



**PARENTS WITH RECURRENT DEPRESSION:
HETEROGENEITY IN COURSE, SEVERITY AND SYMPTOMS
AS RISKS FOR OFFSPRING DEPRESSION**

Becky Mars, Cardiff University

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PhD Supervisors:

Professor Anita Thapar, Cardiff University

Dr Stephan Collishaw, Cardiff University

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Abbreviations

MDD	Major Depressive Disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th edition
PND	Postnatal depression
STAR-D	Sequenced Treatment Alternatives to Relieve Depression
AOO	Age of onset
EPAD	Early Prediction of Adolescent Depression study
GP	General Practitioner
DeCC	Depression Case Control study
DeNT	Depression Network sibling pair study
CAPA	Child and Adolescent Psychiatric Assessment
ADHD	Attention Deficit Hyperactivity Disorder
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
GAF	Global Assessment of Functioning Scale
ICD-10	International Classification of Diseases, 10 th edition
OR	Odds Ratio
CI	Confidence Interval (95%)
B	Beta
β	Standardised beta
p	Probability value
M	Mean
SD	Standard deviation
SEM	Structural Equation Modelling
RCT	Randomised Control Trial

Summary

Depression is a significant global problem and is among the leading causes of disability worldwide. Depression in children and adolescents is associated with wide-ranging impairments and often marks the beginning of a lifelong, chronic illness. Early treatment and prevention of depression is therefore a major public health concern.

Parental depression is one of the most consistently identified risk factors for depression in young people. Although depression is a highly heterogeneous disorder, most studies examining cross-generational depression risk have simply dichotomised parents into 'depressed' and 'non-depressed' groups and clinical characteristics beyond diagnostic status are rarely presented. In this thesis I examine how differences in clinical features of parental depression including variations in depression course, severity, timing and symptom manifestation differentially relate to offspring depression risk.

Data were drawn from the Early Prediction of Adolescent Depression study. A three-wave longitudinal study of the offspring of 337 parents with a history of recurrent unipolar depression. Within this high risk group of offspring, specific clinical features of parental depression were identified that may serve as useful markers of current and/or future offspring depression risk. These included a recent episode of clinical depression, an episode involving severe impairment or hospitalisation and symptoms of appetite or weight loss. In addition, findings from this thesis highlight that there is considerable variability in the course of parent depression over time and suggest that any persistent symptoms of depression in parents, even those at low levels, may be clinically important in indexing offspring risk for depression symptoms.

Findings highlight the importance of considering clinical characteristics of depression in parents beyond diagnostic status when examining cross-generational depression risk. The identification of subgroups of offspring who are at greatest risk can help ensure that clinical services and preventative interventions are targeted to those with greatest need.

Papers relating to the present thesis (published or under review)

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Chapter 1

Introduction

Depression is a significant global problem and is among the leading causes of disability worldwide. It is a common psychiatric disorder, which occurs throughout the lifespan and often becomes a chronic or recurrent condition. This introductory chapter will first describe the importance of child and adolescent depression, referring to epidemiology, clinical presentation and the wide range of negative outcomes that are associated with both clinical depression and depression symptoms in youth. The risk to offspring associated with parental depression is next considered, along with a discussion of inherited and non-inherited influences and strategies for treatment and prevention. Current research investigating the influence of parental depression heterogeneity in cross-generational depression risk will then be summarised including consideration of chronicity, severity, timing, age of onset and symptom presentation. Finally, the implications of adopting a categorical or dimensional approach to the conceptualisation of parent depression will be discussed. The chapter concludes with a summary of aims for the present thesis.

Depression in childhood and adolescence

Depression epidemiology in children and adolescents

Major depressive disorder (MDD) is rare in prepubertal children. A wealth of cross-sectional and longitudinal studies have shown that the transition to adolescence is characterised by a sharp increase in the prevalence of MDD (Birmaher et al., 1996; Costello, Copeland, & Angold, 2011; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Ford, Goodman, & Meltzer, 2003; Hankin et al., 1998; Merikangas et al., 2010b), with median 12 month rates rising from less than

1% in childhood to 4-5% during this developmental period (Thapar, Collishaw, Pine, & Thapar, 2012). By late adolescence, lifetime prevalence rates approach those seen in adult populations and have been estimated to range from 15% to 25% (Hankin et al., 1998; Kessler & Walters, 1998; Lewinsohn, Rohde, & Seeley, 1998a; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). This suggests that for a substantial proportion of adults with MDD, the onset may have occurred during adolescence, a finding that has been supported by retrospective studies of depressed adults (Kim-Cohen et al., 2003; Newman et al., 1996).

Prospective longitudinal studies have suggested that the peak age of onset for depression is mid-adolescence (Hankin et al., 1998). For example in the Oregon Adolescent Depression Project (OADP), a large community study of youth followed to age 24 years, the mean age of onset for MDD was around age 15 years (Lewinsohn, Rohde, & Seeley, 1998a). Similarly, Weismann and colleagues (2006b) compared high and low risk offspring of depressed and non-depressed parents over a period of 20 years and found the peak time for the incidence of MDD in both groups to be between the ages of 15 and 20 years. These studies confirm that adolescence is a key risk period for the development of depression.

During adolescence, the female predominance found in adult depressive disorder becomes evident, with around twice as many females affected as males (Angold & Rutter, 1992; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Hankin et al., 1998; Nolen-Hoeksema & Girgus, 1994; Piccinelli & Wilkinson, 2000). In pre-adolescent children, the prevalence of depression is similar across genders (Angold & Rutter, 1992), with some studies suggesting rates may be slightly higher in boys (Angold, Costello, & Worthman, 1998; Twenge & Nolen-Hoeksema, 2002). In early-mid adolescence (around age 12-13 years) rates of depression in girls begin to rise

sharply while rates in males remain stable or increase much less (Angold & Rutter, 1992; Hankin et al., 1998; Twenge & Nolen-Hoeksema, 2002). This gender difference in MDD becomes more pronounced across adolescence (Merikangas et al., 2010b) and remains significant throughout the lifespan (Fiske, Wetherell, & Gatz, 2009; Kessler, 2003; Kessler et al., 2010; Kessler et al., 1994).

The rising rates of depression and the emergence of gender differences during adolescence are consistent and important epidemiological findings. The reasons underlying these developmental trends are not fully understood, but are likely to be complex, involving cognitive, social, hormonal and genetic factors (Angold, Costello, Erkanli, & Worthman, 1999; Cyranowski, Frank, Young, & Shear, 2000; Hankin & Abramson, 1999; Merikangas, Weissman, & Pauls, 1985; Nolen-Hoeksema & Girgus, 1994; Petersen, Sarigiani, & Kennedy, 1991; Wichstrom, 1999). It is also important to note that the onset of depression may be better predicted by pubertal status than by age per se (Angold & Costello, 2006; Angold, Costello, & Worthman, 1998). Moreover, some researchers have found stronger links with pubertal timing than with developmental stage, with early puberty in females and late puberty in males associated with increased depression symptoms. These findings suggest that there may be psychosocial influences of puberty on the development of depression in addition to hormonal influences (Conley & Rudolph, 2009; Graber, Lewinsohn, Seeley, & Brooks-Gunn, 1997).

Clinical presentation and negative outcomes

Depression in young people is characterised by the presence of persistent low or irritable mood and/or the absence of positive affect (loss of interest or pleasure in activities), usually accompanied by a range of associated cognitive, physical and

behavioural symptoms. Symptoms of depression are common in the population. However, when these symptoms become persistent, are qualitatively different from usual, or interfere with everyday functioning, then they are may be considered to be pathological. Clinical depression is a highly disabling condition that can interfere with a person's ability to function across multiple domains. It is often defined according to criteria specified in classification manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 1994), a widely recognised system that is used for both research and clinical purposes. The DSM-IV diagnostic criteria for MDD in children and adolescents are detailed in Figure 1. The presence of five or more of nine possible symptoms is required for diagnosis, one of which must be a core symptom of either depressed/irritable mood, or loss of interest or pleasure in activities. The clinical and diagnostic features of depression in children/adolescents are broadly comparable with those used for adults (Kovacs, 1996; Lewinsohn, Pettit, Joiner, & Seeley, 2003; Roberts, Lewinsohn, & Seeley, 1995; Thapar, Collishaw, Pine, & Thapar, 2012), although the DSM-IV criteria include irritable mood as a core diagnostic symptom in young people. MDD is one of a number of disorders in the DSM-IV which are primarily characterised by a disturbance in mood. Other related disorders include dysthymia, depressive disorder not otherwise specified, adjustment disorder with depressed mood, bipolar spectrum disorders and cyclothymia.

Depression during childhood or adolescence is associated with substantial and pervasive psychosocial impairment. Difficulties are wide-ranging and can include lower educational attainment, problems in interpersonal relationships, increased rates of early pregnancy, smoking and substance misuse as well as obesity and physical health problems (Asarnow et al., 2005; Birmaher et al., 1996; Fergusson &

Woodward, 2002; Giaconia, Reinherz, Paradis, Hauf, & Stashwick, 2001; Glied & Pine, 2002; Lewinsohn, Rohde, & Seeley, 1998a; Rao, Hammen, & Daley, 1999; Weissman et al., 1999a). The risk of suicidal behaviour is also greatly increased, which is a major public health concern given that suicide is the third leading cause of death amongst young people (Anderson, 2002; Kovacs, Goldston, & Gatsonis, 1993; Lewinsohn, Rohde, & Seeley, 1994).

Figure 1. DSM-IV criteria for Major Depressive Episode in children and adolescents

Five (or more) of the following symptoms must have been present during the same two-week period and represent a change from previous functioning

Core symptoms (at least one must be present)

- Depressed or irritable mood present for 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

Associated symptoms

- Significant weight loss 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 which is observable by others
- 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

Although 90% of adolescents will recover from an index episode of MDD within 1-2 years (Birmaher et al., 1996; Curry et al., 2011; Emslie et al., 1997), recurrence is common, with 50-70% of those who remit developing a subsequent depressive episode within five years (Birmaher et al., 1996; Emslie et al., 1997; Kovacs, 1996; Rao, 2006; Rao & Chen, 2009). Heterotypic continuity is also frequently reported, with increased rates of later substance use and anxiety disorders amongst adolescents with MDD (Copeland, Shanahan, Costello, & Angold,

2009; Fergusson & Woodward, 2002; Kim-Cohen et al., 2003; Lewinsohn, Rohde, Klein, & Seeley, 1999; Pine, Cohen, Gurley, Brook, & Ma, 1998; Rao & Chen, 2009). Evidence for continuity in depression across developmental periods is less clear. Whilst longitudinal studies of both clinical samples (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a; Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Rao, Hammen, & Daley, 1999; Rao et al., 1995; Weissman et al., 1999a) and community samples (Bardone, Moffitt, Caspi, Dickson, & Silva, 1996; Fergusson & Woodward, 2002; Lewinsohn, Rohde, Klein, & Seeley, 1999) have shown adolescent depression to be associated with a 2-7 fold increased odds of depression in adulthood (Rutter, Kim-Cohen, & Maughan, 2006), the evidence for predictive links from childhood-onset disorder to adult depression has been mixed (Birmaher et al., 2004; Harrington, Rutter, & Fombonne, 1996; Weissman et al., 1999b). These findings have contributed to the suggestion that there may be a discontinuity between depression with an onset prior to, or following puberty, with some studies finding differences in causes, correlates and aetiology between childhood and adolescent-onset cases (Harrington et al., 1997; Jaffee et al., 2002; Kaufman, Martin, King, & Charney, 2001; Weissman, 2002).

Childhood and adolescent depression is often comorbid with other mental health conditions such as anxiety, substance use and disruptive behaviour disorders. Comorbidity is present in up to 50-70% of youth with MDD (Birmaher et al., 1996; Ford, Goodman, & Meltzer, 2003; Kessler, Avenevoli, & Merikangas, 2001; Kovacs, 1996; Lewinsohn, Rohde, & Seeley, 1998a; Rao, 2006) and this is important to consider when assessing depression recurrence. Some studies have found that initial predictive links between adolescent and adult depression become non-significant once comorbid disorders are considered (Copeland, Shanahan, Costello,

& Angold, 2009; Pine, Cohen, Gurley, Brook, & Ma, 1998). Other studies have found the presence of comorbid disorders to be associated with a more severe and persistent course of depression (Birmaher, Arbelaez, & Brent, 2002; Birmaher et al., 1996) and found that adolescent depression continues to be predictive of depression in early adulthood after controlling for comorbidity (Lewinsohn, Rohde, Klein, & Seeley, 1999).

Family history of depression has also been shown to be predictive of continuity of MDD into adulthood (Wickramaratne, Warner, & Weissman, 2000). For example, in the Oregon Adolescent Depression Project, Lewinsohn and colleagues (2000) found that adolescents with a family history of recurrent MDD were significantly more likely to experience MDD recurrence in adulthood. Weissman et al (1999b) also found that childhood-onset depressed probands who experienced depression recurrence in adulthood had higher rates of depression in first degree relatives. This is consistent with the suggestion that recurrence may be a characteristic associated with a higher genetic loading for depression (Sullivan, Neale, & Kendler, 2000).

Subthreshold depression symptoms

Depressive symptoms which fall below the threshold for diagnosis are common in adolescence. Community epidemiological surveys indicate that between 20% and 50% of adolescents exceed conventionally established cut-points for clinically significant self-reported depressive symptoms, based on recall periods of 1-6 months (Kessler, Avenevoli, & Merikangas, 2001). This is considerably higher than prevalence rates of MDD obtained from diagnostic interviews, which are in the region of 1-6%. This discrepancy might be explained by the large proportion of young

people who may suffer from subthreshold depression (Kessler, Avenevoli, & Merikangas, 2001). Twelve month prevalence rates of subthreshold depressive disorders in young people range from 3% to 7% (Fergusson, Horwood, Ridder, & Beautrais, 2005; Gonzalez-Tejera et al., 2005; Kessler & Walters, 1998; Oldehinkel, Wittchen, & Schuster, 1999), with lifetime prevalence rates in late adolescence reported to be as high as 26% (Lewinsohn, Shankman, Gau, & Klein, 2004).

There is a lack of consensus regarding the operationalisation and terminology used to describe subthreshold depression, although it can be broadly conceptualised as the presence of depressive symptoms that are insufficient in either number or severity to reach diagnostic criteria. Subthreshold depression has most commonly been defined as either a dimensional score, a score derived from a cut-off on a self-report questionnaire (for example, one or two standard deviations above the mean) or as a 'minor disorder' derived from relaxing the duration, symptomatic or impairment criteria for full syndrome MDD.

Despite differences in definition across studies, subthreshold depressive symptoms in adolescence have consistently been shown to be associated with impaired functioning, treatment seeking and suicidality (Fergusson, Horwood, Ridder, & Beautrais, 2005; Gotlib, Lewinsohn, & Seeley, 1995; Johnson, Cohen, & Kasen, 2009; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Pickles et al., 2001). Prospective longitudinal studies have also shown predictive links with later MDD. For example, in the Christchurch Health and Development Study, a longitudinal study of a birth cohort of over 1200 children in New Zealand followed to age 25 years, Fergusson and colleagues (2005) found subthreshold depressive disorder at age 17-18 years to be predictive of full syndrome MDD at age 25 years. Similarly, in the Children in the Community Study, Johnson et al (2009), found adolescents with

minor depression in adolescence were significantly more likely than those without minor depression to have major depression in adulthood, even after controlling for comorbidity. In the Oregon sample (OADP), the long term consequences of subthreshold depression symptoms have been investigated using a variety of different definitions and measures and predictive links have consistently been shown with later MDD (Gotlib, Lewinsohn, & Seeley, 1995; Klein, Shankman, Lewinsohn, & Seeley, 2009; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Shankman et al., 2009). For example, Klein and colleagues (2009) found that almost half of adolescents with subthreshold depressive disorder in adolescence developed full-syndrome depressive disorder by age 30 years, with an estimated risk of escalation of 67%. Furthermore, familial loading for depression in first degree relatives predicted escalation to full-syndrome depressive disorder, suggesting that it may be particularly important to assess depressive symptoms amongst children and adolescents with a family history of MDD.

Investigating subthreshold conditions can help to establish whether clinical diagnoses are qualitatively distinct from those beneath the threshold, or whether they lie along a continuum of severity. A variety of studies have demonstrated a linear relationship between depressive symptoms and impairment in adolescence (Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Pickles et al., 2001), with Pickles and colleagues (2001) finding no evidence of additional impairment associated with crossing the diagnostic threshold beyond that expected from an increase in symptoms. Similarly, in the Great Smoky Mountains study, a diagnosis was not necessary for there to be impairment in children's functioning (Angold, Costello, Farmer, Burns, & Erkanli, 1999). Studies such as this suggest that subthreshold and full-scale depressive conditions fall on a continuum. They also highlight the

importance of predicting and preventing symptoms of depression in adolescence, in addition to clinical disorder, particularly when there is a family history of MDD.

The severe adverse developmental consequences associated with both depressive symptoms and clinical disorder highlight adolescent depression as a major public health concern. Early identification and treatment of depression in young people is important, as research suggests that youth who recover from MDD and do not relapse, show levels of functioning in adulthood comparable with never depressed individuals (Rao et al., 1995). However most adolescents with depression do not seek treatment (Lewinsohn, Rohde, & Seeley, 1998b; Merikangas et al., 2010a; Merikangas et al., 2011; Olfson, Gameroff, Marcus, & Waslick, 2003; Potter et al., 2012; Wu et al., 2001) and even amongst those who do, adverse secondary effects (such as reduced educational attainment) are likely to have already occurred. This can contribute to the risk of developing future depressive episodes. Prevention of depression is therefore also a paramount goal. In order for preventative interventions to be effectively developed and targeted, the identification of early risk factors that are associated with the onset of MDD is required. One of the most consistently identified and important risk factors for depression in young people is having a parent with depression. Research related to this will now be considered.

Offspring of depressed parents

Numerous studies have reported increased rates of psychiatric disorder and depression in particular, amongst offspring of parents with MDD (Beardslee et al., 1988; Beardslee, Keller, Lavori, Staley, & Sacks, 1993; Beardslee, Versage, & Gladstone, 1998; Goodman et al., 2011; Grigoriu-Serbanescu et al., 1991;

Hammen & Brennan, 2003; Hammen, Burge, Burney, & Adrian, 1990; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Lee & Gotlib, 1989; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Orvaschel, Walsh-Allis, & Ye, 1988; Vandeleur et al., 2012; Weissman et al., 2006b) with most research focusing on the impact of maternal depression. Whilst this is a consistent finding, observed prevalence rates of MDD in offspring vary considerably between studies. This is likely due in part to methodological differences in sampling (for example clinical or community sample, age of offspring), study design (longitudinal or cross-sectional), assessment methods (interview or self-report), taxonomy (e.g. DSM-III or DSM-IV) and length, if any of follow-up. Table 1 provides a summary of the key studies that have been conducted in this area to date.

There are now several longitudinal studies of both clinical and community samples which have investigated the effects of parental depression on offspring psychopathology. Hammen et al (1990) compared outcomes in the 8-16 year old offspring of mothers with unipolar, bipolar or medical disorders and controls over the course of three years and found that the highest rates of MDD and poorest levels of functioning were in the group of children whose mothers had unipolar depression (Anderson & Hammen, 1993; Hammen, Burge, Burney, & Adrian, 1990). Rates of MDD were 45% in children of mothers with unipolar depression compared with 11% in children of non-ill mothers. In one of the longest follow-ups conducted to date, Weissman et al (2006b) evaluated 220 offspring of depressed and non-depressed parents over a period of 20 years (mean offspring age 35 years) and found risk of major depression was three times higher amongst offspring of depressed parents compared with non-depressed controls. Furthermore, this and other studies have

Table 1. Key studies of the offspring of depressed parents

Authors	Study description	Offspring age (years)	Sample size	Details of follow-ups	Child depression outcome
Weissman, et al., 2006b	Twenty year follow-up of the offspring of depressed and non-depressed parents. Probands with moderate/severe depression were selected from outpatient clinics. Non-depressed controls were selected from epidemiological sample of adults from same community.	Aged 6-23 years at baseline	220 offspring from 91 families	Three follow-ups: year two, year ten (mean age 26 years) and year 20 (mean age 35 years)	Offspring of parents with depression had a three-fold higher risk of lifetime MDD than offspring of non-depressed parents. Rates of MDD in offspring were 65% when parental depression compared with 27% when no parental depression.
Hammen, Burge, Burney, & Adrian, 1990	Longitudinal study of the offspring of women with recurrent unipolar depression, bipolar disorder, chronic medical illness or no psychiatric disorder. Mothers with unipolar and bipolar disorders were recruited from inpatient and outpatient clinics and private referrals. Chronically ill mothers included those with diabetes or severe arthritis. Volunteer families were recruited from schools.	Aged 8-16 years at baseline	96 offspring from 68 families	Followed-up at six month intervals for up to three years	45% of offspring of mothers with unipolar depression met criteria for lifetime MDD in comparison with 11% from non-ill mothers, 22% from BPD mothers and 29% from medically ill control mothers. Offspring of mothers with unipolar depression had higher internalising scores than the other three groups and were the most impaired.
Lee & Gotlib, 1989	Study of offspring of women receiving outpatient treatment for MDD, other psychiatric disorders, medical conditions and a no outpatient control group.	Aged 7-13 years at baseline	75 mother-child dyads	One follow-up ten months later	Offspring of depressed mothers had significantly higher internalising problems than offspring of medically ill and non-patient mothers. There were no significant differences between offspring of depressed and non-depressed psychiatric patient mothers.
Orvaschel, Walsh-Allis, & Ye, 1988	Study of offspring of parents with recurrent major depression and controls	Aged 6-17 years	106 offspring from 63 families	No follow-up	Offspring of depressed parents had significantly higher rates of affective disorder (MDD, dysthymia or mania) than offspring of non-depressed parents. Rates of affective disorder were 21.3% compared with 4.3%

Vandeleur, et al., 2012	Study of offspring of parents with bipolar disorder, unipolar depression and controls.	Aged 6-18 years at baseline	376 offspring from 194 families	No follow-up	Lifetime rates of mood disorder (MDD, SAD, dysthymia, minor depression, BPD and subthreshold BPD) were elevated among offspring of BPD probands (35%) and MDD probands (26%) compared with controls (13%).
Grigoriou-Serbanescu, et al., 1991	Offspring of in-patients with unipolar depression and controls. Control offspring were matched for age, sex and socioeconomic status.	Aged 10-17 years	192 offspring from 124 families	No follow-up	One year prevalence rates of offspring depressive disorders (MDD, dysthymia, D-NOS, ADJ-D) were 12% amongst offspring of depressed parents compared with 5% amongst offspring of non-depressed controls. This difference was not statistically significant.
Hammen & Brennan, 2003	Community sample of mothers drawn from a birth cohort study in Brisbane. Mothers were selected when their offspring were aged 15 years to represent women with varying depression histories (including no depression).	Aged 15 years	816 mother-child dyads	Follow-up at age 15 years	Offspring of mothers with depression, dysthymia or minor depression were more likely to have experienced depression or dysthymia than offspring of non-depressed women. Rates of MDD in offspring were 20% when maternal depression compared with 10% when no maternal depression.
Beardslee, et al., 1988	Families with adolescent children randomly selected from a prepaid health plan register. Three groups generated based on parent psychopathology. Those with no lifetime disorder, those with depressive disorder and those with non-depressive disorder.	Aged 6-19 years at baseline	153 offspring from 81 families	Follow-up four years later (mean age 18.5 years)	Baseline rates of offspring affective disorder (lifetime MDD/dysthymia): 30% when either one or both parents had a depressive disorder, 0% when parents had a non-depressive disorder and 2% when parents had no psychiatric disorder. Follow-up rates of offspring affective disorder (lifetime MDD/dysthymia): 26% when either one or both parents had a depressive disorder vs. 10% when parents had no psychiatric disorder.

<p>Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002</p>	<p>The Early Developmental Stages of Psychopathology Study (EDSPS). A prospective, longitudinal study of a representative community sample of adolescents and young adults in Munich. Family supplement conducted at second follow-up.</p>	<p>Aged 14-24 years at baseline</p>	<p>2427 offspring at follow-up</p>	<p>Two follow-up surveys: first follow-up 20 months (for children aged <17 years). Second follow-up 42 months (all sample)</p>	<p>Offspring of either one or two parents with depression had higher rates of lifetime MDD compared with offspring of non-depressed parents.</p> <p>Offspring MDD: OR of 2.5 when 1 parent depressed (26% vs. 12%) and OR of 2.8 when both parents depressed (29% vs. 12%).</p>
<p>Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005</p>	<p>Oregon Adolescent Depression Project (OADP). A prospective, longitudinal study of a representative community sample of adolescents in Oregon. At second follow-up, all offspring with a lifetime history of psychopathology and a random sample of those without were selected for participation. Parental lifetime psychopathology was assessed and offspring of parents with non-affective disorder, bipolar disorder or dysthymia without MDD were excluded.</p>	<p>Aged 14-18 years at baseline</p>	<p>1709 adolescents at baseline, N=775 at follow-up</p>	<p>Three follow-ups: one year later, at age 24 year and at age 30 years</p>	<p>Lifetime rates of offspring MDD when maternal MDD: 61.9% vs. 46.1% in controls (HR = 1.54). Lifetime rates of offspring MDD when paternal MDD: 57.0% vs. 49.6% in controls (HR = 1.11, ns).</p> <p>Paternal MDD was significantly associated with offspring MDD when offspring depression was moderate/severe.</p>

MDD: Major depressive disorder; BPD: Bipolar disorder; SAD: Seasonal affective disorder; D-NOS: Depressive disorder not otherwise specified; ADJ-D: Adjustment disorder with depressed mood

shown that youth depression occurring in the context of parental depression appears to be more severe, chronic and impairing than depression occurring in the youth of non-depressed parents (Hammen & Brennan, 2001; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002). Beardslee and colleagues (1993) found that depressed offspring had longer episodes, earlier onset and more comorbid conditions when they had a parent who was depressed. Weissman et al (1997) found higher work and interpersonal impairment, more persistent and greater severity of depression and a younger age of onset in the depressed offspring of depressed compared with non-depressed parents.

Parental depression has also been associated with increased rates of offspring depression amongst community samples of depressed parents. In a longitudinal study of parents randomly selected from a health plan register, Beardslee and colleagues (1988) found lifetime rates of depression were 30% amongst offspring of parents with depressive disorder compared with only 2% amongst offspring of parents who were not ill. These elevated rates continued to be observed at the four year follow-up where rates of depression in offspring were 26% vs. 10% respectively (Beardslee, Keller, Lavori, Staley, & Sacks, 1993). In a population sample of over 800 women selected to have varying histories of depression, Hammen and colleagues (2003) found rates of depression in 15 year old youth were double amongst offspring of depressed mothers compared with never-depressed mothers (20% vs. 10%). Community samples of adolescents which have assessed parent psychopathology have also found similar associations between parental and offspring depression. In the Early Developmental Stages of Psychopathology Study (EDPS), a large four year follow-up of over 2,000 adolescents aged between 14 and 24 years, Lieb et al (2002) found parental

depression was associated with a 2-3 fold increased risk of offspring MDD. Similarly, in the Oregon Adolescent Depression Project, maternal depression was found to be significantly associated with offspring depression risk (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005).

Most cross-generational depression studies have focused on the risk associated with maternal depression and there are limited studies investigating the impact of paternal depression on offspring. Two meta-analyses (Connell & Goodman, 2002; Kane & Garber, 2004) that have addressed this issue have found depression in fathers to be associated with increased internalising problems in offspring. Adolescent offspring of depressed fathers have also been found to be at increased risk of depression and suicidal behaviour (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Lieb, Isensee, Hofler, Pfister, & Wittchen, 2002; Phares & Compas, 1992; Ramchandani & Psychogiou, 2009; Reeb & Conger, 2009), however evidence suggests that links may be stronger for externalising than internalising offspring outcomes (Brennan, Hammen, Katz, & Le Brocque, 2002; Connell & Goodman, 2002; Ramchandani & Psychogiou, 2009).

Inherited and non-inherited influences on the development of depression

Taken together, these family studies indicate a 3-4 fold increased risk of depressive disorders amongst offspring of depressed parents compared with controls (Rice, Harold, & Thapar, 2002). However, the mechanisms through which parental depression confers risk to offspring are not entirely clear. Genetically sensitive designs such as twin and adoption studies provide evidence that the transmission of depression across generations is likely mediated via a combination of genetic and environmental factors. By comparing rates of a given phenotype in

monozygotic and dizygotic twins, twin studies are able to estimate the proportion of phenotypic variance that is attributable to genetic influences and that which is due to environmental effects. Studies of adolescent twins have shown that depressive symptoms are significantly genetically influenced, with heritability estimates of around 30-50% (Rice, 2010). The only twin study to examine clinical depressive disorder in adolescence obtained a heritability estimate of 40% (Glowinski, Madden, Bucholz, Lynskey, & Heath, 2003) which is similar to the 37% found in a recent meta-analysis of MDD in adults (Sullivan, Neale, & Kendler, 2000). Thus genetic influences for adolescent depression appear to be modest, but they do not fully account for the increased risk to children of depressed parents, suggesting that environmental factors also make an important contribution to the transmission of risk for depression.

Genetic estimates of depressive symptoms vary markedly across studies and this is likely due in part to methodological differences in choice of informant, severity of symptoms and child age. Heritability estimates are generally higher when symptoms are parent-rated than child-rated (Eaves et al., 1997; Rice, Harold, & Thapar, 2002) and environmental influences have been shown to be more important for the development of high depression scores than for those occurring within the normal range (Rice, Harold, & Thapar, 2005). Most studies also find an increase in heritability with age, suggesting that there might be developmental differences in the aetiology of depression (Rice, Harold, & Thapar, 2002; Scourfield et al., 2003; Thapar & McGuffin, 1996). This is potentially due to an increase in gene-environment correlation during adolescence as individuals become more autonomous and able to select and shape their own environments (Rice, Harold, & Thapar, 2003).

Despite modest genetic influences on depression, molecular genetic studies, including genome wide association studies (Muglia et al., 2010; Shi et al., 2011; Shyn et al., 2011; Wray et al., 2012) have failed to identify replicated genetic variants associated with unipolar depression and the biological mechanisms involved in mediating genetic risk remain unclear. It is important to note however that genetic factors can also interact with environmental factors and can therefore influence the development of depression both directly and indirectly. Genetic factors can influence both exposure (gene-environment correlation) and susceptibility (gene-environment interaction) to the environment. For example Caspi and colleagues (2003) found that a polymorphism in the serotonin transporter gene 5-HTT moderated the influence of stressful life events on risk for depression.

The adoption design offers an alternative method of separating environmental from genetic influences. To date there have been only three such studies in children and adolescents which have examined a depression-related phenotype (Eley, Deater-Deckard, Fombonne, Fulker, & Plomin, 1998; Tully, Iacono, & McGue, 2008; van den Oord, Boomsma, & Verhulst, 1994) and all have suggested an important contribution of environmental risk effects in the transmission of depression. The only adoption study to examine clinical depression in adolescents found an elevated risk for MDD in children of affectively ill parents regardless of genetic relatedness (Tully, Iacono, & McGue, 2008). This finding is consistent with a shared environmental component, however, risk for depression was greater (although not significantly so) amongst biologically related offspring, suggesting that inherited factors also contribute. More recently, research has begun to utilise novel research designs including the extended twin design (Rice, Harold, & Thapar, 2005), children of twins design (Silberg, Maes, & Eaves, 2010) and assisted conception design (Lewis, Rice,

Harold, Collishaw, & Thapar, 2011) to examine environmental contributions. These designs also report evidence consistent with the environmental transmission of depression between parents and children.

Depression is clearly familial. Collectively, family, twin and adoption studies have provided evidence for both genetic and environmental effects on the intergenerational transmission of unipolar depression and it is likely that these factors interact in complex ways to influence the onset of depressive disorder and symptoms in adolescence. These findings have implications for the design of treatment and prevention strategies which will now be discussed.

Treatment and prevention of depression in children and adolescents

Even though depression in young people is a major public health concern, it is a disorder which is considerably under-recognised and under-treated (Essau, 2005; Kramer & Garralda, 1998; Lewinsohn, Rohde, & Seeley, 1998b; Merikangas et al., 2010a; Merikangas et al., 2011; Olfson, Gameroff, Marcus, & Waslick, 2003; Potter et al., 2012; Wu et al., 2001). Rates of treatment for depression in community samples of non-referred adolescents have been shown to range from 15% to 65% (Lewinsohn, Rohde, & Seeley, 1998b) and a recent report from the national co-morbidity survey found that less than 40% of depressed youth were receiving treatment (Merikangas et al., 2011). In their study evaluating the effects of parental depression on offspring, Weissman and colleagues (1997) noted that more than 30% of high-risk children with MDD did not receive any treatment for their illness.

Available treatment options for depressed children and adolescents differ from those used to treat depression in adults. This is due in part to controversy over the use of some antidepressant medications in children under the age of 18 years

following possible links with suicidal behaviour (Hammad, Laughren, & Racoosin, 2006; Libby et al., 2007; Whittington et al., 2004). Psychological interventions such as Cognitive Behavioural Therapy (CBT) and Inter-Personal Therapy (IPT) have been shown to be effective in adolescents, particularly when depression is mild (Curry, 2001; Thapar, Collishaw, Potter, & Thapar, 2010). However, when illness is more severe, psychosocial treatments may not offer any additional benefits over pharmacotherapy (Thapar, Collishaw, Potter, & Thapar, 2010; Walkup, 2010). There are also concerns over the limited availability of specialist resources such as CBT and the long term benefits of such interventions have yet to be demonstrated.

Given the challenges associated with treatment of depression in adolescents coupled with the long term cost to individuals, families and society that depression entails, preventative interventions which target individuals prior to the development of depressive disorder are of prime importance. Prevention prior to the onset of depression is also important, given that once depression occurs, individuals may be predisposed to future depressive episodes via kindling effects (Kendler, Thornton, & Gardner, 2000). Prevention programs usually consist of a combination of educational and cognitive-behavioural elements and can be categorised into three types (Institute of Medicine, 1994): 'universal' interventions which are delivered to all members of a population, 'selective' interventions which are administered to those who are considered to be at high risk and 'indicated' interventions which are targeted at individuals manifesting early signs/symptoms, but who do not meet diagnostic criteria for disorder. Several meta-analyses of such programmes have concluded that selective and indicated interventions (collectively referred to as targeted interventions) are more effective than universal programmes in preventing the onset of depression (Horowitz & Garber, 2006; Merry, McDowell, Hetrick, Bir, & Muller,

2004; Stice, Shaw, Bohon, Marti, & Rohde, 2009). However, a recent Cochrane review (Merry et al., 2011) found both targeted and universal interventions to be effective in reducing depressive disorder and symptoms in children and adolescents, with effects sustained at 3-9 months follow-up. Whether effects are sustained over a longer period of time however, remains unclear (Horowitz & Garber, 2006; Merry et al., 2011).

The identification of early risk factors associated with the onset of depression is a clear public health goal. Given the well-established link between parent and child depression, offspring of depressed parents are a logical choice for selective intervention. However, depression is highly prevalent amongst women of childbearing age (Burke, 2003; Weissman & Olfson, 2009) and therefore a large number of children in the UK are likely to be exposed to parental affective illness. To target all these children for intervention is a highly implausible goal. Such an approach is also likely to be unnecessary given that many children of depressed parents do not experience MDD or depressive symptoms. In order for treatment and preventative interventions to be targeted to those at greatest need, it is necessary to identify sub-groups of offspring of depressed parents who are at highest risk. One factor which likely contributes to diversity in child outcomes is variability in the clinical characteristics of parental affective illness. Research relating to this will now be discussed.

Heterogeneity in parent depression and offspring depression risk

The increased risk for MDD among offspring of depressed parents is well documented, however outcomes vary and not all children go on to experience depression themselves. One factor which likely contributes to this diversity is variability in the clinical characteristics of parental affective illness.

Implicit in a categorical approach to depression diagnosis is the assumption that individuals meeting diagnostic criteria are broadly similar to one another and qualitatively different to those who do not meet criteria for disorder (Coghill & Sonuga-Barke, 2012). However, the quality of depression can vary considerably between individuals and across episodes, from a mild disorder with little impairment to a very severe episode that may involve immobilisation, hospitalisation, psychosis or suicidal behaviour. Depression can also be persistent or episodic and episodes can vary in duration from days to months or years. Furthermore, the DSM-IV criteria for MDD are broad, requiring five or more out of a possible nine symptoms. This can mean that two individuals can be diagnosed with the same diagnosis of 'MDD' and yet share only one symptom in common. The timing of a parent's depression in relation to the child's developmental stage may also be important to consider when investigating cross-generational depression risk.

Despite a sound theoretical basis for investigating heterogeneity in parental depression, most intergenerational studies have treated depression as if it were a unidimensional construct and simply dichotomised parents into 'depressed' and 'non-depressed' groups. In doing so, parents who vary not only regarding their current clinical presentation, but also in prior features of depression course, severity and chronicity are grouped together. These are distinct but typically confounded characteristics which are important to examine as they may differentially relate to

children's outcomes. The potential influence of depression heterogeneity has however been difficult to address as there are surprisingly few studies which report additional clinical information about parental depression beyond diagnostic status. Most studies that have examined parent depression heterogeneity have tended to focus on only one or two characteristics (such as recurrence or age of onset) without considering the large degree of overlap between constructs. Moreover, those studies that have attempted to deal with confounding by creating non-overlapping groups are likely to be left with small and somewhat atypical sub-groups. Very few studies have been specifically designed to investigate the influence of heterogeneity on offspring depression risk. One important exception is that of Hammen and Brennan (2003), who recruited a sample of 800 community women with varying depression histories, in order to tease apart the related concepts of severity, chronicity and timing.

There are many different features of parental depression that may influence cross-generational depression risk. These include symptom presentation, severity and impairment, number of episodes, duration of episodes and age at first manifestation. Characteristics such as parent gender, whether there are other mental disorders present alongside depression and whether there is also a co-parent with depression may also be of interest (Landman-Peeters et al., 2008; Merikangas, Weissman, Prusoff, & John, 1988; Sellers et al., 2012). However, adequate consideration of all of these clinical features is beyond the scope of this thesis, which will focus on parental depression course, severity, timing and symptom manifestation. Research relating to these concepts will now be discussed.

Chronicity and severity

There is some evidence to suggest that children of parents with more severe, chronic depression are at greater risk for psychopathology than children whose parents are less seriously affected. Findings from longitudinal studies of the offspring of depressed parents are generally consistent in demonstrating worse outcomes amongst children of mothers with more chronic depression (Brennan et al., 2000; Halligan, Murray, Martins, & Cooper, 2007; Hay, Pawlby, Waters, & Sharp, 2008; Murray et al., 2011; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009) including higher rates of clinical depression. However there is variability across studies in how chronicity has been operationalised which makes comparisons across studies difficult. Chronicity has most commonly been defined in one of two ways; the total number of study periods during which the parent is depressed (Brennan et al., 2000; Bureau, Easterbrooks, & Lyons-Ruth, 2009; Fihrer, McMahon, & Taylor, 2009; Hay, Pawlby, Waters, & Sharp, 2008; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009) or the total number of months spent depressed (Halligan, Murray, Martins, & Cooper, 2007; Hammen & Brennan, 2003; Murray et al., 2011). The term 'chronicity' implies that symptoms are long-lasting, however, it is possible that studies assessing repeated scores might actually be measuring depression recurrence. This is a particular problem when studies have large gaps in between assessments. The possibility that recurrence and total duration might have different effects on offspring risk has not been considered as these concepts have not been examined separately within the same study. Additionally, as depression recurrence is often dichotomised as either 'single episode' or 'multiple episodes', whether the number of recurrences is related to offspring risk is also not clear. This may be important to investigate in relation to offspring risk as the number of depressive episodes is a feature that has

been associated with risk to relatives in some twin studies (Kendler, Gardner, & Prescott, 1999; Kendler, Gatz, Gardner, & Pedersen, 2007; Kendler, Neale, Kessler, Heath, & Eaves, 1994). Thus the relationship between parent depression chronicity and offspring depression risk requires further consideration.

Associations with severity of parental MDD are less clear. There is some evidence from family and twin studies to suggest that the severity of depression is associated with increased familial aggregation for MDD (Janzing et al., 2009; Kendler, Gatz, Gardner, & Pedersen, 2007; Klein, 1990; Lieb, Isensee, Hofler, & Wittchen, 2002). However, overall findings are mixed with some studies failing to find associations (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Weissman et al., 1986) and yet others finding associations between one index of severity but not another (Kendler, Gardner, & Prescott, 1999; Kendler, Neale, Kessler, Heath, & Eaves, 1994; Lieb, Isensee, Hofler, & Wittchen, 2002).

As with chronicity, there are numerous differences in the way in which severity has been operationalised across studies and this may in part account for the mixed findings. Severity can be classified according to the number of depressive symptoms reported, the degree of impairment, whether or not hospitalisation was necessary, or as a mixture of these (as in the DSM-IV severity specifier for MDD). There are also other differences to consider such as whether severity is assessed using questionnaire or interview measures, and whether reports are derived from the worst episode, the current episode, or averaged across multiple episodes/periods. The addition of impairment to MDD symptom criteria may also be important, as this has been shown to increase familial aggregation in family studies (Gershon, Weissman, Guroff, Prusoff, & Leckman, 1986; Weissman et al., 2005). The varieties of ways in

which chronicity and severity have been operationalised mean current findings are hard to interpret and make comparisons across studies difficult.

The potential influence of parental depression severity on cross-generational depression risk has been largely unaddressed. Whilst there are some studies which have demonstrated a positive association between parental depression severity and offspring depression risk (Brennan et al., 2000; Fihrer, McMahon, & Taylor, 2009; Hammen & Brennan, 2003; Keller et al., 1986), few of these have been conducted in adolescence. Moreover, other studies have failed to find associations, for example Pilowsky and colleagues (2006) found parent depression severity and chronicity to be unrelated to offspring depression. However, given the high severity of depression amongst parents in that sample, there may not have been enough variability to detect an effect. This highlights the importance of utilising diverse samples when assessing parent depression heterogeneity.

Overall, the limited evidence available suggests that increasing severity of parental depression is associated with a worse outcome for their children. However it has also been suggested that in some circumstances severe parental depression symptoms may also be protective, through enhancing the child's understanding of their parent as 'ill' (Rutter, 1990). The possibility that children's perceptions may be an important moderator of risk is an area worthy of further study.

In one of the few longitudinal studies to examine parental depression severity Fihrer and colleagues (2009) found that average scores on the Centre for Epidemiological Studies Depression Scale (CES-D) in mothers (assessed at five time points from child age 4 months to age 6-8 years), were associated with greater internalising and externalising scores in their offspring. However, severity was significantly correlated with both chronicity and concurrent symptoms, highlighting

that these concepts are heavily confounded. The high overlap between the concepts of severity and chronicity make it methodologically difficult to disentangle any independent contributions they may have on offspring depression risk. However, it is important to try and separate these two dimensions because they may have somewhat different theoretical and treatment implications. Only a few studies have attempted to do so and these will now be considered.

Brennan et al (2000) separately examined the effects of parent depression chronicity (number of times moderately/severely depressed based on the number of symptoms) and severity (highest number of symptoms reported) on offspring outcomes in a sample of school age children and found both concepts uniquely contributed to poorer child outcomes. The risk to offspring was most apparent when severity and chronicity occurred in combination. In an extension of this study into adolescence, Hammen et al (2003) found parent's highest depression severity (categorised into mild, typical or severe) to be a better predictor of offspring MDD than chronicity (total number of study months depressed), although chronicity was found to be a good predictor of non-depressive disorders. Additional analysis separately examined effects of chronicity in those with mild and those with either moderate or severe depression. Effects of chronicity were found to be dependent upon severity, as a longer duration was required to increase offspring depression risk when parent depression was mild than when depression was moderate/severe.

In a large community sample of mothers, Campbell and colleagues (2007) assessed maternal depression symptoms at regular intervals from offspring age one month to 15 years. These scores were then used to generate different trajectories of maternal depression over time. Chronic parent symptoms of varying severity were found to predict poorer offspring adjustment at age 15 including higher depression

scores. However, Campbell et al assessed symptoms rather than psychiatric disorder in offspring and so it is unclear whether the same pattern of results would apply to offspring MDD.

Despite the considerable methodological differences between studies, overall the evidence suggests that increasing levels of chronicity and severity of parent depression are adversely related to offspring adjustment and psychopathology, including MDD. However, due to the heavily confounded nature of these constructs, more work is required in larger samples of depressed mothers to tease apart their individual effects. These findings could have important implications, as they suggest that successful treatment of parent disorder, to reduce chronicity and severity, has the potential to have a positive effect on offspring outcomes.

Episode timing: exposure to parent depression during the postnatal period

The timing of exposure to parental depression is another feature that may be important for understanding cross-generational depression risk. Most of the literature has focused on the early years, perhaps reflecting a belief that early maternal depression is more influential than exposures in later development. Detailed examination of the potential influence of parental depression during other developmental periods and comparisons of the effects of depression exposure across infancy, childhood and adolescence are lacking.

It has been suggested that exposure to maternal depression during the postnatal period may be particularly detrimental to offspring, as this developmental period is characterised by rapid growth in neurological, physical and emotional systems, is associated with the formation of attachment bonds and is a time when the infant is highly dependent on the primary caregiver to meet their physiological

and emotional needs (Bureau, Easterbrooks, & Lyons-Ruth, 2009; Fihrer, McMahon, & Taylor, 2009; Goodman & Gotlib, 1999). In contrast, first exposure to depression occurring later in life may render children less vulnerable as they may have developed effective emotion regulation and coping strategies, have a broader range of potential social supports (e.g. friends and other adults) and because older children and adolescents have greater independence and spend less time in the home environment (Goodman & Gotlib, 1999; Goodman et al., 2011; Grych & Fincham, 1990; Larson, Richards, Moneta, Holmbeck, & Duckett, 1996).

A large body of research has focused on the effects of postnatal depression (PND) on the developing infant. Reported difficulties are wide ranging and include deficits in attention and cognitive ability, problems with behavioural and emotional development as well as the development of insecure attachments (Barker, Jaffee, Uher, & Maughan, 2011; Goodman, 2007; Goodman & Gotlib, 1999; Martins & Gaffan, 2000; Murray, 1992; Murray & Cooper, 1997; Righetti-Veltema, Bousquet, & Manzano, 2003). Due to the limited number of longitudinal studies, particularly those extending into adolescence, whether or not exposure to PND has enduring effects on later child and adolescent development has not been robustly established. This is particularly salient for examining PND in relation to risk for offspring depression, as the prevalence of depressive disorder before adolescence is very low (Birmaher et al., 1996; Costello, Copeland, & Angold, 2011; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Ford, Goodman, & Meltzer, 2003; Hankin et al., 1998; Merikangas et al., 2010b).

When investigating the influence of early experiences on child development, it is necessary to control for characteristics of the environment under which the child is later tested (Rutter, 1972). This is particularly pertinent to the study of PND as many

mothers with PND go on to experience subsequent depressive episodes (Halligan, Murray, Martins, & Cooper, 2007; Hay, Pawlby, Waters, & Sharp, 2008; Murray et al., 2011). This raises the question of whether it is repeated rather than early exposure which is related to the development of depression in offspring. This is an important consideration, as some longitudinal studies which have examined the effects of PND into adolescence, have found initial associations to be mediated by exposure to later parental depressive episodes (Halligan, Murray, Martins, & Cooper, 2007; Hay, Pawlby, Waters, & Sharp, 2008). However, other investigators have found that effects of early exposure on adolescent depressive symptoms and internalising problems persist, even after controlling for later maternal episodes (Bureau, Easterbrooks, & Lyons-Ruth, 2009; Murray et al., 2011; Verbeek et al., 2012). Thus it is currently unclear whether PND has lasting adverse effects on offspring.

One method of separating the effect of PND and depression recurrence is to examine outcomes in adolescents exposed to only one episode of parental depression. Hammen and Brennan (2003) adopted this approach and compared outcomes in 15 year old offspring exposed to maternal depression either during the first two years of life, between ages 3-5 years, or between ages 6-10 years. They found no differences in either the rates, or characteristics of later MDD between the three groups, although rates of MDD in all three groups were significantly higher than in children of non-depressed mothers. However, the substantial recurrence rates found in the sample resulted in a considerably reduced sample size which may have limited the ability to detect effects. Amongst the sample of over 800 women originally recruited, only 130 mothers experienced depression during only one of the three developmental periods. Moreover, given that recurrence in depression is so common

in the population (Halligan, Murray, Martins, & Cooper, 2007; Hay, Pawlby, Waters, & Sharp, 2008; Murray et al., 2011), these sub-samples of mothers may have been somewhat atypical. In a 13-year longitudinal study following children of postnatally depressed women and women who were not depressed, Halligan and colleagues (2007) similarly found a high degree of recurrence, with many mothers with PND experiencing another depressive episode. They created four non-overlapping groups in order to explore whether there were unique influences of PND on offspring depression at age 13 years. These included a PND only group ($N=18$), a PND plus later depression group ($N=35$), a late depression without PND group ($N=10$) and no depression group ($N=31$). They found an elevated risk of depression only amongst offspring of mothers who had experienced both PND and later depression, which is not consistent with the idea that early life is a primary 'sensitive period' during which exposure to maternal depression has enduring adverse effects on offspring.

A further limitation of many studies concerns the predominant use of self-report rather than interview assessments to measure PND in parents. The importance of accurate depression assessment was highlighted by Pawlby et al (2008), who found PND to be associated with a four-fold increase in risk for offspring psychiatric disorder at age 11 years when assessed using the Clinical Interview Schedule, but no association between PND and offspring disorder when PND was assessed using the Edinburgh Postnatal Depression Scale.

Episode timing: exposure to parent depression during pregnancy

Although the effects of postnatal depression on child development have been widely studied, less attention has been paid to the impact of maternal psychopathology during pregnancy. Prenatal depression has been associated with

elevated cortisol levels in children (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002) and adolescents (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008) suggesting that exposure to depression *in utero* may have long-term effects on neuroendocrine functioning. Furthermore, Van den Bergh (2008) found disruptions in cortisol to be associated with depressive symptoms in female adolescents. This is consistent with theories positing a biologically-mediated risk pathway for depression, for example via disruptions in Hypothalamic Pituitary Adrenal (HPA) axis functioning (Gold, Drevets, & Charney, 2002; Goodyer, Herbert, Tamplin, & Altham, 2000a, 2000b; Harris et al., 2000; Pariante, 2003). The mechanisms underlying associations between prenatal depression exposure and disruptions in hormonal levels such as cortisol in offspring are unknown, but are likely to involve exposure to maternal stress hormones (Field et al., 2004; Gitau, Cameron, Fisk, & Glover, 1998; Sohr-Preston & Scaramella, 2006; Welberg & Seckl, 2001). Additionally, there may be teratogenic effects of depression in pregnancy whereby the mother is more likely to engage in harmful behaviours and expose the foetus to substances such as nicotine and alcohol (Bonari et al., 2004; Zuckerman, Amaro, Bauchner, & Cabral, 1989).

Prenatal depression has primarily been studied in relation to biological outcomes and the risk for development of depression in older offspring has rarely been examined. This is partly due to the lack of longitudinal studies which begin during pregnancy. One of the few longitudinal studies to do so, examined outcomes amongst offspring of 127 women recruited at random from antenatal clinics in South London (Pawlby, Hay, Sharp, Waters, & O'Keane, 2009). One third of mothers experienced a depressive episode during pregnancy and this was associated with a four-fold increase in the risk for offspring MDD at age 16 years. However like PND,

prenatal depression was found to be heavily confounded with later parent depressive episodes with 90% of mothers experiencing a subsequent episode. The association with offspring MDD became non-significant once later exposure was taken into account.

Episode timing: exposure to concurrent parent depression in childhood and adolescence

Many studies of cross-generational risk transmission have looked at prevalence of psychiatric disorders in the offspring of parents with a lifetime history of MDD. This fails to consider the potential importance of exposure to concurrent parental depression symptoms. Current symptoms may be particularly detrimental for offspring as they are associated with impaired parenting and dysfunctional family relationships (Burke, 2003; Downey & Coyne, 1990; Goodman, 2007; Goodman & Gotlib, 1999; Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Most studies which have examined the timing of parent depression in relation to offspring outcomes have not considered concurrent symptoms, or have included concurrent symptoms only as a confounding factor. One exception is a longitudinal study by Korhonen and colleagues (2012) which compared adolescent outcomes in mothers who were depressed prenatally, postnatally or concurrently. They found a stronger relationship between concurrent parent depression symptoms and adolescent internalising symptoms than parent symptoms occurring at other times. However, other investigators have noted that concurrent symptoms are heavily confounded with chronicity and that once this is taken into consideration, initial associations with depressive symptoms or disorder in adolescence become non-significant (Bureau, Easterbrooks, & Lyons-Ruth, 2009; Murray et al., 2011). This highlights the

importance of considering multiple clinical characteristics of parental depression in tandem.

There is also some evidence to suggest that a temporal relationship exists between parent and child depressive episodes. In a three year longitudinal study of depressed mothers, Hammen and colleagues (1991) assessed mother and child depression every six months and found that children tended to experience depression close in time to their mother's depression. However, maternal depression did not precede child depression in all cases. Studies have also shown that the presence of parental depression may act as a moderator in the treatment outcomes of depressed youth, as children undergoing treatment for depression have better outcomes in the absence of current maternal depression (Garber et al., 2009; Kennard et al., 2008). This further suggests that there is an important influence of current parental depression on the mental health in their offspring.

Parental depression treatment studies provide a quasi-experimental method to address whether current parental depression symptoms have an influence on their offspring, however overall findings have been mixed. In a recent review, Gunlicks and Weissman (2008) identified only 10 studies which had investigated associations between treatment of parental depression and child psychopathology, only six of which spanned adolescence and many of which did not report on depression specifically. One of the largest and most well known of these studies is the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) treatment trial child ancillary study (Weissman et al., 2006a), which found parental remission to be associated with a significant reduction in offspring psychopathology as well as improvements in child functioning. This finding is consistent with a significant proximal (i.e. at a particular point in time) influence of parental depression on the

intergenerational transmission of risk for psychopathology in offspring. However, the majority of improvements were found for children with disruptive behaviour disorders and it is less clear whether remission of parental depression is related to offspring depressive outcomes.

There are several other limitations which also need to be addressed. Firstly, most studies included only one or two follow-up points and so it is unclear whether any positive benefits to children associated with remission are sustained over time. Secondly, not all included a non-depressed control group. This is important in order to see whether remission in parents is associated with a return to normal functioning in their children comparable with that of never depressed parents. Thirdly, many studies of concurrent depression are cross-sectional, comparing child outcomes according to remission status rather than examining patterns of change over time, thus they are unable to examine the causal impact of parental depression on the child. Finally, many studies rely on the depressed parent as the primary informant of their child's symptoms. The possibility of shared method variance is particularly pertinent when investigating the effects of concurrent parent depression as it is possible that parent's ratings of their child's mood may be influenced by their own mental state (Boyle & Pickles, 1997; Goodman et al., 2011; Lewis et al., 2012; Najman et al., 2000; Rice, Lifford, Thomas, & Thapar, 2007; Richters & Pellegrini, 1989; Richters, 1992). If so, then this can result in an increase in the correlation between parental and child depressive symptoms. However, whether depressed parents have distorted views of their children's symptoms remains debatable, with some researchers arguing that depressed parents may actually be more sensitive to depression in their children.

Garber and colleagues (2011) addressed many of the above limitations in a parent treatment study which included multiple follow-ups of depressed parents and their offspring over 22 months. Assessments were conducted using blind raters and the study included a non-depressed control group. Individual trajectories of depressive symptoms in parents and children were generated and the relation between these trajectories explored using growth curve analysis. Results indicated that change in parent's depressive symptoms significantly predicted change in children's depressive symptoms over time. Following an initial drop in depressive symptoms, parent's symptoms then began to increase. This increase in parent's depressive symptoms was associated with a parallel increase in children's depressive symptoms, suggesting that improvements in parents' depression may have to be sustained in order for any positive benefits to children to be sustained over time. Garber et al (2011) also examined differences in trajectories according to parental remission status and found that although children of remitted mothers showed improvements, they did not reach the same level of adaptation as offspring of non-depressed parents. Therefore, although treating parents to remission may have associated benefits for their children, it is not sufficient for children to return to levels of normal functioning. The reasons why this might be the case require further exploration.

The finding that reductions in parental depression symptoms are associated with improvements in offspring suggests a likely causal influence of parental depression and indicates a potential environmentally mediated effect in the intergenerational transmission of depression. However such findings do not rule out alternative casual mechanisms. It is possible that the observed associations are explained by a third variable such as a common genetic vulnerability or shared life

stressors. Additionally, it was found in the STAR-D trial that the more severely depressed mothers were less likely to achieve remission following treatment, thus it is important to establish whether there are effects of proximal exposure to parental depression independent of depression severity.

Age of onset of parent depression

An additional factor which may be associated with differential risk for offspring depression is the age at which the parent's depression began. Both family (Kupfer, Frank, Carpenter, & Neiswanger, 1989; Weissman, Warner, Wickramaratne, & Prusoff, 1988; Weissman et al., 1984) and twin (Kendler, Gatz, Gardner, & Pedersen, 2005) studies have shown that an earlier age of onset (AOO) in depressed probands is associated with increased rates of MDD in relatives, suggesting that this phenotype may be indicative of a stronger genetic/familial liability to depression. For example, Kupfer et al (1989) found that the risk of MDD in relatives (parents and siblings) was significantly elevated for early onset probands compared with late onset probands and that the effect became more marked as the cut-off for early AOO was reduced from less than 40 years to less than 20 years. In a sample of parents with MDD, Weissman et al (1988) found a negative relationship between parental AOO and offspring MDD, with the highest risk found amongst children of parents whose depression began before the age of 20 years. Using a cut-off of less than 30 years in the same sample, Wickramaratne (1998) also found that early, but not late onset depression in parents was associated with an increased risk for depression in their offspring. This relationship between early AOO and increased familial risk has been demonstrated for both maternal and paternal depression (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005) and shown in community as well

as in clinical samples (Janzing et al., 2009), however other studies have failed to find an association (Harrington et al., 1997; Kendler, Gardner, & Prescott, 1999; Kendler, Neale, Kessler, Heath, & Eaves, 1994; Milne et al., 2009). These mixed findings may in part reflect methodological differences, as there is a lack of consensus over the threshold for 'early onset' depression, with cut-offs typically ranging from between age 20 and age 60 years. Evidence also suggests that the relationship between AOO and familial depression risk is not linear, as there is little change in risk to relatives once AOO reaches greater than 35 years (Kendler, Gatz, Gardner, & Pedersen, 2005).

It is also important to note that early-onset depression appears to be associated with poorer outcomes of depression, including recurrence, increased total illness duration, a greater number of depressive episodes and longer depressive episodes (Janzing et al., 2009; Korten, Comijs, Lamers, & Penninx, 2012; Sullivan, Neale, & Kendler, 2000; Yang et al., 2011). Thus, AOO is heavily confounded with depression chronicity and so it is unclear the extent to which the increased risk to offspring associated with an earlier AOO in parents represents stronger genetic liability to depression, or greater depression exposure. In a large community study, Janzing and colleagues (2009) found AOO to be associated with increased familial risk of MDD independent of recurrence, however, other studies have not found associations with early AOO and familial risk when other clinical features are considered (Kendler, Gardner, & Prescott, 1999; Lieb, Isensee, Hofler, & Wittchen, 2002). This highlights the importance of controlling for additional parental depression characteristics, as it is currently unclear whether there are effects of early AOO of parent depression on offspring risk that are independent of chronicity.

Specific depression symptoms

The DSM-IV symptomatic criteria for MDD are broad, requiring five out of a possible nine depressive symptoms to be present. Aside from the core symptoms of low mood and loss of interest, the remaining criteria are considered to contribute equitably to diagnosis and are regarded as interchangeable. However, research suggests that there may be important differences in the causes and correlates of different depressive symptoms. For example, within-generation twin studies have shown that the vegetative symptoms (such as changes in appetite/sleep/weight) show greater heritability relative to the other symptoms (Jang, Livesley, Taylor, Stein, & Moon, 2004; Kendler, Neale, Kessler, Heath, & Eaves, 1992). Other researchers have found specific symptoms to increase overall liability to MDD in relatives. In a twin sample, Kendler and Colleagues (2007) found that the symptoms of loss of interest and worthlessness both predicted MDD in co-twins, however, results became non-significant once other clinical characteristics such as age of onset were considered. In another twin sample, recurrent thoughts of death/suicide were found to be the most predictive (Kendler, Gardner, & Prescott, 1999). In one of the few family studies to investigate individual depressive symptoms, Leckman and colleagues (1984) found that the symptoms associated with increased familiarity were appetite loss and feelings of guilt, with rates of MDD doubled amongst first degree relatives of depressed probands who reported these symptoms relative to those without. Thus there is some evidence to suggest that there may be differences in the extent to which symptoms index genetic liability to MDD. However, findings have not been entirely consistent across studies and it is currently not known whether there are specific symptoms which particularly influence cross-generational depression risk.

Genetically informative studies have also highlighted an important environmental contribution to the development of depression as previously discussed (Silberg, Maes, & Eaves, 2010; Tully, Iacono, & McGue, 2008). It is possible that some depressive symptoms in parents, such as loss of interest, may have psychosocial influences on offspring via impacting on the quality of the parent-child relationship. This possibility has not been examined. It is important to gain a greater understanding of the risk to offspring associated with individual depressive symptoms in parents, as this may help elucidate the mechanisms of intergenerational transmission which are at present not well understood.

Conceptualisation of parent depression

There is a longstanding debate over whether depression is best conceptualised as a categorical or continuous construct (Angold & Costello, 2009; Coghill & Sonuga-Barke, 2012; Pickles & Angold, 2003; Rutter, 2011). This is an issue which has gained renewed interest lately due to the forthcoming revision of the DSM and one which has important implications for research in the intergenerational transmission of depression. Those favouring a categorical approach classify individuals according to diagnosis and argue that individuals with disorder differ qualitatively from those without. In contrast, those advocating a continuous approach consider individuals to lie on a linear continuum, viewing disorder as a manifestation of the extremes of normal variation.

Studies that have examined the intergenerational transmission of depression have mostly compared outcomes in offspring of parents with or without a lifetime diagnosis of MDD. This categorical approach provides a clear and consistent framework in which to make distinctions between individuals and ensures

comparability across studies. However, this can result in the assumption that individuals with a disorder are homogeneous. Evidence outlined earlier has highlighted that individuals with the same classification do not necessarily have the same number and pattern of symptoms, the same level of impairment, or the same clinical features, thus it is important to go beyond 'diagnostic status' when assessing cross-generational risk.

There is also an assumption that parents who are currently experiencing a depressive episode differ qualitatively from those in remission. This belief is reflected in parental depression treatment studies which commonly report child outcomes as a function of parental remission status. However, the majority of remitted individuals experience residual depressive symptoms and associated impairment. For example, in the STAR-D study, less than 10% of over 900 remitted patients' achieved asymptomatic status following treatment (Nierenberg et al., 2010). Dichotomising according to remission status results in a loss of potentially important information as it groups together parents who are asymptomatic with those who lie just beneath the diagnostic threshold for MDD. Adopting a dimensional as well as a categorical approach is therefore important in order to gain a better understanding of the relationship between parental depression symptom severity and offspring depression risk.

The conceptualisation of depression over time in parents is also important to consider when examining intergenerational transmission. Depression is commonly assessed cross-sectionally and thought of as an episodic illness, however depressed individuals show marked variation in the course of depression over time (Ashman, Dawson, & Panagiotides, 2008; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009; Judd & Akiskal, 2000; Judd et al., 1998; Nandi, Beard, & Galea, 2009; Rhebergen et

al., 2012; Skipstein, Janson, Stoolmiller, & Mathiesen, 2010). Rather than consisting of periods of episodic illness, depression course may be better conceptualised along a continuum, whereby individuals fluctuate between different levels of symptom severity. This view has repercussions for the way in which chronicity is defined as it suggests that it may be more informative to adopt a dimensional approach and look at patterns of change in parent depressive symptoms over time, rather than a categorical approach which measures episode recurrence.

Although there is some evidence to suggest that depression may be better conceptualised along a continuum, categorising individuals according to MDD diagnosis is useful in both research and clinical practice. The best strategy may therefore be to adopt a mixed approach whereby dimensions and categories are used alongside each other.

Chapter summary

Depression is a significant global problem and is among the leading causes of disability worldwide (Murray & Lopez, 1997). Given the high prevalence of depression during the child-rearing years (Burke, 2003; Weissman & Olfson, 2009), many children are likely to be exposed to an affectively ill parent. This has serious implications for development as the offspring of depressed parents are 3-4 times more likely than controls to experience depression themselves (Rice, Harold, & Thapar, 2002). Precise mechanisms underlying the transmission of depression across generations are not known although evidence from family, twin and adoption studies suggests that it is likely mediated by both genetic and environmental factors (Rice, 2010; Rice, Harold, & Thapar, 2002; Silberg, Maes, & Eaves, 2010; Sullivan, Neale, & Kendler, 2000; Tully, Iacono, & McGue, 2008).

Adolescent depression is associated with pervasive impairments across multiple domains and often marks the beginning of a lifelong, chronic illness (Asarnow et al., 2005; Bardone, Moffitt, Caspi, Dickson, & Silva, 1996; Birmaher et al., 1996; Fergusson & Woodward, 2002; Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a; Giaconia, Reinherz, Paradis, Hauf, & Stashwick, 2001; Glied & Pine, 2002; Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Lewinsohn, Rohde, Klein, & Seeley, 1999; Lewinsohn, Rohde, & Seeley, 1994, 1998a; Rao, Hammen, & Daley, 1999; Rao et al., 1995; Rutter, Kim-Cohen, & Maughan, 2006; Weissman et al., 1999a). Despite the substantial costs to individuals, families and society associated with depression, depression in young people often goes unrecognised and is under-treated (Kramer & Garralda, 1998; Lewinsohn, Rohde, & Seeley, 1998b; Merikangas et al., 2010a; Merikangas et al., 2011; Olfson, Gameroff, Marcus, & Waslick, 2003; Potter et al., 2012; Wu et al., 2001). Early treatment of those with

problems is vital, however some pharmacological treatments are controversial and results are mixed regarding the effectiveness of psychosocial interventions (Thapar, Collishaw, Pine, & Thapar, 2012; Thapar, Collishaw, Potter, & Thapar, 2010). Preventing, or at least delaying the onset of depression is therefore an important goal. Some meta-analyses have suggested that preventative interventions for depression are most effective when they are targeted at high risk groups, such as the offspring of depressed parents (Horowitz & Garber, 2006; Merry, McDowell, Hetrick, Bir, & Muller, 2004; Stice, Shaw, Bohon, Marti, & Rohde, 2009). However, it is unfeasible and likely to be unnecessary to target all such children for intervention. In order for prevention strategies to be targeted more effectively, it is necessary to identify which children of depressed parents are at greatest risk.

Depression is a highly heterogeneous disorder and it is possible that variation in clinical features of parent depression may go some way to explaining variability in offspring outcomes. However, most studies simply dichotomise parents into 'depressed' and 'non-depressed' groups and information about clinical characteristics is rarely presented. Features of parental depression such as chronicity, severity, episode timing, age of onset and symptom presentation have all been examined in relation to offspring risk. However, the range of different definitions used to operationalise these constructs makes it difficult to draw comparisons across studies. Moreover, it is difficult to draw conclusions about their independent effects as these constructs are highly confounded with one another and rarely considered within the same study. There are only a few studies which have attempted to disaggregate parental clinical features, many of which are limited by reduced sample sizes and may end up focusing on atypical sub-groups. Knowledge in this area has also been limited by a lack of longitudinal studies, particularly those which extend

into adolescence. Such studies are of prime importance when examining influences on offspring depression, given that the prevalence of depression increases markedly during adolescence (Birmaher et al., 1996; Costello, Copeland, & Angold, 2011; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Ford, Goodman, & Meltzer, 2003; Hankin et al., 1998; Merikangas et al., 2010b).

The way in which depression is conceptualised, in both parents and children, also has important implications for research about the intergenerational transmission of depression. Parental depression is often defined using cross-sectional assessments, however the course of depression is highly variable over time (Ashman, Dawson, & Panagiotides, 2008; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009; Judd & Akiskal, 2000; Judd et al., 1998; Nandi, Beard, & Galea, 2009; Rhebergen et al., 2012; Skipstein, Janson, Stoolmiller, & Mathiesen, 2010). It remains unclear how this variability in the longitudinal course of parental depression symptoms is related to offspring depression risk. In addition, there are few clinical studies of depressed parents which consider dimensional outcomes in children, despite evidence that subthreshold depression symptoms are associated with impairments and are strongly predictive of future disorder (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Fergusson, Horwood, Ridder, & Beautrais, 2005; Gotlib, Lewinsohn, & Seeley, 1995; Johnson, Cohen, & Kasen, 2009; Klein, Shankman, Lewinsohn, & Seeley, 2009; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Pickles et al., 2001; Shankman et al., 2009). It is therefore important to consider both categorical and dimensional approaches to the measurement of parent and child depression when examining cross-generational depression risk.

The present thesis

Although it is established that parental depression is a risk factor for offspring depression, relatively little is currently known about how heterogeneity in parental depression may moderate offspring risk. The present thesis examines this issue using a prospective, three-wave longitudinal, multi-informant, high-risk sample of the offspring of recurrently depressed parents. Detailed information about the sample is described in chapter 2. This study is well placed to examine the role of parental depression heterogeneity in the intergenerational transmission of depression for several reasons. Firstly, the offspring are followed through adolescence which is a critical risk period for the onset of depressive disorders (Birmaher et al., 1996; Costello, Copeland, & Angold, 2011; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Ford, Goodman, & Meltzer, 2003; Hankin et al., 1998; Merikangas et al., 2010b). Secondly, these offspring have an elevated probability of developing depression by virtue of having an affectively ill parent (Rice, Harold, & Thapar, 2002). This design therefore maximises the potential case yield, increasing the power to identify associations with particular parent features of interest. Additionally, the study uses a three-wave, four year longitudinal design and includes children and adolescents who have not yet developed depression at baseline. This enables an examination of parental risk factors that predict the emergence of new-onset depression in offspring. This is important for the effective targeting of selective preventative intervention strategies. Finally, given that parents in the sample have varying histories of depression, heterogeneity in parental depression and how this relates to offspring risk for depression can be examined in more detail.

The sample examined in this thesis benefits from rigorous interview assessments of parent and child psychopathology which allow both depression

diagnoses and symptom scores to be derived. This enables simultaneous consideration of both categorical and dimensional approaches to measuring depression. The use of multiple informants when assessing psychopathology in children and adolescents is also desirable as some young people may not be developmentally mature enough to understand particular symptoms, or may hold back information about symptoms which they feel are socially undesirable. On the other hand, parents may not be aware of all symptoms, especially a child's internal state (Cantwell, Lewinsohn, Rohde, & Seeley, 1997). Furthermore, this approach reduces problems due to shared method variance, which is of particular concern when investigating associations with current parental depressive symptoms, as parent ratings of their child can be affected by their own mood state (Boyle & Pickles, 1997; Lewis et al., 2012; Najman et al., 2000; Rice, Lifford, Thomas, & Thapar, 2007; Richters & Pellegrini, 1989; Richters, 1992).

Aims

In this thesis, I aim to examine the role of parent depression heterogeneity in the intergenerational transmission of depression. This thesis is divided into three empirical chapters, which each address different questions relating to the role of parent depression heterogeneity in offspring depression risk. The three chapters are stand alone papers that are either published or under review. I analysed the data and wrote all papers. Named co-authors jointly contributed ideas and contributed to the editing of papers. The specific aims of each study were as follows:

Study 1: the aim of study 1 was to investigate whether there is a proximal influence of parental depression (indexed by a recent episode of MDD) on child psychiatric disorder and depression symptoms. Associations were then examined controlling for clinical depression characteristics in parents including age of depression onset, family history of depression, chronicity (number and duration of prior episodes), severity (presence of a severe depressive episode) and timing (depression during the postnatal period and during pregnancy).

Study 2: the aim of study 2 was first to use dimensional assessments of parent depression symptoms over all three waves of the study to identify groups of parents who varied in their depression course over time, and second, to investigate how these differences in parental course are related to parent social and health impairment and offspring risk of mood disorder and depression symptoms.

Study 3: the aim of study 3 was to disaggregate major depressive disorder into its respective DSM-IV symptom criteria and investigate whether there is

differential risk to offspring associated with specific depression symptoms in parents. For this study, all three waves of longitudinal data were used to examine whether specific symptoms in parents at baseline predict a new onset of mood disorder in offspring and future offspring depression symptoms.

Chapter 2

Methodology

The present chapter describes the sample used in this thesis, summarises the procedures used to ascertain, retain and interview the sample, describes the parent and child assessments and provides a brief overview of the statistical methods used to address the key questions. Details of the sample and methodology specific to individual analysis will be described in the relevant chapters.

The Early Prediction of Adolescent Depression study

The data used for this thesis were collected as part of the Early Prediction of Adolescent Depression (EPAD) project conducted at Cardiff University. This is a prospective, longitudinal three-wave study which aims to improve the early detection, monitoring and clinical management of depression in children and adults. Data collection began in April 2007 and was completed in April 2011. Study participants included parents who had suffered from recurrent depression (parents were required to have experienced at least two episodes of depression during their lifetime) and one child aged between 9 and 17 years at the baseline assessment. The study was funded by the Sir Jules Thorn Charitable Trust.

The EPAD sample was recruited by the research team at Cardiff University. I was employed as research assistant on the team prior to the commencement of my postgraduate studies and had a substantial role in the recruitment and assessment of families in the study. As a member of the team I was also responsible for data entry, data management and preparation, as well as analyses and contributing as a co-author to related papers (Lewis et al., 2012; Potter et al., 2012; Sellers et al., 2012).

Recruitment

Study inclusion and exclusion criteria

Parents recruited into the EPAD study were required to have a clinical history of recurrent unipolar depression (a minimum of two depressive episodes) and no prior diagnosis of bipolar affective disorder, schizoaffective disorder or evidence of psychosis (experienced outside of the context of a depressive episode). Families were excluded from the study if the affected parent met criteria for mania or hypomania at interview, or if they received a diagnosis of bipolar affective disorder from a clinician during the study course.

Parents were also required to be living with a child between the ages of 9 and 17 years to whom they were biologically related. If more than one child was willing to participate then the youngest eligible child was chosen. This approach was adopted to eliminate selection bias and to enhance the study's ability to examine the development and natural history of psychopathology longitudinally, across adolescence. There were no diagnostic exclusion criteria for the children in the study, however families were excluded if the participating child had moderate-severe learning difficulties (IQ<50). Three-hundred-and-thirty-nine families were recruited into the EPAD study, however two families were excluded following the baseline assessments due to parental diagnosis of bipolar disorder, leaving an eligible baseline sample of 337 families.

Sampling

Participants were sourced via three methods: through General Practices (GPs) across South Wales, from a research database of individuals with previously identified unipolar depression and a sample of community volunteers. The number of

participants approached and recruited from each of the three sources is summarised in Figure 1. Details of the sampling procedure for each method will now be discussed.

General Practice

Recruitment of primary care surgeries

Approximately 300 primary care surgeries across South Wales were contacted to ask for their assistance with the recruitment of families for the EPAD study. Initial contact was made via an invitation pack sent to the practice manager of the surgery containing information about the study background and aims and a summary of what participation would involve for the practice and their patients should they agree. Contact details for the researchers and information about data confidentiality were also provided. Those practices interested in participating, or wanting more information were asked to complete and return a reply slip.

A second letter was sent to the practice if no correspondence had been received after two weeks. Non-responding practices were then contacted by phone to ascertain their interest and study information was resent if necessary. If requested, a short presentation was given to the resident doctors. In total, 62 GP surgeries agreed to help with recruitment.

Recruitment of participants from General Practice

Suitable participants were identified by practices via one of two methods: a history of at least two prescriptions of antidepressant medication, or appropriate read codes (such as 'recurrent depression'). Searches were limited to adults aged 25-55

years to increase the likelihood that they would have children within the required age range (9-17 years).

Parents identified from the GP database were sent an information pack. The information pack devised by the team was sent from the GP and contained a letter from the doctor explaining why they had been contacted and separate study information sheets for parents and for children (child information sheet contained no mention of parental depression). These contained detailed information about the study background, aims, procedure, data confidentiality and contact information for the researchers. Parents were also sent a voluntary reply slip to return to the researchers should they be willing to participate or wanted more information. A second letter was sent to those individuals who had not responded after two weeks. No further contact was made subsequent to this.

Over 4000 letters were sent to potentially suitable participants from the 62 GP surgeries. Of these, over 700 responses of interest were received. All positive responses were followed up by a telephone call during which participants were screened for suitability. There was no contact made directly from the research team prior to this point. Three-hundred-and-sixty-eight eligible families agreed to participate and were booked in for an appointment, of which 264 were interviewed. One family was later withdrawn post assessment as they met the DSM-IV diagnostic criteria for hypomania at interview.

Database of unipolar depression cases

Participants were selected from a database of adults known to have recurrent unipolar depression. This database was compiled from two previous studies of unipolar depression: The Depression Case Control study (DeCC) and the

Depression Network (DeNT) sibling pair study (Farmer et al., 2004; Korszun et al., 2004).

Subjects recruited into these studies were sourced from three sites across the UK: Cardiff, London and Birmingham. They were recruited via community mental health teams, through advertisements in local media and primary care centres and via patient support organisations such as Depression Alliance. The exclusion criteria for the DeCC and DeNT samples was similar to the core criteria used for other adults in the EPAD study: participants had to be over 18 years and meet diagnostic criteria for major recurrent depressive disorder of at least moderate severity. They were excluded if they a) had a history of psychotic symptoms that were experienced outside mood disturbance or were mood incongruent; b) had a history of intravenous drug dependency; c) experienced depression only as a result of alcohol or substance dependence, or secondary to medical illness or medication; or d) had a first or second degree family member with a diagnosis of bipolar affective disorder, schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders, or schizoaffective disorder. Additionally, as the DeCC and DeNT samples were recruited for molecular genetic studies, participants were required to be of UK/EIRE white ethnicity.

Participants in the DeCC and DeNT studies were first informed about the EPAD study via a newsletter. Participants aged 25-55 years were then contacted via letter and sent an information pack as detailed above. Those parents known to not have children or thought not to have unipolar depression were not approached. Interested parents were asked to return a reply slip. Those who did not respond were firstly sent a second letter and then telephoned by a member of the team to ascertain their interest.

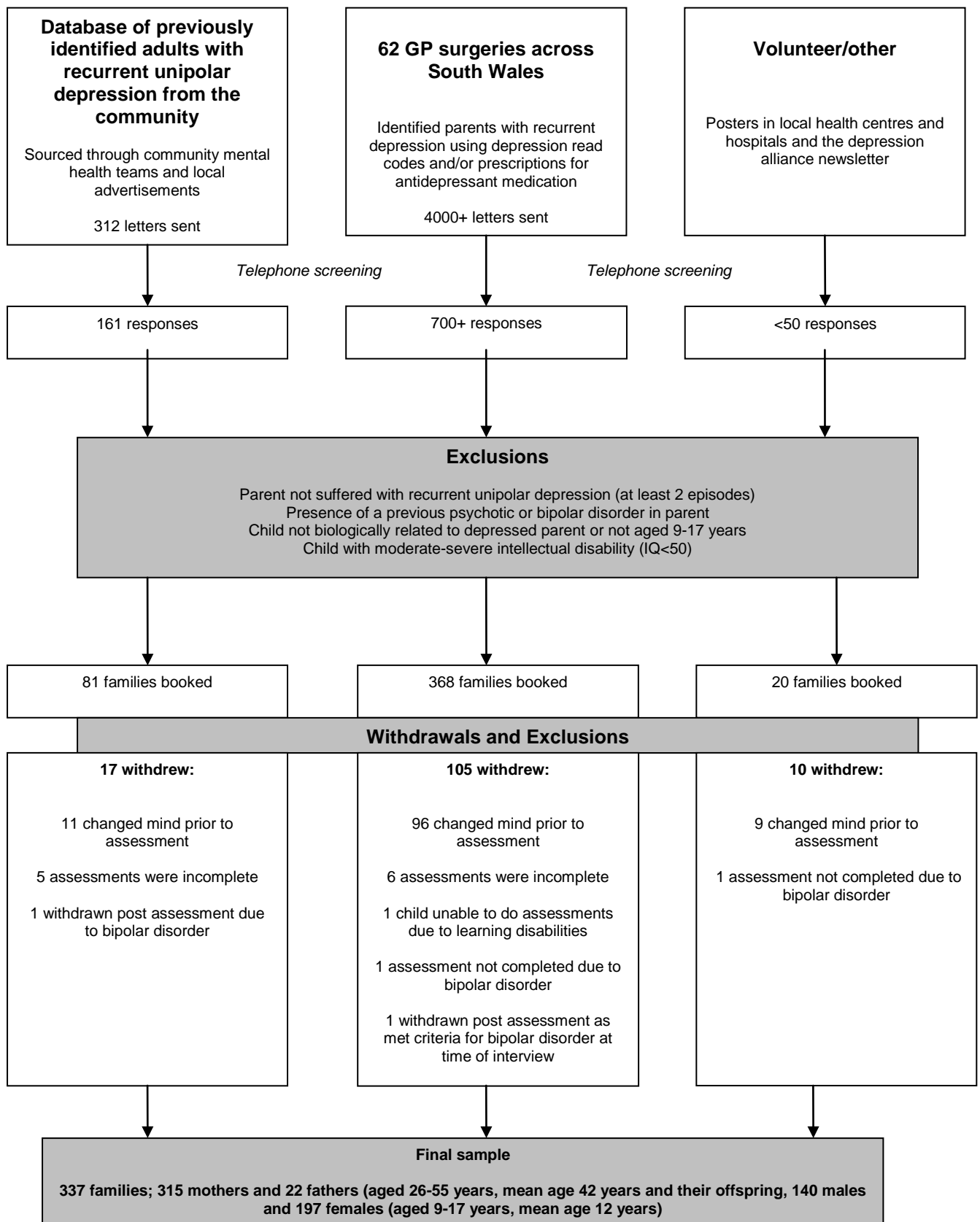
Of the 312 individuals from the database who were contacted, 161 responses of interest were received. All interested parents were telephoned by a member of the team to confirm suitability. Eighty-one eligible families were booked in for an appointment, of which 65 were interviewed. One family was withdrawn post assessment after later revealing to the team that they had received a diagnosis of bipolar disorder.

Volunteer sample

Posters were created advertising the EPAD study. These were placed in locations throughout the University Hospital in Cardiff, in primary care centres across South Wales and in leisure centres in Cardiff. Interested participants could take away a small card containing contact information for the researchers. An article about the EPAD study was also published in the Depression Alliance newsletter.

Individuals who contacted the researchers were sent an information pack as above. Those who returned a reply slip were then contacted via telephone by a member of the research team and screened to ensure suitability. Less than 50 individuals made contact with the research team. Twenty eligible families were booked in for an appointment, of which ten families were interviewed.

Figure 1. Recruitment chart



Interview procedure

Following confirmation of eligibility, appointments were made to visit the family and complete the assessments. A questionnaire pack was sent out two weeks prior to the visit to be collected by the researchers on the day of the appointment. Separate questionnaires were provided for the affected parent, their partner (if applicable) and child, who were instructed to complete them independently and place them in sealed envelopes. Questionnaire assessments were primarily used in the present thesis to ascertain demographic information or to replicate research findings based on diagnostic interviews. Details of assessments specific to individual analysis will be described in the relevant chapters.

The majority of interviews took place in the family home with a small number conducted in the University Hospital in Cardiff (<1%). Assessments were conducted by teams of two interviewers, all of whom were psychology graduates. Interviewers were trained in all child and adult assessments and were monitored throughout the study by two child psychiatrists and one adult psychiatrist. Parent and child interviews were completed independently and conducted in separate rooms where possible. Interviews lasted 2-3 hours on average and participants were compensated for their time (parents and children both received a £10 high street voucher).

Ethical approval and consent

The Multi-centre Research Ethics Committee for Wales reviewed and approved the study protocol (Ref: 06/MRE09/48). Prior to participation, parents and children were provided with a description of the study and written informed consent (parents and children aged 16 years or over) or assent (children aged less than 16

years) was then obtained from all participants as appropriate. Informed consent was obtained from each participant at each of the three time points.

Measures

The EPAD study is a multi-method and multi-informant study. Assessments were conducted separately with parents and children and included a mix of semi-structured diagnostic interviews, self report questionnaires (including demographics, mental and physical health, the social and family environment and school life) and collection of a DNA sample. Children also completed physical health assessments, cognitive assessments and provided cortisol and blood samples. The data used for the present thesis were obtained primarily from the semi-structured interview assessments. These are described in detail below. Details of other measures specific to individual analyses are described in the relevant chapters.

1) Child and Adolescent Psychiatric Assessment (CAPA, parent and child versions)

The Child and Adolescent Psychiatric Assessment (Angold & Costello, 2000) is a semi-structured clinical diagnostic interview designed for use with children aged 9-17 years. Information is collected about the intensity, frequency and onset dates of symptoms pertaining to a wide range of psychiatric diagnoses. Child and parent versions of the interview are available and both were used for the EPAD study. The interviews are similar in design, however symptoms of Attention Deficit Hyperactivity Disorder (ADHD) are reported only by parents. The CAPA rates symptoms present in the three months preceding the interview (termed the primary period) but for certain symptoms (for example truancy, firesetting and use of a weapon) information is also taken outside this period.

The interviewer establishes symptom presence and severity based on detailed definitions provided in a glossary. For most symptoms, intensity is measured according to three criteria: intrusiveness into activities, modifiability and

generalisation. Psychosocial impairment as a result of any reported symptomatology is also rated across 19 different domains of functioning (for example family relationships, self care, school life and spare time activities). The CAPA sections used in the EPAD study included those related to: mood disorders, anxiety disorders, disruptive behaviour disorders, Attention Deficit Hyperactivity Disorder (ADHD), eating disorders and psychosis. Unless otherwise specified, the child outcomes of interest for the present thesis were categorical diagnoses of mood disorders (i.e. major depressive disorder, dysthymia, depressive disorder not otherwise specified, bipolar disorder, cyclothymia or adjustment disorder with depressed mood) and dimensional depression symptom counts (symptoms relating to the DSM-IV diagnosis of MDD).

2) The Schedules for Clinical assessment in Neuropsychiatry (SCAN)

The Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) is a set of instruments and manuals aimed at assessing, measuring and classifying psychopathology and behaviour associated with the major psychiatric disorders in adult life. It can be used for clinical, research and training purposes and was developed within the framework of the World Health Organization. The parts of the SCAN used in the EPAD study include a glossary of differential definitions and a semi-structured clinical interview schedule containing the following sections: depressed mood and ideation, thinking, concentration, energy and interests, bodily functions, expansive mood and ideation, panic and anxiety, obsessional symptoms and psychotic symptoms. The present thesis focuses only on symptoms related to the DSM-IV criteria for MDD, from which a diagnosis of MDD could then be derived.

Responses are matched against the symptom definitions in the glossary and then rated by the interviewer for severity. Most SCAN items are coded according to the following criteria: symptom not present (coded 0), symptom present but below the required threshold (coded 1), symptom present to a moderate degree or symptom is severe but present for less than half of the time (coded 2) and symptom present to a severe degree and present for more than half the time (coded 3). For the present thesis, a symptom was required to be of at least moderate severity to be considered present. The SCAN can be used to assess psychopathology during a number of different periods including present state (the past month), a representative episode and episodes prior to interview. Information about the last month was collected in the EPAD study.

3) The Depression Timeline

A timeline of the affected parent's previous depressive episodes was compiled using a life history calendar approach. This is a method of collecting retrospective information using past experiences (such as births, marriages, deaths) as cues to aid autobiographical recall. Life history calendars are often used in mental health research and have been shown to generate reliable and detailed life history data (Belli, 1998; Caspi et al., 1996; Freedman, Thornton, Camburn, Alwin, & Young-Demarco, 1988).

The timeline was used to rate clinical information about the parent's depression history including number of episodes, duration of episodes, whether they had ever experienced a depressive episode during pregnancy or postnatally, whether they had ever been hospitalised for their depression and details about any treatment received. Following the configuration of the timeline, parents were required

to identify their two worst episodes of depression which were assessed in greater detail. Information was collected about the specific symptoms experienced during these episodes and the associated level of impairment (measured according to the Global Assessment of Functioning Scale (GAF)).

4) The Global Assessment of Functioning scale

The Global Assessment of Functioning scale (American Psychiatric Association, 1994) is a numerical rating scale presented in the DSM-IV which is used subjectively to rate levels of social, occupational and psychological functioning in adults. The 100 point scale operates along a continuum with lower scores indicating greater severity of symptoms and greater impairment in functioning.

Quality control and generating diagnoses

The research team received training and subsequent regular supervision from child psychiatrists Professor Anita Thapar and Dr Robert Potter who supervised the child assessments and from adult psychiatrist Dr Daniel Smith who supervised the adult assessments. Offspring depression symptom counts and psychiatric diagnoses were generated from the CAPA interviews. For depression symptom counts, parent and child CAPA reports were combined at the symptom level using an either/or rule. For offspring diagnoses, parent-reported diagnoses and child-reported diagnoses were established separately and then combined. All children meeting criteria for DSM-IV and ICD-10 diagnoses, together with all subthreshold cases were reviewed by Professor Thapar and Dr Potter. Parent depression symptom counts and parent MDD diagnosis were generated from the SCAN interview.

Inter-rater reliability was formally assessed using joint ratings of a total of 40 CAPA interviews (20 parent-rated and 20 child-rated) and 20 SCAN interviews. Interviews were obtained from both the baseline and follow-up assessments. The average agreement between interviewers for individual CAPA depression symptoms was excellent (mean kappa statistic =.90 for child-rated depression symptoms and .90 for parent-rated depression symptoms). Interviewer agreement for coding parental diagnosis of MDD was perfect (kappa =1).

Methods of analyses

Analyses were performed using SPSS version 16.0 unless otherwise stated. Continuous outcome data that were not normally distributed were transformed prior to analysis using a natural log transformation. Mean imputation was used to calculate total symptom counts for parent depression and child depression where there was one item missing.

The primary analytical techniques used to address the key questions in this thesis were logistic and linear regression. Other methods of statistical analysis used are described in the individual results chapters. In chapter five, Structural Equation Modelling (SEM) was used as a complement to the primary analyses, for which I was aided by Professor Gordon Harold.

The Early Prediction of Adolescent Depression study: sample characteristics at baseline

Following the baseline assessments, the eligible sample included 337 families who met the inclusion/exclusion criteria detailed earlier. The parent sample consisted of 315 mothers and 22 fathers (mean age 41.7 years; SD = 5.45; range 26-55 years) all of whom had a clinical history of recurrent unipolar depression. The child/adolescent sample consisted of 197 females and 140 males (mean age 12.4 years; SD = 2.01; range 9-17 years).

At the time of the baseline assessments 85% of families ($N = 286$) were living in Wales (North Wales $N = 2$; South-West Wales $N = 57$; South Wales $N = 227$) and 15% of families ($N = 51$) were living in England (Midlands $N = 28$; North-West England $N = 3$; South-East England/London $N = 8$; South-West England $N = 12$). Nationality of the sample was not available at baseline, therefore this information was obtained from the first follow-up. Both parents' nationality was British in 96% of the 288 families who participated in the first follow-up ($N = 276$). There were ten families where one or both of the child's biological parents were of another nationality and two families where the nationality of one parent was unknown.

Family composition was comparable to UK norms with 70% of families in the study living in two-parent households (compared with 77% nationally, Office for National Statistics, 2009). Rates of DSM-IV disorder in the children in the EPAD sample are presented in Table 1. Rates of disorder were elevated at each time point compared to normative data from a recent UK epidemiological survey of children aged 11-15 years (Green, McGinnity, Meltzer, Ford, & Goodman, 2005), where prevalence rates of disorder were reported as follows: any disorder 11.7%;

depressive disorders 2.6%; anxiety disorders 4.4%, disruptive behaviour disorders 7.0%; and ADHD 1.5%.

Table 1. Child diagnosis in the EPAD study

Diagnosis	Wave 1		Wave 2		Wave 3	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Sample	Sample	Sample	Sample	Sample	Sample
	N=337	N=288^a	N=288^a	N=288^a	N=283	N=283
Any DSM-IV assessed disorder	80	(23.7)	80	27.9	72	(25.4)
Any mood disorder	16	(4.7)	28	(9.8)	28	(9.9)
Major depressive disorder	12	(3.6)	17	(5.9)	15	(5.3)
Dysthymia	1	(0.3)	1	(0.3)	2	(0.7)
Depressive disorder NOS	2	(0.6)	4	(1.4)	3	(1.1)
Adjustment with depressed mood	0	-	1	(0.3)	4	(1.4)
Bipolar spectrum disorder	1	(0.3)	3	(1.0)	4	(1.4)
Cyclothymia	0	-	2	(0.7)	0	-
Any anxiety disorder	39	(11.6)	38	(13.2)	38	(13.4)
Generalised anxiety disorder	11	(3.3)	16	(5.6)	21	(7.4)
Separation anxiety disorder	12	(3.6)	9	(3.1)	5	(1.8)
Obsessional compulsive disorder	4	(1.2)	4	(1.4)	7	(2.5)
Panic disorder	1	(0.3)	0	-	0	-
Agoraphobia	2	(0.6)	0	-	0	-
Social phobia	15	(4.5)	17	(5.9)	15	(5.3)
Anxiety disorder NOS	4	(1.2)	4	(1.4)	4	(1.4)
Adjustment disorder with anxiety	0	-	0	-	1	(0.4)
Any disruptive behaviour disorder	24	(7.1)	29	(10.1)	23	(8.1)
Oppositional defiant disorder	18	(5.3)	18	(6.3)	19	(6.7)
Conduct disorder	1	(0.3)	0	-	1	(0.4)
Disruptive disorder NOS	5	(1.5)	11	(3.8)	3	(1.1)
Attention Deficit Hyperactivity Disorder	21	(6.2)	19	(6.6)	18	(6.4)
Bulimia	2	(0.6)	0	-	0	-
Eating disorder NOS	1	(0.3)	3	(1.0)	1	(0.4)
Specific phobia	9	(2.7)	21	(7.3)	21	(7.4)

^a One family missing diagnostic information due to missing data; NOS: Not otherwise specified

Any DSM-IV disorder include all assessed DSM-IV disorders apart from specific phobia; mood disorders include major depressive disorder, dysthymia, depressive disorder not otherwise specified, adjustment disorder with depressed mood, bipolar spectrum disorder and cyclothymia; anxiety disorders include generalised anxiety disorder, separation anxiety disorder, obsessional compulsive disorder, panic disorder, agoraphobia, social phobia, anxiety disorder not otherwise specified and adjustment disorder with anxiety; disruptive behaviour disorders include oppositional defiant disorder, conduct disorder and disruptive behaviour disorder not otherwise specified

Differences in the sample according to recruitment source

Table 2 shows sample descriptives and features of parents' depression according to recruitment source. Analysis of variance and Chi-square statistics were used to examine differences between the three groups. Annual household income ($\chi^2(2) = 7.67, p = .022$) and parent age ($F(2, 321) = 3.30, p = .038$) were significantly associated with recruitment source. Post hoc comparisons revealed that families recruited from the databases had significantly higher income ($\chi^2(1) = 7.48, p = .006$) and a significantly older parent age ($M = 43.15, CI = 41.66, 44.65$) than families recruited from primary care ($M = 41.21, CI = 40.55, 41.86, p = .029$).

Table 2. Sample descriptives according to recruitment source *

	Recruitment source			
	General Practice	DeCC and DeNT Databases	Volunteer sample	Whole sample
Percentage of Sample (N)	78 (263)	19.0 (64)	3 (10)	337 (100)
Demographics				
Child age, years, mean (SD)	12.4 (2.0)	12.5 (2.1)	12.8 (2.6)	12.4 (2.0)
Child gender, % female	56.7	60.9	90.0	58.5
Parent age, years, mean (SD)	41.2 (5.3)	43.2 (6.0)	41.9 (5.1)	41.6 (5.5)
Parent gender, % female	94.3	89.1	100.0	93.5
Annual household income < £30,000, %	55.9	36.5	44.4	51.6
Two parent family, %	69.6	76.6	50.0	70.3
Parent depression features				
Mean impairment across worst two depressive episodes, GAF mean (SD)	47.2 (15.4)	42.6 (19.3)	47.7 (13.4)	46.4 (16.2)
Four or more depressive episodes, %	39.0	38.1	60.0	39.4
Mean duration of worst two depressive episodes, months, mean (SD)	16.4 (22.0)	19.9 (31.3)	11.9 (8.5)	16.9 (23.7)
Age of depression onset, years, mean (SD)	26.6 (8.4)	24.3 (7.5)	26.3 (8.3)	26.1 (8.2)
Baseline Psychopathology				
Number of parent DSM-IV depression items, mean (SD)	2.7 (2.7)	2.6 (2.8)	1.8 (2.7)	2.6 (2.7)
Mean number of child DSM-IV depression items, mean (SD)	1.7 (1.9)	1.8 (1.9)	1.6 (1.1)	1.7 (1.9)

* Some numbers may vary due to missing data; GAF: Global Assessment of Functioning Scale

Retention

As described earlier, families were interviewed three times over the course of the study which began in April 2007 and finished in April 2011. The average time between the first and second assessment was 16.2 months (SD = 2.69) and between the second and third assessment was 12.5 months (SD = 1.56). The average time between the baseline and final assessment was 29.3 months (SD = 3.62). Figure 2 summarises the number of families who were interviewed at each phase of the study.

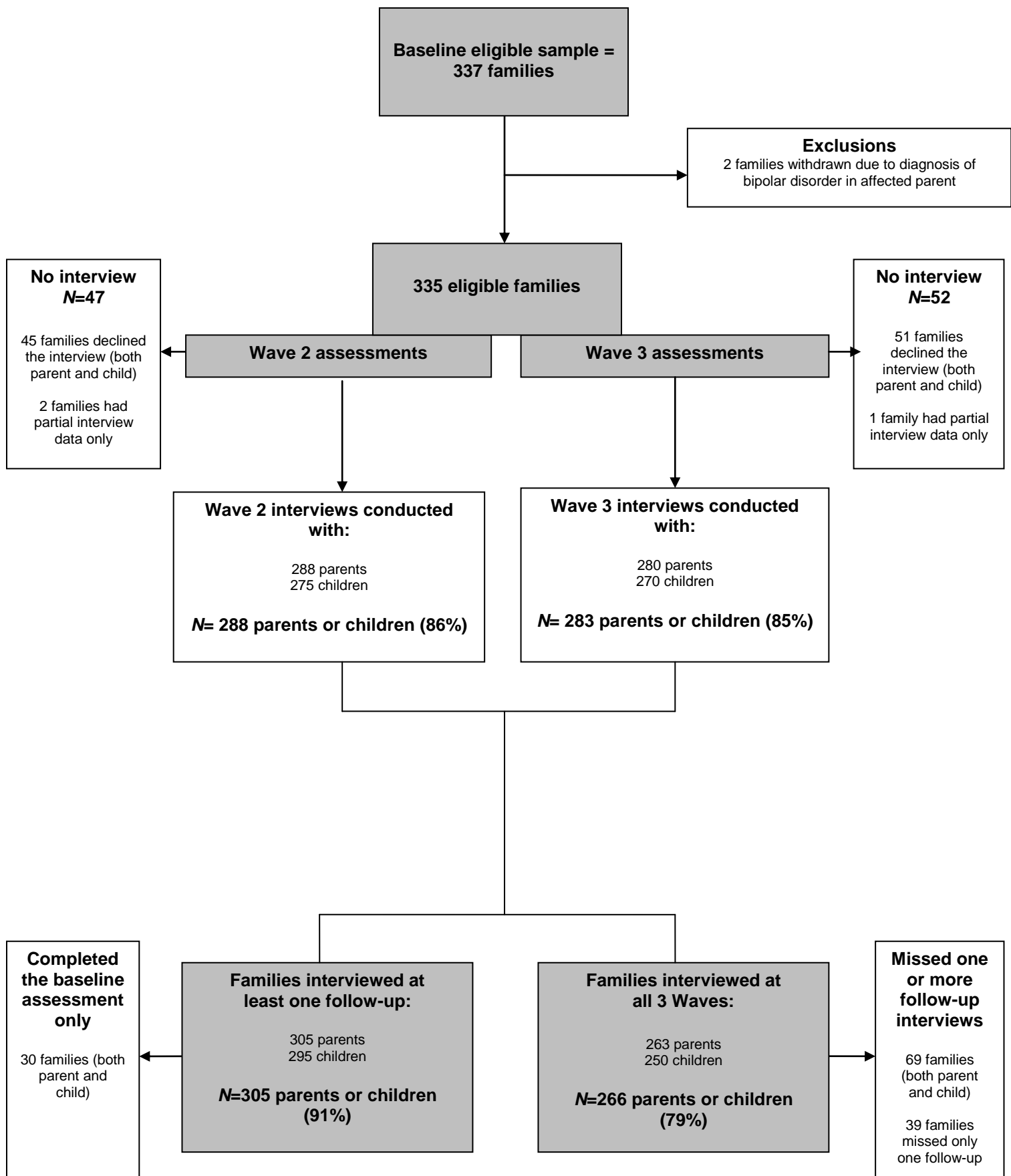
Exclusions

Two families were excluded between the baseline assessment and first follow-up as the affected parent subsequently received a clinician diagnosis of bipolar affective disorder. No further exclusions were made throughout the study.

Re-contacting families

The adolescent depression research team kept in regular contact with all participating families via six-monthly newsletters and Christmas cards. Change of address cards and contact information for the researchers were provided at each time. Towards the end of each wave of assessments, the research team began re-contacting families who were due for their next assessment. Families were contacted sequentially in the order in which they originally participated and were initially sent a reminder card, shortly after which they were contacted via telephone to book an appointment. Families were free to withdraw from the study at any time. The procedure for families with whom the team were unable to make contact is detailed next.

Figure 2. Retention chart



A letter was first sent to the participant's home requesting that they make contact with the team to let them know whether or not they would be interested in continuing with the study. If no response was received then the GP was contacted to confirm their address and telephone number. A further letter was then sent and telephone calls attempted. Following these steps if no contact had been made, the family was considered to be withdrawn from the current wave of the study. Occasionally a family had changed address without informing the team. Wherever possible the new address was obtained via the GP, via an alternative contact provided by the parent previously at interview or via the electoral roll. A letter was then sent to their new address and steps followed as above.

Differences between retained and non-retained families

Differences in sample demographics and features of parents' depression amongst retained and non-retained families are detailed in Table 3. Chi-square and t tests were used to test for significant differences between:

- i) Families who completed only the baseline assessments ($N = 30$) and those who completed one or both follow-ups ($N = 305$).
- ii) Families who completed an interview at each of the three assessments ($N = 266$) and those who declined one or both follow-ups ($N = 69$).

There were no statistically significant differences between those families who completed only the baseline assessment and those who completed either one or both follow-up assessments. Families who completed interviews at all three assessments had significantly lower baseline depression symptoms (parent and child) and a significantly older index parent, than those families with missing data.

Table 3. Differences between retained and not retained samples

Sample <i>N</i> = 335	Families completed baseline only 30 (9%)	Families completed one/both follow-ups 305 (91%)	Test statistic (chi-square / t test) and <i>p</i> value	Families missing one/both follow-ups 69 (21%)	Families completed all waves 266 (79%)	Test statistic (chi-square / t test) and <i>p</i> value
Demographics						
Child age, years, mean (SD)	12.4 (1.9)	12.4 (2.0)	$t(333)=0.01, p=0.98$	12.6 (1.9)	12.4 (2.0)	$t(333)=0.79, p=0.43$
Child gender, % female	56.7	58.7	$\chi^2(1)=0.04, p=0.83$	56.5	59.0	$\chi^2(1)=0.14, p=0.70$
Parent age, years, mean (SD)	40.0 (4.9)	41.8 (5.4)	$t(320)= -1.53, p=0.12$	40.3 (5.3)	41.9 (5.4)	$t(320)= -2.14, p=0.03$
Parent gender, % female	96.7	93.1	$\chi^2(1)=0.56, p=0.45$	95.7	92.9	$\chi^2(1)=0.69, p=0.40$
Annual household income < £30,000, %	66.7	50.2	$\chi^2(1)=2.13, p=0.14$	60.4	49.4	$\chi^2(1)=2.11, p=0.14$
Two parent family, %	56.7	71.5	$\chi^2(1)=2.86, p=0.09$	65.2	71.4	$\chi^2(1)=1.00, p=0.31$
Parent depression features						
Mean impairment across worst two depressive episodes, GAF mean (SD)	42.7 (17.6)	46.9 (16.0)	$t(332)= -1.35, p=0.17$	4.6 (17.0)	47.0 (16.0)	$t(332)= -1.09, p=0.27$
Four or more depressive episodes, %	42.9	38.7	$\chi^2(1)=0.18, p=0.66$	38.5	39.2	$\chi^2(1)=0.01, p=0.90$
Mean duration of worst two episodes, months, mean (SD)	22.6 (37.9)	16.3 (21.9)	$t(30)=0.87, p=0.38$	19.6 (31.0)	16.2 (21.5)	$t(324)=1.06, p=0.29$
Age of depression onset, years, mean (SD)	26.1 (7.6)	26.2 (8.3)	$t(324)= -0.02, p=0.97$	25.6 (6.8)	26.3 (8.5)	$t(123)= -0.73, p=0.46$
Baseline Psychopathology						
Number of parent DSM-IV depression items, mean (SD)	3.3 (2.8)	2.6 (2.7)	$t(312)=1.40, p=0.16$	3.7 (2.8)	2.4 (2.6)	$t(312)= 3.52, p < 0.01$
Number of child DSM-IV depression items, mean (SD)	2.3 (1.9)	1.6 (1.8)	$t(329)=1.77, p=0.07$	2.2 (2.0)	1.6 (1.8)	$t(329)= 2.49, p=0.01$

* Some numbers may vary due to missing data; GAF: Global Assessment of Functioning Scale

Chapter summary

This chapter has described the sample, methods and analytical techniques used to address the key questions in this thesis. The three chapters constituting the empirical body of this thesis are presented next. These chapters are based on stand-alone papers that are either published or under review.

Chapter 3

Offspring of parents with recurrent depression: which features of parent depression index risk for offspring psychopathology?

Paper 1: Mars, B., Collishaw, S., Smith, D., Thapar, A. K., Potter, R., Sellers, R., Harold, G. T., Craddock, N., Rice, F., & Thapar, A. (2012). Offspring of parents with recurrent depression: which features of parent depression index risk for offspring psychopathology? *Journal of Affective Disorders*, 136(1-2), 44-53.

This paper was written whilst the second follow-up was in progress and is therefore based on data from the first two waves of the study. For this paper, offspring DSM-IV psychiatric disorder was used as an outcome measure alongside depression symptoms, as the number of offspring with depressive disorder was too small for meaningful associations with parental depression characteristics to be tested.

Abstract

Background: Parental depression is associated with an increased risk of psychiatric disorder in offspring, although outcomes vary. At present relatively little is known about how differences in episode timing, severity, and course of recurrent depression relate to risk in children. The aim of this study was to consider the offspring of parents with recurrent depression and examine whether a recent episode of parental depression indexes risk for offspring psychopathology over and above these other parental depression features.

Methods: Three hundred and thirty seven recurrently depressed parents and their offspring (aged 9-17) were interviewed as part of an ongoing study, the 'Early Prediction of Adolescent Depression study'. The Child and Adolescent Psychiatric Assessment was used to assess two child outcomes; presence of a DSM-IV psychiatric disorder and number of DSM-IV child-rated depression symptoms.

Results: Children whose parents had experienced a recent episode of depression reported significantly more depression symptoms, and odds of child psychiatric disorder were doubled relative to children whose parents had not experienced a recent episode of depression. Past severity of parental depression was also significantly associated with child depression symptoms.

Limitations: Statistical analyses preclude causal conclusions pertaining to parental depression influences on offspring psychopathology; several features of parental depression were recalled retrospectively.

Conclusions: This study suggests that particular features of parental depression, specifically past depression severity and presence of a recent episode, may be important indicators of risk for child psychiatric disorder and depressive symptoms.

Introduction

Parental depression is one of the strongest identified risk factors for youth psychiatric disorder, with offspring of depressed parents consistently showing heightened rates of anxiety and disruptive behaviour disorders (Weissman et al., 2006b) as well as a 2-3 fold increased risk for depressive disorders when compared with controls (Rice, Harold, & Thapar, 2002). Levels of depressive symptoms which fall short of diagnostic criteria are also elevated in offspring of depressed parents (Connell & Goodman, 2002). Adoption and twin designs suggest that both inherited and environmental factors contribute to this increased risk for offspring psychopathology, with non-inherited factors being particularly important in the intergenerational transmission of depression (Harold et al., 2010; Silberg, Maes, & Eaves, 2010; Tully, Iacono, & McGue, 2008).

Youth depression is associated with severe adverse consequences including psychosocial impairment and an increased risk for suicide and future medical problems (Birmaher et al., 1996; Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001b; Weissman et al., 1999a). Furthermore, longitudinal follow-ups of clinical and community samples demonstrate that depression occurring early in life shows strong continuity into adulthood (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a; Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Pine, Cohen, Gurley, Brook, & Ma, 1998; Rao et al., 1995; Rutter, Kim-Cohen, & Maughan, 2006) and recurrence rates of 60 to 70% (Birmaher et al., 1996). Depressive symptoms that fall below the diagnostic threshold are also often accompanied by impairment and predict escalation to full disorder (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Fergusson, Horwood, Ridder, &

Beautrais, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Pickles et al., 2001; Pine, Cohen, Cohen, & Brook, 1999). The long-term morbidity associated with youth depression highlights it as a serious concern for health professionals and necessitates strategies for early evidence-based intervention and prevention in those children who are at greatest risk.

Despite the robust association found between parental depression and offspring psychopathology, outcomes vary with not all children going on to experience problems. There is inherent heterogeneity within the depression construct meaning that parents meeting criteria for depressive disorder will differ on clinical variables such as episode severity and chronicity, and this may go some way to explaining differences in child outcomes. This possibility is, however, rarely considered, with most studies comparing child outcomes according to parental diagnostic status alone (e.g. depressed compared to non-depressed).

Several longitudinal population-based studies testing links between parent depression and child psychopathology have attempted to disaggregate associations with different depression features and suggest that children of parents who have experienced a more severe, chronic course of illness are at greater risk for psychopathology than children of parents who are less seriously affected. The number, severity and duration of parental depressive episodes as well as early age of depression onset (≤ 20) have all been associated with poorer child outcomes, including an increased risk for psychiatric disorder, higher levels of internalising and externalising symptoms and greater total behavioural problem scores (Brennan et al., 2000; Foster et

al., 2008; Hammen & Brennan, 2003; Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Weissman et al., 1984).

Timing of parental depressive episodes may also differentially index risk in offspring. Many studies have focused on the post-natal period (with most assessing parental depression within one year of birth) as a time when depression exposure may be particularly harmful to children (Brand & Brennan, 2009; Murray et al., 2010; Murray et al., 2011; Murray et al., 1999). However other studies have failed to find associations with offspring depression once later maternal depressive episodes are taken into account (Halligan, Murray, Martins, & Cooper, 2007; Hay, Pawlby, Waters, & Sharp, 2008; Sutter-Dallay et al., 2010). These findings suggest that in addition to testing early associations between maternal depression and offspring outcomes, an important issue is how far depressive episodes occurring later in childhood and adolescence present a continuing index of risk for offspring as they grow older. This may be especially important in the transition to adolescence given that this is an important period for social and emotional development. A crucial question therefore is whether risk to older child and adolescent offspring can be usefully indexed by the presence of a recent episode of parental depression, and if so, whether this adds anything over and above risk associated with previous exposure.

The aim of the present study is to examine a group of parents with recurrent depression, and consider whether a recent episode of parental depression is associated with an increased risk of child psychopathology, over and above any risk associated with other depression characteristics such as past severity and chronicity.

Methods

Sample

This study utilised data from an ongoing high risk study of the offspring of recurrently depressed parents, the 'Early Prediction of Adolescent Depression' (EPAD) study. At baseline, participants included 339 parents, all of whom had a history of recurrent unipolar depression and their adolescent offspring (aged 9-17 years). The sample was recruited predominantly from general practices across South Wales (78%). Additional participants were community volunteers recruited into the study through a database of individuals with previously identified unipolar depression (19% who were originally identified via community mental health teams and through advertisements in local media and primary care centres) with the remainder recruited through a variety of other sources (e.g. notice boards in primary care health centres, 3%, see supplementary Figure 1).

Prior to participation in the study, parents were screened over the telephone to ensure their family fulfilled the inclusion criteria. Parents were required to have suffered from recurrent unipolar depression (at least 2 episodes; later confirmed by diagnostic interview) but need not have been experiencing a depressive episode at the time of recruitment. Additionally, parents had to be currently living with a child (age 9-17 years) to whom they were biologically related. If more than one child was present in the household and willing to participate then the youngest eligible child was selected. This served to eliminate any selection bias that may have arisen from parents suggesting the child with the greatest psychopathology for interview and also enhanced the study's ability to examine the development and natural history of psychopathology

longitudinally, across adolescence. Parents with a psychotic or bipolar diagnosis and those who met DSM-IV criteria for mania/hypomania at the time of interview were excluded from the study. Families were also excluded if the participating child had moderate-severe intellectual disability ($IQ < 50$). There were no diagnostic exclusion criteria for the children at study entry. Following the baseline interview assessments, there was a final sample of 337 families who met these inclusion criteria. The adult sample consisted of 315 mothers and 22 fathers (age 26-55 years, mean 41.7 years) and the child sample consisted of 197 females and 140 males (age 9-17 years, mean 12.4 years). Eighty of the 337 index parents (24%) met DSM-IV criteria for depression at baseline. Family composition was comparable to UK norms, with 70% of families in the study living in 2-parent households (77% in a recent UK epidemiological survey, Office for National Statistics, 2009).

Families were assessed at recruitment then an average of 16 months later ($SD = 2.69$, range 11 to 27). Retention rate at follow-up was 96% ($N = 323$) with full interview data available on 86% of parents ($N = 290$) and 82% of children ($N = 277$). An additional 2 families were excluded as the affected parent had been re-diagnosed as suffering from bipolar disorder between assessments. This resulted in a final sample of 288 parents and 275 children available for analyses. At the time of the second assessment, all of the children were living primarily with the affected parent save one, who had moved out 3 months prior but had remained in frequent contact.

Procedure

The Multi-centre Research Ethics Committee for Wales reviewed and approved the study protocol. Prior to participation, parents and children were provided with a description of the study and written informed consent or assent was then obtained from all participants as appropriate.

Data were collected from parents and children via semi-structured diagnostic interviews. These were completed with the parent and child independently of each other, in separate rooms in most instances and in 99% of cases by separate researchers. Assessments were conducted in the family home (99%) or at the university hospital (1%) by teams of two trained interviewers, all of whom were psychology graduates and were supervised weekly by a team of clinical child and adolescent (AT, RP) and adult (DS) psychiatrists. Interviewers were aware that all parents had experienced recurrent depression but were blind to parent's and children's current psychiatric status at the time of each assessment.

Assessments

Parent depression diagnosis and prior depression episodes:

The index parents' current psychiatric state was assessed using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). This interview was used to assess whether an episode of DSM-IV depression had occurred over the previous month. The interviewer agreement for coding DSM-IV parental depression diagnosis was perfect ($\kappa = 1$). A timeline of the affected parent's previous depressive episodes was compiled using a life history calendar approach which is a method of

collecting information retrospectively where life events are used as markers to aid recall (Belli, 1998; Caspi et al., 1996; Freedman, Thornton, Camburn, Alwin, & Young-Demarco, 1988). Parents were required to provide details about previous episodes of depression (including episode timing, duration and treatment) and identify their worst two depressive episodes. The timeline data was used to provide information about age of depression onset (dichotomised according to previous research into ≤ 20 versus 21 years or older (Weissman et al., 1984)), episode duration (an average of the worst two reported episodes), whether episodes had been frequent (classified as 4 or greater) and any periods of hospitalisation for depression. Information about depression during pregnancy and the postnatal period (up to 1 year after birth) with the index child was also collected from the mothers in the sample.

Severity, impairment and family history:

Information regarding severity and associated level of impairment was ascertained by assessing the two worst depressive episodes in detail. Level of impairment was assessed using the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 1994) which is a numerical scale (range 0-100) used to rate levels of social, occupational and psychological functioning with lower scores indicating greater impairment. A severe episode was defined as an episode involving either severe impairment ($GAF \leq 30$) or hospitalisation due to depression in accordance with previous criteria (Hammen & Brennan, 2003). Family history of depression was also assessed at baseline by asking parents about all first degree relatives of the child

(siblings, parents and grandparents). A count based method was then used to calculate the number of family members affected (Milne et al., 2008).

Recent episode of parental depression:

This was defined using data from the SCAN interview at recruitment and at follow-up. Details of any depressive episodes experienced since the first assessment were retrospectively recalled and documented. Based on this information, parents were categorised according to whether they had experienced a recent episode of depression - defined as meeting DSM-IV criteria for depression at either the baseline (assessing the last month) or follow-up assessment (assessing the last month) or having reported a depressive episode in between. One hundred and sixty-six (57.8%) of the index parents who took part in the follow-up interview (154/268 mothers; 12/20 fathers) had experienced a recent episode of depression. Of these, sixty-three (22%) had a current diagnosis at baseline, fifty-two (18.2%) at follow-up and 158 (55.1%) reported an episode between the assessments. Recent parental depression was used as the primary predictor of child outcomes.

Child outcomes:

The child outcome measures were analysed from data obtained at the follow-up interview (child age range 10-18 years, mean 13.8 years). Child diagnosis and depression symptoms were assessed using the parent and child versions of the Child and Adolescent Psychiatric Assessment [CAPA (Angold & Costello, 2000)]. This is a semi-structured diagnostic interview which was used to assess depressive disorders,

anxiety disorders, oppositional defiant disorder, conduct disorder, ADHD (parent only), bipolar disorder, eating disorders, and psychosis based on symptoms and impairment present in children and adolescents during the preceding three months.

Parent and child rated diagnoses were combined (using an either/or approach) to provide an overall DSM-IV diagnosis as used previously (Angold & Costello, 1995). All cases meeting criteria for diagnosis and all those with sub-threshold symptoms were reviewed by two child psychiatrists and diagnoses were agreed by clinical consensus. Clinician agreement was perfect for both parent-reported and child-reported DSM-IV psychiatric disorder at follow-up (presence/absence). There was only one instance where clinicians differed regarding the specific diagnoses given (one giving a diagnosis of adjustment disorder and the other major depressive disorder).

The agreement between parent and offspring reports for child disorder (presence/absence) at follow-up was low ($\kappa = .120$, $p < .05$). This is consistent with other studies which have generally found low to moderate agreement between informants when assessing child psychiatric disorder (Cantwell, Lewinsohn, Rohde, & Seeley, 1997) and highlights the need to obtain data from multiple informants whenever possible.

The total number of DSM-IV major depression symptoms was also computed from the child CAPA (maximum of 9). The average agreement between interviewers for child-rated CAPA depression symptoms was excellent (mean $\kappa = .90$)

Statistical Analysis

Two child outcomes were analysed: diagnosis of any DSM-IV psychiatric disorder and number of child-rated depression symptoms. The outcome diagnoses included all mood disorders, anxiety disorders, disruptive disorders (ODD and CD) and other disorders (eating disorders and adjustment disorders). In accordance with previous research on the offspring of depressed parents, specific phobias were not included as outcomes (Hammen & Brennan, 2003). Additionally, as ADHD is not assessed by the child CAPA, this outcome was also not included in the primary analyses, although further analyses including parent reports of ADHD were also conducted and similar results were found (supplementary Table 1). A disorder was considered present if reported by either the parent or the child.

The distribution of depression symptoms reported by the child was positively skewed and therefore transformed prior to analysis using a natural log transformation. Logistic and linear regressions were used to analyse disorder and symptom score outcomes respectively. Analysis of Variance and Chi-Square statistics were used to compare parents with and without recent depression on a number of different clinical depression characteristics. These included depression during pregnancy, postnatal depression (with the index child), average episode duration, frequent episodes, severe episodes, early age of onset, and family history of depression. Those variables that were associated with both a recent episode of parental depression and child outcome (psychiatric disorder or depressive symptoms) were included in further multivariate analyses. Age and sex of child at follow-up, and their interaction were included as covariates.

Results

Table 1 presents clinical information regarding the index parent's history of depression and the diagnoses in the children at the follow-up assessment. Rates of any DSM-IV disorder (parent and child disorder combined) were similar for boys and girls (28.7% vs. 27.3%, OR = .934, CI = .55, 1.58, $p = .800$), however girls experienced significantly higher rates of depressive disorders than boys (10.5% vs. 3.5%, OR = 3.24, CI = 1.07, 9.85, $p = .038$). Rates of disorder did not differ significantly between older (≥ 14 years) and younger children (30.7% vs. 24.8%, OR = 1.34, CI = .80, 2.26, $p = .270$). In line with previous studies of children of depressed parents (Beardslee, Versage, & Gladstone, 1998; Goodman & Gotlib, 1999; Weissman et al., 2006b) this study found elevated rates of disorder in offspring when compared with normative data from a recent UK epidemiological survey of children aged 11-15 years (Green, McGinnity, Meltzer, Ford, & Goodman, 2005). Specifically there were higher rates of overall (27.9 % vs. 11.7% $\chi^2 = 61.5$, $p = <.01$), depressive (7.7% vs. 2.6% $\chi^2 = 23.6$, $p = <.01$), anxiety (13.2% vs. 4.4% $\chi^2 = 43.0$, $p = <.01$), disruptive behaviour disorders (conduct disorder and oppositional defiant disorder; 10.1% vs. 7.0% $\chi^2 = 3.8$, $p = .05$) and ADHD (6.6% vs. 1.5% $\chi^2 = 36.9$, $p = <.01$).

Recent parental depression as a predictor of child outcomes

Child diagnoses:

A significant association was found between recent parental depression and child disorder (parent and child combined, Table 2). Children of parents who had recently experienced an episode of depression were significantly more likely to have a

psychiatric disorder than children who had not been recently exposed (OR = 2.00, CI = 1.12, 3.56, $p = .019$).

When analyses excluded children with a psychiatric disorder at baseline, those children who had been recently exposed to a parental depressive episode also showed a higher rate of new-onset psychiatric disorder compared to children who had not been recently exposed, although the association was not significant (21.4% when recent parental depression versus 14.3% when no recent depression, OR = 1.70, CI = .84, 3.42, $p = .140$. Child disorder at baseline is described in supplementary Table 2).

There was no evidence of cross-sectional association between current parental diagnosis of DSM-IV depression (assessed by the SCAN over the preceding month) and child disorder at baseline (OR = 1.59, CI = .87, 2.90, $p = .135$), however a significant cross-sectional association was found between current parental depression and child psychiatric disorder at follow-up (OR = 1.60, CI = 1.15, 2.22, $p = .006$).

Child-rated depression symptom scores:

An interaction was found between child age and sex at follow-up such that older girls were found to report more depressive symptoms ($\beta = .086$, $p = .019$). This interaction term was therefore included in all subsequent analyses. Linear regression analysis revealed a significant association between recent parental depression and child-rated depression symptoms ($\beta = .17$, CI = .03, .31, $p = .017$). Children who had recently been exposed to a parental depressive episode reported significantly more depressive symptoms (untransformed mean = 1.43, SD = 1.73) than children who had not been recently exposed (untransformed mean = 1.00, SD = 1.38). There was no

evidence of cross-sectional association between current parental diagnosis of DSM-IV depression (assessed by the SCAN over the preceding month) at each time point and child-rated depression symptoms (baseline $\beta = .11$, CI = $-.04, .26$, $p = .153$; follow-up $\beta = .09$, CI = $.00, .18$, $p = .051$).

Other features of parent depression associated with child outcomes

Presence of a previous severe depressive episode in the parent was associated with both child disorder (OR = 1.81, CI = 1.01, 3.24, $p = .047$) and child depression symptoms ($\beta = .19$, CI = $.04, .35$, $p = .015$). Family history ($\beta = .10$, CI = $.01, .19$, $p = .038$) was also associated with number of child depression symptoms (Table 3). No associations were found between any of the other features of parental depression examined (postnatal depression, depression during pregnancy, average episode duration, frequent episodes or early age of depression onset) and either child outcome.

Is recent parental depression associated with child outcomes when prior depression features are taken into consideration?

Of the parent depression features associated with child outcomes, only prior depression severity was also associated with recent parental depression (Table 4). Multiple regression analyses were therefore performed to assess the independent contributions of these two variables in predicting child outcomes (Table 5). Age and sex of child at follow-up, and their interaction were included as covariates.

Child diagnoses:

In the multivariate analysis, when both severity and recent parental depression were included as predictors of child disorder, a significant association was found for recent depression. Prior depression severity was found to be marginally associated with child disorder. Further analyses showed no statistically significant interaction between recent depression and past severity (OR = .90, CI = .25, 3.21, $p = .871$), suggesting an additive risk for child disorder (Figure 1, 16.0% if no recent depressive episode and no severe episode, 38.5% when both recent depressive episode and severe episode). Results were similar when only mothers were included in the analyses (supplementary Table 3).

Child-rated depression symptom scores:

In the multivariate analyses, a significant association was found for both predictors, suggesting that both presence of a severe depressive episode and recent parental depression independently predict child depression symptoms (Table 5). Again there was no significant interaction between severity and recent depression ($\beta = -.01$, CI = $-.33, .32$, $p = .967$), suggesting an additive risk also for child depression symptoms (see supplementary Figure 2). Results were similar when only mothers were included in the analyses (supplementary Table 3).

Discussion

Parental depression is one of the best established risk factors for offspring psychopathology with studies repeatedly showing higher rates of psychiatric disorder in the children of depressed parents compared with non-depressed controls (Beardslee, Versage, & Gladstone, 1998; Goodman & Gotlib, 1999; Weissman et al., 2006b). Consistent with this previous research, high rates of psychopathology were found in the children in this sample, with over a quarter meeting criteria for a DSM-IV psychiatric disorder at follow-up. This is more than double the rate reported in a recent UK epidemiological survey of children aged 11-15 years (Green, McGinnity, Meltzer, Ford, & Goodman, 2005) and confirms the expectation that offspring of depressed parents are a high risk group.

Within this high risk sample, features of parents' depression further indexed children's risk for psychopathology. Offspring whose parents had experienced a recent depressive episode reported significantly more child-rated depression symptoms and the odds of child psychiatric disorder were doubled (OR = 2.00, 30% vs.18%) relative to children who had not recently been exposed.

The direct evidence on the importance of recent parental depressive episodes as a risk indicator to children is consistent with other observational and treatment studies (Gunlicks & Weissman, 2008). Genetically informative studies suggest that the association between concurrent parent depression and child depression appears to have a strong environmental explanation along with some evidence of inherited liability (Harold et al., 2010; Silberg, Maes, & Eaves, 2010; Tully, Iacono, & McGue, 2008), and some but not all treatment studies have found reductions in overall levels of psychiatric

disorder (but not depression specifically) in children of mothers whose depression remits after treatment (Gunlicks & Weissman, 2008).

Although the study design does not allow a test of causality, it was possible to examine whether features of parent depression other than the presence of a recent episode were associated with higher offspring risk. All of the index parents in this sample had suffered from recurrent depression at baseline, however, those who experienced episode recurrence over the assessment period appear to have suffered from an overall worse course of affective illness (including a greater likelihood of having an early age of onset (≤ 20), longer episode duration, a greater likelihood of depression during pregnancy and postnatally, and a greater likelihood of having had severe episodes). It is therefore possible that recent parental depression is merely acting as a marker for greater clinical severity, and this could potentially provide a better explanation for the association with child psychopathology.

In this study, presence of a severe parental depressive episode was found to be associated with both child DSM-IV disorder and number of child-rated depression symptoms. However, when examined together, a recent episode of parent depression continued to predict both child disorder and child depression symptoms. Prior episode severity also continued to predict child depression symptoms and was marginally predictive of offspring DSM-IV disorder, suggesting that both these variables may be useful markers of risk in children. For children's depression symptoms, family history (number of 1st degree relatives with depression) was also significantly associated, and not confounded with recent parent depression, suggesting that it might be an additional useful indicator of risk for depression in children. These findings contrast with previous

studies that have found associations between early age of parental depression onset and offspring depression (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Weissman et al., 1984). This may be because there were insufficient numbers of parents with early age of onset to detect an association, or it is possible that age of onset may be a marker of risk for child depressive disorder specifically.

Consistent with the findings from the present study, the only other study to examine multiple features of parent depression (timing, chronicity and severity but not recent depression; (Hammen & Brennan, 2003) also found past depression severity in parents to be a significant predictor of childhood depressive disorders. Overall this study extends previous findings by suggesting that recent parental depression remains a significant predictor of both child depression symptoms and child DSM-IV psychiatric disorder when correlated features of parental depression such as severity are considered. Possible shared rater effects were also ruled out as associations with recent parental depression were confirmed using children's own reports of their depression symptoms.

The reasons for this increased risk in the offspring of depressed parents likely involve a complex interplay of genetic and environmental factors (Lau & Eley, 2010; Tully, Iacono, & McGue, 2008) and to date many mechanisms have been proposed to explain the cross-generational transmission of depression. These could include impaired parenting, difficult parent-child relationships, increased conflict, high levels of family stress, dysfunctional neuroregulatory mechanisms, and exposure to negative parental cognitions, behaviour and affect as well as a genetic predisposition

(Cummings, Keller, & Davies, 2005; Goodman & Gotlib, 1999; Herr, Hammen, & Brennan, 2007; Lovejoy, Graczyk, O'Hare, & Neuman, 2000).

Implications

It is well established that children of depressed parents are at risk for psychopathology (Weissman et al., 2006b). Findings from this study extend this by suggesting that certain features of parent depression, specifically recent episodes and more severe depression (including hospitalization and high levels of impairment) can be useful markers of risk in offspring. Although causal relationships could not be established here, identifying risk markers is also important. Clinicians should be vigilant of these in order to identify children who may warrant monitoring regarding the possibility of psychopathology and who might especially benefit from prevention and early intervention strategies.

Monitoring children who exhibit depression symptoms is crucial as they may be indicative of future problems, particularly when accompanied by psychosocial impairment (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Fergusson, Horwood, Ridder, & Beautrais, 2005; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Pickles et al., 2001; Pine, Cohen, Cohen, & Brook, 1999). Intervening at this stage could potentially prevent subthreshold symptoms from escalating into full depressive disorder, which is likely to have serious adverse consequences for future development.

Effective treatment of depression in parents remains a clinical priority because of the substantial associated suffering and morbidity. However, the results of this study suggest that recent parent depressive episodes may also index a more severe clinical

course. The implication of this is that simply treating current parent depression may not be sufficient to forestall the onset of depressive symptoms or psychiatric disorder in offspring.

Limitations

Several limitations of this study need to be noted; firstly many of the features of recurrent depression that were investigated (such as episode number, duration and timing) were reported retrospectively by the affected parent so there may have been inaccuracies. To minimise this, a life history calendar approach was adopted when generating the depression timeline whereby major events were included as a way of aiding recall. Also, lifetime suicidality in the parents was not assessed, which may be an additional indicator of depression severity.

Secondly, although child outcomes were assessed at 2 time points, these analyses focused only on outcomes measured at the follow-up assessment, thus the direction of association could not be established and possible child effects on parent depression symptoms cannot be ruled out. This approach was adopted to allow for recent parental depression to be defined over a longer time period than one month, since cross-sectionally, current parental depression (occurring over the previous month) was not found to be associated with child psychopathology. This might have been because the numbers of parents with current depression were too few to detect associations with child psychopathology. Alternatively, it is possible that the time frame used to define current parent depression might be too short for any associated risk to children to be detected. A final explanation is that current and recent parental

depression are simply risk markers for child psychopathology, with the latter serving as a better marker.

Thirdly, although rates of child psychiatric disorder are high compared to population norms, there was insufficient power to adequately investigate associations with individual psychiatric disorders. Limited power also prevented examination of potential differences according to child age and parent and child gender which previous research has suggested may be important moderators of risk in the intergenerational transmission of depression (Cortes, Fleming, Catalano, & Brown, 2006; Davies & Windle, 1997; Fergusson, Horwood, & Lynskey, 1995; Jenkins & Curwen, 2008; Lewis, Rice, Harold, Collishaw, & Thapar, 2011). It should also be noted that the children in this sample were aged 10-18 years at the time of assessment and so have yet to pass fully through the optimal age of risk for depression.

Finally, given that clinical features of depression such as timing, chronicity and severity are inextricably linked, this study was not able to fully disentangle the risk to children uniquely associated with recent parental depression. However, disaggregating these features is a considerable problem for the majority of study designs, and therefore, empirically establishing a causal relationship between specific clinical variants of parental depression and child outcomes is likely to prove extremely difficult. Additionally, it is also possible that there are other unmeasured and untested third variables which could be contributing to the association, including other co-occurring parental psychopathology (Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005).

Summary

This study extended previous research by investigating associations between recent parental depression and offspring psychopathology in a community sample of recurrently depressed parents. Other depression factors were also considered. Recent parental depression was found to be significantly associated with both child psychiatric disorder and child-rated depression symptoms. Prior severity of parent depression was also associated with child depression symptoms. Furthermore these associations were also found using child ratings of their own psychopathology. These indicators of risk might be helpful where treatment resources are limited and when prevention and early intervention strategies for offspring of recurrently depressed parents need to be targeted towards those at greatest risk.

Table 1. Parent and child clinical characteristics at follow-up^a

Parent depression characteristics (N=288)	Sample mean (SD) or % (N)
Depression during pregnancy with index child, % (N)	10.2 (27/264)
Postnatal depression with index (within 1 year), % (N)	42.4 (112/264)
Average episode duration (months), mean (SD)	16.6 (22.3)
4 or more depressive episodes, % (N)	38.4 (108/281)
Severe depressive episode: severe impairment (GAF<30) or hospitalised for depression, % (N)	27.9 (79/283)
Family history of depression - number of affected first degree relatives of the child, mean (SD)	1.5 (0.7)
1 family member, % (N)	59.4 (171)
2 family members, % (N)	30.9 (89)
3 or more family members, % (N)	9.6 (28)
Early age of depression onset, ≤ 20 , % (N)	27.0 (76/282)
Recent episode of depression, % (N)	57.8 (166/287)
DSM-IV depression at baseline, % (N)	22.0 (63/287)
DSM-IV depression at follow-up, % (N)	18.2 (52/285)
Depressive episode in between assessments, % (N)	55.1 (158/287)
Child diagnoses at follow-up^b	% (N)
Any child DSM-IV disorder (not including specific phobias)	27.9 (80)
Depressive disorders	7.7 (22)
Anxiety Disorders	13.2 (38)
Disruptive behaviour disorders	10.1 (29)
ADHD	6.6 (19)
Other disorders	3.1 (9)
Specific Phobias	7.3 (21)

^a Numbers vary due to missing data

^b Depressive disorders includes Major Depressive Disorder, Dysthymia and Depression not otherwise specified; Anxiety disorders includes Generalised Anxiety Disorder, Separation Anxiety, Social Phobia, Panic Disorder, Agoraphobia, Obsessive Compulsive Disorder and Anxiety Disorder not otherwise specified; Disruptive Behaviour Disorders includes Oppositional Defiant Disorder, Conduct Disorder and Disruptive Behaviour not otherwise specified; Other disorders includes Bipolar Spectrum Disorders (3), Cyclothymia (2), Eating disorders (3) and Adjustment Disorders (1)

Table 2. Rates of child DSM-IV psychiatric disorder according to recent parental depression

DSM-IV Psychiatric Disorder ^a	Recent parental depressive episode, % (N)			
	Yes	No	OR (95% CI)	p value
Parent and child combined diagnosis	<i>N</i> =166	<i>N</i> =121		
Any DSM-IV disorder	30.3% (50)	18.2% (22)	2.00 (1.12, 3.56)	.019
Any Depressive disorder	9.1% (15)	5.8% (7)	1.58 (0.61, 4.05)	.345
Any Anxiety disorder	15.8% (26)	9.9% (12)	1.71 (0.82, 3.56)	.150
Any Disruptive disorder	13.3% (22)	5.8 % (7)	2.59 (1.06, 6.30)	.036

Analyses adjusted for child age, sex and their interaction measured at follow-up

^a *Any DSM-IV disorder include all assessed DSM-IV disorders apart from ADHD and specific phobias; depressive disorders includes major depressive disorder, dysthymia and depressive disorder not otherwise specified; anxiety disorders include generalised anxiety disorder, separation anxiety disorder, social phobia, panic disorder, agoraphobia, obsessional compulsive disorder and anxiety disorder not otherwise specified; disruptive behaviour disorders include oppositional defiant disorder, conduct disorder and disruptive behaviour disorder not otherwise specified*

Table 3. Association between clinical features of parental depression and child outcome

Parent depression characteristics ^a	Child disorder (parent and child combined ratings) % (N) or mean (SD)				Child-rated depression symptoms	
	Yes (N=72)	No (N=215)	OR (95% CI)	p value	β value (95% CI)	p value
Depression during pregnancy with index child, % (N)	11.9 (8)	9.7 (19)	1.25 (0.51, 3.10)	.509	-.037 (-.27, .20)	.754
Postnatal depression with index child (within 1 year), % (N)	47.8 (32)	40.8 (80)	1.52 (0.84, 2.75)	.163	.066 (-.08, .21)	.386
Average episode duration, mean (SD) months	18.6 (21.8)	15.9 (22.6)	1.01 (1.00, 1.02)	.218	-.001 (-.01, .00)	.411
4 or more episodes % (N)	42.9 (30)	36.7 (77)	1.41 (0.80, 2.47)	.236	.124 (-.02, .27)	.090
Severe depressive episode: severe impairment (GAF<30) or hospitalised for depression, % (N)	38.0 (27)	24.6 (52)	1.81 (1.01, 3.24)	.047	.193 (.04, .35)	.015
Family history of depression (number of 1 st degree family members), mean (SD)	1.6 (0.78)	1.5 (0.73)	1.17 (0.82, 1.66)	.400	.100 (.01, .19)	.038
Early age of depression onset, <20, % (N)	30.6 (22)	25.4 (53)	1.26 (0.69, 2.31)	.446	.089 (-.07, .25)	.271

Analyses adjusted for child age, sex and their interaction measured at follow-up

^a *Numbers vary due to missing data*

Table 4. Association between parental depression features and recent parental episode

Parent depression characteristics ^a	Recent episode of parental depression % (N) or Mean (SD)		p value
	Yes	No	
Depression during pregnancy with index child, % (N)	13.8 (23)	6.2 (7)	.047
Postnatal depression with index (within 1 year), % (N)	47.3 (79)	36.6 (41)	.077
Average episode duration (months), mean (SD)	20.0 (29.5)	12.4 (10.5)	.007
4 or more depressive episodes, % (N)	41.8 (74)	35.0 (42)	.238
Severe depressive episode by wave 2 (GAF<30, hospitalised or serious suicide attempt), % (N)	34.7 (59)	22.3 (27)	.022
Family history of depression - number of family members, mean (SD)	1.59 (.77)	1.46 (.68)	.142
Early age of depression onset, <20, % (N)	30.7 (55)	20.3 (24)	.047

^a Numbers vary due to missing data

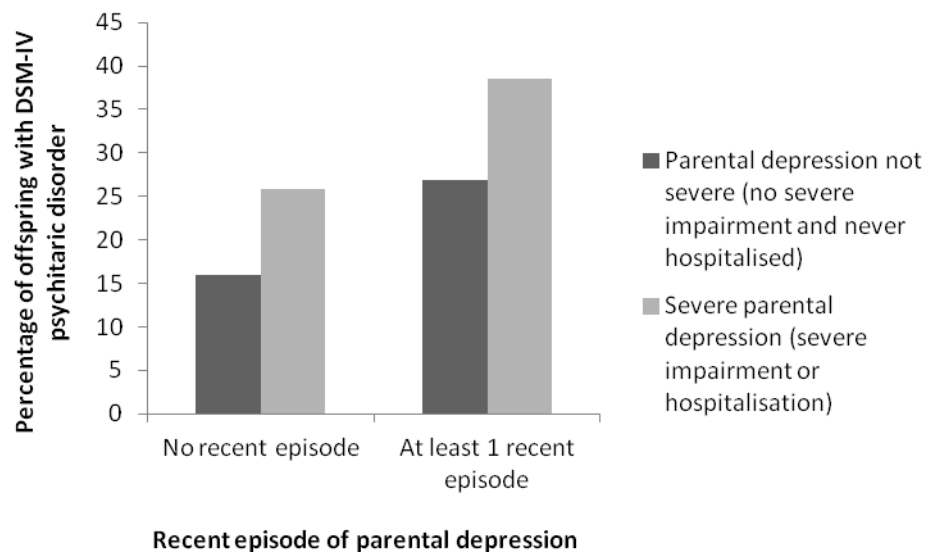
Analyses were conducted using Analysis of variance/chi-square

Table 5. Univariate and Multivariate analyses predicting child outcomes

DSM-IV Psychiatric Disorder <i>Parent and child combined reports</i>	Univariate Analyses			Multivariate Analyses		
	OR (95% CI)	p value	R²	OR (95% CI)	p value	R²
Recent parental depressive episode	2.00 (1.12, 3.56)	.019	.048	1.93 (1.07 3.47)	.029	.062
Severe depression history	1.81 (1.01, 3.24)	.047	.045	1.67 (.92, 3.02)	.092	
Depression symptom score <i>Child-rated</i>	β Value (95% CI)	p value	R²	β Value (95% CI)	p value	R²
Recent parental depressive episode	.168 (.03, .31)	.017	.088	.149 (.01, .29)	.036	.107
Severe depression history	.193 (.04, .35)	.015	.096	.169 (.01, .32)	.033	

Analyses adjusted for child age, sex and their interaction measured at follow-up

Figure 1. Percentage of children with a disorder according to both past episode severity and recent parental depression



Supplementary material

Supplementary Table 1. Univariate and Multivariate analyses predicting child DSM-IV psychiatric disorder (including diagnosis of ADHD)

DSM-IV Psychiatric Disorder <i>Parent and child combined reports</i>	Univariate Analyses			Multivariate Analyses		
	OR (95% CI)	<i>p</i> value	R ²	OR (95% CI)	<i>p</i> value	R ²
Recent parental depressive episode	1.99 (1.14, 3.47)	.015	.048	1.86 (1.06, 3.28)	.031	.061
Severe depression history	1.88 (1.06, 3.31)	.030	.045	1.73 (.97, 3.08)	.062	

Analyses adjusted for child age, sex and their interaction measured at follow-up

Supplementary Table 2. Description of child DSM-IV diagnosis at the baseline assessment

Child DSM-IV diagnoses at baseline (N=337)^a	% (N)
Any child DSM-IV disorder (not including specific phobias)	23.7 (80)
Depressive disorders	4.5 (15)
Anxiety disorders	11.6 (39)
Disruptive behaviour disorders	7.1 (24)
ADHD	6.2 (21)
Other disorders	1.2 (4)
Specific phobias	2.7 (9)

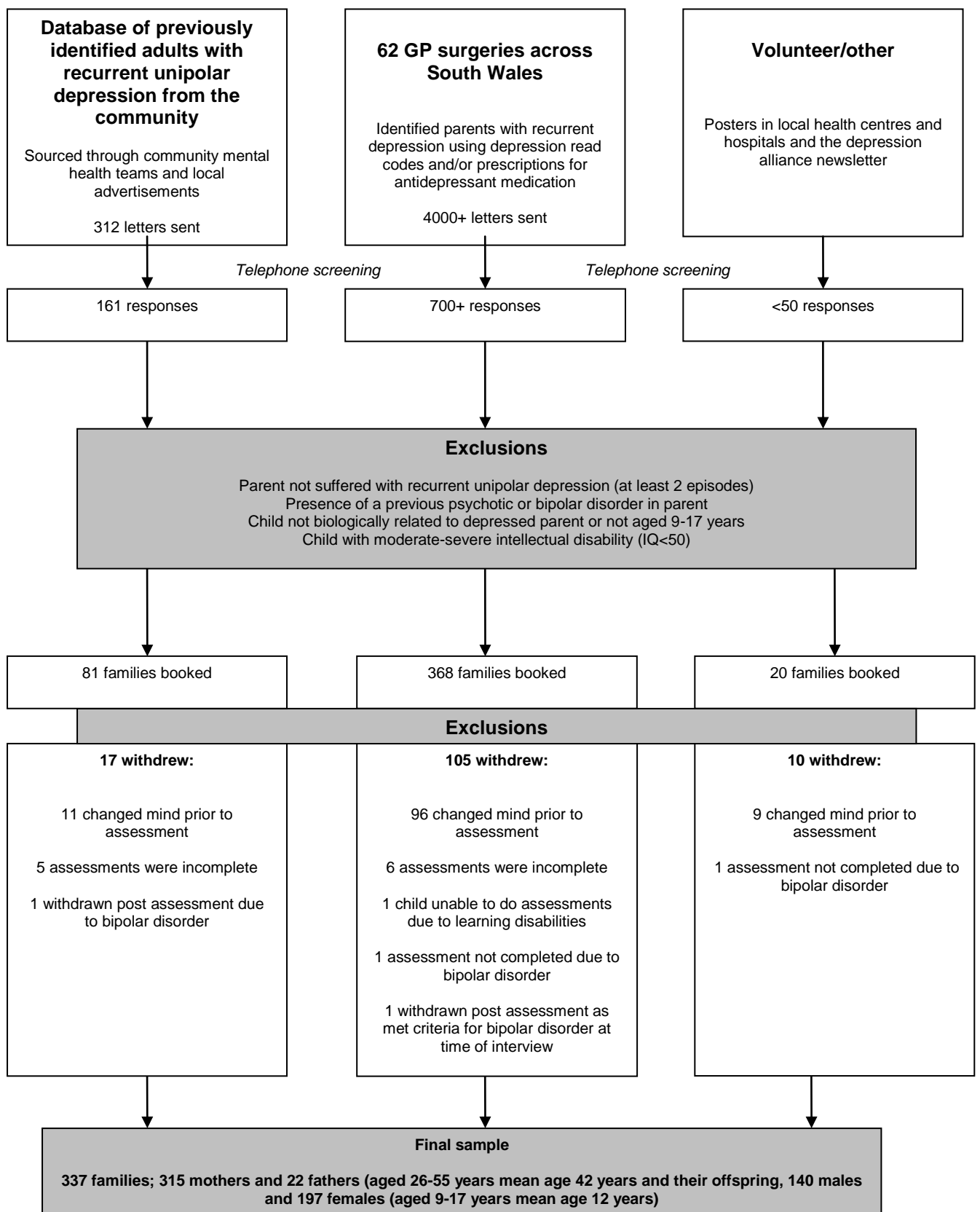
^a*Depressive disorders include major depressive disorder, dysthymia and depression not otherwise specified. Anxiety disorders include generalised anxiety disorder, separation anxiety, social phobia, panic disorder, agoraphobia, obsessional compulsive disorder and anxiety disorder not otherwise specified. Disruptive behaviour disorders include oppositional defiant disorder, conduct disorder and disruptive behaviour not otherwise specified. Other disorders include bipolar spectrum disorders (1), and eating disorders (3).*

Supplementary Table 3. Univariate and Multivariate analyses predicting child outcomes. Mothers only

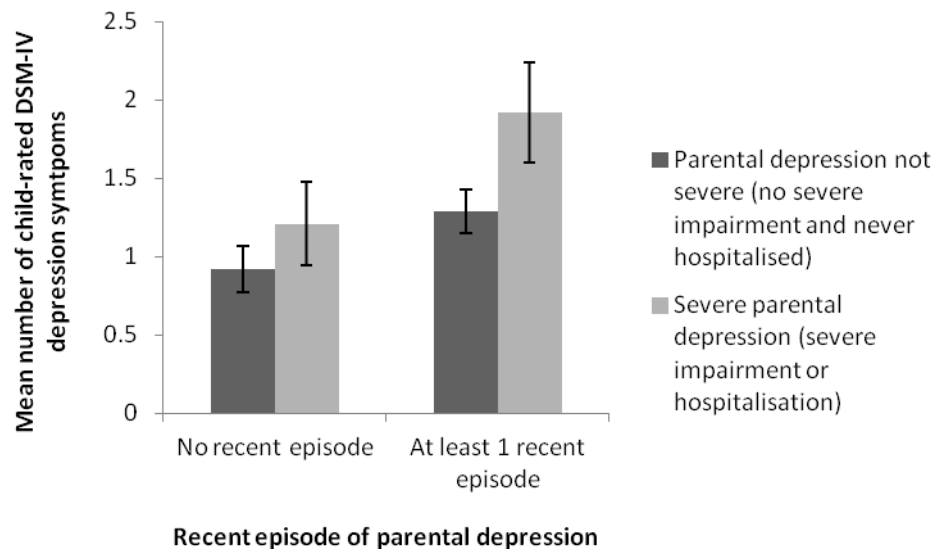
DSM-IV Psychiatric Disorder <i>Parent and child combined reports</i>	Univariate Analyses			Multivariate Analyses		
	OR (95% CI)	p value	R²	OR (95% CI)	p value	R²
Recent maternal depressive episode	1.98 (1.09, 3.60)	.025	.053	1.95 (1.06, 3.55)	.031	.063
Severe depression history	1.75 (.96, 3.19)	.068	.046	1.62 (.88, 2.99)	.120	
Depression symptom score <i>Child-rated</i>	β Value (95% CI)	p value	R²	β Value (95% CI)	p value	R²
Recent maternal depressive episode	.147 (.03, .32)	.016	.089	.132 (.01, .30)	.031	.100
Severe depression history	.143 (.03, .35)	.020	.088	.126 (.01, .33)	.040	

Analyses adjusted for child age, sex and their interaction measured at follow-up

Supplementary Figure 1. Recruitment chart



Supplementary Figure 2. Mean number of child-rated depression symptoms according to both past episode severity and recent parental depression



Chapter 4

Parent depression symptom course, impairment and risk of depression in adolescent offspring

Paper 2: Mars, B., Collishaw, S., Rice, F., Harold, G. T., Smith, D., Bevan Jones, R., Sellers, R., Potter, R., Craddock, N., Thapar, A. K., & Thapar, A. Parent depression symptom course, impairment, and risk of depression in adolescent offspring.

Manuscript was submitted for publication in August 2012 and is currently under review

This paper was written following completion of the second follow-up and is based on data from the full three waves of the study. For this paper, the child outcomes of interest were offspring mood disorder occurring throughout the study and number of DSM-IV depression symptoms at final follow-up.

Abstract

Background: Major depressive disorder (MDD) shows considerable heterogeneity in its course over time. Little is currently known about how variability in course relates to adult health and social impairment and offspring depression risk.

Methods: Data were drawn from the Early Prediction of Adolescent Depression study: a prospective longitudinal study of high-risk offspring of 337 parents with recurrent depression. Families were assessed on three occasions over four years. Seventy percent ($N = 233$) provided complete interview data at all time points. Hierarchical cluster analysis was used to identify distinct longitudinal parent depression symptom profiles. Adult health and social impairment and child depression outcomes were compared for these profiles using logistic and linear regression analyses. Adult health and social impairment were derived from the Euroqol and a measure of employment status. Child outcomes were assessed using the Child and Adolescent Psychiatric Assessment.

Results: Three symptom profiles were identified (chronic high, moderate, minimal) as well as an asymptomatic group. Adult symptom profiles were significantly associated with features of clinical severity (age of onset, past severity, treatment), parent health and social impairment and mood disorder onset and depression symptoms in their offspring.

Conclusions: Recurrent depressive disorders have a heterogeneous clinical course. Distinct depression symptom profiles in parents are related not only to their own health and social impairment, but also to depressive symptoms and disorder in

their children. Longitudinal assessments of depressive symptoms as an augmentation to diagnosis could help identify those most in need of prevention, and enhance management strategies for parent and offspring depression.

Introduction

Major depressive disorder (MDD) is a serious and increasing global health issue, resulting in substantial costs to individuals, families and society (Murray & Lopez, 1997; Thapar, Collishaw, Pine, & Thapar, 2012). Depression when its onset is in adolescence is especially problematic given high rates of recurrence into adulthood, challenges with treatment and associated impairments including suicidality (Thapar, Collishaw, Pine, & Thapar, 2012). Prevention of adolescent depression is therefore a priority, especially in high-risk populations (National Research Council & Institute of Medicine, 2009). Evidence from family and twin studies suggests that depression is a familial disorder (Rice, Harold, & Thapar, 2002; Sullivan, Neale, & Kendler, 2000) and one of the best established risk factors for depression in young people is having an affectively ill parent (Beardslee, Versage, & Gladstone, 1998).

Much of the research regarding the intergenerational transmission of depression has compared the rates of diagnoses in children of parents with and without MDD (Rice, Harold, & Thapar, 2002). However, depression is highly heterogeneous in its presentation and course and this may partly explain differences in child outcomes. The implications of variations in age of onset, severity and timing of parent depression on the risk of depression in their children have all received attention (Brennan et al., 2000; Halligan, Murray, Martins, & Cooper, 2007; Hammen & Brennan, 2003; Mars et al., 2012; Weissman et al., 1984). In addition, it is well established that the life course of adult depression is highly variable over time (Judd et al., 1998). When considered in terms of discrete episodes of major depressive disorder, depression typically follows an episodic and recurrent course. However, depression may also be considered dimensionally in terms of continuous variation in

symptom severity (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Pickles et al., 2001; Ruscio & Ruscio, 2000). The advantages of refining this continuous variation over time into patterns (“profiles”) has been highlighted (Muthen & Muthen, 2000) and the existence of distinct depression profiles, characterised by different levels of symptom severity over time are now being increasingly used (Nandi, Beard, & Galea, 2009). For example, in a sample of adults with unipolar depression drawn from the Netherlands Study of Depression and Anxiety, Rhebergen et al (2012) identified remitted, moderate, severe and decreasing depression profiles using retrospective reports of depressive symptoms over the previous 24 months. However, retrospective reports of depression severity are limited by mood-congruent reporter effects (Fergusson, Lynskey, & Horwood, 1993). Although there is some existing work examining the links between longitudinal depression profiles in parents and offspring outcomes, this existing work has either looked at general population samples (Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009), examined mental health outcomes in very young children (Ashman, Dawson, & Panagiotides, 2008), or has focused on normal variation in symptoms (Campbell, Morgan-Lopez, Cox, & McLoyd, 2009). No cross-generational longitudinal studies have examined the risk of clinical depression in the offspring of parents with a history of recurrent depressive disorder in relation to parent depression symptom profiles over time. This is likely to be particularly important in adolescence, given that this is a key risk period for the onset of depressive disorders (Thapar, Collishaw, Pine, & Thapar, 2012).

If distinct depression symptom profiles in adults with a history of recurrent depression can be identified, two important questions remain largely unaddressed. Firstly, are there meaningful differences between these different depression

symptom profiles in terms of other clinical features of depression and in terms of associated impairment? Second, what are the implications of these depression symptom profiles for risk of depression in offspring?

The present study utilised data from a longitudinal three-wave study of families where one parent had at least two episodes of MDD. The aims were:

1) To test whether it is possible to derive distinct groups of parents who differ in their depression symptom profiles over time.

2) To examine associations between symptom course and measures of adult impairment and clinical severity of depression.

3) To examine the relationship between longitudinal parent symptom profiles and risk for future depressive symptoms and depressive disorder in their adolescent offspring.

Methods

Sample

Data were drawn from the Early Prediction of Adolescent Depression study: a prospective longitudinal study of the high-risk offspring of recurrently depressed parents (Mars et al., 2012). Families were recruited predominantly from primary care practices across South Wales, UK (78%). Remaining families were recruited from a sample with previously identified unipolar depression (19%) and community volunteers (3%). Parents with a history of psychotic disorder or bipolar disorder or those who met DSM-IV criteria for mania/hypomania were excluded. There were no diagnostic exclusion criteria for the children in the study, although the participating child was required to have an IQ ≥ 50 .

The eligible baseline sample included 337 parents with recurrent unipolar depression (315 mothers and 22 fathers; age 26-55 years, mean 41.7 years) and their adolescent offspring (197 females and 140 males; age 9-17 years, mean 12.4 years). Parental history of recurrent unipolar depression was confirmed at interview (two or more lifetime MDD episodes).

Families were assessed at three time points between April 2007 and April 2011. The average time between the baseline assessment and first follow-up was 16.2 months (SD 2.69) and between the first and second follow-up was 12.5 months (SD 1.56). Two families were excluded at follow-up as the affected parent received a clinician diagnosis of bipolar affective disorder. Response rates were excellent, with over 90% of families providing interview or questionnaire data at each follow-up. The present study focuses on the 70% of eligible families ($N = 233$) with complete parent interview data at each of the three time points (94% of which also had complete child interview data). Families with missing data had higher baseline parent depression

scores $t(314) = -2.96, p = .003$, but there were no differences in terms of baseline child depression symptoms $t(331) = -1.45, p = .155$.

The Multi-Centre Research Ethics Committee for Wales reviewed and approved the study protocol. Written informed consent/assent was obtained from each participant at each of the three assessments. More detailed information about study recruitment, sample characteristics and assessment procedures has been reported elsewhere (Mars et al., 2012).

Assessments

Child mood disorder and depression symptom scores:

The Child and Adolescent Psychiatric Assessment (CAPA), parent and child versions (Angold & Costello, 2000) were used to assess two child outcomes in the three months prior to each assessment - i) the presence of child mood disorder during the study (major depressive disorder, dysthymia, depressive disorder not otherwise specified, adjustment disorder with depressed mood, bipolar spectrum disorders and cyclothymia) and ii) the total number of DSM-IV child depression symptoms reported at final follow-up.

Offspring mood disorder was considered present if DSM-IV criteria for a diagnosis were met according to either parent or child CAPA interview reports at any of the three time points of the study. All cases meeting criteria for diagnosis, together with all subthreshold cases, were reviewed by two child and adolescent psychiatrists (AT and RP).

For offspring depression symptoms, parent and child reports were combined at the symptom level to generate a total DSM-IV depression symptom count at the final follow-up (range 0-9). Mean imputation was used where there was one missing

value and the data were transformed using a natural log transformation to correct for positive skew.

Parent depression symptoms:

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) diagnostic interview was used at each assessment to assess the current number of parent DSM-IV depressive symptoms occurring over the previous month. Assessments and diagnoses were reviewed by an experienced adult psychiatrist (DS).

Parent depression - clinical history and associated impairment at follow-up:

The SCAN was used to assess presence of major depressive disorder occurring over the previous month. Age of depression onset and presence of a severe past depressive episode [defined as Global Assessment of Functioning score (American Psychiatric Association, 1994) less than 30 or hospitalisation for depression] were ascertained at baseline from a timeline of the parent's previous depressive episodes, generated using a life history calendar approach (Belli, 1998; Caspi et al., 1996). Information about current depression treatment (medication and psychotherapy) was obtained at each time-point.

A measure of health impairment was derived from the EuroQol 5D 3L questionnaire (The EuroQol Group, 1990). This asks about level of problems related to mobility, self care, usual activities, pain/discomfort and level of anxiety/depression. Response categories are "no difficulty", "some difficulty" and "a lot of difficulty" (scored as 0, 1 and 2 respectively). A crude "health impairment" score was derived from the totals with the anxiety/depression score omitted from the total score. The

parent's current employment status was ascertained by questionnaire report on each occasion and used as a measure of social impairment.

Family adversity:

The study also considers several potential confounding sociodemographic factors including household income (dichotomised according to median annual household income at baseline), family composition (two-parent vs. one-parent households), change in family composition (from a two-parent to a one-parent household) over the course of the study and the number of stressful family life events affecting both parent and child (e.g. death of a grandparent, N=41) occurring over the course of the study. This was assessed using a cumulative count of stressful family life events occurring between time 1 and time 2 and between time 2 and time 3 (maximum of 21 at each time point), derived from parent and child combined reports.

Statistical Analysis

Hierarchical cluster analysis was used to classify parents according to similarities in depression scores over the three time points of the study. Those parents who remained asymptomatic throughout the course of the study were selected as a comparison group (16.3% of sample, $N = 38$).

Cluster analysis is a person-centred approach used to identify sub-groups (or clusters) of individuals within a sample. Clusters are constructed according to differences/similarities between individuals so that there is a strong degree of association between individuals within each subgroup and weak association between individuals in different groups. The cluster analysis was conducted using

Ward's method with squared Euclidian distance as a measure of dissimilarity (Everitt, Landau, Leese, & Stahl, 2011). A three-cluster solution was selected based on the agglomeration schedule and visual inspection of the dendrogram. The analysis was then rerun accordingly to ensure allocation of each case to one of the three identified parent depression symptom profile groups. As shown in Figure 1, these reflected minimal, moderate and chronic high symptom courses.

Logistic and linear regression analyses tested associations between parent symptom course (coded 0 "asymptomatic", 1 "minimal", 2 "moderate", 3 "high") and measures of parental clinical severity and impairment and offspring mood disorder and depression symptom totals. Where significant associations were found, further analyses compared each of the three parent symptom profiles with the asymptomatic comparison group. Analyses controlled for baseline child age, sex and their interaction. Additional analyses also tested measures of shared family adversity as potential contributors to associations.

Results

All of the index parents in the sample had a history of recurrent depression confirmed at interview (at least two lifetime episodes of MDD). Of the 233 parents with complete information at each of the three study time points, 33.3% ($N = 77$) experienced an episode of DSM-IV depression over the course of the study (22.4%, $N = 52$ at time 1; 19.5%, $N = 45$ at time 2; and 17.2%, $N = 40$ at time 3).

Empirical derivation of parental symptom profiles

Cluster analysis identified three distinct parent depression symptom profiles in addition to the asymptomatic comparison group. The longitudinal depression symptom profiles are shown in Figure 1 and descriptive names were assigned as follows: “chronic high symptoms”, “moderate symptoms” and “minimal symptoms”. Each profile showed a distinct pattern of mean depression symptom scores although, interestingly, there appear to be no differences in the level of symptoms between the minimal symptom and moderate symptom profiles on the basis of cross-sectional time 3 data alone. All parents with a chronic high symptom profile experienced an episode of depression over the course of the study ($N = 32$), compared with 56% ($N = 34$) of parents with a moderate symptom profile, 11% ($N = 11$) with a minimal symptom profile and 0% ($N = 38$) in the asymptomatic group. Similar symptom profiles were also identified using an alternative measure of parental depression [the depression subscale of the Hospital Anxiety and Depression scale (Zigmond & Snaith, 1983), Supplementary Figure 1].

Parental symptom course and patterns of clinical severity and impairment

Parent symptom course was associated with features of illness severity and impairment (Table 1). Further analyses revealed that relative to the asymptomatic group of parents, the moderate and chronic symptom profiles were associated with a younger age of depression onset, higher rates of treatment and greater impairment in terms of quality of life and unemployment (Table 1, p all $<.05$). The group of parents with chronic high symptoms were also significantly more likely to have experienced an episode of severe depression. There were no significant differences between the minimal symptoms group and the asymptomatic group.

Relationship between parent depression group and child outcomes

Child mood disorder:

17.7% ($N = 41$) of children met criteria for mood disorder on at least one occasion (4.3% at baseline, 10.0% at time 2 and 9.4% at time 3). Overall, baseline parental diagnosis of DSM-IV MDD was significantly associated with offspring mood disorder (31.4% vs. 13.3%; OR = 2.80, CI = 1.33, 5.90, $p = .007$). Figure 2 shows the percentage of children meeting criteria for mood disorder during the course of the study for each of the four parent symptoms profiles, indicating a stepped increase in prevalence across these groups. Logistic regression analysis, where parent group was coded using an ordinal scale, revealed a significant effect of parent symptom course on child mood disorder (OR = 1.85, CI = 1.25, 2.75, $p = .002$). As shown in Table 2, significantly more children of parents with chronic high symptoms experienced mood disorder than children of parents in the asymptomatic group (35.5% vs. 5.3%; OR = 9.33, CI = 1.85, 47.13, $p = .007$). Although the pattern of effects was in the expected direction, differences between children in the

asymptomatic group and either the minimal (15.0% vs. 5.3%; OR = 3.03, CI = .65, 14.14, $p = .158$) or moderate symptoms groups of parents (20.6% vs. 5.3%; OR = 4.26, CI = .89, 20.34, $p = .069$) did not achieve conventional levels of statistical significance.

Child depression symptoms:

Figure 3 shows the mean number of child depression symptoms reported at the final follow-up for each of the four parent symptom profiles. Linear regression analysis revealed a significant association between parent symptom course and child depression symptoms at final follow-up ($\beta = .20$, $B = .14$, CI = .06, .23, $p = .002$). As shown in Table 2, the number of child depression symptoms was significantly higher in each of the three parent symptom profile groups than in the asymptomatic parent group.

Additional analyses tested the extent to which cross-generational associations might be explained by recent experience of adversity shared between parent and child (supplementary Table 1). There were no significant associations between parent symptom course and family composition at baseline (OR = .80 CI = .58, 1.09, $p = .150$) nor change in family composition (OR = 1.32, CI = .89, 1.96, $p = .163$). Parent symptom profile was, however, significantly associated with household income (OR = .53, CI = .38, .72, $p < .001$) and the number of stressful shared life events occurring over the study ($\beta = .14$, $B = .42$, CI = .02, .81, $p = .039$). Annual household income was significantly more likely to be below the median (<£30,000) in each of the three parent symptom profile groups than in the group of parents who

were asymptomatic. There were no significant differences in the number of life events between the three profiles and the asymptomatic group.

Further multivariate analyses adjusting for household income and shared life events revealed a similar pattern of results between parent symptom course and both child mood disorder (OR = 1.63, CI = 1.04, 2.54, $p = .034$) and depression symptoms at follow-up ($\beta = .15$, B = .11, CI = .01, .21, $p = .026$).

Discussion

In this study of parents with recurrent depressive disorder (at least two episodes of MDD), using cluster analysis, substantial longitudinal heterogeneity was found and distinct depression symptom profiles were identified. Three profiles were identified in addition to an asymptomatic group: “chronic high” (14% of individuals), “moderate” (27% of individuals) and “minimal” (43% of individuals). Parents’ depression symptom profiles were associated with their own health and social impairment and with risk of mood disorder and depression symptoms in their children.

Several other studies have examined the heterogeneity of adult depression over time, although not necessarily those with recurrent depression, by using a longitudinal profile based approach (Ashman, Dawson, & Panagiotides, 2008; Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009; Nandi, Beard, & Galea, 2009; Rhebergen et al., 2012; Skipstein, Janson, Stoolmiller, & Mathiesen, 2010) and findings are broadly similar, despite differences in sample characteristics and design. Using a seven year follow-up of a clinical sample of depressed mothers, Ashman et al (2008) also identified three distinct courses of depression; chronic high, stable mild and a group whose depression symptoms decreased to moderate level. Mothers who did not experience depression symptoms were removed from their analysis and so, unlike the present study, they did not also have an asymptomatic group. Rhebergen et al (2012) identified five distinct depression profiles (remitted, chronic high, moderate group and two classes characterised by decreasing symptoms). The decreasing profiles were not identified in this sample, but this may have been because the participants in Rhebergen et al’s study were required to have a MDD/dysthymia episode within the

preceding six months and to be experiencing symptoms in the month prior to baseline. Findings from this study are also in line with those from population-based studies (Campbell, Morgan-Lopez, Cox, & McLoyd, 2009; Skipstein, Janson, Stoolmiller, & Mathiesen, 2010). All of these studies highlight that the course of depression is highly heterogeneous. This study suggests that even those with a history of recurrent MDD show substantial heterogeneity that would not ordinarily be captured by conventional assessments.

The parent longitudinal symptom profiles that were derived show validity, as parent symptom course was found to be associated with other measures of past clinical severity, including age of depression onset, severe depression and treatment for depression. More than two-thirds of parents in each of the three profile groups received medication during the study course. This suggests that depression symptoms can persist over time despite continuing treatment of the depression. Associations between more severe illness course and earlier age of onset also highlight the importance of early detection and intervention of depression, especially in those with a younger age of onset.

This study extends previous research by investigating parent health and social impairment. Parents in the moderate and the chronic high groups reported higher levels of health impairment than parents in the asymptomatic group and were more likely to be unemployed. These findings are consistent with earlier work that has highlighted the importance of sub-syndromal depression as a predictor of not only major depressive disorder, but also psychosocial disability (Judd & Akiskal, 2000; Judd et al., 1998).

Whilst many studies have documented an association between parental and offspring depression (Beardslee, Versage, & Gladstone, 1998; Mars et al., 2012;

Weissman et al., 2006b), there are few longitudinal studies which have examined parental depression course in relation to cross-generational risk. In this study, parent symptom course was significantly associated with both mood disorder and elevated depression symptoms in their high-risk offspring. Although all parents in the sample had a history of recurrent depression, only a small proportion of parents experienced depression symptoms that remained consistently high. Rates of child mood disorder were particularly elevated in this subgroup.

Parental depression course was also associated with future offspring depression symptoms. The number of offspring DSM-IV depression symptoms at the final wave of assessment was significantly higher in each of the three profile groups than in the asymptomatic comparison group, suggesting that even minimal symptoms in parents that persist over time are associated with increased offspring depression symptoms. It is also important to note that low levels of continuing parent symptoms were associated with increased offspring depression risk, even though there were no differences on measures of parental impairment and depression severity between the asymptomatic and minimal groups. These findings highlight the importance of monitoring dimensional levels of depression symptoms in parents over time, in addition to assessing diagnoses and suggest that for parents with any level of persisting depression symptomatology, clinicians should consider the possibility of depression in their offspring.

Results appear consistent with previous reports from different types of population samples. For example, Hammen and Brennan (2003) found brief exposure to severe maternal depression had deleterious effects on offspring mood, whereas longer exposure to milder maternal symptoms was required for negative effects on child mood to emerge. Similar to the findings from the present study,

Campbell et al (2009) found that chronic maternal depression symptoms occurring at varying levels of severity were associated with greater internalising symptoms, depression symptoms and loneliness scores in their adolescent children, compared to offspring of never-depressed mothers. This study provides an important extension to these previous findings by showing that variation in parental symptom course predicts offspring depression symptoms and depressive disorder in a high-risk clinical sample of parents with recurrent depressive disorder, a form of MDD that might be considered especially homogeneous yet still shows substantial heterogeneity.

Parent symptom profile was associated with multiple measures of parent impairment and some indicators of socio-economic position and adversity. Thus, there is a gradient of symptom and impairment severity which also co-occurs with markers of social adversity. Although it is not possible or necessarily appropriate to include all possible covariates (particularly as some may be unknown or unmeasured), it is important to observe that the associations between parent symptom course and child mood symptoms and disorder found in this study were not solely attributable to measures of social adversity.

Strengths and limitations

Using a longitudinal design allowed parent depression symptom profiles to be generated and enabled us to examine the effect of different parental depression symptom profiles in relation to outcomes in the parents and their high-risk offspring. Such studies are rare, especially in high-risk samples, which are helpful when the outcomes (adolescent-onset mood disorder) are relatively rare in the general population. The advantages of using longitudinal profile assessments over single

time-point assessments have been highlighted (Muthen & Muthen, 2000), as has the importance of chronic versus non-chronic depression (Klein, Shankman, & Rose, 2006). Given the high prevalence of depression symptoms at any single point in time (Kessler, Avenevoli, & Merikangas, 2001; Kessler et al., 2003), this is potentially a powerful method of studying effects of different levels of persisting symptoms and capturing some aspects of depression heterogeneity. This study also comprehensively assessed families on three occasions over four years using multiple informants and assessments of parent and child depression derived from diagnostic interview.

However, results must also be interpreted in light of several possible limitations. First, the number of children in the sample with mood disorder was still small and this reduced power to detect significant differences in risk for offspring MDD between the parent profile groups. However, to date, this is the largest longitudinal family study of offspring of parents with recurrent depressive disorder and diagnoses were established rigorously. Second, the study was unable to determine the direction of effects underlying intergenerational associations. It is possible that depression symptoms in children may exacerbate problems in their parents. Third, the majority of parents in the sample were mothers recruited from primary care and caution is required in generalising findings to children of depressed fathers or to community samples. Fourth, the analysis is based on data at three time points with little information about symptoms in-between assessments and this may affect the depression profiles generated. Finally, as not all of the children in the sample had passed through the peak risk period for the onset of depression by the final assessment, it is likely that some children may go on to develop disorder in the future. This may be particularly relevant for children of parents experiencing

continuing minimal symptoms, as it is possible that continued exposure over longer periods of time may be required for associations with child mood disorder to emerge.

Summary and implications

Recurrent depression is a heterogeneous disorder in terms of long-term clinical course and it may be helpful clinically to capture some aspects of this heterogeneity by identifying sub-groups based on longitudinal patterns of symptoms. Findings from this study have shown that, within a sample of parents with a history of recurrent depression, multiple distinct depression profiles can be identified and that these depression profiles not only predict parental health and social impairment, but also predict depression symptoms and disorder in their children. These differences in parental symptom course are associated with other markers of social and economic adversity, but this does not account for the association with child mood disorder or symptoms.

These findings highlight the need to follow up and monitor depression symptoms in parents with recurrent depression and, for those with any level of persisting symptoms, ensure that the possibility of depression in their children is also considered. This may be particularly important when parents report chronically high levels of depression symptoms. Sub-grouping recurrent depression in this way could also help with the development of new treatment approaches for both adult and adolescent depression. For example, it may be that parents with chronic high symptoms of depression will require a much more intensive family-based intervention in order to address both parental and offspring depressive symptoms and improve long-term functioning. More research is needed on the potential utility of longitudinal dimensional assessments of depression as an augmentation to

diagnosis in order to help with prevention and management strategies for both parent and offspring disorder.

Table 1. Differences in features of clinical severity and impairment according to parent symptom profile

	OR or β, B (95% CI)	p value	Asymptomatic	Minimal	Moderate	Chronic high	Comparisons with asymptomatic parent group
			a	b	c	d	
Impairment/quality of life							
Euroqol (minus depression item), baseline, mean (SD)	.50, .78 (.60, .96)	<.001	0.3 (0.6)	0.7 (1.0)	1.3 (1.5)	2.8 (1.7)	c, d >a
Euroqol (minus depression item), time 2, mean (SD)	.50, .82 (.63, 1.02)	<.001	0.4 (0.7)	0.7 (1.0)	1.4 (1.4)	3.0 (2.0)	c, d >a
Euroqol (minus depression item), time 3, mean (SD)	.47, .77 (.58, .96)	<.001	0.5 (0.9)	0.7 (1.1)	1.3 (1.3)	2.9 (2.0)	c, d >a
Unemployment							
Unemployment of index parent, baseline, % (N)	2.47 (1.66, 3.69)	<.001	5.4 (2)	12.1 (12)	22.6 (14)	46.9 (15)	c, d >a
Unemployment of index parent, time 2, % (N)	2.56 (1.72, 3.80)	<.001	5.6 (2)	16.5 (15)	25.9 (15)	57.1 (16)	c, d >a
Unemployment of index parent, time 3, % (N)	1.99 (1.39, 2.84)	<.001	10.8 (4)	18.2 (18)	26.7 (16)	50.0 (15)	d >a
Parent depression features							
Age of depression onset, years, mean (SD)	-.27, -2.50 (-3.69, 1.30)	<.001	29.7 (8.0)	27.1 (8.0)	24.4 (8.7)	22.2 (9.3)	c, d <a
Severe depression (GAF <30 or hospitalisation), % (N)	1.75 (1.26, 2.43)	.001	15.8 (6)	23.5 (23)	29.0 (18)	53.1 (17)	d >a
Treatment							
Medication taken during study, % (N)	1.78 (1.26, 2.51)	.001	55.3 (21)	69.0 (69)	76.2 (48)	90.6 (29)	c, d >a
Psychological treatment during study, % (N)	2.75 (1.88, 4.02)	<.001	7.9 (3)	14.0 (14)	30.2 (19)	59.4 (19)	c, d >a

OR refers to odds ratio; β refers to the standardised coefficient; B refers to the un-standardised coefficient; 95% CI refers to 95% confidence intervals

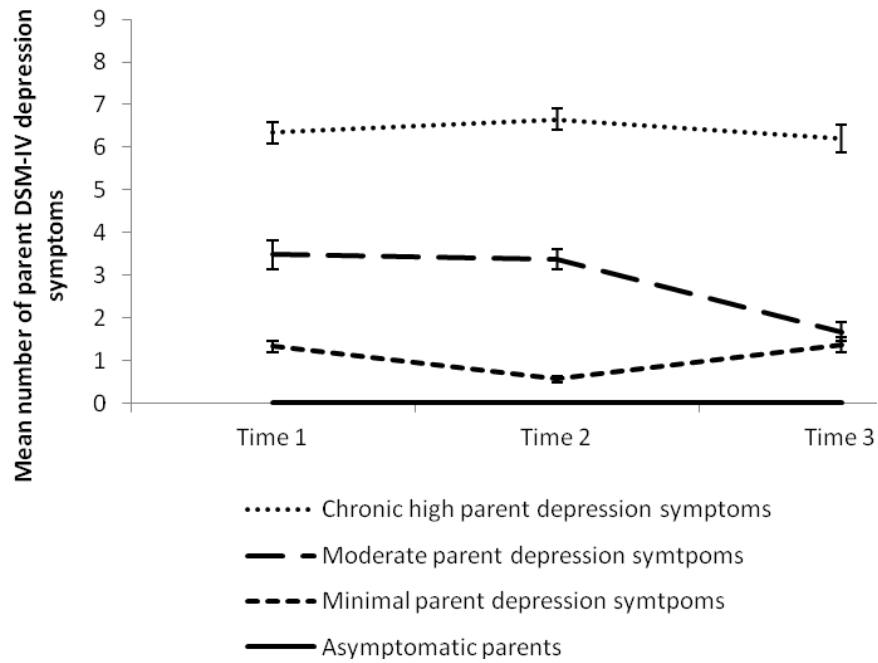
Table 2. Comparisons between parent symptom profiles and asymptomatic parent group for child mood disorder and depression symptoms

	Child mood disorder at any time point			Child depression symptoms at time 3	
	% with mood disorder	OR (95% CI)	<i>p</i> value	β , B (95% CI)	<i>p</i> value
Asymptomatic 16% (<i>N</i> =38) (reference category)	5.3 (<i>N</i> =2)	-	-	-	-
Minimal symptoms 43% (<i>N</i> =100)	15.0 (<i>N</i> =15)	3.03 (.65,14.14)	.158	.20, .26 (.03, .50)	.030
Moderate symptoms 27% (<i>N</i> =63)	20.6 (<i>N</i> =13)	4.26 (.89, 20.34)	.069	.23, .34 (.09, .60)	.009
Chronic high symptoms 14% (<i>N</i> =32)	35.5 (<i>N</i> =11)	9.33 (1.85, 47.13)	.007	.25, .48 (.18, .78)	.002

Analysis controlled for child age, sex and their interaction at baseline

OR refers to odds ratio; β refers to the standardised coefficient; B refers to the un-standardised coefficient; 95% CI refers to 95% confidence interval

Figure 1. Mean number of parent DSM-IV depression symptoms at each time point according to parent symptom profile



Error bars refer to standard error of the mean

Figure 2. Rates of child mood disorder during the study according to parent symptom profile

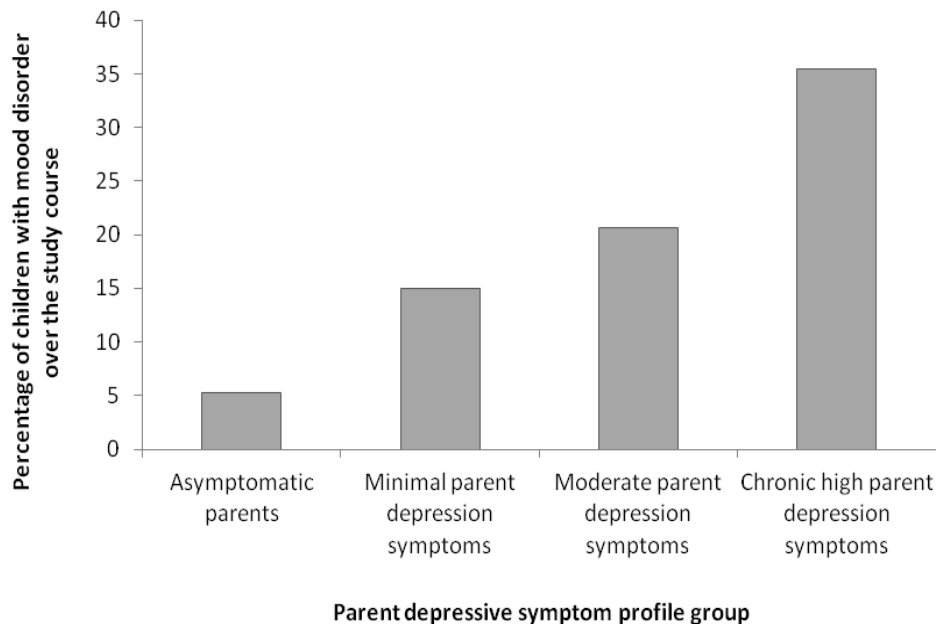
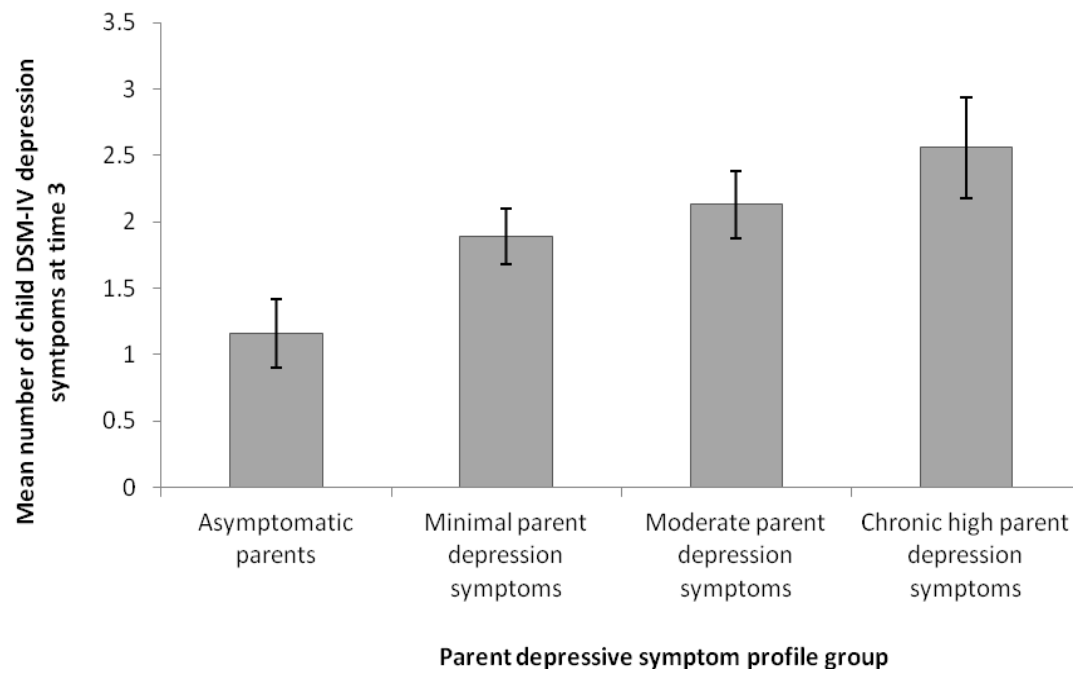


Figure 3. Mean number of child DSM-IV depression symptoms at time 3 according to parent symptom profile



Error bars refer to standard error of the mean

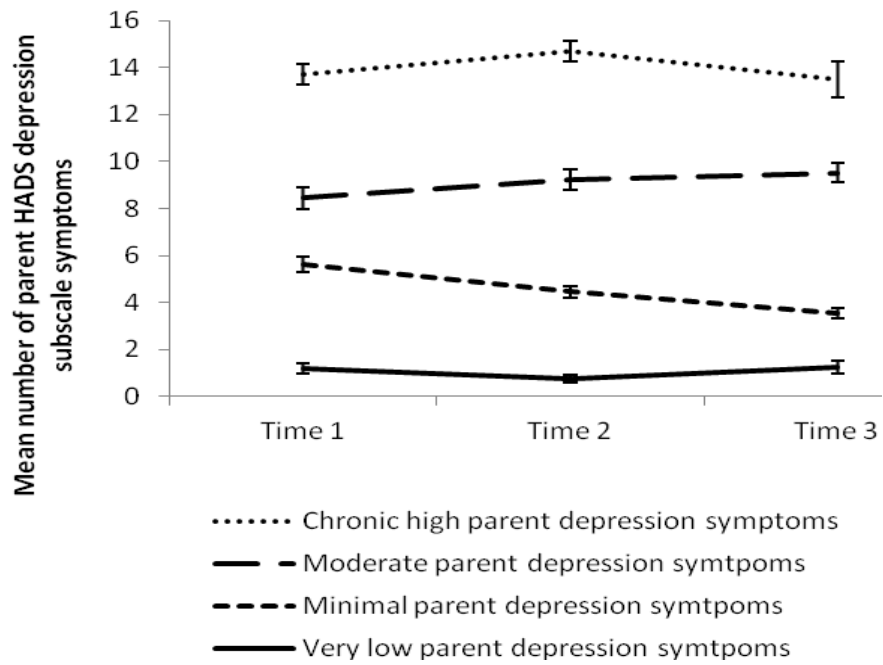
Supplementary material

Supplementary Table 1. Differences in treatment and sociodemographic risk factors according to parent symptom profile

	OR or β , B (95% CI)	<i>p</i> value	Asymptomatic a	Minimal b	Moderate c	Chronic high d	Comparisons with asymptomatic parent group
Sociodemographic risk factors							
Annual household income below median (<30.000), % (n)	.53 (.38, .72)	<.001	25.0 (9)	48.5 (48)	55.0 (33)	76.7 (23)	b, c, d >a
Two parent family at baseline, % (n)	.80 (.58, 1.09)	.150	86.8 (33)	69.7 (69)	66.7 (42)	71.9 (23)	-
Change to 1 parent family, % (n)	1.32 (.89, 1.96)	.163	16.1 (5)	23.9 (16)	19.5 (8)	38.1 (8)	-
Shared life events, mean (SD)	.14, .42 (.02, .81)	.039	2.8 (2.0)	2.9 (2.7)	3.7 (2.8)	3.8 (2.8)	b, c, d not significantly different to a

OR refers to odds ratio; β refers to the standardised coefficient; B refers to the un-standardised coefficient; 95% CI refers to 95% confidence intervals

Supplementary Figure 1. Mean number of parent HADS depression subscale symptoms at each time point according to parent symptom profile



Error bars refer to standard error of the mean; HADS: hospital anxiety and depression scale

Chapter 5

Specific parental depression symptoms as risk markers for new-onset depression in high-risk offspring

Paper 3: Mars, B., Harold, G. T., Elam, K. K., Sellers, R., Owen, M. J., Craddock, N., Thapar, A. K., Rice, F., Collishaw, S., & Thapar, A. Specific parental depression symptoms as risk markers for new-onset depression in high-risk offspring.

Manuscript was submitted for publication in September 2012 and is currently under second review

This paper is based on data from the full three waves of the study. For this paper, the child outcomes of interest were new-onset offspring mood disorder and number of DSM-IV depression symptoms at final follow-up.

Abstract

Objective: To disaggregate the depression construct and investigate whether specific depression symptoms in parents with a history of recurrent depression are clinical risk markers for future depression in their high-risk offspring. The hypothesis was that parent symptoms of the type that might impact on the child would likely be most important.

Methods: Data were drawn from a longitudinal high-risk study. Families were mainly recruited from primary care and included 337 parents with recurrent unipolar depression and their offspring (aged <18 years). Three assessments were conducted between April 2007 and April 2011. Ninety-one percent of families ($N = 305$) provided full interview data at baseline and at least one follow-up of which 291 were included in the primary analysis. The main outcome measure was new-onset child DSM-IV mood disorder which was assessed using the Child and Adolescent Psychiatric Assessment.

Results: Of the 9 DSM-IV depression symptoms, parent appetite/weight change, specifically loss of appetite/weight loss most strongly predicted new-onset child mood disorder (OR = 4.47, CI = 2.04, 9.79, $p < .001$) and future child depression symptoms. The cross-generational association was not accounted for by measures of parent depression severity (total depression symptom score, episode recurrence, age of onset, past impairment/hospitalisation) or other potential confounds (parent physical health, eating disorder, or medication).

Conclusions: Findings from this study suggest appetite/weight loss in parents with a history of recurrent depression is a marker of risk for depression in their offspring. The findings highlight the importance of examining depression heterogeneity. The biological and environmental mechanisms underlying this finding require investigation.

Introduction

Parental depression is one of the best established risk factors for depression in young people (Thapar, Collishaw, Pine, & Thapar, 2012). Family studies have typically examined offspring risk according to parental depression diagnosis or total symptom scores. However, depression shows substantial heterogeneity in its presentation. Although research has examined whether age of onset, chronicity and severity differentially predict risk of illness in offspring (Brennan et al., 2000; Hammen & Brennan, 2003; Mars et al., 2012; Weissman et al., 1984), studies investigating specific parental depression symptoms are rare.

Within-generation twin studies of adult and juvenile depression have shown that some depressive symptoms are more heritable than others. There has been evidence suggesting that vegetative symptoms or those that reflect physiological functions such as loss of appetite show the greatest heritability (Jang, Livesley, Taylor, Stein, & Moon, 2004; Kendler, Neale, Kessler, Heath, & Eaves, 1992). Specific depression symptoms have also been shown to influence overall familial liability to disorder. Leckman et al (1984) found that rates of major depressive disorder (MDD) were doubled amongst first degree relatives of depressed probands who reported symptoms of appetite disturbance and excessive guilt compared with relatives of depressed individuals lacking these symptoms. To date however, no study has explicitly examined whether there are differences in risk for offspring depression associated with specific depression symptoms in parents.

Although twin and family studies of adult depression suggest that the vegetative symptoms of depression are especially heritable, genetically informative cross-generational designs highlight the importance of non-inherited environmental risk factors in the inter-generational transmission of depression (Harold et al., 2010;

Lewis, Rice, Harold, Collishaw, & Thapar, 2011; Silberg, Maes, & Eaves, 2010; Tully, Iacono, & McGue, 2008). Depressive symptoms that impact on quality of relationships, such as loss of interest could be thought to contribute to the development of depression via environmentally mediated effects, although this has not been tested. A greater understanding of the risk associated with individual parental depression symptoms may help elucidate the mechanisms of intergenerational transmission which at present are not well understood (Stein, Ramchandani, & Murray, 2008; Thapar, Collishaw, Pine, & Thapar, 2012). Such an approach could also give clues as to intervention/prevention targets in this high-risk group of children (Stein, Ramchandani, & Murray, 2008). This is an important goal given the severe long-term morbidity associated with depression in young people (Beardslee, Gladstone, & O'Connor, 2011; Garber et al., 2009; Weissman et al., 1999a). For example, if loss of interest and disengagement of the parent from her/his child were found to be risk factors, this might suggest intervention efforts could be usefully directed at the quality of parent-child engagement.

This study utilises data from a longitudinal study of the offspring of recurrently depressed parents (Mars et al., 2012). The aim was to investigate whether particular depression symptoms in parents are clinical risk markers of future depression in their offspring. It was hypothesised that parent depression symptoms of the type that might impact on the child, for example loss of interest, would likely be most important.

Methods

Sample

The 'Early Prediction of Adolescent Depression' study is a prospective high-risk study of the offspring of recurrently depressed parents (Mars et al., 2012). Families were recruited predominantly from primary care (78%) and included 337 parents with a clinical history of recurrent unipolar depression (at least 2 depressive episodes confirmed at interview; 315 mothers and 22 fathers, age 26-55 years, $M = 41.7$ years, $SD = 5.5$) and their offspring (197 females and 140 males; age 9-17 years, $M = 12.4$ years, $SD = 2.0$). Detailed information about sample recruitment and inclusion/exclusion criteria are included in Figure 1 and have been previously described (Mars et al., 2012). Assessments of parents and children were conducted at three time points (T1, T2, T3). The average time between assessments was 16 months ($SD = 2.69$) and 13 months ($SD = 1.56$) respectively. Ninety-one percent ($N = 305$) of families provided full interview data at baseline and at least one follow-up assessment. Families with interview data at follow-up did not differ from those who participated only at baseline with regard to parent or child baseline depression symptoms. Ethical approval was obtained from the Multi-centre Research Ethics Committee for Wales. Parents provided written consent and their children assent at each assessment.

Assessments

Child diagnosis and depression scores

The Child and Adolescent Psychiatric Assessment parent and child versions (Angold & Costello, 2000) were used to assess child DSM-IV mood disorder (major depressive disorder, dysthymia, depressive disorder not otherwise specified, bipolar

disorder, cyclothymia, or adjustment disorder with depressed mood) and number of DSM-IV child depression symptoms (maximum nine) at each assessment. Child mood disorders were considered to be present if a diagnosis was made based on either the parent or child interview (Angold & Costello, 1995). All diagnoses and sub-threshold cases were reviewed by two child psychiatrists. The main outcome measure was new-onset child mood disorder at either T2 or T3. For these analysis, to ensure assessed parent symptoms preceded child disorder, the small number of children with a baseline diagnosis of mood disorder ($N = 14/305$) were removed, leaving a final sample of 291 families.

Parent and child reports were also used to produce a total symptom count. Child depression symptom scores at the final assessment was the secondary outcome measure. Mean imputation was used to generate symptom counts where there was one missing value. To address positive skew, symptom counts were transformed using a natural log transformation.

Parent depression symptoms

The Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990), a semi-structured clinical interview was used to assess DSM-IV parental depression symptoms and MDD diagnosis occurring over the previous month at each assessment. Symptoms were considered present only if they were of moderate or severe intensity (SCAN rating >1). All parents had experienced at least two episodes of depression. Twenty-three percent ($N = 68/291$) of parents met criteria for a depressive episode at the time of the baseline assessment. Fifty-eight percent ($N = 120$) of parents not meeting criteria for MDD at interview reported at least one depressive symptom during the preceding month. Each of the nine DSM-IV criteria

for MDD at baseline were tested as independent variables. Specific symptoms were endorsed by between 8% (retardation, $N = 23/291$) and 45% (sleep, $N = 122/270$) of parents.

Parent depression features

Information about prior depressive episodes was obtained retrospectively at baseline using a life history calendar approach (Belli, 1998; Caspi et al., 1996). This confirmed parental history of recurrent depression and provided information about age of depression onset, impairment during the worst two episodes (using the Global Assessment of Functioning scale (American Psychiatric Association, 1994)) and any periods of hospitalisation for depression. This approach was also used at T2 and T3 to assess any depressive episodes that occurred between assessments.

Further recurrence of parental depression over the course of the study:

Depression recurrence was defined as a new episode of depression during the study period. This included parents who met DSM-IV diagnostic criteria for depression using the SCAN at either follow-up interview or in-between the assessments. Sixty-five percent of parents ($N = 190/291$) experienced episode recurrence.

History of severe impairing depression:

In accordance with previous research (Hammen & Brennan, 2003; Mars et al., 2012), a severe depressive episode was defined as an episode that involved severe impairment (Global Assessment of Functioning score ≤ 30) or hospitalisation

due to depression. Twenty-seven percent of parents had experienced a severe depressive episode by the baseline assessments ($N = 78/291$).

Age of depression onset:

The mean age of depression onset in the parent sample was 26 years ($SD = 8.3$, range 7-48 years).

Statistical Analysis

Logistic regression analyses tested associations between specific parental depression symptoms at baseline and new-onset child mood disorder. Primary analyses were conducted with baseline parent symptoms so they preceded offspring mood disorder. Symptoms that were significantly associated were then examined using further multivariate analysis whilst covarying for parents' total depression score.

Linear regression analyses tested associations between parental depression symptoms at baseline and the child depression symptom count at T3 as a secondary outcome measure. This analysis included the subsample of families who participated at baseline and T3 ($N = 283$). All analyses controlled for child age (at baseline), gender and their interaction.

I further examined whether associations between parental depression symptoms and new-onset child mood disorder could be better explained by other features of parental depression course (age of depression onset, prior episode impairment/hospitalisation and future episode recurrence).

Results

Description of child outcomes

Rates of mood disorder in offspring rose over the course of the study from 4.6% ($N = 14/305$) at baseline, to 9.8% ($N = 28/287$) at T2 and 9.9% ($N = 28/283$) at T3. Excluding those with a mood disorder at baseline, 12.7% ($N = 37$) developed a new-onset mood disorder at T2 or T3. The mean number of child DSM-IV depression symptoms reported at T3 was 2.0 (SD 2.0, range 0-9).

Parent symptoms as predictors of new-onset child mood disorder

The mean number of parent DSM-IV depression symptoms at baseline was 2.5 (SD = 2.6, range 0-9). Total parent depression symptom count was associated with increased risk for new-onset mood disorder in offspring (OR = 1.14, CI = 1.00, 1.29, $p = .04$). I next separately tested each of the nine DSM-IV depression symptoms (Table 1). Of the specific parent depression symptoms at baseline, only change in appetite/weight (OR = 3.21, CI = 1.56, 6.59, $p = .002$) and change in concentration/ indecisiveness (OR = 2.47, CI = 1.18, 5.20, $p = .017$) significantly predicted new-onset child mood disorder. The association between appetite/weight change and child new-onset mood disorder remained significant after Bonferonni correction for multiple testing (nine tests, significant adjusted p value $<.005$).

I further tested the extent to which the association between total parent depression symptom count and new-onset child mood disorder was accounted for by the appetite/weight change and loss of concentration/indecisiveness items. When these two items were removed from the total score, this variable (consisting of the remaining seven DSM-IV items) no longer predicted new-onset child mood disorder

(OR = 1.12, CI = .95, 1.31, $p = .177$). Multivariate analysis including appetite/weight change, loss of concentration/indecisiveness and parent's remaining total depression item score as predictors revealed appetite/weight change as the only significant predictor (Table 2).

Secondary outcome - Child depression symptom count at T3

A similar pattern of results was found for child depression symptom scores at final follow-up. Parent appetite/weight change ($\beta = .17$, B = .25, CI = .09, .41, $p = .003$), change in concentration/indecisiveness ($\beta = .13$, B = .20, CI = .02, .37, $p = .027$) and loss of interest/anhedonia ($\beta = .11$, B = .17, CI = .00, .33, $p = .049$) at baseline predicted future child depression symptoms (Table 3). Change in appetite/weight remained significant after Bonferonni correction for multiple testing (nine tests, significant adjusted p value $<.005$) and was the only symptom that remained associated with future child depression symptoms in the multivariate analysis (Table 4).

Direction of appetite/weight change

Clinical interview data allowed us to separately examine appetite/weight gain ($N = 35$) and appetite/weight loss ($N = 46$). Nine parents reported fluctuating or inconsistent symptoms and were not included in the analysis. Further analysis revealed no significant association between gain in appetite/weight and new-onset child mood disorder (OR = .93, CI = .31, 2.85, $p = .903$) or future child depression symptoms ($\beta = .09$, B = .17, CI = -.05, .39, $p = .132$). In contrast, loss of appetite/weight was significantly associated with new-onset child mood disorder (OR = 4.47, CI = 2.04, 9.79, $p <.001$); thirty percent of children whose parents reported

appetite/weight loss at baseline experienced a new-onset mood disorder at follow-up, compared with only nine percent of children whose parents did not report appetite/weight loss. Loss of appetite/weight in parents was also associated with future child depression symptoms ($\beta = .12$, $B = .21$, $CI = .00, .42$, $p = .050$).

Further sensitivity analysis revealed that parental appetite/weight loss measured at the second assessment again prospectively predicted child depression symptoms at final follow-up ($\beta = .13$, $B = .28$, $CI = .03, .52$, $p = .027$) and showed a trend in the same direction for mood disorder ($OR = 2.73$, $CI = .90, 8.31$, $p = .077$). In contrast, parental appetite/weight gain at time 2 was not associated with either child outcome ($p > .600$).

Adjusting for other features of parent depression

Finally, I tested whether the observed associations between parent appetite/weight loss and new-onset child mood disorder could be better accounted for by age of onset, past severity or future recurrence of parent depression. Appetite/weight loss was significantly associated with a younger age of parent depression onset ($OR = .94$, $CI = .90, .98$, $p = .003$) and recurrence of parental depression at follow-up ($OR = 3.40$, $CI = 1.46, 7.93$, $p = .005$) but not past depression impairment/hospitalisation ($OR = 1.53$, $CI = .78, 3.00$, $p = .216$). None of these parent depression features were however associated with new-onset child mood disorder (age of onset $OR = .97$, $CI = .93, 1.01$, $p = .151$; depression recurrence $OR = 1.30$, $CI = .61, 2.77$, $p = .497$; past impairment/hospitalisation $OR = 1.56$, $CI = .74, 3.28$, $p = .238$).

Associations between parents' appetite/weight loss and new-onset child mood disorder were also not accounted for by parent antidepressant medication use, presence of long term physical health problems, or eating disorder in the parent. Appetite/weight loss in parents was significantly associated with antidepressant medication use (OR = 2.47, CI = 1.22, 5.01, $p = .012$) however, a similar pattern of association was observed between parent appetite/weight loss and new-onset child mood disorder amongst parents who were taking antidepressant medication (OR = 3.65, CI = 1.40, 9.56, $p = .008$) and those who were not taking antidepressant medication (OR = 5.30, CI = 1.12, 25.16, $p = .036$). Parent appetite/weight loss was not associated with either parent physical health problems (OR = 1.83, CI = .95, 3.50, $p = .071$) or parent eating disorder (OR = 1.52, CI = .31, 7.56, $p = .608$).

The pattern of association between appetite/weight loss and new-onset child mood disorder was similar when only mothers were included in the analysis ($N = 270/291$, OR = 3.64, CI = 1.60, 8.26, $p = .002$), when parents meeting DSM-IV depression criteria at baseline assessment were excluded (OR = 4.77, CI = 1.44, 15.76, $p = .010$), when those children with a new-onset diagnosis of bipolar disorder, cyclothymia or adjustment disorder were excluded (excluded $N = 8/37$, OR = 3.50, CI = 1.45, 8.48, $p = .005$) and when specific parent symptoms were derived from questionnaires (Beck Depression Inventory, Beck & Steer, 1993b) rather than interview (OR = 2.55, CI = 1.25, 5.21, $p = .010$).

Discussion

Depression symptom heterogeneity is widely recognised but rarely investigated, particularly in relation to offspring risk for depression. Within this high-risk sample, the findings suggest that specific parental depressive symptoms differentially predict risk for future, new-onset offspring mood disorder. Parent appetite/weight loss emerged as a particularly important marker of risk: thirty percent of children whose parents reported baseline appetite/weight loss experienced a new-onset mood disorder at follow-up, compared with only nine percent of children whose parents did not report appetite/weight loss. This association remained after accounting for parents' overall level of depressive symptoms. Moreover, removing appetite/weight change from the total symptom count removed the association with new-onset mood disorder, suggesting that this item was contributing substantially to the initial observed relationship.

Parent appetite/weight loss is a feature that many would consider unlikely to have a direct negative impact on children, however the finding that this symptom appears to be an especially important marker of offspring depression risk is consistent with evidence from family and twin studies. For example, Leckman et al (1984) found that appetite disturbance was the symptom most discriminative of MDD in relatives of depressed probands and appetite/weight disturbance has been previously highlighted as a symptom associated with greater depression severity (Cole et al., 2011). On balance, research suggests that the vegetative symptoms (including appetite and weight disturbance) also appear to be more heritable than the other depression symptoms (Jang, Livesley, Taylor, Stein, & Moon, 2004; Kendler, Neale, Kessler, Heath, & Eaves, 1992; Korszun et al., 2004).

Depression with an early age of onset is also thought to be associated with increased familial aggregation and greater heritability than depression with an onset later in life (Weissman et al., 1984; Wickramaratne & Weissman, 1998). In this study, parent appetite/weight loss was associated with a younger age of onset in parents. Thus, this symptom may be a marker for a stronger genetic liability to early onset depression, not only in parents but also in offspring. However, appetite/weight loss could also be a marker of some additional unmeasured variable that has environmental effects on children.

It was originally hypothesised parent depression symptoms that might have the greatest psychosocial impact on children, such as loss of interest, would be the most important predictors. I did not find evidence in favour of this in this high-risk adolescent sample. Although parents who are depressed have been shown to be more disengaged, withdrawn and less responsive in their interactions with their children (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Stanley, Murray, & Stein, 2004; Stein et al., 1991), the majority of research has been conducted with infants or preschool age children. Findings from twin research suggest that the influence of genetic factors on depression symptoms increases in adolescence, while the importance of the family environment diminishes. This is possibly due to an increase in gene-environment correlation as adolescents become more autonomous and more able to seek-out and shape their own environments (Rice, 2010; Rice, Harold, & Thapar, 2002). Thus it is possible that during this developmental stage, offspring depression risk may be better indexed by the more heritable symptoms in parents, even though environmental factors also contribute. In addition, the impact of proximal, environmentally mediated parental depression symptoms may reduce as adolescents spend more time outside of the family home.

Although parental appetite/weight loss appears to be an important marker of risk, it is only possible to speculate as to the mechanisms that might be involved. Appetite regulation and depression share some common neurochemical and neurophysiological underpinnings (Adam & Epel, 2007; Arora & Anubhuti, 2006; Gurevich et al., 2002; Lam, Garfield, Marston, Shaw, & Heisler, 2010; Pariante, 2003; Ressler & Nemeroff, 2000). For example, serotonergic pathways (Gurevich et al., 2002; Lam, Garfield, Marston, Shaw, & Heisler, 2010; Ressler & Nemeroff, 2000) and the hypothalamo-pituitary-adrenal axis (Adam & Epel, 2007; Pariante, 2003) are systems which are involved in the regulation of appetite and have also been linked to depression. Thus appetite/weight loss may represent a core underlying feature of depression vulnerability. Although, it is also possible that appetite/weight loss may be a marker of unmeasured environmental adversity.

Strengths and limitations

Very few studies have considered which features of parental depression are the best predictors of future onset of depression in offspring. The current 4 year longitudinal study featured very high rates of retention and involved multiple informants and multiple measures of offspring depression derived from diagnostic interview. Several potential confounding factors were also addressed. The findings must however be interpreted in light of several study limitations. The number of children with new-onset mood disorder in this sample was small ($N = 37$) which may have limited the power to detect smaller effect sizes. However, similar results were found when using the child depression symptom count as the outcome measure. The small number of children with new-onset mood disorder also precluded the ability to examine associations separately according to offspring age and gender

which may be important moderators of intergenerational depression risk. For example, cross-generational links appear to be stronger between mothers and daughters (Lewis, Rice, Harold, Collishaw, & Thapar, 2011).

Some studies have suggested that symptoms are variable across depressive episodes (Oquendo et al., 2004), however other researchers have found symptom presentations to be similar (Korszun et al., 2004; Minor, Champion, & Gotlib, 2005) and in the present study, correlation coefficients for parent appetite/weight loss were highly significant across depressive episodes ($p < .001$). Moreover, sensitivity analysis looking at parental appetite/weight loss at T2 showed a consistent pattern of findings.

As the majority of parents participating in the study were mothers ($N = 270/291$), it is not possible to generalise the findings to offspring of depressed fathers. Also, the present study focuses on an important clinical sample: parents with a history of recurrent depression, who although identified from primary care rather than from tertiary services, will still likely be a much more severely affected group than population-based samples. It is plausible that risk markers for child depression symptoms in the general population are not the same as those for depressive disorder in offspring in high-risk families. If this is the case, it highlights the need for both clinically informative samples such as that used in the present study, as well as population-based studies.

Summary

The present study identified parent appetite/weight loss as an important marker of risk for future depression in their offspring. Although there are some plausible biological links, it is unlikely that loss of parent appetite/weight itself would

have a direct negative impact on children. Further research is therefore required to identify and characterise the genetic, familial, social and biological mechanisms that might explain the link between parental appetite/weight loss and offspring depression risk.

Table 1. Univariate associations between baseline parent depression symptoms and new-onset child mood disorder

Baseline parent depression (N=291)	New-onset child mood disorder N=37	
	OR (95% CI)	p value
Parent low mood (N=107, 36.8%)	1.59 (.79, 3.22)	.19
Parent loss of interest/anhedonia (N=84, 28.9%)	1.35 (.65, 2.83)	.42
Parent loss of energy (N=67, 23.0%)	1.67 (.78, 3.57)	.19
Parent change in appetite/weight (N=90, 31.3%)	3.21 (1.56, 6.59)	.002
Parent change in sleep (N=122, 45.2%)	1.95 (.94, 4.06)	.07
Parent low self esteem/guilt (N=103, 37.7%)	1.53 (.75, 3.12)	.24
Parent suicidality (N=39, 14.2%)	1.24 (.47, 3.26)	.66
Parent retardation (N=23, 7.9%)	0.97 (.27, 3.48)	.96
Parent loss of concentration/indecisiveness (N=67, 23.0%)	2.47 (1.18, 5.20)	.02

^a Numbers vary due to missing data

Analysis adjusted for child age, sex and their interaction measured at baseline

Table 2. Multivariate model predicting new-onset child mood disorder

	New-onset child mood disorder		
	OR (95% CI)	<i>p</i> value	R ²
Change in appetite/weight	2.99 (1.35, 6.61)	.007	.056
Loss of concentration/indecisiveness	1.86 (.67, 5.16)	.24	
Remaining DSM-IV depression symptoms (total score, max of 7 items)	0.94 (.75, 1.18)	.60	

Analysis adjusted for child age, sex and their interaction measured at baseline

Table 3. Univariate associations between baseline parent depression symptoms and child depression symptoms at follow-up

Baseline parent depression (N=283) ^a	Child depression symptoms at follow-up	
	β , B (95% CI)	p value
Parent low mood (N=98, 34.6%)	.03, .04 (-.11, .20)	.58
Parent loss of interest/anhedonia (N=81, 28.6%)	.11, .17 (.00, .33)	.05
Parent loss of energy (N=66, 23.3%)	.10, .15 (-.03, .32)	.10
Parent change in appetite/weight (N=84, 29.9%)	.17, .25 (.09, .41)	.003
Parent change in sleep (N=112, 42.7%)	.10, .13 (-.03, .29)	.11
Parent low self esteem/guilt (N=96, 36.4%)	.05, .07 (-.09, .23)	.40
Parent suicidality (N=37, 13.9%)	-.02, -.05 (-.27, .18)	.69
Parent retardation (N=22, 7.8%)	.08, .18 (-.09, .46)	.19
Parent loss of concentration/indecisiveness (N=68, 24.0%)	.13, .20 (.02, .37)	.03

^a numbers vary due to missing data

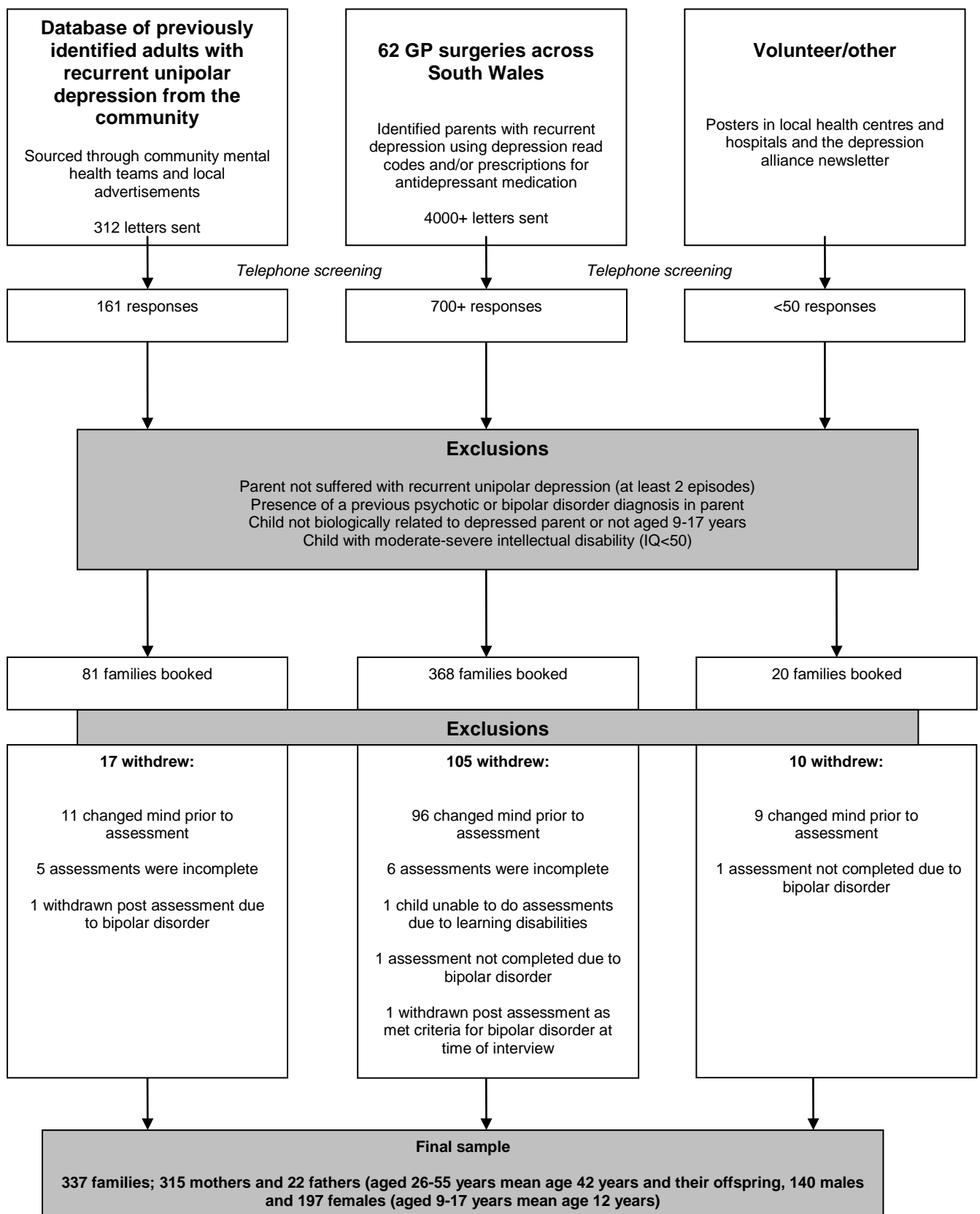
Analysis adjusted for child age, sex and their interaction measured at baseline

Table 4. Multivariate model predicting child depression symptoms at follow-up

	Child depression symptoms at follow-up		
	β , B (95% CI)	<i>p</i> value	R ²
Change in appetite/weight	.16, .22 (.05, .40)	.01	.094
Loss of concentration/indecisiveness	.09, .13 (-.11, .37)	.29	
Loss of interest/anhedonia	.09, .13 (-.10, .36)	.27	
Remaining DSM-IV depression symptoms (total score, max of 6 items)	-.08, -.03 (-.09, .04)	.37	

Analysis adjusted for child age, sex and their interaction measured at baseline

Figure 1. Recruitment chart



Appendix

Additional analysis: structural equation modelling

As a complementary means of addressing the same primary question, associations between parent depression symptoms and child depression symptoms were examined using structural equation modelling (SEM), under the guidance of Professor Gordon Harold. Here, the starting point was a latent depression variable capturing variation in parent DSM-IV depression symptoms, such that all underlying DSM symptom scores contribute equitably to an overall index of depression. SEM using polychoric correlations and weighted least squares estimation based on the dichotomous profile of underlying symptom score indices (Flora & Curran, 2004; Jöreskog & Sörbom, 1996) was first used to simultaneously test the relationship between a latent variable indexed by all 9 DSM items and new-onset offspring mood disorder. Then, a series of nested models were tested where the latent variable was indexed by specific subsets of the DSM-IV items to identify the parsimonious subset of underlying items (or single individual item) that best captured the parental latent variable relationship with offspring depression relative to the estimation that included all nine DSM items.

Results from structural equation models

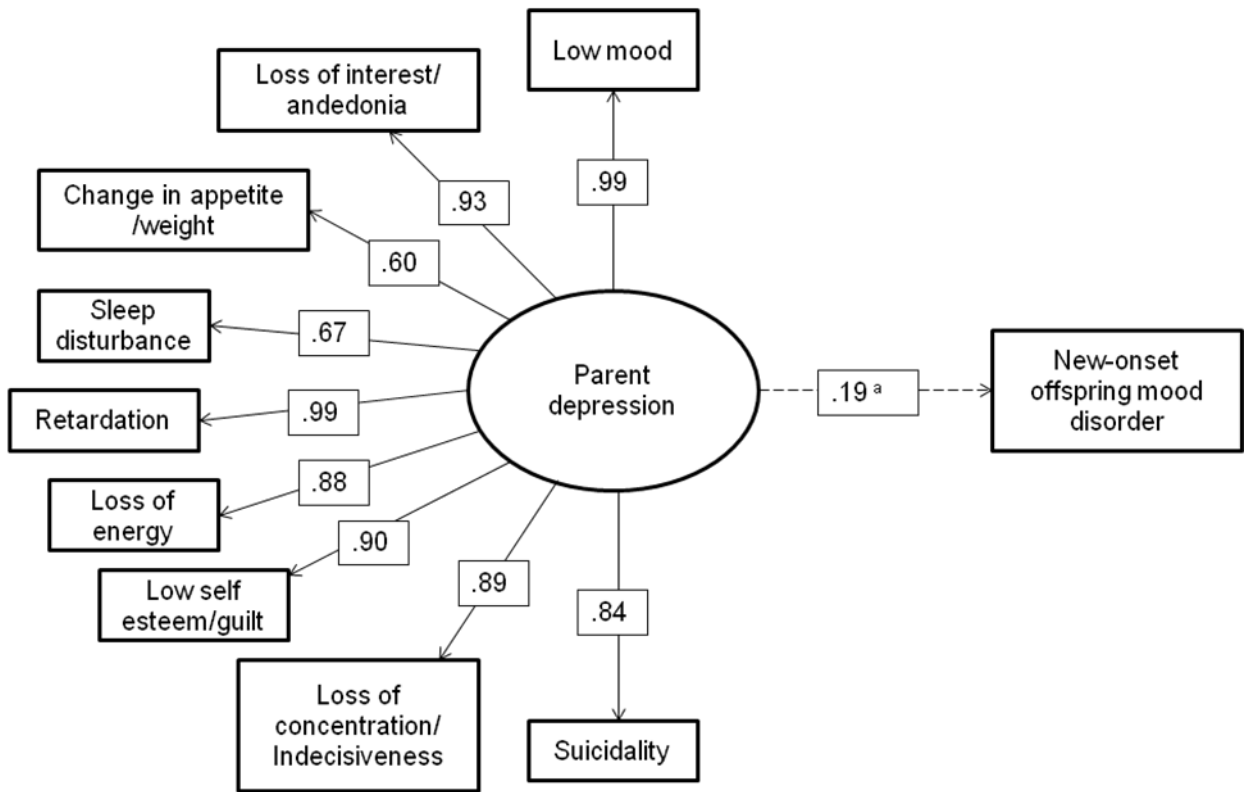
Full results of all SEM analyses (all nested models) are included in Figures 1 and 2. A latent variable indexed by all DSM-IV items showed a non-significant association (trend level, $p < .10$) with new-onset offspring mood disorder (See Figure 1). All DSM-items showed high and statistically significant factor loadings as indices of the underlying latent depression variable. Seven items loaded equivalently (factor loadings(γ) $> .84$). However, two items, change in appetite/weight and sleep

disturbance loaded at a lower level to these items ($\gamma < .67$) suggesting further analyses specific to these two items to examine possible differential function when considered separately to each of the other 7 items. A latent variable represented by both of these items showed significant association with new-onset offspring mood disorder (Figure 2 Panel A). When each item was tested individually, only change in appetite/weight remained a significant predictor (Figure 2 Panel B). A latent variable captured by the remaining DSM-IV symptom items (Figure 2 Panel C) showed no association with offspring mood disorder.

Conclusions

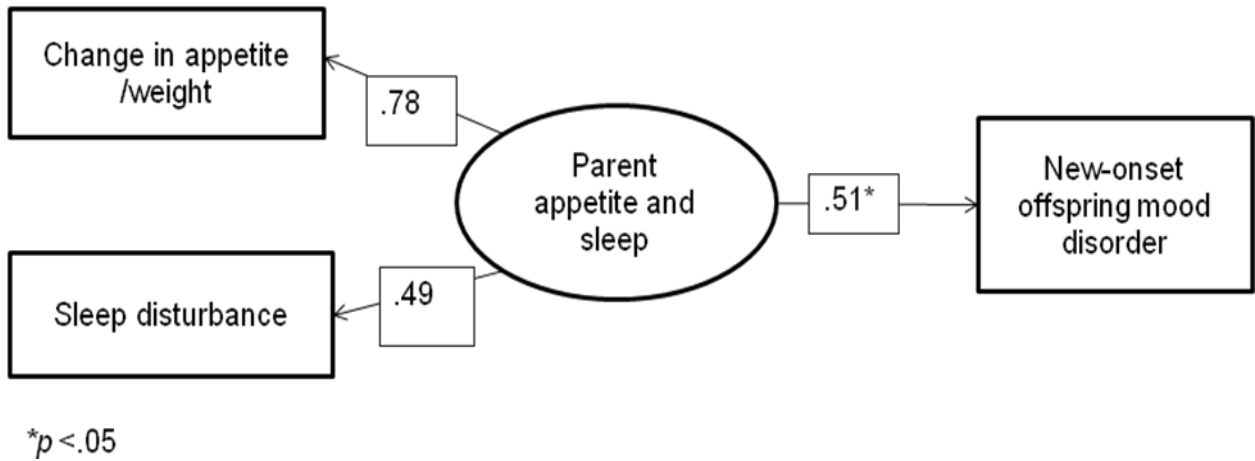
Results from the structural equation models were consistent with those from the logistic regression analysis. This confers additional support for the finding that appetite/weight change in parents is a variable which appears to be particularly associated with offspring depression risk. Moreover, in both analyses, associations between parental depression and offspring mood disorder became non-significant once appetite/weight change was removed, suggesting that this variable was contributing substantially to the initial observed relationship between parent and child depression.

Appendix Figure 1. Polychoric weighted least squares estimation of full latent specification model



^a= $p < .10$

Appendix Figure 2. Panel A. Polychoric weighted least squares estimation of 2-indicator reduced model



Appendix Figure 2. Panel B1 and B2. Single indicator estimation of parent risk (change in appetite/weight, sleep disturbance) on new-onset offspring mood disorder

Figure 2, Panel B1

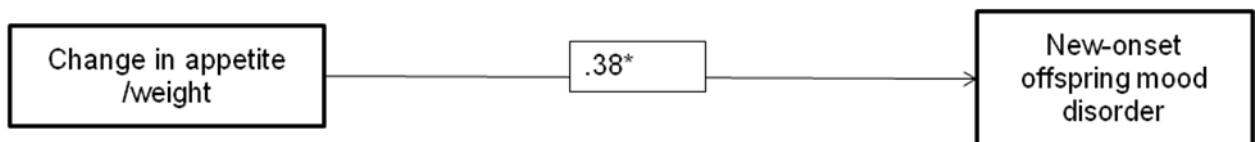
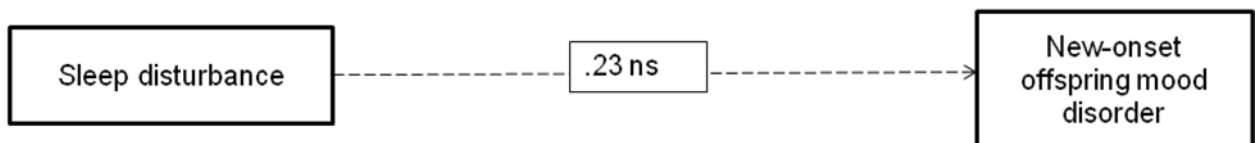
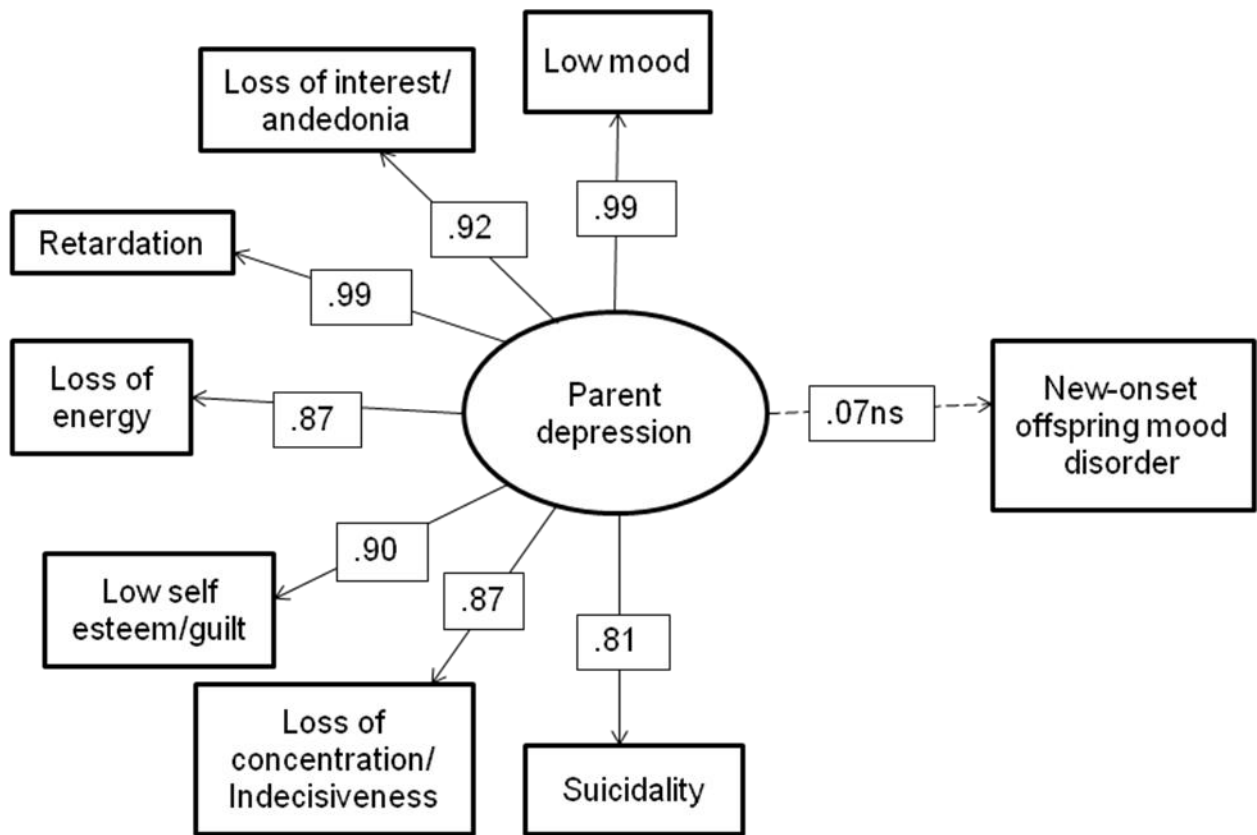


Figure 2, Panel B2



* $p < .05$

Appendix Figure 2. Panel C. Polychoric weighted least squares estimation of 7-indicator reduced model



Chapter 6

Overall discussion

The purpose of this thesis was to examine the impact of parental depression heterogeneity on risk for offspring depression and investigate how differences in clinical features including course, severity, timing and symptom presentation differentially relate to offspring depression risk. This chapter will summarise the findings from the three empirical papers that comprise the body of this thesis. The clinical implications of the work will next be discussed, before a consideration of the strengths and limitations. Finally, this chapter will conclude with a section on possible future directions.

Summary of aims and findings

Depression is a serious mental health problem common throughout adolescence. Both depression symptoms and clinical disorder are associated with a range of negative outcomes for young people and often mark the beginning of a chronic lifelong illness. Early identification, treatment and prevention of depression in children and adolescents who are at risk are important in order to alleviate current distress and prevent future problems.

Several meta-analyses have suggested that prevention efforts for child and adolescent depression are most effective when targeted at those who are high risk (Horowitz & Garber, 2006; Merry, McDowell, Hetrick, Bir, & Muller, 2004; Stice, Shaw, Bohon, Marti, & Rohde, 2009). Thus, in order for interventions to be effectively targeted, risk factors must first be identified. One of the most well established risk factors for depression in young people is the presence of parental depression, with the offspring of depressed parents typically showing a 3-4 fold

elevated risk of depression relative to controls (Rice, Harold, & Thapar, 2002). This group therefore represents a logical target for prevention and treatment strategies. Moreover, given that many parents with depression are already engaged with services, this should, in theory, be an easily accessible high risk group. Other high risk groups of children, for example those with elevated depression symptoms or those exposed to chronic adversity may be more difficult to identify.

Although offspring of depressed parents show elevated rates of depression relative to controls, outcomes are variable with not all children going on to experience depressive symptoms or disorder. The identification of features of depression in parents that account for this variation in offspring risk is therefore important, as it can lead to more precise identification of sub-groups likely to be most in need of early intervention. However, many studies of intergenerational transmission simply compare outcomes in children of depressed and non-depressed parents and do not report features of the disorder beyond diagnostic status.

Previous research has suggested that there may be a proximal (i.e. at a particular point in time) influence of parental depression on offspring depression. For example, studies of depressed children who are receiving Cognitive Behaviour Therapy have found treatment to be less effective where a parent is currently depressed (Garber et al., 2009; Kennard et al., 2008). Moreover, some, but not all treatment trials of depressed mothers have shown reductions in child psychopathology and/or improvements in functioning following remission of maternal depression (Gunlicks & Weissman, 2008; Weissman et al., 2006a). However, most of these studies have not focused on offspring depression specifically. In addition, many have failed to take account of prior features of maternal depression such as severity, chronicity or current symptom levels and so it is possible that those parents

whose depression remitted may have been less severely depressed than those whose did not remit, potentially confounding the results. The first aim of this thesis was to examine whether there is a proximal influence of parental depression (indexed by a recent episode of parent MDD) on offspring psychiatric disorder generally and depression symptoms specifically, over and above other clinical depression characteristics. Recent parental depression was found to be significantly associated with both child outcomes after taking into account features of parent depression, including timing, chronicity, age of onset and severity, as well as family history. In addition, a history of severe depression in parents (defined in terms of severe impairment or hospitalisation for depression) was also associated with offspring depression symptoms, suggesting that both these factors are important markers of offspring depression risk.

Depression is often assessed cross-sectionally and categorically. However, studies that have modelled the course of depression longitudinally have shown that it is highly variable, with individuals fluctuating in the number of depressive symptoms experienced over time (Ashman, Dawson, & Panagiotides, 2008; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009; Judd et al., 1998; Nandi, Beard, & Galea, 2009; Rhebergen et al., 2012; Skipstein, Janson, Stoolmiller, & Mathiesen, 2010). The risk to offspring associated with differences in parental depression course has rarely been investigated. The second aim of this thesis was to use dimensional assessments of parent depression symptoms over the three waves of the study to examine heterogeneity in the course of parent depression over time. Parent symptom profiles were then examined in relation to offspring mood disorder, offspring depression symptoms and patterns of parental impairment. Distinct parental depression profiles were identified using cluster analysis, including an

asymptomatic comparison group, a minimal symptoms group, a moderate group and a group characterised by chronic high depression symptoms. Findings suggested that children whose parents experienced chronic high depression symptoms showed an elevated risk of mood disorder and experienced significantly more depression symptoms than children whose parents remained asymptomatic throughout the course of the study. Results also suggested that any persistent symptoms of depression in parents, even those at low levels, may be clinically important in indexing offspring risk for depression symptoms. This highlights the utility of dimensional assessments of parent depression over time as an augmentation to diagnosis when assessing offspring risk. In addition, parent depression profiles characterised by moderate and chronic high symptoms were also related to greater levels of parental health and social impairment.

The DSM-IV criteria for MDD consist of nine possible depressive symptoms, of which five are required for diagnosis. Aside from the core symptoms of low mood and loss of interest, the remaining symptoms are often considered to be interchangeable. However, research suggests that there may be differences between symptoms in the extent to which they index familial liability to depression. The final aim of the thesis was to investigate whether there are differences in the risk for future offspring mood disorder and depression symptoms associated with specific parental depression symptoms. Of the nine DSM-IV MDD symptom criteria, parent appetite/weight change (specifically appetite/weight loss) was a particularly important marker of offspring risk in this sample.

Taken together, these findings highlight the importance of considering clinical characteristics of depression in parents, beyond diagnostic status when examining cross-generational depression risk. Within this high risk group of offspring, specific

clinical features of parental depression were identified that may serve as useful markers of current and/or future offspring psychopathology and depression risk.

Clinical implications

Depression is one of the most common psychiatric disorders in the UK. Given that depression is particularly prevalent during the childbearing years (Burke, 2003; Weissman & Olfson, 2009) and is often a chronic recurrent condition, many children in the UK will be exposed to one or more episodes of parental depression. Thus it is important to understand the potential consequences this may have for offspring development. Research consistently shows parental depression to be associated with an elevated risk of depression in their offspring, with approximately a 3-4 fold elevated risk relative to offspring of non-depressed controls (Rice, Harold, & Thapar, 2002). Consistent with previous studies of the offspring of depressed parents, rates of depression amongst the children in the EPAD sample were significantly elevated compared with normative data from a recent UK epidemiological survey (Green, McGinnity, Meltzer, Ford, & Goodman, 2005). This pattern was found at each of the three time points and confirmed the expectation that this is a high risk group. Parental depression must therefore be recognised as a major public health concern.

Depression that occurs at a young age is associated with a wide range of negative outcomes and often persists into adulthood (Asarnow et al., 2005; Bardone, Moffitt, Caspi, Dickson, & Silva, 1996; Birmaher et al., 1996; Fergusson & Woodward, 2002; Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001a; Giaconia, Reinherz, Paradis, Hauf, & Stashwick, 2001; Glied & Pine, 2002; Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Lewinsohn, Rohde, Klein, & Seeley, 1999; Lewinsohn, Rohde, & Seeley, 1994, 1998a; Rao, Hammen, & Daley, 1999; Rao et al., 1995; Rutter, Kim-Cohen, & Maughan, 2006; Weissman et al., 1999a). Findings from paper 1 add to evidence that parental depression continues to be a

proximal risk during adolescence, highlighting the need for prevention and treatment strategies during this key developmental stage.

Many young people with depression do not engage with services and even among those who do, depression is frequently missed (Essau, 2005; Kramer & Garralda, 1998; Lewinsohn, Rohde, & Seeley, 1998b; Merikangas et al., 2010a; Merikangas et al., 2011; Olfson, Gameroff, Marcus, & Waslick, 2003; Potter et al., 2012; Wu et al., 2001). As many parents with MDD receive treatment through primary care services (Ohayon, Priest, Guilleminault, & Caulet, 1999), consultations with parents provide an excellent opportunity for GPs to identify children who may be currently in need of treatment, as well as those who may be at risk of developing depression in the future. Findings from the present thesis suggest that GPs should utilise information about clinical characteristics of depression in parents, in addition to diagnostic status and be particularly vigilant to the possibility of depression in offspring when a parent's depression is characterised by severe impairment or hospitalisation, symptoms of appetite/ weight loss, a recent episode of clinical depression, or if parents present with any level of persisting depression symptoms.

It is vital that the process through which offspring at high depression risk are identified in primary care is simple and feasible. Given that it is not feasible and likely to be unnecessary to target treatment and prevention efforts at all offspring of depressed parents, a primary translational aim of the EPAD study was to develop a simple identification tool which could be used to effectively identify which offspring of depressed parents are at greatest risk and may warrant consultation with the GP themselves. To be of use, such a tool must be brief, require minimum training and have high sensitivity and specificity. Work arising from this thesis has directly contributed to the development of the identification tool and 'parent hospitalisation' is

currently included alongside six other items that were identified by members of the research team. Together these items provide clinicians with a calculated risk score for the child. The identification tool will be piloted in several GP practices in South Wales. It is hoped that this will help to facilitate access to services, raise awareness in clinicians and parents about the possibility of depression in young people and highlight the need to integrate adult and child services better.

There is also an important role for other services, in addition to primary care in the detection of depression in young people. An additional published paper based on data from the EPAD project (Potter et al., 2012), found that almost two thirds of children in the sample with psychiatric disorder were not in contact with any services at all, with only 11% in contact with their GP. Moreover, of those children with a mood disorder, only 63% were in touch with services, suggesting that even amongst a high risk group of children whose parents are known to have a history of depression, depression in their children often goes unrecognised and untreated. The most frequently accessed services by children with a psychiatric disorder were teachers and special educational needs services. This highlights an important role of schools in the identification of depression in young people and suggests a need for better integration of existing services.

The findings from this thesis also highlight effective treatment of parental depression as a clinical priority, as many parents in the sample with a history of recurrent depression continued to display depression symptoms. In paper 1, recent parental depressive episodes were associated with an increased risk for offspring psychiatric disorder and depression symptoms, suggesting a proximal risk of parental depressive episodes on offspring psychopathology. This might suggest that there are potential benefits to offspring of treating parental depression, as well as

benefits to the affected parent, even when there has been previous exposure to parental depressive episodes. However, it is also possible that observed associations between recent parental depression and offspring risk could be due to other inherited or non-inherited background risk factors, for example common genetic vulnerability.

Findings from paper 2 extended this, by showing that there is risk to offspring associated with any level of persistent depression symptoms in parents. This suggests that in order to achieve the most favourable child outcomes, treatment strategies for parent depression should continue beyond diagnostic remission, with an aim to achieve asymptomatic status. Moreover, whilst alleviation of parental depression symptoms is important, maintaining these gains is also a paramount goal, as offspring depression risk was considerably lower amongst those parents who remained symptom free over the four-year period of the study. Educating parents about the potential benefits to offspring associated with reductions in their own depression symptoms may encourage parents to seek treatment when they would not otherwise have done so.

This thesis has highlighted that there is considerable variability in the course of depression over time, even amongst those parents who have experienced recurrent depression. However, most current tools used in practice assess depression cross-sectionally which does not adequately capture this longitudinal variability in symptom scores. A second translational aim of the EPAD project was to develop a tool which could be used by individuals and practitioners to monitor levels of depression over time. Findings from this thesis highlight the potential benefits of monitoring depression in this way. Firstly, via identifying offspring who may be at particularly high risk of depression by virtue of having a parent with chronic high

depression scores, or at low risk by virtue of having a parent who remains asymptomatic over time. Secondly, the use of a monitoring tool may make parents more aware of their depression symptoms and encourage them to seek treatment sooner. Early recognition and treatment of parental depression is important as it could help to prevent further deterioration in symptoms and in doing so, reduce the likelihood of hospitalisation and severe impairment which was found in this thesis to be associated with offspring depression risk.

Strengths

A main strength of this thesis was the use of a large well characterised high risk sample. Depression is clearly a familial disorder (Rice, Harold, & Thapar, 2002) and examining the offspring of parents with recurrent depression maximised the prevalence of depressive symptoms and disorders in offspring, enhancing the ability to detect associations with parental depression features of interest. The use of a large, diverse sample of recurrently depressed parents with rich phenotypic information also allowed for an examination of a wide range of clinical depression features in relation to offspring depression risk. Many studies investigating the intergenerational transmission of depression to date have simply dichotomised parents into 'depressed' and 'non- depressed' groups. The few studies which have considered parent depression heterogeneity have typically focused on only one or two aspects of depression course, such as postnatal depression or depression recurrence. Moreover, clinical characteristics of depression are frequently heavily confounded and studies that have attempted to disentangle these dimensions by creating non-overlapping groups are often left with smaller sample sizes, or samples that may be atypical in terms of depression course.

Many studies of the offspring of depressed parents have measured parent depression at only one time point and thus examined cross-sectional associations with offspring depression. The longitudinal research design used for this thesis allowed for an examination of differences in the pattern of parental depression symptoms over time. Whilst depression symptom profiles such as this have been investigated in a number of studies (Judd & Akiskal, 2000; Nandi, Beard, & Galea, 2009; Rhebergen et al., 2012), parental profiles have rarely been considered in relation to cross-generational depression risk (Ashman, Dawson, & Panagiotides,

2008; Campbell, Morgan-Lopez, Cox, & McLoyd, 2009). The longitudinal design also allowed for an investigation of parental depression features associated with future-onset mood disorders in their offspring. Establishing temporal precedence by identifying features that predict future depression risk is especially relevant for the targeting of preventative intervention strategies.

The use of rigorous, semi-structured diagnostic assessments for both parent and child depression is an additional strength. Psychiatric diagnosis and symptom counts can be derived from the interviews simultaneously, enabling depression to be characterised both as a categorical and a dimensional construct. Interviewer led clinical assessments are often considered the 'gold standard' when diagnosing MDD. Information obtained from interviews is more detailed, has greater reliability and validity and is less prone to misinterpretation than data collected from self-report questionnaires (Cicchetti & Cohen, 2006; Costello, Egger, & Angold, 2005; Rutter et al., 2009). In addition, consistency across raters can also be measured statistically and interviewer agreement was found to be excellent in the EPAD sample.

A final strength of this thesis is the inclusion of data from multiple informants. This is particularly salient given the low-moderate agreement between parents and children for ratings of child depression (Cantwell, Lewinsohn, Rohde, & Seeley, 1997; Lewinsohn, Rohde, & Seeley, 1998a). Many previous studies of the offspring of depressed parents have been limited by a reliance on parental reports of their own and their child's symptoms, introducing the issue of shared method variance. For example, parent ratings of their child can be affected by their own mood state, although it remains debatable whether depressed parents over-estimate depressive symptoms in their offspring or whether they are actually more sensitive to such symptoms when depressed (Boyle & Pickles, 1997; Goodman et al., 2011; Lewis et

al., 2012; Najman et al., 2000; Rice, Lifford, Thomas, & Thapar, 2007; Richters & Pellegrini, 1989; Richters, 1992). Inclusion of child reports alongside parental reports is therefore important when investigating the effects of current parental depression symptoms in order to eliminate potential negative affectivity bias. It is noteworthy however, that an additional published paper from the EPAD project (Lewis et al., 2012) found parent-reports of their child's depression symptoms at baseline to be significantly predictive of new-onset mood disorder in their offspring. Moreover, for younger children, parent-reports were found to be significantly more predictive of future mood disorder than children's own reports. These findings suggest that parents with depression are not necessarily unreliable informants and are able to provide clinically useful information about depression symptoms in offspring.

Limitations

Results should be interpreted in light of several limitations. Firstly, although features of parent depression were identified that were associated with increased risk for offspring depression, it cannot be claimed that these associations are causal. Experimental methodologies such as randomised controlled trials are needed in order to demonstrate causal effects. Causality could also have been more confidently inferred if the direction of effects between parent and offspring depression symptoms had been investigated. It is possible that children's own depressive symptoms may impact negatively on their parents' depression rather than the converse, or there may be bidirectional effects (Bell, 1968; Ge, Conger, Lorenz, Shanahan, & Elder Jr, 1995; Hughes & Gullone, 2010) and this possibility was not tested here. In addition, it is also possible that some unmeasured third variable could have contributed to the associations found between parent depression features and child outcomes, thus providing an alternative explanation for the results. It is not however possible to account for all potential confounding factors.

An additional limitation concerns the wide age range of the children in the sample. Children were aged between 9 and 17 years at baseline. Therefore, by the end of the study many children had not yet passed through the peak risk period for the emergence of depression. It is possible that some children in this sample may go on to develop depressive disorders or symptoms in the future and this may have resulted in reduced power to detect associations with parental depression risk factors of interest. Although rates of depressive disorders were high in the children in this sample compared with those in the general UK population (Green, McGinnity, Meltzer, Ford, & Goodman, 2005), absolute values were relatively small. The small numbers of children with depressive disorders precluded the ability to investigate

potential differences in associations according to child gender. This is important as research has suggested that the risk factors and mechanisms may be different for males and females (Cortes, Fleming, Catalano, & Brown, 2006; Davies & Windle, 1997; Goodman, 2007; Lewis, Rice, Harold, Collishaw, & Thapar, 2011). Moreover, although the sample included some depressed fathers, the number of fathers was too small to examine associations separately according to parent gender. It is therefore unclear whether the markers of risk identified in this thesis would also apply to offspring of depressed fathers. Whilst there are a limited number of studies that have investigated the influence of paternal depression on offspring depression risk, very few have examined different paternal depression features (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Lieb, Isensee, Hofler, & Wittchen, 2002; Ramchandani & Psychogiou, 2009) This is an area which warrants further research.

Parents in the sample were recruited predominantly from primary care practices and all had received treatment for depression. This makes the study especially relevant because this is the setting where most depression is diagnosed and treated (Ohayon, Priest, Guilleminault, & Caulet, 1999). However, many adults with depression do not seek treatment (Kessler et al., 2003; Ohayon, Priest, Guilleminault, & Caulet, 1999) meaning help-seeking bias may be an issue. It is possible that those who seek help for depression may differ in important ways from those who do not seek help (Blumenthal & Endicott, 1996; Kendler, 1995; Ohayon, 2007). For example, Kendler and colleagues (1995) found that women with depression who sought treatment were older, had higher levels of education, were more likely to have a co-morbid disorder, had more depressive symptoms and were more impaired than non treatment seeking women. Thus the generalisability of the results to community samples may be limited. Moreover, the majority of patients

approached did not agree to take part in the study and therefore volunteer bias may also be a problem. This may have served to increase or decrease the severity of depression in the parent sample; however, as information about non-respondents was not available, it was not possible to investigate this further.

A further limitation which is common in longitudinal studies concerns sample attrition and missing data. There was some evidence for selective attrition in this sample, for example higher baseline parent and child depression scores were found amongst families with missing data at follow-up. However, overall retention of families in the sample was excellent. At each follow-up assessment over 85% of families completed an interview, with full interview data obtained at all three time points from approximately 80% of families.

Although the study involved rigorous prospective assessments, with semi-structured interviews used to establish parent and child depression diagnosis and symptoms, some of the parent depression characteristics that were investigated were assessed retrospectively (e.g. age of onset). A life history calendar approach was adopted when collecting information about prior depressive episodes and whilst this approach has been shown to aid autobiographical recall (Belli, 1998; Caspi et al., 1996), it is possible that some information may not have been recalled accurately.

In addition, although several markers of offspring depression risk were identified, there are other features in parents which may influence offspring depression risk that were not investigated here. One example is comorbidity of parent depression with other mental health problems which has been examined by other members of the research team. (Sellers et al., 2012).

An exploration of the mechanisms through which clinical features of parental depression may have an effect on offspring was also beyond the scope of this thesis. However, the identification of risk features is an important first step before mechanisms can be investigated.

Future directions

This thesis identified several features of parental depression that are markers of risk for depression in their offspring. Identification of risk factors is important for detecting those children who may be in need of treatment, as well as for the targeting of selective intervention strategies aimed at preventing depression onset.

The intergenerational transmission of depression from parents to offspring is very likely mediated via a combination of genetic and environmental factors. Evidence from twin, family and adoption studies suggests that there are modest genetic influences on depression, whilst also highlighting that environmental factors make an important contribution (Rice, 2010; Rice, Harold, & Thapar, 2002; Silberg, Maes, & Eaves, 2010; Sullivan, Neale, & Kendler, 2000; Tully, Iacono, & McGue, 2008). Many mechanisms have been proposed to explain the link between parent and offspring depression, including impaired parenting, problems in the parent-child relationship, increased exposure to conflict and stress, modelling of parental depression affect and cognitions, as well as genetic predisposition (Cummings, Keller, & Davies, 2005; Downey & Coyne, 1990; Goodman, 2007; Goodman & Gotlib, 1999; Herr, Hammen, & Brennan, 2007; Lovejoy, Graczyk, O'Hare, & Neuman, 2000). It is possible that the mechanisms of cross-generational transmission may be different for different features of parental depression. Although the identification of risk factors is important for the targeting of treatment and intervention strategies, an understanding of the underlying genetic, familial, social and biological mechanisms is also a paramount goal in order for such interventions to be effectively designed. Future research also needs to make use of genetically sensitive designs such as adoption and twin studies to examine potential mechanisms, since family studies such as this one are unable to distinguish genetic

from environmental influences. This is important given that modifiable environmentally mediated risk and protective mechanisms are likely to be the most useful targets for treatment and prevention strategies.

It is also important to investigate moderators of risk. For example, research has suggested that the risk factors and mechanisms involved in the intergenerational transmission of depression may vary according to both parent and child gender (Cortes, Fleming, Catalano, & Brown, 2006; Davies & Windle, 1997; Landman-Peeters et al., 2008; Lewis, Rice, Harold, Collishaw, & Thapar, 2011; Reeb, Conger, & Wu, 2010). Large samples of the offspring of both mothers and fathers with depression are needed in order to adequately investigate gender-specific models of depression risk. The presence of a co-parent is also a potential moderator which warrants further study. It is possible that children's depression risk may be further elevated when both parents suffer with depression (Burke, 2003; Landman-Peeters et al., 2008; Merikangas, Weissman, Prusoff, & John, 1988; Nomura, Warner, & Wickramaratne, 2001). This is particularly salient, given findings suggesting there may be assortative mating in depression, whereby depressed individuals are more likely to choose partners who also have a history of psychopathology (Brennan, Hammen, Katz, & Le Brocque, 2002; Mathews & Reus, 2001; Merikangas, Prusoff, & Weissman, 1988). Conversely, a supportive co-parent, or alternative support such as from a sibling, friend or grandparent may provide a buffering effect against any negative effects of depression from the affected parent (Chang, Halpern, & Kaufman, 2007; Gass, Jenkins, & Dunn, 2007; Goodman & Gotlib, 1999; Tannenbaum & Forehand, 1994). A better understanding of protective as well as risk factors and the interplay between them is important for the design of interventions. Although there are some studies which have examined predictors of offspring resilience in relation

to parental depression (Brennan, Le Brocque, & Hammen, 2003; Conrad & Hammen, 1993; Pargas, Brennan, Hammen, & Le Brocque, 2010), this is an area which requires further investigation.

This thesis identified clinical features of depression in parents that are markers of risk for offspring depression, however it cannot be claimed that effects are causal. Further research could make use of statistical techniques such as cross-lagged panel analysis which can be useful for inferring causality. These techniques allow for a test of the direction of effects between parent and child symptoms as well as testing for the possibility of bidirectional associations. Randomised Controlled Trials (RCTs) are often considered the optimal method for establishing causal effects (Rutter et al., 2009) however, random assignment is not possible when examining cross-generational depression risk. There are many RCTs that have been conducted into parent depression treatment, several of which have also assessed changes in offspring psychopathology (Gunlicks & Weissman, 2008). Parental depression remission following treatment has been associated with improvements in offspring functioning and reductions in psychiatric disorder (Garber, Ciesla, McCauley, Diamond, & Schloedt, 2011; Gunlicks & Weissman, 2008; Weissman et al., 2006a). However, not all findings are consistent and questions remain regarding the causal mechanisms which underlie these associations. Moreover, offspring of parents who are in remission show poorer functioning relative to controls (Garber, Ciesla, McCauley, Diamond, & Schloedt, 2011) highlighting that treating parents to remission, although undoubtedly worthwhile, is not likely to be sufficient for children to reach levels of adaptation that are comparable with children of non-depressed parents.

Findings from the present thesis suggest that depression symptoms at lower levels in parents may also impact on offspring depression risk. Future trials are needed which extend parental depression treatment beyond traditional remission cut-offs. This is important to see if there is any additional benefit to children that can be achieved from further treatment of depression in parents. In addition, it is important to examine patterns of change in parent and child depression symptoms over time and for this, multiple follow-ups are required. There are many sophisticated statistical techniques now available such as latent growth curve modelling which are able to use longitudinal data to generate and compare parent and child depression trajectories. The use of these statistical methods will result in a better understanding of the relationship between parental depression severity and offspring depression risk, however, these techniques ideally require more than three data points and are sensitive to discrepancies in duration between assessments.

Finally, although this sample benefits from a three-wave longitudinal design spanning four years across adolescence, future work would benefit from a longer follow-up of this sample as studies which follow high risk offspring from adolescence into adulthood are relatively rare (Weissman et al., 2005). An extended follow-up of this sample would allow for an examination of whether certain depression characteristics in parents are associated not only with elevated risk of depression in offspring, but also with differences in offspring depression course. It would also be of interest to examine whether features of depression that are observed in parents are mirrored across generations and also observed in offspring who are depressed in adulthood.

Conclusion

Parent depression is associated with a significant risk of depression in their offspring. Studies such as EPAD provide an opportunity to better understand under what circumstances offspring are at greatest risk. This can help ensure effective targeting of clinical services and preventative interventions to those with greatest need.

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