**Title Page**

Title: Anxiety and depressive disorders in offspring of parents with anxiety disorders: a meta-analysis

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CC and PL are supported by an NIHR Research Professorship to CC (NIHR-RP 2014-04-018).

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The NIHR had no involvement in any aspect of this paper.

PL, KM and CC have no competing or potential conflicts of interest to declare.

Acknowledgements: The authors thank Chloe Williams, Caitlin Thompson and Lucy Feighery for help with abstract screening, data extraction and quality rating; and Sally Smith for help with bibliographic / literature search issues. We also thank Drs Joseph Biederman, David Brent, Helen Dodd, Daniel Klein, Susanne Knappe, Autumn Kujawa, Anna Manelis, Daniel Pine, Krishnamachari Srinivasan, Lisa Starr and Erin Tone for responding to our requests for data.

Keywords: Anxiety Disorders; Depression; Risk Factors; Child; Adolescent

Objective: We conducted meta-analyses to assess risk of anxiety disorders among offspring of parents with anxiety disorders and to establish whether there is evidence of specificity of risk for anxiety disorders as opposed to depression in offspring, and whether particular parent anxiety disorders confer risks for particular child anxiety disorders. We also examined whether risk was moderated by offspring age, gender, temperament and the presence of depressive disorders in parents.

Method: We searched PsycINFO, PubMed and Web of Science in June, 2016 and July, 2017 (PROSPERO CRD42016048814). Study inclusion criteria: published in peer-reviewed journals; contained at least one group of parents with anxiety disorders and at least one comparison group of parents who did not have anxiety disorders; reported rates of anxiety disorders in offspring, and used validated diagnostic tools to ascertain diagnoses. We used random and mixed-effects models and evaluated study quality.

Results: We included 25 studies (7285 offspring). Where parents had an anxiety disorder, offspring were significantly more likely to have anxiety (RR: 1.76, 95% CI = 1.58-1.96) and depressive disorders (RR: 1.31, 95% CI = 1.13-1.52) than offspring of parents without anxiety disorders. Parent Panic Disorder and Generalized Anxiety Disorder appeared to confer particular risk. Risk was greater for offspring anxiety than depressive disorders (RR: 2.50, 95% CI = 1.50-4.16), and specifically for offspring Generalized Anxiety Disorder, Separation Anxiety Disorder and Specific Phobia, but there was no evidence that children of parents with particular anxiety disorders were at increased risk for the same particular anxiety disorders. Moderation analyses were possible only for offspring age, gender and parental depressive disorder; none were significant.

Conclusions: Parent anxiety disorders pose specific risks of anxiety disorders to offspring. However, there is limited support for transmission of the same particular anxiety disorder. These results support the potential for targeted prevention of anxiety disorders.

Introduction

Anxiety disorders are the most common psychiatric disorders among children and adolescents 1, with a median age of onset of 11 years 2. They are associated with increased risk of other psychiatric disorders including mood disorders, substance abuse and psychosis 3-5 and have a significant global economic burden 6. Prevention of these common and serious disorders will advance with an improved understanding of risk factors.

One risk factor for anxiety disorders in children, examined in family aggregation studies, is anxiety disorders in parents 7. In the first study to examine this risk, Turner and colleagues reported the odds of anxiety disorders to be more than seven times greater in children of parents with anxiety disorders than in children of psychiatrically healthy parents 8. Other studies examining risks posed by parent anxiety disorders have also found an increased risk of depression in offspring 9,10. However, some studies of parents with anxiety disorders have found lower, and some insignificant, odds of offspring anxiety disorders and / or depression, relative to offspring of healthy parents 9,11 and to offspring of parents without anxiety disorders but with other psychiatric disorders 12,13. These discrepant findings regarding risk of anxiety and depressive disorders in offspring of parents with anxiety disorders have been addressed in a single previous meta-analysis of nine studies, including 972 offspring 14. Children of parents with anxiety disorders were found to be at increased risk of anxiety disorders generally (OR: 3.91, 95% CI= 2.51–6.1), depressive disorders (OR: 2.67, 95% CI = 1.69–4.23) and Agoraphobia, GAD, Panic Disorder, Separation Anxiety Disorder, Social Phobia and Specific Phobias, relative to offspring of parents without psychiatric disorders. Here, we update our understanding of the issues examined by Micco and colleagues 14 regarding risks posed by parent anxiety disorders generally for research question (RQ) 1) offspring anxiety disorders generally, RQ 2) offspring depressive disorders and, RQ 3) offspring particular anxiety disorders. Further, we address three questions (RQ 4 – RQ6) not previously addressed in the literature regarding specific risks posed by parent anxiety disorders generally and particular parent anxiety disorders.

First, regarding disorder class, Murray et al. 15 raised the question of whether parent anxiety disorders are associated uniquely with offspring anxiety disorders or with child internalizing disorders more broadly. Rates of anxiety and depressive disorders have both been found to be raised in the offspring of parents with anxiety disorders, with greater odds of anxiety than depressive disorders 14. However, the previous meta-analysis did not directly compare the rates from studies where offspring were assessed for *both* anxiety and depressive disorders. So, what has not been addressed meta-analytically is whether parent anxiety disorders pose a greater risk to offspring of anxiety disorders or of depressive disorders. Thus, we ask RQ 4) whether offspring whose parents have anxiety disorders are at greater risk of anxiety disorders or of depressive disorders (in studies where both are assessed).

Our second novel question focuses on whether *particular* parent anxiety disorders place offspring at increased risk of anxiety disorders. Longitudinal cohort studies have examined this for parent Panic Disorder 10,16,17 in the ‘Massachusetts General Hospital at-risk study’, and for parent Social Anxiety Disorder in the ‘Reading Longitudinal Study’ 18-20 and the German ‘Early Developmental Stages of Psychopathology study’, in which parental GAD was also examined 21-24. Thus, we ask: RQ 5) are the rates of anxiety disorders higher in offspring of parents with particular anxiety disorders compared to offspring of non-anxious parents.

Third, there is evidence of increased risk of first-degree relatives (for example, sibling or avuncular relatives) having the *same* particular anxiety disorder as each other, including Social Anxiety Disorder 25-27 and Specific Phobia 28. More specifically, particular *parent* anxiety disorders, including Social Anxiety Disorder and Separation Anxiety Disorder, have been found to pose a specific risk of the *same* particular anxiety disorder to offspring 10,23. Thus, we ask: RQ 6) where parents have a particular anxiety disorder, are offspring more likely to have that *same* particular anxiety disorder, or only different anxiety disorders?

Longitudinal studies have shown the importance of risk factors other than parent anxiety disorder for the development of offspring anxiety disorders, of which we examine four. First, rates of anxiety disorders have repeatedly been found to be greater in females than males 29,30. Second, the temperamental style of behavioural inhibition has been implicated in the development of anxiety disorders 31,32, including in the context of parent anxiety disorders 33. Third, age is associated with different rates of particular anxiety disorders 34,35. Fourth, parental depressive disorders have been associated with an increased risk of offspring anxiety disorders 14,36. Here, we examine whether the presence of parental depressive disorders moderates risks to offspring of particular outcomes from different parent risk groups. In particular we ask, in non-anxious parents, as the rate of parent depressive disorder increases, does the risk of offspring anxiety disorder increase; and, in anxious parents, as the rate of depressive disorder increases, does this modify the relative risk of anxiety versus depressive disorders in offspring? Thus, we set out to sharpen the focus of our meta-analysis by examining these four potential moderators for each of the risk relationships specified in questions 1) to 6).

In summary, we examine the risks posed by parent anxiety disorders generally (i.e. any, but no specific, anxiety disorder’) for 1) offspring anxiety disorders generally and 2) offspring depressive disorders. We clarify issues of specificity by asking 3) whether parent anxiety disorders place offspring at greater risk of *particular* anxiety disorders and, 4) whether offspring whose parents have anxiety disorders are at greater risk of anxiety disorders or of depressive disorders (in studies where both are assessed). We examine the risk posed by particular parent anxiety disorders to offspring for 5) anxiety disorders generally and 6) the same particular anxiety disorder (see figure 1 for diagrams of the relationships in questions 1-6). Finally, we examine whether these relationships are weaker or stronger in the presence of other risk factors.

INSERT FIGURE 1 ABOUT HERE

Method

Protocol

We specified methods, inclusion and exclusion criteria and analyses in advance; and registered them in a protocol on the International Prospective Register of Systematic Reviews (PROSPERO; protocol number: CRD42016048814). We adapted the original protocol to account for the narrower scope of this systematic review. Specifically, this report focusses only on studies reporting diagnostic outcomes for anxiety. Examining the risks of continuous features of anxiety is conceptually separate from our focus here, so those studies which met the criteria in our registered protocol but reported only continuous outcomes will be reported separately.

Eligibility Criteria

We included articles which

1. were published in peer-reviewed journals 37
2. contained at least one group of parents with anxiety disorders and at least one comparison group of parents who did not have anxiety disorders.
3. reported rates of anxiety disorders in offspring.
4. used validated diagnostic tools to ascertain diagnoses.

We excluded articles where

1. participants were identified in light of issues other than parent psychiatric disorder (e.g., child anxiety disorder, parental cancer, diabetes, dental surgery).
2. parents had no anxiety disorder classified in DSM5 (where neither post traumatic stress disorder nor obsessive compulsive disorder are classified as ‘anxiety disorders’).

Information Sources and Search Terms

The electronic databases: PsycINFO (1967 onward), PubMed (no date restriction) and Web of Science Core Collection (1970 onward) were searched in the second week of June, 2016 and third week of July, 2017, (this rerun yielded a single extra paper 38) for reports published in English in a peer reviewed journal. The search strategies and syntax for each database are contained in the online supplementary materials (Supplement 1). We also completed a hand search of references from previous reviews and papers included in this review. We contacted study authors where data in a paper were reported in a format we could not analyse.

Outcome measures

The primary outcomes for this review were offspring anxiety disorder diagnoses and depressive disorder diagnoses.

Study selection

PL retrieved references, which were all independently screened and rated by PL and one of two research assistants. There was 100% agreement between raters.

Study quality assessment

PL and a research assistant both assessed study quality of all papers using an adapted version of the ‘Standard Quality Assessment Criteria for Evaluating Primary Research Papers’ for quantitative studies 39. Items on the checklist that were irrelevant to studies included in this review were removed (for example, ‘If interventional and random allocation was possible, was it described?’), and other items’ wording was modified for the purpose of this review (for example, from ‘Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias?’ to ‘anxiety disorder diagnostic interviews clearly defined?’). We kept items regarding study design, sample selection, sample description and the methods of assessment of anxiety disorders. The items were:

1. Is the study design evident and appropriate?
2. Is the method of participant selection described and appropriate?
3. Are the participant characteristics sufficiently described?
4. Are the anxiety disorder diagnostic interviews clearly defined?
5. Are the anxiety disorder diagnostic tools of high quality / robust?

For all studies, each item was rated as:

1. No - study did not resolve this item.
2. Partial - study addressed query partially.
3. Yes - study addressed query to high standard.

Data extraction and statistical analyses.

We extracted data for each outcome as well as relevant information about the participants, as summarized in Table 1. All data were extracted by both PL and a research assistant. Any disagreement was resolved by CC. A full list of data extracted is available from the authors.

 We used the R statistical environment, with the metafor package for meta-analysis 40 and its ‘weightr’ package for weighted sensitivity analyses.

We calculated Risk Ratios (RR) for diagnostic outcome reports using random effects meta-analyses 37. We used the Knapp and Hartung adjustment because random-effects modelling meta-analysis is known to increase the type-I error rate, especially when there is heterogeneity of variance or a small number of studies 41. We used the *I*2 statistic to calculate the impact of heterogeneity of effect sizes between studies 42. We conducted meta-regressions (mixed effects meta-analyses) to assess for moderation of effects by continuous variables (rate of depressive disorders in parents, offspring age, proportion of female to male offspring participants).

Publication Bias

We used funnel plots and Egger tests to assess the risk of publication bias and used *a priori* weight functions for sensitivity analyses 43.

Results

In total, 53 papers met our inclusion criteria. Table 1 provides characteristics of studies retained in analyses. (Table S1 provides characteristics of studies meeting inclusion criteria, but which did not provide data for analysis). Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. Of these, 26 were reports from follow-up studies. We removed multiple reports from the same cohorts to retain the most recent reports. We were unable to extract analysable data from two papers 44,45. Two papers reporting results from the same sample were retained because we could extract data for offspring anxiety disorders from only one of them 46 and data for offspring depressive disorders from only the other 47. Thus, we retained 25 papers from 24 studies with 7285 unique offspring. Table 2 contains a summary of the results.

INSERT FIGURE 2 ABOUT HERE

 Regarding RQ 1), children of parents with anxiety disorders were at significantly greater risk of anxiety disorders (1.76, 95% CI = 1.58-1.96, k = 22, n = 6674), with low heterogeneity between studies (*I2* = .01%) (Figure 3); and, regarding RQ 2), were at greater risk of depressive disorders (RR: 1.31, 95% CI = 1.13-1.52, k = 17, n = 5009) with low heterogeneity (*I2* = 28%) (Figure 4), than children of parents without anxiety disorders. Regarding RQ 3), offspring of parents with anxiety disorders were at risk of GAD (RR: 2.19, 95% CI = 1.58 - 3.04, k = 5, n = 3330, *I2*=0%), , Separation Anxiety Disorder (RR: 2.94, 95% CI = 1.26 - 6.86, k = 7, n = 424, *I2*=39%) and Specific Phobia (RR: 2.29, 95% CI = 1.11 - 4.75, k = 4, n = 269, *I2*=0%) compared to offspring of parents without an anxiety disorder, but there were no significant differences in risks for offspring Panic Disorder (RR: 2.17, 95% CI= .97 – 4.87, k = 6, n = 400, *I2*=0%) and Social Anxiety Disorder (RR: 2.98, 95% CI = .80 – 11.08, k = 5, n = 295) where heterogeneity was moderate (*I2*=49%). Regarding RQ 4), where studies assessed for anxiety *and* depressive disorders, the risk for anxiety disorders was significantly greater than the risk of depressive disorders (RR: 2.50, 95% CI = 1.50 – 4.16, k = 13, n = 3220) with high heterogeneity (*I2* =88 %) (Figure 5). Regarding RQ 5), there was significant risk of anxiety disorders in offspring of parents with Panic Disorder (RR: 1.82, 95% CI = 1.30 – 2.55, k = 6, n = 773) with moderate heterogeneity (*I2*=95%) or GAD (RR: 2.54, 95% CI = 1.86, 3.45, k = 2, n = 3614,) with moderate heterogeneity (*I2*=50%), but not Social Anxiety Disorder (RR: 3.49, 95% CI = .27 – 45.67, k = 2, n = 3157) where heterogeneity between studies was high (*I2*=72%) compared to offspring of parents without an anxiety disorder. We could not examine the risk to offspring associated with parental Specific Phobia or Separation Anxiety Disorder because there were no eligible studies. Finally, regarding RQ 6), where offspring had at least one anxiety disorder and their parents had a particular anxiety disorder, there was no evidence that children were at greater risk of the same particular anxiety disorder than of all other anxiety disorders. For GAD (RR: .39, 95% CI = .19 - .83, k = 3, n = 792), although heterogeneity was high (*I2*=85%), and Panic Disorder (RR: .26, 95% CI = .18 - .39, k = 4, n = 530, *I2*=0%) there was a greater chance that offspring would have a different disorder to their parents than have the same disorder, and for Social Anxiety Disorder there was not a significant difference in the risk of same versus other anxiety disorder (RR: .61, 95% CI .35 – 1.09, k = 3, n = 730), although heterogeneity was high (*I2*=75%).

INSERT TABLES 1 AND 2 ABOUT HERE

INSERT FIGUERS 3, 4 AND 5 ABOUT HERE

 Regarding rating study quality, inter-rater reliability was good (Cohen’s K = .779, 95% CI = .632 - .925).Studies were generally highly rated in four domains: evident and appropriate designs; descriptions of participant characteristics; definitions of anxiety disorder diagnostic tools; quality of diagnostic tools (Figure S1, available online). The main area of concern was that 11 studies were scored as only ‘partially addressing’ their methods of participant selection.

 Funnel plots (Figures S2 and S3, available online) and Egger test results were consistent with publication bias for studies reporting offspring anxiety (*z* = 3.36, *p* < .0001) and for those reporting offspring depressive disorders (*z* =2.15, *p* = .003). The bias appears to reflect studies with medium or larger standard errors (i.e., those with a smaller n) with null results being under-reported in the published literature. We used Vevea and Woods’ weight-function model to analyse sensitivity 43. The estimates for offspring anxiety (RR: 1.75 – 1.78) and depressive disorders (RR: 1.26 – 1.32) proved robust. This is consistent with publication bias being an unlikely influence on results.

 There was no support for offspring mean age moderating the risk of any outcome. Temperament was reported in too few studies to examine it as a moderator. There was limited evidence of moderation by i) offspring gender of the risk posed by parent anxiety disorders for offspring anxiety disorders, and ii) the presence of parent depressive disorders of the risk posed by parent anxiety disorder for offspring Separation Anxiety Disorder in particular (Figures S4 and S5, available online). The association between anxiety disorders in parents and offspring was higher when there was a greater proportion of female offspring in the study (QM(1) = 5.63, p = 0.02). This finding appeared to be accounted for by one study with only female participants 48 and the moderation effect was no longer significant when this study was excluded (QM(1) = 2.93, p = 0.09). The relationship between anxiety disorders in parents and Separation Anxiety Disorder in offspring was weaker where parents also had depressive disorders. However, when two outlying studies - which included no psychiatrically healthy parents - were removed, the moderation effect became non-significant (p=.20).

Discussion

Consistent with the previous meta-analysis by Micco and colleagues 14 we found that children of parents with anxiety disorders are at increased risk of both anxiety and depressive disorders. We extended the findings of the previous meta-analysis by demonstrating that the risk for offspring anxiety disorders is higher than the risk for offspring depression (RR: 2.50). The effect sizes we obtained for risk of offspring anxiety (RR: 1.76) and depressive disorders (RR: 1.31) are smaller than those reported in the previous meta-analysis (anxiety; OR: 3.91; depression; OR: 2.67). This is likely to reflect the greater number of included studies (an additional 11 studies with 3877 offspring). Indeed the effect sizes reported in many of these more recent studies are smaller than those in earlier studies, consistent with Ioannidis’ concept of the ‘decline effect’ 49.

 As well as identifying this general risk, it is scientifically and clinically important to examine the specific risks posed (i) for particular child anxiety disorders, and (ii) by particularparent anxiety disorders, in order to inform prevention programmes for at risk offspring. Regarding particular child anxiety disorders, Micco and colleagues had found that, compared to children of psychiatrically healthy parents, children of parents with anxiety disorders were at increased risk of all particular anxiety disorders. However, when compared to children of psychiatric control parents, children of parents with anxiety disorders were at increased risk of no particular anxiety disorders14. We found that offspring of parents with anxiety disorders, compared to offspring of parents without anxiety disorders, were at increased risk of GAD, Separation Anxiety Disorder and Specific Phobia, but not Social Anxiety Disorder or Panic Disorder, irrespective of whether parents had depressive disorders. The important implication for prevention of anxiety disorders in offspring at risk in light of parent anxiety disorders generally is that prevention programmes could focus on targeting specific mechanisms implicated in the development of GAD, Separation Anxiety Disorder and Specific Phobia, but may not necessarily need to focus specifically on the prevention of Social Anxiety Disorder or Panic Disorder.

 In terms of the risks posed by *particular* parent anxiety disorders, rather than parent anxiety disorders generally, we were able to examine the risks posed by three particular parent anxiety disorders: GAD, Panic Disorder and Social Anxiety Disorder. Our meta-analyses indicated that two of these, parent GAD and Panic Disorder, when compared to no parent anxiety disorder, place offspring at increased risk of anxiety disorders in general, while parent Social Anxiety Disorder did not significantly increase this risk. This is surprising, because previous studies of familial aggregation of anxiety disorders have found increased rates of anxiety disorders in first degree relatives of probands with Social Phobia 25-27,50. We could only include data from two studies in this analysis, yielding a large confidence interval around the point risk estimate of 3.49, which may explain this discrepancy. (Although many more than two studies included parents with Social Phobia in their high risk groups, we were unable to ascertain the rates of anxiety disorders in *their* offspring, so could not calculate the risk associated with parent Social Phobia in these studies.) Further, for parent GAD and Panic Disorder, offspring were significantly less likely to have the same particular anxiety disorder as their parent (i.e., GAD or Panic Disorder) than to have differentanxiety disorders. For parent Social Anxiety Disorder, offspring were not significantly more likely to have any of the other anxiety disorders than to have Social Anxiety Disorder. These results are also surprising, given the significant associations found between particular parent anxiety disorders and the same particular anxiety disorders in their offspring in some previous studies (for example, 10,20,51). It is possible that we failed to find a significant risk of the same particular disorder in offspring and parents because we had to set a higher bar for conclusions to be drawn about this than in individual studies. We required the risk of the same particular anxiety disorder in offspring to be greater than the combined risk for all other anxiety disorders. This is a higher bar than is typically set in individual studies where the risk of having the same particular anxiety disorder as a parent is compared to the risk of having another *individual* particular anxiety disorder. We were unable to assess for specificity of risk in this same way, because we had only group level data, not individual participant level data. As highlighted by Bloch 52, such individual participant level data are essential to clarifying meta-analyses, allowing finer grained analyses to be conducted. Without these data, we cannot conclude whether or not particular parent anxiety disorders increase the risk of the same particular anxiety disorder in their offspring compared to any other particular anxiety disorder.

 Our findings must be considered in light of the following limitations. The included studies did not report the age of onset of anxiety disorders in offspring, but the age of participation at the time of assessment. In particular, our analyses of risks for particular anxiety disorders could have failed to identify true moderation effects, because particular anxiety disorder have different median ages of onset (see 35). Second, few studies reported the rates of diagnoses of the full range of anxiety disorders so we were unable to examine which particular anxiety disorder is most commonly seen in the offspring of parents with a given particular anxiety disorder. Third, samples varied in terms of whether one or multiple children and one or two parents per family were included in study samples. This is problematic because including siblings or more than one parent might lead to increased estimates of risk, due to both sibling and parent similarities 53. Further, where only one parent was included, we were not always able to establish whether this was a mother or a father. While studies have found anxiety disorders in mothers and fathers to be equally important in explaining transmission of toddlers’ observed anxious behaviours 54, to our knowledge, top down studies have not reported differential risks for offspring anxiety disorders posed by maternal versus paternal anxiety disorders. Fourth, we were unable to assess whether offspring temperament moderated risk because it was reported in too few studies. Fifth, while we examined four particular moderators of the associations between parent and child disorders, we did not examine potential influences of a broader range of environmental factors (e.g. adversity, trauma, cultural factors). Furthermore, none of the studies we identified reported parent physical illness, so we were unable to examine how this context may influence risks to offspring. The generalizability of our findings is limited by differences between studies in whether families were recruited from clinics or the community, what diagnostic system was used, and whether current or lifetime disorder was assessed. Where lifetime anxiety disorders were not assessed, this would likely make our effects sizes more conservative estimates of the risks.

 We chose to examine risk for anxiety disorders based on studies using a family design, not twin designs, so are unable to conclude anything about the extent to which transmission of risk for anxiety disorders from parents to offspring might be genetically or environmentally mediated. Although notably a recent and pioneering children of twins study found that the transmission of risk of anxiety symptoms in adolescents was mediated solely by environmental factors 55. This is consistent with other studies that have found shared and non-shared environmental factors to be important in the development of anxiety disorders (e.g., 56).

 We focused here on categorical diagnoses of anxiety and depression, as predictor, moderator and outcome variables. Anxiety and depression can also be examined via dimensional constructs, such as symptom / trait measures and broader domains as highlighted by the United States of America National Institute for Mental Health Research Domain Criteria (RDoC) [58]. It will be important to establish whether the patterns of risk we have found here for categorical diagnoses are similar for dimensional features of anxiety and depression. Further investigation of specific dimensions will be important because evidence currently suggests that different dimensional features of anxiety and depression might be explained by different mechanisms. For example, twin studies examining dimensional features of anxiety and depression have found that stable genetic effects account for the *stability* of anxiety sensitivity, fear and negative affect from childhood to adolescence, while environmental factors account for *changes* in anxiety and depression symptoms over time 57-59.

 In summary, our meta-analyses found that parent anxiety disorders pose a greater risk of anxiety than depressive disorders to offspring; and that the risk was significant for some particular anxiety disorders in offspring (GAD, Separation Anxiety Disorder and Specific Phobia), but not others (Panic Disorder or Social Anxiety Disorder). Parent GAD and Panic Disorder, but not Social Anxiety Disorder, posed a risk of anxiety disorders in offspring, but not for the same particular anxiety disorder. These findings build on those from a recent meta-analysis 60 in which the only prevention programme which effectively lowered the rate of onset of child anxiety disorders was one in which at risk offspring were targeted in light of parent anxiety disorders 61. Although this does not establish a causal mechanism, it does demonstrate that targeting children at risk of anxiety disorders in light of parent anxiety disorders can be effective. Our findings suggest that there may be value in developing prevention programmes which i) identify offspring in light of particular parent anxiety disorders, and ii) target the prevention of particular anxiety disorders in offspring.

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Table 1 Characteristics of Studies Included in Meta-Analysis

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Offspring (n) | Age range (m) | Gender(%F) | Ethnicity | Parent Dx Tool | ADParent Dxs | Control Parent Dxs | Offspring Dx Tool | Recruitment |
| \*Beesdo et al., 2010  | 3021 | 21-34 | - | German sample | CAPI DIA-x / M-CIDI | Phobias or PD; GAD | Depression; Substance Use; No Psychiatric Disorder | CAPI DIA-x / M-CIDI | Community |
| Beidel & Turner, 1997 | 129 | 7-12 (9.6) | 44 | 83% European American15% AF-AM;2% E Indian | SCID (DSM III) | PD, Social Phobia, OCD; MDD & GAD; MDD & OCD | Depression; No Psychiatric Disorder | K-SADS | Clinical & Community |
| \*Bhat & Srinivasan, 2006  | 117 | 11-16 | 46 | 100% Indian | CIDI | PD | Depression; No Psychiatric disorder | MAGIC | Clinical |
| Biederman et al., 1991 | 121 | (9.2) | 41.3 | 100 Caucasian | NIMH-DIS | PD W Ag; PD + MDD | MDD; Other Psych; No Psychiatric disorder | DICA-P | Clinical & Community |
| Biederman et al., 2006 | 319 | 7-18 | 46 | 95 Caucasian | SCID | PD/AG; PD/AG + MDD | MDD; No PD/AG or MDD | K-SADS E | Clinical & Community |
| Biederman et al., 2007 | 233 | 7-18 (10.9) | - | 95 Caucasian | SCID | PD/AG; PDD + MDD | MDD; No PD/AG or MDD | K-SADS-E (<18 years) SCID (>17 years) | Clinical & Community |
| Breslau et al., 1987 | 331 | 8-23 | - | 80 Caucasian | DIS | GAD; GAD + MDD | No GAD or MDD | DISC | Probands from control group in study of children with disabilities |
| Buckley & Woodrfuff-Borden, 2006 | 49 | 6-12 (8.4) | 55 | 80 Caucasian | ADIS-IV | GAD, PD, Soc, Specific Phobia | Never psychiatrically ill | ADIS-IV-P/C | Community |
| Capps et al., 1996 | 32 | 8-14 | 67 | 69 Caucasian13 African-Am; 13 Asian-Am; 6 Latino | ADIS-R | PD/AG | Never psychiatrically ill | DISC-2.1 | Clinical & Community |
| Chapman et al., 2012 | 100 | 6-17 | 51 | 100 African-Am | ADIS-IV | PD/AG, Soc, GAD, OCD, Specific Phobia (various); PTSD; MDD | No Psychiatric Diagnosis | ADIS-IV-P/C | Community |
| \*Cox et al., 2012a  | 352 | 10+ (18) | 49 | 66 Caucasian | SCID; SCID-II | Not specified | Mood Disorder | KSADS-PL | Clinical |
| \*Hudson & Dodd, 2012  | 160 | 8-9 | 50 | 64 Oceanic; 20 European; 10 Asian | ADIS | AD | No anxiety disorder | ADIS-P-IV | Community |
| Kaplan et al., 1996 | 50 | 6-18 (9.5) | 67 | - | SADS-L | AG; MDD; SUD; Bipolar Disorder, OCD | No anxiety disorder | DICA-P | Clinical & Community |
| Klein et al., 2005 | 775 | 24 | - | - | K-SADS; LIFE | Any Anxiety Disorder | MDD, Alcohol dependence, Drug dependence | SCID-NP | Community |
| \*Kujawa et al., 2014  | 407 | (9) | 45 | 89.7 Causcasian; 7.6 African-Am; 2.7 Asian | SCID | AD; AD+MDD | MDD; No maternal anxiety or depression | K-SADS-PL | Community |
| \*Manelis et al., 2015  | 81 | 7-17(13.8) | 58 | - | SCID-IV | AD; AD+Bipolar Disorder | Bipolar Disorder; No family history of any major psychiatric diagnosis | K-SADS-PL | Clinical & Community |
| McClellan et al., 1990 | 163 | 7-17 | 51 | - | DIS | PD | MDD; No major psychiatric diagnosis | DICA; DICA-P | Clinical & Community |
| Merikangas et al., 1998 | 192 | 7-18 | 49 | 100 Caucasian | SADS | PD/AG; Soc and / or GAD | Substance abuse or dependence; Never psychiatrically ill | K-SADS-E | Clinical & Community |
| Mogg et al., 2012 | 119 | 9-14 (11.8) | 100 |  | SCID | PD | No psychiatric diagnosis | ADIS-P | Clinical & Community |
| Mufson et al., 1992 | 214 | 6-23 | 53 | - | SADS | PD + MDD | MDD; Never psychiatrically ill | K-SADS-E | Community |
| Murray et al., 2014 | 136 | 4-5 | 56.7 | >99 Caucasian | SCID | Social Phobia | No anxiety disorder | ADIS? | Community |
| Pine et al., 2005 | 142 | 9-19 | - | - | SCID | PD; PD+MDD | MDD; Psychiatrically healthy parents | PARIS | Clinical, Dental, Community |
| Schneider et al., 2009 | 107 | 13-23 | - | German sample | Mini-DIPS | PD/AG | No psychiatric disorder | F-DIPS | Clinical & Community |
| Schrock & Woodruff-Borden, 2010 | 158 | 3-12 | 44.3 | 76 Caucasian; 16 African-Am; 3 Hispanic; 1 Asian; 1 Native-Am; 3 other | ADIS | PD/AG; Social Phobia; GAD; Specific Phobia | No anxiety disorder, No diagnoses | ADIS-P (3-5 years) ADIS/PC (6-12 years) | Clinical & Community |
| Turner et al., 1987 | 59 | 7-12 | 42 | 93 Caucasian; 7 African-Am | ADIS | AG; OCD | Dysthymic Disorder; No DSM-III Diagnoses | CAS | Clinical & Community |
| Whaley et al., 1999 | 36 | 7-14 (10.3) | 44 | 78 Caucasian; 11 Latino; 6 Asian Am; 6 Other | ADIS-IV | AD (inc PD/AG, OCD, GAD, Social Phobia, Specific Phobia, Hypochondriasis and MDD | Psychologically healthy | K-SADS | Clinical & Community |

**Column heading key:**

Parent Dx Tool: Tool used to assess psychiatric disorders in parents

AD Parents Dxs: Diagnoses in parents with anxiety disorders

Control Parent Ds: Psychiatric disorders in parents without anxiety disorders

Offspring Dx Tool: Tool used to assess psychiatric disorders in offspring

Recruitment: Source(s) of participants

**Assessment tool abbreviations**:

ADIS(-R): Anxiety Disorders Interview Schedule (for DSM III-R);

ADIS-IV: Anxiety Disorders Interview Schedule (for DSM-IV);

CAS: Children’s Assessment Schedule;

CIDI: Composite International Diagnostic Interview;

Computer-Assisted Personal Interview (CAPI) version of the (DIA-X / M-CIDI) Munich-Composite International Diagnostic Interview;

DICA-P: Diagnostic Interview for Children and Adolescents – Parent Version;

DIPS (German version of ADIS-R);

DIPS: German version of ADIS-R

DIS: Diagnostic Interview Schedule;

DISC: Diagnostic interview Schedule for Children;

F-DIPS: German version of ADIS for DSM-IV

Kinder DIPS (German Child version of ADIS-R);

Kinder-DIPS: German version of Child ADIS-R

LIFE: Longitudinal Interval Follow-up Evaluation;

MAGIC: Missouri Assessment of Genetics Interview for Children;

Mini-DIPS: (German translation of ADIS-IV-L)

NIMH-DIS: National Institute of Mental Health Diagnostic Interview Schedule;

NYHRSFHI: New York High Risk Study Family History Interview;

PAPA: Preschool Age psychiatric Assessment;

PARIS: Parent As Respondent Informant Schedule;

SADS-L: Schedule for Affective Disorders and Schizophrenia - Lifetime Version.

SCID: Structured Clinical Interview for DSM (NP-Nonpatient version);

**Disorder abbreviations:**

AD: Anxiety Disorder

ASPD: Anti-Social Personality Disorder;

CD: Conduct Disorder

GAD: Generalized Anxiety Disorder

MDD: Major Depressive Disorder

SUD: Substance Use Disorder

\*Data provided by authors

Table 2 Summary of Results

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Offspring Outcome TABLE 2 Summary of Results | Parent risk group  | Parent control group  |  | Risk | Heterogeneity |
|  |  |  | *Studies, k* | *RR* | *95%CI* | *p* | *I2%* |
| AD | AD | without AD | 22*Sensitivity analyses* 2121 | **1.76**lowest 1.74highest 1.84 | 1.58, 1.961.57, 1.931.55, 2.18 | <.0001<.0001<.0001 | 0026 |
| Depressive disorder | AD | without AD | 17*Sensitivity analyses* 1616 | **1.31**lowest 1.29 highest 1.54 | 1.13, 1.521.10, 1.521.05, 2.25 | .001.004.03 | 0024 |
| GAD | AD | without AD | 15*Sensitivity analyses* 44 | **2.19**lowest 2.03highest 2.25 | 1.58, 3.04.88,4.681.59, 3.19 | <.0001.09<.0001 | 000 |
| Panic Disorder | AD | without AD | 6*Sensitivity analyses* 55 | 2.02lowest 1.87highest 3.31 | .87, 4.67.81, 4.35.87, 12.6 | .1.24.18 | 000 |
| Separation Anxiety Disorder | AD | without AD | 7*Sensitivity analyses* 66 | **2.94**lowest 4.32highest 2.16 | 1.26, 6.861.56, 11.961.07, 4.36 | .01.01.03 | 394422 |
| Social Anxiety Disorder | AD | without AD | 5*Sensitivity analyses* 44 | 2.98lowest 2.17highest 4.74 | .80, 11.08.56, 8.401.83,12.29 | .1.26.001 | 49470 |
| Specific Phobia | AD | without AD | 4*Sensitivity analyses*  33 | **2.29**lowest 1.62highest 2.83 | 1.11, 4.75.67, 3.91.27, 6.29 | .03.28.01 | 000 |
| Offspring Outcome  | **Parent risk group**  | **Parent control group**  |  | **Risk** | **Heterogeneity** |
|  |  |  | *Studies, k* | *RR* | *95%CI* | *p* | *I2%* |
| AD vs Depressive disorder | AD  |  - | 10*Sensitivity analyses*  99 |  **2.50**lowest 2.16 highest 2.77 | 1.50, 4.161.32, 3.51 1.69, 4.54 | .004.002.005 | 888479 |
| AD | GAD | without AD | 2*Sensitivity analyses -*  | **2.54**-  | 1.86, 3.45- | <.001- | 99- |
| AD | Panic Disorder | without AD | 6*Sensitivity analyses* 55 | **1.82**lowest1.54 highest 2.05 | 1.30, 2.561.24,1.911.37, 3.06 | <.0001<.0001.005 | 95655 |
| AD | Social AD | without AD | 3*Sensitivity analyses* 22 | 3.49lowest1.29 highest 19.9 | .27, 45.71.1,1.531.12, 330 | .34.002.037 | 9900 |
| GAD vs AD without GAD | GAD |  - | 2*Sensitivity analyses* - | **.39**-  | .19, .83- | .015- | 99- |
| Panic Disorder vs AD without Panic Disorder | Panic Disorder |  - | 4*Sensitivity analyses* 33 | **.25**lowest .23 highest .26 | .17, .36.13, .39.17, .39 | .<.0001.<.0001.<.0001 | 7600 |
| Social AD vs AD without Social AD | Social AD |  - | 3*Sensitivity analyses* 22 | .61lowest .46 highest .82 | .35, 1.09.31,.69.55, 1.24 | .09.0002.035 | 7500 |
| Key: AD: Anxiety Disorder; GAD: Generalized Anxiety Disorder; Sensitivity analyses used the leave-one-out method; significant results in bold. |