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Association between parental mental illness and autoimmune diseases in the offspring – A nationwide register-based cohort study in Sweden

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ABSTRACT

Mental illness has been previously linked with autoimmune diseases, yet the associations between parental mental illness and offspring's risk of autoimmune diseases is largely unknown. We conducted a population-based cohort study of 2,192,490 Swedish children born between 1991 and 2011 and their parents to determine the associations between parental mental illness and risk of autoimmune diseases among the offspring. Time-dependent diagnoses of parental mental illness (psychosis, alcohol/drug misuse, depression, anxiety, eating disorders, personality disorders, attention deficit hyperactivity disorder, autism spectrum disorder) and offspring autoimmune diseases (type 1 diabetes (T1D), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, psoriasis, multiple sclerosis, inflammatory bowel disease (IBD), coeliac disease) were identified from inpatient/outpatient healthcare visits. Associations were measured by hazard ratios (HRs) adjusted for potential confounders. Overall, parental mental illness was associated with a small increase in risk of offspring's autoimmune diseases (HR 1.05, 95% CI 1.02–1.08). However, parental common mental disorder (anxiety/depression) was associated with higher risk of JIA, psoriasis, and T1D (HR T1D 1.11, 95% CI 1.01–1.22), while maternal psychosis with reduced risk of coeliac disease (HR 0.68, 95% CI 0.49–0.95) and paternal alcohol/drug misuse with reduced risk of IBD (HR 0.80, 95% CI 0.64–0.99). Maternal eating disorders were associated with a markedly increased risk for T1D (HR 1.41, 95% CI 1.05–1.89). Further studies are needed to confirm these findings and to understand underlying mechanisms. There is a need for greater clinical awareness about potential risk of JIA, psoriasis, and T1D among children of parents with common psychiatric morbidity.

Authorship statement

Alicia Nevriana: Conceptualisation, methodology, software, formal analysis, visualisation, writing – original draft, writing – review and editing. Matthias Pierce: Conceptualisation, methodology, writing – review and editing. Kathryn M Abel: Conceptualisation, methodology, writing – review and editing, supervision, funding acquisition. Marios Rossides: Conceptualisation, methodology, writing – review and editing. Susanne Wicks: Conceptualisation, methodology, resources, data curation, writing – review and editing. Christina Dalman: Conceptualisation, methodology, writing – review and editing, funding acquisition. Kyriaki Kosidou: Conceptualisation, methodology, writing – original draft, writing – review and editing, supervision.

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, Hazard Ratio; IBD, Inflammatory Bowel Disease; ICD, International Classification of Diseases; JIA, Juvenile Idiopathic Arthritis; NPR, National Patient Register; SLE, Systemic Lupus Erythematosus; T1D, Type 1 Diabetes.

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1. Introduction

Autoimmune diseases in childhood have the potential to limit children's development through school absences (Nordal et al., 2019), lower quality of life (Kuhlmann et al., 2016), and incur substantial healthcare costs (Kuhlmann et al., 2016). However, relatively little is known about the determinants of these diseases (Bogdanos et al., 2012).

There is increasing interest in understanding potential link between autoimmune diseases and mental illness, especially common mental disorders. Individuals who suffer from mental illness have a higher risk subsequently of developing autoimmune diseases (Benros et al., 2014; Cullen et al., 2019; Song et al., 2018). Also, studies that have included first-degree relatives of individuals with mental disorders indicate evidence of familial clustering of mental illness and autoimmune disease (Ji et al., 2018; Mataix-Cols et al., 2018; Sadik et al., 2022). Theories linking these disorders include shared genetics (Benros et al., 2014; Cullen et al., 2019; Mataix-Cols et al., 2018), lifestyle factors (e.g. smoking) (Benros et al., 2014; Song et al., 2018), or dysregulation of the immune system (Song et al., 2018).

Recent studies estimate that between 10 and 20% of children have at least one parent with a mental illness (Abel et al., 2019; Pierce et al., 2020a). Children and adolescents with parental mental illness are a vulnerable group. Compared to other children, their risk of developing mental illness is greater (Lawrence et al., 2019), as is their risk of physical ill-health (Pierce et al., 2020b), or healthcare utilisation (Hope et al., 2021). A meta-analysis (Pierce et al., 2020b) has indicated higher risks of asthma and injuries among children with parental mental illness but evidence on other somatic health outcomes is scarce.

Children and adolescents with parental mental illness may also have a higher risk of developing an autoimmune disease, but evidence is scarce. A Danish study (Benros et al., 2014) found that individuals with parents or siblings with schizophrenia had a slightly higher risk for autoimmune disease, driven by higher risks for primary biliary cirrhosis, autoimmune hepatitis, systemic lupus erythematosus (SLE), Sjögren's syndrome, pernicious anaemia, iridocyclitis, and type 1 diabetes (T1D). By contrast, a Swedish study found a slightly lower risk for rheumatoid arthritis in the offspring of parents with schizophrenia, but no differences were reported for offspring of parents with schizoaffective or bipolar disorder (Sellgren et al., 2014).

This study of 2 million Swedish children and their parents aimed to examine the associations between a broad spectrum of maternal and paternal mental illnesses and the risk of several autoimmune diseases in children. We were able to study the risks while incorporating rich information on confounders, such as socioeconomic factors and familial history of autoimmune disease.

2. Material and methods

2.1. Study design, settings, and population

We conducted a longitudinal population-based cohort study using Swedish national health and administrative registers, linked through the

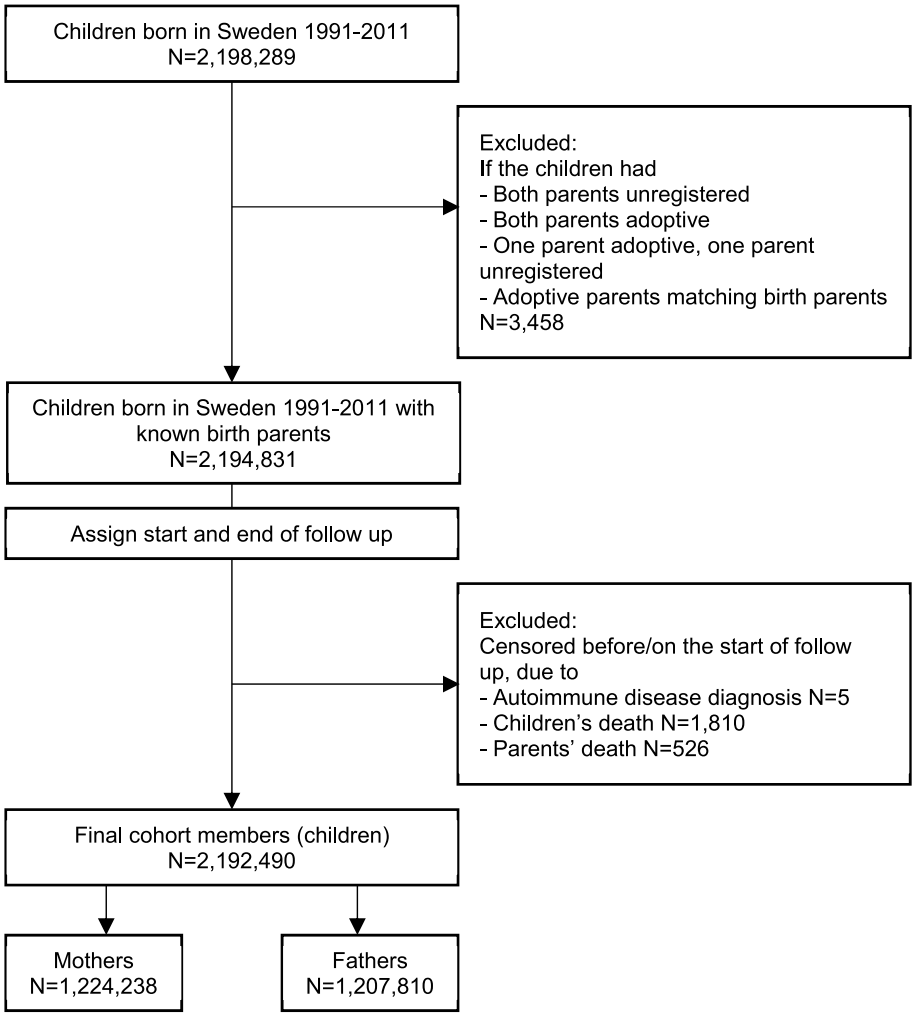

Fig. 1. Flowchart depicting the derivation of the analytical sample.

unique personal identification number assigned to all Swedish residents. We identified all children born in Sweden over twenty years between 1991 and 2011 (N = 2,198,289) and their parents from the Total Population (Ludvigsson et al., 2016) and Multi-Generation Register (Ekbom, 2011). We excluded 3458 children (0.15%) without known parents or with adoptive parents since we wanted to capture potential genetic and environmental factors that might influence the associations. The final analytical sample included 2,192,490 children, 1,224,238 mothers and 1,207,810 fathers (Fig. 1). Children were followed-up from their date of birth until the first date of emigration or death (of either parent or child), their 18th birthday, or 31 December 2016, whichever was earliest.

2.2. Parental mental illness

Information on parental mental illness was obtained from the National Patient Register (NPR), which contains data from all publicly funded secondary inpatient (complete coverage since 1973 for psychiatric disorders, since 1987 for somatic disorders) and specialised outpatient care (near-complete coverage for adults since 2006) (Ludvigsson et al., 2011). The NPR has been validated for mental illness diagnoses (Dalman et al., 2002; Kouppis and Ekselius, 2020; Ruck et al., 2015; Sellgren et al., 2011; Vilaplana-Pérez et al., 2020). Diagnoses in the NPR are recorded with the ICD codes, however, within clinical practice in Sweden, mental disorder diagnoses are made according to the DSM criteria. Parental mental illness was categorised based on the similarities of diagnostic categories, according to symptoms described in the ICD and DSM. This was grouped into non-affective psychotic disorders (including schizophrenia), affective psychotic disorders (including bipolar disorders), alcohol/substance use disorders, depressive disorders (excluding those with psychotic symptoms), anxiety/stress-related disorders, eating disorders, personality disorders, attention deficit hyperactivity disorder, or autism spectrum disorder (Table S1). We grouped non-affective and affective psychotic disorders into 'psychotic disorders'; and depressive and anxiety/stress-related disorders into 'common mental disorders.'

Parental mental illness was used as a time-varying exposure: children were exposed when their mothers or fathers received their first mental illness diagnosis (beginning one year before birth) and remained exposed until the end of follow up.

2.3. Children's autoimmune diseases

We *a priori* selected the following autoimmune diseases diagnoses that are likely to be diagnosed in paediatric populations, or known to have paediatric onset (although the majority might be diagnosed in adults): T1D, juvenile idiopathic arthritis (JIA), SLE, psoriasis, multiple sclerosis (MS), inflammatory bowel disease, or coeliac disease. These diagnoses were identified using ICD codes (Table S2) for inpatient or outpatient visits in NPR. Studies comparing the recorded autoimmune disease diagnoses within the NPR and patients' medical records have shown high validity of the registered diagnoses (Ceder et al., 2021; Jakobsson et al., 2017; Lindström et al., 2015; Murley et al., 2019; Waldenlind et al., 2014).

2.4. Covariates

We obtained the following demographic data from the Total Population Register: child's birth year, parental country of birth (Sweden/other), and parental age at childbirth. Parental education and household disposable income were obtained from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) (Ludvigsson et al., 2019). Maternal and paternal education was ascertained in the year before childbirth and categorised into compulsory (≤9 years), secondary (10–12 years) and university education (≥13 years). A single variable representing the highest maternal or paternal education level was included in the analysis. Household disposable income was defined as the yearly sum of income and public benefits earned by all family members after taxes, categorised into quintiles for each calendar year. We defined parental history of autoimmune disease as any visit in the NPR in mothers or fathers before childbirth where an autoimmune disorder was recorded (Table S3). We defined childhood psychopathology as the presence of any mental illness diagnosis in the NPR for the index child throughout the follow-up period (Table S4).

2.5. Statistical analysis

We calculated crude incidence rates of autoimmune diseases by parental mental illness exposures. The association between parental mental illness and offspring autoimmune disease, overall and by individual pairs of prespecified diagnoses, was estimated using rate differences and hazard ratios (HRs). Since these associations were specified *a priori* based on putative mechanisms, we did not adjust for multiple comparisons, which might be necessary when there is no sound theoretical basis for the associations (Rothman, 2014). Instead, we chose to present all the estimates from the prespecified associations (Haneuse and Rothman, 2021). Hazard ratios were estimated using Cox proportional hazard models, with children's age as the underlying time scale. Adjusted hazard ratios were calculated by including potential confounders in the regression model (Calixto and Anaya, 2014; Muntaner et al., 2004): child's birth year, parental country of birth, parental age at childbirth, parental education, household disposable income and parental history of autoimmune disease. Familial homogeneity was accounted for in the standard errors by using Huber-White adjustments, clustering on maternal or paternal ID. We included missing observations as a separate category (ranged from <0.1% in parental country of birth to 2.1% in parental education). We considered interval estimates that did not cross 1.00 as statistically significant.

We conducted two sensitivity analyses. First, to limit misclassification, we applied a stricter criterion for outcome definition requiring at least two registered diagnoses for the same autoimmune disease. Second, to minimise the risk of reverse causality, as outcomes and the exposures were obtained from registers and the date of diagnosis might not accurately reflect disease onset, we only included parental mental illness exposure that was diagnosed at any time point up until childbirth, i.e., children were considered exposed/unexposed at birth, and we did not consider any parental mental illness diagnoses that were obtained afterwards.

We performed two supplementary analyses. First, we stratified by childhood psychopathology to explore effect measure modification, as parental mental illness is known to be associated with psychopathology in the offspring (Rasic et al., 2014; van Santvoort et al., 2015); and mental disorders and autoimmune diseases tend to co-occur (Cullen et al., 2019). Thus, we hypothesized that a potentially increased risk for autoimmune diseases in children of mentally ill parents might be confined to the subgroup of children who also have psychopathology. Second, we performed a *post hoc* analysis stratified by parental educational level and household disposable income, to determine whether there were differences in the associations between parental mental illnesses and risk of autoimmune disease by differences in parental socioeconomic position.

Data management and analyses were performed using SAS version 9.4, Stata version 16.1, and R version 3.6.1.

2.6. Ethical considerations

We assert that all procedures contributing to this work were carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the Regional Ethics Review Board in Stockholm, Sweden (DNR: 2010/1185–31/5, 2013/1118–32, 2016/987–32). The need to obtain informed consent is waived in register-based studies in Sweden, as stipulated in the ethics approval.

3. Results

3.1. Study population

About one in five children and adolescents in the study population had at least one parent with a mental illness diagnosis during follow-up (Table S6), most commonly, anxiety/stress-related disorders (13.7%) and depressive disorders (9.3%). A higher proportion of mothers (12.7%) than fathers (9.2%) had a mental illness diagnosis during follow-up.

Children and adolescents with parental mental illness were more likely to have parents with lower education or to live in households in the lowest income quintile (Table 1). A slightly higher proportion of parents with mental illness also had a history of autoimmune disease (5.1% vs 4.2%; Table 1). Children and adolescents with parental mental illness were also more likely to have a diagnosis of childhood psychopathology during follow-up, compared to their peers without parental mental illness (15.3% vs 6.2%; Table 1).

Autoimmune disease was more common in girls (54.3 vs 45.7%) and among children and adolescents with parental history of autoimmune disease (7.1% vs 4.3%; Table S5). Around 4% of children and adolescents with autoimmune disease were diagnosed with childhood psychopathology during follow up (compared to 8.1% among children and adolescents without autoimmune disease, Table S5).

Table 1
Demographic, socioeconomic, and health characteristics of children (N = 2,192,490), according to parental mental illness exposure.

Variables	Categories	Any parental mental illness over follow-up			
		Yes		No	
		N = 424,708		N = 1,767,782	
		n	%	n	%
Children characteristics					
Follow up time (years)	Mean (SD)	13.6	4.4	12.9	5.0
Sex	Female	205,023	48.3	860,886	48.7
	Male	219,685	51.7	906,896	51.3
Birth year	1991–1995	100,366	23.6	478,011	27.0
	1996–2000	99,604	23.5	355,631	20.1
	2001–2005	105,558	24.9	387,527	21.9
	2006–2011	119,180	28.1	546,613	30.9
Autoimmune disease during follow up	No	418,510	98.5	1,723,206	97.5
	Yes	6198	1.5	44,576	2.5
Family characteristics					
Parental country of birth	All known parents born outside Sweden	62,388	14.7	231,281	13.1
	All known parents born in Sweden	301,923	71.1	1,334,809	75.5
	One parent born outside and one parent born inside Sweden	60,396	14.2	201,643	11.4
	Missing	1	0.0	49	0.0
Maternal age at birth (years)	Mean (SD)	29.3	5.6	30.2	5.0
Paternal age at birth (years)	Mean (SD)	32.5	6.7	33.1	6.0
Highest parental education	Compulsory	47,095	11.1	88,298	5.0
	Secondary	219,850	51.8	774,124	43.8
	University	149,038	35.1	871,159	49.3
	Missing	8725	2.1	34,201	1.9
Household disposable income in quintiles	Q1 (lowest)	85,178	20.1	252,285	14.3
	Q2	123,358	29.1	462,483	26.2
	Q3	99,904	23.5	431,528	24.4
	Q4	64,454	15.2	343,439	19.4
	Q5 (highest)	47,308	11.1	261,071	14.8
	Missing	4506	1.1	16,976	1.0
Parental history of autoimmune diseases	No	403,097	94.9	1,693,634	95.8
	Yes	21,611	5.1	74,148	4.2
Childhood psychopathology	No	359,961	84.8	1,657,845	93.8
	Yes	64,747	15.3	109,937	6.2

3.2. Associations between parental mental illness and children's autoimmune disease

Among children and adolescents with parental mental illness, we identified 6198 children diagnosed with autoimmune disease during 13 years of follow up (incidence rate 218.6, 95% CI 213.2–224.1 per 100,000 person-years; Tables 1 and S7). Among other children, 44,576 were diagnosed with an autoimmune disease (incidence rate 172.9, 95% CI 171.3–174.6 per 100,000 person-years). This corresponds to an incidence rate difference of 45.7 (95% CI 40.0–51.4) per 100,000 person-years.

For most parental mental disorders, there was little evidence of an association with autoimmune diseases (as demonstrated by confidence intervals crossing one, Fig. 2, Table S7). However, 8 parental mental disorders were associated with significantly increased risk of specific autoimmune diseases. The largest increase in risk was observed for T1D among children with parental eating disorders (HR 1.36, 95% CI 1.02–1.83); followed by psoriasis among children with parental depressive disorders (HR 1.18, 95% CI 1.08–1.28), alcohol/substance use disorders (HR 1.16, 95% CI 1.02–1.31) and anxiety/stress-related disorders (HR 1.11, 95% CI 1.03–1.19), JIA among the offspring of parents with depressive disorders (HR 1.14, 95% CI 1.03–1.26), and inflammatory bowel disease among offspring of parents with anxiety/stress-related disorders (HR 1.10, 95% CI 1.01–1.21). Further, we had evidence for positive associations for psoriasis (HR 1.13, 95% CI 1.06–1.21) and JIA (HR 1.09, 95% CI 1.01–1.18) when depressive and anxiety disorders were grouped as common mental disorders. Conversely, a lower relative risk of inflammatory bowel disease was observed among children with parental alcohol/substance use disorders (HR 0.83, 95% CI 0.70–0.99).

Similar to results for parental exposure, for most maternal or paternal mental disorders there was little evidence of association with autoimmune diseases in the children (Fig. 3, Table S8). However, an increased risk was observed for T1D among children with maternal eating disorders (HR 1.41, 95% CI 1.05–1.89) and maternal depressive disorders (HR 1.11, 95% CI 1.01–1.22). We also observed an increased risk for psoriasis among children with maternal depressive disorders (HR 1.19, 95% CI 1.08–1.32), anxiety/stress-related disorders (HR 1.11, 95% CI 1.01–1.21), or both disorders combined (HR 1.14, 95% CI 1.06–1.23). Reduced risk of coeliac disease was identified among children with maternal non-affective psychotic disorders (HR 0.68, 95% CI 0.49–0.95).

For paternal mental illness exposure, the largest increase in risk was observed for psoriasis among children with paternal depressive disorder (HR 1.18, 95% CI 1.04–1.34) followed by common mental disorders (HR 1.11, 95% CI 1.01–1.22). A decreased risk was observed for inflammatory bowel disease among children with paternal alcohol/substance use disorders (HR 0.80, 95% CI 0.64–0.99; Fig. 3, Table S9).

3.3. Secondary analysis

The associations between parental, maternal, and paternal mental illness and child autoimmune diseases were generally similar in sensitivity analyses where we applied a stricter outcome definition requiring ≥2 registered ICD-coded visits (Table S10) or restricted to parental mental disorders diagnosed before childbirth (Table S11). In addition to associations identified in the main analyses, an increased relative risk was observed for inflammatory bowel disease associated with paternal alcohol/substance use disorders diagnosed solely before childbirth.

In the supplementary analyses, we did not observe any notable differences in the HRs when we stratified by childhood psychopathology (e.

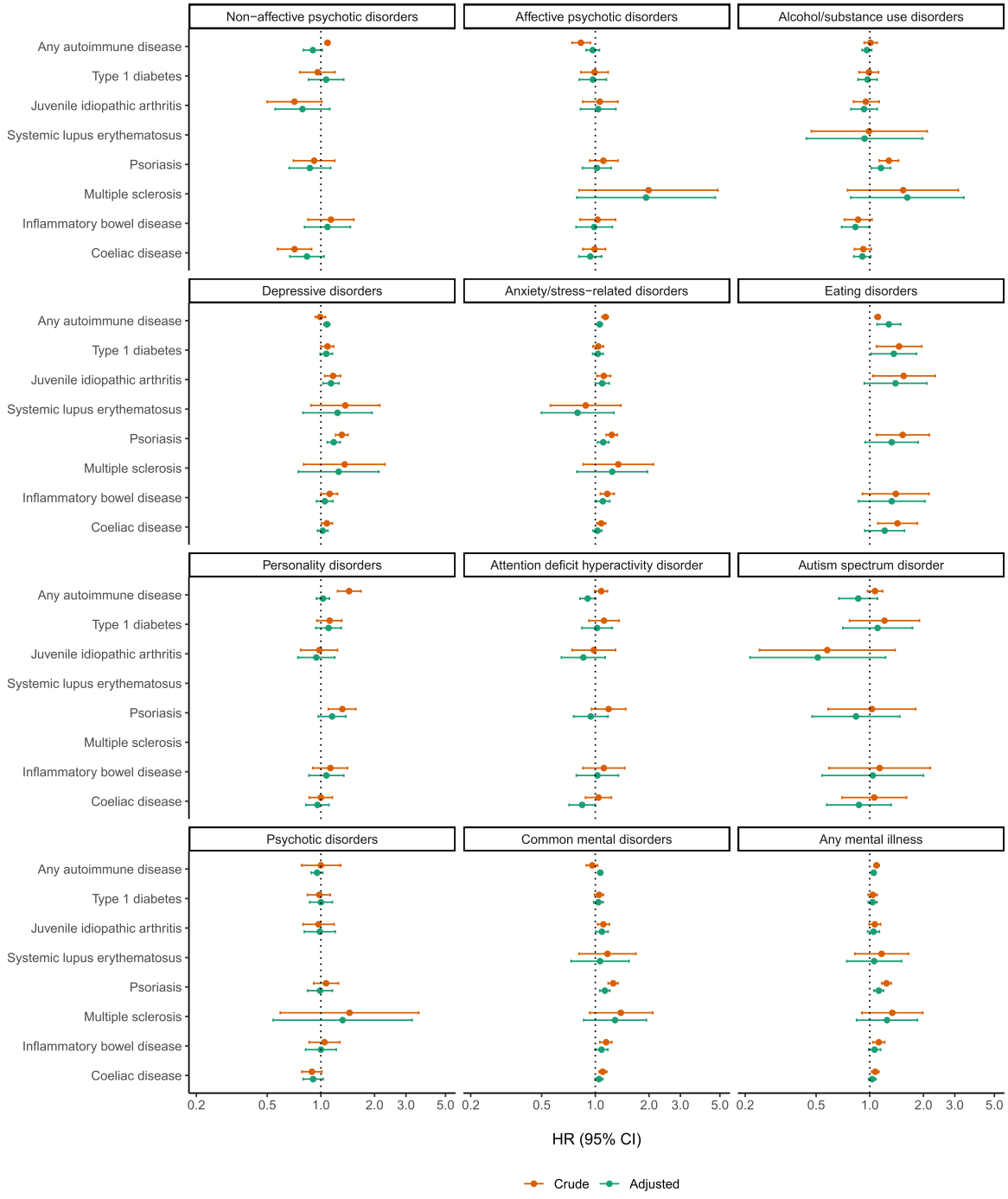

Fig. 2. Hazard ratios and 95% confidence intervals for the association between parental mental illness and risk of autoimmune diseases among the children. Adjusted models controlled for birth year, parental age, parental country of birth, parental education, household disposable income, and parental history of autoimmune disease. We did not present the estimates if there were <5 cases in an exposure category. The exact estimates can be found in Table S7.

g., HR for the association between parental eating disorders and type 1 diabetes for those with childhood psychopathology 1.75, 95% CI 0.78–3.92, and those without childhood psychopathology 1.40, 95% CI 1.03–1.91, Table S12). Lastly, we did not observe any notable differences in the HRs by parents' educational level or household income (Tables S13–S14).

4. Discussion

This nationwide population-based study is the most comprehensive investigation of autoimmune disease among children with parental mental illness, to date. Our findings suggest that most types of parental mental illness show no relationship with any additional risk of autoimmune disease in offspring.

Nevertheless, we report evidence for several noteworthy associations. First, we found increase in risk for both JIA and psoriasis if a parent suffered from anxiety, depression or drug and alcohol use disorders. Second, we observed increase in risk for T1D if the mother were diagnosed with depression or eating disorders. The greatest excess relative risk for T1D in offspring (41%) was observed for mothers with

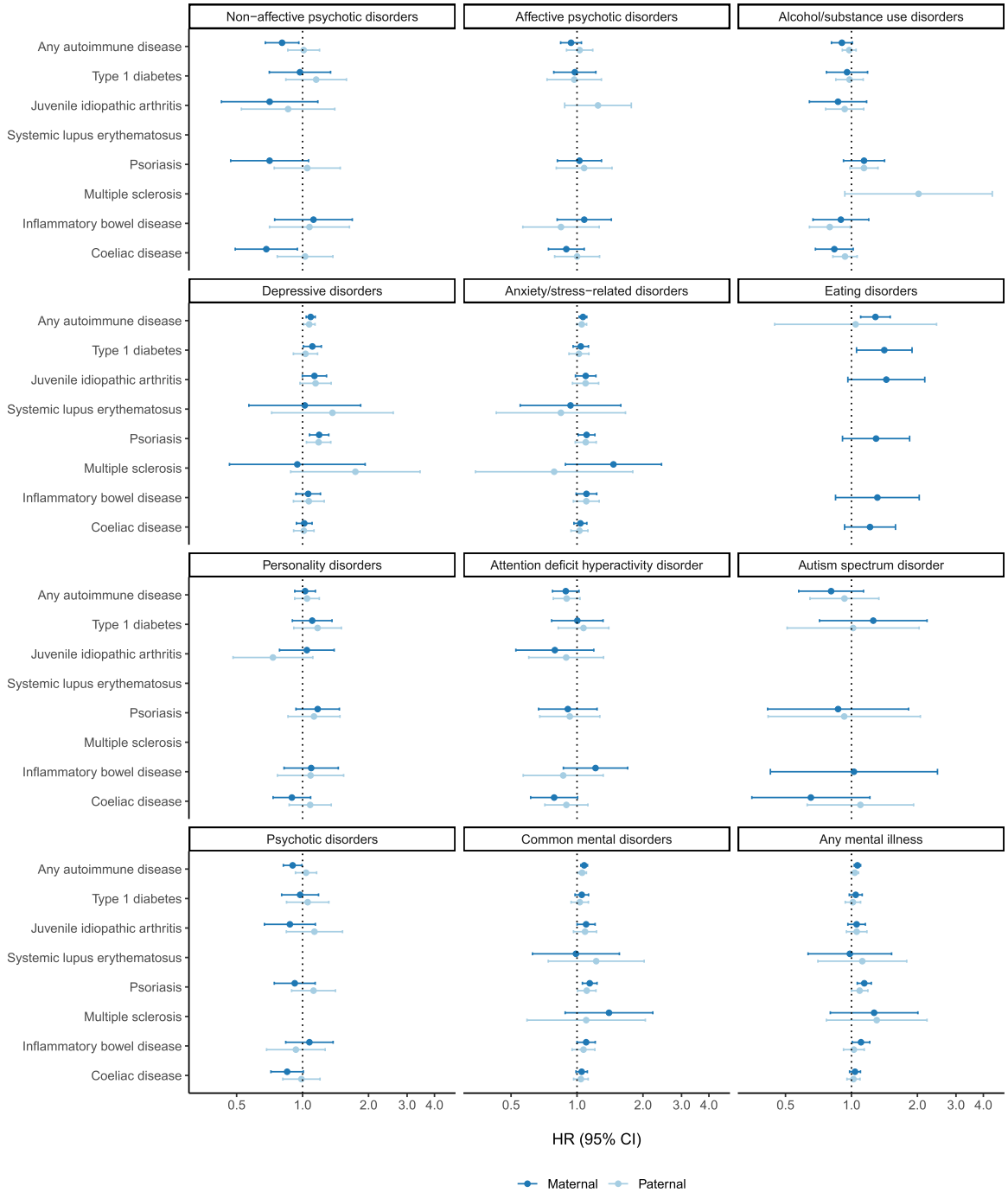

Fig. 3. Adjusted hazard ratios and 95% confidence intervals for the association between maternal and paternal mental illness and the risk for autoimmune diseases among the children. Controlled for birth year, parental age, parental country of birth, parental education, household disposable income and parental history of autoimmune disease. We did not present the estimates if there were <5 cases in an exposure category. The exact estimates can be found Table S8 (maternal) and Table S9 (paternal).

an eating disorder. As far as we are aware, neither finding has been previously reported. We also observed a lower risk of inflammatory bowel disease in children with parental alcohol/substance use disorders, especially when the father carried the diagnosis and for coeliac disease among children of mothers with non-affective psychotic disorders.

Our results appear to contrast with some of those reported in a previous Danish study (Benros et al., 2014) which found an increased risk of coeliac disease among individuals with first degree relatives (parents/siblings) with schizophrenia; we report a lower risk of coeliac disease in children of parents, particularly mothers, with non-affective psychosis. However, the confidence intervals of both these estimates are wide (HR Sweden 0.84, 95% CI 0.67–1.04; IRR Denmark 1.02, 95% CI 0.79–1.29) so this difference may result from random variation.

Explanatory mechanisms for our findings are likely to be complex. First, although children and adolescents with parental mental illness are likely to be exposed to more adversity and deprivation in childhood, this does not appear overall to increase autoimmune disease risk. This is important because a growing literature links depression and stress-

related disorders to early adversity and deprivation with subsequent altered inflammatory and immune responses (McEwen, 2007; Song et al., 2018). If higher levels of psychosocial adversity and/or stress are triggering autoimmune disease among children and adolescents with parental mental illness, we would have expected the highest rates of autoimmune diseases among those with childhood psychopathology, as well as among those with lower parental education or household income, which are both linked to childhood adversity (Pierce et al., 2020a). However, childhood psychopathology was actually less common in children diagnosed with autoimmune disease and there were similar increases in overall risk of autoimmune diseases among children and adolescents with and without childhood psychopathology. Additionally, we did not observe significant differences in the risk across different strata of parental socioeconomic position.

Furthermore, the two most notable and, as far as we are aware, previously unreported associations between maternal eating disorder and T1D and parental anxiety/depressive/alcohol-drug disorders with psoriasis may implicate novel interactions between environment and genetics altering immune mechanisms. Microorganisms in the gut (part of the so-called 'microbiome') may be important endocrine modulators of the immune system. Eating disorders, drug and alcohol dependence, as well as mood disorders, may plausibly alter gut microbiota and influence dysregulation of the immune system (Cruz-Pereira et al., 2020). For example, HPA axis activation in depression has been reported to increase the pro-inflammatory immune mediators and impair the neurotransmitter transmission, which could potentially lead to disturbance in the signalling mechanisms within the gut and alter the gut microbiota (Cruz-Pereira et al., 2020). Whether or not alterations in maternal or paternal microbiota also can seed relevant changes in offspring microbiota to influence their immune responses requires far more research but transgenerational passage of microbiota has been described (Alberts et al., 2019).

Genetic factors may underlie some of the increased risks. For example, a statistically insignificant positive correlation was observed between risk alleles for major depression and psoriasis (Tylee et al., 2018). However, the same study also found a statistically significant positive correlation between schizophrenia and coeliac disease (Tylee et al., 2018), while we found that maternal psychosis was associated with lower risk of coeliac disease in children. The same study also showed no significant genetic correlations between anorexia nervosa and T1D (Tylee et al., 2018), yet another genome-wide association study (Duncan et al., 2017) identified one significant locus for anorexia nervosa, which has also been associated with T1D. Epigenetic changes might also be implicated in the development of autoimmune diseases, including type 1 diabetes (Karagianni and Tzioufas, 2019; Knip et al., 2017; Xie et al., 2020). Additionally, certain environmental factors, such as maternal nutrition and eating disorders have been linked to epigenetic changes during the fetal development period (Sebastiani et al., 2020; Stevenson et al., 2020). Although more research is needed, it may be possible that the observed association between maternal eating disorders and T1D in the child can be partly explained by epigenetic mechanisms occurring during fetal development.

Within index individuals, it has indeed been hypothesized that alcohol use might influence changes in the blood-brain barrier permeability (Vore and Deak, 2021) and increased blood-brain permeability has been implicated in the aetiology of certain autoimmune diseases (Simka, 2009). However, the mechanisms that might link alcohol use in the parents with risk for autoimmune disease in children are currently unknown and need to be addressed in research, if future studies confirm these findings.

Alternative mechanisms for the effects we describe could include differences in health-seeking behaviour between parents (mothers or fathers) with and without mental illnesses. For example, the lower estimates of autoimmune disease among children with parental psychotic disorder or substance misuse overall could be accounted for by the fact the most serious conditions prevent parental help-seeking or reduce parental vigilance on behalf of their children's health needs. This is consistent with previous study which found lower vaccination uptake for children with maternal mental illness (Osam et al., 2020). However, the opposite might be true for parents with common mental illness who may be more vigilant and more likely to seek help for their children (Hope et al., 2021). Health-seeking behaviour is unlikely to explain differences in risk of T1D in children of mothers with eating disorders or depression since these children inevitably present to health care.

Lastly, we cannot rule out the possibility of residual confounding. For example, parental smoking has been implicated in the aetiology of some mental illnesses (Boksa, 2017) and autoimmune diseases (Mårild et al., 2019). Besides, smoking is often a consequence of mental illness (Fluharty et al., 2017) and may, therefore, be considered a mediator. Therefore, it could be difficult to rule out its associations with parental mental illness.

This study has several strengths. By using linkage from various national registers, we were able to include more than 2 million children, alongside their parents, which allowed for sufficient statistical power to analyse rare outcomes and exposures. Moreover, the usage of several registers also meant that we had access to a variety of demographics and socioeconomic variables both at the individual and household level, which we utilized in our analyses to control for potential confounders.

Nevertheless, this study is not without limitations. We might have missed parents with mental illness if they were treated exclusively within primary care; this is especially true for less severe types of parental mental illness. This implies that we may only be able to generalise results to parental mental illness severe enough to be treated in secondary care. Similarly, we may have missed children treated for autoimmune disease exclusively within primary care. However, our sample is likely to have captured most children with autoimmune diseases as most are diagnosed and treated in secondary care. Another limitation of using register-based diagnoses was that the recorded date of diagnosis might not reflect the actual date of disease onset. It is possible, therefore, that some of the associations might be explained by reverse causation, with difficult to diagnose autoimmune disease in children leading to mental illness in the parent. However, this is unlikely because findings from the sensitivity analysis using parental mental illness exposure before birth were in line with the results from the main analysis. Given the number of reported associations, we acknowledge that there might be a possibility of chance findings. Therefore, and although our study utilized a very large and nationwide study sample, our findings might need to be confirmed in future studies using separate and potentially larger datasets i.e. pooled data from more countries. It is also possible that the associations between parental mental illness and autoimmune diseases might be different for comorbid mental disorders in the parents. However, we chose not to include these analyses in the current study that already presents several associations between parental mental disorders in parents and autoimmune diseases in offspring. Nevertheless, this should be addressed in future studies. Finally, we were not able to assess if familial confounding (i.e., genetics or shared environment) played a role in the associations we observed, which might be important in determining the potential causality of the reported associations.

We observed increased risks for T1D among children with maternal eating disorders or depression, and JIA and psoriasis among children with parental common mental disorders. Lower risks were seen for coeliac disease among children with maternal non-affective psychosis, and for inflammatory bowel disease among children with paternal alcohol/substance use disorders. Albeit these findings need further investigation and replication in other settings/datasets, they, nevertheless, show a need for greater clinical awareness about risks of autoimmune diseases, and especially T1D, in children of parents with common psychiatric morbidity. Further studies are needed to understand potential mechanisms underlying these associations, for example by conducting familial studies to disentangle potential genetic and environmental influences.

Declarations

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Conflicts of interests

MR reports non-promotional speaker fees from Teva, outside this work. All other authors declared no competing interests.

Data statement

Due to Swedish legal restrictions and the current ethical approval for the study, data are not publicly available to share.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.04.017.

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