

The genetic aetiology of childhood depression: a review

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Background: We review the evidence for the familiarity of major depressive disorder (MDD) and the genetic aetiology of depressive symptoms in children and adolescents. **Methods:** Databases and reference lists were searched for family, twin and adoption studies of childhood MDD and childhood depressive symptoms. Data from independent family studies that fulfilled specified inclusion criteria were pooled and odds ratios were calculated for top-down and bottom-up family studies. **Results:** Estimates of familial risk differ by control group and by study design (odds ratio range 1.70, 3.98). Twin studies show that depressive symptoms in young people are heritable although rater and measurement issues are important. Adoption studies show little evidence for a genetic influence on depressive symptoms. **Conclusions:** MDD in young people is familial although control group and study design affect the magnitude of the familial risk. Estimates of heritability from twin and adoption studies vary widely and few firm conclusions can be made regarding the genetic aetiology of depressive symptoms in childhood. Areas that require future work include the examination of rater effects, measurement issues, the effects of age and comorbidity and reasons for the discrepancy between twin and adoption findings. **Keywords:** Adolescence, adoption, childhood, depression, family, genetics, meta-analysis, twins. **Abbreviations:** CAPA: Child and Adolescent Psychiatric Assessment; CDI: Child Depression Inventory; DICA-P: Diagnostic Interview for Children and Adolescents Parent Version; DISC: Diagnostic Interview Schedule for Children; DZ: dizygotic; FDR: first-degree relative; FH-RDC: Family History Research Diagnostic Criteria; HR: high risk; K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia; LR: low risk; MDD: major depressive disorder; MFQ: Moods and Feelings Questionnaire; MZ: monozygotic; NIMH-DIS: National Institute for Mental Health Diagnostic Interview Schedule; OR: odds ratio; RDC: Research Diagnostic Criteria; SADS-L: Schedule for Affective Disorders and Schizophrenia lifetime version; VTSABD: Virginia Twin Study of Adolescent Behavioural Development.

There is consensus from family and twin studies that major depressive disorder (MDD) in adulthood is both familial and heritable (McGuffin & Katz, 1989; Kendler, Neale, Heath, Kessler, & Eaves, 1992; Kendler et al., 1994; McGuffin, Katz, Watkins, & Rutherford 1996; Kendler & Prescott, 1999; Sullivan, Neale, & Kendler, 2000). Results from family and epidemiological studies have led to the suggestion that early-onset depression may be more strongly genetically influenced than adult-onset MDD. First, childhood MDD shows strong continuity with depression in adulthood (Harrington et al., 1993; Van Os, Jones, Lewis, Wadsworth, & Murray, 1997; Wickramaratne & Weissman, 1998; Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001). Second, some (Neuman, Geller, Rice, & Todd, 1997) but not all (Harrington et al., 1997) family studies have found an increased risk of MDD in the relatives of early-onset cases compared to the relatives of adult-onset cases. Third, increased familiarity has been reported in the offspring of early-onset MDD cases (onset before 30 years) compared with the offspring of later-onset cases (Weissman, Warner, Wickramaratne, & Prusoff, 1988; Wickramaratne & Weissman, 1998). These findings coupled with the observation that an earlier age of onset is often the result of a more strongly

genetically influenced disorder (e.g., Alzheimer's disease, breast cancer, diabetes) have led to suggestions that early-onset MDD cases should be targeted for molecular genetic studies. However, family studies include both environmental and genetic influences, and twin and adoption studies of depressive symptoms in children and adolescents do not report converging findings.

In this paper we examine the evidence that childhood depression is genetically influenced. More specifically we sought to examine the following important questions: 1. How robust is the evidence that depressive disorder in childhood and adolescence is familial and what estimate of relative risk for depression do we obtain from a meta-analysis of family study data? 2. What evidence is there that depressive symptoms and disorder in childhood and adolescence are heritable and is there sufficient evidence to conclude that molecular genetic studies of depression in children are worthwhile?

Family studies

How robust is the evidence that childhood depression is familial?

Family studies of early-onset MDD can be differentiated according to their strategy; 1) 'bottom-up'

studies of the relatives of child probands with a diagnosis of major depressive disorder (MDD), or 2) 'top-down' studies of the children of depressed parents (usually depressed mothers). On the whole, both types of family study have reported an elevated risk of MDD in these groups in comparison to controls.

Bottom-up studies

Studies of the relatives of child probands with MDD (Puig-Antich et al., 1989; Kutcher & Marton, 1991; Harrington et al., 1993; Goodyer, Cooper, Vize, & Ashby, 1993; Williamson et al., 1995; Kovacs, Devlin, Pollock, Richards, & Mukerj, 1997; Harrington et al., 1997; Weissman et al., 1999; Wickramaratne, Greenwald, & Weissman, 2000a; Klein, Lewinsohn, Seeley, & Rohde, 2001) report an increased prevalence of MDD of around twofold in first-degree relatives (FDR) compared to non-affective psychiatric controls, and to the relatives of never psychiatrically ill controls. Two studies differ in that they found no significant difference in the familial rate of MDD in young MDD probands compared to young non-affective psychiatric controls (Mitchell, McCauley, Burke, Calderon, & Schloredt, 1989; Puig-Antich et al., 1989). Mitchell et al. (1989) found no increased risk for lifetime Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robbins 1978) based diagnoses of MDD in the directly interviewed parents of early-onset probands versus parents of a psychiatric control group, although other first-degree relatives were not studied. Similarly, Puig-Antich et al. (1989) found that lifetime morbidity risk for MDD was marginally but not significantly higher in the relatives of an MDD group compared to those of a non-affective psychiatric control group. However, age-adjusted rates were not analysed and were more highly elevated in the relatives of the proband group compared to the psychiatric control group.

Top-down studies

Studies of the offspring of parents with MDD (Weissman, Leckman, Merikangas, Gammon, & Prusoff, 1984; Keller et al., 1986; Weissman et al., 1987; Hammen et al., 1987; Weissman, Warner, Wickramaratne, & Prusoff, 1988; Orvaschel, Walsh-Allis, & Ye, 1989; Hammen, Burge, Burney, & Adrian, 1990; Biederman, Rosenbaum, Bolduc, Faraone, & Hirshfield, 1991; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992; Mufson, Weissman, & Warner, 1992; Warner, Mufson, & Weissman, 1995; Beidel & Turner, 1997; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997; Wickramaratne & Weissman, 1998; Warner, Weissman, Mufson, & Wickramaratne, 1999; Wickramaratne, Warner, & Weissman, 2000b) have reported higher levels of MDD in the offspring of depressed parents compared to offspring of parents with no psychopathology

(relative risk/odds ratio range 0.9–8.8, median 2.75). Compared to psychiatric (Biederman et al., 1991; Mufson et al., 1992) or medical control groups (Hammen et al., 1990) an increased risk of around twofold to offspring of depressed parents has been reported. Taken overall then, there is reasonably consistent evidence from both bottom-up and top-down studies that childhood depression is familial.

What estimate of relative risk for depression do we obtain from a meta-analysis of family study data?

Method

Inclusion criteria for family studies in the meta-analysis (some of which were specified by Sullivan et al. (2000) in their review of adult MDD) were: 1) distinction between unipolar and bipolar depression; 2) systematic recruitment of probands and relatives; 3) systematic recruitment of a control group; 4) use of operationalized criteria. Medline, Web of Science, Psych. lit. databases and reference lists were searched for relevant studies for all years recorded. Combinations of the following keywords were used: depress*, parent*, mother, father, mat*, pat*, fam*, offspring, child*, adolesc*, internal*, external*, CBCL, twin, genetic*, adopt*.

Eight relevant and independent parent-to-offspring studies were identified of which four could be included in the meta-analysis (see Table 1). Studies that did not use diagnoses as outcome measures were not included in the meta-analysis (see Beardslee, Bemporad, Keller, & Klerman, 1983; Downey & Coyne, 1990; Downey & Walker, 1992) to minimise effect size variability due to measurement differences. Studies that used the same sample cohort as part of separate analyses were not included to reduce the possibility of effect sizes being weighted by the specifics of a single study. In the case of the analyses of the same cohort, preference was given to papers that presented raw data, employed direct interviews rather than family history only and that included the youngest offspring. Full references are given.

Nine independent bottom-up studies were identified of which six fulfilled the inclusion criteria and were thus included in the meta-analysis (see Table 2). In papers where both raw and age-adjusted rates have been reported, the age-adjusted rates have been taken. Full references are given. Some of the studies included in the meta-analysis included data on comorbidity. However, as most of the papers did not provide information of diagnoses additional to MDD, this could not be taken account of. In addition, correction for sample size was not undertaken in the present analysis. While sample size differences may influence effect size estimates, it should be noted that, with the exception of one very large bottom-up study, all the individual studies included did not differ greatly in sample size within study type, thus reducing variability. For family studies using normal control groups, our meta-analysis gives an odds ratio (OR) of 3.98 for top-down studies and 2.30 for bottom-up studies (only three bottom-up studies used a normal control group). Two of the four top-down studies used a psychiatric control group; the third paper included in the estimate used a medically ill control group. The overall OR for these studies was estimated

Table 1 Top-down studies

Authors	Method	N Children	Age of offspring (mean)	Measures	N MDD children in high-risk (a) group	N MDD children in low-risk (b) group	N MDD children in other psychiatric/medical group	OR (c) HR vs. LR (confidence interval)	OR HR vs. psych control (confidence interval)
Hammen et al. (1990)	Longitudinal (up to 3 years) Direct interview	94	8-16 (12.6)	SADS-L mother and child separately Lifetime DSM-III	10/22	4/38	4/14	3.975 (2.44, 5.51)	1.704 (-0.46, 3.87)
Biederman et al. (1991)	Interview with parent	107	4-20 (9.6)	NIMH-DIS parent Mother as informant for child DICA-P Lifetime DSM-III	7/37	0/47	4/23		
Mufson et al. (1992)	Direct interview	135	6-23 (16.8)	SADS-L mother and child separately C-GAS Lifetime DSM-III	54/153	9/41	5/20		
Warner et al. (1995)	Direct interview	145	6-23 (14)	As above Lifetime DSM-III	10/32	5/36	N/A		

(a) High risk = children of MDD parents

(b) Low risk = children of never psychiatrically ill parents

(c) Odds ratio

Table 2 Bottom-up studies

Authors	Method & Measures	N probands	N FDR (a) relatives	Mean age of relative	MDD in FDR of MDD probands	MDD in psychiatric controls	MDD in FDR normal controls	OR FDR proband vs. normal control (confidence interval)	OR FDR proband vs. FDR psych control (confidence interval)
Mitchell et al. (1989)	Direct interviews SADS-L	94 MDD 38 psych	180	39.6	65/133	22/47	N/A	2.122 (1.58, 2.66)	1.829 (1.22, 2.43)
Puig-Antich et al. (1989)	Family history for all relatives except informant (usually mother of proband) FH-RDC	48 MDD 20 psych 27 normal	188	35.7	55/104	12/41	12/43		
Harrington et al. (1993)	Direct interviews & family history SADS-L RDC-L	62 MDD 69 non-affective psych	399	47.6	23/128	7/151	N/A		
Goodyer et al. (1993)	Direct interviews Epidemiological DISC (level 2 items) DSM-III-R	19 MDD 17 partial syndrome 46 normal controls	141	60.8 (MDD) 54.9 (control)	16/30	N/A	16/82		
Kovacs et al. (1997)	Family history for all relatives except mother SADS-L	125 MDD 55 psych 26 bipolar	313	37.8	106/197	51/116	N/A		
Klein et al. (2001)	Direct telephone interviews. Family history if unavailable. Epidemiological. Age 14–18 SADS-L Age 18+ SCID DSM-IV	360 MDD 284 psych 457 normal controls	2202	40.0	293/864	85/350	209/988		

(a) FDR = first-degree relative

as 1.70. Five of the six bottom-up studies used a psychiatric control group; the pooled OR was 1.85.

Several issues raised by family studies are particularly important if we are to use family data to supplement (twin and adoption) studies that directly estimate heritability and to inform future molecular genetic studies. Namely, 1) Is the familial risk identified specific to MDD or does it merely reflect an increased risk of general psychopathology? 2) Is the magnitude of familial risk for MDD in young people similar compared to that in adults? That is, as has been suggested, do young people with MDD represent a group with higher familial loading? 3) In what way does the phenomenology and course of MDD influence familiarity? 4) To what extent is the familial link due to adverse family circumstances rather than genetic factors? We address these issues briefly below.

1) Specificity of risk for MDD

Significantly higher rates of any disorder or of problem behaviours in the offspring of those with MDD in comparison to normal control groups (Weissman et al., 1984; Radke-Yarrow et al., 1992) and to medically ill control groups (Hammen et al., 1990) have been reported. In addition, some studies have reported elevated risks of anxiety disorders (Weissman et al., 1997; Beidel & Turner, 1997; Rende, Warner, Wickramaratne, & Weissman 1999), of substance abuse (Weissman et al., 1984) and of alcoholism (Puig-Antich et al., 1989; Kovacs et al., 1997; Weissman et al., 1999). However, there are also many studies that support the specificity of transmission of MDD from parent to offspring (e.g., Orvaschel et al., 1988; Biederman et al., 1991; Warner et al., 1995). The odds ratio that we obtain also suggests some degree of diagnostic specificity since (although lower than compared to a normal control group), it remains significant for bottom-up studies when the comparison group is a non-affective psychiatric group.

2) Is prepubertal MDD more familial than adolescent or adult MDD?

Some studies have found evidence of greater familial loading in the relatives of childhood MDD probands compared to adult probands. For instance, Neuman et al. (1997) compared rates of MDD in the first-degree relatives of child probands (mean age 10.3, range 6–12) to adult probands and found that rates were more than twice as high than in the relatives of the childhood cases. In contrast, Harrington and colleagues (1997) found no difference in the rate of MDD in first-degree relatives of prepubertal probands (14.9%) and postpubertal probands (16.8%); however, higher levels of criminality (as measured by police records) and of family discord were found in the prepubescent relatives. Similarly, Wickramaratne et al. (2000a) found no difference in the rates of MDD in first-degree relatives of prepubertal (40.6%) and adolescent MDD cases (46.9%) (odds ratio 0.7, 95% CI 0.4–1.2). However, looking more closely, Wickramaratne et al. (2000a, b) have found some evidence suggesting that recurrent prepubescent MDD may be more familial. On the whole there seems to be little definitive evidence to

substantiate the claim that prepubertal MDD is more familial than adolescent or adult MDD.

3) Influence of comorbidity on relative risk for MDD

Conduct disorder. Family study findings suggest that MDD comorbid with conduct disorder (CD) may represent a distinct form of depression. Puig-Antich et al. (1989) first noted that the lowest levels of MDD in family members were found in MDD child probands with comorbid CD and associated suicidality (defined as a concrete plan and/or attempt in present episode). In those probands with MDD and CD, levels of MDD in their relatives were nearly identical to those of the normal control group. Findings from a follow-up study are also consistent with the conjecture that MDD comorbid with CD represents a distinct form of MDD (Harrington, Fudge, Rutter, Pickles, & Hill, 1990). Lower rates of continuity of MDD into adulthood were found in children with MDD plus CD compared to those with MDD only. However, recent findings from an older, mainly adolescent cohort differ in that both pure MDD and MDD comorbid with CD were shown to have strong continuities with adult depression (Fombonne et al., 2001).

Anxiety. Some family studies suggest that anxiety and depression may represent the same underlying familial liability. For example, Rende et al. (1999) found sibling aggregation for comorbid anxiety disorder and MDD in a high-risk offspring group (by virtue of parental MDD) but not a low-risk group (neither parent ever psychiatrically ill). In this cohort, the median onset of anxiety disorders was 8 years while it was 12 years of age for major depression. The authors note that this is consistent with assertions that familial liability for depressive disorder may be initially revealed through anxiety. Similarly, Warner et al. (1999), in a study of three generations, found that rates of anxiety disorders were elevated in the children of MDD parents and the grandchildren of MDD grandparents while rates of MDD were not. Nonetheless it may simply be that anxiety is a precursor of MDD regardless of familiarity of MDD. For instance, Wickramaratne et al. (2000b) found that high rates of anxiety disorders preceded child and adolescent MDD in both high- and low-risk groups. On the other hand, several studies report elevated rates of anxiety only in the offspring of parents with MDD and panic disorder and not in offspring of parents with pure MDD (Weissman et al., 1984; Biederman et al., 1991; Warner et al., 1995). Thus it is unclear whether anxiety disorder in children is influenced by family loading for MDD or by clinical features of parental MDD.

Continuity and recurrence of MDD. Continuity over time with the depressive phenotype in adulthood needs to be established if child-onset MDD cases are to be selected for molecular genetic studies. The Maudsley long-term follow-up studies have shown continuity of depression into adulthood (Harrington et al., 1990; Fombonne et al., 2001). Weissman and

colleagues have examined the familiarity of recurrent versus non-recurrent MDD in several studies (Warner et al., 1995; Wickramaratne et al., 2000a) and calculated a higher risk to relatives of recurrent MDD cases (e.g., Warner et al., 1995). Following up individuals from the original Puig-Antich (1989) study into adulthood, Wickramaratne et al. (2000a) found that familial loading was associated with recurrence and continuity in only the prepubescent MDD probands but not in the adolescent probands. Again, following this same cohort longitudinally, Weissman et al. (1999) found an elevated prevalence of mood disorders in the first-degree relatives of prepubescent MDD probands with recurrent illnesses compared to those without a recurrence. These findings have led Weissman and colleagues to suggest that a recurrent form of prepubescent MDD is familial (Weissman et al., 1999; Wickramaratne et al., 2000a, b). However, given the observations of nearly equal rates of MDD in relatives of both prepubescent and postpubescent MDD (Wickramaratne et al., 2000a; Harrington et al., 1997), this finding needs replication in other studies that examine recurrence. Thus overall, there is good evidence that MDD in young people shows continuity into adulthood. It seems that recurrent depression may be associated with an increased familial risk compared to non-recurrent depression.

4) Family adversity

Family studies only provide an upper limit to heritability estimates since they do not allow the separation of genetic and shared environmental influences. However, some family studies have directly measured within-family factors. For instance, Warner et al. (1995) found that 'chaotic family environment' as measured by the Family Adaptability and Cohesion Scale (Olson, Sprenkle, & Russel, 1979) was an independent predictor of dysthymia in offspring when parental MDD was controlled for. Depressed parents have also been described as less involved with their children, showing increased hostility and irritability and decreased interaction and affection (see Downey & Coyne, 1990 for a review). Specific family factors such as marital discord have been implicated as mediating the relationship between parental and child psychopathology (e.g., Davis & Windle, 1997). Nevertheless, genetic as well as environmental factors affect personal interactions (e.g., O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998a). Hence, risk factors likely comprise a complex interplay of genetic and environmental influences. In addition, influences that were once thought of as purely environmental (e.g., negative life events) have now been shown to also be affected by genetic factors (e.g., Thapar, Harold, & McGuffin, 1998). However, it is noteworthy that indicators of risk (genetic and environmental) such as parental psychopathology and family discord are uninformative about the mechanisms of risk, and the impact of family risk factors could differ across family members.

Summary of family study findings

In summary, there is consistent evidence that childhood depression is familial although our meta-analysis

suggests that the familial risk for childhood depression is not substantially greater than for adult depression (adult odds ratio = 2.84, Sullivan et al., 2000). So far there are insufficient data to support the distinction of prepubertal and postpubertal depression although there is tentative evidence that recurrent prepubescent MDD may be more familial than other forms of childhood MDD. There is some evidence to suggest that MDD comorbid with CD may be less familial at least in children.

In family studies, similarities in rates of depression across biological relatives may be due to adverse environmental influences as well as due to inherited genetic factors. There is clear evidence that family adversity is strongly associated with childhood depression (see e.g., Rutter, 2000; Davis & Windle, 1997) and a family study design does not allow us to disentangle the influences of genes and environmental influences. Twin and adoption studies allow the variance of a behavioural trait to be apportioned to genetic, non-shared environmental and shared environmental factors. Shared environmental factors are those that serve to make members of the same family alike and non-shared environmental factors are those that tend to make family members different from each other. Twin and adoption evidence is needed to address the question of whether childhood depression is genetically influenced.

What evidence is there that depressive symptoms and disorder in childhood and adolescence are heritable?

Twin studies

There have been at least ten independent published twin studies of depression in children and adolescents (Wierzbicki, 1987; Hewitt, Silberg, Neale, Eaves, & Erickson, 1992; Rende, Plomin, Reiss, & Hetherington, 1993; Thapar & McGuffin, 1994; Edelbrock, Rende, Plomin, & Thopmson, 1995; Schmitz, Fulker, & Mrazek, 1995; Murray & Sines, 1996; Eley, 1997; Gjone & Stevenson, 1997, Eaves et al., 1997) of which six have been based on depression-specific questionnaires (Moods and Feelings Questionnaire (MFQ) (Costello & Angold, 1988); Child Depression Inventory (CDI) (Kovacs, 1991)) and four that have used internalising symptom scores from the Child Behavior Checklist (CBCL) (Achenbach, 1991). Unlike family study samples that have been based on clinical, referred populations, all the twin study findings are based on non-clinical samples and most have utilised questionnaire measures.

Figures 1 and 2 illustrate heritability estimates from adequately sized twin studies that included parent- and self-rated depressive symptoms separately. Overall, twin studies have shown modest to high heritability estimates for parent-rated depressive symptoms (range 30–80%). However, heritability estimates from most (but not all) studies have been generally lower for self-reported symptoms (range

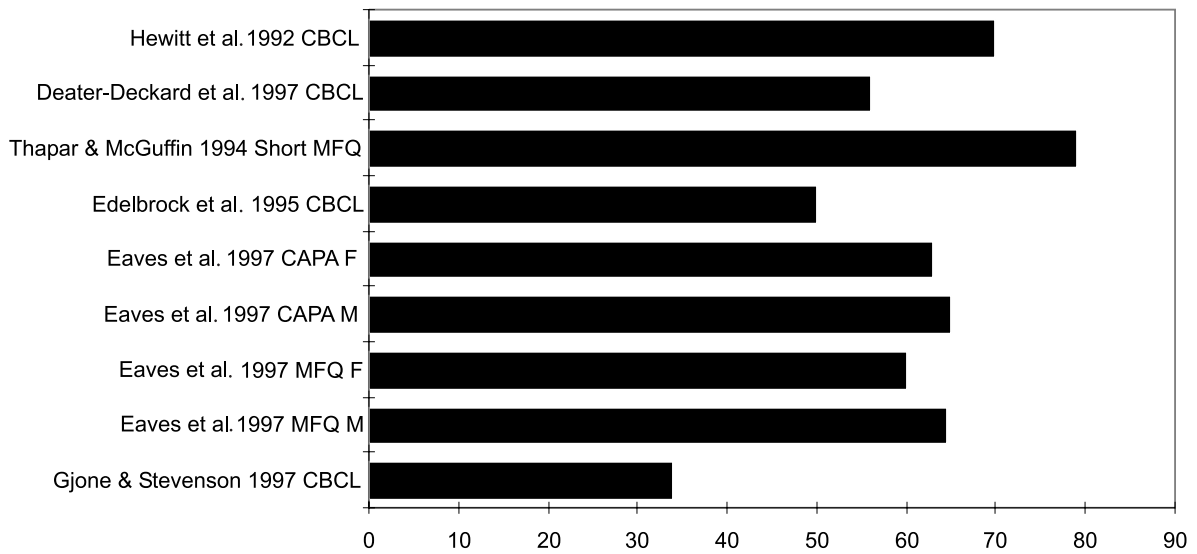


Figure 1 Heritability estimates for parent-rated depressive symptoms

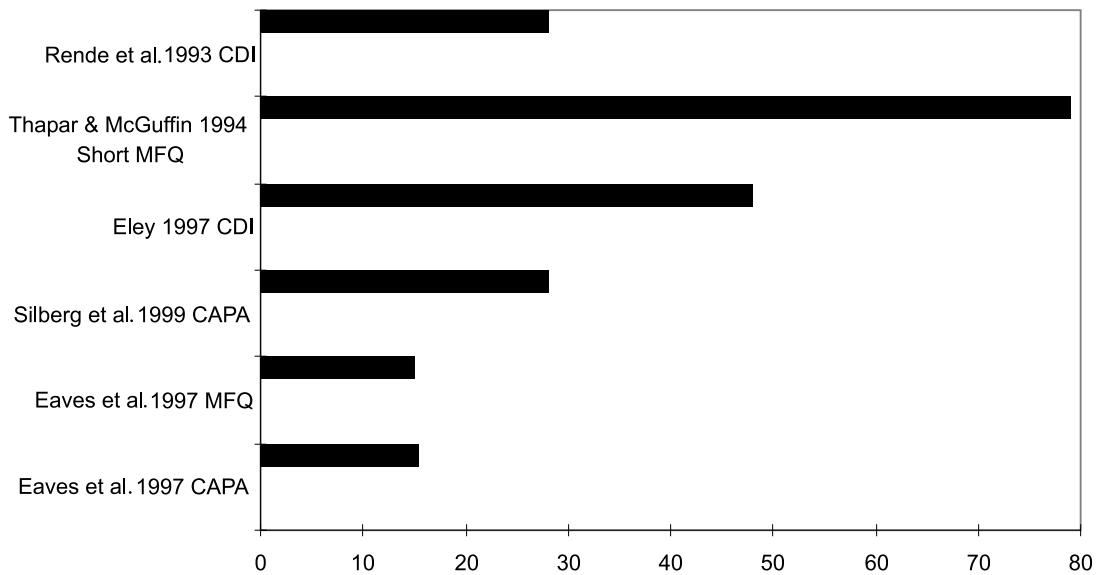


Figure 2 Heritability estimates of self-reported depressive symptoms

15–80%). Some variation in heritability estimates is not surprising since heritability estimates are specific to the population being studied and these papers include different populations. However, it is unclear why heritability estimates are higher for parent-rated symptoms, though measurement may be a factor since few studies have used the same measurement instrument across different raters. The issue of why heritability estimates differ according to rater is obviously important since it has implications for behaviour and molecular genetic research.

The largest twin study of childhood depressive symptoms is The Virginia Twin Study of Adolescent Behavioural Development (VTSABD) (Eaves et al., 1997) which used the semi-structured Child and Adolescent Psychiatric Assessment (CAPA) (Angold &

Costello, 2000) to generate DSM-III-R (American Psychiatric Association, 1987) symptom scores in a sample of 1412 twins aged 8–16 years. Overall heritability was estimated at 60% (parent-rated range 54–72%) although estimates differed across informants with estimates for self-reported symptoms being particularly low (boys 11%, girls 19%). Eaves and colleagues also looked at heritability as measured by The Moods and Feelings Questionnaire (MFQ) which is a 34-item questionnaire designed to cover the symptoms of DSM-III-R depression. Again, Eaves and colleagues found that heritability estimates were substantially lower for self-reported symptoms (boys 16%, girls 15%) than proxy reports from either parent (range 60–65%). Similarly, Thapar & McGuffin (1994) used the shortened MFQ and reported an overall heritability estimate for parent-rated data of

79% (although their self-rated symptoms yielded a similar heritability estimate of 70%). Heritability estimates for parent-rated CBCL scores range from 34 to 70% (Hewitt et al., 1992; Edelbrock et al., 1995; Schmitz, Fulker, & Mrazek, 1995; Deater-Deckard, Reiss, Hetherington, & Plomin, 1997; Gjone & Stevenson, 1997) and for self-reported CDI scores, heritability estimates range from 32–48% (Wierzbicki, 1987; Rende et al., 1993; Eley, 1997).

Age effects

Epidemiological and behaviour–genetic evidence suggests that differences in the relative contribution of genetic and environmental influences to depression in young people might be expected to vary as a function of age. Epidemiological studies show differences in the prevalence and the sex ratio of depressive disorder and depressive symptoms in children compared to adolescents (see e.g., Harrington, 1994). More generally, behaviour–genetic studies of other phenotypes most notably of IQ have found shared environmental influences to decrease and genetic influences to increase with age.

Five studies have stratified twins according to age. In a study of 411 twins aged 8–16 years (Thapar & McGuffin, 1994), overall heritability for maternally rated depressive symptoms was 79%. However, when the sample was stratified according to age, shared environmental factors accounted for the majority of the variance for children's symptoms (8–11 years). In contrast, for adolescent's symptoms, both self and maternally rated, genetic factors were substantial. This suggests that developmental change may be of importance. It has been suggested that this may be due to gene–environment correlation¹ increasing with age (gene–environment correlation is included in heritability estimates in twin studies).

Two other groups have reported similar findings. Eley & Stevenson (1999) examined self-reported CDI scores in 490 pairs of twins aged 8–16 and found the importance of additive genetic factors increased with age in males but decreased with age in females. Using a subset of the VTSABD, Silberg et al. (1999) found heritability to increase with age in females. However, findings of increased heritability in adolescence have not been consistent and two groups report a decrease in heritability with increasing age. Using the internalising scale of the CBCL Gjone, Stevenson, Sundet, & Eilertsen (1996) found the

significance of genetic factors decreased with age in a younger cohort (range 5–15 years) of 526 MZ and 389 DZ twins. Similarly, O'Connor, McGuire, Reiss, Hetherington, & Plomin (1998b) and O'Connor, Neiderhiser, Reiss, & Hetherington (1998c) found the importance of genetic influences decreased over a three-year period in a longitudinal mixed twin and family study ($h^2 = 48\%$ at wave 1; $h^2 = 22\%$ at wave 2). Thus the importance of developmental change and the influence of gender is unclear.

Gene–environment correlation and age. Genes and environmental risk factors may correlate. The decrease in the proportion of variance accounted for by shared environmental factors as age increases has previously been documented (Plomin, 1986). It may be that heritability increases with age in twin studies since heritability estimates using twin methodology include gene–environment correlation. Simply, this refers to the fact that genetic and environmental influences covary, that is children inherit genes from their parents but are also exposed to environments that are shaped by their own and their parent's genetic makeup. It is possible that gene–environment correlation increases with age as children become more autonomous and have more control in choosing their environments, or 'niche-fitting'.

Silberg et al. (1999) studied the relationship between stressful life events (maternally rated) and self-reported DSM-III-R symptoms derived from the CAPA. The relationship between depressive symptoms and life events was genetically influenced in only the pubertal girls and not the younger children or boys. This finding is consistent with the conjecture that gene–environment correlation increases with age. Importantly, the common genetic influence in this study could not be attributed to shared rater bias or error (criterion contamination) since different informants rated depressive symptoms and life events. However, the conflicting findings reported by Gjone & Stevenson (1997), O'Connor et al. (1998a, b) and by Eley & Stevenson (1999) for girls are confusing, although measurement issues may be important. Gjone & Stevenson (1997) used the internalising scale of the CBCL while the other studies used depression-specific questionnaires. Eley & Stevenson (1999) used self-reported depressive symptoms which they note may have been a difficult task for the younger children in the study; O'Connor et al. (1998a, b) used a composite of parent- and self-rated CDI symptoms and observational measures. Thus findings are not consistent regarding the importance of developmental change on the aetiology of depressive symptoms but some of the inconsistency may be attributed to different measurement instruments and informants.

In addition to gene–environment correlation, gene–environment interaction is also included in the genetic estimate in twin studies. Simply, gene–environment interaction refers to differential genetic

¹Several types of gene–environment correlation have been identified. For example, sociable parents pass on genes to their children but may also provide an environment that encourages sociability in their children (passive gene–environment correlation). A sociable child may also actively seek out circumstances that further increase sociability (active gene–environment correlation). A sociable child may also evoke sociable or friendly reactions from others (evocative gene–environment correlation.)

susceptibility to environmental risks. Statistically, gene–environment interaction is very difficult to detect in the presence of gene–environment correlation (Rutter, Silberg, O'Connor, & Simonoff, 1999). Nevertheless, evidence for a significant gene–environment interaction between independent negative life events and depressive symptoms in female adolescent twins has recently been reported (Silberg, Rutter, Neale, & Eaves, 2001).

Extreme groups

There has been no twin study of depressive disorder in childhood. The DeFries & Fulker regression method (DeFries & Fulker, 1985, 1988) provides a means of at least examining the genetic aetiology of high depression symptom scores. However, twin studies of selected extreme groups report conflicting findings. Rende et al. (1993), Deater-Deckard et al. (1997) and Eley (1997) all found that high scores were less genetically influenced than scores within the normal range (range for extremes 20–35) and that the importance of shared environmental factors increased with extreme scores (Rende and Deater-Deckard analysed data from the same cohort and some of these individuals were included in the Eley study). However, Gjone et al. (1996) reported a trend in the opposite direction, with extreme scores being more genetically influenced than individual differences. Thus there are insufficient consistent findings to draw conclusions about the genetic aetiology of extreme depression symptom scores.

Comorbidity. Bivariate genetic analysis has been used to examine the aetiology of co-occurring symptoms. This allows the examination of the extent to which genetic and environmental influences account for the covariation of two behavioural measures such as anxiety and depression symptoms.

Anxiety. As in adults, most of the covariation between depressive and anxious symptoms can be explained by common genetic influences (Thapar & McGuffin, 1997; Eley & Stevenson, 1999). However, neither of these studies used a longitudinal approach which would provide greater insight into the relationship between anxiety and depression.

Conduct disorder. Gjone & Stevenson (1997) examined the heritability of extreme scorers on parent-rated Child Behaviour Checklist (CBCL) symptoms in a population-based twin sample. For extreme scorers, heritability was lower for children with comorbid internalising and externalising problems than for those with internalising problems only. No significant difference between the fraternal (dizygotic; DZ) and identical (monozygotic; MZ) correlation was observed, indicating that comorbid internalising and externalising problems are less genetically influenced than internalising behaviours

only. These results are consistent with those from family studies in suggesting that depression or depressive symptoms when comorbid with conduct problems may represent a less familial and thus possibly less heritable subtype (e.g., Puig-Antich et al., 1989; Harrington et al., 1990). The authors also examined the genetic and environmental contribution to covariation between internalising and externalising symptoms and found that this was primarily due to shared environmental factors, particularly in the younger twins. In contrast, O'Connor et al. (1998c) found about 50% of the covariation between antisocial behaviour and depressive symptoms to be explained by a common genetic influence. However, there were specific non-shared environmental factors for both behaviours. There was also evidence for an important shared environmental influence on antisocial behaviour but not depressive symptoms. Few twin studies of depression in young people have used comorbidity data and even fewer have a longitudinal design, therefore, few conclusions can be drawn.

Conclusion from twin studies

Twin studies show evidence for an influence of genetic factors on the aetiology of depressive symptoms using both depression-specific questionnaires and the internalising scale of the CBCL, when reports are obtained from parents. The majority of studies have found that heritability estimates are lower for self-rated symptoms than parent-rated symptoms, suggesting that rater and measurement issues are important. There have been no twin studies of clinical depression in children and adolescents and there are no consistent findings for extreme depressive symptom scores. It is evident that future work is needed to examine why findings are so inconsistent and particularly in relation to why results differ according to informant. Findings of changes in heritability with age are frustratingly inconclusive.

Adoption studies

There have been two adoption studies of depressive symptoms in childhood (van den Oord, Boomsma, & Verhulst, 1994; Eley, Deater-Deckard, Fombonne, Fulker, & Plomin, 1998), both of which have found little evidence for an important genetic component. The first studied parental ratings of a modified version of the CBCL in three groups of international adoptees, singletons (N = 94), biological siblings (N = 222) and non-biological siblings (N = 442) (mean age 12.4, mean age at placement 2.3 years). Correlations for the internalising scale were equal across biological and non-biological different sex siblings but were higher in the unrelated same sex dyads indicating little genetic influence and a shared environment component to parent-rated internalising

behaviours. There were significant differences across groups in the number of changes in care setting before adoption and in the amount of abuse and neglect children had been exposed to before adoption. Since it is known that stressful life events and chronic adversity are related to depressive symptoms and disorder, it is possible that these group differences may have affected results.

Eley et al. (1998) studied the Colorado Adoption Project cohort using both a sibling and a parent offspring design. Parents completed the CBCL when their children were aged 7, 9 and 10 years (mean age at placement 29 days). Children also completed a 10-item self-report questionnaire containing items from three separate questionnaires. Mothers completed the 16 Personality Factor Questionnaire (Cattell et al., 1970) to derive their neuroticism scores. Correlations between biological siblings and between biologically related parents and offspring were low (the correlation with mother's neuroticism scores and self-rated depression was near zero for all groups), consistent with a substantial non-shared environmental component. Correlations were compared across three different measurement instruments, which might have reduced correlations between individuals and increased measurement error.

Thus twin and adoption studies have reported different findings, with adoption studies showing little evidence for an important influence of genetic factors on depressive symptoms in childhood. It may be that heritability estimates are increased in twin studies due to gene-environment correlation. Passive gene-environment correlation is the phenomenon whereby parents provide an environment related to their own genes and therefore to their child's genes. Adoption studies are thought not to include passive gene-environment correlation in heritability estimates since passive gene-environment correlation arises when children live with their biological relatives and this is not the case with adopted children. Other potential sources of inconsistencies are rater and measurement issues. In addition, both twin and adoption studies tend to under represent high-risk environments (Rutter et al., 1999; Rutter, 2000). However, this is especially true of adoption studies.

Conclusion

Initially we set out to review the literature on the genetic basis of childhood depression. Our conclusion is based upon our original questions. We first asked, 'How robust is the evidence that depressive disorder in childhood and adolescence is familial and what estimate of relative risk for depression do we obtain from a meta-analysis of family study data?' Most family studies report that MDD in childhood and adolescence is familial although estimates of risk vary across studies and according to how the sample is stratified. Our estimate of

familiality differs according to the type of control group used. Compared to a normal control group, for top-down studies there is a nearly fourfold increase in risk of depression among first-degree relatives (OR=3.98) and a twofold increase for bottom-up studies (OR=2.12). Compared to a psychiatric or medical control group there is nearly a twofold increase in risk although not all top-down studies use such control groups (OR range 1.70–1.83). These results suggest a measure of diagnosis specificity in the bottom-up group (which has the largest number of studies) since the odds ratio remains significant when the comparison group is a non-affective psychiatric control group. Our estimates may underestimate familial risk since no formal adjustment for age has been made, although if available, age-adjusted rates have been used from the original papers. Furthermore, data were collected from papers rather than from the original data sets. This reduced the statistical analyses available to us and our results simply represent a pooling of available data. A larger number of studies could be included in the bottom-up analysis and these tended to have larger sample sizes than the top-down studies (N range bottom-up; MDD cases, 19–125; FDR 141–313 with one very large study of 360 cases; FDR 2202; N range top-down, 94–145 children). This resulted in narrower confidence intervals for odds ratios derived from the bottom-up studies. Only three top-down studies were included in the analysis based on comparisons with a psychiatric control group (although one of these included a medical control rather than a psychiatric control group), resulting in a wide confidence interval (and a non-significant odds ratio). As mentioned earlier, sample size was not corrected for in this analysis; however, since the individual studies included did not differ greatly in sample size, we did not expect sample size differences to introduce variability.

Family studies have found that recurrence of MDD and age of onset in early adulthood in family members are factors which are likely to be present in familial rather than non-familial MDD. There is some unreplicated evidence to suggest that familial loading may only affect recurrence of prepubertal- rather than adolescent-onset MDD. A trend has been observed for lower rates of familiality in relatives of younger probands with comorbid conduct disorder and MDD, suggesting that MDD with conduct disorder may represent a distinct subtype at least in children.

In conclusion there is consistent evidence, from family studies and our analyses of pooled data, that MDD in children and adolescence is familial. Importantly for molecular genetic studies, long-term follow-ups of child and adolescent MDD cases have shown that MDD continues into adulthood. Nevertheless, it is noteworthy that these studies examine continuity at a group level rather than an individual

level. For the concept of continuity to be reliably established, ideally information about intra-individual differences should be incorporated when assessing inter-individual variability. Techniques such as growth curve analysis allow individual trajectories to be assessed while incorporating estimates of group-level variability (e.g., Ge, Lorenz, Conger, Elder, & Simons, 1994).

We next set out to answer the question 'Are depressive symptoms and disorder in childhood and adolescence heritable and is there sufficient evidence to conclude that molecular genetic studies of depression in children are worthwhile?'

Twin studies show that normal variation in depressive symptoms is genetically influenced although heritability estimates tend to be quite low for self-rated symptoms and estimates vary widely. No clear conclusion can be drawn regarding the aetiology of extreme scores. The two adoption studies of depressive symptoms show no evidence for a substantial genetic influence on depressive symptoms. Taken together, twin and adoption studies suggest that commencing molecular genetic studies of depression in children and adolescents should not be a priority.

Although twin studies show that depressive symptoms are heritable, the question as to why heritability estimates are nearly always lower for child-rated symptoms than for parent-rated symptoms, the issues of age and comorbidity effects and the discrepancy between twin and adoption study findings all require further investigation.

Rater effects

Parent-child agreement on symptom ratings and diagnostic interviews for internalising disorders is often low to moderate (e.g., Cantwell, Lewinsohn, Rohde, & Seeley, 1997). This could arise for many reasons: It may be that parents and children are rating different phenotypes or endorsing different symptoms. For instance, it could be that children or adolescents rate the symptoms of their current mood while parents may tend to rate their child's behavioural tendencies over a longer time period. Most studies have relied on retrospective recall of symptoms. Thus, remembering the depressive episode accurately is an issue for both parent- and self-ratings. Retrospective recall may be a particular issue for the cognitive symptoms of depression. Indeed, some psychological theories (e.g., Persons & Miranda, 1992) suggest that cognitive symptoms can only be accurately recollected when in a depressed mood (either as a result of a new depressive episode or of undergoing a mood induction). Proxy ratings of psychopathology may be biased by factors such as the current mental state of the informant (e.g., Hay et al., 1999). There are also particular types of bias relevant to twin studies that arise when a rater compares pairs of individuals, either contrasting

twins and rating them as more dissimilar from one another or by rating them as more similar than they appear when more objective observational measures are used. These are potential explanations for rater differences in heritability estimates that require further investigation.

Measurement

Since different studies and different types of study (e.g., family versus twin) differ in the measurement instruments they use, it is entirely plausible that differences between studies and study types are at least partly due to measurement issues. Family studies have used the family-history method, structured interviews and semi-structured interviews. Twin studies have used depression-specific questionnaires and the internalising scale of the CBCL. The two adoption studies used different questionnaires. These different measures have different psychometric properties (validity, reliability, sensitivity, specificity) and these differences may introduce variability in effect sizes. Thus, at least some inconsistency in findings is attributable to different phenotypic measures.

Given that there has been no twin or adoption study of clinical MDD in children or adolescents, we cannot draw any conclusions about whether or not clinical depression in this age group is a genetically influenced disorder. Twin studies of depression are difficult to conduct and this is partly due to the relatively low prevalence of MDD in young people (especially in children) compared to other psychiatric disorders (e.g., Foley et al., 2001). This low prevalence means that extremely large samples would need to be screened from the community or from clinical settings to allow a twin study of MDD. The nearest approximation we have to twin studies of depressive disorder is the analyses of high depression scores based on questionnaires. Unfortunately these have not yielded conclusive findings. Thus the trend of increasing heritability with increasing severity of depression that has been reported in the adult literature has not been established in children and adolescents.

The failure to replicate this finding in children and adolescents might suggest that there is genetic heterogeneity between depression in young people and depression in adults. These findings suggest that pooling early- and late-onset cases in molecular studies is not advisable. Factors such as measurement methods, the age and sex of the sample, and comorbidity clearly need to be taken account of in future work. Consistency of findings across different studies and a variety of study designs is required before conclusions can be drawn with confidence and this is still lacking for many key questions. There is thus clearly a need for much more work on the aetiology of depression in childhood and adolescence.

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