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ORIGINAL RESEARCH

Offspring exposure to Crohn's disease during pregnancy and association with milder psychiatric regulatory disturbances in childhood

Elin Skott[1,2,3] | Gustav Söderberg[4,5] | MaiBritt Giacobini[1,2,3] | Samson Nivins[6] | Xinxia Chen[7] | Daniel Lindqvist[4,8] | Mika Gissler[1,2,9,10] | Klas Sjöberg[5,11] | Catharina Lavebratt[1,2]

[1]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

[2]Center for Molecular Medicine, Karolinska University Hospital Solna, Stockholm, Sweden

[3]Prima Vård AB, Malmö, Sweden

[4]Department of Clinical Sciences Lund, Psychiatry, Faculty of Medicine, Lund University, Lund, Sweden

[5]Department of Gastroenterology and Nutrition, Skåne University Hospital, Malmö, Sweden

[6]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[7]School of Nursing and Rehabilitation, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

[8]Department of Psychiatry, Skåne University Hospital, Lund, Sweden

[9]Department of Data and Analytics, Finnish Institute for Health and Welfare, Helsinki, Finland

[10]Research Centre for Child Psychiatry, University of Turku, Turku, Finland

[11]Department of Clinical Sciences Malmö, Lund University, Sweden

Correspondence
Catharina Lavebratt, Department of Molecular Medicine and Surgery,

Abstract

Introduction: Prenatal exposure to inflammatory states has been suggested to influence offspring neurodevelopment. The aim was to investigate if offspring exposure to maternal Inflammatory bowel disorder (IBD), or specifically the IBD disorder Crohn's disease, during gestation is associated with neurodevelopmental or psychiatric disorders in childhood.

Material and Methods: We conducted a population-based registry study in Finland. All live births from 1996 until 2014 in Finland were included and followed up until December 2018. Exposure was maternal IBD or Crohn's disease. Outcome was a broad range of neurodevelopmental and psychiatric disorders in offspring. Cox proportional hazards regression was applied to assess association. Sensitivity analyses included assessing, for example, exposure to severe episode of IBD or Crohn's disease, the outcome psychotropic medication for the children, and influence from perinatal risk factors.

Results: Of the participants ($N = 1\,105\,997$), 0.55% ($N = 6067$) were exposed to maternal IBD 0.18% ($N = 1959$) to maternal Crohn's disease. Among the children exposed to IBD or the subgroup Crohn's disease, 6.3% or 7.3%, respectively, had received an outcome diagnosis during the follow-up. There were higher risks for Sleeping disorders HR = 1.77 (95% CI, 1.13–2.78), Other feeding disorders HR = 1.83 (95% CI, 1.19, 2.19), and Incontinence HR = 1.42 (95% CI, 1.02–1.97) in children exposed to maternal Crohn's disease compared to unexposed children. This was supported by even higher point risk estimates for Incontinence HR = 2.43 (95% CI, 1.34–4.38) and Other feeding disorders HR = 2.83 (95% CI, 1.35–5.91) in offspring where the

Abbreviations: AD, autoimmune or autoinflammatory disorder; ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ATC, anatomic therapeutic chemical; CD, Crohn's disease; CI, confidence interval; HILMO, Finnish Care Registers for Health Care; HR, hazard ratio; IBD, inflammatory bowel disorder; ICD-10, International Statistical Classification of Diseases and Related Health Problems version 10; MBR, Medical Birth Register; PRF, perinatal risk factor; RRD, Finnish Register on Reimbursed Drugs; SGA, small for gestational age.

Karolinska University Hospital, Stockholm, Sweden.
Email: catharina.lavebratt@ki.se

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mother was hospitalized for Crohn's disease during pregnancy. Furthermore, there was a higher risk of dispensed antipsychotic, anxiolytic, hypnotic, and/or sedative medications for children with maternal Crohn's disease HR = 1.38 (95% CI, 1.03–1.85). These associations were not explained by cesarean section, preterm birth, or small birth size.

Conclusions: Offspring exposed to maternal Crohn's disease during pregnancy had modestly higher risks of early sleeping, continence, and feeding disturbances. The exposure had no detectable association with any of the other psychiatric disorders studied.

KEYWORDS
Crohn's disease, pregnancy, feeding disorder, incontinence, maternal, sleeping disorder

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated chronic inflammatory gastrointestinal disease mainly comprised of Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by inflammation and ulceration of the gut epithelium.[1] The peak incidence of IBD occurs between 20 and 29 years of age,[2] the population incidence has increased in Western countries during the 20th century, and in Finland, 2020 the prevalence was estimated to be ~1% of the population.[3,4] The etiology of IBD involves a complex interaction between genetic and environmental factors, with a disrupted gut microbiome and an insufficient barrier function with systemic effects.[5,6] There is a high comorbidity between IBD and psychiatric disorders.[7–11] A systematic review and meta-analysis shows that psychiatric symptoms in IBD are more prevalent in active disease episodes compared to milder periods and more common in CD compared to UC.[7] CD can affect the entire gastrointestinal tract, whereas UC is limited to the colon and rectum; furthermore, systemic effects are more common in CD.[12] Women with IBD have an increased risk of psychiatric disorder debut during pregnancy compared to those without IBD.[13] Maternal IBD active during conception and pregnancy is associated with adverse birth outcomes including preterm birth and low birthweight,[14] while quiescent IBD implies a much smaller risk.[15,16] Corticosteroid medication of IBD in pregnant women was reported to be associated with more preterm birth, but not with birth size or Apgar score; however, medication could also reflect the severity of IBD.[17] Through animal models, it is established that immune mediators are critical for normal neurodevelopment and that abnormal immune activation in utero can cause altered neurodevelopment in offspring resulting in structural and functional alterations.[18,19] However, to the best of our knowledge, no published study has investigated the association between prenatal exposure to IBD, or CD specifically, and specific offspring neurodevelopmental and psychiatric disorders beyond Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). In addition, no study has estimated the effect sizes on offspring psychopathology of exposure to severe episodes of maternal IBD or CD. A systematic review and meta-analysis reported associations for several parental autoimmune or autoinflammatory disorders (ADs) to offspring ASD and ADHD, with the strongest association for maternal ADs, but no association was found for IBD.[20] Furthermore, three nationwide registry studies from Denmark and Sweden investigated associations for maternal ADs to offspring neurodevelopmental and, to some extent, psychiatric disorders; He et al. found a small increased risk by maternal IBD or CD for psychiatric disorders overall when combined as one outcome (HR = 1.08 (95% CI, 1.00–1.17)); however, they did not assess specific psychiatric diagnoses with exposure to IBD or CD specifically.[21] Jolving et al. found no association between maternal IBD and offspring psychiatric disorder when studying a number of selected diagnoses and grouping them, for example, ASD, personality disorder, and agoraphobia as one outcome group, with a relatively short follow-up time (median 9.7 years).[22] Finally, Sadik et al. found that exposure to parental, primarily maternal, IBD or CD specifically, was associated with an increased risk of ASD; Maternal IBD: HR = 1.32 (95% CI, 1.24–1.40); Paternal IBD HR = 1.11 (1.03–1.18); Maternal CD: HR = 1.19 (95% CI, 1.05–1.35); Paternal CD HR = 1.16 (95% CI, 1.02–1.33).[23] Mendelian randomization analyses indicated that the aforementioned associations reflected in-part a causal genetic liability.[24]

Key message

Crohn's disease is an inflammatory bowel disorder. Offspring exposed prenatally to maternal Crohn's disease had modestly higher risks of early sleeping, continence, and feeding disturbances. This was supported by even higher point estimates when the mothers were hospitalized during pregnancy.

The aim of this study was to examine whether maternal IBD, and specifically the most severe IBD diagnosis: CD, is associated with a wide spectrum of psychiatric and neurodevelopmental disorders in offspring. For this, we conducted a nationwide observational

register-based cohort study in Finland. Hospitalization due to IBD during pregnancy, potentially an increased burden of abnormal in utero immune activation, was used as an indicator of severe IBD during pregnancy. Presence of preterm birth, caesarian section, or small birth size was considered to possibly influence the association.

2 | MATERIAL AND METHODS

2.1 | Study population and data source

This nationwide registry-based cohort study included all live offspring, $N = 1\,105\,997$, born between January 1, 1996 and December 31, 2014 in Finland, identified from the Medical Birth Register (MBR). The offspring were followed up until December 31, 2018 using the Finnish Care Registers for Health Care (HILMO) and until December 31, 2014 using the Finnish Register on Reimbursed Drugs (RRD). MBR and HILMO are kept by the Finnish Institute for Health and Welfare, and RRD is kept by the Social Insurance Institution of Finland. This study followed reporting guidelines provided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for cohort studies.[25] Data analysis was conducted between June 2022 and December 2023. Study population characteristics of the total cohort are shown in Table 1.

2.2 | Exposures

Main exposures included maternal IBD (CD and UC combined) and CD diagnosis, obtained before or during pregnancy identified using the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10), with the codes K50 (CD) and K51 (UC) from HILMO and MBR. Further exposures were maternal inpatient care during pregnancy identified using K50 (CD), K51 (UC) and O99.6 (diseases of the digestive system during pregnancy) from HILMO and MBR. For the birth cohorts 1996 and 1997, only inpatient maternal diagnoses were available. Since 1998 also outpatient visits in public hospitals were also in the registers. MBR recorded maternal diagnoses during pregnancy and birth only for the 2004–2014 birth cohorts. Paternal diagnoses were not available. Characteristics of the mothers with IBD and their births, stratified for inpatient care during pregnancy, are shown in Table S1.

2.3 | Outcomes and covariates

Diagnoses were identified from HILMO, and information on dispensations of psychotropic medications, defined as Anatomical Therapeutic Chemical (ATC)-groups, were obtained from RRD. Outcome variables were neurodevelopmental and psychiatric disorders in offspring identified using ICD-10 diagnosis codes during

TABLE 1 Characteristics of offspring and their mothers for all live births 1996–2014 in Finland.

	Maternal IBD		No maternal IBD	
Variable	***N* = 6067**	**(%)**	***N* = 1 099 930**	**(%)**
Offspring year of birth				
1996–2000	85	1.4	289 591	26.3
2001–2005	1461	24.0	280 804	25.5
2006–2010	2256	37.1	296 263	26.9
2011–2014	2265	37.3	233 272	21.2
Offspring biological sex				
Boy	3198	52.7	562 298	51.1
Girl	2869	47.3	537 632	48.9
No. of offspring with IBD	15	0.2	729	0.1
Offspring age at IBD diagnosis (years)				
Median (25th-75th percentile)	3.4 (2.5–4.3)		2.3 (0.9–3.7)	
Perinatal problems[a]				
Yes	1097	18.1	141 763	12.9
No	4970	81.9	958 167	87.1
Number of fetuses				
1	5856	96.5	1 067 350	97.0
2	210	3.5	31 944	2.9
3	1	0.0	632	0.1
4	0	0.0	4	0.0
Mode of delivery				
Vaginal	4177	68.8	834 306	75.9
Instrumental	533	8.8	80 350	7.3
Planned CS	619	10.2	79 459	7.2
Other CS	734	12.1	104 396	9.5
Missing	4	0.1	1419	0.1
Maternal age (years)				
<20	58	1.0	27 933	2.5
20–24	593	9.8	175 696	16.0
25–29	1952	32.2	348 701	31.7
30–34	2190	36.1	343 404	31.2
35–55	1274	21.0	204 195	18.6
Parity				
0	2706	44.6	454 179	41.3
1	2103	34.7	369 023	33.5
2	835	13.8	167 488	15.2
3	263	4.3	58 003	5.3
4 or more	225	3.7	50 053	4.6
Missing	8	0.1	1184	0.1
Maternal marital status				
Married	3536	58.3	654 145	59.5
Cohabiting	1939	32.0	319 377	29.0
Other	564	9.3	105 185	9.6
Missing	28	0.5	21 223	1.9
Maternal country of birth				
Finland	5885	97.0	1 015 582	92.3
Other	182	3.0	84 348	7.7
Maternal smoking				
No	5135	84.6	907 708	82.5
Stopped in 1 trimester	295	4.9	41 018	3.7

(Continues)

TABLE 1 (Continued)

Variable	Maternal IBD N = 6067	(%)	No maternal IBD N = 1099930	(%)
Continued	500	8.2	123214	11.2
Missing	137	2.3	27990	2.5
Maternal systemic inflammatory disorders[b]				
Yes	126	2.1	11614	1.1
No	5941	97.9	1088316	98.9
Maternal psychiatric disorders[c]				
Yes	171	2.8	24498	2.2
No	5896	97.2	1075432	97.8
Maternal psychotropics during pregnancy[d]				
Yes	442	7.3	49511	4.5
No	5625	92.7	1050419	95.5
Maternal preeclampsia[e]				
Yes	255	4.2	30928	2.8
No	5812	95.8	1069002	97.2
Maternal diabetes[f]				
PGDM	45	0.7	5882	0.5
T2DM	67	1.1	8655	0.8
GDM	817	13.5	150323	13.7
No DM	5138	84.7	935070	85.0
Maternal obesity diagnosis (ICD-10 E65–66)				
Yes	154	2.5	29557	2.7
No	5913	97.5	1070373	97.3
Socioeconomic status				
Upper white-collar	1103	18.2	183314	16.7
Lower white-collar	2352	38.8	392451	35.7
Blue-collar	720	11.9	159629	14.5
Other[g]	1892	31.2	191321	33.1

Abbreviations: CS, caesarian section; GDM, gestational diabetes mellitus; IBD, inflammatory bowel disease (ICD-10: K50–51); No DM, none of PGDM, T2DM or GDM; PGDM, pre-gestational diabetes mellitus; T2DM, pre-gestational type 2 diabetes mellitus.

[a]Perinatal problem: birth before gestational week 37 or birth weight <2500 g or small for gestational age (SGA) being a birth weight and/or length more than 2 standard deviations (SD) below the sex- and gestational age-specific reference mean (Sankilampi et al. 2013) according to the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society (Clayton et al. 2007).

[b]Maternal systemic inflammatory disorder: ICD-10 M30–M36 in 1996–2014 as primary or secondary diagnoses.

[c]Maternal psychiatric disorders: inpatient care due to mental health disorders before pregnancy according to ICD-8: 290–317 in 1969–198, ICD-9: 290–319 in 1987–1995, and ICD-10: F00–F99 in 1996–2014.

[d]Maternal prescription of ATC N05 or N06 during pregnancy (antipsychotics, anxiolytics, hypnotics, sedatives, antidepressants, stimulants or nootropics).

[e]Maternal pre-eclampsia was identified by ICD-10 diagnosis codes O11 and O14.

[f]Maternal diabetes: PGDM was defined as the purchase of insulin due to diabetes before pregnancy. Mothers with T2DM were defined as those with at least one of the ICD-10 diagnoses O24.1, E11, and E14 before pregnancy and/or a drug purchase of the Anatomic Therapeutic Chemical (ATC) class A10B (blood glucose lowering drugs other than insulin) before pregnancy. GDM was identified through ICD-10 diagnosis O24.4.

[g]Undefined.

the period from birth to 2018. The following categories with appurtenant ICD-10 codes were used: Mood disorders (F30–39, F92), Anxiety disorders (F40–43, F93), Eating disorders (F50), Sleeping disorders (F51), Specific developmental disorders (F80–83), ASD (F84), ADHD and conduct disorders (F90–91) and Other behavioral and emotional disorders (F98). Outcome variables were analyzed in groups of diagnoses with high symptom similarities to enhance power in statistical analyses. For example, the category Mood disorders comprised F30–F39 and F92 (e.g., major depressive disorder and bipolar disorder). Similarly, in sensitivity analyses, subdiagnoses under other behavioral and emotional disorders (F98) were grouped. For example, all incontinence diagnoses (F98.0–F98.1) were analyzed together. Pica (F98.3) was recorded for only 26 children, none of whom were exposed to IBD, and was therefore not considered. Dispensations of psychotropics until 2014 were identified as codes N05 (antipsychotic, anxiolytic, hypnotic, and sedative medications), N06A (antidepressants) and N06B (psychostimulants and nootropic medication). Covariates in Model 1 were offspring birth year (continuous), sex (boy/girl), number of fetuses (1/2 or more), maternal age group at delivery (<20/20–24/25–29/30–34/35–55 years), parity (continuous), socioeconomic status (SES, based on maternal occupation: upper white-collar/lower white-collar/blue-collar/other), unmarried not cohabiting mother at birth (yes/no), mother's country of birth (Finland or other), maternal smoking anytime during pregnancy (yes/no), maternal psychiatric disorder (yes/no), and maternal use of psychotropic medication during pregnancy (ATC N05 or N06, yes/no). Model 2 additionally included maternal obesity (ICD-10 E65–66, yes/no), maternal pregestational diabetes (ICD-10 O24.1, E11 and E14 or ATC class A10B, yes/no), and maternal systemic inflammatory disease (ICD-10 M30–36, yes/no), see Figure S1. In Model 3, the analyses were adjusted as in Model 1 with the addition of anti-CD medication (any of ATC codes A07E (intestinal anti-inflammatory agents), H02A (corticosteroids for systemic use), L04A (immunosuppressants) [yes/no]) dispensed either within (i) 3 months before pregnancy (B3) or trimester 1 (T1), or (ii) T2–T3, while Model 4 was Model 1 with the addition of child IBD diagnosis (yes/no). Maternal psychiatric in- and outpatient diagnoses were identified as ICD-8290–317 in 1969–1986, ICD-9290–319 in 1987–1995, and ICD-10 codes F00–F99 from 1996 until delivery. The information other than diagnoses and medications was obtained from the MBR. Perinatal risk factors (yes/no) referred to birth weight below 2500 g, birth size small for gestational age (SGA, below 5th percentile), cesarean section, and/or birth before the 37th gestational week. Missing data was handled as an own category.

2.4 | Statistical analyses

Cox proportional hazards modeling, considering time to event, was used to estimate the effect sizes of association between exposure to maternal IBD (any IBD or CD) and outcome offspring neurodevelopmental or psychiatric diagnosis. The proportional hazards assumption was tested. All statistical analyses were performed with SAS

statistical software version 9.4 (SAS institute). Crude and adjusted Hazard Ratios (HRs) were reported with 95% CI as measures of effect size. Two-sided $p < 0.05$ was considered statistically significant. Sensitivity analyses were performed on offspring diagnoses which were found associated with maternal IBD. The sensitivity analyses included (i) analyzing the exposure to hospitalization due to severe episodes of IBD during pregnancy, (ii) analyzing the association between maternal IBD and risk for offspring psychotropic medication dispensations, (iii) stratifying the IBD exposure on perinatal risk factors (yes/no), (iv) adjusting for offspring IBD, (v) assessing the influence of mothers' hospitalization 0–2 years postpartum and (vi) analysis of the birth cohorts 2003–2014 excluding the early years with low numbers of IBD births to reduce the risk of exposure misclassification, (vii) in later onset diagnosis groups (mood, anxiety and eating disorder) consider diagnoses set from 10 years of age studying those followed 10 years or longer (birth cohorts 2003–2008) to reduce the risk of outcome misclassification, and (viii) calculating e-values to assess the robustness of detected associations against possible unmeasured confounding.[26]

3 | RESULTS

3.1 | Study population characteristics

All live births from 1996 to 2014 in Finland were followed up for psychiatric diagnoses until 2018. The median follow-up time was 12.1 (IQR: 7.6–17.3) years. Of the 1 105 997 births in this study, 6067 (0.55%) offspring were born to mothers with IBD and 1 099 930 (99.5%) were born to mothers without IBD, and in total 106 521 (9.6%) offspring had an ICD-10 psychiatric or neurodevelopmental diagnosis (F00–F99). Mothers with IBD were older, more often born in Finland, and had higher rates of cesarean section and perinatal problems (premature birth, and/or small birth size) compared to mothers without IBD. The IBD-exposed offspring had a higher risk of receiving an IBD diagnosis during the follow-up compared to unexposed (0.2% vs. 0.1%). The proportion with IBD diagnosis among women giving birth increased gradually over time from 0.1% in 1996 to 4.6% in 2003 and 9.5% in 2014, likely reflecting the improved registration and the reported increase in incidence of IBD in Finland (Table 1).[4] All live births in the cohort were included in the analysis.

3.2 | Association between maternal IBD and neurodevelopmental and psychiatric diagnoses in offspring

In unadjusted models, maternal IBD diagnosis was associated with an increased risk for all F-diagnosis categories except for Eating disorders (F50). In adjusted models, there was a 48% higher risk for Sleeping disorders (F51; Model 1 HR = 1.48 (95% CI, 1.10–1.98); Model 2 HR = 1.46 (95% CI, 1.09–1.95)), and a 23% higher risk for Other behavioral and emotional disorders (F98; Model 1 HR = 1.23 (95% CI, 1.06–1.42), Model 2 HR = 1.21 (95% CI, 1.05–1.40)) (Figure 1 and Table S2a). The associations were driven by CD; CD was associated with Sleeping disorders (F51; HR = 1.77 (95% CI, 1.13–2.78)) and with Other behavioral and emotional disorders (F98; HR = 1.45 (95% CI, 1.15–1.82)), whereas UC was not associated with either of these two offspring disorder groups. Model 2 was not reported in the CD-specific analyses as there was only a small difference between Model 1 and Model 2 in the aforementioned IBD analyses of both CD and UC combined (Table S2a,b). There was no detectable association between maternal IBD and the other categories of F-diagnoses (Figure 1).

Because of the increased risk for Other behavioral and emotional disorders (F98) diagnosis, we analyzed the four subdiagnoses separately (Table S2b). The F98 diagnosis Other behavioral and emotional problems is used for early onset disorders, for example, impairment of essential regulatory areas (F98.0–F98.1 Incontinence and F98.2 food intake) and Attention deficit disorder (ADD, F98.8). IBD was associated with Other feeding disorders (F98.2; HR = 1.40 (95% CI, 1.05–1.86)). Again, CD implied a higher point-wise estimate: Other feeding disorders (F98.2; HR = 1.83 (95% CI, 1.19–2.19)), and CD was associated also with Incontinence (F98.0-F98.1; HR = 1.42 (95% CI, 1.02–1.97)) (Figure 1). Notably, the age at onset in the population (median, 25th–75th percentile) was low for Sleeping disorders (2.0, 0.78–11.7 years), Incontinence (6.6, 5.4–8.2 years) and Other feeding disorders (0.8, 0.2–6.7 years) (Table S3, Figure 2). Of the births exposed to CD, 29.7% had mothers with anti-CD medication in B3-T1, and 29.9% had mothers with such dispensation in T2 or T3. In an attempt to explore if this medication contributed to the detected offspring risks for Sleeping disorders, Incontinence, or Other feeding disorders, we added any such medication (yes/no) dispensed either in (i) B3-T1 or (ii) T2–T3 to Model 1 (Model 3). Anti-CD medication was associated with an increased risk for Sleeping disorders ($HR_{B3\text{-}T1}$ = 1.40 (1.12–1.75), $HR_{T2\text{-}T3}$ = 1.50 (1.18–1.92)), Incontinence ($HR_{B3\text{-}T1}$ = 1.16 (1.00–1.34), $HR_{T2\text{-}T3}$ = 1.11 (0.93–1.33)), and Other feeding disorders ($HR_{B3\text{-}T1}$ = 1.32 (1.05–1.66), $HR_{T2\text{-}T3}$ = 1.41 (1.08–1.84)). After adjusting for this medication, the association for CD remained with Other feeding disorders ($HR_{B3\text{-}T1}$ = 1.67 (1.08–2.02), $HR_{T2\text{-}T3}$ = 1–63 (1.05–1.98)), partly with Sleeping disorders ($HR_{B3\text{-}T1}$ = 1.58 (1.00–2.51), $HR_{T2\text{-}T3}$ = 1.54 (0.97–2.45)), but not with Incontinence ($HR_{B3\text{-}T1}$ = 1.36 (0.97–1.89), $HR_{T2\text{-}T3}$ = 1.38 (0.98–1.92)).

We conducted a sensitivity analysis in offspring exposed to maternal IBD with inpatient hospital care for IBD during pregnancy as a measure of offspring exposure to more severe disease episodes (N = 1377). Maternal IBD with hospitalization was associated with Other behavioral and emotional disorders (F98; HR = 1.54 (95% CI, 1.15–2.06)) (Table S4a) driven by Incontinence (F98.0-F98.1; HR = 1.74 (95% CI, 1.16–2.59)), (Figure 3 and Table S4b). Again, maternal CD was driving the IBD-hospitalization effect on Other behavioral and emotional disorders (F98; N = 417, HR = 1.98 (95% CI, 1.26–3.11)) (Figure 3). Consistently, the CD-hospitalization association with Other behavioral and emotional disorders F98 was explained by Incontinence (F98.0, F98.1; HR = 2.43 (95% CI,

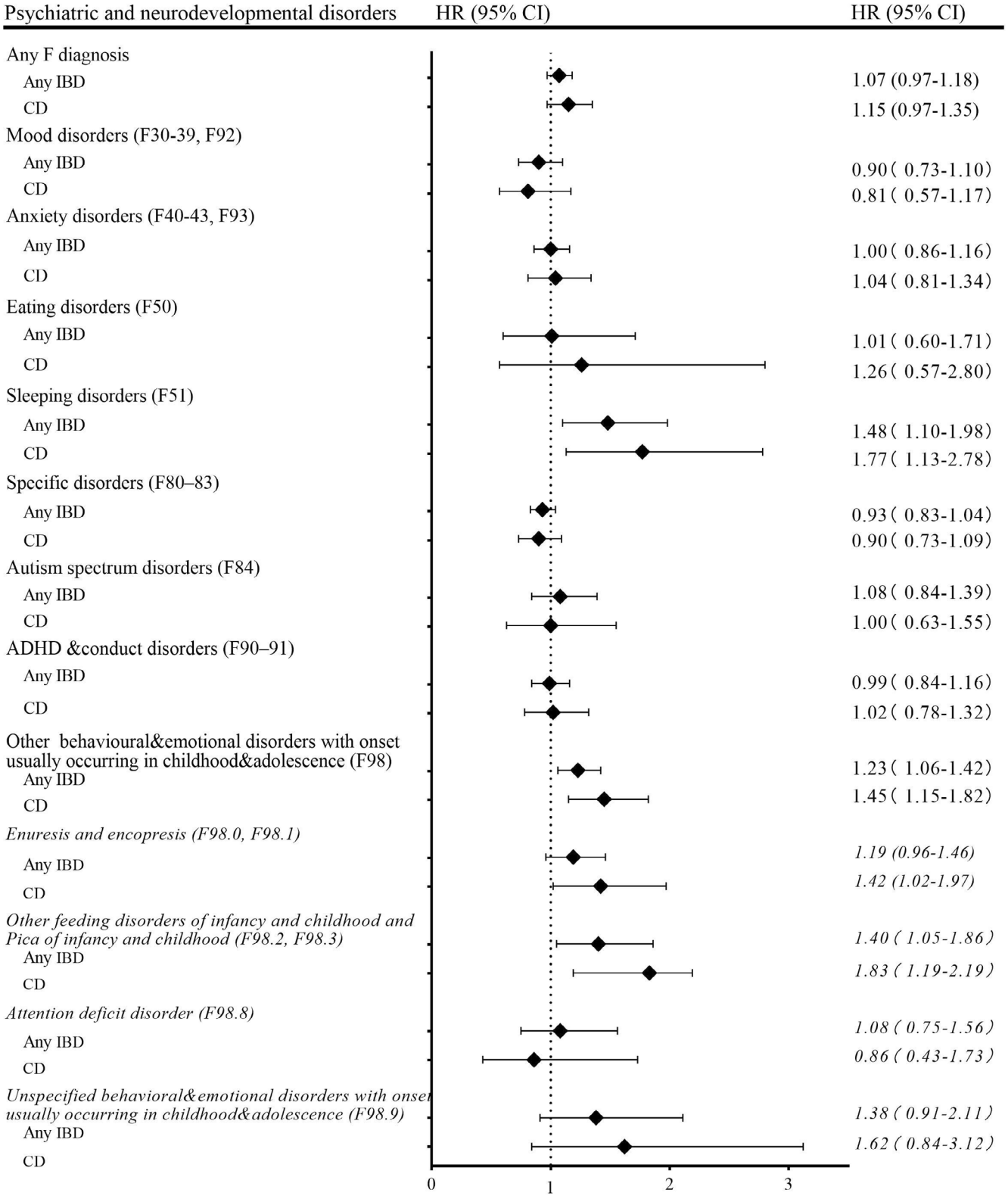

FIGURE 1 Psychiatric and neurodevelopmental disorders in offspring with exposure to maternal inflammatory bowel disease (IBD) and Crohn's disease (CD). Cox proportional hazard model shows significantly increased hazard ratios for Sleeping disorders (ICD-10: F51) and Other behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F98). Subdiagnoses of Other behavioral and emotional disorders F98 are shown in italics. IBD: ICD-10K50-K51; CD: ICD-10K50; Reference: No ICD-10K50 or K51. The analyses were adjusted for offspring birth year, sex, number of fetuses, maternal age group at delivery, parity, unmarried mother at birth, mother's occupation, mother's country of birth, maternal smoking, maternal in- or outpatient psychiatric disorder, and maternal use of psychotropic medication during pregnancy (ATC N05/N06). All live births in Finland 1996–2014 followed up until December 2018. For details see Table S2.

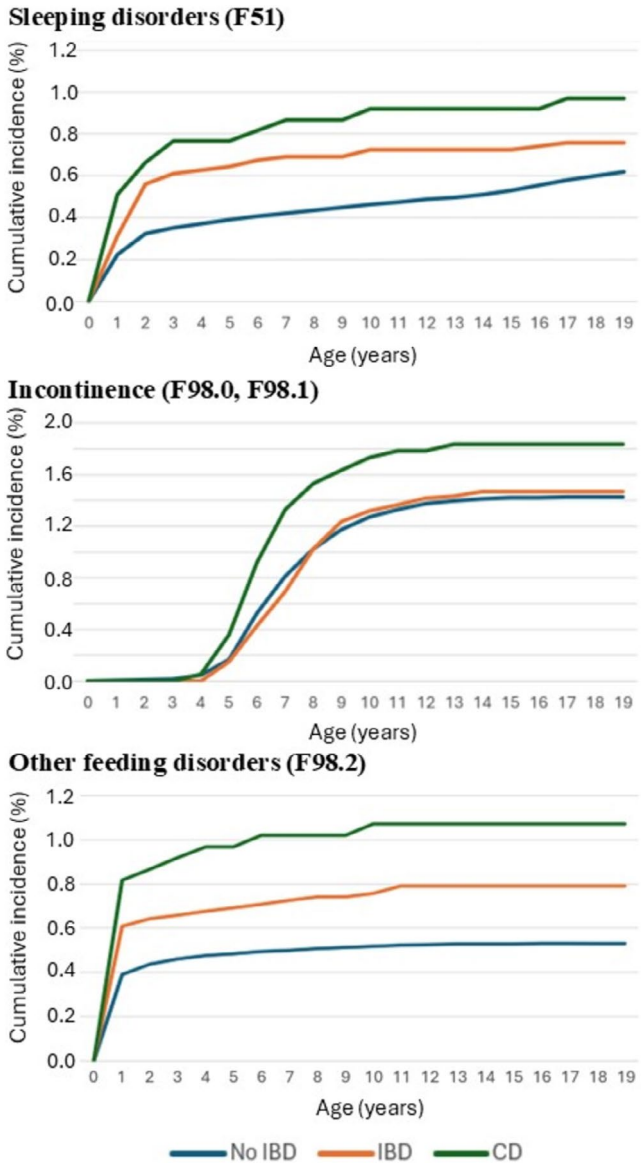

FIGURE 2 Cumulative incidence of Sleeping disorders, Incontinence and Other feeding disorders in children exposed in utero to maternal inflammatory bowel disease (IBD) and Crohn's disease (CD).

1.34–4.38)) and Other feeding disorders (F98.2; HR = 2.83 (95% CI, 1.35–5.91)), (Figure 3 and Table S4b). While the point-wise HRs for Sleeping disorders, Incontinence, and Other feeding disorders were higher for the hospitalized CD group than the non-hospitalized CD group, these differences were not statistically significant ($p > 0.05$, Table S4c). In addition to the aforementioned risk of Sleeping disorders in offspring to maternal CD, offspring exposed to maternal CD had a higher rate of dispensations of ATC N05 which includes antipsychotics, anxiolytics, hypnotics, and sedatives (HR = 1.38 (95% CI, 1.03–1.85)) (Table S5), in the follow-up until December 2014. The patterns of cumulative incidence curves of dispensation of N05 medications were similar to that of Sleeping disorders, proposing that part of the N05 medications were dispensed to children with Sleeping disorders (Figure S2).

To explore if perinatal risk factors influenced the CD-associated risk for offspring, we stratified the births by the presence of perinatal risk factors (yes/no). Offspring with perinatal risk factors without maternal IBD had an increased risk of Sleeping disorders (F51; HR = 1.20 (95% CI, 1.13–1.27)) and Other behavioral disorders (F98.0-F98.1; HR = 1.24 (95% CI, 1.20–1.29); F98.2; HR = 1.94 (95% CI, 1.83–2.05)). Importantly, the IBD- and CD-associated offspring F-diagnosis risks for Sleeping and Feeding disorders were present also in births without perinatal risk factors $HR_{F51} = 2.09$ (95% CI, 1.23–3.53) and $HR_{F98.2} = 2.40$ (95% CI, 1.45–3.99) (Figure 4 and Table S6). In the stratified analysis, there was no association for CD with Incontinence in those without perinatal risk factors (F98.0-F98.1; HR = 1.09 (95% CI, 0.69–1.73)); however, exposure to both CD and perinatal risk factors entailed an almost doubled HR for Incontinence HR = 2.39 (95% CI, 1.51–3.79) compared to exposure to only perinatal risk factors HR = 1.24 (95% CI, 1.20–1.29) (Figure 4 and Table S6).

Sensitivity analyses, adjusting for child IBD diagnosis, showed that the associations reported in Figure 1 were not significantly influenced by child IBD diagnosis (Table S7a,b), nor did the exclusion of the 1996–2002 birth cohort, nor the exclusion of mood, anxiety, or eating disorders in offspring with onset before 10 years of age affect the results (Table S8a,b). Furthermore, maternal hospitalization after birth was unlikely to explain the results in Figures 1 and 3 as there was no association for maternal hospitalization postpartum (0–2 years) with either Sleeping disorders (F51; HR = 1.06 (95% CI, 0.45–2.53)) nor Other behavioral and emotional disorders (F98; HR = 0.84 (95% CI, 0.52–1.36)) in children. Finally, the e-values of the associations for maternal CD with sleeping, continence, and feeding disturbances were 2.9, 2.2, and 3.1, indicating that the associations were robust against unmeasured confounding.

4 | DISCUSSION

We investigated the association between prenatal exposure to maternal IBD and CD with a wide spectrum of neurodevelopmental and psychiatric disorders (ICD-10 F-diagnoses) in offspring. Studying 13.8 million person-years, we detected a higher risk of Incontinence (F98.0–F98.1), Other feeding disorders (F98.2) and Sleeping disorders (F51) in offspring exposed to maternal CD during gestation (Figure 1). One-third were prenatally exposed to anti-CD medication, which was associated with a higher risk for all three disorders. The medication use could reflect a more severe CD. In support, children born to mothers who were hospitalized due to severe CD episodes during pregnancy had twofold to threefold point-wise risk estimates for Incontinence (F98.0–F98.1) and Other feeding disorders (F98.2) diagnoses (Figure 3). The associations for maternal CD to Other behavioral and emotional disorders (F98) and Other feeding disorders (F98.2) survived an attempt to correct for multiple testing (statistical significance at $\alpha = 0.01$, as indicated in Tables S2 and S4). Furthermore, in addition to a higher risk of offspring Sleeping disorders (F51), the children exposed to maternal CD were dispensed

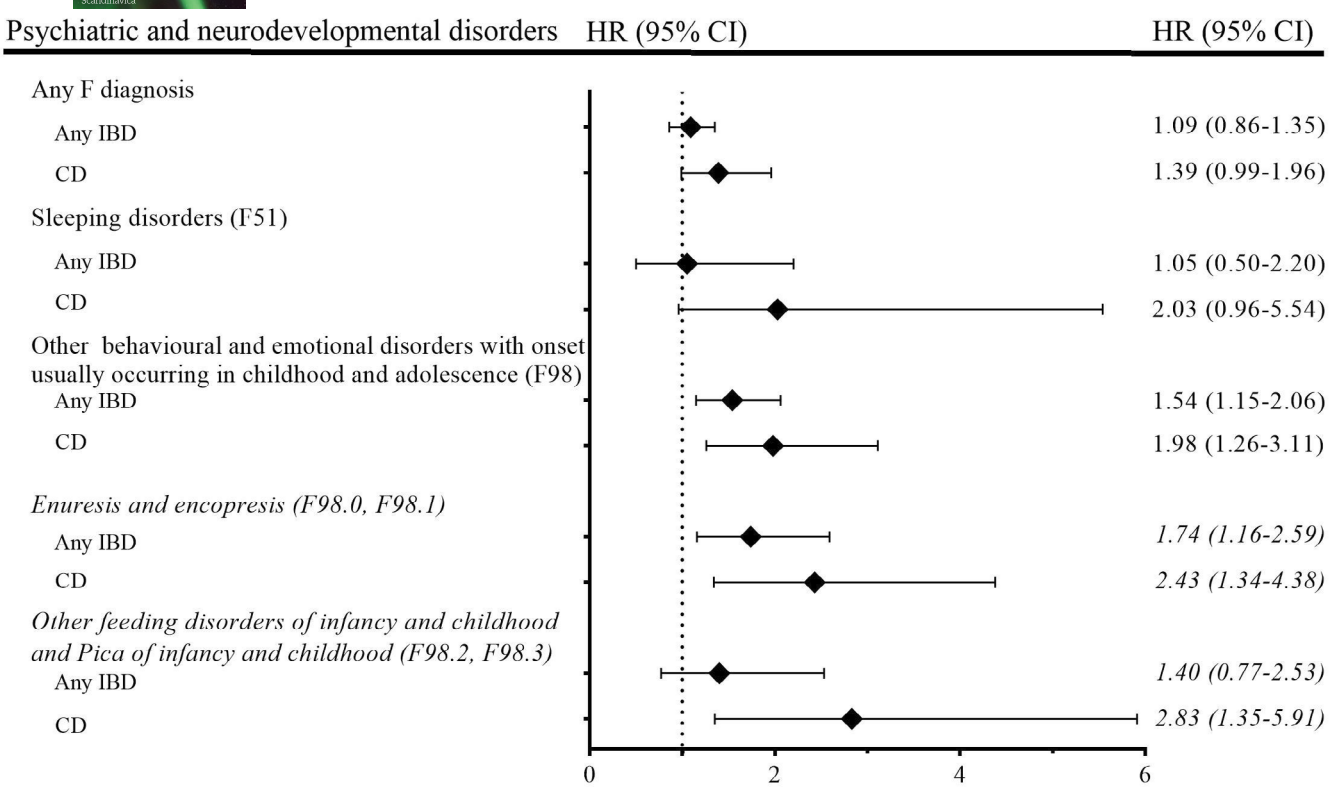

FIGURE 3 Psychiatric and neurodevelopmental disorders in offspring with exposure to severe maternal Inflammatory bowel disease (IBD) or Crohn's disease (CD) during pregnancy. Cox proportional hazard model shows significantly increased hazard ratios for Other behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F98) with exposure to severe IBD during pregnancy. Subdiagnoses of Other behavioral and emotional disorders F98 are shown in italics. IBD: ICD-10K50-K51; CD: ICD-10K50; Reference: No ICD-10K50 or K51. The analyses were adjusted for offspring birth year, sex, number of fetuses, maternal age group at delivery, parity, unmarried mother at birth, mother's occupation, mother's country of birth, maternal smoking, maternal in or outpatient psychiatric disorder and maternal use of psychotropic medication during pregnancy (N05/N06). All live births in Finland 1996–2014 followed up until December 2018. For details see Table S4.

more antipsychotics, anxiolytics, hypnotics, and/or sedatives (N05) (Table S5). The rise in cumulative incidence by age for those exposed to IBD or CD was similar for N05 and Sleeping disorders, proposing that part of the N05 medications were dispensed to children with Sleeping disorders (Figure S1). However, as the curves for N05 became approximately twofold compared to the Sleeping disorder curves, a significant part of N05 medications were dispensed to cases with diagnoses that we failed to detect to be associated with IBD and/or CD. Antipsychotics are not uncommonly used off-label in low doses in child psychiatry to reduce behavioral problems.[27]

One possible explanation for the higher risk of Other behavioral and emotional disorders F98.0–F98.2 and Sleeping disorders F51 in offspring to mothers hospitalized during pregnancy could be maternal hospitalization, and thereby absence, in early childhood; however, we could exclude that maternal hospitalization the first 2 years of the child's life confounded these associations. As aforementioned, mothers with IBD more often have preterm birth and offspring with small birth size,[14] which are per se risk factors for some neurodevelopmental and psychiatric disorders.[28,29] By stratifying for these perinatal risk factors, we could exclude that these risk factors completely explained the higher risks of offspring Other feeding disorders F98.2 and Sleeping disorders F51 in mothers with CD (Figure 4). A higher risk for particularly intellectual disability by preterm birth has been reported earlier both in children in utero exposed to IBD,[30] and in children not exposed to IBD.[31]

Notably, we found no association between in utero CD exposure and childhood diagnosis other than the early onset Sleeping disorders, Incontinence, and Other feeding disorders. That could indicate a mild and temporary effect of CD exposure. Previously, a systematic review and meta-analysis found no associations for IBD to offspring neurodevelopmental disorders, but several other maternal autoimmune or autoinflammatory disorders were associated with offspring ASD and ADHD.[20] But, Sadik et al. reported that exposure to parental IBD increased the risk for offspring ASD.[23] While our ASD information source was validated,[32] our lack of association with ASD might be due to the effect of also subdiagnostic IBD as we used IBD diagnosis before delivery as exposure, whereas Sadik et al. used lifetime exposure.[23] However, there seems to not be coherent evidence of a causal relationship in general between maternal plasma immune activation during pregnancy and offspring ASD.[33,34] Maternal IBD association to other specific offspring psychiatric disorders than ADHD and ASD is, to our knowledge, not well explored, but Friedman et al studied motor or cognitive function impairment at 6, 18 months, or 7 years of age in exposed children and found no difference compared to unexposed children.[35]

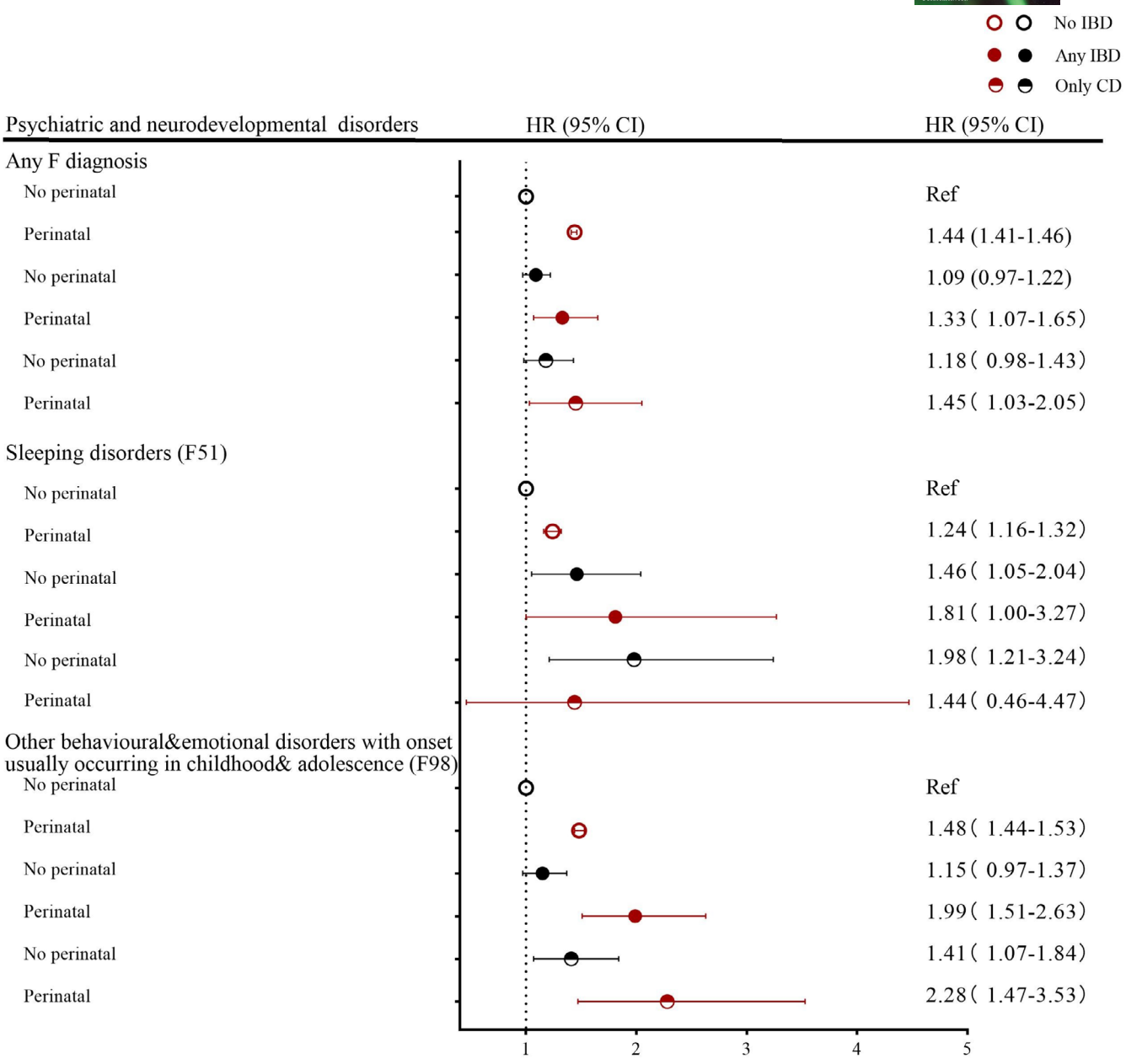

FIGURE 4 Psychiatric and neurodevelopmental disorders in offspring in relation to exposure to maternal Inflammatory bowel disease (IBD) and Crohn's disease (CD) stratified by perinatal risk factors. Cox proportional hazard model shows that the CD-associated offspring risks for Sleeping and Feeding disorders were present also in births without perinatal risk factors. Perinatal risk factors (yes/no) referred to birthweight below 2500 g, birth small for gestational age (SGA) and/or birth before the 37th gestational week. IBD: ICD-10K50-K51; CD: ICD-10K50; Reference: No ICD-10K50 or K51, and no perinatal risk factor. The forest plot shows hazard Ratios (HR) adjusted for offspring birth year, biological sex, number of fetuses, maternal age group at delivery, parity, unmarried mother at birth, mother's occupation, mother's country of birth, maternal smoking, maternal in or outpatient psychiatric disorder, and maternal use of psychotropic medication during pregnancy (N05/N06). All live births in Finland 1996–2014 followed up until December 2018. For details see Table S6.

It is possible that sleeping, continence, and feeding disturbances have a neurodevelopmental origin. Mechanisms of how in utero IBD exposure could affect offspring neurodevelopment are still to be elucidated, but lower maternal levels of vitamin B or D, maternal immune activation, and their links to the maternal intestinal microbiome have been proposed.[36] Maternal circulating immune activity molecules can affect the placenta, pass to the fetus, and can be essential for adequate fetal brain development.[37] In IBD and CD, levels of circulating proinflammatory interleukin (IL)-17 are elevated.[38] From studies in animal models, IL17, passing the placenta, appears to be a primary actor evoking impact on fetal brain development. Embryonic brain microglial cells, key in neurodevelopment, appear particularly sensitive to maternal immune activity and metabolites from the maternal microbiome.[39] However, we found maternal anti-inflammatory medication to be associated with offspring risk increase. As we could not control for

the severity of CD, we cannot exclude the possibility of medication reflecting a more severe CD and more active immune imbalance despite medication. Another less probable possibility could be a negative impact of the immune-suppressing medication per se on brain development and behavior; for example, the potent TNF inhibitor thalidomide has detrimental teratogenic effects. However, the invented most potent immune suppressants are not yet in clinical use, and the ones currently used are without reported teratogenic effect, why this association is less probable. The association reported between corticosteroid medication and risk for preterm birth for pregnant women with IBD,[17] is unlikely to fully explain our findings, as we detected an increased risk for psychiatric outcomes also in those without perinatal risk factors (Figure 4). While CD is in part genetically heritable,[40] and psychiatric comorbidities are overrepresented in IBD,[7–11] our data propose that our association findings (maternal CD–offspring Incontinence, Other feeding disorders F98.0–F98.2 and Sleeping disorders F51) were not explained by known IBD diagnoses in the offspring. Also, the size of the reported genetic correlation between CD and psychiatric disorders is as yet known very low.[41] Still, we cannot exclude the possibility that the early feeding disturbances and incontinence may be a consequence of early prodromal CD.

A major strength is the prospective nationwide cohort of more than 1 million births followed up to 22 years, providing good generalizability. Both IBD and CD, and also specific neurodevelopmental and psychiatric diagnoses were studied separately. In addition to adjusting for putative confounding factors, the data allowed us to study the effect of a proxy for severity of IBD exposure, namely hospitalization for IBD during pregnancy, as well as offspring outcome not only using diagnosis but also dispensed medications.

There are several limitations of the study. Notably, as the prevalence of IBD markedly increased 1996–2003 (Table 1), mothers with undiagnosed IBD were possibly misclassified as controls before 2003, increasing the risk for false negative findings. However, our analyses restricted to births in 2003–2014 confirmed our finding from the complete cohort of 1996–2014. We had no data on medication during hospitalization. We detected no association between IBD and the individual F-diagnosis groups studied other than sleeping disorders and Other behavioral and emotional disorders F98 (Table S2a). The more late onset disorders mood, anxiety, and eating disorders were captured to a lower extent (40%–55%) due to the mean follow-up time of 12.4 years (Table S3) with a risk for outcome misclassification. However, using a sub-cohort of those births followed at least 10 years, we could confirm the lack of IBD association. The proportion captured of individual neurodevelopmental disorders (specific neurodevelopmental disorders, ASD or ADHD) was >87% and thus, their lack of association with maternal CD is more robust. The diagnoses for which we detected an association with CD had estimated capture rates of 100% for Other behavioral and emotional disorders (F98) and 63% for Sleeping disorders F51 (Table S3). Furthermore, information on breastfeeding, maternal IBD medication, maternal hospitalization after 2 years postpartum, and paternal data were not available, and, albeit a publicly funded health-care system for equal availability, the health-care seeking behavior for the offspring might be higher in mothers with IBD. A sibling-pair analysis to account for unmeasured shared familial confounding was not possible due to the low number of exposure-discordant singleton sibling pairs ($n = 339$, of 429 721). Some children included in this study might have had subdiagnostic IBD-pathology, since the peak age at onset of IBD occurs after 20 years of age.[2] Therefore, we cannot exclude the possibility that the associations between maternal IBD and offspring sleeping disorders, incontinence, and other feeding disorders are explained by undiagnosed IBD-related pathology in the child. The nature of the analyses does not allow conclusion about causality.

5 | CONCLUSION

Prenatal exposure to maternal CD was associated with a 42%–85% higher risk for a diagnosis of Sleeping disorders as well as Incontinence and Other feeding disorders with onset usually in early childhood. When the mother, due to CD, had been hospitalized during pregnancy, the risks for these offspring disorders were approximately twofold compared to those with no maternal IBD. These associations were not explained by cesarean section, preterm birth, or small birth size. Thus, there were only modestly higher risks for milder child psychiatric regulatory disturbances despite exposure to more severe CD. However, our findings need to be replicated. Future large cohort studies should follow children even longer to investigate prenatal IBD exposure associations with also late onset psychiatric disorders, such as eating disorders with onset in later childhood and adolescence.

AUTHOR CONTRIBUTIONS

Concept and design: Skott, Söderberg, Giacobini, Lindqvist, Gissler, Sjöberg, and Lavebratt.

Drafting of the manuscript: Skott and Söderberg. Acquisition, analysis, or interpretation of data, and critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Gissler. Obtained funding: Skott, Lindqvist, and Lavebratt. Administrative, technical, or material support: Gissler and Lavebratt. Supervision: Lindqvist, Sjöberg and Lavebratt. Responsible for original manuscript submission: Skott and Lavebratt. Responsible for manuscript revision: Lavebratt.

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CONFLICT OF INTEREST STATEMENT

None reported.

DATA AVAILABILITY STATEMENT

Data and ethical permit are available upon request and from Findata (findata.fi).

ETHICS STATEMENT

This study was approved by the data protection and ethics review authorities in Finland (the Finnish Social and Health data Permit Authority (Findata)) and Sweden (the Swedish Ethics Review Authority) according to the following reference numbers with indicated dates of approval: Findata: THL/1662/5.05.00/2015 (May 11, 2016), THL/1853/5.05.00/2016 (January 18, 2017), THL/1496/5.05.00/2019 (February 24, 2020), THL/3922/14.06.00/2022 (December 29, 2022), THL/5391/14.02.00/2022 (May 5, 2023). Swedish ethics review board: 2023-03041 (August 28, 2023). Since the present study was strictly register-based, informed consent was not required according to Finnish law.

ORCID

Catharina Lavebratt https://orcid.org/0000-0003-4987-2718

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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