Title: The impact of parental mental illness across the full diagnostic spectrum on externalising and internalising vulnerabilities in young offspring

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Abstract

Background: The intergenerational risk for mental illness is well established within diagnostic categories, but risk is unlikely to respect diagnostic boundaries and may be reflected more broadly in early life vulnerabilities. We aimed to establish patterns of association between externalising and internalising vulnerabilities in early childhood and parental mental disorder across the full spectrum of diagnoses.

Methods: A cohort of Australian children (n=69,116) entering the first year of school in 2009 were assessed using the Australian Early Development Census (AEDC), providing measures of externalising and internalising vulnerability. Parental psychiatric diagnostic status was determined utilising record-linkage to administrative health datasets.

Results: Parental mental illness, across diagnostic categories, was associated with all child externalising and internalising domains of vulnerability. There was little evidence to support interaction by parental or offspring sex.

Conclusions: These findings have important implications for informing early identification and intervention strategies in high-risk offspring and for research into the causes of mental illness. There may be benefits to focusing less on diagnostic categories in both cases.

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Introduction

The intergenerational clustering of specific mental illnesses has long been observed¹ and has provided support for the pursuit of diagnosis-specific causal mechanisms. Intergenerational risk of mental illness extending beyond concordant diagnoses to risk of diagnostically-related illnesses is now well established, with offspring of parents diagnosed with schizophrenia having an elevated risk of developing bipolar disorder, for example². Whether such overlap extends even further to include apparently diagnostically unrelated disorders is less clear but a number of recent studies suggest the inherited risk for mental disorders may well span a broad spectrum of diagnoses^{3,4}. Such findings have important implications, not only for understanding the extent to which current diagnostic approaches have utility when applied to the identification of the causes of mental illness, but also for informing early identification and intervention strategies. Accumulating evidence of a lack of concordance in parent-offspring psychiatric diagnoses is also consistent with the notion of a general factor of psychopathology (the p factor) underlying the apparent overlap in symptoms across diagnoses^{5,6}, and thought likely to have a strong genetic basis⁷. It may be that this general factor of psychopathology is shared between parents and offspring, giving rise to a lack of diagnosis-specific intergenerational associations. Further, while mental disorders in adult offspring of affected parents have been well studied, it is increasingly understood that manifestations of intergenerational risk, including sub-clinical signs of emerging psychopathology, may appear much earlier in the lives of offspring, bolstering the potential for early identification of those at risk. The evidence to support early life antecedents of mental illness in those at elevated familial risk arises predominantly from studies focused on specific diagnostic groups, such as the high-risk longitudinal studies of offspring born to parents, usually mothers, with severe mental illnesses^{8,9}. Fewer studies have examined antecedents in offspring born to parents affected by other disorders, with the exception of perinatal depression¹⁰, while studies that have simultaneously included the full spectra of diagnoses in parents and domains of vulnerability in children are lacking. In addition, few studies have examined the impact of affected fathers

and thus the potentially important role of assortative mating on the developmental trajectory of mental disorders¹¹, at least partly on the basis that mothers with mental illness are often assumed to have a greater impact on offspring development.

The current study aimed to examine the nature of vulnerabilities emerging in early childhood across the externalising and internalising spectrum emerging in relation to parental mental illness across the full range of diagnoses, in a large population-based intergenerational cohort. We hypothesised that offspring externalising and internalising vulnerabilities would be associated with all types of parental mental health diagnoses, that associations would be present for offspring with affected mothers or affected fathers, and that these associations would be relatively greater where both parents were mentally ill.

Methods

Design and sample

The New South Wales Child Development Study (NSW-CDS) is a longitudinal population-based cohort study utilising multi-agency, inter-generational record linkage methodology¹². The child cohort includes all those children who entered their first year of full time schooling in the state of New South Wales in Australia in 2009 (aged approximately 5 years) and who were assessed by their teachers using the Australian Early Development Census (AEDC)¹³. The AEDC was completed for the vast majority of children entering school across the state (approximately 99%, N=87,026), providing the basis for a whole-of-population cohort (full sample and study details are provided in a published cohort profile paper¹²).

Cohort children were linked to a variety of population-based administrative databases. Linkage to parental information was possible for those children with NSW birth registration records (N=72,245). Parental records for this subsample were also linked to a variety of administrative databases including the NSW Ministry of Health's Mental Health Ambulatory (detailing community mental health contacts but not emergency department or primary care contacts) and Admitted Patients Data Collections (detailing all hospital admissions). The sample for the current study was further restricted by excluding those children identified as having special needs by teachers completing the AEDC (i.e. those children with chronic medical, physical, or intellectually disabling conditions, for whom limited AEDC data are available). The socio-demographic profile of the subsample of the NSW-CDS cohort used for the current study (n=69,116) has been compared to the full cohort and to the general population at the state and national level with no major group differences identified¹².

All data linkage for child and parent cohort members was undertaken by an independent government agency, the Centre for Health Record Linkage (CHeReL: www.cherel.org.au/), which obtained data directly

from data custodians in order that the researchers would not have access to any identifying information. The CHReL employed probabilistic linkage methods to match individuals across different datasets relying on the identifying information provided on individuals by each data custodian. Matching variables, including name, date of birth, residential address and sex, were obtained for each dataset, where available. Definite and possible matches between datasets were identified on the basis of matching probabilities (0.75 was set as the upper probability threshold for assigning 'true matches' and 0.25 the lower threshold for assigning 'false matches'. Clerical reviews were conducted on all pairs with probabilities between the thresholds. Optimal linkage rates were achieved using this process (see details provided in the published cohort description for more information¹²). Data provided to researchers for analysis was in de-identified form only. Ethical approval for the research was obtained from the NSW Population and Health Services Research Ethics Committee (HREC/11/CIPHS/14) and the University of New South Wales Human Research Ethics Committee (HC11409), with data custodian approvals granted by the relevant Government Departments.

Assessment of mental illness in parents

Data on the mental health of parents, including ICD-10 diagnoses, were obtained from the NSW Ministry of Health's Mental Health Ambulatory (for the years 2001-2009) and Admitted Patients (years 2000-2009) Data Collections. Details on each admission to hospital with a psychiatric diagnosis (ICD 10 Chapter V, F00-99 codes) listed as either a primary or additional diagnosis and each episode of ambulatory (i.e. community or outpatient) mental health service contact (episodes defined within 3-month calendar periods)¹⁴ were obtained up to the 31 December 2008 (the year prior to AEDC assessment) for all mothers and fathers of children in the cohort. Any psychiatric diagnosis assigned to a hospital admission episode and the primary diagnosis occurring latest in a 3-month calendar period for ambulatory contact were considered the relevant diagnoses for an episode of care. After exclusion of specific ICD-10 diagnostic code categories included in the raw data (those relating to physical health diagnoses only, those coded as health contact

for contextual reasons, and those where a psychiatric diagnosis was coded as not applicable), the following broad psychiatric diagnostic categories were developed (see Supplementary Table 1 for ICD-10 codes included in each broad group):

1. Severe mental illness;
2. Common mental disorder;
3. Personality disorder;
4. Substance abuse;
5. All other adulthood-onset illness (e.g. organic disorders, eating disorders, sleep disorders, disorders not otherwise classified or not yet allocated);
6. All other childhood-onset illness (e.g. hyperkinetic disorders, conduct disorders, mental retardation, pervasive developmental disorders);

Whilst these 6 broad groupings were comprised of mutually exclusive sets of ICD-10 codes (i.e. codes for schizophrenia appeared only in Group 1, and codes for anxiety disorders appeared only in Group 2), the groups created for analysis were not mutually exclusive. That is, offspring could appear in more than one broad parental diagnosis group if a parent was diagnosed with more than one psychiatric diagnosis belonging to more than one broad group throughout the course of available data collections. Sensitivity analyses were undertaken with mutually exclusive versions of the same categories created on the basis of *the last episode* of parental mental health contact occurring prior to the end of 2008¹⁴.

Assessment of early childhood outcomes

The Australian Early Development Census (AEDC) is a modified version of a validated Canadian instrument¹⁵ which is completed by teachers on the basis of at least one month's knowledge of the child (typically, teachers have at least five months' knowledge of the child). The AEDC is an instrument designed

to measure development in five key domains: physical health and wellbeing, social competence, emotional maturity, language and cognitive development, and communication skills and general knowledge. Subdomains within each of the five domains have also been identified. Three specific subdomains covering both externalising and internalising features were selected from the AEDC emotional maturity domain: aggressive problems, hyperactive and inattentive behaviour and, anxious and fearful behaviour¹⁶. For each subdomain, children were classified as vulnerable (in the lowest 10th centile) or not (remaining 90th centile) of the national 2009 AEDC sample. Supplementary Table 2 lists the individual teacher-rated items included in each of the three subdomains of interest. Between 437 and 469 children had invalid data on one of the three AEDC subdomain classifications due to inadequate completion of relevant AEDC items; these children were excluded from analyses involving the relevant subdomain data.

Consideration of covariates

The following socio-demographic factors were considered potential confounders of relationships between history of parental mental illness and externalising/internalising vulnerabilities: mother's age at birth of the child cohort member (three levels: ≤ 26.0 , > 26.0 and ≤ 36.9 , > 36.9 years), child age at AEDC assessment (three levels: < 5 , 5 and > 5 years), having English as a Second Language, and SEIFA (Socio-Economic Index for Area), a five-level (quintile) area-based index of socio-economic disadvantage¹⁷. The latter three variables were obtained from the AEDC dataset, and the mother's age from birth registration data.

Statistical analyses

Logistic regression models were used in all analyses of the hypothesised associations between offspring history of parental mental illness and externalising/internalising vulnerabilities. These analyses provided odds ratios (ORs) and their 95% confidence intervals (CIs); results were statistically significant if the 95% CI did not cross 1.00. The unexposed reference group for all analyses comprised the group of children without any history of parental mental illness. The impact of parental diagnostic group on children born to at least

one parent with any mental disorder was considered and then results were stratified first by sex of the affected parent and then by offspring sex. Offspring of two affected parents were also considered where numbers allowed. The main effect of parental diagnoses (in either parent) was adjusted for the selected covariates. Departure from the multiplicative logistic regression models was used to formally test the potential interaction of parental diagnosis with sex of the offspring (by adding an interaction term to the multivariate model) and sex of the affected parent (by formally comparing the stratified models for affected fathers and mothers). Finally, a series of sensitivity analyses were undertaken to determine the impact of restricting parental diagnostic classification to mutually exclusive categories of parental mental illness.

Results

Of the 69,116 children in the sample, 15.3% (n=10,563) had at least one parent with a psychiatric diagnosis; 4,127 (5.97%) had an affected father, 7,498 (10.85%) an affected mother, and 1,184 (1.71%) had both parents with a psychiatric diagnosis.

Broad diagnostic categories of parental mental illness and early childhood psychopathology

Compared to children with no mental disorder in either parent, those with at least one parent with any mental disorder had elevated risks of vulnerability across all three subdomains of interest: OR 1.87 (95%CI 1.75-1.99) for aggressive behaviour, OR 1.75 (95%CI 1.65-1.86) for hyperactive and inattentive behaviour, and OR 1.53 (95%CI 1.44-1.62) for anxious and fearful behaviour. When each of the six broad diagnostic categories were considered, significant associations were found for all categories in relation to all three subdomains (Table 1). The strongest effect appeared to be for children born to at least one parent with a childhood-onset disorder although the cell sizes in this diagnostic category were the smallest. Effect sizes were generally stronger for the two externalising domains. Adjustment for covariates reduced the strength of associations but all associations remained statistically significant (Table 2).

Impact of having two affected parents, sex of the affected parent and sex of offspring

The presence of mental disorder in a parent was positively associated with mental disorder in the other parent ($p < 0.001$). Children born to two parents with any mental disorder (n=1,184; 1.71%) had almost three times the odds (unadjusted) of being vulnerable in terms of aggressive behaviour than children without parental mental disorder (OR 2.85, 95%CI 2.45-3.31), with elevated risk also seen for the other two subdomains (Supplementary Table 3).

Repeated analyses stratified by parental sex indicated that significant associations between all categories of parental mental disorder and all subdomains were present for both offspring with affected mothers and offspring with affected fathers (Table 3; raw numbers in supplementary Table 4). Interaction by parental sex was formally tested (by comparing the models stratified by parental sex) and a statistically significant interaction was identified in the specific case of parental history of substance use disorder with the effect of maternal disorder being greater than paternal for each of the two externalising subdomains. A sensitivity analysis using parental diagnosis based on the most recent mental health contact, with results stratified by sex of the affected parent, was also conducted and these results were similar to those initially produced (tables available from authors on request).

The main analysis was repeated with stratification by offspring sex. Having at least one parent with a history of any mental disorder was associated with offspring vulnerability across the three subdomains for both male and female offspring (Table 4; raw numbers in Supplementary Table 5). For most associations, the size of effect appeared to be greater for female compared to male offspring, particularly in the case of vulnerability in the two externalising subdomains. When interaction by offspring sex was formally tested in the fully adjusted model (by adding an interaction term to the unstratified model), statistically significant interaction was identified for three specific associations – the effect on hyperactive/inattentive vulnerability was greater for female than male offspring with at least one parent having a common mental disorder, substance use disorder or personality disorder.

Discussion

In this population-based intergenerational record linkage study we have demonstrated that emerging psychopathology in early childhood, of both externalising and internalising type, is associated with a history of parental mental illness spanning the entire psychiatric diagnostic spectrum. Both mothers and fathers with mental illness had an impact on vulnerability in their children; those born to two parents affected by mental illness were at even greater risk. The impact of a history of parental mental illness on male and female offspring was comparable for most associations, with some limited evidence of increased vulnerability for girl, with parental history of common mental disorder, substance use disorder and personality disorder.

Main findings

Overall, our findings support the notion that intergenerational risk of psychopathological vulnerability in offspring is not specific to any particular type of parental mental disorder. This may reflect a degree of commonality among causes of mental illnesses, undermining diagnostic specificity¹⁸, although it remains possible that different underlying mechanisms give rise to common overt signs of vulnerability, particularly early in development. This will be an important issue to examine in future when the children in this cohort reach critical ages for onset of particular mental disorders in adolescence and adulthood. While most previous studies of emerging psychopathology and antecedents of mental illness in high-risk offspring have focused on particular diagnoses in parents^{19,20}, a lack of specificity has been noted in the few studies where different diagnoses of parents are compared and in a recent systematic review found evidence to support a range of shared risk factors and antecedents for non-affective and affective psychoses²¹. Our findings also accord with studies focused on older offspring during later stages of development, where evidence of risk for psychiatric disorders spanning traditional diagnostic categories comes from intergenerational studies of discordant but diagnostically-related mental illnesses, including from a number of the high-risk

follow-up studies of offspring born to parents with certain severe mental illnesses³. While few studies have considered the full diagnostic spectrum in both parents and offspring⁴, evidence for commonality in offspring diagnostic outcomes across parental diagnostic groups does come from systematic reviews of studies focused on a range of parental diagnoses²².

The lack of interaction by parental sex in the current study is of particular interest given that the impact of mental illness on offspring is often assumed to be greater for those with affected mothers than fathers. While the literature to date has been dominated by studies focused on mothers²³, a recent meta-analysis of maternal versus paternal psychopathology in relation to child outcomes has reported stronger associations for affected mothers on child internalizing, but not externalizing, problems and the former identified difference for internalising problems was small²⁴. In our study, the one circumstance in which parental sex had a significant interaction effect was in the case of mothers with substance use disorders, where a stronger impact on all types of offspring psychopathology was found. This finding has not been highlighted in previous studies and requires further replication and exploration, including the potential for an explanation to be found in maternal substance use during pregnancy. We also found evidence for an impact of assortative mating such that children born to two affected parents had particularly high risk of vulnerability, although we were unable to look in further detail at whether particular combinations of parental diagnoses influenced offspring vulnerability. Overall, our findings highlight the importance of considering the impact of both mothers' and fathers' mental illness on child development.

While we found evidence of associations between all parental diagnostic groups and all three subdomains of externalising and internalising vulnerabilities, there were a number of apparent variations in the strength of associations. For example, across all parental diagnostic groups, the strength of associations appeared higher for externalising than internalising vulnerability in offspring, consistent with an early classic study of children of mentally ill parents²⁵. It may be, however, that externalising behaviours are

simply a more conspicuous response to stress or vulnerability in childhood and are thus more easily detected by teachers (who provided the AEDC ratings). The lack of multiple raters of child vulnerability is also an issue here, particularly given the evidence that correlations between teacher and parent reports is less robust for internalising problems²⁶. We also found some evidence, albeit on the basis of relatively small numbers, that parents with childhood-onset disorders (ADHD, conduct disorder, pervasive developmental disorders) had the greatest impact on offspring vulnerability across subdomains. This finding may reflect a degree of emerging concordance between parent and offspring psychopathology. Alternatively, the finding may reflect the impact of timing of onset (or duration) of parental mental disorder on vulnerabilities in offspring, such that parents with mental disorder beginning in childhood may have experienced particular challenges in developing effective parenting skills, for example^{24,25}. In support of the latter hypothesis, the associations between personality disorder in parents and offspring vulnerabilities were also strong.

Potential mechanisms underlying shared risks across diagnoses

While our study cannot separate genetic from environmental mechanisms underlying the associations between parental diagnoses and offspring vulnerabilities, the findings do have important implications for exploring potential mechanisms of the intergenerational transmission of mental disorders. In particular, our findings are consistent with the general factor of psychopathology or p factor literature^{5,6}, for which there is evidence to indicate a likely genetic basis⁷.

In our study we were able to include a range of socio-demographic variables in adjusted analyses and found that shared socio-demographic risk was evident across parental diagnostic groups but was not sufficient to explain individual associations. We were not able to consider a range of other potential mechanisms including marital or other family discord, prenatal factors, exposure to maladaptive parental

affect, behaviour and cognitions, and contextual (or indirect) stressors^{25,27}. Parenting itself has been a focus of investigation in studies attempting to understand the mechanisms underlying intergenerational patterns of mental health risk²⁸⁻³¹. Whilst apparently environmental in nature, these latter mechanisms may themselves have underlying genetic contributions.

Strengths and limitations

The current study benefits from the advantages of population-based sampling and record-linkage methodology, in which selection biases (both sampling and attrition) and information biases are minimised, and generalizability enhanced. The sample is large and enables investigation of associations between relatively uncommon exposures and outcomes as well as subgroup analyses and formal tests for interaction. The findings presented here were limited to those children in the NSW-CDS cohort with birth registration in NSW and for whom AEDC subdomain information was available but we found no differences in socio-demographic profile between the subsample used and either the wider cohort or the general population¹². It should be noted that our measure of emerging childhood psychopathology relied on assessment by class teachers and did not benefit from other sources of information on the child. Misclassification of individuals as unexposed (i.e. without parental history of mental illness) is also possible for those parents where incorrect or inadequate identifying information was available in the birth registration dataset resulting in apparently failed linkage, where contact with health services occurred only prior to the period of reliable data collection or, importantly, where contact for mental illness treatment occurred only in primary care, emergency departments or with private mental health care providers. Such misclassification is likely to underestimate any association between parental mental illness and offspring psychopathology and is more likely to impact older parents and those with less severe mental illnesses or those otherwise excluded by services. We were also limited by a lack of information on potential mechanisms, including an inability to separate genetic from environmental effects, and on detailed information relating to parental psychopathology beyond diagnosis³².

Implications

Parental mental illnesses across the diagnostic spectrum are associated with externalising and internalising vulnerabilities in early childhood, among offspring born to affected mothers and affected fathers. These findings have important implications for developing effective strategies for identifying and intervening with young people at risk of later development of mental illness. Such strategies should not be focused on particular psychiatric diagnoses in the parent(s), should not ignore the impact of paternal mental illness or assortative mating, and should not expect emerging psychopathology in offspring to necessarily concord with parental diagnoses. It may be that intervening early in children presenting with evidence of developmental vulnerabilities will have an impact on a wider range of diagnostic and other outcomes, rather than demonstrating specificity for prevention of particular mental illnesses. Our findings provide support for the notion that different psychiatric diagnoses likely share causal mechanisms adding further weight to the argument that future research may benefit by focusing less on diagnostic categories in the search for the causes of mental illness. Nonetheless, common patterns of vulnerability may still reflect a number of different and possibly specific underlying mechanisms, especially early in development. This complexity needs to be considered if causal mechanisms and potential targets for prevention and intervention are to be successfully delineated.

References

1. Rutter M. *Children of sick parents: An environmental and psychiatric study*. London, Oxford U. P; 1966.
2. Van Snellenberg JX, de Candia T. Meta-analytic evidence for familial coaggregation of schizophrenia and bipolar disorder. *Archives of General Psychiatry*. 2009;66(7):748-755.
3. Rasic D, Hajek T, Alda M, Uher R. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophrenia bulletin*. 2013;sbt114.
4. Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E, Pedersen CB. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of General Psychiatry*. 2010;67(8):822-829.
5. Murray AL, Eisner M, Ribeaud D. The development of the general factor of psychopathology ‘p factor’ through childhood and adolescence. *Journal of abnormal child psychology*. 2016;44(8):1573-1586.
6. Caspi A, Houts RM, Belsky DW, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical Psychological Science*. 2014;2(2):119-137.
7. Pettersson E, Larsson H, Lichtenstein P. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. *Molecular psychiatry*. 2016;21(5):717-721.
8. Welham J, Isohanni M, Jones P, McGrath J. The Antecedents of Schizophrenia: A Review of Birth Cohort Studies. *Schizophrenia Bulletin*. 2009;35(3):603-623.
9. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. *Am J Psychiatry*. 2013;170(5):542-549.
10. Luoma I, Tamminen T, Kaukonen P, et al. Longitudinal Study of Maternal Depressive Symptoms and Child Well-Being. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(12):1367-1374.
11. Plomin R, Krapohl E, O’Reilly PF. Assortative mating—a missing piece in the jigsaw of psychiatric genetics. *JAMA Psychiatry*. 2016;73(4):323-324.
12. Carr VJ, Harris F, Raudino A, et al. New South Wales Child Development Study (NSW-CDS): an Australian multiagency, multigenerational, longitudinal record linkage study. *BMJ open*. 2016;6(2):e009023.
13. Brinkman SA, Gregory TA, Goldfeld S, Lynch JW, Hardy M. Data Resource Profile: The Australian Early Development Index (AEDI). *International Journal of Epidemiology*. 2014;43(4):1089-1096.
14. Sara G, Luo L, Carr VJ, et al. Comparing algorithms for deriving psychosis diagnoses from longitudinal administrative clinical records. *Social psychiatry and psychiatric epidemiology*. 2014;49(11):1729-1737.
15. Janus M, Offord DR. Development and psychometric properties of the Early Development Instrument (EDI): A measure of children's school readiness. *Canadian Journal of Behavioural Science / Revue canadienne des sciences du comportement*. 2007;39(1):1-22.
16. Janus M. Estimating prevalence of behaviour problems in kindergarten children based on population-level data. Paper presented at: Proceedings from the XIV European conference on developmental psychology 2010.
17. Pink B. *Socio-Economic Indexes for Areas (SEIFA) 2011: Technical Paper*. Canberra: Commonwealth of Australia; 2013.
18. Dean CE. The death of specificity in psychiatry: cheers or tears? *Perspectives in biology and medicine*. 2012;55(3):443-460.
19. Fergusson DM, Lynskey MT. The effects of maternal depression on child conduct disorder and attention deficit behaviours. *Social Psychiatry and Psychiatric Epidemiology*. 1993;28(3):116-123.
20. Hameed MA, Lewis AJ. Offspring of Parents with Schizophrenia: A Systematic Review of Developmental Features Across Childhood. *Harvard review of psychiatry*. 2016;24(2):104-117.

21. Laurens KR, Luo L, Matheson SL, et al. Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses. *BMC Psychiatry*. 2015;15(1):1-20.
22. van Santvoort F, Hosman CM, Janssens JM, van Doesum KT, Reupert A, van Loon LM. The Impact of Various Parental Mental Disorders on Children's Diagnoses: A Systematic Review. *Clinical child and family psychology review*. 2015;18(4):281-299.
23. Phares V, Compas BE. The role of fathers in child and adolescent psychopathology: make room for daddy. *Psychological bulletin*. 1992;111(3):387.
24. Connell AM, Goodman SH. The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychological bulletin*. 2002;128(5):746.
25. Rutter M, Quinton D. Parental psychiatric disorder: Effects on children. *Psychological medicine*. 1984;14(04):853-880.
26. Grietens H, Onghena P, Prinzie P, et al. Comparison of mothers', fathers', and teachers' reports on problem behavior in 5-to 6-year-old children. *Journal of Psychopathology and Behavioral Assessment*. 2004;26(2):137-146.
27. Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychological review*. 1999;106(3):458.
28. Vostanis P, Graves A, Meltzer H, Goodman R, Jenkins R, Brugha T. Relationship between parental psychopathology, parenting strategies and child mental health. *Social Psychiatry and Psychiatric Epidemiology*. 2006;41(7):509-514.
29. Fudge E, Falkov A, Kowalenko N, Robinson P. Parenting is a mental health issue. *Australasian Psychiatry*. 2004;12(2):166-171.
30. Smith M. Parental mental health: disruptions to parenting and outcomes for children. *Child & Family Social Work*. 2004;9(1):3-11.
31. Johnson JG, Cohen P, Kasen S, Smailes E, Brook JS. Association of maladaptive parental behavior with psychiatric disorder among parents and their offspring. *Archives of General Psychiatry*. 2001;58(5):453-460.
32. Nordahl HM, Ingul JM, Nordvik H, Wells A. Does maternal psychopathology discriminate between children with DSM-IV generalised anxiety disorder or oppositional defiant disorder? The predictive validity of maternal axis I and axis II psychopathology. *European child & adolescent psychiatry*. 2007;16(2):87-95.

Table 1: Offspring with history of parental mental disorder (in either parent) and subdomain vulnerability (unadjusted associations)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
<i>Either parent with history of:</i>	No. cases (row N)	OR (95% CI)	No. cases (row N)	OR (95% CI)	No. cases (row N)	OR (95% CI)
Any mental disorder	1,374 (10,468)	1.87 (1.75-1.99)	1,643 (10,473)	1.75 (1.65-1.86)	1,516 (10,466)	1.53 (1.44-1.62)
Severe mental disorder	208 (1,311)	2.33 (2.00-2.71)	251 (1,312)	2.23 (1.94-2.56)	224 (1,311)	1.86 (1.61-2.15)
Common mental disorder	838 (6,586)	1.80 (1.67-1.95)	1,020 (6,589)	1.73 (1.60-1.85)	963 (6,586)	1.54 (1.43-1.66)
Substance use disorder	632 (3,779)	2.48 (2.27-2.72)	744 (3,781)	2.31 (2.12-2.51)	598 (3,776)	1.70 (1.55-1.86)
Personality disorder	142 (744)	2.92 (2.42-3.51)	167 (745)	2.72 (2.29-3.24)	129 (744)	1.89 (1.56-2.29)
Other adulthood-onset disorder	621 (4,045)	2.24 (2.05-2.46)	725 (4,048)	2.05 (1.89-2.24)	624 (4,046)	1.64 (1.50-1.80)
Childhood-onset disorder	49 (227)	3.40 (2.48-4.68)	56 (227)	3.08 (2.28-4.18)	49 (227)	2.48 (1.81-3.41)
No mental disorder in either parent (ref)	4,355 (58,196)	1.00	5,588 (58,206)	1.00	5,810 (58,181)	1.00

Note: No. = number; OR = odds ratio; CI = confidence interval; ref = reference category

Table 2: Offspring with history of parental mental disorder (in either parent) and subdomain vulnerability (adjusted for child sex, maternal age at birth, child English as a Second Language, and Socio-Economic Index for Areas)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
<i>Either parent with a history of:</i>	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Any mental disorder	1.88 (1.77-2.01)	1.73 (1.62-1.85)	1.77 (1.67-1.88)	1.65 (1.55-1.76)	1.54 (1.45-1.64)	1.45 (1.36-1.55)
Severe mental disorder	2.26 (1.93-2.66)	2.15 (1.84-2.51)	2.21 (1.90-2.56)	2.09 (1.80-2.42)	1.75 (1.49-2.05)	1.73 (1.49-2.00)
Common mental disorder	1.78 (1.64-1.93)	1.72 (1.58-1.86)	1.70 (1.58-1.84)	1.68 (1.56-1.75)	1.56 (1.45-1.68)	1.49 (1.38-1.61)
Substance use disorder	2.52 (2.29-2.78)	2.19 (1.99-2.42)	2.35 (2.14-2.57)	2.10 (1.92-2.29)	1.64 (1.48-1.81)	1.55 (1.41-1.71)
Personality disorder	2.77 (2.14-3.58)	2.65 (2.18-3.20)	2.63 (2.07-3.35)	2.52 (2.10-3.02)	1.91 (1.47-2.48)	1.75 (1.44-2.13)
Other adulthood-onset disorder	2.15 (1.96-2.35)	2.01 (1.83-2.21)	1.99 (1.82-2.16)	1.88 (1.72-2.05)	1.63 (1.49-1.78)	1.54 (1.41-1.69)
Childhood-onset disorder	3.44 (2.31-5.13)	2.88 (2.07-3.99)	2.74 (1.85-4.06)	2.69 (1.96-3.69)	3.05 (2.09-4.45)	2.24 (1.63-3.08)
No mental disorder in either parent (ref)	1	1	1	1	1	1

Note: No. = number; OR = odds ratio; CI = confidence interval; ref = reference category; Adjusted analyses are undertaken on a reduced sample due to missing data for maternal age at birth (n=617 missing)

Table 3: Offspring with paternal and maternal history of mental disorder and subdomain vulnerability (unadjusted associations)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
	Affected Father	Affected Mother	Affected father	Affected mother	Affected father	Affected mother
Parent with a history of:	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any mental disorder	1.98 (1.81-2.17)	1.81 (1.68-1.95)	1.81 (1.66-1.97)	1.75 (1.64-1.87)	1.54 (1.40-1.68)	1.54 (1.43-1.65)
Severe mental disorder	1.87 (1.48-2.36)	2.12 (1.71-2.64)	1.82 (1.47-2.25)	2.20 (1.81-2.67)	1.50 (1.20-1.89)	1.73 (1.40-2.13)
Common mental disorder	1.85 (1.61-2.13)	1.58 (1.44-1.73)	1.73 (1.51-1.97)	1.55 (1.43-1.69)	1.64 (1.43-1.88)	1.47 (1.36-1.60)
Substance use disorder	2.10 (1.84-2.38)	2.71 (2.39-3.07)	1.96 (1.74-2.21)	2.64 (2.35-2.97)	1.39 (1.22-1.59)	1.69 (1.48-1.92)
Personality disorder	2.73 (1.82-4.11)	2.29 (1.65-3.17)	2.69 (1.84-3.93)	2.18 (1.60-2.95)	1.90 (1.25-2.89)	1.79 (1.30-2.47)
Other adulthood-onset disorder	2.20 (1.92-2.53)	1.87 (1.68-2.08)	2.04 (1.80-2.32)	1.77 (1.60-1.96)	1.61 (1.41-1.85)	1.53 (1.38-1.70)
Childhood-onset disorder	3.41 (1.98-5.88)	2.90 (1.64-5.12)	2.63 (1.53-4.54)	2.24 (1.27-3.96)	2.80 (1.64-4.77)	3.01 (1.78-5.08)
No mental disorder in either parent (ref)	1	1	1	1	1	1

Note: No. = number; OR = odds ratio; CI = confidence interval; ref = reference category; the raw numbers for each cell can be found in Supplementary Table 4

Table 4: Female and male offspring with parental history of mental disorder (in either parent) and offspring subdomain vulnerability (unadjusted associations)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
	Female offspring	Male offspring	Female offspring	Male offspring	Female offspring	Male offspring
<i>Either parent with a history of:</i>	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any mental disorder	2.08 (1.85-2.35)	1.83 (1.69-1.98)	2.07 (1.86-2.31)	1.69 (1.57-1.81)	1.53 (1.40-1.68)	1.53 (1.40-1.66)
Severe mental disorder	2.95 (2.28-3.81)	2.16 (1.79-2.61)	2.80 (2.20-3.58)	2.11 (1.77-2.51)	1.88 (1.51-2.33)	1.85 (1.51-2.25)
Common mental disorder	2.04 (1.77-2.35)	1.76 (1.60-1.94)	2.11 (1.85-2.40)	1.64 (1.50-1.79)	1.62 (1.46-1.81)	1.48 (1.34-1.64)
Substance use disorder	2.83 (2.40-3.32)	2.44 (2.18-2.73)	3.02 (2.61-3.50)	2.14 (1.92-2.38)	1.57 (1.37-1.81)	1.81 (1.60-2.04)
Personality disorder	3.31 (2.38-4.58)	2.86 (2.27-3.60)	3.80 (2.85-5.08)	2.42 (1.93-3.02)	2.02 (1.53-2.67)	1.79 (1.37-2.32)
Other adulthood-onset disorder	2.34 (1.97-2.77)	2.25 (2.01-2.51)	2.32 (1.98-2.72)	2.01 (1.81-2.23)	1.63 (1.43-1.87)	1.65 (1.46-1.86)
Childhood-onset disorder	3.09 (1.69-5.65)	3.71 (2.51-5.49)	4.09 (2.46-6.80)	2.83 (1.92-4.17)	3.01 (1.92-4.71)	2.08 (1.32-3.26)
No mental disorder in either parent (ref)	1	1	1	1	1	1

Note: No. = number; OR = odds ratio; CI = confidence interval; ref = reference category; the raw numbers for each cell can be found in Supplementary Table 5

Table 5: Offspring with a history of parental mental disorder (in either parent) and number of subdomain vulnerabilities (unadjusted associations)

	1 of 3 vulnerabilities		2 of 3 vulnerabilities		3 of 3 vulnerabilities	
<i>Either parent with a history of:</i>	No. cases (row N)	OR (95% CI)	No. cases (row N)	OR (95% CI)	No. cases (row N)	OR (95% CI)
Any mental disorder	1,870 (10,461)	1.52 (1.43-1.60)	860 (10,461)	1.95 (1.80-2.11)	310 (10,461)	2.46 (2.15-2.81)
Severe mental disorder	246 (1,310)	1.69 (1.47-1.96)	136 (1,310)	2.62 (2.18-3.15)	54 (1,310)	3.63 (2.74-4.83)
Common mental disorder	1,172 (6,583)	1.50 (1.41-1.61)	527 (6,583)	1.89 (1.72-2.09)	195 (6,583)	2.45 (2.09-2.87)
Substance use disorder	724 (3,774)	1.74 (1.60-1.90)	396 (3,774)	2.66 (2.38-2.98)	150 (3,774)	3.52 (2.95-4.21)
Personality disorder	156 (743)	2.02 (1.68-2.42)	87 (743)	3.15 (2.50-3.97)	35 (743)	4.43 (3.12-6.29)
Other adulthood-onset disorder	738 (4,043)	1.60 (1.47-1.74)	374 (4,043)	2.27 (2.03-2.55)	160 (4,043)	3.40 (2.85-4.04)
Childhood-onset disorder	50 (227)	2.30 (1.66-3.18)	34 (227)	4.37 (2.99-6.38)	12 (227)	5.39 (2.97-9.77)
No mental disorder in either parent (ref)	7,779 (58,169)	1	2,740 (57,734)	1	786 (57,734)	1

Note: No. = number; OR = odds ratio; CI = confidence interval; ref = reference category

Supplementary Table 1: Broad parental mental illness diagnostic category definitions

Broad Diagnostic Group	Diagnostic categories	ICD-10 codes
Severe Mental Disorders	Schizophrenia and other psychotic disorders	F20, F22, F23, F24, F28, F29
	Schizoaffective Disorders	F25, F25.0, F25.1, F25.2, F25.8, F25.9
	Psychotic Affective Disorders	F30, F31
	Psychotic Disorders related to Substance Use	F10.5, F11.5, F12.5, F13.5, F14.5, F15.5, F15.50, F15.51, F15.59, F15.70, F16.5, F17.5, F18.5, F19.5, F19.7
Common Mental Disorders	Non-psychotic Affective Disorders	F32, F33, F34, F34.0, F34.8, F34.9, F38.0, F38.1, F38.8, F39, F53
	Neurotic and stress-related (anxiety) disorders	F40, F41, F42, F43, F44, F45, F48
Personality Disorders	Cluster A	F21, F60.0, F60.1
	Cluster B	F60.2, F60.3, F60.30, F60.31, F60.4
	Cluster C	F60.5, F60.6, F60.7
	Other Personality Disorders	F60, F60.8, F60.09, F60.9, F61, F62, F62.0, F62.1, F62.8, F62.9, F68.0, F68.1, F68.8, F69
Substance Use Disorders	Substance Intoxication and Use Disorders	F10, F11, F12, F13, F14, F15 F16, F17, F18, F19, F55.9
Other Adult Onset Disorders	Other postnatal conditions	F53, F53.8, F53.9
	Other Disorders not elsewhere classified	F99, F99.1
	Other Adult onset disorders (e.g. organic disorders, eating disorders, sleep disorders)	F00, F01, F03, F04, F05, F06, F07, F09, F50, F51, F52, F54, F55, F59, F63, F64, F65, F66
	Self-harm	R45.81, X84
	Mental health diagnosis not yet allocated	99.1
Other Childhood Onset Disorders	Hyperkinetic disorders	F90
	Conduct Disorders	F91, F92
	Other Childhood Disorders (e.g. hyperkinetic disorders, conduct disorders, mental retardation, pervasive developmental disorders)	F70, F71, F73, F78, F79, F80, F81, F82, F83, F84, F88, F89, F93, F94, F95, F98

Supplementary Table 2: Australian Early Development Census items constituting the three subdomains of childhood vulnerability

<i>Aggressive behaviour</i>	<i>Hyperactive and inattentive behaviour</i>	<i>Anxious and fearful behaviour</i>
C34. Would you say that this child gets into physical fights?	C39. Would you say that this child can't sit still, is restless?	C47. Would you say that this child seems to be unhappy, sad or depressed?
C35. Would you say that this child bullies or is mean to others?	C40. Would you say that this child is distractible, has trouble sticking to any activity?	C48. Would you say that this child appears worried?
C36. Would you say that this child kicks, bites, hits other children or adults?	C43. Would you say that this child is impulsive, acts without thinking?	C49. Would you say that this child cries a lot?
C37. Would you say that this child takes things that do not belong to him/her?	C44. Would you say that this child has difficulty waiting turns in games or groups?	C50. Would you say that this child is nervous, highly-strung or tense?
C38. Would you say that this child laughs at other's discomfort?	C45. Would you say that this child cannot settle to anything for more than a few moments?	C51. Would you say that this child is incapable of making decisions?
C41. Would you say that this child is disobedient?	C46. Would you say that this child is inattentive?	
C42. Would you say that this child has temper tantrums?		

Supplementary Table 3: Offspring with parental mental disorder (in both parents) and subdomain vulnerability (unadjusted associations)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
Both parents with a history of:	No. cases (row N)	OR (95% CI)	No. cases (row N)	OR (95% CI)	No. cases (row N)	OR (95% CI)
Any mental disorder	219 (1,170)	2.85 (2.45-3.31)	261 (1,171)	2.70 (2.35-3.12)	215 (1,169)	2.03 (1.75-2.36)
Severe mental disorder*	5 (35)	-	10 (36)	3.62 (1.75-7.51)	5 (36)	-
Common mental disorder*	68 (382)	2.68 (2.06-3.49)	78 (383)	2.41 (1.88-3.09)	78 (383)	2.31 (1.80-2.96)
Substance use disorder*	94 (442)	3.34 (2.65-4.20)	120 (443)	3.50 (2.83-4.32)	71 (443)	1.72 (1.33-2.22)
Personality disorder*	3 (17)	-	5 (18)	-	5 (18)	-
Other adulthood-onset disorder*	49 (258)	2.90 (2.12-4.00)	61 (259)	2.90 (2.17-3.87)	48 (259)	2.05 (1.50-2.81)
Childhood-onset disorder*	1 (2)	-	0 (2)	-	2 (2)	-
No mental disorder in either parent (ref)	4,355 (58,196)	1	5,588 (58,206)	1	5,810 (58,181)	1

Note: No. = number; OR = odds ratio; CI = confidence interval; ref = reference category; *Each parent had a diagnosis in the same broad category for these comparisons; Results of regression analyses are not reported where the number of cases is <= 5

Supplementary Table 4: Offspring with paternal and maternal history of mental disorder and subdomain vulnerability (raw numbers)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
	Affected Father	Affected Mother	Affected father	Affected mother	Affected father	Affected mother
Parent with a history of:	No. cases (row N)	No. cases (row N)	No. cases (row N)	No. cases (row N)	No. cases (row N)	No. cases (row N)
Any mental disorder	600 (4,125)	993 (7,513)	696 (4,129)	1,208 (7,515)	622 (4,126)	1,109 (7,509)
Severe mental disorder	114 (771)	118 (702)	140 (772)	148 (703)	136 (771)	122 (703)
Common mental disorder	289 (2,024)	640 (5,133)	338 (2,026)	787 (5,135)	337 (2,026)	746 (5,132)
Substance use disorder	402 (2,589)	365 (1,950)	465 (2,591)	440 (1,951)	369 (2,588)	337 (1,949)
Personality disorder	75 (401)	80 (452)	91 (402)	99 (453)	66 (401)	80 (453)
Other adulthood-onset disorder	291 (1,853)	389 (2,563)	340 (1,856)	459 (2,564)	289 (1,855)	400 (2,563)
Childhood-onset disorder	27 (145)	26 (118)	31 (145)	28 (118)	32 (145)	25 (118)
No mental disorder in either parent	4,355 (58,196)	4,355 (58,196)	5,588 (58,206)	5,588 (58,206)	5,810 (58,181)	5,810 (58,181)

Note: No. = number

Supplementary Table 5: Female and male offspring with parental mental disorder (in either parent) and subdomain vulnerability (row numbers)

	Aggressive behaviour		Hyperactive and inattentive behaviour		Anxious and fearful behaviour	
	Female offspring	Male offspring	Female offspring	Male offspring	Female offspring	Male offspring
<i>Either parent with a history of:</i>	No. cases (row N)	No. cases (row N)	No. cases (row N)	No. cases (row N)	No. cases (row N)	No. cases (row N)
Any mental disorder	394 (5,209)	977 (5,259)	470 (5,213)	1,173 (5,260)	679 (5,211)	837 (5,255)
Severe mental disorder	68 (651)	140 (660)	77 (652)	174 (660)	10 (652)	123 (659)
Common mental disorder	246 (3,295)	592 (3,291)	302 (3,297)	718 (3,292)	451 (3,296)	512 (3,290)
Substance use disorder	189 (1,878)	443 (1,901)	237 (1,880)	507 (1,901)	250 (1,879)	348 (1,897)
Personality disorder	42 (363)	100 (381)	56 (364)	111 (381)	60 (364)	69 (380)
Other adulthood-onset disorder	167 (1,970)	454 (2,075)	197 (1,972)	528 (2,076)	271 (1,971)	353 (2,075)
Childhood-onset disorder	12 (110)	37 (117)	18 (110)	38 (117)	25 (110)	24 (117)
No mental disorder in either parent	1,097 (28,803)	3,258 (29,393)	1,314 (28,806)	4,274 (29,400)	2,562 (28,792)	3,248 (29,389)

Note: No. = number