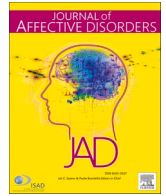




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Research paper

Parental psychopathology and offspring anxiety disorders in childhood and adolescence: A Finnish nationwide register study

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ABSTRACT

Background: Research suggests an association between parental psychiatric disorders and offspring anxiety disorders, yet comprehensive studies are limited. This study aims to investigate the associations between various parental psychiatric disorders and anxiety disorders in their offspring.

Method: Using Finnish register data, this nested case-control study analyzed 867,175 singleton live births from 1992 to 2006, identifying 21,671 cases of anxiety disorders diagnosed between 1998 and 2016. Matched with four controls each ($n = 72,414$) based on age and biological sex, the study adjusted for demographic and prenatal factors using conditional logistic regression models to calculate odds ratios (aORs).

Results: There was a significant association between parental psychiatric disorders and increased risk of anxiety disorders in offspring. The risk was notably higher when both parents had psychiatric disorders (aOR = 5.04; 95 % CI, 4.70–5.39; $p < .001$). Maternal psychiatric disorders were strongly associated with offspring anxiety than paternal disorders (aOR 1.52; 95 % CI 1.43–1.61; $p < .001$). This association was consistent regardless of timing of parental diagnosis. Significant associations were observed between any parental psychiatric disorder and increased risks in offspring for specific phobia, social phobia, generalized anxiety disorder, separation anxiety, and panic disorder. Maternal psychiatric disorders showed elevated risk for panic disorder and social phobia among girls and separation anxiety and generalized anxiety among boys.

Conclusion: The findings emphasize the significant impact of parental psychiatric health on offspring anxiety disorders, highlighting the influence of genetic and environmental factors. Addressing parental mental health is crucial in preventing childhood anxiety disorders.

1. Introduction

Anxiety disorders represent a predominant psychiatric condition among school-aged children (Chiu et al., 2016) affecting 6.5 % of children and adolescents globally (Polanczyk et al., 2015). Untreated anxiety in childhood can contribute to the development or aggravation of other mental health conditions during adulthood such as depression, substance abuse, suicidality, and eating disorders (Kendall et al., 2010; Riordan and Singhal, 2018).

Globally, approximately 15 % to 23 % of children reside in households where at least one parent has been diagnosed with a mental health

disorder (Maybery and Reupert, 2018). Such children are met with a potential risk, estimated to be as high as 50 %, of developing their own mental health problems (Leijdesdorff et al., 2017). While genetic research has yielded valuable insights into the pathogenetic mechanisms of other psychiatric conditions, the high comorbidity of anxiety disorders with other psychiatric and somatic illnesses limits the comprehensive understanding of their neurobiological mechanisms (Koskinen and Hovatta, 2023). Nonetheless, available evidence suggests that similar to other mental health disorders, the etiology of anxiety disorders involves a complex interplay between genetic and environmental risk factors (Oliver-Parra et al., 2020; Allen et al., 2018).

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Most studies on the association between parental psychopathology and offspring anxiety either focused on more severe parental psychiatric disorders such as schizophrenia (Hans et al., 2004), bipolar disorder (Vandeleur et al., 2012; Henin et al., 2005), depressive disorder (Glasheen et al., 2013) and attention deficit hyperactivity disorder (ADHD) (Powell et al., 2023) or a specific group of child anxiety such as social phobia (Lieb et al., 2000), selective mutism (Koskela et al., 2020) and panic disorder/agoraphobia (Biederman et al., 2005). These studies revealed that various psychiatric disorders in either or both parents are associated with anxiety disorders in their offspring.

Only three population-based studies based on Swedish (Li et al., 2008) and Danish register data (Steinhausen et al., 2009; Helenius et al., 2014) examined the association between parental psychiatric disorders and anxiety disorders in offspring. They reported increased risk of anxiety disorders in the offspring when both parents had anxiety disorders. While Swedish study included large cases of anxiety disorders, the parental diagnoses was only limited to anxiety disorders. Similarly, Helenius et al. (2014) also focused exclusively on parental anxiety disorders as exposure, limiting the understanding of the impact of other parental psychiatric conditions on offspring anxiety disorders. Although Steinhausen et al. (2009) included multiple parental psychiatric disorders, both Danish studies (Steinhausen et al., 2009; Helenius et al., 2014) had a small number of offspring diagnosed with anxiety disorders, resulting in reduced statistical power and limited generalizability. Moreover, Steinhausen et al. (2009) included broader diagnostic codes

for neurotic disorders, not limited to anxiety disorders only. Additionally, while all three studies accounted for demographic and socioeconomic confounders, they did not consider other potential confounding related to maternal prenatal and perinatal factors such as maternal age, smoking during pregnancy and gestational age, which could influence the development of anxiety disorders in offspring.

There are no large population-based studies that have examined the association between parental psychiatric disorders diagnosed before and after the child's birth and offspring anxiety disorders. This gap restricts our understanding of the effect of prenatal influences, early childhood adversities, parent-child interactions problems and other environmental factors related to parents' psychiatric disorders and offspring anxiety disorders. Furthermore, the association between a broad spectrum of parental psychiatric disorders and subgroup of anxiety disorders in the offspring has yet to be examined. These findings could enhance our understanding of a complex intergenerational mental health landscape.

The first aim of this study was to investigate how various parental psychiatric disorders were associated with offspring anxiety disorders, in general and by specific diagnostic groups. The second aim was to compare the effect of maternal versus paternal psychiatric disorders on offspring anxiety disorders. Finally, we examined the association between parental psychiatric disorders diagnosed for the first time before and after child's birth and offspring anxiety disorders. We hypothesized that a wide range of parental psychiatric disorders would be associated with offspring anxiety disorders showing intergenerational

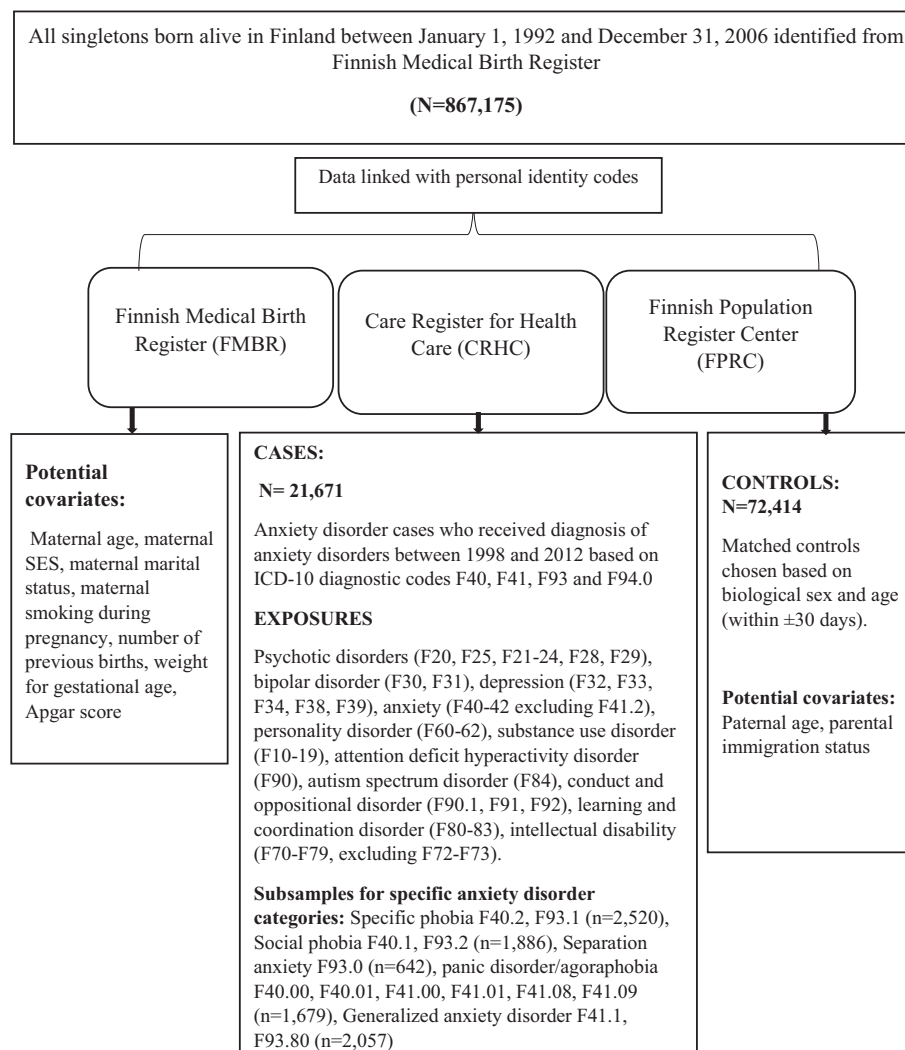


Fig. 1. Flowchart of study design.

unspecificity.

2. Methods

2.1. Study design

This study was a part of Finnish Prenatal Study of Anxiety (FIPS-ANX), a nationwide birth cohort study with a nested case-control design. Cases were all individuals diagnosed with anxiety disorders identified from the 1992–2006 birth cohort. For each case, four matching controls were selected from the same birth cohort based on age (± 30 days) and biological sex (Fig. 1).

2.1.1. Data sources

Data for this study were obtained from three national registers:

- The Finnish Care Register for Health Care (CRHC), providing information on diagnosis and treatment in both inpatient and outpatient specialized healthcare services in Finland.
- The Finnish Medical Birth Register (FMBR), containing standardized data on the prenatal and perinatal period for all live and stillbirths.
- The Finnish Central Population Register (FCPR), comprising demographic, social, and household information on Finnish citizens and residents.

The linkage between these registers was accomplished using personal identity codes, assigned to all Finnish residents. The use and linkage of data was approved by the Data Protection Ombudsman and ethical approval for the study was obtained from the Ethics Committee of the Hospital District of Southwest Finland. Previous studies from Finland based on these registers have demonstrated good validity for conditions such as schizophrenia and bipolar disorder (Pihlajamaa et al., 2008), autism (Lampi et al., 2010), Tourette syndrome (Leivonen et al., 2014), ADHD (Joelsson et al., 2016) and selective mutism (Koskela et al., 2020). The quality of CRHC data (formerly known as Finnish Hospital Discharge Register) has been studied previously, and that the study reported positive predictive value for common diagnoses between 75 and 99 % (Sund, 2012).

2.2. Study subjects

The study sample was a birth cohort of 867,175 singleton live birth in Finland between January 1992 and December 2006. We identified cases who were born in Finland and received diagnosis of anxiety disorder between 1998 and 2012 based on International Classification of Disease, Tenth Revision (ICD-10) diagnostic codes F40, F41, F93 and F94.0. Four age (within ± 30 days) and biological sex matched control were selected for each case. Controls had to be alive and residing in Finland at the time of the cases' anxiety disorders diagnosis. Controls who received anxiety disorders diagnoses during the follow-up period of 2012 to 2016 were excluded. Study subjects with severe or profound intellectual disabilities (ICD-10: F72-F73), as determined by CRHC, and those with incomplete information on both parents were excluded from both case and control groups. The final study cohort comprised of 21,671 cases and 72,414 controls.

2.3. Exposures

We used two approaches to categorize parental psychiatric disorders. First, parental psychiatric disorders were categorized as only mother, only father, both parents and with no psychiatric diagnoses. Second, both paternal and maternal psychiatric disorders were examined separately in the following categories: psychotic disorders (schizophrenia, schizoaffective disorders, and other psychoses combined), bipolar disorder, depression, anxiety disorders, personality disorders, substance use disorder, attention deficit hyperactivity disorder (ADHD), autism

spectrum disorder (ASD), conduct disorders, learning and coordination disorders, and intellectual disability. If a parent was diagnosed with psychotic disorders, he or she would not be assigned to another category. We used hierarchical model: schizophrenia spectrum disorders, schizoaffective disorders and psychosis were given highest priority. For example, if the parent had been diagnosed both with severe depression and schizophrenia, she/he was assigned to the schizophrenia spectrum category. In other cases, parents could be assigned into multiple diagnostic categories. We used this approach based on the severity and chronicity of the disorders. Similar categorization was done in several Finnish Prenatal Studies (FIPS) (Jokiranta et al., 2013; Sucksdorff et al., 2014; Joelsson et al., 2017; Leivonen et al., 2017; Koskela et al., 2020). Finally, maternal and paternal disorders were classified as before or after the child's birth based on when they received the diagnosis for adulthood onset psychiatric disorders, except for psychotic disorders. Childhood onset disorders were excluded as it is self-explanatory that their symptoms have been present before child's birth. The diagnostic codes for each exposure category are provided in Fig. 1 and Supplementary Table 1.

2.4. Anxiety disorders subgroup

We also examined the subgroup of anxiety disorders that included: specific phobia [F40.2, F93.1 ($n = 2520$)], social phobia [F40.1, F93.2 ($n = 1886$)], separation anxiety [F93.0 ($n = 642$)], generalized anxiety disorder [F41.1, F93.80 ($n = 2057$)] and panic disorder/agoraphobia [F40.00, F40.01, F41.00, F41.01, F41.08, F41.09 ($n = 1679$)].

2.5. Covariates

Based on previous evidence and literature several potential confounding factors associated with offspring anxiety and parental psychiatric disorders were considered as covariates. These included parents age at birth of study child (Malaspina et al., 2015; Tearne et al., 2016), maternal socio-economic status (SES) (Reiss et al., 2019; Khanal et al., 2022), maternal marital status (Khanal et al., 2022), maternal smoking during pregnancy (Joelsson et al., 2017; Corrêa et al., 2022), parents immigration status (Lehti et al., 2016), number of previous childbirths (Ståhlberg et al., 2022a), offspring weight for gestational age (GA) (Ståhlberg et al., 2022b) and their Apgar score at 1 min (Kingston et al., 2015).

2.6. Statistical analysis

We used chi-square test to examine the association between potential covariates and parental psychiatric disorders in general among controls (Table S2), whereas we used conditional logistic regression to test the associations between covariates and offspring's diagnosed anxiety disorders in the case-control model (Table S3). Conditional logistics regression is particularly suited for matched case-control study and it allows for the estimation of odds ratio while controlling for confounding factors of the matching variables (Hosmer et al., 2013). The covariates showing a significant association ($p < .1$) with both offspring anxiety disorder and parental psychopathology were included in the final model.

To determine if the analyses should be stratified by offspring biological sex, interactions between parental psychiatric disorders (only mother and only father) and offspring biological sex were tested, revealing significant interactions ($p < .1$) for any parental psychiatric disorder and specific maternal (psychotic disorders, conduct, learning, and coordination disorders) and paternal disorders (psychotic and substance use disorders). Accordingly, analyses were stratified by biological sex.

Using conditional logistic regression models for matched sets, odds ratios (OR) and corresponding two-sided 95 % confidence intervals (95 % CI) were calculated to estimate the strength of associations between

parental psychiatric disorders (overall and by specific disorders) and offspring anxiety disorders (any anxiety disorder and anxiety subgroup). Comparisons were made between offspring where both parents, only mothers, and only fathers had psychiatric disorders against offspring where neither parent had disorders. Specific parental disorders were analyzed separately, followed by comparisons of maternal and paternal diagnoses within corresponding categories. Finally, the association between parental psychiatric disorders registered for the first time before and after child's birth and offspring anxiety disorder was compared. All statistical analyses were conducted using SAS software, version 9.4.

3. Results

The age range at first anxiety diagnosis of study subjects was between 5 and 20 years and the mean age was 12.7 years (SD ±3.7). Of total cases 56.5 % were female and 43.5 % were male. Among total cases 11.6 % were accounted for specific phobia, 8.7 % social phobia, 9.5 % generalized anxiety disorder, 3.0 % separation anxiety and 7.7 % for panic disorder/agoraphobia.

The associations between any parental psychiatric disorders and offspring anxiety disorders stratified by offspring biological sex are shown in Table 1. In adjusted analysis and compared to controls, only mother, only father, or both parents' psychiatric disorders were associated with offspring anxiety disorders in boys and girls. Only mothers' psychiatric disorders showed significantly stronger association with offspring anxiety disorders compared to only fathers' psychiatric disorders for boys and girls (Table 1). Psychiatric disorders in both parents showed a stronger association with offspring anxiety disorders

Table 1
Association between any parental psychiatric disorders and offspring anxiety disorder.

	Cases n = 21,671 n (%)	Controls n = 72,414 n (%)	Cases vs. Controls Adjusted OR (95 % CI)	Only maternal vs. Only paternal ^a Adjusted OR (95 % CI)
Total sample				
None	11,848 (54.6)	56,838 (78.5)	Ref.	
Only mother	4384 (20.2)	6659 (9.2)	2.97 (2.84–3.11)***	1.52 (1.43–1.61)***
Only father	3111 (14.4)	6998 (9.7)	1.96 (1.86–2.06)***	
Both parents	2328 (10.7)	1919 (2.6)	5.04 (4.70–5.39)***	
Boys	9427 (%)	32,449 (%)		
None	5008 (53.1)	25,467 (78.5)	Ref.	
Only mother	1999 (21.2)	3066 (9.4)	3.10 (2.89–3.32)***	1.48 (1.35–1.62)***
Only father	1362 (14.4)	3013 (9.3)	2.09 (1.94–2.26)***	
Both parents	1058 (11.2)	903 (2.8)	4.98 (4.50–5.52)***	
Girls	12,244 (%)	39,965 (%)		
None	6840 (55.9)	31,371 (78.5)	Ref.	
Only mother	2385 (19.5)	3593 (9.0)	2.88 (2.71–3.06)***	1.55 (1.43–1.68)***
Only father	1749 (14.3)	3985 (10.0)	1.86 (1.74–1.98)***	
Both parents	1270 (10.4)	1016 (2.5)	5.11 (4.65–5.61)***	

Models were adjusted for maternal age, paternal age, maternal SES, maternal marital status, maternal smoking during pregnancy, number of previous births, weight for gestational age, parental immigration status.

^a Comparison among cases OR: Odds ratio, CI: Confidence interval.

*** $p < .001$.

compared to only mothers' and only fathers' psychiatric disorders for boys [aOR 4.98, 95 % CI, 4.50–5.52, $p < .001$] and girls [aOR 5.11, 95 % CI, 4.65–5.61, $p < .001$].

Tables 2, S4 and S5 display the associations between specific maternal and paternal psychiatric disorders and anxiety disorders in the offspring (Table 2), and among boys and girls (Tables S4 and S5). All specific parental disorders were associated with offspring anxiety disorders. Some non-significant associations emerged when the analyses were stratified by parental and offspring biological sex (Tables S4 and S5). When comparing mothers and fathers, the associations were stronger for specific maternal psychiatric disorders compared to paternal psychiatric disorders (Table 2). Specifically, for intellectual disability [aOR 1.95, 95 % CI 1.11–3.42, $p < .05$], personality disorder [aOR 1.76, 95 % CI 1.56–1.99, $p < .001$], bipolar disorder [aOR 1.67, 95 % CI 1.40–2.00, $p < .001$], substance use disorder [aOR 1.42, 95 % CI 1.30–1.55, $p < .001$], depression [aOR 1.31, 95 % CI 1.23–1.40, $p < .001$] and psychotic disorders [aOR 1.24, 95 % CI 1.07–1.44, $p < .01$].

The associations between any parental psychiatric disorders and the risk of different sub-groups of anxiety disorders in offspring by biological sex are displayed in Table 3. In the adjusted analyses significant associations were observed across all anxiety subgroup for both parents with psychiatric disorders compared to parental absence of psychiatric disorders. The risk was higher for separation anxiety [aOR 2.80, 95 % CI 1.73–4.53, $p < .001$] and generalized anxiety [aOR 2.02, 95 % CI, 1.52–2.69, $p < .001$] among boys for maternal psychiatric disorders compared to paternal psychiatric disorders. Similarly, the risk was higher for panic disorder [aOR = 1.71, 95 % CI, 1.30–2.25, $p < .001$] and social phobia [aOR 1.67, 95 % CI, 1.26–2.19, $p < .001$] among girls for maternal psychiatric disorders compared to paternal psychiatric disorders.

Finally, when the timing of a first parental diagnoses was examined (Table 4), the association between specific parental psychiatric disorders diagnosed for the first time before versus after the child's birth- and offspring anxiety disorder did not show significant differences.

4. Discussion

To our knowledge this is the first nationwide register-based study using nested case-control design to report a wide spectrum of parental psychiatric disorders and their associations with offspring anxiety disorders. Our study had some important findings. First, we observed that the risk of anxiety disorders in children and adolescents was higher when both parents have psychiatric disorders. Second, maternal psychiatric disorders overall showed stronger associations with offspring anxiety disorders compared to paternal psychiatric disorders. Third, the impact of parental psychiatric disorders on offspring anxiety disorders was consistent regardless of whether these diagnoses were made before or after the child's birth.

Both paternal and maternal psychiatric disorders were associated with increased risk of anxiety disorder among offspring. The risk of offspring being diagnosed with anxiety disorder was particularly high when both parents had any psychiatric disorder. This finding corroborates existing studies highlighting the influence of parental psychiatric disorders on offspring mental health (Wickersham et al., 2020; Lejdesdorff et al., 2017; Wolicki et al., 2021; Ramchandani and Psychogiou, 2009; Rangyen et al., 2015). A Norwegian study examining the inter-generational transmission of mental health disorders found that parental psychiatric disorder was associated with a 40 % higher likelihood of a psychiatric diagnosis in their children (Bütikofer et al., 2023). This observed association has several plausible pathways. Epidemiological and genetic studies have reported the development of anxiety disorders as multifactorial, involving genetic, environmental, and psychological factors (Hettema et al., 2001; Penninx et al., 2021; Wang et al., 2024). This suggests that given the genetical vulnerability, exposure to certain environmental factors increases the risk of disorder. Children exposed to four or more adverse childhood experiences (ACEs) are four times likely

Table 2
Association between specific parental psychiatric disorder and offspring anxiety disorder.

		Cases n = 21,671	Controls n = 72,414	Cases vs. Controls	Maternal vs. Paternal
Parental psychiatric disorders		n (%)	n (%)	Adjusted OR (95 % CI)	Adjusted OR (95 % CI)
Psychotic disorders	Maternal	835 (3.9)	835 (1.2)	2.78 (2.50–3.09)***	1.24 (1.07–1.44)**
	Paternal	668 (3.1)	863 (1.2)	2.08 (1.86–2.33)***	
Bipolar disorder	Maternal	720 (3.3)	606 (0.8)	3.32 (2.95–3.73)***	1.67 (1.40–2.00)***
	Paternal	384 (1.8)	579 (0.8)	1.83 (1.59–2.11)***	
Depression	Maternal	4571 (21.1)	5572 (7.7)	2.80 (2.67–2.93)***	1.31 (1.23–1.40)***
	Paternal	2591 (12.0)	4208 (5.8)	1.79 (1.69–1.89)***	
Personality disorder	Maternal	1339 (6.2)	959 (1.3)	3.86 (3.53–4.23)***	1.76 (1.56–1.99)***
	Paternal	1086 (5.0)	1320 (1.8)	2.04 (1.87–2.23)***	
Anxiety disorder	Maternal	1879 (8.7)	2385 (3.3)	2.42 (2.26–2.58)***	1.20 (1.09–1.33)***
	Paternal	1130 (5.2)	1689 (2.3)	1.91 (1.76–2.08)***	
Substance use disorder	Maternal	1525 (7.0)	1629 (2.2)	2.38 (2.20–2.57)***	1.42 (1.30–1.55)***
	Paternal	2521 (11.6)	4028 (5.6)	1.67 (1.58–1.77)***	
ADHD	Maternal	147 (0.7)	106 (0.1)	3.80 (2.90–4.97)***	1.34 (0.91–1.98)
	Paternal	108 (0.5)	104 (0.1)	2.42 (1.80–3.25)***	
ASD	Maternal	17 (0.1)	15 (0.02)	3.28 (1.56–6.87)**	0.90 (0.26–3.09)
	Paternal	8 (0.04)	8 (0.01)	3.27 (1.19–9.01)*	
Conduct disorder	Maternal	75 (0.3)	55 (0.1)	2.94 (2.01–4.29)***	1.22 (0.75–1.98)
	Paternal	86 (0.4)	91 (0.1)	2.06 (1.49–2.86)***	
Learning and coordination disorder	Maternal	68 (0.3)	72 (0.1)	2.39 (1.68–3.40)***	1.31 (0.83–2.08)
	Paternal	77 (0.4)	113 (0.2)	1.84 (1.34–2.53)***	
Intellectual disability	Maternal	56 (0.3)	42 (0.1)	3.41 (2.23–5.22)***	1.95 (1.11–3.42)*
	Paternal	54 (0.2)	66 (0.1)	1.62 (1.10–2.40)*	

Models were adjusted for maternal age, paternal age, maternal SES, marital status, smoking, previous births, weight for gestational age, maternal immigrant status and paternal immigrant status. Cases vs. Controls models were also adjusted by the other parent's any psychiatric disorder. OR: adjusted odds ratio; CI: Confidence interval.

* p < .05.
** p < .01.
*** p < .001.

Table 3
Association between any parental psychiatric diagnoses and offspring's anxiety subcategories across gender.

	Boys			Girls		
	Cases N = 9427	Controls N = 32,449	Adjusted OR (95 % CI)	Cases N = 12,244	Controls N = 39,965	Adjusted OR (95 % CI)
Anxiety disorders	N (%)	N (%)		N (%)	N (%)	
Specific phobia	1294 (13.7)	4478 (13.8)	^b 1.48 (1.15–1.91)*	1226 (10)	3956 (10)	^b 1.48 (1.14–1.92)*
Only mother	248 (19.2)	432 (9.6)	2.50 (2.07–3.02)***	238 (19.4)	359 (9.1)	2.81 (2.31–3.43)***
Only father	174 (13.4)	409 (9.1)	1.69 (1.37–2.08)***	168 (13.7)	372 (9.4)	1.90 (1.54–2.34)***
Both parents	122 (9.4)	135 (3.01)	3.63 (2.75–4.80)***	112 (9.1)	88 (2.2)	4.55 (3.33–6.22)***
Social phobia	765 (8.1)	2623 (8.1)	^b 1.14 (0.83–1.56)	1121 (9.2)	3636 (9.1)	^b 1.67 (1.26–2.19)***
Only mother	128 (16.7)	258 (9.8)	2.16 (1.68–2.77)***	205 (18.3)	310 (8.5)	2.72 (2.21–3.35)***
Only father	131 (17.1)	273 (10.4)	1.90 (1.48–2.43)***	144 (12.8)	359 (9.9)	1.63 (1.31–2.04)***
Both parents	60 (7.8)	71 (2.7)	3.12 (2.11–4.60)***	103 (9.2)	83 (2.3)	4.81 (3.47–6.66)***
Generalized anxiety	951 (10.1)	3307 (10.2)	^b 2.02 (1.52–2.69)***	1106 (9)	3611 (9)	^b 1.73 (1.31–2.28)***
Only mother	237 (24.9)	300 (9.1)	4.24 (3.40–5.27)***	236 (21.3)	310 (8.6)	3.77 (3.06–4.66)***
Only father	131 (13.8)	313 (9.5)	2.10 (1.64–2.67)***	155 (14.01)	348 (9.6)	2.18 (1.47–2.73)***
Both parents	113 (11.9)	88 (2.6)	5.88 (4.25–8.15)***	136 (12.3)	118 (3.3)	5.64 (4.24–7.50)***
Separation anxiety	374 (3.9)	1254 (3.9)	^b 2.80 (1.73–4.53)***	268 (2.2)	865 (2.2)	^b 2.21 (1.24–3.93)*
Only mother	101 (27)	113 (9)	4.95 (3.43–7.11)***	64 (24)	75 (8.7)	4.46 (2.91–6.83)***
Only father	45 (12.03)	129 (11)	1.76 (1.17–2.65)*	32 (12)	88 (10.2)	2.02 (1.23–3.30)**
Both parents	36 (9.6)	35 (2.8)	4.43 (2.54–7.72)***	32 (12)	26 (3)	7.93 (4.04–15.57)***
Panic disorder	488 (5.2)	1686 (5.2)	^b 1.01 (0.67–1.52)	1191 (9.7)	3920 (9.8)	^b 1.71 (1.30–2.25)***
Only mother	74 (15.2)	159 (9.4)	1.94 (1.40–2.68)***	203 (17)	347 (8.8)	2.35 (1.92–2.88)***
Only father	80 (16.4)	166 (9.8)	1.92 (1.40–2.62)***	143 (12)	390 (9.9)	1.37 (1.10–1.72)*
Both parents	39 (8)	56 (3.3)	3.30 (2.04–5.36)***	85 (7.4)	84 (2.1)	3.88 (2.78–5.41)***

OR: Odds ratio; CI: Confidence interval.

^a Adjusted for: maternal age, paternal age, maternal SES, maternal marital status, maternal smoking during pregnancy, number of previous births, weight for gestational age, parental immigration status.

^b Adjusted OR comparing only mother versus only father. Missing values for anxiety disorders ranged between 9–100 for boys and 3–91 for girls.

* p < .05.
** p < .01.
*** p < .001.

of having anxiety or depressive disorders compared to children that are not exposed to ACEs (Hughes et al., 2017). Similarly, parenting also might have its impact on the development of anxiety disorders. Parental overprotection (Beesdo et al., 2010) and parental rejection (Guzick

et al., 2022) may undermine the children's sense of safety and competence by further stimulating their fear, which increases the risk of anxiety. These parenting behaviors are associated with parental psychiatric disorders such as depression (Hanington et al., 2010), anxiety (Aktar

Table 4
Association between parental psychiatric diagnoses registered before and after childbirth and offspring anxiety disorder.

		Before birth vs. Never	After birth vs. Never	Before birth vs. After birth
		Adjusted OR (95 % CI)	Adjusted OR (95 % CI)	Adjusted OR (95 % CI)
Psychotic disorder	Maternal	2.51 (2.01–3.12)***	2.86 (2.54–3.22)***	0.88 (0.68–1.12)
	Paternal	1.82 (1.46–2.27)***	2.18 (1.91–2.48)***	0.84 (0.65–1.08)
Bipolar disorder	Maternal	1.93 (0.93–4.03)	3.36 (2.99–3.78)***	0.58 (0.27–1.21)
	Paternal	2.05 (1.13–3.71)*	1.82 (1.57–2.10)***	1.13 (0.61–2.08)
Depression	Maternal	3.04 (2.64–3.52)***	2.77 (2.64–2.91)***	1.10 (0.95–1.27)
	Paternal	1.74 (1.49–2.02)***	1.80 (1.69–1.91)***	0.97 (0.82–1.13)
Personality disorder	Maternal	3.42 (2.73–4.29)***	3.95 (3.58–4.36)***	0.87 (0.68–1.11)
	Paternal	1.98 (1.75–2.25)***	2.10 (1.86–2.38)***	0.94 (0.79–1.12)
Anxiety disorders	Maternal	2.64 (2.19–3.18)***	2.39 (2.22–2.56)***	1.11 (0.91–1.35)
	Paternal	1.91 (1.66–2.21)***	1.91 (1.73–2.11)***	1.00 (0.84–1.19)
Substance use disorder	Maternal	2.15 (1.79–2.58)***	2.43 (2.23–2.64)***	0.89 (0.73–1.08)
	Paternal	1.76 (1.56–1.99)***	1.65 (1.55–1.76)***	1.07 (0.93–1.22)

Models were adjusted for the other parent's any psychiatric disorder, maternal age, paternal age, maternal marital status, smoking during pregnancy, number of previous births, weight for gestational age; maternal immigration status, paternal immigration status; OR: Odds ratio, CI: Confidence interval.

* p < .05.
*** p < .001.

et al., 2013), bipolar (Arman et al., 2018) and substance use disorder (Bountress and Chassin, 2015). The components and complexity of family environment doubles when both parents suffer from any psychiatric disorder compared to a single parent, thus shaping the neurodevelopmental outcome in children.

We found that maternal psychiatric disorder overall showed stronger association to offspring anxiety than paternal psychiatric disorder. Disorders such as maternal intellectual disability, personality disorder, bipolar disorder, substance use disorder (SUD) and depression were especially associated to a heightened risk of anxiety among offspring. Consistent to our findings, it has been reported that intellectual disability as well as maternal personality disorder increased risk of anxiety among offspring (Sheerin, 1998; Pearson et al., 2018). Pearson et al. (2018) reported higher levels of maternal but not paternal dysfunctional personality traits associated with anxiety in offspring independently of other confounders. Mothers with personality disorders often exhibit impulsive and hostile behaviors along with over-reactive and inconsistent parenting (Chen and Johnston, 2007), and can result in behavioral issues such as anxiety disorder in their children. Similarly, previous research has consistently shown that children of parents with bipolar disorder, especially when both parents were affected, have a significantly heightened risk of developing anxiety disorders, with those having mothers with the bipolar being nearly three times more likely to be diagnosed (Park et al., 2015; Lau et al., 2018; Kendler et al., 2022; Bastos et al., 2022; Birmaher et al., 2009). This could possibly be due to the genetic correlation, as significant genetic overlaps have been found between anxiety and bipolar disorders (Kendler et al., 2022).

We also found a strong association between maternal SUD and anxiety disorders in offspring. This suggests that substance abuse possibly impairs parents' ability to form healthy relationships with their children and could lead to emotional and behavioral issues in children,

including internalizing problems (Lander et al., 2013). A Swedish study further supports this by linking parental substance abuse with an increased risk of intellectual disability in offspring, which is significant as anxiety disorders are notably prevalent among individuals with intellectual disabilities (27–50 %) (Khemiri et al., 2023; Groves et al., 2022). Additionally, maternal SUD can disrupt emotional regulation strategies crucial for mother-infant interactions, leading to emotional dysregulations in children (Punamäki et al., 2021). Our research further reveals that both maternal and paternal depression are linked to offspring anxiety, differing from previous findings that either focused solely on maternal depression (Ohannessian et al., 2005) or did not find a significant link with parental depression, except for specific phobia (Hirshfeld-Becker et al., 2012). However, we observed a stronger association with maternal depression compared to paternal, corroborating reports that children of depressed mothers tend to exhibit higher anxiety levels (Silver et al., 2020). This could be due to stress-induced epigenetic changes in the offspring, which may alter gene regulation related to stress (Fitzgerald et al., 2020; Rogers et al., 2020). Such epigenetic changes, including DNA methylation and histone modifications, can have lasting effects (Richards, 2006; Talbert and Henikoff, 2006), and have been associated with anxiety disorders through changes in specific genes (Ziegler and Domschke, 2018). Additionally, intrauterine factors, particularly those affecting the hypothalamic-pituitary-adrenal (HPA) axis during early infancy, play a crucial role in cognitive development (Finegood et al., 2017). Stress induced HPA axis during pregnancy produces high level of cortisol potentially affecting fetal brain development, increasing the risk of internalizing disorders (Lester et al., 2013). The stressful environments created by depressive symptoms in mothers can profoundly impact children (Delagneau et al., 2023) and exposure to maternal depression during pregnancy also significantly increases the likelihood of child maltreatment, resulting in anxiety (Plant et al., 2015).

Our study also noted biological sex specific risks, maternal psychiatric disorders were associated with higher risk of separation anxiety and generalized anxiety in boys and social phobia and panic disorder in girls. While separation anxiety tends to run in families (Manicavasagar et al., 2001), factors such as parental intrusiveness and over-protectiveness might contribute to these outcomes (Wood, 2006; Stone et al., 2015; Orgilés et al., 2018). Prevalence of panic disorder is higher in girls, and familial factors, as well as an overprotective family environment, may serve as psychological vulnerability factor for panic disorder (Joyce et al., 1989; Hettema, 2008; Schneider et al., 2009; Vizard et al., 2018).

The number of parents with childhood onset diagnosis in our study was relatively small and we did not observe significant difference in maternal and paternal childhood onset disorder and their association with offspring anxiety. We also did not observe differences in the associations between offspring anxiety and parental psychiatric diagnoses given before or after childbirth, this could also be suggestive more towards environmental transmission of anxiety disorders.

The major strength of our study is that the sample was population based, and the population-based case-controls studies minimize the probabilities of recall bias. Besides, our data was drawn from different national databases which enabled us to capture large sample of cases with anxiety disorder, parents with wide range of psychiatric disorder diagnoses and account for different covariates. The healthcare services in Finland are universally available and financed by the state or local municipalities, and children are not subject to the generally modest patient fees. As a result, it is likely that most children experiencing anxiety would have accessed the public healthcare system. However, certain limitations should be considered in interpreting our findings. This was a register-based study which means it didn't represent every case of anxiety disorder among the Finnish population. This study includes the anxiety cases that sought specialized health care services and likely to represent more severe cases of anxiety disorders. Although Finnish children regularly attend child health clinics where routine

screenings are conducted, the reliance on specialized service may overlook a certain portion of the population with anxiety disorders. Our analysis focused on subjects diagnosed between the ages six and twenty. This age restriction limits the applicability of our findings outside this age range as the developmental trajectory of anxiety disorders can vary significantly across life stages. Most of the cases analyzed in our study were unspecified anxiety disorders. This lack of specificity restricts to draw a robust conclusion regarding the association between parental psychiatric disorders and specific anxiety subgroup hence this should be cautiously interpreted. While our analysis included parental psychiatric disorders before and after the child's birth, it did not account for the possibility that parents may have been diagnosed with other psychiatric disorders at different points of time. This could obscure the true impact of parental mental health on offspring anxiety disorder. Additionally, we could not control for other potential confounders such as genetic and other biological factors, childhood adversities, (e.g. abuse, neglect, or exposure to violence), parenting practices and family dynamics through register data.

Given the limitations, longitudinal, multi-generational studies could provide deeper insights into hereditary and environmental influences, as well as integrating register-based data with self-reported measures, diagnostics interviews, and other data sources could enhance the understanding of anxiety disorders.

5. Conclusion

Our research adds to the current evidence that a wide range of parental psychiatric disorders are associated with offspring anxiety disorder. Maternal psychopathology showing stronger association underscores the importance of maternal mental health for child well-being. Given that parental psychopathology and behavior may impact child anxiety, it is important to develop prevention programs for at-risk children and develop family-based treatment programs.

CRedit authorship contribution statement

Prakash Khanal: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Conceptualization. **Tiia Ståhlberg:** Writing – review & editing, Validation, Methodology. **Subina Upadhyaya:** Writing – review & editing, Validation. **Emmi Heinonen:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Ana Ortin-Peralta:** Writing – review & editing, Visualization, Validation. **Andre Sourander:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The author(s) report no conflicts of interest.

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Appendix A. Supplementary data

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References

- Aktar, E., Majdandžić, M., de Vente, W., Bögels, S.M., 2013. The interplay between expressed parental anxiety and infant behavioral inhibition predicts infant avoidance in a social referencing paradigm. *J. Child Psychol. Psychiatry* 54, 144–156. <https://doi.org/10.1111/j.1469-7610.2012.02601.x>.
- Allen, J.L., Sandberg, S., Chhoa, C.Y., et al., 2018. Parent-dependent stressors and the onset of anxiety disorders in children: links with parental psychopathology. *Eur. Child Adolesc. Psychiatry* 27, 221–231. <https://doi.org/10.1007/s00787-017-1038-3>.
- Arman, S., Salimi, H., Maracy, M.R., 2018. Parenting styles and psychiatric disorders in children of bipolar parents. *Advances in Biomedical Research* 7, 147. <https://doi.org/10.4103/abr.abr.131.18>.
- Bastos, R.A., Campos, L.S., Faria-Schützer, D.B., Brito, M.E., da Silva, D.R., Dos Santos-Junior, A., Turato, E.R., 2022. Offspring of mothers with bipolar disorder: a systematic review considering personality features. *Brazilian Journal of Psychiatry* 44 (1), 94–102. <https://doi.org/10.1590/1516-4446-2020-1465>.
- Beesdo, K., Pine, D.S., Lieb, R., Wittchen, H.U., 2010. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Arch. Gen. Psychiatry* 67 (1), 47–57. <https://doi.org/10.1001/archgenpsychiatry.2009.177>.
- Biederman, J., Petty, C., Faraone, S.V., Hirshfeld-Becker, D.R., Henin, A., Dougherty, M., Rosenbaum, J.F., 2005. Parental predictors of pediatric panic disorder/agoraphobia: a controlled study in high-risk offspring. *Depress. Anxiety* 22 (3), 114–120. <https://doi.org/10.1002/da.20122>.
- Birmaher, B., Axelson, D., Monk, K., et al., 2009. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring study. *Arch. Gen. Psychiatry* 66, 287–289.
- Bountress, K., Chassin, L., 2015. Risk for behavior problems in children of parents with substance use disorders. *Am. J. Orthopsychiatry* 85 (3), 275–286. <https://doi.org/10.1037/ort0000063>.
- Bütikofer, A., Ginja, R., Karbownik, K., & Landaud, F. (2023). (Breaking) intergenerational transmission of mental health (NBER Working Paper No. 31446). National Bureau of Economic Research. Retrieved from <http://www.nber.org/papers/w31446>.
- Chen, M., Johnston, C., 2007. Maternal inattention and impulsivity and parenting behaviors. *J. Clin. Child Adolesc. Psychol.* 36 (3), 455–468. <https://doi.org/10.1080/15374410701448570>.
- Chiu, A., Falk, A., Walkup, J.T., 2016. Anxiety disorders among children and adolescents. *Focus (American Psychiatric Publishing)* 14 (1), 26–33. <https://doi.org/10.1176/appi.focus.20150029>.
- Corrêa, M.L., da Silva, B.G.C., Wehrmeister, F.C., Horta, B.L., Gonçalves, H., Barros, F., Menezes, A.M.B., 2022. Maternal smoking during pregnancy and children's mental health at age 22 years: results of a birth cohort study. *J. Affect. Disord.* 300, 203–208. <https://doi.org/10.1016/j.jad.2021.12.125>.
- Delagneau, G., Twilhaar, E.S., Testa, R., van Veen, S., Anderson, P., 2023. Association between prenatal maternal anxiety and/or stress and offspring's cognitive functioning: a meta-analysis. *Child Dev.* 94, 779–801. <https://doi.org/10.1111/cdev.13885>.
- Finewood, E.D., Wyman, C., O'Connor, T.G., Blair, C.B., Family Life Project Investigators, 2017. Salivary cortisol and cognitive development in infants from low-income communities. *Stress* 20 (2), 112–121. <https://doi.org/10.1080/10253890.2017.1286325>.
- Fitzgerald, M., London-Johnson, A., Gallus, K.L., 2020. Intergenerational transmission of trauma and family systems theory: an empirical investigation. *J. Fam. Ther.* 42, 406–424. <https://doi.org/10.1111/1467-6427.12303>.
- Glasheen, C., Richardson, G.A., Kim, K.H., Larkby, C.A., Swartz, H.A., Day, N.L., 2013. Exposure to maternal pre- and postnatal depression and anxiety symptoms: risk for major depression, anxiety disorders, and conduct disorder in adolescent offspring. *Dev. Psychopathol.* 25 (4pt1), 1045–1063. <https://doi.org/10.1017/S0954579413000369>.
- Groves, L., Moss, J., Oliver, C., et al., 2022. Divergent presentation of anxiety in high-risk groups within the intellectual disability population. *J. Neurodev. Disord.* 14, 54. <https://doi.org/10.1186/s11689-022-09462-w>.
- Guzick, A.G., Chabaud, S., Garrett, C., Storch, E.A., 2022. Anxiety, depression, and rejection towards parents among individuals who grew up in a hoarded home. *Ann. Clin. Psychiatry* 34 (1), 77–88. <https://doi.org/10.12788/acp.0053>.
- Hanington, L., Ramchandani, P., Stein, A., 2010. Parental depression and child temperament: assessing child to parent effects in a longitudinal population study. *Infant Behav. Dev.* 33 (1), 88–95. <https://doi.org/10.1016/j.infbeh.2009.11.004>.
- Hans, S.L., Auerbach, J.G., Styr, B., Marcus, J., 2004. Offspring of parents with schizophrenia: mental disorders during childhood and adolescence. *Schizophr. Bull.* 30 (2), 303–315. <https://doi.org/10.1093/oxfordjournals.schbul.a007080>.
- Helenius, D., Munk-Jørgensen, P., Steinhausen, H.C., 2014. Family load estimates and risk factors of anxiety disorders in a nationwide three generation study. *Psychiatry Res.* 216 (3), 351–356. <https://doi.org/10.1016/j.psychres.2014.02.026>.
- Henin, A., Biederman, J., Mick, E., Sachs, G.S., Hirshfeld-Becker, D.R., Siegel, R.S., McMurrich, S., Grandin, L., Nierenberg, A.A., 2005. Psychopathology in the

- offspring of parents with bipolar disorder: a controlled study. *Biol. Psychiatry* 58 (7), 554–561. <https://doi.org/10.1016/j.biopsych.2005.06.010>.
- Hettema, J.M., 2008. What is the genetic relationship between anxiety and depression? *Am. J. Med. Genet. C Semin. Med. Genet.* 148C, 140–146. <https://doi.org/10.1002/ajmg.c.30171>.
- Hettema, J.M., Neale, M.C., Kendler, K.S., 2001. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am. J. Psychiatry* 158, 1568–1578.
- Hirshfeld-Becker, D.R., Micco, J.A., Henin, A., Petty, C., Faraone, S.V., Mazursky, H., Biederman, J., 2012. Psychopathology in adolescent offspring of parents with panic disorder, major depression, or both: a 10-year follow-up. *Am. J. Psychiatry* 169 (11), 1175–1184.
- Hosmer, D.W., Lemeshow, S., Sturdivant, R.X., 2013. *Applied Logistic Regression*, 3rd ed. vol. 398. Wiley.
- Hughes, K., Bellis, M.A., Hardcastle, K.A., et al., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* 2 (8), e356–e366. [https://doi.org/10.1016/S2468-2667\(17\)30118-4](https://doi.org/10.1016/S2468-2667(17)30118-4).
- Joelsson, P., Chudal, R., Gyllenberg, D., Kesti, A.K., Hinkka-Yli-Salomäki, S., Virtanen, J. P., Huttunen, J., Ristkari, T., Parner, E., Sourander, A., Sillanpää, M., 2016. Demographic characteristics and psychiatric comorbidity of children and adolescents diagnosed with ADHD in specialized healthcare. *Child Psychiatry Hum. Dev.* 47 (4), 574–582. <https://doi.org/10.1007/s10578-015-0591-6>.
- Joelsson, P., Chudal, R., Uotila, J., Suominen, A., Sucksdorff, D., Gyllenberg, D., Sourander, A., 2017. Parental psychopathology and offspring attention-deficit/hyperactivity disorder in a nationwide sample. *J. Psychiatr. Res.* 94, 124–130. <https://doi.org/10.1016/j.jpsychires.2017.07.004>.
- Jokiranta, E., Brown, A.S., Heinimaa, M., Cheslack-Postava, K., Suominen, A., Sourander, A., 2013. Parental psychiatric disorders and autism spectrum disorders. *Psychiatry Res.* 207 (3), 203–211. <https://doi.org/10.1016/j.psychres.2013.01.005>.
- Joyce, P.R., Bushnell, J.A., Oakley-Browne, M.A., Wells, J.E., Hornblow, A.R., 1989. The epidemiology of panic symptomatology and agoraphobic avoidance. *Compr. Psychiatry* 30 (4), 303–312. [https://doi.org/10.1016/0010-440x\(89\)90054-0](https://doi.org/10.1016/0010-440x(89)90054-0).
- Kendall, P.C., Compton, S.N., Walkup, J.T., Birmaher, B., Albano, A.M., Sherrill, J., Ginsburg, G., Rynn, M., McCracken, J., Gosch, E., Keeton, C., Bergman, L., Sakolsky, D., Suveg, C., Iyengar, S., March, J., Piacentini, J., 2010. Clinical characteristics of anxiety disordered youth. *J. Anxiety Disord.* 24 (3), 360–365. <https://doi.org/10.1016/j.janxdis.2010.01.009>.
- Kendler, K.S., Ohlsson, H., Sundquist, J., Sundquist, K., 2022. Risk for mood, anxiety, and psychotic disorders in individuals at high and low genetic liability for bipolar disorder and major depression. *JAMA Psychiatry* 79 (11), 1102–1109. <https://doi.org/10.1001/jamapsychiatry.2022.2873>.
- Khanal, P., Ståhlberg, T., Luntamo, T., et al., 2022. Time trends in treated incidence, sociodemographic risk factors and comorbidities: a Finnish nationwide study on anxiety disorders. *BMC Psychiatry* 22, 144. <https://doi.org/10.1186/s12888-022-03743-3>.
- Khemiri, L., Kujala-Halkola, R., Larsson, H., Butwicka, A., Tideman, M., D’Onofrio, B.M., Lichtenstein, P., 2023. Parental substance use disorder and risk of intellectual disability in offspring in Sweden: a national register study. *EclinicalMedicine* 63. <https://doi.org/10.1016/j.eclinm.2023.102170>.
- Kingston, D., Heaman, M., Brownell, M., Ekuma, O., 2015. Predictors of childhood anxiety: a population-based cohort study. *PLoS One* 10 (7), e0129339. <https://doi.org/10.1371/journal.pone.0129339>.
- Koskela, M., Chudal, R., Luntamo, T., et al., 2020. The impact of parental psychopathology and sociodemographic factors in selective mutism - a nationwide population-based study. *BMC Psychiatry* 20, 221. <https://doi.org/10.1186/s12888-020-02637-6>.
- Koskinen, M.K., Hovatta, I., 2023. Genetic insights into the neurobiology of anxiety. *Trends in Neuroscience* 46 (4), 318–331. <https://doi.org/10.1016/j.tins.2023.01.007>.
- Lampi, K., Sourander, A., Gissler, M., Niemelä, S., Rehnström, K., Pulkkinen, E., Peltonen, L., Von Wendt, L., 2010. Brief report: validity of Finnish registry-based diagnoses of autism with the ADI-R. *Acta Paediatr.* 99 (9), 1425–1428. <https://doi.org/10.1111/j.1651-2227.2010.01835.x>.
- Lander, L., Howsare, J., Byrne, M., 2013. The impact of substance use disorders on families and children: from theory to practice. *Soc. Work Public Health* 28 (3–4), 194–205. <https://doi.org/10.1080/19371918.2013.759005>.
- Lau, P., Hawes, D.J., Hunt, C., et al., 2018. Prevalence of psychopathology in bipolar high-risk offspring and siblings: a meta-analysis. *Eur. Child Adolesc. Psychiatry* 27, 823–837. <https://doi.org/10.1007/s00787-017-1050-7>.
- Lehti, V., Chudal, R., Suominen, A., Gissler, M., Sourander, A., 2016. Association between immigrant background and ADHD: a nationwide population-based case-control study. *J. Child Psychol. Psychiatry* 57, 967–975. <https://doi.org/10.1111/jcpp.12570>.
- Leijdesdorff, S., van Doesum, K., Popma, A., Klaassen, R., van Amelsvoort, T., 2017. Prevalence of psychopathology in children of parents with mental illness and/or addiction: an up-to-date narrative review. *Curr. Opin. Psychiatry* 30 (4), 312–317. <https://doi.org/10.1097/YCO.0000000000000341>.
- Leivonen, S., Voutilainen, A., Hinkka-Yli-Salomäki, S., Timonen-Soivio, L., Chudal, R., Gissler, M., Huttunen, J., Sourander, A., 2014. A nationwide register study of the characteristics, incidence and validity of diagnosed Tourette syndrome and other tic disorders. *Acta Paediatr.* 103 (9), 984–990. <https://doi.org/10.1111/apa.12708>.
- Leivonen, S., Scharf, J.M., Mathews, C.A., Chudal, R., Gyllenberg, D., Sucksdorff, D., Suominen, A., Voutilainen, A., Brown, A.S., Sourander, A., 2017. Parental psychopathology and Tourette syndrome/chronic tic disorder in offspring: a nationwide case-control study. *J. Am. Acad. Child Adolesc. Psychiatry* 56 (4), 303.e4. <https://doi.org/10.1016/j.jaac.2017.01.009>.
- Lester, B.M., Conrad, E., Marsit, C.J., 2013. Epigenetic basis for the development of depression in children. *Clin. Obstet. Gynecol.* 56 (3), 556–565. <https://doi.org/10.1097/GRF.0b013e318299d2a8>.
- Li, X., Sundquist, J., Sundquist, K., 2008. Age-specific familial risks of anxiety. A nationwide epidemiological study from Sweden. *Eur. Arch. Psychiatry Clin. Neurosci.* 441–445. <https://doi.org/10.1007/s00406-008-0817-8>.
- Lieb, R., Wittchen, H.U., Höfler, M., Fuetsch, M., Stein, M.B., Merikangas, K.R., 2000. Parental psychopathology, parenting styles, and the risk of social phobia in offspring: a prospective-longitudinal community study. *Arch. Gen. Psychiatry* 57 (9), 859–866. <https://doi.org/10.1001/archpsyc.57.9.859>.
- Malaspina, D., Gilman, C., Kranz, T.M., 2015. Paternal age and mental health of offspring. *Fertil. Steril.* 103 (6), 1392–1396. <https://doi.org/10.1016/j.fertnstert.2015.04.015>.
- Manicavasagar, V., Silove, D., Rapee, R., Waters, F., Momartin, S., 2001. Parent-child concordance for separation anxiety: a clinical study. *J. Affect. Disord.* 65 (1), 81–84. [https://doi.org/10.1016/S0165-0327\(00\)00241-x](https://doi.org/10.1016/S0165-0327(00)00241-x).
- Maybery, D., Reupert, A.E., 2018. The number of parents who are patients attending adult psychiatric services. *Curr. Opin. Psychiatry* 31 (4), 358–362. <https://doi.org/10.1097/YCO.0000000000000427>.
- Ohanessian, C.M., Hesselbrock, V.M., Kramer, J., Kuperman, S., Bucholz, K.K., Schuckit, M.A., Nurnberger, J.I., 2005. The relationship between parental psychopathology and adolescent psychopathology: an examination of gender patterns. *J. Emot. Behav. Disord.* 13 (2), 67–76. <https://doi.org/10.1177/10634266050130020101>.
- Oliver-Parra, A., Dalmáu-Bueno, A., Ruiz-Muñoz, D., García-Altés, A., 2020. Relationship between parents’ mental disorders and socioeconomic status and offspring’s psychopathology: a cross-sectional study. *PLoS One* 15 (10), e0240681. <https://doi.org/10.1371/journal.pone.0240681>.
- Orgilés, M., Penosa, P., Morales, A., Fernández-Martínez, I., Espada, J.P., 2018. Maternal anxiety and separation anxiety in children aged between 3 and 6 years: the mediating role of parenting style. *J. Dev. Behav. Pediatr.* 39 (8), 621–628. <https://doi.org/10.1097/DBP.0000000000000593>.
- Park, M.H., Sanders, E., Howe, M., Singh, M., Hallmayer, J., Kim, E., Chang, K., 2015. Association of anxiety symptoms in offspring of bipolar parents with serotonin transporter-linked polymorphic region (5-HTTLPR) genotype. *J. Child Adolesc. Psychopharmacol.* 25 (6), 458–466. <https://doi.org/10.1089/cap.2014.0115>.
- Pearson, R.M., Campbell, A., Howard, L.M., Bornstein, M.H., O’Mahen, H., Mars, B., Moran, P., 2018. Impact of dysfunctional maternal personality traits on risk of offspring depression, anxiety and self-harm at age 18 years: a population-based longitudinal study. *Psychol. Med.* 48 (1), 50–60. <https://doi.org/10.1017/S0033291717001246>.
- Penninx, B.W., Pine, D.S., Holmes, E.A., Reif, A., 2021. Anxiety disorders. *Lancet* 397 (10277), 914–927. [https://doi.org/10.1016/S0140-6736\(21\)00359-7](https://doi.org/10.1016/S0140-6736(21)00359-7).
- Pihlajamaa, J., Suvisaari, J., Henriksson, M., Heilä, H., Karjalainen, E., Koskela, J., Cannon, M., Lönnqvist, J., 2008. The validity of schizophrenia diagnosis in the Finnish Hospital Discharge Register: findings from a 10-year birth cohort sample. *Nord. J. Psychiatry* 62 (3), 198–203. <https://doi.org/10.1080/08039480801983596>.
- Plant, D.T., Pariante, C.M., Sharp, D., Pawlby, S., 2015. Maternal depression during pregnancy and offspring depression in adulthood: role of child maltreatment. *Br. J. Psychiatry* 207 (3), 213–220. <https://doi.org/10.1192/bjp.bp.114.156620>.
- Polanczyk, G.V., Salum, G.A., Sugaya, L.S., Caye, A., Rohde, L.A., 2015. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J. Child Psychol. Psychiatry* 56 (3), 345–365. <https://doi.org/10.1111/jcpp.12381>.
- Powell, V., Lennon, J., Bevan Jones, R., Stephens, A., Weavers, B., Osborn, D., Allardyce, J., Potter, R., Thapar, A., Collishaw, S., Thapar, A., Heron, J., Rice, F., 2023. Following the children of depressed parents from childhood to adult life: a focus on mood and anxiety disorders. *JCPP Advances*. <https://doi.org/10.1002/jcv2.12182> (Advance online publication).
- Punamäki, R.L., Flykt, M., Belt, R., Lindblom, J., 2021. Maternal substance use disorder predicting children’s emotion regulation in middle childhood: the role of early mother-infant interaction. *Heliyon* 7 (4), e06728. <https://doi.org/10.1016/j.heliyon.2021.e06728>.
- Ramchandani, P., Psychogiou, L., 2009. Paternal psychiatric disorders and children’s psychosocial development. *The Lancet* 374 (9690), 646–653. [https://doi.org/10.1016/S0140-6736\(09\)60238-5](https://doi.org/10.1016/S0140-6736(09)60238-5).
- Ranøyen, I., Stenseng, F., Klöckner, C.A., Wallander, J., Jozefiak, T., 2015. Familial aggregation of anxiety and depression in the community: the role of adolescents’ self-esteem and physical activity level (the HUNT Study). *BMC Public Health* 15, 78. <https://doi.org/10.1186/s12889-015-1431-0>.
- Reiss, F., Meyrose, A.K., Otto, C., Lampert, T., Klasen, F., Ravens-Sieberer, U., 2019. Socioeconomic status, stressful life situations and mental health problems in children and adolescents: results of the German BELLA cohort-study. *PLoS One* 14 (3), e0213700. <https://doi.org/10.1371/journal.pone.0213700>.
- Richards, E., 2006. Inherited epigenetic variation — revisiting soft inheritance. *Nat. Rev. Genet.* 7, 395–401. <https://doi.org/10.1038/nrg1834>.
- Riordan, D.M., Singhal, D., 2018. Anxiety-related disorders: an overview. *J. Paediatr. Child Health* 54, 1104–1109. <https://doi.org/10.1111/jpc.14167>.
- Rogers, A., Obst, S., Teague, S.J., Rossen, L., Spry, E.A., Macdonald, J.A., Olsson, C.A., 2020. Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis. *JAMA Pediatr.* 174, 1082–1092. <https://doi.org/10.1001/jamapediatrics.2020.2910>.
- Schneider, S., Houweling, J.E.G., Gommlich-Schneider, S., et al., 2009. Effect of maternal panic disorder on mother–child interaction and relation to child anxiety and child

- self-efficacy. *Arch. Womens Ment. Health* 12, 251–259. <https://doi.org/10.1007/s00737-009-0072-7>.
- Sheerin, F., 1998. Parents with learning disabilities: a review of the literature. *J. Adv. Nurs.* 28, 126–133. <https://doi.org/10.1046/j.1365-2648.1998.00636.x>.
- Silver, J., Olino, T.M., Carlson, G.A., Klein, D.N., 2020. Offspring of mothers with histories of chronic and non-chronic depression: symptom trajectories from ages 6 to 15. *Front. Psych.* 11, 601779. <https://doi.org/10.3389/fpsy.2020.601779>.
- Ståhlberg, T., Upadhyaya, S., Khanal, P., Sucksdorff, M., Luntamo, T., Suominen, A., Sourander, A., 2022a. Associations between delivery modes, birth outcomes and offspring anxiety disorders in a population-based birth cohort of children and adolescents. *Front. Psych.* 13, 917299. <https://doi.org/10.3389/fpsy.2022.917299>.
- Ståhlberg, T., Upadhyaya, S., Khanal, P., Sucksdorff, M., Luntamo, T., Suominen, A., Sourander, A., 2022b. Preterm birth, poor foetal growth and anxiety disorders in a Finnish nationwide register sample. *Acta Paediatr.* 111 (8), 1556–1565. <https://doi.org/10.1111/apa.16377>.
- Steinhausen, H.C., Foldager, L., Perto, G., et al., 2009. Family aggregation of mental disorders in the nationwide Danish three-generation study. *Eur. Arch. Psychiatry Clin. Neurosci.* 259, 270–277. <https://doi.org/10.1007/s00406-008-0865-0>.
- Stone, L.L., Otten, R., Soenens, B., Engels, R.C., Janssens, J.M., 2015. Relations between parental and child separation anxiety: the role of dependency-oriented psychological control. *J. Child Fam. Stud.* 24 (11), 3192–3199. <https://doi.org/10.1007/s10826-015-0122-x>.
- Sucksdorff, D., Chudal, R., Suominen, A., et al., 2014. Bipolar disorder and parental psychopathology. *Soc. Psychiatry Psychiatr. Epidemiol.* 49, 1973–1984. <https://doi.org/10.1007/s00127-014-0885-1>.
- Sund, R., 2012. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand. J. Public Health* 40 (6), 505–515. <https://doi.org/10.1177/1403494812456637>.
- Talbert, P., Henikoff, S., 2006. Spreading of silent chromatin: inaction at a distance. *Nat. Rev. Genet.* 7, 793–803. <https://doi.org/10.1038/nrg1920>.
- Tearne, J.E., Robinson, M., Jacoby, P., Allen, K.L., Cunningham, N.K., Li, J., McLean, N.J., 2016. Older maternal age is associated with depression, anxiety, and stress symptoms in young adult female offspring. *J. Abnorm. Psychol.* 125 (1), 1–10. <https://doi.org/10.1037/abn0000119>.
- Vandeleur, C., Rothen, S., Gholam-Rezaee, M., Castela, E., Vidal, S., Favre, S., Preisig, M., 2012. Mental disorders in offspring of parents with bipolar and major depressive disorders. *Bipolar Disord.* 14 (6), 641–653. <https://doi.org/10.1111/j.1399-5618.2012.01048.x>.
- Vizard, T., Pearce, N., Davis, J., 2018. *Mental Health of Children and Young People in England, 2017*. Health and Social Care Information Centre, Leeds.
- Wang, F., Ma, X., Zhao, L., Li, T., Fu, Y., Zhu, W., 2024. The influence of genetic and environmental factors on anxiety among Chinese adolescents: a twin study. *J. Genet. Psychol.* <https://doi.org/10.1080/00221325.2024.2319235>.
- Wickersham, A., Leightley, D., Archer, M., Fear, N.T., 2020. The association between paternal psychopathology and adolescent depression and anxiety: a systematic review. *J. Adolesc.* 79, 232–246. <https://doi.org/10.1016/j.adolescence.2020.01.007>.
- Wolicki, S.B., Bitsko, R.H., Cree, R.A., Danielson, M.L., Ko, J.Y., Warner, L., Robinson, L.R., 2021. Mental health of parents and primary caregivers by sex and associated child health indicators. *Advances in Resilience Science* 2 (2), 125–139. <https://doi.org/10.1007/s42844-021-00037-7>.
- Wood, J.J., 2006. Parental intrusiveness and children's separation anxiety in a clinical sample. *Child Psychiatry Hum. Dev.* 37, 73–87. <https://doi.org/10.1007/s10578-006-0021-x>.
- Ziegler, C., Domschke, K., 2018. Epigenetic signature of MAOA and MAOB genes in mental disorders. *J. Neural Transm.* 125, 1581–1588. <https://doi.org/10.1007/s00702-018-1929-6>.