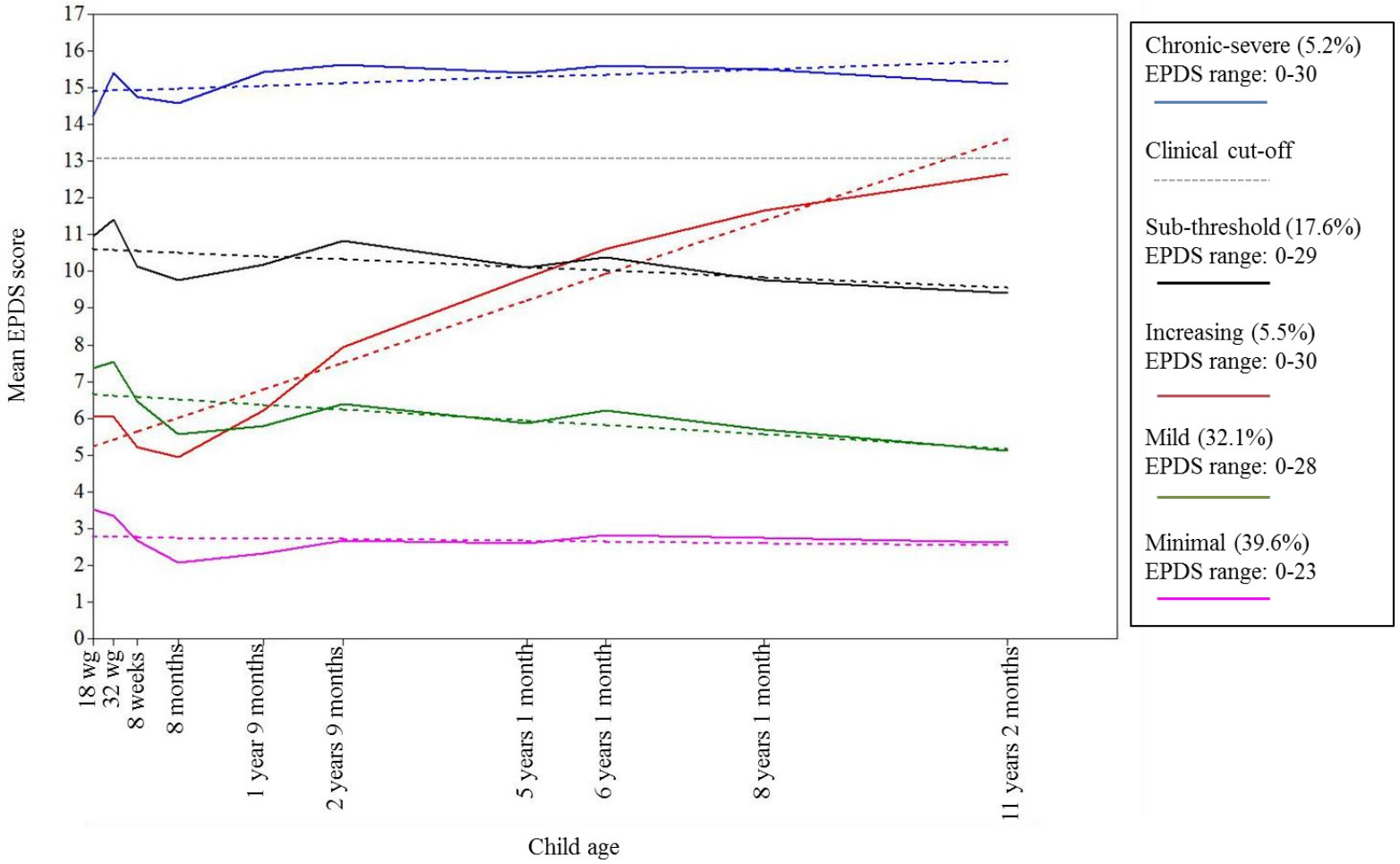


Figure 3.1 - Five class model of maternal depression symptoms measured using the Edinburgh Postnatal Depression Scale (EPDS) from 18 weeks gestation to child age 11 years; figure shows both model fitted estimated linear growth trajectories for each class (dotted line) and the observed pseudo-class trajectories for the identified classes (solid line); N = 10,559

3.4.2: Validation of latent classes of maternal depression symptoms

Table 3.2 shows that the pattern of association between the classes of maternal depression symptoms and other clinical and sociodemographic measures used in analyses was consistent with the pattern expected. There was a stepped increase in prevalence for most measures with increasing severity of maternal depression symptom trajectories. Compared to mothers with *minimal* depression symptoms, mothers with *chronic-severe* symptoms were more likely to make a suicide attempt, live in rented accommodation, be single, smoke in pregnancy, have less education, have a psychiatric disorder before pregnancy, have a family history of depression and be known to services due to depression. Offspring of mothers with *chronic-severe* depression were also more likely to have a diagnosis of MDD. The pattern of association was similar for mothers with *mild, increasing* and *sub-threshold* symptoms compared to mothers with *minimal* symptoms with a few exceptions. There was no evidence that mothers with *mild* and *increasing* symptoms had less education than mothers with *minimal* symptoms. Additionally, there was no evidence that mothers with *increasing* symptoms were more likely to be single or have a family history of depression compared to mothers with *minimal* symptoms.

Table 3.2 - Pattern of maternal suicide attempt, offspring Major Depressive Disorder (MDD), housing tenure, marital status, maternal smoking in pregnancy, maternal education, maternal psychiatric disorder before pregnancy, maternal family history of depression and maternal depression-related service use by classes of maternal depression symptoms; imputed N = 10,559

	Minimal (n = 4,177)	Mild (n = 3,384)	Increasing (n = 583)	Sub-threshold (n = 1,863)	Chronic-severe (n = 552)
Maternal suicide attempt (%)	0.34	1.09***	4.12***	3.98***	10.87***
Offspring MDD (%)	2.14	3.06#	5.87***	7.08***	14.34***
Housing tenure (% rented)	16.05	22.77***	19.89*	27.45***	37.08***
Marital status (% single)	16.54	22.33***	18.89	28.54***	32.37***
Smoked in pregnancy (%)	16.86	22.90***	24.79***	29.85***	35.92***
Maternal education (% < O-level)	24.27	25.77	23.83	31.01***	36.76***
Maternal past psychiatric disorder (%)	4.59	10.16***	11.22***	21.45***	37.63***
Maternal family history of depression (% both of child's maternal grandparents)	1.23	2.14**	1.95	3.40***	5.97***
Maternal service use:					
From birth of child to age 3 years (%)	4.68	14.20***	18.14***	30.18***	55.66***
From child age 3 years to 9 years (%)	9.67	20.67***	41.98***	39.20***	62.84***

#$p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$ with minimal class as the reference group

3.4.3: Prevalence of offspring suicide-related behaviour

The number of adolescents that reported lifetime suicidal ideation by age 16 years was 867/4,588 (19%; 214 males and 653 females). Of these, 78% reported suicidal ideation within the last year. All the analyses in this thesis focus on children who reported suicidal ideation in the previous year to preserve the time ordering of the analysis.

The number of adolescents that reported past year suicidal ideation at the age 16 years assessment was 672/4,588 (15%; 174 males and 498 females). Of these, 81% reported specifically that they had thought about killing themselves. Of the adolescents that reported suicidal ideation in the past year (n = 672), 25% had made a suicide plan in their lifetime and 35% had made a suicide attempt. Additionally, 92% had not reported lifetime suicidal ideation at age 11 years (i.e. new onset cases).

The number of adolescents that reported a lifetime suicide attempt at the age 16 years assessment was 302/4,588 (7%; 61 males and 241 females). Of these, 15% were included as making a lifetime suicide attempt because they reported 'wanting to die' as a reason why they hurt themselves on purpose on the most recent occasion but did not report that they had ever seriously wanted to kill themselves. As has been reported previously (Mars, Heron, Crane, Hawton, Kidger, et al., 2014), of those adolescents that reported a lifetime suicide attempt (n = 302), 28% reported that they swallowed pills or something poisonous the last time that the hurt themselves on purpose, 84% cut themselves on this occasion, 13% burnt themselves and 16% did something else (including an excess of alcohol or drugs, self-battery, jumping or dangerous behaviour and hanging, strangulation or suffocation). Additionally, 54% of the adolescents who had made a lifetime suicide attempt had ever tried to get help from someone about hurting themselves or wanting to kill themselves, and 92% also reported lifetime suicidal ideation.

The number of children that reported suicidal ideation at age 11 years was 272/5,613 (5%; 144 males and 128 females). Of those that reported suicidal ideation (n = 272), 8.1% had also made a suicide plan.

The overall prevalence for offspring suicide-related behaviour was very similar in fully imputed models taking account of missing data – the estimated prevalence for past year suicidal ideation at age 16 years was 15% (95% CI 14, 17%; 11% of males and 20% of females) and the estimated prevalence for lifetime suicide attempt at age 16 years was 8% (95% CI 7, 9%; 5% of males and 11% of females). Finally, the estimated prevalence for suicidal ideation by age 11 years was 6% (95% CI 5, 6%; 6% of males and 5% of females).

3.4.4: Association between latent classes of maternal depression symptoms, maternal suicide attempt and offspring MDD with offspring past year suicidal ideation at age 16 years

Figure 3.2 shows an increase in prevalence of offspring suicidal ideation at age 16 years with increasing severity of maternal depression symptom trajectories. The pattern is similar for males and females, although a higher percentage of females report suicidal ideation across all classes. In total, 18% of offspring of mothers with *chronic-severe, sub-threshold, increasing* or *mild* symptoms reported suicidal ideation, resulting in a PAR of 23% (95% CI 17, 30%).

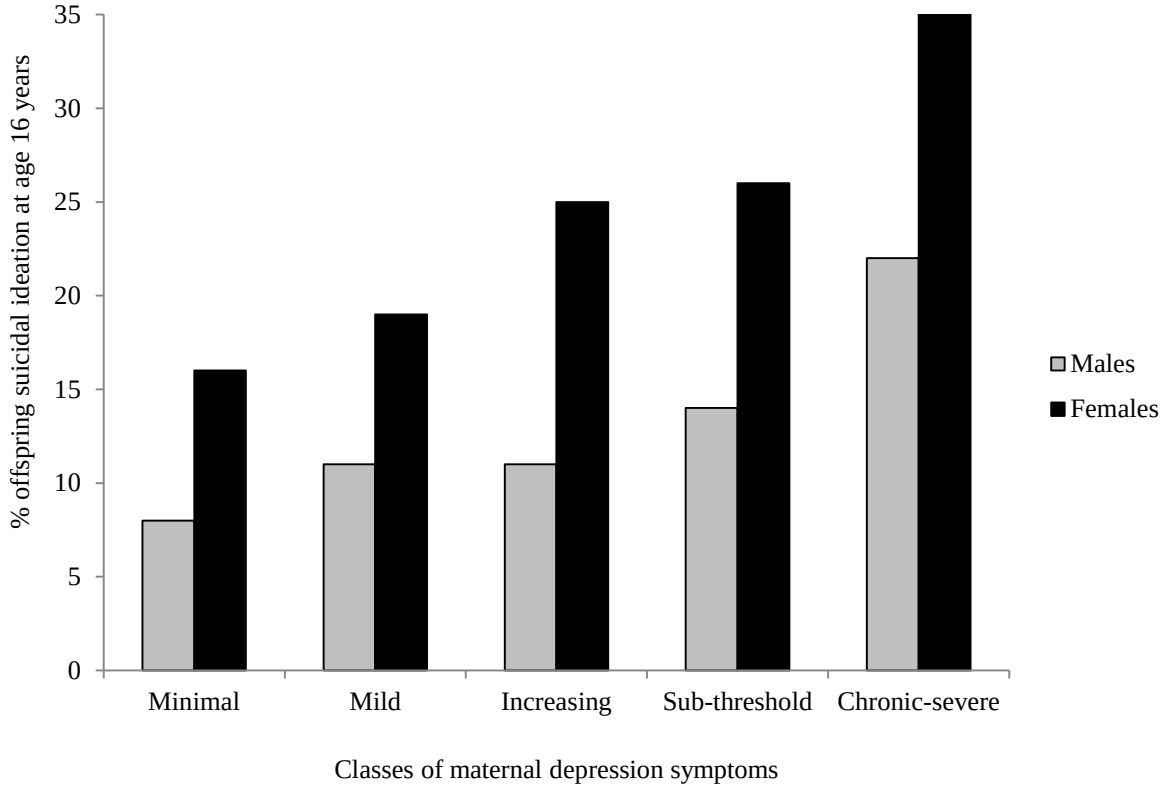


Figure 3.2 - Percentage of male and female offspring with past year suicidal ideation at age 16 years for each of the classes of maternal depression symptoms; imputed *N* = 10,559

In order to examine whether the increase in prevalence of suicidal ideation at age 16 years with increasing severity of maternal depression symptom trajectories was solely due to an increase in prevalence of offspring depressive disorder, the pattern of findings was examined in non-depressed offspring. A similar pattern of results was found when the percentage of offspring with suicidal ideation, but no previous diagnosis of MDD was examined [*minimal:* 11% (95% CI 10, 13%)*; mild*: 14% (95% CI 12, 16%); *increasing*: 16% (95% CI 12, 21%); *sub-threshold*: 18% (95% CI 15, 22%); *chronic-severe:* 26% (95% CI 20, 32%)].

Table 3.3 shows evidence of associations between maternal suicide attempt, offspring MDD, housing tenure and maternal smoking in pregnancy, past psychiatric disorder before pregnancy and family history of depression with offspring suicidal ideation at age 16 years.

Table 3.3 – Associations between maternal suicide attempt, offspring Major Depressive Disorder (MDD), housing tenure, marital status, maternal smoking in pregnancy, maternal education, maternal psychiatric disorder before pregnancy and maternal family history of depression with offspring suicidal ideation at age 16 years (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed N = 10,559

	No suicidal ideation	Suicidal ideation	OR (95% CI)
Maternal suicide attempt (%)	1.51	4.56	3.10 (2.03, 4.74)***
Offspring MDD (%)	3.02	10.35	3.69 (2.50, 5.45)***
Housing tenure (% rented)	20.28	28.35	1.55 (1.29, 1.88)***
Marital status (% single)	21.00	24.07	1.19 (0.98, 1.45)
Smoked in pregnancy (%)	21.18	29.89	1.59 (1.31, 1.92)***
Maternal education (% < O-level)	26.29	28.07	1.16 (0.96, 1.41)
Maternal past psychiatric disorder (%)	10.42	17.08	1.77 (1.40, 2.24)***
Maternal family history of depression (% both)	1.76	4.56	2.88 (1.89, 4.38)***

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

Next, a logistic regression analysis was performed between the classes of maternal depression symptoms (with *minimal* class as the reference group) and offspring suicidal ideation at age 16 years. Table 3.4 shows evidence for increased risk of suicidal ideation in offspring of mothers from each of the depression classes in comparison to the offspring of mothers with *minimal* symptoms (model 1). These associations were attenuated only marginally when adjusted for potential confounders (model 2). Additionally, the associations were not fully explained through maternal suicide attempt (model 3) or offspring MDD (model 4). When examining associations in those offspring who did not report suicidal ideation at age 11 years (i.e. new onset cases), findings were similar; however there was no evidence for an association between the *mild* and *increasing* classes with offspring suicidal ideation after adjusting for covariates (see Appendix 4).

Table 3.4 - Logistic regression analyses showing associations between each class of maternal depression symptoms in comparison to minimal class (reference group) and subsequent offspring past year suicidal ideation at age 16 years (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 10,559

	OR (95% CI)			
Maternal depression class	Model 1 (unadjusted)	Model 2 [a]	Model 3 [b]	Model 4 [c]
Minimal (*n* = 4,177)	Reference group			
Mild (*n* = 3,384)	1.31 (1.09, 1.59)**	1.23 (1.01, 1.49)*	1.22 (1.01, 1.49)*	1.22 (1.00, 1.48)*
Increasing (*n* = 583)	1.59 (1.16, 2.19)**	1.47 (1.06, 2.04)*	1.43 (1.02, 1.99)*	1.37 (0.97, 1.92) [#]
Sub-threshold (*n* = 1,863)	1.85 (1.50, 2.27)***	1.60 (1.29, 1.99)***	1.57 (1.26, 1.95)***	1.51 (1.21, 1.88)***
Chronic-severe (*n* = 552)	3.04 (2.19, 4.21)***	2.38 (1.68, 3.37)***	2.23 (1.57, 3.19)***	2.01 (1.40, 2.87)***

[#]$p \leq .10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] Adjusting for confounders assessed in pregnancy (housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy)

[b] Additionally adjusting for maternal suicide attempt (from pregnancy to child age 11 years)

[c] Additionally adjusting for a diagnosis of MDD in offspring (assessed using the DAWBA at ages 7, 10, 13 and 15 years)

Sensitivity checks were then performed by rerunning analyses using alternative approaches to dealing with missing data. Table 3.5 shows associations between the classes of maternal depression symptoms and offspring suicidal ideation (after adjusting for potential confounders, maternal suicide attempt and offspring MDD) across the different sample sizes. Results were comparable when only imputing data for those offspring that were sent the questionnaire measure at age 16 years (N = 8,475; sample 2). The pattern of findings was also similar when using only those with complete data on outcome and covariates, however, wider confidence intervals in complete case analysis meant that there was no evidence for an association between the *mild* and i*ncreasing* classes with offspring suicidal ideation after adjusting for all covariates (N = 3,735; sample 3).

Table 3.5 - Logistic regression analyses showing associations between each class of maternal depression symptoms in comparison to minimal class (reference group) and subsequent offspring past year suicidal ideation at age 16 years using alternative approaches to dealing with missing data (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed)

	OR (95% CI) [a]		
Maternal depression class	Sample 1 (using full imputed data; *N* = 10,559) [b]	Sample 2 (imputing those that were sent Q; *N* = 8,475) [c]	Sample 3 (complete cases; *N* = 3,735) [d]
Minimal	Reference group		
Mild	1.22 (1.00, 1.48)*	1.22 (0.98, 1.50) [#]	1.17 (0.93, 1.47)
Increasing	1.37 (0.97, 1.92) [#]	1.38 (0.96, 1.97) [#]	1.27 (0.84, 1.90)
Sub-threshold	1.51 (1.21, 1.88)***	1.50 (1.19, 1.90)***	1.58 (1.20, 2.09)***
Chronic-severe	2.01 (1.40, 2.87)***	2.08 (1.43, 3.02)***	2.03 (1.31, 3.15)**

[#]$p \leq .10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] All results adjusted for confounders assessed in pregnancy, maternal suicide attempt and a diagnosis of MDD in offspring

[b] Sample 1 shows the fully adjusted results using the full imputed dataset

[c] Sample 2 shows the fully adjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years

[d] Sample 3 shows the fully adjusted results using only those with complete data on all variables in analysis

Next, a logistic regression analysis was performed between classes of maternal depression symptoms (this time with the *chronic-severe* class as the reference group) and offspring past year suicidal ideation at age 16 years. There was evidence for decreased risk of suicidal ideation in offspring of mothers from each of the depression classes in comparison to the offspring of mothers with *chronic-severe* symptoms [*minimal:* OR 0.33 (95% CI 0.24, 0.46); *mild*: OR 0.43 (95% CI 0.31, 0.60); *increasing*: OR 0.52 (95% CI 0.34, 0.81); *sub-threshold*: OR 0.61 (95% CI 0.43, 0.86)]. Finally, when directly comparing offspring of mothers with *mild, increasing* and *sub-threshold* symptoms, there was no evidence for a difference in risk of suicidal ideation.

3.4.5: Association between latent classes of maternal depression symptoms, maternal suicide attempt and offspring MDD with offspring lifetime suicide attempt by age 16 years

A similar set of analyses also investigated associations with offspring suicide attempt. Figure 3.3 shows an increase in prevalence of offspring suicide attempt at age 16 years with increasing severity of maternal depression symptom trajectories. Again, the pattern is similar for males and females, although a higher percentage of females report making a suicide attempt across all classes. In total, 10% of offspring of mothers with *chronic-severe, sub-threshold, increasing* or *mild* symptoms reported a suicide attempt, resulting in a PAR of 35% (95% CI 24, 45%).

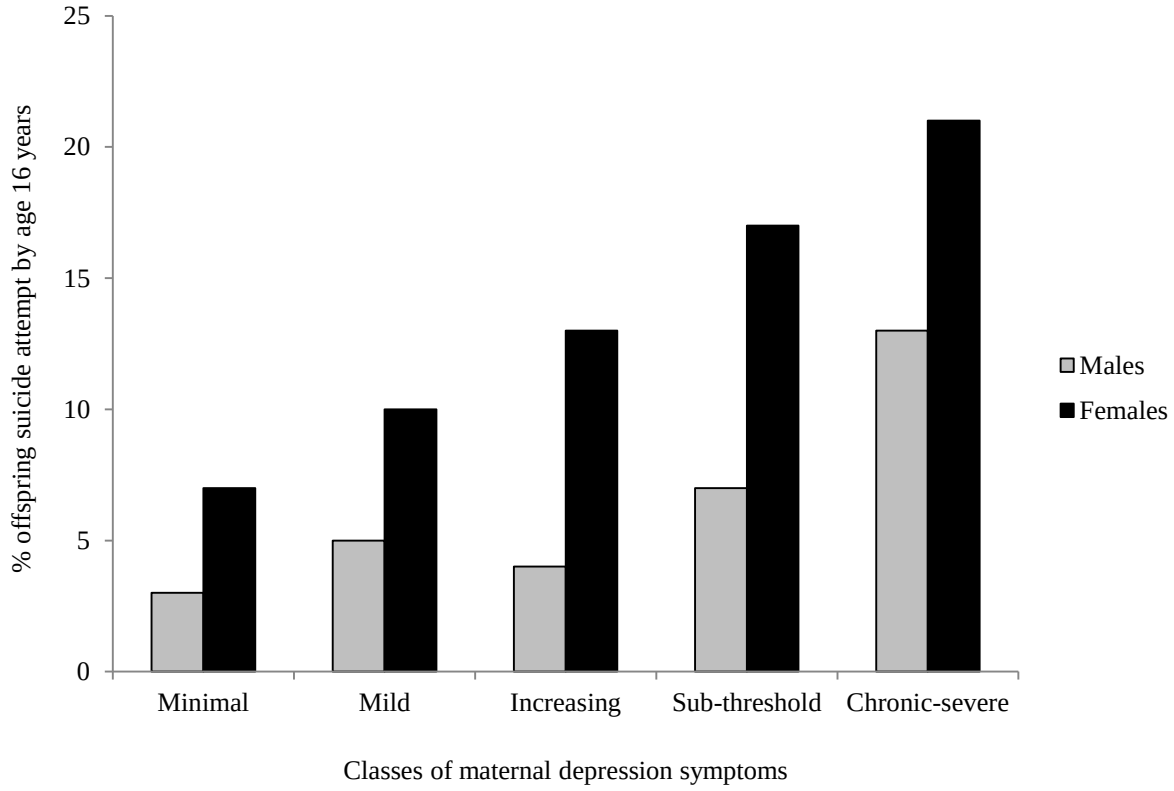


Figure 3.3 - Percentage of male and female offspring with lifetime suicide attempt by age 16 years for each of the classes of maternal depression symptoms; imputed *N* = 10,559

Table 3.6 shows evidence of associations between maternal suicide attempt, offspring MDD, housing tenure, marital status and maternal smoking in pregnancy, past psychiatric disorder before pregnancy and family history of depression with offspring suicide attempt by age 16 years.

Table 3.6 – Associations between maternal suicide attempt, offspring Major Depressive Disorder (MDD), housing tenure, marital status, maternal smoking in pregnancy, maternal education, maternal psychiatric disorder before pregnancy and maternal family history of depression with offspring suicide attempt by age 16 years (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed N = 10,559

	No suicide attempt	Suicide attempt	OR (95% CI)
Maternal suicide attempt (%)	1.54	7.13	4.86 (2.97, 7.97)***
Offspring MDD (%)	3.17	15.73	5.68 (3.90, 8.27)***
Housing tenure (% rented)	20.49	33.71	1.97 (1.55, 2.51)***
Marital status (% single)	20.79	29.55	1.60 (1.26, 2.03)***
Smoked in pregnancy (%)	21.31	36.80	2.15 (1.73, 2.67)***
Maternal education (% < O-level)	26.29	29.82	1.32 (0.99, 1.76)#
Maternal past psychiatric disorder (%)	10.67	20.59	2.17 (1.65, 2.85)***
Maternal family history of depression (% both)	1.93	5.25	3.02 (1.74, 5.24)***

#$p \leq .10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

Table 3.7 shows evidence for increased risk of suicide attempt in offspring of mothers with *mild, sub-threshold* and *chronic-severe* symptoms in comparison to the offspring of mothers with *minimal* symptoms after adjusting for potential confounders, maternal suicide attempt and offspring MDD.

Table 3.7: Logistic regression analysis showing associations between each class of maternal depression symptoms in comparison to minimal class (reference group) and offspring lifetime suicidal attempt by age 16 years (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 10,559

	OR (95% CI)			
Maternal depression class	Model 1 (unadjusted)	Model 2 [a]	Model 3 [b]	Model 4 [c]
Minimal (*n* = 4,177)	Reference group			
Mild (*n* = 3,384)	1.50 (1.14, 1.96)**	1.35 (1.02, 1.78)*	1.34 (1.01, 1.76)*	1.33 (1.01, 1.76)*
Increasing (*n* = 583)	1.80 (1.12, 2.87)*	1.60 (0.99, 2.58) [#]	1.51 (0.93, 2.46) [#]	1.41 (0.86, 2.31)
Sub-threshold (*n* = 1,863)	2.55 (1.92, 3.38)***	2.05 (1.53, 2.76)***	1.97 (1.46, 2.66)***	1.85 (1.37, 2.50)***
Chronic-severe (*n* = 552)	3.79 (2.48, 5.78)***	2.64 (1.71, 4.08)***	2.35 (1.51, 3.67)***	1.97 (1.25, 3.12)**

[#]$p \leq 0.10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] Adjusting for confounders assessed in pregnancy (housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy)

[b] Additionally adjusting for maternal suicide attempt (from pregnancy to child age 11 years)

[c] Additionally adjusting for a diagnosis of MDD in offspring (assessed using the DAWBA at ages 7, 10, 13 and 15 years)

Finally, sensitivity checks were performed by rerunning analyses using alternative approaches to dealing with missing data. Table 3.8 shows associations between the classes of maternal depression symptoms and offspring suicide attempt (after adjusting for potential confounders, maternal suicide attempt and offspring MDD) across the different sample sizes. Results were comparable when only imputing data for those offspring that were sent the questionnaire measure at age 16 years (N = 8,475; sample 2). The pattern of findings was also similar when using only those with complete data on outcome and covariates, however, wider confidence intervals in complete case analysis meant that there was no evidence for an association between the *mild* class and offspring suicide attempt after adjusting for all covariates (N = 3,735; sample 3).

Table 3.8 - Logistic regression analyses showing associations between each class of maternal depression symptoms in comparison to minimal class (reference group) and subsequent offspring lifetime suicide attempt by age 16 years using alternative approaches to dealing with missing data (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed).

	OR (95% CI) [a]		
Maternal depression class	Sample 1 (using full imputed data; *N* = 10,559) [b]	Sample 2 (imputing those that were sent Q; *N* = 8,475) [c]	Sample 3 (complete cases; *N* = 3,735) [d]
Minimal	Reference group		
Mild	1.33 (1.01, 1.76)*	1.32 (0.98, 1.78)	1.28 (0.92, 1.80)
Increasing	1.41 (0.86, 2.31)	1.40 (0.83, 2.35)	1.08 (0.58, 2.02)
Sub-threshold	1.85 (1.37, 2.50)***	1.85 (1.34, 2.56)***	1.81 (1.23, 2.66)**
Chronic-severe	1.97 (1.25, 3.12)**	2.02 (1.24, 3.31)**	2.30 (1.28, 4.12)**

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

[a] All results adjusted for confounders assessed in pregnancy, maternal suicide attempt and a diagnosis of MDD in offspring

[b] Sample 1 shows the fully adjusted results using the full imputed dataset

[c] Sample 2 shows the fully adjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years

[d] Sample 3 shows the fully adjusted results using only those with complete data on all variables in analysis

3.5: Discussion

In this population sample, five distinct classes of maternal depression symptoms were identified. Four classes showed stable levels of depression symptoms but differed in the level of severity and one class showed a change in severity, with increasing levels of depression symptoms over time. Variation in maternal depression symptom course was associated with subsequent offspring suicidal ideation at age 16 years, with greatest risk of suicidal ideation for offspring of mothers with *chronic-severe* depression symptoms. However, there were also smaller increases in risk for offspring of mothers with *sub-threshold*, *increasing* and *mild* symptoms in comparison to offspring of mothers with *minimal* symptoms. Results were similar when examining associations with offspring lifetime suicide attempt. This is an important finding because more than half of this population cohort of teenagers had experienced maternal depression at sub-threshold levels; in fact, the PAR was 35% for offspring suicide attempt suggesting that if levels of maternal depression symptoms in the *chronic-severe, sub-threshold, increasing* and *mild* classes, could be reduced to levels of depression in the *minimal* class (assuming the associations are causal, estimates are unbiased and everything else remained the same), 35% of cases of adolescent suicide attempt could be prevented. Associations between maternal depression and offspring suicide-related behaviour were not completely explained through maternal suicide attempt or a diagnosis of depression in the offspring.

This is one of the first studies to examine whether there is an association between variation in maternal depression symptom course over time and subsequent offspring suicidal ideation. The results extend the findings of previous longitudinal studies that have found an association between maternal depressive disorder and offspring suicidal ideation (Garber et al., 1998; Wilcox et al., 2010). The identified trajectories also extend the majority of wider research on the course of maternal depression in the general population in terms of the time scale and number of assessments used. Other population-based samples that have examined trajectories of maternal depression symptoms across shorter time spans, or fewer assessments in relation to other outcomes in offspring have also identified a small class of mothers with chronic and severe depression symptoms and a number of more common classes of mothers with stable symptoms across time that differ in level of severity (Barker, 2013; Campbell et al., 2007; Cents et al., 2013; Matijasevich et al., 2015; Skipstein et al., 2010; van der Waerden, Galéra, Saurel-Cubizolles, Sutter-Dallay, & Melchior, 2015). A trajectory-based approach is useful for longitudinal cohort data where repeated assessments of mental health symptoms are available (Nandi et al., 2009). The approach means that symptom levels across time rather than a single time point can be used and therefore provides a more robust measure of depression as measurement error is accounted for when deriving trajectories. Additionally, the classes that

have emerged in the mothers were meaningful in that they discriminated a group of offspring at high risk of developing suicide-related behaviour.

In the derivation of the latent classes, although maternal depression trajectories were mostly stable, one group of mothers did exhibit meaningful change in symptom levels over time. Fewer studies have identified a group of mothers with increasing symptoms over time (Campbell et al., 2007; Matijasevich et al., 2015; Skipstein et al., 2010; van der Waerden et al., 2015) and it could be that this group is more likely to emerge with a longer time span of assessment (Campbell et al., 2007). Additionally, the classes that emerged in the current study support findings from two recent studies that examined trajectories of maternal depression symptoms (also assessed using the EPDS) from pregnancy to approximately child age 6 years (Matijasevich et al., 2015; van der Waerden et al., 2015). Both studies, one using a community sample of mothers in Brazil (Matijasevich et al., 2015) and the other of mothers in France (van der Waerden et al., 2015), identified a group of mothers whose depression symptoms began to rise in the child's preschool period, with the offspring of these mothers being at similar risk for later psychiatric disorder as the offspring of mothers with depression symptoms that started high and decreased over the study (Matijasevich et al., 2015). In the current study, offspring of mothers with *increasing* symptoms were nearly two times more likely to have suicidal ideation at age 16 years compared to offspring of mothers with *minimal* symptoms. It should be noted however, that not only did mothers with *increasing* symptoms have the most uncertainty in group membership in the derivation of classes, but also, wider confidence intervals meant there was more uncertainty in the association with offspring suicidal ideation, especially when using only those with complete data, and when excluding offspring with earlier suicidal ideation. In addition, there was only weak evidence for increased risk of suicide attempt in offspring of mothers with *increasing* symptoms after adjusting for potential confounders.

Previous studies have provided strong evidence that both a diagnosis of depression (Evans et al., 2004; Nock et al., 2013) and maternal suicide attempt (Geulayov et al., 2012; Geulayov et al., 2014) increase risk for suicide-related behaviour in adolescents. In this study, associations between differing levels of maternal depression and later offspring suicide-related behaviour were slightly attenuated when including maternal suicide attempt and offspring depression diagnosis in the analysis, especially for the *chronic-severe* class. However, there was still evidence for an association between the classes of maternal depression symptoms and offspring suicide-related behaviour after accounting for these potential mediators. These findings extend results from studies that have found that maternal depression and maternal suicide attempt, assessed retrospectively, have independent links with offspring suicidal ideation and behaviour (Gureje et al., 2011). Furthermore, these results provide support for the view that maternal depression, in addition to contributing to risk for a diagnosis of depression in the offspring, may

also contribute to risk for suicide-related behaviour through other routes (Gureje et al., 2011; Wilcox et al., 2010). The results from this chapter showed that offspring of mothers with *chronic-severe* depression symptoms were at highest risk of suicide-related behaviour with these offspring being two times more likely to have suicidal ideation and make a suicide attempt compared to offspring of mothers with *minimal* symptoms. In addition, there was evidence that offspring of mothers with *chronic-severe* symptoms were also at increased risk of suicidal ideation when compared to offspring of mothers with *sub-threshold, increasing* and *mild* symptoms. This is unsurprising as not only are chronic and severe symptoms of depression likely to indicate higher genetic risk, but also offspring exposed to chronic symptoms are more likely to be exposed to a variety of environmental risk factors such as a negative family environment (Goodman & Gotlib, 1999). Genetic confounding was not something that we were able to account for in this study; however it is an important consideration given evidence that longitudinal stability in depression symptoms is mainly attributable to genetic factors (Nivard et al., 2014).

These findings need to be considered in the light of some additional limitations. Firstly, as with most cohort studies, there was selective attrition over time; however, potential bias arising from missing data was dealt with using multiple imputation, utilising a large amount of additional information to make the assumption of MAR as plausible as possible (White et al., 2011). Previous studies have recommended using multiple imputation to deal with potential bias arising from missing data, especially when data are thought to be MAR (conditional on the other variables included in the model) (Moodie, Delaney, Lefebvre, & Platt, 2008). Additionally, analyses were repeated using only those with complete data and the pattern of findings was the same except for weaker evidence of an association for the *increasing* and *mild* classes after adjusting for all covariates. This pattern of findings across imputed and complete case samples has been shown previously in studies using the same sample that have reported that the association between maternal and offspring depression may be underestimated in complete case analyses (Pearson et al., 2013). Second, it is important to consider the possibility of reverse causation i.e. offspring suicidal ideation having an adverse effect on maternal depression symptom course. Even though offspring suicidal ideation was assessed approximately five years after the maternal depression trajectories, some offspring may already have experienced suicidal ideation at earlier time points. When excluding offspring that reported suicidal ideation at age 11 years all associations were attenuated slightly, however conclusions remained the same, at least for offspring of mothers with *chronic-severe* and *sub-threshold* symptoms suggesting that reverse causation is unlikely to fully explain these associations. Third, the importance of offspring depression as a mediator of intergenerational links may be underestimated. Although the presence of offspring MDD was assessed repeatedly from age 7

to age 15 years findings may not account for offspring that had an episode of depression between assessments or at age 16 years when suicide-related behaviour was assessed. It is also possible that concurrent sub-threshold symptoms of offspring depression at age 16 years could further explain associations. However, diagnostic measures of depression were unavailable at age 16 years and broader symptom screens typically also tap into a range of other related psychopathology, personality traits and cognitive processes. The overlap between suicidal ideation and depression symptoms in adolescents is difficult to disentangle and is something that future research should investigate more thoroughly. Fourth, we treated the derived classes of maternal depression symptoms as observed groups in analyses examining the association with offspring suicide-related behaviour. This approach means that the uncertainty in latent class membership is not taken into account and can inflate differences between classes that are not well separated. However, when the posterior probability scores for each trajectory group are high, as in the current study, this indicates clear separation of classes and provides justification for the approach that was taken. Therefore, it is unlikely that not taking account of the uncertainty in class membership would substantially bias the findings. Finally, risk to offspring from paternal depression was not considered, and this could reflect an important confounding factor for associations between maternal depression and offspring suicide-related behaviour.

In summary, variation in maternal depression symptoms over time was associated with subsequent offspring suicidal ideation and suicide attempt, with greatest risk for offspring of mothers with *chronic-severe* symptoms. However, suicide risk should be considered in offspring, even when maternal depression symptoms are below clinical levels. Offspring of mothers with subclinical levels of depression symptoms are an important group to consider as these offspring may be less likely to be known to services as mothers may have never been diagnosed with clinical depression. In this sample, only half of mothers with *sub-threshold* symptoms were known to services. However, as expected, it is offspring of mothers with both chronic and severe depression symptoms that are most at risk and a priority for preventive interventions. Additionally, as 26% of non-depressed adolescents in this group reported suicidal ideation at age 16 years, this highlights the importance of enquiring about suicidal ideation in offspring of depressed mothers, even when offspring do not have a diagnosis of depression. Given that the majority of mothers from the *chronic-severe* class were already known to services, this would be an easily identified high-risk group to target (Potter et al., 2012). These results may have implications for adult mood disorder clinics, GPs and schools. The findings highlight the importance of GPs being aware of potential problems in children of mothers with chronic depression, and the need for adult services to consider risks in adolescent offspring of mothers with severe and chronic depression. Identifying barriers to effective communication between adult and child services will be important. The results also highlight the importance of

educating schools in being able to identify children at high suicide risk, and knowing the appropriate course of action to take, given that, for some children at risk, it is possible that neither parent nor child will already be known to services. Given that maternal suicide attempt and offspring depressive disorder did not fully explain associations between maternal depression and offspring suicide-related behaviour in this chapter, examining other potential mechanisms that may help to explain why offspring of mothers with depression are at increased risk for suicide-relate behaviour is an important next step.

Chapter 4: Pathways to suicide-related behaviour in offspring of depressed mothers: the role of offspring psychopathology

The work presented in this chapter has been published: Hammerton, G., Zammit, S., Mahedy, L., Pearson, R., Sellers, R., Thapar, A., & Collishaw, S. (2015). Pathways to suicide-related behaviour in offspring of depressed mothers: the role of offspring psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry, 54*(5), 385-393.

The published article has been edited for this chapter in order to include additional results (previously available as supplementary materials) and to reduce the amount of repetition across Chapter 2 and section 4.3 in this chapter. However, there is some repetition of content in section 4.2 and the thesis introduction (Chapter 1).

Please see http://www.jaacap.com/article/S0890-8567(15)00078-7/abstract for the full published article.

4.1: Summary

Offspring of mothers with depression are a high-risk group for the development of suicide-related behaviour. These offspring are therefore a priority for preventive interventions; however pathways contributing to risk, including specific aspects of offspring psychopathology, remain unclear. Chapter 3 highlighted that differing levels of maternal depression symptoms were associated with later suicidal ideation and suicide attempt in offspring even after accounting for maternal suicide attempt and offspring depression. The following chapter builds on these findings by examining whether heterotypic transmission of risk for psychopathology more generally plays an important role. The specific aim of this chapter was to examine whether offspring symptoms of MDD, GAD, DBD, ADHD and alcohol abuse independently mediate the association between maternal depression and offspring suicide-related behaviour. Data were again utilised from ALSPAC. In Chapter 3, five distinct classes of maternal depression symptoms were identified (minimal, mild, increasing, sub-threshold, chronic-severe). It was found that offspring of mothers from each of the depression classes were at increased risk of later suicide-related behaviour compared to offspring of mothers with *minimal* symptoms. In addition, it was found that offspring of mothers with *chronic-severe* symptoms were at greatest risk; however there was no difference in risk between offspring of mothers with *mild*, *increasing* and *sub-threshold* symptoms. Therefore, for all remaining analyses, the *mild*, *increasing* and *sub-threshold* classes were collapsed and three groups of maternal depression symptoms were compared (minimal, moderate, chronic-severe). This was done to simplify analyses using structural equation models with multiple mediators and to reduce the number of models examined. Offspring psychopathology was assessed at age 15 years and suicide-related

behaviour was assessed at age 16 years. The association between maternal *chronic-severe* depression symptoms and offspring suicidal ideation was independently mediated by offspring MDD, GAD and DBD symptoms. The same mechanisms were found for offspring of mothers with moderate depression symptoms over time. Results were similar for offspring suicide attempt except for additional evidence of an indirect effect through offspring ADHD symptoms. Findings highlight that suicide prevention efforts in offspring of mothers with depression should not only be targeted at offspring with MDD; it is also important to consider offspring with other forms of psychopathology.

4.2: Chapter introduction

It is well-established that offspring of mothers with depression are at increased risk for the development of suicide-related behaviour (Garber et al., 1998; Kerr et al., 2008; Klimes-Dougan et al., 1999, 2008; Mittendorfer-Rutz et al., 2012, 2008; Wilcox et al., 2010) and are therefore a priority for preventive interventions. However the reasons why they are at increased risk, including the role of specific aspects of offspring psychopathology, remain unclear. Offspring of mothers with depression are at increased risk for a range of mental health problems (including depression, anxiety, disruptive behaviour disorders, ADHD and alcohol abuse) (Goodman et al., 2011; Low et al., 2012), and there is some evidence that each of these disorders is associated with both suicidal ideation and suicide attempt in adolescence (Boden et al., 2007; Gould et al., 1998; Nock et al., 2013; Verona & Javdani, 2011). Studies have consistently shown that depressive disorder is associated with suicide-related behaviour when taking account of other psychopathology (Gould et al., 1998; Nock et al., 2013), however findings as to whether the effects of other disorders are independent of depression and each other have been inconsistent.

A recent national survey of US adolescents (Nock et al., 2013) found no independent effect of GAD, assessed retrospectively, on suicide-related behaviour in adolescents. However, a longitudinal sample of adolescents (Boden et al., 2007), found that GAD was associated with later suicide-related behaviour after adjusting for the presence of other psychopathology. Findings for substance abuse have also been inconsistent with some studies showing an association with suicidal ideation (Nock et al., 2013) and others only with suicide attempt (Gould et al., 1998; Verona & Javdani, 2011). ADHD has generally been combined with other disruptive behaviour disorders (Gould et al., 1998; Verona & Javdani, 2011) meaning it is difficult to draw conclusions about the independent effects; however, the national survey of US adolescents (Nock et al., 2013) examined the disorders separately and found an independent effect of ODD on later suicidal ideation but that ADHD was only associated with the transition

from ideation to attempt (Nock et al., 2013). Previous studies have not fully taken account of the co-occurrence of offspring psychopathology by examining the effects of each disorder whilst adjusting for covariance between them. Given evidence that disorders tend to co-occur in adolescents (Caron & Rutter, 1991) and that high levels of comorbidity are associated with suicide (Cavanagh et al., 2003), taking account of this co-occurrence is important to examine the independent effects of specific aspects of offspring psychopathology.

Longitudinal studies examining the influence of maternal depression on offspring suicidal ideation have found that adjustment for offspring depression symptoms did not fully account for risk effects (Kerr et al., 2008; Wilcox et al., 2010). However, the mediating role of other types of offspring psychopathology has rarely been investigated. One longitudinal case-control study using Swedish inpatient care registers found that the association between maternal affective disorder and offspring suicide attempt was attenuated although still present, when adjusted for whether offspring had been hospitalised due to a range of different psychiatric disorders (Mittendorfer-Rutz et al., 2008). A cross-sectional study found a similar pattern of results when examining suicidal ideation and suicide attempt in adult offspring of parents with depression with adjustment for the presence of lifetime offspring psychiatric disorder (Gureje et al., 2011). However, more research is needed to examine the relative or differential importance of specific types of offspring psychopathology in explaining the association between maternal depression and subsequent offspring suicidal ideation and suicide attempt in adolescence. This is important given that offspring of mothers with depression show a broad range of psychopathology. Additionally, it is an essential first step to establishing whether treating specific symptoms in offspring of depressed mothers is likely to lead to a reduction in suicide-related behaviour. There is evidence that more chronic and severe symptoms of maternal depression have a greater impact on offspring development (Stein et al., 2014) highlighting the importance of testing mechanisms for this group. However, it is not known whether risk mechanisms underlying links with offspring suicide-related behaviour vary by maternal depression severity.

Therefore, the present investigation uses a large population cohort to examine how much of the association between differing levels of maternal depression symptoms, over the first eleven years of their child's life, and later offspring suicidal ideation and suicide attempt is explained by proximal offspring psychopathology including symptoms of MDD, GAD, DBD, ADHD and alcohol abuse. It is expected that offspring MDD symptoms will account for most of the indirect effect. However, given evidence that suicide-related behaviour can occur outside the context of depression (Lewinsohn et al., 1996), it is also expected that other symptom types will show additional independent mediating effects.

4.3: Chapter methods

4.3.1: Sample

Data were utilised from a large UK birth cohort study; ALSPAC. Further detail on the sample is given in Chapter 2 (section 2.1).

4.3.2: Measures

Maternal depression symptom trajectories

In Chapter 3, LCGA was used to identify qualitatively distinct patterns of depression symptoms in mothers over time. Based on fit statistics, size of the latent classes and parsimony, a five class model represented the best fit to the data. In Chapter 3 it was found that offspring of mothers from each of the depression classes were at increased risk of later suicide-related behaviour compared to offspring of mother with *minimal* symptoms. In addition, it was found that offspring of mothers with *chronic-severe* symptoms were at greatest risk; however there was no difference in risk between offspring of mothers with *mild, increasing* and *sub-threshold* symptoms. Therefore, in this and the next chapter, the five classes were collapsed to form a 3-level categorical variable: 0 "minimal"; 1 "moderate (including *mild, increasing* and *sub-threshold* classes)"; 2 "chronic-severe". Approximately 40% of the sample belonged to the *minimal* class, 55% of the sample belonged to the *moderate* group and 5% of the sample belonged to the *chronic-severe* class. In all analyses the *minimal* class is treated as the reference group. Further detail on the derivation and validation of classes is given in Chapter 3.

Offspring suicide-related behaviour

Suicide-related behaviour at age 16 years was assessed via a self-report postal questionnaire (Kidger et al., 2012). Further detail is given in Chapter 2 (section 2.4.3).

Possible mediating variables: offspring psychopathology

Offspring psychopathology was assessed using the DAWBA (Goodman et al., 2000) parent and child versions. Different time spans are used across the DAWBA sections to follow DSM-IV criteria. At age 15 years, parent versions of the DAWBA were used to assess symptoms of DBD (ODD over the past 6 months or conduct disorder over the past year; symptom range: 0-31) and symptoms of ADHD over the past 6 months (range: 0-30). Child versions of the DAWBA were used to assess symptoms of MDD over the past month (range: 0-25) and symptoms of GAD over the past 6 months (range: 0-33). Parent versions were used for DBD and ADHD and child versions were used for MDD and GAD as this was what was available as part of the ALSPAC

data collection at age 15 years. Each DAWBA section contains 20-25 questions with skip rules so that the full set of questions is only administered when adolescents meet criteria for initial screening questions (Goodman et al., 2000). Where questions were skipped, they were coded as zero. The questions follow the diagnostic criteria operationalised in the DSM-IV and ICD-10. Continuous symptom scores were derived from the sum of all symptom items within the relevant section of the DAWBA. Symptoms of alcohol abuse over the last two years were assessed at the same time point using questions taken from the Semi Structured Assessment of the Genetics of Alcoholism interview (Bucholz et al., 1994; Hesselbrock, Easton, Bucholz, Schuckit, & Hesselbrock, 1999) that correspond relatively well to DSM-IV criteria for alcohol abuse and dependence (Dick et al., 2013) (range 0-88).

Potential confounders

Maternal questionnaires completed during pregnancy were used to assess housing tenure (owned vs. rented), marital status (married vs. single), maternal level of education (below O-level, O-level or above O-level), self-reported psychiatric disorder before pregnancy (yes/no; including drug addiction, alcoholism, schizophrenia, anorexia nervosa, severe depression or any other psychiatric disorder), maternal family history of depression (neither, one or both parents) and smoking in pregnancy (smoked tobacco in either the first three months or the last two weeks of pregnancy).

4.3.3: Statistical analyses

The starting sample for these analyses included mothers who had information on the latent classes of maternal depression symptoms (N = 10,559). Of the starting sample, 4,588 offspring had complete data on suicide-related behaviour at age 16 years (43%; 1,904 males and 2,684 females; mean age: 16.7 years, standard deviation: 0.2 years). Of these, 2,445 offspring also had complete data on symptoms of psychopathology at age 15 years. Given that list-wise deletion of families can increase sample bias (White et al., 2011), missing data for offspring suicide-related behaviour and psychopathology and other covariates were imputed using MICE (Van Buuren & Oudshoom, 2000). Further detail on the imputation procedure is given in Chapter 2 (section 2.2.2). Main results are presented for four different imputation approaches (1. full imputation, N = 10,559; 2. imputation for those sent questionnaires at 16, N = 8,475; 3. imputation for those with complete outcome data, N = 4,588; 4. complete case analysis, N = 2,445).

Following multiple imputation, symptom counts were standardised to allow estimates to be comparable. Univariable logistic and linear regression analyses were then performed, as appropriate, to examine initial associations between variables. Next, a multiple mediation model was run using SEM in M*plus* to assess effects of *moderate* or *chronic-severe* maternal

depression symptoms (with *minimal* class as the reference group) on offspring past year suicidal ideation at age 16 years. Models include both direct and indirect paths through offspring symptoms of psychopathology at age 15 years and simultaneously adjust for residual covariance between symptoms. A weighted least squares estimator (WLSMV) was used due to its robustness in analysing both continuous and categorical measures in SEM (Muthén & Muthén, 1998-2012). Results from path analyses with a categorical outcome (including indirect effects) are presented as probit regression coefficients (referred to throughout as B). Probit coefficients refer to the strength of the association between an exposure and probability of group membership. Therefore, the coefficient represents the difference that a 1-unit change in the exposure variable makes in the cumulative normal probability of the outcome variable. Indirect effects were calculated using bias-corrected bootstrapping with 500 replications. To examine if the indirect effects within the same model differed in strength, post-hoc Wald Chi square tests were used to test the assumption of equality between constrained indirect effects. Secondary analyses examined offspring lifetime suicide attempt as the outcome. Analyses were conducted using Stata version 13 (StataCorp, 2013) and M*plus* version 7 (Muthén & Muthén, 1998-2012).

4.4: Results

4.4.1: Descriptive data for maternal depression, offspring psychopathology and offspring suicidal ideation

The prevalence of past year suicidal ideation at the age 16 years assessment was 15% (95% CI: 14-17%; 11% of males and 20% of females). Table 4.1 shows means, standard deviations and correlations between offspring symptoms of psychopathology at age 15 years.

Table 4.1 –Means, standard deviations and correlations between offspring symptoms of psychopathology; imputed N = 10,559

	1	2	3	4	5
1. MDD symptoms	-				
2. GAD symptoms	.52***	-			
3. DBD symptoms	.21***	.14***	-		
4. ADHD symptoms	.12***	.09***	.59***	-	
5. Alcohol abuse symptoms	.22***	.11***	.29***	.21***	-
Mean (sd)	3.06	2.87	1.54	2.59	3.22
	(6.10)	(5.63)	(5.52)	(6.77)	(11.22)

$^{\#}p \leq 0.10$; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$

Table 4.2 shows mean depression symptoms at each assessment for mothers in each of the three groups of maternal depression.

Table 4.2 - Mean depression symptoms (with 95% Confidence Intervals) at each assessment for mothers in the chronic-severe class, moderate group and minimal class; *N* = 10,559; clinical cut-off on Edinburgh Postnatal Depression Scale (EPDS) = 13

Child age at EPDS assessment	Mean (95% CI)		
	Chronic-severe (5.2%)	Moderate (55.2%)	Minimal (39.6%)
18 weeks gestation	14.3 (13.9, 14.7)	8.4 (8.3, 8.5)	3.5 (3.4, 3.6)
32 weeks gestation	15.5 (15.1, 15.9)	8.7 (8.6, 8.8)	3.3 (3.2, 3.4)
8 weeks	14.8 (14.4, 15.2)	7.5 (7.4, 7.6)	2.6 (2.5, 2.7)
8 months	14.7 (14.3, 15.1)	6.9 (6.8, 7.0)	2.0 (2.0, 2.1)
1 year 9 months	15.5 (15.2, 15.9)	7.3 (7.2, 7.4)	2.3 (2.2, 2.4)
2 years 9 months	15.7 (15.3, 16.1)	8.0 (7.9, 8.2)	2.6 (2.6, 2.7)
5 years 1 month	15.4 (15.0, 15.9)	7.7 (7.6, 7.8)	2.6 (2.5, 2.6)
6 years 1 month	15.6 (15.2, 16.1)	8.1 (7.9, 8.2)	2.8 (2.7, 2.9)
8 years 1 month	15.6 (15.0, 16.1)	7.7 (7.6, 7.8)	2.7 (2.6, 2.8)
11 years 2 months	15.2 (14.7, 15.8)	7.4 (7.2, 7.5)	2.6 (2.5, 2.8)

4.4.2: Associations between maternal depression, offspring psychopathology and offspring suicidal ideation

Twenty nine percent (95% CI 23, 35%) of offspring of mothers with *chronic-severe* depression symptoms reported past year suicidal ideation at age 16 years, compared to 17% (95% CI 15, 18%) of offspring of mothers with *moderate* depression symptoms and 12% (95% CI 10, 13%) of mothers with *minimal* symptoms over time.

Before conducting the mediation models, univariable associations between exposure, mediators and outcome were examined. There was evidence for increased risk of suicidal ideation in offspring of mothers with *chronic-severe* depression symptoms [OR 3.04 (95% CI 2.19, 4.21)] and offspring of mothers with *moderate* symptoms [OR 1.51 (95% CI 1.30, 1.75)] in comparison to offspring of mothers with *minimal* symptoms (Table 4.3). Table 4.3 also shows evidence of a positive association between offspring symptoms of MDD, GAD, DBD, ADHD and alcohol abuse at age 15 years and offspring suicidal ideation at age 16 years.

Table 4.3 - Univariable logistic regression analyses between each group of maternal depression symptoms in comparison to minimal class (reference group) and offspring symptoms of psychopathology (as the exposures) and offspring past year suicidal ideation at age 16 years as the outcome (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 10,559

Exposures	OR (95% CI)
Maternal depression group	
Minimal	Reference group
Moderate	1.51 (1.30, 1.75)***
Chronic-severe	3.04 (2.19, 4.21)***
Offspring psychopathology	
MDD symptoms	2.22 (1.99, 2.48)***
GAD symptoms	1.83 (1.67, 1.99)***
DBD symptoms	1.50 (1.38, 1.63)***
ADHD symptoms	1.26 (1.14, 1.38)***
Alcohol abuse symptoms	1.38 (1.27, 1.51)***

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

Next, the association between maternal depression and offspring symptoms of psychopathology was examined. Table 4.4 shows evidence for increased risk of all symptoms of psychopathology at age 15 years in offspring of mothers with *chronic-severe* depression symptoms and offspring of mothers with *moderate* symptoms in comparison to offspring of mothers with *minimal* symptoms.

Table 4.4 - Univariate linear regression analyses between each group of maternal depression symptoms in comparison to minimal class (reference group) and offspring symptoms of psychopathology at age 15 years (Beta coefficients (β) and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 10,559

Maternal depression group (exposure)	β (95% CI)				
	MDD symptoms	GAD symptoms	DBD symptoms	ADHD symptoms	Alcohol abuse symptoms
Minimal	Reference group				
Moderate	.17 (.11, .22)***	.18 (.13, .23)***	.29 (.24, .34)***	.31 (.26, .36)***	.10 (.04, .16)***
Chronic-severe	.38 (.25, .51)***	.41 (.27, .56)***	.80 (.66, .94)***	.75 (.62, .87)***	.29 (.15, .43)***

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$; all symptoms counts are standardised therefore a coefficient of 0.38 means that *chronic-severe* depression (compared to *minimal* depression) is associated with an increase of 0.38 standard deviations in offspring MDD symptoms

4.4.3: Mediation of effect of maternal depression on offspring suicidal ideation

Next, a multiple mediation model was run to assess effects of the groups of maternal depression symptoms (with *minimal* class as the reference group), on subsequent offspring past year suicidal ideation (at age 16 years) both directly and indirectly, through offspring symptoms of psychopathology at age 15 years. Figure 4.1 shows results from the structural model examining the direct effect of maternal *chronic-severe* depression symptoms on offspring suicidal ideation, and the indirect effects through offspring symptoms of MDD, GAD, DBD, ADHD and alcohol abuse. There was evidence that offspring of mothers with *chronic-severe* symptoms were at increased risk for all symptom types compared to offspring of mothers with *minimal* symptoms. Figure 4.1 also shows evidence that offspring symptoms of MDD, GAD, DBD and alcohol abuse were independently associated with offspring suicidal ideation. However, there was still evidence of a direct effect of maternal *chronic-severe* depression on offspring suicidal ideation not mediated through offspring symptoms of psychopathology [probit coefficient B 0.36 (95% CI 0.17, 0.55); $p < 0.001$]. A probit coefficient of 0.36 indicates that for each unit increase in the exposure (i.e. from *minimal* to *chronic-severe* depression), there is an increase of 0.36 standard deviations in the predicted z score of the cumulative normal distribution of offspring suicidal ideation.

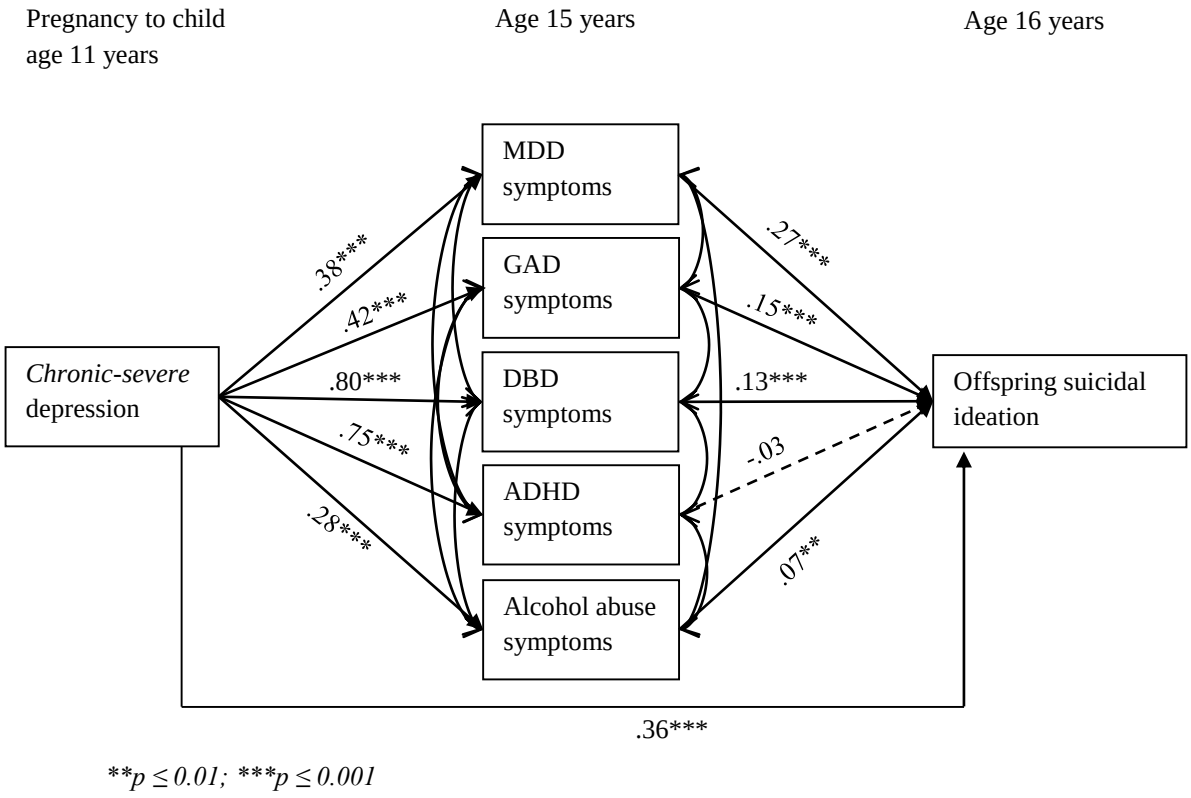


Figure 4.1 – Structural model showing the direct effect of maternal chronic-severe depression symptoms (with minimal class as the reference group) on offspring past year suicidal ideation, and the indirect effects through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse; Residual covariance coefficients not shown on diagram; imputed *N* = 10,559; non-standardised probit regression coefficients presented for categorical outcome (offspring suicidal ideation); linear regression coefficient presented for continuous outcomes (offspring symptoms)

Table 4.5 (model 1a) shows the indirect effects of maternal *chronic-severe* depression on offspring suicidal ideation through offspring symptoms of MDD, GAD, DBD, ADHD and alcohol abuse. There was evidence of an indirect effect through offspring symptoms of MDD [B 0.10 (95% CI 0.06, 0.15)], GAD [B 0.06 (95% CI 0.03, 0.09)] and DBD [B 0.11 (95% CI 0.06, 0.16)] and weak evidence of an indirect effect via symptoms of alcohol abuse [B 0.02 (95% CI 0.00, 0.04)]. Of the total effect [B 0.63 (95% CI 0.44, 0.82)], 17% was explained through MDD, 10% was explained through GAD, 17% was explained through DBD and 3% was explained through alcohol abuse. Table 4.5 (model 1b) shows that indirect effects via MDD, GAD and DBD symptoms were slightly attenuated but strong evidence of effects remained when adjusted for potential confounders assessed in pregnancy. Post-hoc Wald Chi-square tests were then performed to compare the strength of parameters for the indirect effects with one another (again

adjusting for potential confounders). There were no differences in effect sizes for the indirect effects via MDD, GAD and DBD symptoms (all $p \geq 0.12$); however, there was evidence that the indirect effects via MDD, GAD and DBD symptoms were each stronger than the indirect effects through symptoms of ADHD and alcohol abuse (all $p \leq 0.04$). Findings were comparable across different imputation samples (Table 4.5, models 2 and 3).

When using complete cases (Table 4.5, model 4), although all indirect effects were weaker, conclusions were similar. There was again evidence of an indirect effect through offspring symptoms of GAD [B 0.04 (95% CI 0.01, 0.10)] and DBD [B 0.10 (95% CI 0.05, 0.18)]. However, there was no longer evidence of an indirect effect through offspring symptoms of MDD [B 0.03 (95% CI -0.03, 0.08)]; this was due to a weaker association between maternal *chronic-severe* depression and offspring symptoms of MDD in complete case analyses (not shown).

Table 4.5 - Indirect effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring suicidal ideation through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse (probit regression coefficient and 95% Confidence Intervals (95% CI) displayed)

Model [a]	Indirect effects via offspring symptoms (probit coefficient (95% CI))				
	MDD	GAD	DBD	ADHD	Alcohol abuse
Model 1a: using full imputed data; unadjusted (*N* = 10,559) [b]	.10 (.06, .15)	.06 (.03, .09)	.11 (.06, .16)	-.02 (-.06, .02)	.02 (.00, .04)
Model 1b: adjusted for confounders (*N* = 10,559) [c]	.07 (.04, .11)	.04 (.01, .07)	.08 (.04, .12)	-.01 (-.04, .03)	.01 (-.00, .02)
Model 2: as Model 1a, imputing those that were sent questionnaire (*N* = 8,475)	.10 (.06, .15)	.06 (.03, .10)	.10 (.05, .14)	-.03 (-.07, .01)	.02 (-.00, .03)
Model 3: as Model 1a, imputing those with complete outcome data (*N* = 4,588)	.06 (.00, .11)	.05 (.01, .08)	.09 (.04, .14)	-.02 (-.06, .01)	.01 (-.01, .02)
Model 4: as Model 1a, complete cases (*N* = 2,445)	.03 (-.03, .08)	.04 (.01, .10)	.10 (.05, .18)	-.05 (-.12, -.02)	.00 (-.01, .02)

[a] Model 1a shows the unadjusted results using the full imputed dataset; model 1b shows results after adjusting for confounders assessed in pregnancy; model 2 shows the unadjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years; model 3 shows the unadjusted results using imputed data for mediators in those that had complete outcome data; model 4 shows the unadjusted results using only those with complete data on all variables in analysis

[b] Adjusting only for covarying offspring psychopathology as per Figure 4.1

[c] Adjusting for confounders assessed in pregnancy (child gender, housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy)

The pattern of results was similar when examining indirect effects of maternal *moderate* depression symptoms on offspring suicidal ideation with evidence of indirect effects through offspring symptoms of MDD [B 0.05 (95% CI 0.03, 0.06)], GAD [B 0.03 (95% CI 0.02, 0.04)] and DBD [B 0.04 (95% CI 0.02, 0.06)] (Table 4.6, model 1a). Again, there was still evidence of a direct effect of maternal *moderate* depression on offspring suicidal ideation not mediated through offspring symptoms of psychopathology [probit coefficient B 0.11 (95% CI 0.03, 0.20); $p = 0.006$]. Of the total effect [B 0.22 (95% CI 0.14, 0.30)], 20% was explained through MDD, 12% was explained through GAD and 17% was explained through DBD. These indirect effects remained after adjusting for confounders (Table 4.6, model 1b). Findings were again comparable across different imputation samples (Table 4.6, models 2 and 3) and when using complete cases (Table 4.6, model 4). When running analyses in those offspring who did not report suicidal ideation at age 11 years (i.e. new onset cases), conclusions remained the same (see Appendix 5).

Finally, for ease of interpretation, probit coefficients within the path diagram (Figure 4.1) were converted to odds ratios using the scaling factor proposed by Amemiya and colleagues (1981); by multiplying a probit coefficient by 1.6, it can be made to approximate the log odds ratio coefficients of a logistic regression (Amemiya, 1981; Ntzoufras, Dellaportas, & Forster, 2003; Rassen, Schneeweiss, Glynn, Mittleman, & Brookhart, 2009). However, a probit coefficient does not have constant odds, and there is a lack of consensus on the scaling factor that should be used, therefore, this calculation is a rough approximation. Appendix 6 shows the structural model from Figure 4.1 but with the probit coefficients converted to odds ratios.

Table 4.6 - Indirect effect of maternal moderate depression symptoms (with minimal class as the reference group) on offspring suicidal ideation through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse (probit regression coefficient and 95% Confidence Intervals (95% CI) displayed)

Model [a]	Indirect effects via offspring symptoms (probit coefficient (95% CI))				
	MDD	GAD	DBD	ADHD	Alcohol abuse
Model 1a: using full imputed data; unadjusted (*N* = 10,559) [b]	.05 (.03, .06)	.03 (.02, .04)	.04 (.02, .06)	-.01 (-.03, .01)	.01 (.00, .01)
Model 1b: adjusted for confounders (*N* = 10,559) [c]	.04 (.02, .05)	.02 (.01, .03)	.03 (.02, .04)	-.00 (-.02, .01)	.00 (-.00, .01)
Model 2: as Model 1a, imputing those that were sent questionnaire (*N* = 8,475)	.05 (.03, .06)	.03 (.01, .04)	.04 (.02, .05)	-.01 (-.03, .01)	.01 (.00, .01)
Model 3: as Model 1a, imputing those with complete outcome data (*N* = 4,588)	.04 (.02, .06)	.02 (.01, .03)	.03 (.01, .05)	-.01 (-.03, .01)	.00 (-.00, .01)
Model 4: as Model 1a, complete cases (*N* = 2,445)	.03 (.01, .05)	.02 (.01, .03)	.03 (.02, .06)	-.02 (-.05, -.01)	.00 (-.00, .01)

[a] Model 1a shows the unadjusted results using the full imputed dataset; model 1b shows results after adjusting for confounders assessed in pregnancy; model 2 shows the unadjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years; model 3 shows the unadjusted results using imputed data for mediators in those that had complete outcome data; model 4 shows the unadjusted results using only those with complete data on all variables in analysis

[b] Adjusting only for covarying offspring psychopathology

[c] Adjusting for confounders assessed in pregnancy (child gender, housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy)

4.4.4: Mediation of effect of maternal depression on offspring lifetime suicide attempt

The prevalence of lifetime suicide attempt at the age 16 years assessment was 8% (95% CI 7, 9%; 5% of males and 11% of females). There was evidence for increased risk of suicidal attempt in offspring of mothers with *chronic-severe* depression symptoms [OR 3.79 (95% CI 2.48, 5.78)] and offspring of mothers with *moderate* symptoms [OR 1.85 (95% CI 1.47, 2.34)] in comparison to offspring of mothers with *minimal* symptoms (Table 4.7). Table 4.7 also shows evidence of a positive association between offspring symptoms of MDD, GAD, DBD, ADHD and alcohol abuse at age 15 years with offspring lifetime suicidal attempt by age 16 years.

Table 4.7 - Univariable logistic regression analyses between each group of maternal depression symptoms in comparison to minimal class (reference group) and offspring symptoms of psychopathology (as the exposures) and offspring lifetime suicide attempt at age 16 years as the outcome (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed N = 10,559

Exposures	OR (95% CI)
Maternal depression group	
Minimal	Reference group
Moderate	1.85 (1.47, 2.34)***
Chronic-severe	3.79 (2.48, 5.78)***
Offspring psychopathology	
MDD symptoms	2.72 (2.35, 3.14)***
GAD symptoms	1.83 (1.67, 1.99)***
DBD symptoms	1.79 (1.61, 2.00)***
ADHD symptoms	1.63 (1.43, 1.87)***
Alcohol abuse symptoms	1.48 (1.34, 1.64)***

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

Table 4.8 (model 1a) shows evidence of an indirect effect of maternal *chronic-severe* depression symptoms on offspring suicide attempt through offspring symptoms of MDD [B 0.11 (95% CI 0.06, 0.16)], GAD [B 0.07 (95% CI 0.03, 0.11)], DBD [B 0.11 (95% CI 0.06, 0.16)] and ADHD [B 0.06 (95% CI 0.01, 0.12)] and weak evidence of an indirect effect via symptoms of alcohol abuse [B 0.02 (95% CI -0.00, 0.03)]. There was also evidence of a direct effect of maternal *chronic-severe* symptoms on suicide attempt not mediated through offspring symptoms of psychopathology [B 0.31 (95% CI 0.10, 0.52); p = 0.003]. Of the total effect [B 0.68 (95% CI 0.45, 0.90)], 16% was explained through MDD, 10% was explained through GAD, 16% was

explained through DBD, 9% was explained through ADHD and 2% was explained through alcohol abuse. Strong evidence of indirect effects via MDD, GAD, DBD and ADHD persisted after adjustment for confounders (model 1b). Findings were comparable across different imputation samples (models 2 and 3).

When using complete cases (Table 4.8, model 4), all indirect effects were weaker. However, there was still evidence of an indirect effect through offspring symptoms of GAD [B 0.04 (95% CI 0.01, 0.09)] and DBD [B 0.07 (95% CI 0.02, 0.15)]. There was only weak evidence of an indirect via ADHD symptoms [B 0.03 (95% CI -0.01, 0.09)] and again there was no longer evidence of an indirect effect through offspring symptoms of MDD [B 0.03 (95% CI -0.03, 0.09)] due to the weaker association between maternal *chronic-severe* depression and offspring symptoms of MDD in complete case analyses.

Table 4.8 - Indirect effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring suicide attempt through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse (probit regression coefficient and 95% Confidence Intervals (95% CI) displayed)

Model [a]	Indirect effects via offspring symptoms (probit coefficient (95% CI))				
	MDD	GAD	DBD	ADHD	Alcohol abuse
Model 1a: using full imputed data; unadjusted (*N* = 10,559) [b]	.11 (.06, .16)	.07 (.03, .11)	.11 (.06, .16)	.06 (.01, .12)	.02 (-.00, .03)
Model 1b: adjusted for confounders (*N* = 10,559) [c]	.08 (.04, .12)	.05 (.02, .08)	.08 (.04, .13)	.07 (.02, .12)	.01 (-.00, .02)
Model 2: as Model 1a, imputing those that were sent questionnaire (*N* = 8,475)	.11 (.06, .16)	.07 (.03, .10)	.10 (.05, .15)	.05 (.01, .10)	.01 (-.01, .03)
Model 3: as Model 1a, imputing those with complete outcome data (*N* = 4,588)	.06 (.00, .12)	.06 (.01, .10)	.08 (.03, .13)	.04 (.00, .08)	.00 (-.01, .01)
Model 4: as Model 1a, complete cases (*N* = 2,445)	.03 (-.03, .09)	.04 (.01, .09)	.07 (.02, .15)	.03 (-.01, .09)	.01 (-.00, .04)

[a] Model 1a shows the unadjusted results using the full imputed dataset; model 1b shows results after adjusting for confounders assessed in pregnancy; model 2 shows the unadjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years; model 3 shows the unadjusted results using imputed data for mediators in those that had complete outcome data; model 4 shows the unadjusted results using only those with complete data on all variables in analysis

[b] Adjusting only for covarying offspring psychopathology

[c] Adjusting for confounders assessed in pregnancy (child gender, housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy)

Finally, in order to identify which offspring with suicidal ideation were most at risk for making a suicide attempt, analyses with offspring suicide attempt were rerun only on the subsample of adolescents that had reported lifetime suicidal ideation by age 16 years (n = 416). Thirty one percent of adolescents that reported suicidal ideation in their lifetime also reported making a suicide attempt. Again, there was evidence of an indirect effect of maternal *chronic-severe* depression on offspring suicide attempt through offspring symptoms of ADHD [B 0.17 (95% CI 0.05, 0.42)], however, there was no evidence of an indirect effect via offspring symptoms of MDD [B 0.03 (95% CI -0.01, 0.13)], GAD [B 0.04 (95% CI -0.02, 0.18)], DBD [B -0.02 (95% CI -0.15, 0.10)] or alcohol abuse [B 0.02 (95% CI -0.01, 0.13)].

4.5: Discussion

Children exposed to chronic and severe maternal depression symptoms across childhood were at considerably increased risk for suicidal ideation later in adolescence. This association was, in part, explained through offspring proximal symptoms of psychopathology. Importantly, however, there was still evidence of a direct effect of maternal *chronic-severe* depression not mediated by offspring proximal psychiatric symptoms. A further novel and important finding was that closer examination of different aspects of psychiatric symptomatology showed that there were independent indirect effects not only through offspring symptoms of MDD, but also symptoms of GAD and DBD after accounting for covariation of child symptomatology and potential confounding factors. In addition, the indirect effects through GAD and DBD symptoms were of equal importance to MDD symptoms in terms of explaining the link between maternal depression and adolescent suicidal ideation. This chapter found no evidence of an indirect effect on offspring suicidal ideation through offspring symptoms of ADHD or alcohol abuse over and above other symptoms in the offspring and potential confounders. Mechanisms were similar for offspring of mothers with less severe levels of depression symptoms with evidence of an indirect effect of maternal *moderate* depression symptoms on offspring suicidal ideation via offspring symptoms of MDD, GAD, and DBD after adjusting for potential confounders. Lastly, findings were similar when investigating indirect effects on offspring suicide attempt in the whole sample, with the exception of an independent indirect effect of maternal depression on offspring suicide attempt via offspring symptoms of ADHD.

Consistent with previous literature (Gureje et al., 2011; Mittendorfer-Rutz et al., 2008), this chapter found evidence for a direct effect of maternal depression on offspring suicidal ideation after accounting for offspring symptoms of psychopathology. However, the findings in this chapter extend prior research by examining the relative importance of specific aspects of offspring psychopathology in explaining the association between maternal depression and subsequent offspring suicidal ideation and suicide attempt in adolescence. The results extend

studies that have examined whether the association is explained through offspring depression symptoms (Kerr et al., 2008; Wilcox et al., 2010) or psychiatric disorder (Gureje et al., 2011) and provides further evidence that mood, anxiety and disruptive behaviour disorders are independently associated with suicide-related behaviour in adolescents after taking account of the co-occurrence of offspring symptoms. These findings also add to prior research by showing that the same mechanisms are important for offspring of mothers with sub-threshold levels of depression symptoms over time. Contrary to our expectation that the strongest indirect effect would be through offspring MDD symptoms, there was no evidence that the indirect effect via MDD symptoms was stronger than via GAD or DBD symptoms. In the current chapter, offspring symptoms of ADHD mediated the association with offspring suicide attempt but not ideation. Given that studies often combine ADHD with ODD and conduct disorder (Gould et al., 1998; Verona & Javdani, 2011), differential effects on suicidal ideation and suicide attempt may be missed. The current findings indicate that it may be more informative to examine ADHD separately from other disruptive behaviour disorders when examining associations with suicide-related behaviour. Additionally, it was only ADHD symptoms that were associated with risk for suicide attempt among ideators. This supports previous findings that indicate ADHD is associated with the transition from ideation to attempt (Nock et al., 2013). It should be noted however, that the sample size used here to examine risk for suicide attempt among ideators was small given complexity of analyses. Therefore, findings are preliminary and require replication in bigger samples. Previous findings regarding offspring alcohol abuse have been inconsistent. In this chapter, there was little evidence of an indirect effect through offspring symptoms of alcohol abuse for offspring suicidal ideation or attempt, mainly due to a lack of association between maternal depression and offspring symptoms of alcohol abuse after adjusting for confounders. In this chapter, there was evidence for a direct effect of maternal depression on offspring suicidal ideation and suicide attempt after accounting for proximal offspring psychopathology. This could be explained by the direct effect of exposure to maternal depression; however, this 'direct' path could also be explained through other mediating pathways or by offspring psychopathology at other ages or measurement error in the assessment of symptoms at age 15 years.

The findings need to be considered in the light of several limitations. First, offspring symptoms of DBD and ADHD were parent-reported whereas MDD, GAD and alcohol abuse were self-reported. Therefore, shared-rater bias may have affected associations between maternal depression and offspring symptoms of ADHD and DBD or between symptoms of MDD, GAD and alcohol abuse and suicide-related behaviour. Second, as with most cohort studies, there was selective attrition over time; however, potential bias arising from missing data was dealt with using multiple imputation, utilising a large amount of additional information to make the

assumption of MAR as plausible as possible (White et al., 2011). Findings from different imputation models and from complete case analyses were mostly comparable. However, it is important to note where differences were found. Firstly, there was only weak evidence of an indirect effect on offspring suicide attempt via ADHD symptoms in complete case analyses. However, the indirect effect via ADHD symptoms was present in complete case analyses when examining risk for offspring suicide attempt within those that reported suicidal ideation. This finding therefore strengthens the conclusion regarding the importance of ADHD symptoms in predicting which offspring are most at risk for making a suicide attempt. Additionally, in complete case analyses there was no evidence of an association between maternal *chronic-severe* depression and offspring depression symptoms. Previous studies using the same sample have reported that the association between maternal and offspring depression may be underestimated in complete case analyses because families where both the mother and the child are depressed are more likely to have missing data (Pearson et al., 2013). In addition, findings were comparable across each imputation sample, and under the MAR assumption, made more plausible by the variables used to predict missingness, multiple imputation should help correct for biases that may be present in complete case analyses (Sterne et al., 2009). Third, in these analyses although we adjusted for socio-demographic and familial measures, residual confounding by measurement error in these variables, or by other unmeasured characteristics, cannot be ruled out. Finally, although this study allowed for the time-ordering of effects to be examined, it is still important to consider the possibility of reverse causation i.e. young people's suicide-related behaviour may have adverse effects on their own mental health and on maternal depression symptom course (Algorta et al., 2011). When excluding offspring that reported suicidal ideation by age 11 years, conclusions remained unchanged; however, it was not possible to exclude offspring that experienced suicide-related behaviour between the ages of 11 and 15 years.

In this population-based sample, adolescent suicidal ideation and psychopathology were common in young people exposed to sustained periods of maternal depression in childhood. Clinicians treating mothers with ongoing depression symptoms should therefore consider the likelihood of psychopathology and potential risk for suicide-related behaviour in offspring. Offspring proximal symptoms of MDD, GAD and DBD all independently mediated the association between maternal chronic and severe depression symptoms and subsequent offspring suicide-related behaviour. In addition, an indirect effect via ADHD symptoms was found for suicide attempt but not ideation. The same mechanisms were found to be important when mothers experienced less severe but sustained levels of depression symptoms over time. These results highlight that suicide prevention efforts in offspring of mothers with depression should not only be targeted at adolescents with depression symptoms but also those with other

forms of psychopathology, such as anxiety or disruptive behaviour symptoms. It is also important for clinicians to consider that offspring of mothers with depression may be at increased risk for making a suicide attempt if they have symptoms of ADHD. Knowledge about the unique contribution of different types of psychiatric symptoms also helps to inform understanding of the mechanisms by which psychopathology might lead to suicide-related behaviour in adolescents.

Chapter 5: Pathways to suicidal ideation in offspring of depressed mothers: the role of maternal suicide attempt, peer victimisation and the parent-child relationship

The work presented in this chapter has been published: Hammerton, G., Zammit, S., Thapar, A., & Collishaw, S. (2015). Explaining risk for suicidal ideation in adolescent offspring of mothers with depression. *Psychological Medicine*, *25*, 1-11.

The published article has been edited for this chapter in order to include additional results (including peer victimisation as a mediator and results previously available as supplementary materials) and to reduce the amount of repetition across Chapter 2 and section 5.3 in this chapter. However, there is some repetition of content in section 5.2 and the thesis introduction (Chapter 1).

Please see http://journals.cambridge.org/download.php?file=%2FPSM%2FS0033291715001671a.pdf&code=49b7ac86995c8ed7c3e652438a6bb5dd for the full published article.

5.1: Summary

It is well-established that offspring of mothers with depression are at increased risk for suicidal ideation. However, pathways involved in the transmission of risk are poorly understood. Previous chapters have highlighted the importance of both maternal suicide attempt and offspring psychopathology. This chapter builds on these findings by examining the contribution of the parent-child relationship and peer victimisation, in addition to maternal suicide attempt and proximal offspring psychiatric disorder. Data were utilised from ALSPAC. Three distinct groups of maternal depression symptoms across the first eleven years of the child's life had already been identified: minimal, moderate (including the original *mild, increasing* and *sub-threshold* classes), chronic-severe. Offspring suicidal ideation was assessed at age 16 years. Data were analysed using SEM. The majority of the association between maternal *chronic-severe* depression and offspring suicidal ideation was explained through maternal suicide attempt and offspring psychiatric disorder. However, there was also evidence for indirect effects via both the parent-child relationship and peer victimisation in middle childhood. There was no longer evidence of a direct effect of maternal depression on offspring suicidal ideation after accounting for all mediators. The pattern of results was similar when examining mechanisms for maternal *moderate* depression symptoms. Findings highlight that suicide prevention efforts in offspring of depressed mothers should be particularly targeted at both offspring with a psychiatric disorder and offspring whose mothers have made a suicide attempt. Interventions aimed at improving the parent-child relationship, or reducing peer victimisation may also be beneficial.

5.2: Chapter introduction

It is well-established that offspring of mothers with depression are at increased risk for suicidal ideation (Garber et al., 1998; Gureje et al., 2011). However, the pathways that explain suicidal risk in the offspring of mothers with depression are poorly understood. The most commonly assessed explanations of increased risk for suicide-related behaviour are the emergence of depression or other psychiatric disorder in the offspring or exposure to suicide attempts by the mother (Gureje et al., 2011; Mittendorfer-Rutz et al., 2008). However, evidence from Chapters 3 and 4 of this thesis and from previous literature (Gureje et al., 2011) suggests that the association between maternal depression and offspring suicidal ideation is not entirely explained by offspring psychiatric disorder or maternal suicide attempt suggesting that additional mechanisms are important to consider. However, research investigating other mediating pathways is lacking.

The quality of the parent-child relationship is likely to play a role with studies showing that maternal depression can impact on family relationships (Keenan-Miller et al., 2010; Lovejoy et al., 2000), and that a negative parent-child relationship is associated with adolescent suicidal ideation, independently from the adolescent's own psychopathology (Boeninger, 2013; Connor & Rueter, 2006; Thompson et al., 2005). However, only one study that we are aware of has examined whether the association between maternal depression and offspring suicidal ideation can be explained by aspects of the family environment (Garber et al., 1998). This study found that mother and child perceptions of the family environment at baseline fully mediated the association between maternal history of mood disorder and offspring suicidal symptoms one year later when also adjusting for offspring suicidal symptoms at baseline (Garber et al., 1998). There is also strong evidence for an association between peer victimisation and later negative outcomes including suicidal ideation (Klomek et al., 2010; Takizawa et al., 2014; van Geel et al., 2014); however it is currently less clear whether the effects of maternal depression spread outside of the family and impact on peer relationships. Some studies have shown that maternal depression is associated with maladaptive interpersonal cognitions and skills in the child (Hammen & Brennan, 2001) and increased risk of peer victimisation (Lereya & Wolke, 2012). It is likely that these associations are due, in part, to maladaptive interactions between mother and child (Hammen & Brennan, 2001; Lereya & Wolke, 2012). Additionally, one recent study found an indirect effect of maternal MDD on suicidal ideation in daughters via both relational and overt victimisation in childhood (Tsypes & Gibb, 2015). However, no studies have examined how both peer victimisation and the parent-child relationship simultaneously contribute to explaining the association between maternal depression and adolescent suicidal ideation.

There is considerable heterogeneity in the severity and course of adult depression, and this has not been considered in studies of mechanisms explaining offspring risk for suicide-related behaviour. This thesis so far has shown that risk for adolescent suicide-related behaviour is not confined to families where the parent is affected by severe clinical depression, but also extends to adolescents of mothers who suffer from milder but sustained, sub-threshold levels of depression. Previous studies of risk mechanisms have focused on mothers with a lifetime diagnosis of depression (Garber et al., 1998; Gureje et al., 2011; Tsypes & Gibb, 2015). It is important to establish if family and peer mechanisms underlying the link between maternal depression and offspring suicidal ideation in unselected population cohorts vary according to maternal depression symptom severity. Given that a number of different inter-related pathways are likely involved in the aetiology of adolescent suicidal ideation, testing competing mechanisms together is especially important. We anticipate that these will include mothers' own suicidal behaviour, adolescent psychiatric problems, chronic peer victimisation and the relationship between at-risk children and their parents.

The present chapter uses a large, prospective, population cohort to examine hypothesised mediators that might contribute to the association between differing levels of maternal depression in childhood and offspring suicidal ideation in adolescence. These mediators were assessed across childhood and adolescence and include maternal suicide attempt across the first eleven years of their child's life, the parent-child relationship and peer victimisation in middle childhood and offspring psychiatric disorder in adolescence (see Figure 1.2 in Chapter 1 for the theoretical model displaying all hypothesised pathways). We hypothesise that there will be indirect effects via offspring psychiatric disorder, via the parent-child relationship, via peer victimisation and via maternal suicide attempt. Finally, it is expected that together these risk mediators will account for a large part of the association between maternal depression and adolescent suicidal ideation.

5.3: Chapter methods

5.3.1: Sample

Data were utilised from a large UK birth cohort study; ALSPAC. Further detail on the sample is given in Chapter 2 (section 2.1).

5.3.2: Measures

Maternal depression symptom trajectories

For the purposes of these analyses, the three trajectory class groupings of depression used in Chapter 4 were compared: mothers with chronic and severe levels of symptoms "chronic-

severe", those with sub-threshold but sustained depression symptoms over time (including the *mild, increasing* and *sub-threshold* classes) "moderate", and those with very low levels of depression symptoms "minimal". Approximately 40% of the sample belonged to the *minimal* class, 55% of the sample belonged to the *moderate* group and 5% of the sample belonged to the *chronic-severe* class. In all analyses the *minimal* class is treated as the reference group. Although a five class model provided the best to the data, three groups are compared here to simplify analyses using SEM with multiple mediators and to reduce the number of models examined. Further detail on the derivation and validation of the five classes of maternal depression is given in Chapter 3.

Offspring suicidal ideation

Suicidal ideation at age 16 years was assessed via a self-report postal questionnaire (Kidger et al., 2012). Further detail is given in Chapter 2 (section 2.4.3).

Offspring psychiatric disorder

Offspring psychiatric disorder was assessed at age 15 years using the DAWBA (Goodman et al., 2000) parent and child versions. For the purpose of this chapter, the focus is on child psychopathology generally, defined as 'any psychiatric disorder'. This was done for the sake of simplicity when examining a model with additional mediators (maternal suicide attempt, the parent-child relationship and peer victimisation), and because analyses using symptom subtypes are presented in the previous chapter. 'Any disorder' (including depressive disorder, anxiety disorders, disruptive behaviour disorders, ADHD and eating disorder) was derived using a well-defined computerised algorithm that predicts the probability of a clinical rater assigning each child an ICD-10 or DSM-IV diagnosis from symptoms for each disorder.

Maternal suicide attempt

Maternal suicide attempt was assessed at 10 time points (from pregnancy to child age 11 years) using a self-report life events questionnaire in which the mother was asked if she had attempted suicide since the previous assessment (beginning in pregnancy). All available time points were combined to create a binary 'yes/no' variable.

Child perceived relationship with parents

The parent-child relationship was assessed using nine questions to the child about their perceptions of their relationship with parents at age 9 years. The questionnaire asked the child to rate how true a number of sentences were (on a 5-point scale). Items included quality and frequency of time spent together (e.g. *my parents and I spend a lot of time together*), support

(e.g. *my parents are easy to talk to*) and disapproval (e.g. *my parents are usually unhappy or disappointed with what I do*). Positive questions were reverse coded so that, for all items, a score of 4 represented a negative parent-child relationship and items were added up to create a total score (range 0-36). A factor analysis was performed on the nine items and indicated a single factor solution (see Appendix 7) and the scale showed good internal consistency (α = 0.79).

Peer victimisation

Peer victimisation was assessed during research clinics at age 10 and 12 years using the Bullying and Friendship Interview Schedule (Wolke, Woods, Bloomfield, & Karstadt, 2000). At both time points, children were asked 9 questions regarding overt and relational bullying by peers over the previous 6 months. A child was classed as an overt victim, if he/she was on the receiving end of any of the five components of overt bullying frequently (several times a month) or very frequently (several times a week). The four items relating to relational victimisation were combined in the same way. Chronicity of being bullied was then defined on a 3-point scale as has been done previously (Lereya et al., 2013): never been bullied (59%); overt or relational bullying at one time point (30%); overt or relational bullying at both time points (11%).

Potential confounders

Maternal questionnaires completed during pregnancy were used to assess housing tenure (owned vs. rented), marital status (married vs. single), maternal level of education (below O-level, O-level or above O-level), self-reported psychiatric disorder before pregnancy (yes/no; including drug addiction, alcoholism, schizophrenia, anorexia nervosa, severe depression or any other psychiatric disorder), maternal family history of depression (neither, one or both parents) and smoking in pregnancy (smoked tobacco in either the first three months or the last two weeks of pregnancy).

5.3.3: Statistical analyses

The starting sample for these analyses included mothers who had information on the latent classes of maternal depression symptoms (N = 10,559). Of the starting sample, 2,599 offspring had complete data on offspring suicidal ideation and all potential mediators. Given that list-wise deletion of families can increase sample bias (White et al., 2011), missing data for offspring suicide-related behaviour and psychopathology and other covariates were imputed using MICE (Van Buuren & Oudshoom, 2000). Further detail on the imputation procedure is given in Chapter 2 (section 2.2.2). Main results are presented for four different imputation approaches (1. full imputation, N = 10,559; 2. imputation for those sent questionnaires at 16, N = 8,475; 3.

imputation for those with complete outcome data, *N* = 4,588; 4. complete case analysis, *N* = 2,599).

Following multiple imputation, the parent-child relationship scale was standardised to aid interpretation. Univariable binary or ordinal logistic and linear regression analyses were then performed, as appropriate, to examine initial associations between variables. Next, a single mediation model was run using SEM in M*plus* to assess effects of *moderate* or *chronic-severe* maternal depression symptoms on offspring suicidal ideation both directly and indirectly, through the parent-child relationship (at age 9 years). A weighted least squares estimator (WLSMV) was used due to its robustness in analysing both continuous and categorical measures in SEM (Muthén & Muthén, 1998-2012). Results from path analyses with a continuous outcome are presented as linear regression coefficients and results with a categorical outcome (including indirect effects) are presented as probit regression coefficients (referred to throughout as B). Indirect effects were calculated using a non-parametric bootstrapping approach with 500 replications. Next, a multiple mediation model was run including offspring psychiatric disorder in the model together with the parent-child relationship. Another single mediation model was then run to assess effects of *moderate* or *chronic-severe* maternal depression symptoms on offspring suicidal ideation both directly and indirectly, through peer victimisation (from age 10 to 12 years), followed again by a multiple mediation model including offspring psychiatric disorder in the model together with peer victimisation. Next, another multiple mediation model was run including peer victimisation in the model together with offspring disorder and the parent-child relationship. Finally, the full structural model was run including all mediators: offspring psychiatric disorder, peer victimisation, the parent-child relationship and maternal suicide attempt. The full model was also rerun without using bootstrapping in order to calculate model fit statistics (RMSEA and CFI). Analyses were conducted using Stata version 13 (StataCorp, 2013) and M*plus* version 7 (Muthén & Muthén, 1998-2012).

5.4: Results

Fifteen percent of adolescents (95% CI 14, 17%; 11% of males and 20% of females) reported past year suicidal ideation at the age 16 years assessment and 9% of adolescents (95% CI 8, 10%) met DSM-IV or ICD-10 criteria for 'any disorder' (including depressive disorder, anxiety disorders, DBD, ADHD or eating disorder) at 15 years. Two percent of mothers made a suicide attempt between pregnancy and child age 11 years.

Table 5.1 shows an increase in offspring suicidal ideation, offspring psychiatric disorder, maternal suicide attempt, peer victimisation and parent-child relationship difficulties with

increasing severity of maternal depression symptoms. Odds of suicidal ideation and psychiatric disorder were elevated approximately 2- to 6-fold in moderate and severely depressed risk groups. Table 5.2 shows the associations between offspring psychiatric disorder, maternal suicide attempt, peer victimisation and parent-child relationship difficulties with offspring suicidal ideation.

Table 5.1 – Pattern of offspring suicidal ideation at age 16 years, offspring psychiatric disorder at age 15 years, maternal suicide attempt from pregnancy to child age 11 years, peer victimisation from age 10 to 12 years (coded 0, 1, 2) and parent-child relationship at age 9 years by groups of maternal depression symptoms (Odds Ratios (OR) or beta coefficient (β) and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 10,559

	Minimal	Moderate	Chronic-severe	Moderate vs minimal OR (95% CI)	Chronic-severe vs minimal OR (95% CI)
Offspring suicidal ideation (%)	11.74	16.69	28.81	1.51 (1.30, 1.75)***	3.04 (2.19, 4.21)***
Offspring psychiatric disorder (%)	4.89	10.31	22.10	2.24 (1.79, 2.80)***	5.51 (3.92, 7.74)***
Maternal suicide attempt (%)	0.34	2.32	10.87	7.05 (4.06, 12.25)***	36.26 (20.12, 65.37)***
Peer victimisation (% chronic)	9.07	12.83	16.63	1.34 (1.21, 1.48)***	1.66 (1.30, 2.11)***
				β (95% CI)	β (95% CI)
Parent-child relationship (mean)	2.94	3.46	4.15	0.14 (0.09, 0.19)***	0.26 (0.15, 0.37)***

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

Table 5.2 – Association between offspring psychiatric disorder, maternal suicide attempt, peer victimisation (coded 0, 1, 2) and the parent-child relationship with offspring suicidal ideation at age 16 years (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed N = 10,559

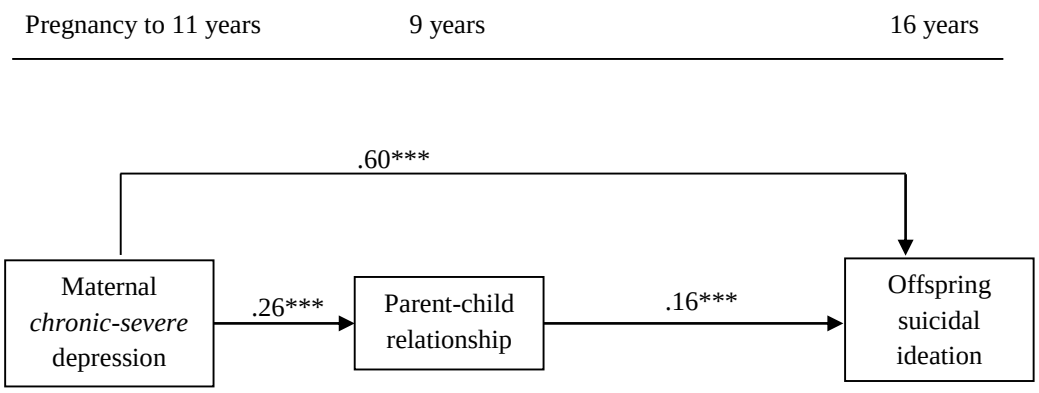
	No suicidal ideation	Suicidal ideation	OR (95% CI)
Offspring psychiatric disorder (%)	6.33	22.27	4.23 (3.18, 5.64)***
Maternal suicide attempt (%)	1.51	4.56	3.10 (2.03, 4.74)***
Peer victimisation (% chronic)	10.01	19.96	1.68 (1.48, 1.91)***
Parent-child relationship (mean)	3.09	4.41	1.36 (1.24, 1.50)***

$^{\#}p \leq 0.10$; $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$

5.4.1: Mediation of effect of maternal depression on offspring suicidal ideation

Parent-child relationship and offspring psychiatric disorder

Figure 5.1 shows results from the structural model examining the direct effect of maternal *chronic-severe* depression (with *minimal* class as the reference group), on offspring past year suicidal ideation at age 16 years, and the indirect effect through the parent-child relationship at age 9 years. There was evidence of an indirect effect through the parent-child relationship [B 0.04 (95% CI 0.02, 0.07)] and a direct effect not mediated by the parent-child relationship [B 0.60 (95% CI 0.40, 0.79); $p < 0.001$].



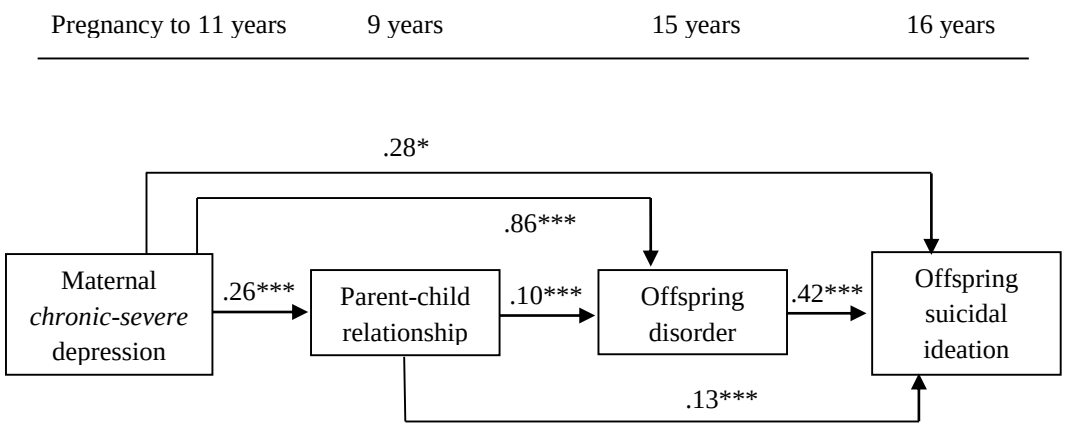
**p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001*

Figure 5.1 - Structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effect through the parent child relationship at age 9 years; imputed *N* = 10,559; non-standardised probit regression coefficients presented for categorical outcomes; linear regression coefficient presented for continuous outcome (parent-child relationship)

A similar pattern of results was found for offspring of mothers with *moderate* depression symptoms over time (in comparison to offspring of mothers with *minimal* symptoms*)* with evidence of an indirect effect through the parent child relationship [B 0.02 (95% CI 0.01, 0.03)]. There was also evidence of a direct effect of maternal *moderate* symptoms on offspring suicidal ideation after accounting for the parent-child relationship [B 0.20 (95% CI 0.12, 0.28); $p < 0.001$].

Figure 5.2 shows results from the structural model examining the direct effect of maternal *chronic-severe* depression on offspring suicidal ideation, and the indirect effects through the parent-child relationship at age 9 years and offspring psychiatric disorder at age 15 years. There was evidence of indirect effects via only the parent-child relationship [B 0.03 (95% CI 0.01,

0.06)], via offspring disorder alone [B 0.36 (95% CI 0.23, 0.49)], and via both parent-child relationship and offspring disorder [B 0.01 (95% CI 0.003, 0.02)].



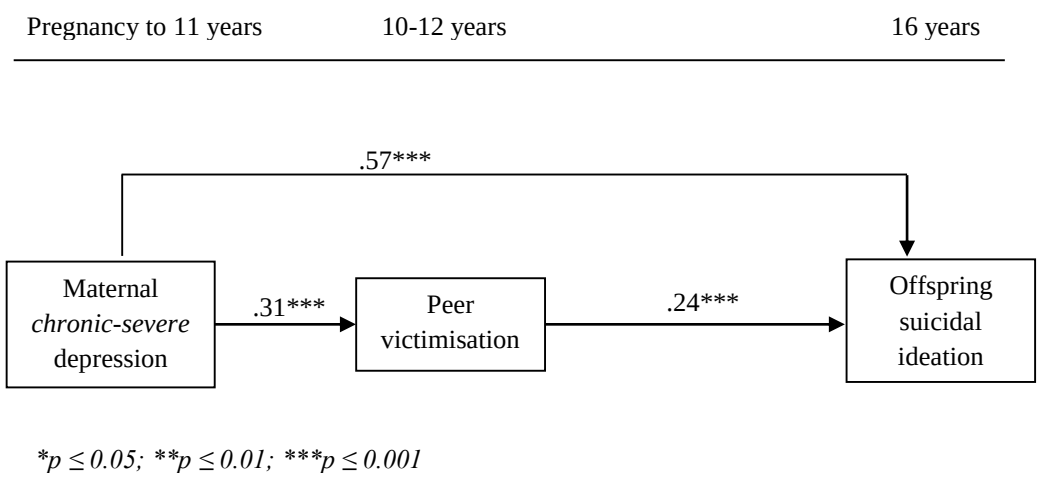
**p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001*

Figure 5.2 – Structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effects through parent-child relationship at age 9 years and offspring psychiatric disorder at age 15 years; imputed *N* = 10,559; non-standardised probit regression coefficients presented for categorical outcomes; linear regression coefficient presented for continuous outcome (parent-child relationship)

A similar pattern of results was found for offspring of mothers with *moderate* symptoms over time (in comparison to offspring of mothers with *minimal* symptoms*)* with evidence of an indirect effect via only the parent-child relationship [B 0.02 (95% CI 0.01, 0.03)], via offspring disorder alone [B 0.16 (95% CI 0.10, 0.22)], and via both parent-child relationship and offspring disorder [B 0.01 (95% CI 0.002, 0.01)].

Peer victimisation and offspring psychiatric disorder

Figure 5.3 shows results from the structural model examining the direct effect of maternal *chronic-severe* depression (with *minimal* class as the reference group), on offspring past year suicidal ideation at age 16 years, and the indirect effect through peer victimisation from age 10 to 12 years. There was evidence of an indirect effect through peer victimisation [B 0.07 (95% CI 0.03, 0.11)] and a direct effect not mediated by peer victimisation [B 0.57 (95% CI 0.38, 0.77); $p < 0.001$].

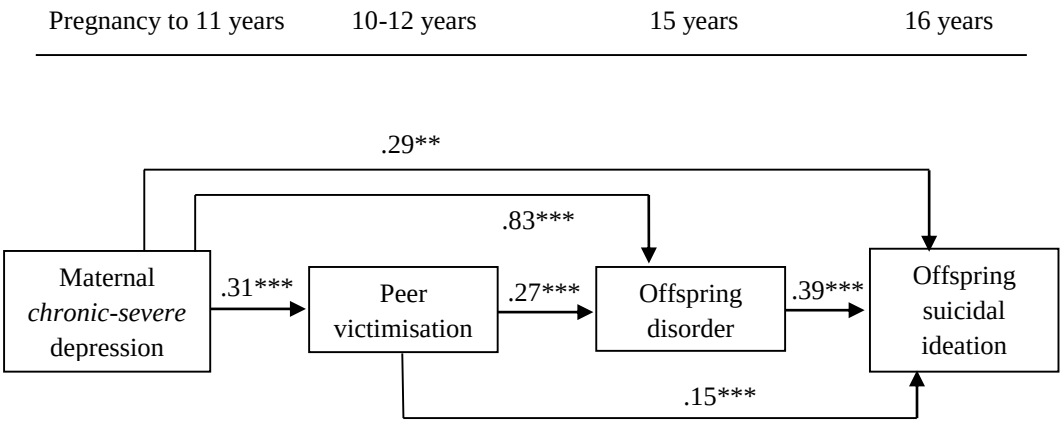


*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$*

Figure 5.3 - Structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effect through peer victimisation from age 10 to 12 years; imputed *N* = 10,559; non-standardised probit regression coefficients presented

A similar pattern of results was found for offspring of mothers with *moderate* depression symptoms over time (in comparison to offspring of mothers with *minimal* symptoms*)* with evidence of an indirect effect through peer victimisation [B 0.04 (95% CI 0.02, 0.06)]. There was also evidence of a direct effect of maternal *moderate* symptoms on offspring suicidal ideation after accounting for peer victimisation [B 0.19 (95% CI 0.10, 0.27); $p < 0.001$].

Figure 5.4 shows results from the structural model examining the direct effect of maternal *chronic-severe* depression on offspring suicidal ideation, and the indirect effects through peer victimisation and offspring psychiatric disorder. There was evidence of indirect effects via only peer victimisation [B 0.05 (95% CI 0.01, 0.08)], via offspring disorder alone [B 0.32 (95% CI 0.20, 0.45)], and via both peer victimisation and offspring disorder [B 0.03 (95% CI 0.01, 0.05)].



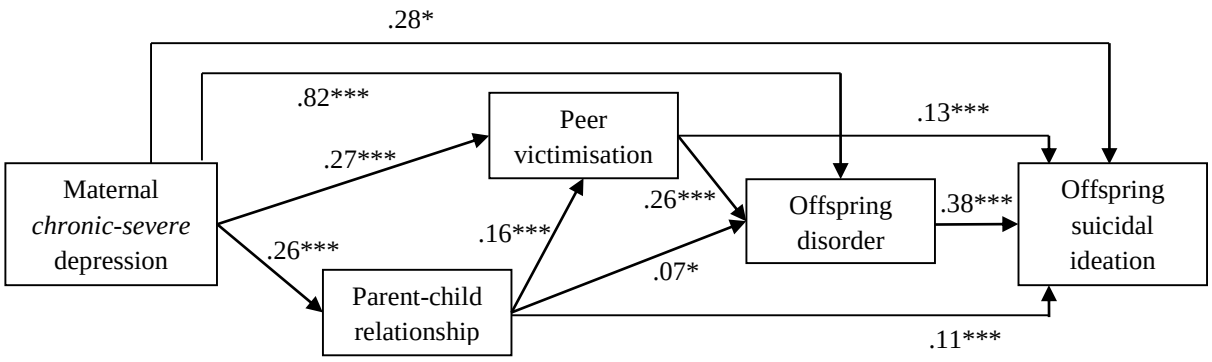
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

Figure 5.4 – Structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effects through peer victimisation from age 10 to 12 years and offspring psychiatric disorder at age 15 years; imputed N = 10,559; non-standardised probit regression coefficients presented

A similar pattern of results was found for offspring of mothers with *moderate* symptoms over time (in comparison to offspring of mothers with *minimal* symptoms*)* with evidence of an indirect effect via only peer victimisation [B 0.03 (95% CI 0.01, 0.04)], via offspring disorder alone [B 0.14 (95% CI 0.08, 0.20)], and via both peer victimisation and offspring disorder [B 0.02 (95% CI 0.01, 0.03)].

<u>The parent-child relationship, peer victimisation and offspring disorder</u>

Figure 5.5 shows results from the structural model examining the direct effect of maternal *chronic-severe* depression on offspring suicidal ideation, and the indirect effects through offspring disorder, the parent-child relationship and peer victimisation. There was evidence of indirect effects via only offspring disorder [B 0.31 (95% CI 0.19, 0.44)], via the parent-child relationship alone [B 0.03 (95% CI 0.01, 0.05)], via peer victimisation alone [B 0.04 (95% CI 0.01, 0.07)], and via both peer victimisation and offspring disorder [B 0.03 (95% CI 0.01, 0.04)]. Finally, there was evidence of weak indirect effects via both the parent-child relationship and offspring disorder [B 0.01 (95% CI 0.00, 0.01)], via the parent-child relationship and peer victimisation [B 0.01 (95% CI 0.001, 0.01)], and via the parent-child relationship, peer victimisation and offspring disorder [B 0.004 (95% CI 0.002, 0.006)].



** p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001*

Figure 5.5 - Structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effects through offspring psychiatric disorder, the parent-child relationship and peer victimisation; imputed *N* = 10,559; non-standardised probit regression coefficients presented for categorical outcomes; linear regression coefficient presented for continuous outcome (parent-child relationship)

A similar pattern of results was found for offspring of mothers with *moderate* symptoms over time (in comparison to offspring of mothers with *minimal* symptoms*)* with evidence of an indirect effect via only offspring disorder [B 0.13 (95% CI 0.07, 0.20)], via the parent-child relationship alone [B 0.02 (95% CI 0.02, 0.03)], via peer victimisation alone [B 0.02 (95% CI 0.005, 0.04)], and via both peer victimisation and offspring disorder [B 0.02 (95% CI 0.01, 0.02)]. Finally, there was evidence of weak indirect effects via both the parent-child relationship and offspring disorder [B 0.003 (95% CI -0.00, 0.01)], via the parent-child relationship and peer victimisation [B 0.003 (95% CI 0.001, 0.005)], and via the parent-child relationship, peer victimisation and offspring disorder [B 0.002 (95% CI 0.00, 0.004)].

<u>Offspring disorder, maternal suicide attempt, the parent-child relationship and peer victimisation</u>

Figure 5.6 shows results from the full structural model examining the direct effect of maternal *chronic-severe* depression on offspring suicidal ideation, and the indirect effects through offspring disorder, maternal suicide attempt, the parent-child relationship and peer victimisation. There was no evidence of a direct effect of maternal *chronic-severe* depression on offspring suicidal ideation after accounting for all potential mediators [B -0.04 (95% CI -0.33,

0.25); $p = 0.79$]. Model fit statistics indicated a good fit to the data (RMSEA = 0.007; CFI = 0.999).

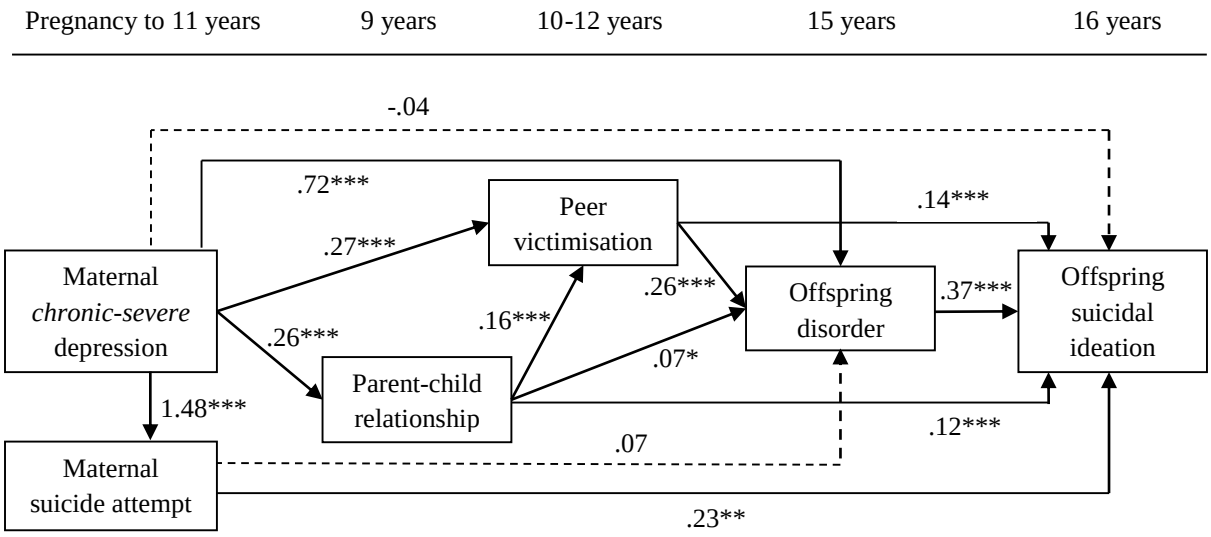


Figure 5.6 – Full structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effects through offspring psychiatric disorder, maternal suicide attempt, the parent-child relationship and peer victimisation; imputed $N = 10,559$; non-standardised probit regression coefficients presented for categorical outcomes; linear regression coefficient presented for continuous outcome (parent-child relationship)

Next, the total indirect effect via each of the four mediators (offspring disorder, maternal suicide attempt, the parent-child relationship, peer victimisation) was calculated. For example, the total indirect effect via peer victimisation consists of the indirect effect via only peer victimisation, the indirect effect via both peer victimisation and offspring disorder, the indirect effect via the parent-child relationship and peer victimisation and the indirect effect via the parent-child relationship, peer victimisation and offspring disorder. Table 5.3 (model 1a) shows the unadjusted indirect effects through all possible combinations of potential mediators. Table 5.3 (model 1b) shows that the pattern of results was the same after adjusting for potential confounders assessed in pregnancy (child gender, housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy). Sensitivity checks were performed by rerunning the full model using alternative approaches to dealing with missing data. Findings were comparable

when only imputing data for those offspring that were sent the questionnaire measure at age 16 years (N = 8,475; Table 5.3, model 2) and when only imputing mediators for those offspring with complete outcome data (N = 4,588; Table 5.3, model 3). Finally, although indirect effects were generally weaker when using complete cases (N = 2,599; Table 5.3, model 4), conclusions remained unchanged with the exception of the indirect effect through maternal suicide attempt (due to a weaker association between maternal suicide attempt and offspring suicidal ideation in complete case analyses) and the indirect effect through peer victimisation (due to a weaker association between maternal *chronic-severe* depression and peer victimisation in complete case analyses). Appendix 8 shows the full structural model using complete data.

Table 5.3 - Indirect effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring suicidal ideation through all possible combinations of mediators (non-standardised probit regression coefficient and 95% Confidence Intervals (95% CI) displayed)

Model [a]	Indirect effects of maternal chronic-severe depression on suicidal ideation via mediators (probit coefficient (95% CI))				
Total indirect effect via:	Model 1a: full imputed data; unadjusted (*N* = 10,559)	Model 1b: adjusted for confounders (*N* = 10,559) [b]	Model 2: as Model 1a, imputing those sent questionnaire (*N* = 8,475)	Model 3: as Model 1a, imputing those with complete outcome data (*N* = 4,588)	Model 4: as Model 1a, complete cases (*N* = 2,599)
Offspring disorder	.35 (.21, .48) [c]	.25 (.14, .36)	.31 (.19, .43)	.27 (.12, .42)	.18 (.02, .35)
Maternal suicide attempt	.37 (.16, .58) [d]	.25 (.07, .43)	.36 (.13, .59)	.34 (.07, .61)	.20 (-.13, .54)
Parent-child relationship	.05 (.02, .07) [e]	.06 (.03, .08)	.04 (.02, .07)	.05 (.01, .08)	.07 (.03, .14)
Peer victimisation	.07 (.03, .12) [f]	.05 (.01, .09)	.07 (.03, .11)	.04 (-.01, .09)	.02 (-.03, .07)

[a] Model 1a shows the unadjusted results using the full imputed dataset; model 1b shows results after adjusting for confounders assessed in pregnancy; model 2 shows the unadjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years; model 3 shows the unadjusted results using imputed data for mediators in those that had complete outcome data; model 4 shows the unadjusted results using only those with complete data on all variables in analysis;

[b] Adjusting for confounders assessed in pregnancy (child gender, housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy);

[c] Consists of the indirect effect via only offspring disorder [B (95% CI) =.27 (.12, .42)], via maternal suicide attempt and offspring disorder [B (95% CI) =.04 (-.05, .13)]; via the parent-child relationship and offspring disorder [B (95% CI) =.01 (.00, .01)], via peer victimisation and offspring disorder [B (95% CI) =.03 (.01, .04)] and via the parent-child relationship, peer victimisation and offspring disorder [B (95% CI) =.004 (.002, .01)];

[d] Consists of the indirect effect via only maternal suicide attempt [B (95% CI) =.33 (.12, .55)] and via maternal suicide attempt and offspring disorder [B (95% CI) =.04 (-.05, .13)];

[e] Consists of the indirect effect via only the parent-child relationship [B (95% CI) =.03 (.01, .05)], via the parent-child relationship and offspring disorder [B (95% CI) =.01 (.00, .01)]; via the parent-child relationship and peer victimisation [B (95% CI) =.01 (.002, .01)] and via the parent-child relationship, peer victimisation and offspring disorder [B (95% CI) =.004 (.002, .01)];

[f] Consists of the indirect effect via only peer victimisation [B (95% CI) =.04 (.01, .07)], via peer victimisation and offspring disorder [B (95% CI) =.03 (.01, .04)]; via the parent-child relationship and peer victimisation [B (95% CI) =.01 (.002, .01)] and via the parent-child relationship, peer victimisation and offspring disorder [B (95% CI) =.004 (.002, .01)]

The pattern of results was similar when examining indirect effects of maternal *moderate* depression symptoms on offspring suicidal ideation through offspring disorder, maternal suicide attempt, the parent-child relationship and peer victimisation (Table 5.4, model 1a). Again, the pattern of results was the same after adjusting for potential confounders (Table 5.4, model 1b). Findings were comparable across different imputation samples (Table 5.4, models 2 and 3). Again, indirect effects were weaker when using complete cases (Table 5.4, model 4), however, conclusions remained unchanged with the exception of the indirect effect through maternal suicide attempt for the reasons outlined previously. When running analyses in those offspring who did not report suicidal ideation at age 11 years (i.e. new onset cases; N = 5,341), conclusions were the same; however there was weaker evidence for an indirect effect of maternal depression on offspring suicidal ideation via maternal suicide attempt [maternal *chronic-severe* depression: B 0.24 (95% CI -0.02, 0.51); maternal *moderate* depression: B 0.14 (95% CI -0.02, 0.30)].

Finally, for ease of interpretation, probit coefficients within the path diagram (Figure 5.6) were converted to odds ratios using the procedure described in Chapter 4, section 4.4.3. Appendix 9 shows the structural model from Figure 5.6 but with the probit coefficients converted to odds ratios. As can be seen in the Appendix, offspring with a psychiatric disorder were nearly two times more likely to have suicidal ideation at age 16 years compared to offspring without a psychiatric disorder, after taking into account the other variables in the model; whereas, offspring of mothers that had made a suicide attempt were just under 1.5 times more likely to have suicidal ideation compared to offspring of mothers who had not made a suicide attempt, in the context of the model.

Table 5.4 - Indirect effect of maternal moderate depression (with minimal class as the reference group) on offspring suicidal ideation through all possible combinations of mediators (non-standardised probit regression coefficient and 95% Confidence Intervals (95% CI) displayed)

Model [a]	Indirect effects of maternal moderate depression on suicidal ideation via mediators (probit coefficient (95% CI))				
Total indirect effect via:	Model 1a: full imputed data; unadjusted (*N* = 10,559)	Model 1b: adjusted for confounders (*N* = 10,559) [b]	Model 2: as Model 1a, imputing those sent questionnaire (*N* = 8,475)	Model 3: as Model 1a, imputing those with complete outcome data (*N* = 4,588)	Model 4: as Model 1a, complete cases (*N* = 2,599)
Offspring disorder	.15 (.09, .22) [c]	.12 (.06, .17)	.14 (.08, .20)	.12 (.05, .19)	.08 (.02, .15)
Maternal suicide attempt	.18 (.07, .29) [d]	.13 (.03, .22)	.18 (.05, .31)	.16 (.01, .30)	.12 (-.09, .32)
Parent-child relationship	.03 (.01, .04) [e]	.03 (.01, .04)	.02 (.01, .03)	.02 (.01, .03)	.02 (.004, .04)
Peer victimisation	.04 (.02, .06) [f]	.03 (.01, .05)	.04 (.02, .06)	.03 (.01, .06)	.02 (.01, .05)

[a] Model 1a shows the unadjusted results using the full imputed dataset; model 1b shows results after adjusting for confounders assessed in pregnancy; model 2 shows the unadjusted results using imputed data for those offspring that were sent the questionnaire at age 16 years; model 3 shows the unadjusted results using imputed data for mediators in those that had complete outcome data; model 4 shows the unadjusted results using only those with complete data on all variables in analysis;

[b] Adjusting for confounders assessed in pregnancy (child gender, housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy);

[c] Consists of the indirect effect via only offspring disorder [B (95% CI) =.11 (.04, .19)], via maternal suicide attempt and offspring disorder [B (95% CI) =.02 (-.02, .06)]; via the parent-child relationship and offspring disorder [B (95% CI) =.003 (.001, .01)], via peer victimisation and offspring disorder [B (95% CI) =.02 (.01, .02)] and via the parent-child relationship, peer victimisation and offspring disorder [B (95% CI) =.002 (.00, .004)];

[d] Consists of the indirect effect via only maternal suicide attempt [B (95% CI) =.16 (.05, .27)] and via maternal suicide attempt and offspring disorder [B (95% CI) =.02 (-.02, .06)];

[e] Consists of the indirect effect via only the parent-child relationship [B (95% CI) =.02 (.01, .03)], via the parent-child relationship and offspring disorder [B (95% CI) =.003 (.001, .01)]; via the parent-child relationship and peer victimisation [B (95% CI) =.003 (.001, .005)] and via the parent-child relationship, peer victimisation and offspring disorder [B (95% CI) =.002 (.00, .004)];

[f] Consists of the indirect effect via only peer victimisation [B (95% CI) =.02 (.01, .04)], via peer victimisation and offspring disorder [B (95% CI) =.02 (.01, .02]; via the parent-child relationship and peer victimisation [B (95% CI) =.003 (.001, .005] and via the parent-child relationship, peer victimisation and offspring disorder [B (95% CI) =.002 (.00, .004)]

5.5: Discussion

Consistent with previous research (Garber et al., 1998; Gureje et al., 2011), offspring in this unselected population cohort that were exposed to chronic and severe maternal depression symptoms were at considerably increased risk for later suicidal ideation in adolescence. Although the majority of the association between maternal *chronic-severe* depression and offspring suicidal ideation was explained through maternal suicide attempt and offspring psychiatric disorder, there was also evidence for independent indirect effects via both the parent-child relationship and peer victimisation in middle childhood. There was no longer evidence of a direct effect of maternal *chronic-severe* depression on offspring suicidal ideation after accounting for all mediators. Maternal *moderate* depression symptoms were considerably more common affecting half of children in this cohort. These offspring were also at increased risk for suicidal ideation, highlighting the importance of considering suicidal ideation and related risk pathways in mothers with sub-threshold but sustained symptoms of depression. Findings showed that the same mechanisms accounted for risks in this group. Again, maternal suicide attempt, offspring psychiatric disorder, problems in the parent-child relationship and being bullied by peers together fully accounted for the association between maternal *moderate* depression and adolescent suicidal ideation.

In this population sample, offspring proximal psychiatric disorder and maternal suicide attempt explained the majority of the association between maternal depression and offspring suicidal ideation. This supports previous studies that have highlighted the importance of both these mechanisms (Geulayov et al., 2014; Gureje et al., 2011; Mittendorfer-Rutz et al., 2008). As has been found previously (Brent et al., 1996; Brent & Mann, 2005; Brent et al., 2014; Christiansen et al., 2011; Kuramoto et al., 2010; Mittendorfer-Rutz et al., 2008; Petersen et al., 2014; Tidemalm et al., 2011), there was evidence that the transmission of suicide-related behaviour from mother to offspring was not accounted for by the transmission of psychopathology. The direct path between maternal suicide attempt and offspring suicidal ideation could be explained by the impact of direct exposure to a suicide attempt in a parent, however evidence suggests that the intergenerational transmission of suicidal behaviour is unlikely to be explained by imitation alone (Brent & Mann, 2005; Brent & Melhem, 2008; Burke et al., 2010; Statham et al., 1998). Additionally, it was not examined here whether the child was aware that their mother had made a suicide attempt. There may also be a genetic component, possible involving liability to impulsive aggression (Brent et al., 1996; Brent & Melhem, 2008; Brent & Mann, 2006). It is also possible that maternal suicide attempt has an impact on child victimisation or impaired family relationships (Brent & Mann, 2005; Brent & Melhem, 2008). Preliminary analyses showed that there was no association between maternal suicide attempt and either the parent-child relationship or peer victimisation in this sample; however, it was beyond the scope of this

thesis to examine further explanations for the association between maternal suicide attempt and offspring suicidal ideation.

Few studies have examined potential mechanisms of the association between maternal depression and offspring suicidal ideation, other than offspring psychiatric disorder and maternal suicide attempt. The direct association between the parent-child relationship and offspring suicidal ideation found in this chapter supports previous literature that has shown that disruption to the parent-child relationship predicts suicidal ideation independently to the adolescent's own psychopathology (Boeninger, 2013; Connor & Rueter, 2006; Thompson et al., 2005). The findings in the current chapter extend this research, first by showing enduring risk effects seven years later, and second, by demonstrating a small, yet robust indirect effect of maternal depression on offspring suicidal ideation via the child perceived parent-child relationship in middle childhood that was not fully accounted for by offspring psychiatric disorder. The remaining direct effect of the parent-child relationship on suicidal ideation could be explained by a number of factors. A negative parent-child relationship may lead the child to feel like an expendable member of the family (Van Orden et al., 2010); alternatively lack of support and communication with parents may lead the child to feel that thoughts of suicide are the only method of escape (Garber et al., 1998).

This chapter also found a direct association between peer victimisation and offspring suicidal ideation. Again, this supports past research that has shown a direct effect of peer victimisation on suicidal ideation after accounting for offspring psychopathology (Turner et al., 2012; van Geel et al., 2014; Winsper et al., 2012). There was also evidence that maternal depression was associated with peer victimisation both directly, and via the impact on the parent-child relationship, although the direct association was weakened slightly after accounting for potential confounding factors. The association between maternal depression and peer victimisation via problems in the parent-child relationship may be explained by the child learning poor social skills and maladaptive behavioural responses through negative interactions with a parent (Putallaz & Heflin, 1990). The remaining direct effect of maternal depression on peer victimisation could be explained by offspring acquiring maladaptive interpersonal cognitions and skills through observation of their mother, and her interactions with others (Hammen & Brennan, 2001; Lereya & Wolke, 2012), or by the direct effect of maternal depression in pregnancy, which may increase vulnerability to later victimisation through altering the child's stress response (Lereya & Wolke, 2012). In addition, it has been found previously that mothers with depression provide fewer cognitive restructuring suggestions (i.e. thinking positively) and more cognitive avoidance suggestions (i.e. directing thoughts away from stress) to children who were dealing with peer victimisation (Monti, Rudolph, & Abaied, 2014) which may exacerbate both the bullying and the distress resulting from bullying.

Two important studies that utilised the same sample (ALSPAC) found that maternal prenatal mental health increased risk of later peer victimisation both directly and indirectly via early maladaptive parenting (Lereya & Wolke, 2012) and that the association between an adverse early family environment and self-harm in adolescence was partially mediated by peer victimisation (Lereya et al., 2013). The current findings extend these studies in three important ways. First, the findings show that the family and peer mechanisms are also important in relation to adolescent suicidal ideation, in addition to self-harm. Second, the current analyses examined these family and peer mechanisms in a model together with maternal depression, maternal suicide attempt and offspring suicidal ideation, therefore showing evidence of independent indirect effects of maternal depression on offspring suicidal ideation via each of the mechanisms. Finally, the results in this chapter show that the same mechanisms are important for offspring of mothers with sub-threshold but sustained levels of depression symptoms over time. This finding also builds on previous studies that identified family functioning (Garber et al., 1998) and peer victimisation (Tsypes & Gibb, 2015) as mediators of the association between maternal depression diagnosis and offspring suicidal ideation by showing that these mechanisms are also important to consider for offspring of mothers with less severe levels of depression symptoms that may have never been diagnosed with depression.

The findings need to be considered in the light of several limitations. First, as the parent-child relationship, peer victimisation and suicidal outcome measure were reported by the child, shared-rater bias may have inflated associations with offspring suicidal ideation (even though reported from four to seven years apart). However, it is widely agreed that children's own perceptions of relationships are particularly important when considering risk for negative outcomes (Harold, Shelton, Goeke-Morey, & Cummings, 2004; Mueller, Jouriles, McDonald, & Rosenfield, 2014; White, Shelton, & Elgar, 2014). In addition, a recent meta-analysis examining the association between peer victimisation and suicidal ideation found that there was no difference in effect size between studies using only self-report of victimisation and those using another reporter (van Geel et al., 2014). Second, as with most cohort studies, there was selective attrition over time, and only a minority of cohort members provided data on all measures across childhood and adolescence; however, potential bias arising from missing data was dealt with using multiple imputation, utilising a large amount of additional information to make the assumption of MAR as plausible as possible. Findings were comparable across three different samples of imputed data. Although most indirect effects were weaker in complete case analyses, as has been reported previously (Pearson et al., 2013), the pattern of findings was similar (with the exception of a weaker association between maternal *chronic-severe* depression and peer victimisation and between maternal suicide attempt and offspring suicidal ideation in those with complete data). Third, the effect sizes found for some of the indirect effects were very small.

This is often the case when investigating indirect effects, especially when examining pathways via a number of mediators, and is in keeping with other similar studies (Lereya et al., 2013; Sellers et al., 2014). However, given that the parent-child relationship and peer victimisation accounted for only a small proportion of the association between maternal depression and offspring suicidal ideation, it is important to consider whether these effects are clinically meaningful. Indirect effects via either of these mechanisms together accounted for approximately 16% of the total effect of maternal *chronic-severe* depression on offspring suicidal ideation. However, both of these factors have been shown to be important in predicting suicide risk outside of the context of maternal depression (Boeninger, 2013; Connor & Rueter, 2006; Klomek et al., 2010; McLoughlin et al., 2015; Takizawa et al., 2014; Thompson et al., 2005; van Geel et al., 2014). Additionally, it could be that family and peer support more generally is important, and this might not have been captured by the specific measures and timings used in this thesis. For example, given that peer victimisation was assessed between the ages of 10 and 12 years, the impact may have been underestimated as new onset victimisation in adolescence was not considered. It is also important to note that prevention of bullying and parent-child difficulties is crucial due to other deleterious outcomes (Burt, McGue, Krueger, & Iacono, 2005; Goodman & Gotlib, 1999; Harold et al., 2013; Lewis, Collishaw, Thapar, & Harold, 2013; Sellers et al., 2014; Takizawa et al., 2014; Woolfenden, Williams, & Peat, 2001). Fourth, although this study allowed for the time-ordering of effects to be examined, it is still important to consider the possibility of reverse causation as the direction of effects between the potential mediators examined is not well-established. It is important to note that when repeating analyses after excluding offspring with suicidal ideation at age 11 years, the indirect effect of maternal depression on offspring suicidal ideation via maternal suicide attempt was attenuated. However, this weaker effect might have been due, in part, to the impact of missing data as the children that did not complete the suicide-related behaviour questionnaire at age 11 years were also excluded from these analyses. It is also possible that earlier suicidal behaviour impacted on offspring psychiatric disorder as has been reported previously in the same sample (Mars, Heron, Crane, Hawton, Lewis, et al., 2014) as it was not possible to exclude children that had experienced suicide-related behaviour between ages 11 and 15 years. Additionally, it is likely that exposure to bullying due to maternal depression reflects, in part, child evocative effects (Ball et al., 2008; Bowes et al., 2013). Finally, although this chapter assessed a number of competing mechanisms which together fully accounted for the association between maternal depression and offspring suicidal ideation, there are additional mechanisms that were not assessed here that may also lie on these pathways and contribute to explaining the association. These might include offspring temperament and personality and cognitive behavioural factors such as coping skills. In addition, given the complexity of the models relative to the sample size, gender differences were not examined. This is something that future research could address. The

focus of this chapter was also on risk for offspring suicidal ideation; therefore additional mechanisms, such as impulsive aggression (Brent et al., 2014), that may contribute to explaining the association between maternal depression and offspring suicide attempt were not considered.

The results in the current chapter suggest that parent, peer, child and family-related mechanisms explain the association between maternal depression and offspring suicidal ideation. These findings have implications for future theory development and model testing. Genetically sensitive designs such as those involving children-of-twins (Silberg et al., 2010), children born by assisted conception (Thapar et al., 2007) and adoption studies (Elam et al., 2014) will be especially helpful in replicating these observational findings because they can take into account genetic contributors to cross-generational associations (Rutter & Thapar, 2015). As expected, offspring with a psychiatric disorder or whose mothers had made a suicide attempt were most at risk for future suicidal ideation indicating that suicide prevention efforts in offspring of mothers with depression should be targeted at these subgroups. However, given findings that two-thirds of adolescents with suicidal ideation did not have any contact with mental health services in the previous year (Husky et al., 2012), better identification of those with a disorder will be important.

In this chapter, there was also evidence for additional pathways from maternal depression to offspring suicidal ideation via the parent-child relationship and peer victimisation in middle childhood. These are important findings given that both these mechanisms are potentially modifiable (Scott & Gardner, 2015; Smith et al., 2003) and therefore could be a focus of preventive interventions. A recent review highlighted that successful interventions aimed at reducing suicidal ideation and suicide attempt in adolescents often had a focus on family interactions (Brent et al., 2013). Therefore interventions in offspring of depressed mothers aimed at improving support and communication between mother and child as well as treating child psychopathology may be beneficial in reducing adolescent suicide risk within this high-risk group. Additionally, there is evidence that anti-bullying interventions in schools addressing school policy or class rules, along with more focused interventions, such as curriculum work on awareness can have a positive impact on reducing victimisation, especially in primary schools before pupils have entered into stable victim roles (Smith et al., 2003). Therefore, interventions aimed at reducing peer victimisation and teaching children how to better deal with being victimised may also be beneficial in reducing adolescent suicide risk. Targeting these children early, before the onset of suicidal behaviour, is also likely to be valuable given the long term negative consequences of adolescent suicidal ideation (Reinherz et al., 2006). The importance of early intervention for offspring of depressed parents has also been highlighted for other outcomes (Beardslee, Gladstone, Wright, & Cooper, 2003; Cicchetti, Rogosch, & Toth, 2000).

In addition to reducing risk, enhancing resilience by fostering supportive relationships with parents and peers may also be helpful (Collishaw et al., 2015). These results also highlight the importance of different services working together. Identifying barriers to effective communication between adult and child services will be important. Additionally, the need for collaboration between researchers and practitioners with expertise in school bullying and peer conflicts and those involved in youth suicide prevention has been highlighted (Hong et al., 2014; Turner et al., 2012). This is especially important given evidence that the risk effects of maternal depression can spread outside of the family. Finally, results also generalised to offspring of mothers with less severe levels of depression symptoms. These offspring are an important group to consider as they may be less likely to be known to services if mothers have never been diagnosed with clinical depression.

Chapter 6: General discussion

The overall goal of this thesis was to investigate mechanisms of the association between maternal depression symptom course and adolescent suicidal ideation and suicide attempt using a large, population-based birth cohort. This chapter will summarise the findings from the three results chapters before discussing the potential implications of the findings, followed by the strengths and limitations of the thesis. Suggestions for future work will then be highlighted**,** followed by final conclusions.

6.1: Summary of aims and findings

Suicide-related behaviour is common in adolescence and suicide is now the second leading cause of death in this age group (World Health Organization, 2014). Evidence from both community samples (Garber et al., 1998; Gureje et al., 2011; Wilcox et al., 2010) and population registers (Mittendorfer-Rutz et al., 2012, 2008) has highlighted that maternal depressive disorder is a robust risk factor for both offspring suicidal ideation and suicide attempt. However, given that the majority of previous literature has examined the impact of a lifetime diagnosis of maternal depression on offspring suicide risk (Garber et al., 1998; Wilcox et al., 2010), the heterogeneity in the course, timing and severity of depression has not been taken into account. Therefore, the first aim of this thesis was to identify trajectories of maternal depression symptoms over the first eleven years of their child's life and then to examine the association between maternal depression symptom course and adolescent suicidal ideation and suicide attempt. In Chapter 3, five distinct classes of maternal depression symptoms were identified; four showed stable levels of depression symptoms but differed in the level of severity (*minimal, mild, sub-threshold, chronic-severe*) and one showed a change in severity, with increasing levels of depression symptoms over time (*increasing*). Variation in maternal depression symptom course was associated with subsequent offspring suicidal ideation and attempt, with greatest risk for offspring of mothers with *chronic-severe* depression symptoms and intermediate risk for offspring of mothers with moderate symptoms (*sub-threshold, increasing* and *mild* symptom trajectories) compared to offspring of mothers with *minimal* symptoms. These findings extend results from previous studies by showing that risk for adolescent suicide-related behaviour is not only confined to families where the parent is affected by severe clinical depression, but extends to adolescents of mothers who suffer from milder but sustained sub-threshold levels of depression. Findings from the first results chapter also advances previous literature by showing that associations were not completely explained by a number of background socio-demographic and familial confounders, by earlier suicidal ideation in the offspring or through maternal suicide attempt or offspring depression diagnosis, at least for offspring of mothers with *chronic-severe* and *sub-threshold* symptoms.

Identifying which offspring are most at risk of suicide-related behaviour is essential to ensure prevention programs are targeted effectively. However, in order to inform the development of such programs, it is necessary to establish potentially modifiable mechanisms that explain the intergenerational transmission of risk. Currently, the pathways involved in the transmission of risk for suicide-related behaviour from depressed mothers to offspring, including the role of specific aspects of offspring psychopathology, remain unclear. Therefore, the second aim of this thesis was to examine how much of the association between differing levels of maternal depression symptoms and adolescent suicidal ideation and suicide attempt was explained through proximal offspring psychopathology, including symptoms of MDD, GAD, DBD, ADHD and alcohol abuse. Findings from Chapter 4 showed that the association between maternal *chronic-severe* depression and offspring suicidal ideation was independently mediated by offspring MDD, GAD and DBD symptoms. The same mechanisms were found for offspring of mothers with *moderate* depression symptoms over time (when combining *mild, increasing* and *sub-threshold* trajectory classes together). Results were similar for offspring suicide attempt except for additional evidence of an indirect effect through offspring ADHD symptoms. There was still evidence for a direct effect of maternal depression on offspring suicide-related behaviour after accounting for offspring symptoms of psychopathology. This finding supports other studies that have shown that risk for both offspring suicidal ideation (Gureje et al., 2011) and attempt (Mittendorfer-Rutz et al., 2008) from maternal depression is not completely explained through a psychiatric disorder in the offspring. However, this study extends prior research by examining the relative importance of specific aspects of offspring psychopathology in explaining the association between maternal depression and subsequent offspring suicidal ideation and suicide attempt in adolescence, and by showing that the same mechanisms are important for offspring of mothers with depression symptoms below clinical levels.

Findings from this thesis and from previous literature have highlighted that the association between maternal depression and offspring suicidal ideation is not completely explained through offspring psychiatric disorder or maternal suicide attempt (Gureje et al., 2011; Mittendorfer-Rutz et al., 2012, 2008). Therefore additional mechanisms may also be important to consider. Given that a number of different inter-related pathways are likely involved in the aetiology of adolescent suicidal ideation, testing competing mechanisms *together* is especially important. However, few studies have examined competing mediators across a long developmental time span, covering the course of childhood and adolescence. Additionally, given that most studies examining risk mechanisms have focused on mothers with a lifetime diagnosis of depression (Garber et al., 1998; Gureje et al., 2011; Tsypes & Gibb, 2015), it is not

known whether mechanisms underlying the link between maternal depression and offspring suicide-related behaviour vary according to maternal depression symptom severity. Therefore, the third aim of this thesis was to examine the role of additional hypothesised mediators that might contribute to explaining the association between differing levels of maternal depression across childhood and offspring suicidal ideation in adolescence. These mediators included maternal suicide attempt across the first eleven years of their child's life, the parent-child relationship and peer victimisation in middle childhood and offspring psychiatric disorder in adolescence. Findings from Chapter 5 showed that the majority of the association between maternal *chronic-severe* depression and offspring suicidal ideation was explained through maternal suicide attempt and offspring psychiatric disorder, however, there was also evidence for independent indirect effects via both the parent-child relationship and peer victimisation. Again, the same mechanisms were found for offspring of mothers with less severe levels of depression symptoms over time.

Overall, the results from this thesis highlight that offspring exposed to chronic and severe levels of maternal depression symptoms throughout childhood are at considerably increased risk for both suicidal ideation and suicide attempt in adolescence. However, suicide risk should be considered in offspring, even when maternal depression symptoms are below clinical levels. Risk mechanisms for both of these groups of offspring were similar and highlighted that offspring with a psychiatric disorder and whose mothers have made a suicide attempt are important groups to target for early intervention and prevention. However, peer victimisation and the parent-child relationship are also important mechanisms to consider given that they are potentially modifiable and amenable to intervention. Further implications of these findings will be discussed next.

6.2: Potential implications

Identifying key risk factors for adolescent suicide-related behaviour will highlight those most at risk to target for early intervention and prevention. Offspring exposed to chronic and severe levels of maternal depression symptoms throughout childhood were at greatest risk of suicide-related behaviour. The offspring of these mothers are an easily identified high-risk group, given that the majority of mothers were known to services; therefore these offspring are a priority for preventive interventions. These findings highlight the need for effective treatment and ongoing monitoring of maternal depression and the importance of GPs and adult services being aware of potential problems in children of mothers with chronic and severe depression, especially when the mother has also made a suicide attempt. However, the findings from this thesis also highlight that risk to the child extends beyond maternal depressive disorder. This is an important finding because more than half of this population cohort of adolescents had experienced

maternal depression symptoms that fell below clinical levels. In fact, estimates of the PAR suggested that suicidal ideation in adolescents could be reduced by 23% and suicide attempt by 35% if levels of depression symptoms in mothers with *chronic-severe, sub-threshold, increasing* or *mild* depression could be decreased to the level of symptoms of mothers in the *minimal* class (assuming associations are causal, estimates are unbiased and everything else remained the same). Although this is an unrealistic scenario, it nevertheless provides us with some information about the potential importance of improving parental mental health care for child outcomes. It is also important to note that the majority of mothers with sub-clinical levels of depression symptoms in the ALSPAC sample were not in contact with services due to depression, therefore the offspring are less likely to be identified as being at risk.

After identifying offspring at risk, an important next step is establishing potentially modifiable mechanisms to explain the intergenerational transmission of risk. The results from this thesis suggest that parent, peer, child and family-related mechanisms explain the association between maternal depression and offspring suicidal ideation. These findings highlight the importance of multicomponent interventions for reducing suicide risk in offspring of mothers with depression. In the recent report by the World Health Organization, 2014, it was highlighted that interventions that consist of multiple prevention strategies may be particularly helpful in reducing suicide rates. Similarly, multifaceted strategies for promoting resilience in offspring of depressed parents are important (Collishaw et al., 2015).

One key mechanism highlighted in the current findings was offspring psychiatric disorder and symptoms. Prevention programmes in offspring of depressed parents tend to focus on offspring depression as the outcome (Beardslee et al., 2013; Garber et al., 2009); however the findings from this thesis highlight the importance of considering additional psychopathology in the offspring including anxiety, disruptive behaviour and ADHD. The early identification and effective management of mental health disorders is already a priority in suicide prevention (World Health Organization, 2014). However, preventing and treating mental health disorders in adolescents is difficult, especially given that the majority of adolescents with suicidal ideation are not in contact with mental health services (Husky et al., 2012). The findings from this thesis also suggest that additional risk pathways are important after accounting for the presence of a psychiatric disorder in the offspring. However, it is important to note that in the current thesis, offspring psychiatric disorder and maternal suicide attempt explained the majority of the association between maternal depression and offspring suicidal ideation. The current findings support other important studies that have shown that the intergenerational transmission of suicide-related behaviour is distinct to the transmission of depression (Brent et al., 2014; Geulayov et al., 2014; Mittendorfer-Rutz et al., 2008), and highlight the importance of

considering suicide-related behaviour in offspring of mothers who have made a suicide attempt, even when the offspring do not have a psychiatric disorder. Given that few interventions currently exist for adolescent suicide-related behaviour, an important next step will be adding suicide-related outcome measures to relevant prevention trials (National Action Alliance for Suicide Prevention, 2014), especially those targeting the offspring of mothers with depression.

6.3: Strengths and limitations

This study extends prior research by using a prospective, population sample to examine the indirect effect of differing levels of maternal depression across childhood on subsequent offspring suicide-related behaviour in adolescence via a number of competing hypothesised mechanisms. Pathways of risk spanning the whole of childhood were examined using a variety of measurement techniques, whilst controlling for a number of potential familial and demographic confounders. The specific strengths of the study design that allowed the aims of the current thesis to be addressed will be discussed in more detail below.

First, the longitudinal design and prospectively assessed measures not only allowed for the temporal precedence of measures to be established, but also meant that the heterogeneity in maternal depression symptom course across the whole of childhood could be examined. By utilising repeated measures of maternal depression symptoms it was possible not only to derive a robust measure of depression course, but also to identify distinct groups of offspring at high risk for the development of suicide-related behaviour. Utilising prospective assessments of maternal depression symptoms also limited recall bias, which is particularly important given that recall of past depression could be affected by current mood state (Newport et al., 2008; Raphael & Cloitre, 1994). Additionally, repeated measures of offspring suicide-related behaviour were available, enabling offspring with earlier suicidal ideation to be excluded from analyses in order to address the possibility of reverse causation.

Second, in the ALSPAC sample, a large amount of information on socio-demographic and familial background risk was collected in pregnancy. This allowed alternative explanations for observed associations to be examined by adjusting for potential confounders. These alternative explanations are important to consider when the goal is to identify potential modifiable intervention targets. Third, given that ALSPAC is a large, population-based sample, this meant that there was enough power to examine rarer outcomes in the general population such as the presence of a suicide attempt in both mother and offspring. Identifying risk factors for adolescent suicide-related behaviour in community samples is essential so as not to exclude the large number of adolescents who do not seek treatment (Burless & De Leo, 2001; Hawton et al., 2002; Kidger et al., 2012; Potter et al., 2012).

Finally, potential mechanisms were assessed using a variety of measurement techniques, including interview and questionnaire measures. Maternal depression symptoms and offspring suicide-related behaviour were both assessed using self-report questionnaires meaning that shared-rater bias was reduced when examining initial associations. Additionally, the assessment of offspring suicide-related behaviour in ALSPAC may have led to less under-reporting than other techniques. Adolescents are more likely to disclose suicide-related behaviour with the anonymity of self-report questionnaire rather than in face-to-face interview (Breton et al., 2002; Klimes-Dougan, 1998; Prinstein et al., 2001). It has also been highlighted previously (Kidger et al., 2012) that the strict anonymity and confidentiality procedures in ALSPAC may have encouraged adolescents to provide honest answers to the questions minimising under-reporting.

However, the findings also need to be considered in the light of several limitations. Firstly, as with most cohort studies, there was selective attrition over time; however, potential bias arising from missing data was dealt with using multiple imputation. Previous studies have recommended using multiple imputation to deal with potential bias arising from missing data, especially when data are thought to be MAR (conditional on the other variables included in the model) (Moodie et al., 2008; Sterne et al., 2009). Additionally, all analyses were repeated using only those with complete data and the pattern of findings was similar. Any differences observed between complete case and imputed data have been discussed in the relevant results chapter. It is also important to note that approximately 3000 families were excluded from the study initially due to substantial missing data on maternal depression symptoms and other measures in analyses. Those participants excluded from the study had higher levels of socio-demographic risk factors than those that remained in, meaning that even the associations observed in the fully imputed sample may reflect conservative estimates. However, these mothers were excluded to ensure that some data were available on depression symptoms for each mother across the whole childhood period. Additionally, Table 2.1 showed that the imputed sample of 10,559 was representative of the original ALSPAC cohort.

Second, there are some limitations regarding the assessment of suicide-related behaviour in ALSPAC. Only information on lifetime suicide attempt was available, and this retrospective assessment might be subject to recall bias (Klimes-Dougan, 1998). Additionally, adolescent self-report was used to assess suicidal intent. It has been noted previously that this could introduce bias into associations observed if, for example, adolescents with depression were more likely to interpret their motivations for self-harm as suicidal (Kidger et al., 2012; Mars, Heron, Crane, Hawton, Kidger, et al., 2014). Additionally, 15% of adolescents that had made a suicide attempt reported ‘wanting to die’ as a reason why they hurt themselves on purpose on the most recent occasion but did not report that they had ever seriously wanted to kill

themselves. These adolescents were still classified as making a suicide attempt as it has been recommended that behaviours are classified as suicidal when there is any evidence for suicidal intent (Nock, 2010). The procedure used in this thesis to classify suicide attempt is also in keeping with other studies using the ALSPAC cohort (Mars, Heron, Crane, Hawton, Kidger, et al., 2014; Mars, Heron, Crane, Hawton, Lewis, et al., 2014). In addition, for the purposes of this thesis, suicidal ideation was considered present if adolescents reported either wishing to be dead or thoughts of killing self. The majority of adolescents classed as having suicidal ideation reported experiencing both of these things in the past year; however, 19% of adolescents only reported wishing to be dead. Including this more passive form of suicidal thoughts in the outcome may have resulted in more conservative estimates of associations; however, findings were similar when only examining risk for adolescents that specifically reported thoughts of killing self. Additionally, it was not possible to examine which of the adolescents that reported suicidal ideation or suicide attempt will go on to die by suicide. This is important to consider given that risk mechanisms for suicide may differ from those identified for suicidal ideation or suicide attempt, and currently, very little is known regarding factors that increase risk for suicide.

Third, despite utilising a longitudinal design with measures assessed across a period of 16 years, adjusting for a range of potential confounders and considering the possibility of reverse causation, it still cannot be assumed that associations observed in this observational study are necessarily causal. A wide range of socio-demographic and familial confounders assessed in pregnancy were taken into account, however residual confounding by measurement error in these variables, or by other unmeasured characteristics, cannot be ruled out. Fourth, the ALPSAC cohort is largely white European (above 96%) so it cannot be assumed that the results generalise to other ethnic groups. Additionally, the results from this thesis only generalise to Western countries. Although research into suicide-related behaviour in low- and middle-income countries is currently limited, some important differences from high-income countries have been identified, such as the gender ratio for suicide and methods used (Beautrais, 2006; Hendin et al., 2008; Phillips, Liu, & Zhang, 1999; Phillips, Li, & Zhang, 2002; World Health Organization, 2014). Fifth, there are a number of additional mechanisms that may also contribute to explaining the association between maternal depression and offspring suicide-related behaviour that were not examined here including offspring temperament and personality and cognitive behavioural factors such as coping skills. Additionally, the focus of this thesis was on normative aspects of disrupted relationships such as an impaired relationship between parent and child and peer victimisation. However, stronger effects may have been found had childhood maltreatment been considered. Previous studies have highlighted robust links between childhood maltreatment and suicidal ideation (Miller, Adams, Esposito-Smythers, Thompson, & Proctor,

2014; Turner et al., 2012) and suicide attempts (Johnson et al., 2002; Mars, Heron, Crane, Hawton, Kidger, et al., 2014) in adolescence, and it has been found that offspring of mothers who experienced both antenatal depression and childhood maltreatment were at increased risk for childhood maltreatment themselves (Plant, Barker, Waters, Pawlby, & Pariante, 2012). Another aspect of the family environment that was not considered was inter-parental conflict. Previous studies have highlighted the importance of considering this as a mechanism of the association between parental depression and offspring psychological adjustment (Cummings, Keller, & Davies, 2005; Shelton & Harold, 2008); additionally, inter-parental conflict is likely to impact on the child's perception of their relationship with their parents (Shelton & Harold, 2008). These additional mechanisms are something that future research could consider. Finally, it was beyond the scope of this thesis to examine whether initial associations or specific mechanisms differed by gender. There is some evidence from previous studies that mechanisms observed here may be stronger for girls. For example, the indirect effect of maternal depression on offspring suicidal ideation via peer victimisation has been shown to be stronger in girls compared to boys (Tsypes & Gibb, 2015). There is also some evidence that familial transmission of psychopathology (Lewis et al., 2011) and the association between the parent-child relationship and child psychological adjustment (Shelton & Harold, 2008) are both stronger in parents and children of the same sex. However, there is little evidence that the association between parental and child suicide-related behaviour is moderated by child gender (Geulayov et al., 2012). Further suggestions for future work are described next.

6.4: Suggestions for future work

6.4.1: The role of fathers

In this thesis, risk to offspring from paternal depression was not considered. Paternal psychiatric disorder (Lewinsohn et al., 2005; Mittendorfer-Rutz et al., 2008; Qin et al., 2002; Rohde et al., 2005) and suicide attempt (Geulayov et al., 2012; Qin et al., 2002) have both been shown to be associated with offspring suicide-related behaviour, even when maternal psychiatric disorder is controlled for (Lewinsohn et al., 2005; Mittendorfer-Rutz et al., 2008; Qin et al., 2002; Rohde et al., 2005). Studies have generally shown that risk to offspring is greater from maternal compared to paternal suicidal behaviour and psychiatric disorder (Geulayov et al., 2012; Geulayov et al., 2014; Mittendorfer-Rutz et al., 2008; Stenager & Qin, 2008); however, the difference in effect size is rarely statistically compared and when it has been, no difference has been found (Geulayov et al., 2014). There are a number of reasons why investigating risk to offspring from both maternal and paternal depression is important. First, a difference in risk in relation maternal compared to paternal depression indicates a possible environmental cause given that both parents contribute equally to offspring's genotype (Geulayov et al., 2012).

Second, selective mating means that a mother with depression is more likely than a non-depressed mother to select a partner with depression (Mathews & Reus, 2001), and risk to offspring may be greater where both parents have a psychiatric disorder (Stenager & Qin, 2008). Third, if offspring of fathers with depression are at increased risk for suicide-related behaviour, regardless of whether the mother has depression, this indicates that these offspring are also an important priority for preventive interventions. Few studies have examined mechanisms of the association between paternal depression and offspring suicide-related behaviour, therefore it is important to test if mechanisms differ from those identified here for maternal depression. Finally, a positive relationship between father and child may be an important protective factor against offspring suicide-related behaviour, especially when the mother is depressed (Collishaw et al., 2015; Mahedy et al., 2015). Therefore, investigating the role of fathers in explaining risk for offspring suicide-related behaviour is an important area for future research.

6.4.2: Maternal comorbidity

The focus of this thesis was on the impact of maternal depression; however depression is highly comorbid with other psychiatric disorders such as anxiety, antisocial behaviour and substance abuse (Rohde, Lewinsohn, & Seeley, 1991; Sellers et al., 2013). The total number of parental psychiatric disorders has been shown to increase risk for offspring suicide-related behaviour (Gureje et al., 2011; Santana et al., 2015) and psychiatric disorder (McLaughlin et al., 2012; Sellers et al., 2013). In this thesis, adjusting for the presence of a psychiatric disorder in mothers before pregnancy had little impact on the results; however, the influence of maternal psychiatric disorders, other than depression, on offspring suicide risk was not specifically considered. Studies using both community samples and population registers have shown that a range of psychiatric disorders in parents (including anxiety, antisocial behaviour, substance abuse, schizophrenia and personality disorders) are independently associated with suicide-related behaviour in offspring (Gureje et al., 2011; Mittendorfer-Rutz et al., 2008; Santana et al., 2015; Stenager & Qin, 2008; von Borczyskowski et al., 2011). In a large, cross-sectional study that utilised data collected at interview across 21 nationally representative samples around the world (Gureje et al., 2011), it was found that parental antisocial and anxiety disorders predicted suicide attempt among ideators. In a more recent study utilising a retrospective, cross sectional household survey of adults living in Brazil, it was found that parental GAD and antisocial personality independently predicted suicidal ideation, whereas only parental panic disorder independently predicted suicide attempt among ideators (Santana et al., 2015). There is also evidence that parental substance abuse is associated with offspring suicide attempt (Mittendorfer-Rutz et al., 2008; Santana et al., 2015) and suicide (von Borczyskowski et al., 2011), and this association appears to be mediated by the post-natal environment (von

Borczyskowski et al., 2011). Therefore, parental psychiatric disorders other than depression are important predictors of offspring suicidal behaviour, however, few studies have examined mechanisms for these associations other than a psychiatric disorder in the offspring (Gureje et al., 2011; Mittendorfer-Rutz et al., 2008; Santana et al., 2015). It may be that the traits underlying the different disorders (i.e. rumination or impulsivity) are important for explaining the association between the particular disorder in the parent and suicide-related behaviour in the offspring (Gureje et al., 2011; Santana et al., 2015).

6.4.3: Mechanisms linking offspring psychiatric symptoms to suicide-related behaviour

It was beyond the scope of this thesis to examine why maternal depression exerted an indirect effect on offspring suicide-related behaviour through offspring symptoms of MDD, GAD and DBD. Whilst mental health disorders may lead to suicide-related behaviour because of the distress or impairment that result from living with the disorder (Nock et al., 2011), this would not explain the weaker indirect effect found in this thesis for symptoms of alcohol abuse or the differential effect of ADHD on offspring suicidal ideation and suicide attempt. Alternatively, it has been noted that the underlying mechanisms linking internalising symptoms and externalising symptoms to suicide-related behaviour may differ (Verona, Sachs-Ericsson, & Joiner, 2004). For example, hopelessness may explain the effects of internalising symptoms on suicide-related behaviour (Verona, Sachs-Ericsson, & Joiner, 2004), whereas anger may be an important mechanism for the association between DBD symptoms and suicide-related behaviour (Jang et al., 2014). Future research should investigate what might explain the indirect effects observed in this thesis. Additionally, given that it was only ADHD symptoms that were associated with risk for suicide attempt among ideators, identifying mechanisms for this group may be especially important for suicide prevention strategies. Previous literature has hypothesised that the link between offspring ADHD and suicide attempt may be explained by the impulsivity and related deficits in executive functioning, such as attentional problems, that are characteristic of ADHD (Brent et al., 2014; Goldston & Daniel, 2009; Goodman, Gerstadt, Pfeffer, Stroh, & Valdez, 2008). Alternatively, the association between ADHD and suicide attempt might be partly explained by other mechanisms such as interpersonal problems, or reckless behaviour associated with hyperactivity or aggression (Goodman et al., 2008).

6.4.4: Genetic confounding and gene-environment correlation

Existing evidence highlights the importance of both genetic and environmental factors in explaining the association between parental psychiatric disorder and offspring suicide-related behaviour. In this thesis, it was not possible to separate genetic and environmental effects. Additionally, the indirect effects of maternal depression on offspring suicidal ideation via the

parent-child relationship and peer victimisation may be due to gene-environment correlation. Gene-environment correlation refers to the fact that genetic and environmental risk factors covary i.e. children inherit genes from their parents, but also are exposed to environments that are shaped by their parents' and their own genetic makeup (Rice et al., 2002). Evocative gene-environment correlation is where the child's genetically influenced characteristics elicit certain reactions from others (Rutter, 2007), for example, an adolescent's genetically influenced behaviour may evoke differences in parenting or victimisation by peers. This highlights the possibility that identified environmental risk factors for suicidal ideation (such as the parent-child relationship or peer victimisation) are actually markers for shared genetic risk. However, this does not necessarily negate the possible role of evoked environmental exposures (Rutter, Pickles, Murray, & Eaves, 2001), for example, child evoked victimisation may still impact on suicidal ideation via environmental mechanisms. Genetically sensitive designs such as those involving children-of-twins (Silberg et al., 2010), children born by assisted conception (Thapar et al., 2007) and adoption studies (Elam et al., 2014) will be especially helpful in replicating these observational findings because they can take into account genetic contributors to cross-generational associations (Rutter & Thapar, 2015). A number of twin studies have provided evidence that the association between disruptive behaviour and aggression with peer relationship difficulties in childhood is mainly accounted for by genetic factors (Boivin et al., 2013; Brendgen et al., 2011). A similar pattern of findings has been shown for genetic risk for depression symptoms and increased peer rejection (Brendgen et al., 2009), however, the association between peer victimisation and later psychotic symptoms at age 12 years has been found to be independent of the confounding effect of genetic susceptibility to developing psychotic illnesses (Arseneault et al., 2011). In addition, the importance of a warm parent-child relationship in protecting children from the negative consequences of being bullied has been highlighted, and it has been shown that this protective effect is environmentally mediated (Bowes, Maughan, Caspi, Moffitt, & Arseneault, 2010). Finally, a longitudinal sample of children adopted at birth found that children's genetically influenced characteristics in childhood elicited hostile parenting in adoptive parents, however, the hostile parenting in turn impacted on children's later disruptive peer behaviour via environmental mechanisms (Elam et al., 2014). Therefore, future research investigating the genetic and environmental contribution to the mechanisms identified in this thesis will be useful to identify potentially modifiable environmentally mediated risk mechanisms of the association between maternal depression and offspring suicidal ideation.

6.5: Conclusion

Community studies are essential to identify which offspring to target for prevention interventions. This thesis highlights that risk for suicide-related behaviour should be considered

in offspring of mothers with ongoing depression symptoms even when below clinical levels. Once those offspring at risk have been identified, it is important to identify potentially modifiable mechanisms, so that effective interventions can be developed. In this thesis, maternal suicide attempt and offspring psychiatric disorder were found to explain the majority of the association between maternal depression and offspring suicidal ideation. However, the findings suggest that interventions focused on improving support and communication between parents and children or reducing peer victimisation and teaching children how to cope with being bullied may also be beneficial in reducing risk of suicide-related behaviour.

Appendices

Appendix 1 – DSM-5 symptoms of Major Depressive Disorder (MDD)

Core symptoms	Depressed mood most of the day, nearly every day
	Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
Additional symptoms	Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
	Insomnia or hypersomnia nearly every day
	Psychomotor agitation or retardation nearly every day
	Fatigue or loss of energy nearly every day
	Feelings of worthlessness or excessive or inappropriate guilt nearly every day
	Diminished ability to think or concentrate, or indecisiveness, nearly every day
	Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Appendix 2 – Items included in the Edinburgh Postnatal Depression Scale (EPDS)

1. I have been able to laugh and see the funny side of things
2. I have looked forward with enjoyment to things
3. I have blamed myself unnecessarily when things went wrong
4. I have been anxious or worried for no good reason
5. I have felt scared or panicky for no very good reason
6. Things have been getting on top of me
7. I have been so unhappy that I have had difficulty sleeping
8. I have felt sad or miserable
9. I have been so unhappy that I have been crying
10. The thought of harming myself has occurred to me

Appendix 3 – Relevant sections of the self-report questionnaire assessing suicide-related behaviour at age 16 years

L3. a) Have you **ever** hurt yourself on purpose **in any way** (e.g. by taking an overdose of pills, or by cutting yourself)?

Yes ☐ No ☐ ⟶ **If no, go to L6a)**

If yes,

b) How many times have you done this in the last year? Please mark **one** box only.

Once ☐ 2-5 times ☐ 6-10 times ☐ More than 10 times ☐

c) When was the **last time** you hurt yourself on purpose? Please mark **one** box only.

In the last week ☐ More than a week ago but in the last year ☐ More than a year ago ☐

d) The **last time** you hurt yourself on purpose, which of the actions below best describes what you did? Please mark **all** boxes that apply.

i) Swallowed pills or something poisonous ☐

ii) Cut yourself ☐

iii) Burnt yourself, e.g. with cigarette ☐

iv) Something else, please say what: ☐

_____

e) Do **any** of the following reasons help to explain why you hurt yourself on that occasion? Please mark **all** boxes that apply.

i) I wanted to show how desperate I was feeling ☐

ii) I wanted to die ☐

iii) I wanted to punish myself ☐

iv) I wanted to frighten someone ☐

v) I wanted to get relief from a terrible state of mind ☐

vi) Some other reason, please say what: ☐

_____

f) After you had hurt yourself on that occasion, how did you feel? Please mark **one** box only.

Better than before ☐ The same as before ☐ Worse than before ☐

g) The last time you hurt yourself in any way (e.g. by taking an overdose of pills, or by cutting yourself) did you seek medical help / first aid from any of the following? Please mark **all** boxes that apply.

i) GP (Family doctor) ☐
ii) Hospital casualty / emergency department ☐
iii) Other health professional, please say what their job was: ☐

_____

L4. On **any** of the occasions when you have hurt yourself on purpose, have you **ever** seriously wanted to kill yourself?

Yes ☐ No ☐

L5. a) Have you **ever** tried to get help from someone or somewhere about hurting yourself on purpose, or about wanting to kill yourself?

Yes ☐ No ☐ ⟶ **If no, go to L6a)**

If yes,

b) Who have you been to for help? Please mark all boxes that apply.

i) Mum or Dad ☐
ii) Brother or sister ☐
iii) Someone else in your family ☐
iv) A friend ☐
v) A teacher ☐
vi) A school counsellor ☐
vii) Peer supporter/mediator at school ☐
viii)A GP (family doctor) ☐
ix) A social worker ☐
x) A psychologist or psychiatrist ☐
xi) A telephone help line ☐
xii) Somewhere else (e.g. internet, book, magazine, other person, etc.), please say what or who: ☐

_____

L6. a) Have you **ever** felt that life was not worth living?

Yes ☐ No ☐ ⟶ **If no, go to end**

If yes,

L6. b) When was the **last time** you felt like this? Please mark **one** box only.

In the last week ☐ More than a week ago but in the last year ☐ More than a year ago ☐

L7. a) Have you **ever** found yourself wishing you were dead and away from it all?

Yes ☐ No ☐ ⟶ **If no, go to end**

If yes,

b) When was the last time you felt like this? Please mark one box only.

In the last week ☐ More than a week ago but in the last year ☐ More than a year ago ☐

L8. a) Have you **ever** thought of killing yourself, even if you would not really do it?

Yes ☐ No ☐ ⟶ **If no, go to end**

If yes,

b) When was the **last time** you felt like this? Please mark **one** box only.

In the last week ☐ More than a week ago but in the last year ☐ More than a year ago ☐

L9. Have you **ever** made plans to kill yourself?

Yes ☐ No ☐

Appendix 4 - Logistic regression analyses showing associations between each class of maternal depression symptoms in comparison to minimal class (reference group) and subsequent offspring past year suicidal ideation at age 16 years in offspring with no suicidal ideation at age 11 years (Odds Ratios (OR) and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 5,341

	OR (95% CI)			
Maternal depression class	Model 1 (unadjusted)	Model 2 [a]	Model 3 [b]	Model 4 [c]
Minimal	Reference group			
Mild	1.25 (0.99, 1.58) [#]	1.16 (0.91, 1.47)	1.15 (0.90, 1.47)	1.15 (0.90, 1.47)
Increasing	1.45 (0.97, 2.17) [#]	1.32 (0.87, 1.98)	1.29 (0.86, 1.95)	1.23 (0.81, 1.86)
Sub-threshold	1.83 (1.40, 2.39)***	1.56 (1.17, 2.06)**	1.54 (1.16, 2.04)**	1.48 (1.11, 1.97)**
Chronic-severe	2.58 (1.68, 3.95)***	2.06 (1.32, 3.23)**	2.00 (1.27, 3.13)**	1.76 (1.11, 2.78)*

[#]$p \leq .10$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

[a] Adjusting for confounders assessed in pregnancy (housing tenure, marital status, maternal level of education, smoking in pregnancy, maternal family history of depression and maternal psychiatric disorder before pregnancy)

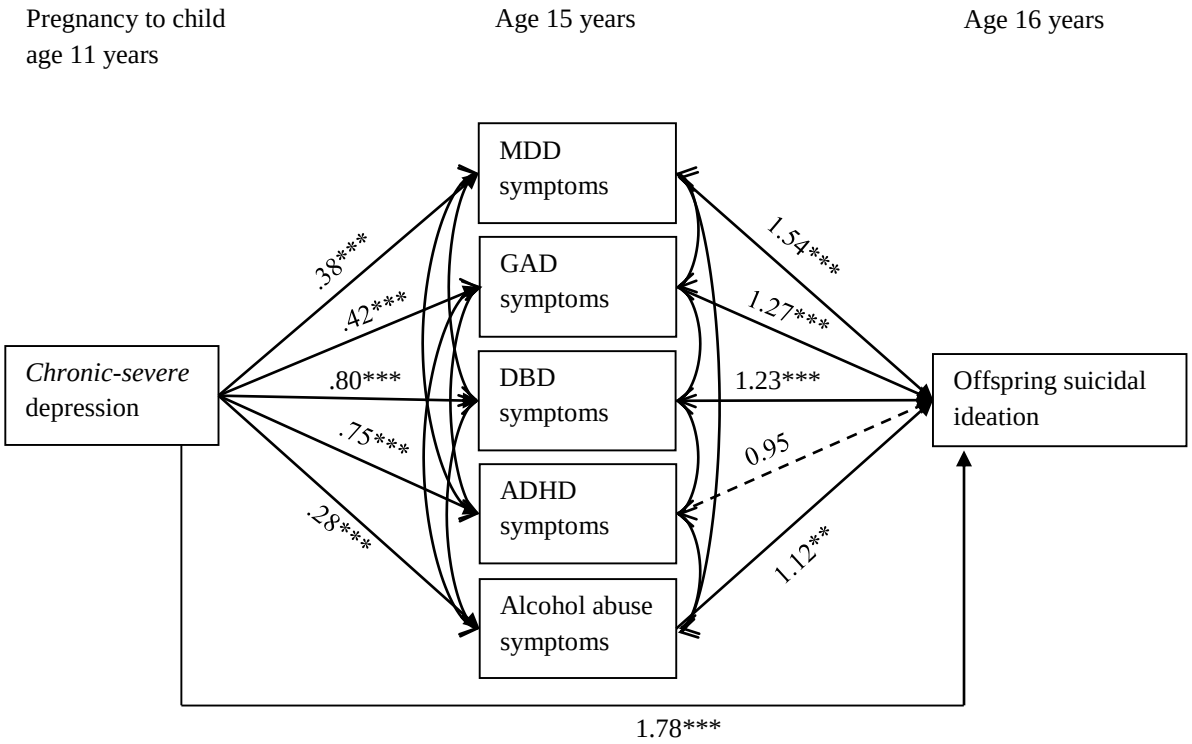
[b] Additionally adjusting for maternal suicide attempt (from pregnancy to child age 11 years)

[c] Additionally adjusting for a diagnosis of MDD in offspring (assessed using the DAWBA at ages 7, 10, 13 and 15 years

Appendix 5 - Indirect effect of maternal depression (with minimal class as the reference group) on offspring suicidal ideation through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse in offspring with no suicidal ideation at age 11 years (probit regression coefficient and 95% Confidence Intervals (95% CI) displayed); imputed *N* = 5,341

	Unadjusted indirect effects via offspring symptoms (probit coefficient (95% CI))				
	MDD	GAD	DBD	ADHD	Alcohol abuse
Maternal *chronic-severe* depression	.08 (.04, .13)	.05 (.02, .09)	.08 (.03, .13)	-.01 (-.05, .03)	.01 (-.005, .03)
Maternal *moderate* depression	.04 (.02, .05)	.03 (.01, .04)	.03 (.01, .05)	-.01 (-.02, .01)	.01 (.00, .01)

Appendix 6 - Structural model showing the direct effect of maternal chronic-severe depression symptoms (with minimal class as the reference group) on offspring past year suicidal ideation, and the indirect effects through offspring symptoms of Major Depressive Disorder (MDD), Generalised Anxiety Disorder (GAD), Disruptive Behaviour Disorder (DBD), Attention Deficit Hyperactivity Disorder (ADHD) and alcohol abuse; Residual covariance coefficients not shown on diagram; imputed N = 10,559; odds ratios presented for categorical outcome (offspring suicidal ideation); linear regression coefficient presented for continuous outcomes (offspring symptoms)

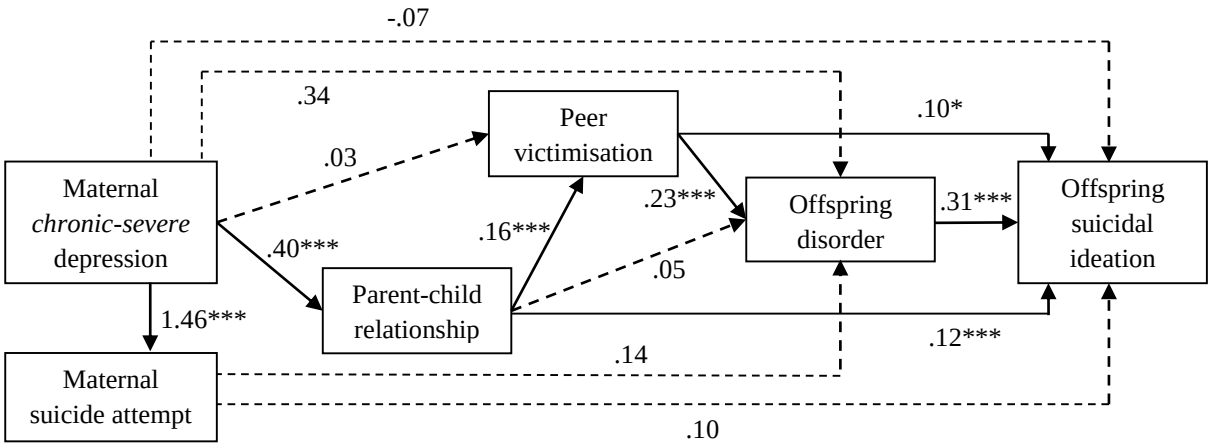


***p ≤ 0.01; ***p ≤ 0.001*

Appendix 7 - Factor analysis of nine items assessing the parent-child relationship at age 9 years

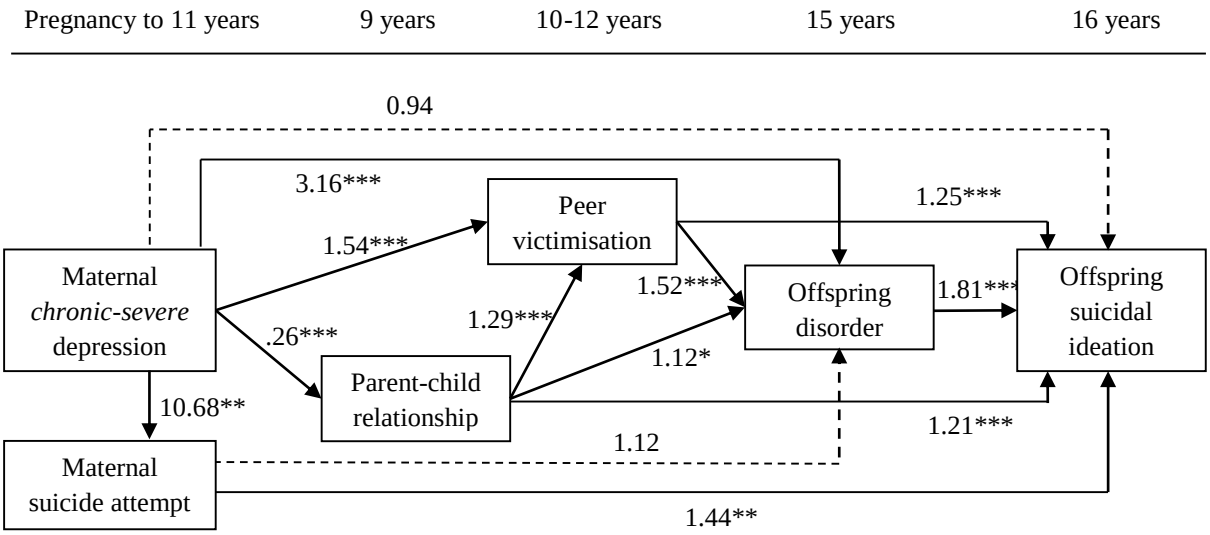
Question	Factor loadings
1. My parents understand me	0.58
2. My parents are usually unhappy or disappointed with what I do	-0.37
3. I like my parents	0.54
4. My parents like me	0.50
5. If I have children of my own, I want to bring them up like my parents have brought me up	0.42
6. My parents and I spend a lot of time together	0.59
7. My parents are easy to talk to	0.68
8. I get along well with my parents	0.73
9. My parents and I have a lot of fun together	0.68
Eigenvalue	2.99

Appendix 8 – Full structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effects through offspring psychiatric disorder, maternal suicide attempt, the parent-child relationship and peer victimisation using complete data; *N* = 2,599; non-standardised probit regression coefficients presented for categorical outcomes; linear regression coefficient presented for continuous outcome (parent-child relationship)



**p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001*

Appendix 9 - Full structural model showing the direct effect of maternal chronic-severe depression (with minimal class as the reference group) on offspring past year suicidal ideation at age 16 years, and the indirect effects through offspring psychiatric disorder, maternal suicide attempt, the parent-child relationship and peer victimisation; imputed *N* = 10,559; odds ratios presented for categorical outcomes; linear regression coefficient presented for continuous outcome (parent-child relationship)



*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$*

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