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Exposures during pregnancy and at birth are associated with the risk of offspring eating disorders

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Abstract

Background: Eating disorders (ED) are severe psychiatric disorders, commonly debuting early. Aberrances in the intrauterine environment and at birth have been associated with risk of ED. Here, we explore if, and at what effect size, a variety of such exposures associate with offspring ED, that is, anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS).

Methods: This population-based cohort study, conducted from September 2021 to August 2023, used Finnish national registries of all live births in 1996–2014 ($N = 1{,}097{,}753$). Cox proportional hazards modeling was used to compare ED risk in exposed versus unexposed offspring, adjusting for potential confounders and performing sex-stratified analyses.

Results: A total of 6614 offspring were diagnosed with an ED; 3668 AN, 666 BN, and 4248 EDNOS. Lower risk of offspring AN was seen with young mothers, continued smoking, and instrumental delivery, while higher risk was seen with older mothers, inflammatory disorders, prematurity, small for gestational age, and low Apgar. Offspring risk of BN was higher with continued smoking and prematurity, while lower with postmature birth. Offspring risk of EDNOS was lower with instrumental delivery, higher for older mothers, polycystic ovary syndrome, insulin-treated pregestational diabetes, antibacterial treatment, prematurity, and small for gestational age. Sex-specific associations were found.

Conclusions: Several prenatal and at birth exposures are associated with offspring ED; however, we cannot exclude confounding by maternal BMI. Nevertheless, several exposures selectively associate with risk of either AN, BN, or EDNOS, and some are sex-specific, emphasizing the importance of subtype- and sex-stratified analyses of ED.

Public Significance: We define environmental factors involved in the development of different ED, of importance as preventive measure, but also in order to aid in defining the molecular pathways involved and thus in the longer perspective contribute to the development of pharmacological treatment of ED.

KEYWORDS
anorexia nervosa, bulimia nervosa, eating disorder not otherwise specified, eating disorders, perinatal risk factors, prenatal risk factors

1 | INTRODUCTION

Eating disorders (ED) are severe psychiatric disorders characterized by abnormal eating behavior and disturbed weight and body perception (Klump et al., 2009). The etiology of ED remains weakly defined, likely related to its complexity with both genetics and environmental factors known to be involved (Schaumberg et al., 2017). Genetic studies have been able to define important players and pathways (Trace et al., 2013). The latest Genome-wide Association Study (GWAS) on anorexia nervosa (AN) rephrased it as a metabopsychiatric disorder since genetic variants associated with AN also associate with several metabolic traits, as well as other psychiatric disorders (Trace et al., 2013). However, more research into environmental factors involved in the development of ED is essential, as a preventive measure, but also to aid in defining the molecular pathways involved and thus contribute to developing the currently lacking evidence-based pharmacological treatment of ED. These drugs can be combined with psychological interventions for a more efficient treatment.

The complex wiring of the mature brain is dependent on the timely and precise processes of neurodevelopment occurring pre- and postnatally and can be affected by a range of external and internal factors. A deviant neurodevelopment has been linked to a variety of psychiatric disorders, including attention deficit hyperactivity disorder (ADHD) (Purper-Ouakil et al., 2011) and schizophrenia (Rapoport et al., 2012). In addition, specific exposures during pregnancy and at birth are associated with offspring's risk of several psychiatric disorders (Chen et al., 2020; Kong et al., 2018; Kong, Chen, et al., 2020; Kong, Nilsson, et al., 2020). Indeed, changes in brain connectivity have been shown in ED (Frank et al., 2013; King et al., 2017; Shott et al., 2016) including in areas related to the reward aspects (Frank et al., 2016) and hypothalamic circuits involved in the regulation of weight and food intake (Florent et al., 2020; Frank et al., 2016). However, to what extent such changes have their origin in the post- or perinatal period is not known.

Association studies of in utero and perinatal exposures and offspring ED are to date at large inconclusive (Goodman et al., 2014; Krug et al., 2013). However, a systematic review (Marzola et al., 2021) concluded robust associations between offspring risk of AN and higher maternal age (Cnattingius et al., 1999; Goodman et al., 2014; Lindberg & Hjern, 2003; Razaz & Cnattingius, 2018; Tenconi et al., 2015), preeclampsia (Favaro et al., 2006; Lindberg & Hjern, 2003; Tenconi et al., 2015), preterm birth (Cnattingius et al., 1999; Foley et al., 2001; Lindberg & Hjern, 2003; Nosarti et al., 2012; Razaz & Cnattingius, 2018), multiparity (Goodman et al., 2014; Razaz & Cnattingius, 2018), hypoxic complications (Favaro et al., 2006; Lindberg & Hjern, 2003), and small for gestational age (SGA)/low birth weight (Cnattingius et al., 1999). For bulimia nervosa (BN) robust association was reported only with maternal stress during pregnancy, while most associations have been non-replicable likely due to low frequencies (Krug et al., 2013; Marzola et al., 2021; Raevuori et al., 2014). Including eating disorder not otherwise specified (EDNOS) is very rare. In addition, despite the clear sex difference in a majority of ED, with more females than males diagnosed, we find only one previous study stratifying by sex (Larsen et al., 2021), likely because of too small sample sizes for males. We here hypothesize that in utero exposures affecting the development of neurocircuitries involved in, for example, the reward aspects of food intake, energy homeostasis and body image perception increase the offspring risk of ED in a sex-specific pattern. Thus, here we assess if exposures during pregnancy and at birth are associated with offspring's risk of developing an ED; AN, BN, and EDNOS, estimate the effect sizes, and perform sex-stratified analyses, using Finnish national registries.

2 | METHODS

2.1 | Study population

This population-based register cohort study was based on the Finnish registers (Artama et al., 2011), originating from the Medical Birth Register (MBR), the Finnish Care Register for Health Care (HILMO), and the Finnish Register on Reimbursement Drugs (RRD). The study database includes all live births in Finland, registered 1996–2014 (1,097,753 offspring from 590,939 mothers), and followed until 2018. The data analyses were conducted from September 2021 to August 2023. Information on maternal and offspring diagnoses were obtained from the HILMO by using the *International Classification of Diseases*, *8th* (1969–1986), *9th* (1987–1995), and *10th* (from 1996) *Revision* (*ICD-8*, *ICD-9*, and *ICD-10*). Data on purchases of reimbursed medications were identified using Anatomical Therapeutic Chemical (ATC) codes from the RRD.

Register data were combined using the personal identification numbers assigned to all Finnish citizens and permanent residents. Linkages between registers were carried out as described in the registers' consent (Social Insurance Institution and Finnish Institute for Health and Welfare [THL]). Finland's data protection authorities and the steering committee of the drugs and pregnancy database approved this study. Informed consent was not required due to data anonymization.

2.2 | Variables

Data on offspring ED were obtained from HILMO using *ICD-10* diagnosis codes. Outcome variables were defined as; any ED (F50), AN (F50.0, F50.1), BN (F50.2, F50.3), and EDNOS (F50.8, F50.9). A low number (.74%) of offspring was diagnosed with ED in the group followed only until the age of six or younger (Table S1). They were included in the main analysis despite possible misclassification with feeding disorders in infancy and childhood, however we performed a sensitivity analysis of the cohort of offspring born 1996–2008, thus followed until the age of 10 years or older (see further details below).

The definition and source of exposure variables including maternal variables and birth characteristics are found in Table 1. Covariates (Tables S1 and S2) were selected based on their potential contribution to the development of ED (Brainstorm et al., 2018; Culbert et al., 2021; Koch et al., 2022; Trace et al., 2013). Maternal and birth

TABLE 1 Register linkage and definitions of exposures.

Exposure	Definition	Categories	*ICD-9/10* diagnoses	ATC group	Register
Maternal preexisting and gestational conditions					
Maternal age	Maternal age at birth in years	<20, 20–24, 25–29,[a] 30–34, ≥35			MBR
Mode of conception	Spontaneous conception or medically assisted conception	Spontaneous,[a] assisted			MBR
Smoking	Maternal smoking during pregnancy	No,[a] stopped in first trimester, yes			MBR
Polycystic ovary syndrome	Maternal polycystic ovary syndrome and anovulatory infertility	No,[a] yes	*ICD-9*: 256.4, 628.0 *ICD-10*: E28.2, N97.0		HILMO
Inflammatory disorders	Maternal preexisting systemic connective tissue disorders and noninfective enteritis and colitis	No,[a] yes	*ICD-10*: M30-M36, K50, K51, K52.3		HILMO
Hypertension	Maternal hypertensive disorders during pregnancy, including preexisting hypertension and pre-eclampsia	No,[a] yes	*ICD-10*: O10, O11, or O14		HILMO
Diabetes	Maternal pregestational and gestational diabetes	No[a]			HILMO, RRD
		Insulin-treated pregestational	*ICD-10*: O24.0	A10A	
		Type-2 pregestational	*ICD-10*: E11, E14. O24.1	A10B	
		Gestational	*ICD-10*: O24.4		
Antibacterial treatment during pregnancy	Maternal antibacterial medication during pregnancy for systemic use	No,[a] yes		J01A-J01X	RRD
Birth characteristics					
Mode of delivery	Vaginal birth, instrumental vaginal birth, elective or acute cesarean section	Vaginal,[a] instrumental, elective cesarean section, acute cesarean section			MBR
Multiple births	Number of offspring given birth to	Singleton,[a] multiples			MBR
Gestational age at delivery	Gestational age in weeks at delivery	22–32, 33–36, 37–41,[a] ≥42			MBR
Birth weight for gestational age	Birth weight for gestational age estimates an infant's growth relative to gestational age. Small or large for gestational age fall below or above the normal range, respectively.	Small, appropriate,[a] large			MBR
Apgar score	A test given 1 and 5 min after birth to see if extra medical care for the newborn is needed.	0–6, 7–10[a]			MBR

[a]The category group used as reference.
Abbreviations: ATC, Anatomical Therapeutic Chemical; HILMO, Finnish Care Register for Health Care; *ICD-9*, *International Classification of Disease, 9th Revision*; *ICD-10*, *International Classification of Disease, 10th Revision*; MBR, Medical Birth Register; RRD, Finnish Register on Reimbursement Drugs.

covariates registered in MBR included marital status, maternal country of birth, maternal socioeconomic status (SES), offspring birth year, and sex, as well as parity. Maternal ED diagnoses were obtained from HILMO by *ICD-8*: 306.50, 306.58, 306.59; *ICD-9*: 3071A, 3071B, 3071E; and *ICD-10*: F50. Maternal in- or outpatient psychiatric diagnoses were indicated by *ICD-8*: 290–317; *ICD-9*: 290–319; *ICD-10*: F00–F99.

2.3 | Statistical analysis

We used Cox proportional hazard modeling to obtain hazard ratios (HRs) with 95% Wald's confidence intervals (CIs) of the associations between prenatal and at birth exposures, and risk of the three offspring ED by evaluating the exposure effects to their respective

reference (ref). The obtained crude estimates (non-adjusted model) were subsequently adjusted in three different models. In model 1, we adjusted for all other exposure variables. In model 2, we adjusted as in model 1 plus offspring birth year and sex, parity, marital status, maternal country of birth, SES, and maternal ED diagnosis. In model 3, we adjusted as in model 2 plus other maternal in- and outpatient psychiatric diagnoses. Additionally, we conducted a sex-stratified analysis for which we excluded offspring sex as adjusting variables in models 2 and 3. $p < .05$ was considered statistically significant. SAS version 9.4 (SAS Institute, Inc., Cary, NC) was used for the data analysis.

The rate of missing data for all exposures and covariates in the total cohort was <1%, except for marital status (1.9%), maternal smoking during pregnancy (2.5%), and SES (15.8%). To address the issue of missing data, the main analyses were conducted with an additional "missing category" for marital status and SES. Subsequently, we performed a sensitivity analysis for adjusted model 3 excluding the individuals with missing data from the cohort ($N = 906{,}912$). To address the short follow up time for the younger offspring in the full cohort, we performed a sensitivity analysis of adjusted model 3 including only offspring born 1996–2008 ($N = 742{,}982$).

3 | RESULTS

3.1 | Study population

Until 4–22 years of age, 6614 (.60%) offspring were diagnosed with an ED, of which 58.7% exclusively with an ED and no other psychiatric disorder. All were included in this analysis. 3668 (55.5%) were diagnosed with AN, 666 (10.1%) BN, 4248 (64.2%) EDNOS, and 65 (.98%) with no specification of ED subdiagnosis. Due to sample size limitations, offspring diagnosed with more than one ED were included. Fifty-four offspring were diagnosed with both AN and BN, 1532 with AN and EDNOS, and 159 with BN and EDNOS. One hundred and forty-four offspring were diagnosed with all three ED (Figure S1A). The overall median age at first diagnosis for these individuals was 17.0 years (Interquartile range [IQR] 13.7–18.9) (Table S3). Of the individuals with an ED, 85.3% and 14.7% were females and males, respectively (Figure S1B). Frequencies of exposures and covariates are represented in Table 2 and Table S1, stratified by sex in Table S2.

In the following sections, we present AN, BN, and EDNOS, separately. All estimated HRs with 95% CI values are displayed in Figure 1, Table 3, stratified by sex in Figure S2B as well as Tables S6–S8. *p*-values are presented in Figure S3. In the text, we present only the associations that are significant with model 3 ($HR_{adj\text{-}3}$) since this model takes most potential confounders into account. We note, however, those instances when the significance appears only after the covariate adjustments. Further, based on low N for male offspring with BN we exclude these results. Results on the risk of offspring ED as one group can be found in Figure S2A, Tables S4 and S5.

3.2 | Offspring AN

Premature birth between gestational weeks 22–32 [$HR_{adj\text{-}3}$ 1.55, 95% CI 1.14–2.11], Apgar score 0–6 [HR_{adj3} 1.38, 95% CI 1.13–1.68], SGA [$HR_{adj\text{-}3}$ 1.26, 95% CI 1.06–1.50], maternal inflammation [$HR_{adj\text{-}3}$ 1.32, 95% CI 1.02–1.70], and high maternal age (≥35 years) [$HR_{adj\text{-}3}$ 1.19, 95% CI 1.08–1.31] were all significantly associated with increased offspring AN (Figure 1, Table 3). Continued smoking throughout pregnancy [$HR_{adj\text{-}3}$ .82, 95% CI .74–.92], instrumental delivery [$HR_{adj\text{-}3}$ .82, 95% CI .70–.96], and young maternal age (20–24 years) [$HR_{adj\text{-}3}$ .86, 95% CI .77–.96] were associated with reduced risk. Very young maternal age (<20 years) was associated with lower offspring risk of AN, however exclusively in the most adjusted model [$HR_{adj\text{-}3}$ .77, 95% CI .60–.98]. The sex-stratified analyses revealed some sex-specific findings (Figure S2B,C, Table S6). Maternal inflammatory disorders [$HR_{adj\text{-}3}$ 2.39, 95% CI 1.23–4.65] and multiple births [$HR_{adj\text{-}3}$ 1.93, 95% CI 1.14–3.24] were associated with an increased risk of male offspring AN. SGA [$HR_{adj\text{-}3}$ 1.25, 95% CI 1.04–1.50], low Apgar (0–6) [$HR_{adj\text{-}3}$ 1.40, 95% CI 1.13–1.73], and high maternal age (≥ 35) [$HR_{adj\text{-}3}$ 1.20, 95% CI 1.08–1.33] both associated with increased female offspring AN. Continued smoking during pregnancy [$HR_{adj\text{-}3}$ .79, 95% CI .70–.89], and young maternal age (20–24) [$HR_{adj\text{-}3}$ .87, 95% CI .78–.97] were both associated with lower risk of female offspring AN. Instrumental delivery was associated with reduced female offspring AN only after the adjustments in models 2 and 3 [$HR_{adj\text{-}2\&3}$ .84, 95% CI .71–1.00]. Elective cesarean section was associated with a lower risk of male AN [$HR_{adj\text{-}3}$ .60, 95% CI .37–.99], but only in the two most adjusted models. Finally, very young maternal age (<20) was associated with reduced female offspring AN exclusively in model 3 [$HR_{adj\text{-}3}$ .76, 95% CI .58–.98].

3.3 | Offspring BN

Preterm birth at gestational week 22–32 [$HR_{adj\text{-}3}$ 1.97, 95% CI 1.04–3.73] and smoking during pregnancy [$HR_{adj\text{-}3}$ 1.32, 95% CI 1.06–1.64] were associated with increased offspring risk of BN (Figure 1, Table 3). Postmature birth, on the other hand, was associated with a reduced risk of offspring BN [$HR_{adj\text{-}3}$ .50, 95% CI .30–.84]. When exploring only female offspring (Figure S2B, Table S7), the association between BN risk and postmature birth remained [$HR_{adj\text{-}3}$ .53, 95% CI .32–.89], but not with maternal smoking [$HR_{adj\text{-}3}$ 1.30, 95% 1.03–1.63].

3.4 | Offspring EDNOS

Preterm birth at gestational week 22–32 [$HR_{adj\text{-}3}$ 1.98, 95% CI 1.54–2.53], insulin-treated pregestational diabetes (PGD) [$HR_{adj\text{-}3}$ 1.75, 95% CI 1.24–2.47], SGA [$HR_{adj\text{-}3}$ 1.38, 95% CI 1.18–1.60], polycystic ovary syndrome (PCOS) [$HR_{adj\text{-}3}$ 1.29, 95% CI 1.05–1.58], antibiotic treatment during pregnancy [$HR_{adj\text{-}3}$ 1.13, 95% CI 1.06–1.21], and high maternal age (≥35) [$HR_{adj\text{-}3}$ 1.16, 95% CI 1.05–1.27] were all associated with increased offspring EDNOS (Figure 1, Table 3).

TABLE 2 Frequencies of exposures in the cohort and by eating disorder diagnosis.

Total, N[a]	Total cohort 1,097,753	Any ED 6614	AN 3668	BN 666	EDNOS 4248
Exposures[b]	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Maternal preexisting and gestational conditions					
Maternal age					
<20	27,797 (2.53)	164 (2.48)	73 (1.99)	13 (1.95)	123 (2.90)
20–24	175,165 (15.96)	1034 (15.63)	500 (13.63)	127 (19.07)	684 (16.10)
25–29	348,233 (31.72)	2062 (31.18)	1179 (32.14)	207 (31.08)	1333 (31.38)
30–34	342,889 (31.24)	2044 (30.90)	1179 (32.14)	195 (29.28)	1295 (30.48)
≥35	203,668 (18.55)	1310 (19.81)	737 (20.09)	124 (18.62)	813 (19.14)
Missing data	1 (.00)	0 (.00)	0 (.00)	0 (.00)	0 (.00)
Mode of conception					
Natural	1,071,581 (97.62)	6431 (97.23)	3555 (96.92)	652 (97.90)	4127 (97.15)
Assisted	26,172 (2.38)	183 (2.77)	113 (3.08)	14 (2.10)	121 (2.85)
Smoking					
No	905,994 (82.53)	5528 (83.58)	3155 (86.01)	530 (79.58)	3534 (83.19)
Stopped in first trimester	41,070 (3.74)	142 (2.15)	69 (1.88)	15 (2.25)	97 (2.28)
Continued	122,757 (11.18)	783 (11.84)	349 (9.51)	103 (15.47)	517 (12.17)
Missing data	27,932 (2.54)	161 (2.43)	95 (2.59)	18 (2.70)	100 (2.35)
Polycystic ovary syndrome					
No	1,073,071 (97.75)	6476 (97.91)	3605 (98.28)	656 (98.50)	4154 (97.79)
Yes	24,682 (2.25)	138 (2.09)	63 (1.72)	10 (1.50)	94 (2.21)
Inflammatory disorder					
No	1,086,245 (98.95)	6511 (98.44)	3607 (98.34)	656 (98.50)	4192 (98.68)
Yes	11,508 (1.05)	103 (1.56)	61 (1.66)	10 (1.50)	56 (1.32)
Hypertension					
No	1,052,116 (95.84)	6330 (95.71)	3511 (95.72)	645 (96.85)	4074 (95.90)
Yes	45,637 (4.16)	284 (4.29)	157 (4.28)	21 (3.15)	174 (4.10)
Diabetes					
No	931,964 (84.90)	5744 (86.85)	3211 (87.54)	576 (86.49)	3687 (86.79)
Insulin-treated PG	5927 (.54)	48 (.73)	25 (.68)	2 (.30)	35 (.82)
Type 2 PG	8722 (.79)	84 (1.27)	45 (1.23)	12 (1.80)	52 (1.22)
Gestational	151,140 (13.77)	738 (11.16)	387 (10.55)	76 (11.41)	474 (11.16)
Antibacterial treatment during pregnancy					
No	815,602 (74.30)	4880 (73.78)	2755 (75.11)	481 (72.22)	3102 (73.02)
Yes	282,151 (25.70)	1734 (26.22)	913 (24.89)	185 (27.78)	1146 (26.98)
Birth characteristics					
Mode of delivery					
Vaginal	832,778 (75.86)	5144 (77.77)	2876 (78.41)	519 (77.93)	3319 (78.13)
Instrumental	80,234 (7.31)	323 (4.88)	167 (4.55)	27 (4.05)	208 (4.90)
Elective cesarean section	79,207 (7.22)	540 (8.16)	319 (8.70)	56 (8.41)	328 (7.72)
Acute cesarean section	104,120 (9.48)	601 (9.09)	304 (8.29)	64 (9.61)	388 (9.13)
Missing data	1414 (.13)	6 (.09)	2 (.05)	0 (.00)	5 (.12)
Multiple births					
Singleton	1,065,271 (97.04)	6382 (96.49)	3525 (96.10)	646 (97.00)	4101 (96.54)
Multiples	32,482 (2.96)	232 (3.51)	143 (3.90)	20 (3.00)	147 (3.46)

(Continues)

TABLE 2 (Continued)

Total, N[a] / Exposures[b]	Total cohort 1,097,753 N (%)	Any ED 6614 N (%)	AN 3668 N (%)	BN 666 N (%)	EDNOS 4248 N (%)
Gestational age at delivery					
22–32	10,982 (1.00)	106 (1.60)	45 (1.23)	11 (1.65)	74 (1.74)
33–36	49,563 (4.51)	330 (4.99)	184 (5.02)	30 (4.50)	216 (5.08)
37–41	983,361 (89.58)	5908 (89.33)	3291 (89.72)	606 (90.99)	3773 (88.82)
≥42	50,127 (4.57)	238 (3.60)	140 (3.82)	15 (2.25)	160 (3.77)
Missing data	3720 (.34)	32 (.48)	8 (.22)	4 (.60)	25 (.59)
Birth weight for gestational age					
Small	34,795 (3.17)	267 (4.04)	136 (3.71)	17 (2.55)	182 (4.28)
Appropriate	1,025,820 (93.45)	6096 (92.17)	3392 (92.48)	620 (93.09)	3899 (91.78)
Large	32,373 (2.95)	207 (3.13)	125 (3.41)	24 (3.60)	132 (3.11)
Missing data	4765 (.43)	44 (.67)	15 (.41)	5 (.75)	35 (.82)
Apgar score					
0–6	55,059 (5.02)	272 (4.11)	108 (2.94)	29 (4.35)	188 (4.43)
7–10	1,039,552 (94.70)	6320 (95.55)	3547 (96.70)	635 (95.35)	4048 (95.29)
Missing data	3142 (.29)	22 (.33)	13 (.35)	2 (.30)	12 (.28)

Abbreviations: AN, anorexia nervosa; Any ED, eating disorder diagnosis of any kind; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; PG, pregestational; *N* (%), number of cases (percentage to the total of the category).

[a]The total case numbers of the cohort and the diagnostic categories for eating disorders (Any ED, AN, BN, EDNOS).

[b]The exposure frequencies are represented as case numbers and percentage and are represented in two categories, maternal preexisting and gestational conditions, and birth characteristics.

While instrumental delivery [$HR_{adj\text{-}3}$ .84, 95% CI .72–.97] was significantly associated with reduced risk, although not in the sex-stratified analysis (Figure S2B,C, Table S8). Gestational diabetes was associated with a higher risk of male offspring EDNOS exclusively [$HR_{adj\text{-}3}$ 1.25, 95% CI 1.01–1.54], whereas a reduced risk was seen with large for gestational age (LGA) [$HR_{adj\text{-}3}$ .48, 95% CI .27–.86], and postmature birth [$HR_{adj\text{-}3}$ .60, 95% CI .38–.95]. The positive association between EDNOS and high maternal age (≥35) remained for males [$HR_{adj\text{-}3}$ 1.34, 95% CI 1.08–1.68] and for females only in the most adjusted models [$HR_{adj\text{-}3}$ 1.12, 95% CI 1.01–1.24].

3.5 | Sensitivity analysis

To determine the potential effect of the missing values in two covariates; maternal SES (15.8%) and marital status (1.9%), we analyzed model 3 excluding the individuals with missing values for these categories, ending up with $N = 906{,}912$ individuals with frequencies of subdiagnoses (Table S9). Estimated HR with 95% CI values of the adjusted model 3 in the full cohort and matched sensitivity model 3 without missing data (HR_{sen}) are represented in Table S10. Only 5 of the 19 significant HRs within the three diagnoses groups did not remain, and one new appeared in the cohort without missing data, all HRs being very close to the significance threshold in model 3 of both the full cohort and the cohort without missing data. To determine a potential effect of the short follow-up time for the younger individuals in the cohort, we analyzed model 3 including only the offspring born 1996–2008, ending up with $N = 742{,}982$ individuals (Table S11). Estimated HR in the full cohort and matched sensitivity cohort are comparable, and only one association, that is, maternal inflammatory disorder and offspring AN, did not remain significant (Table S12).

4 | DISCUSSION

In this nation-wide cohort study, we evaluated exposures prenatally and at birth in relation to offspring's risk of three ED diagnoses; AN, BN, and EDNOS. We assessed each exposure in a non-adjusted and three adjusted models in which we controlled for all exposures and other covariates suspected to mediate the association. A few of the significant associations were common for all three ED, but several diagnosis- and sex-specific associations were also documented. Below we focus the discussion on the novel associations that remained significant in the most adjusted model. The significant associations that already were supported by robust evidence in a recent systematic review (see introduction) (Marzola et al., 2021), even if only for offspring AN, that is, high maternal age, preterm birth, and SGA, are discussed in the Supplementary Discussion.

Smoking was associated with offspring risk of AN and BN, interestingly in opposite directions. The risk was reduced with approximately 20% for offspring AN and increased with approximately 30% for BN, and similar were seen when analyzing the cohort excluding

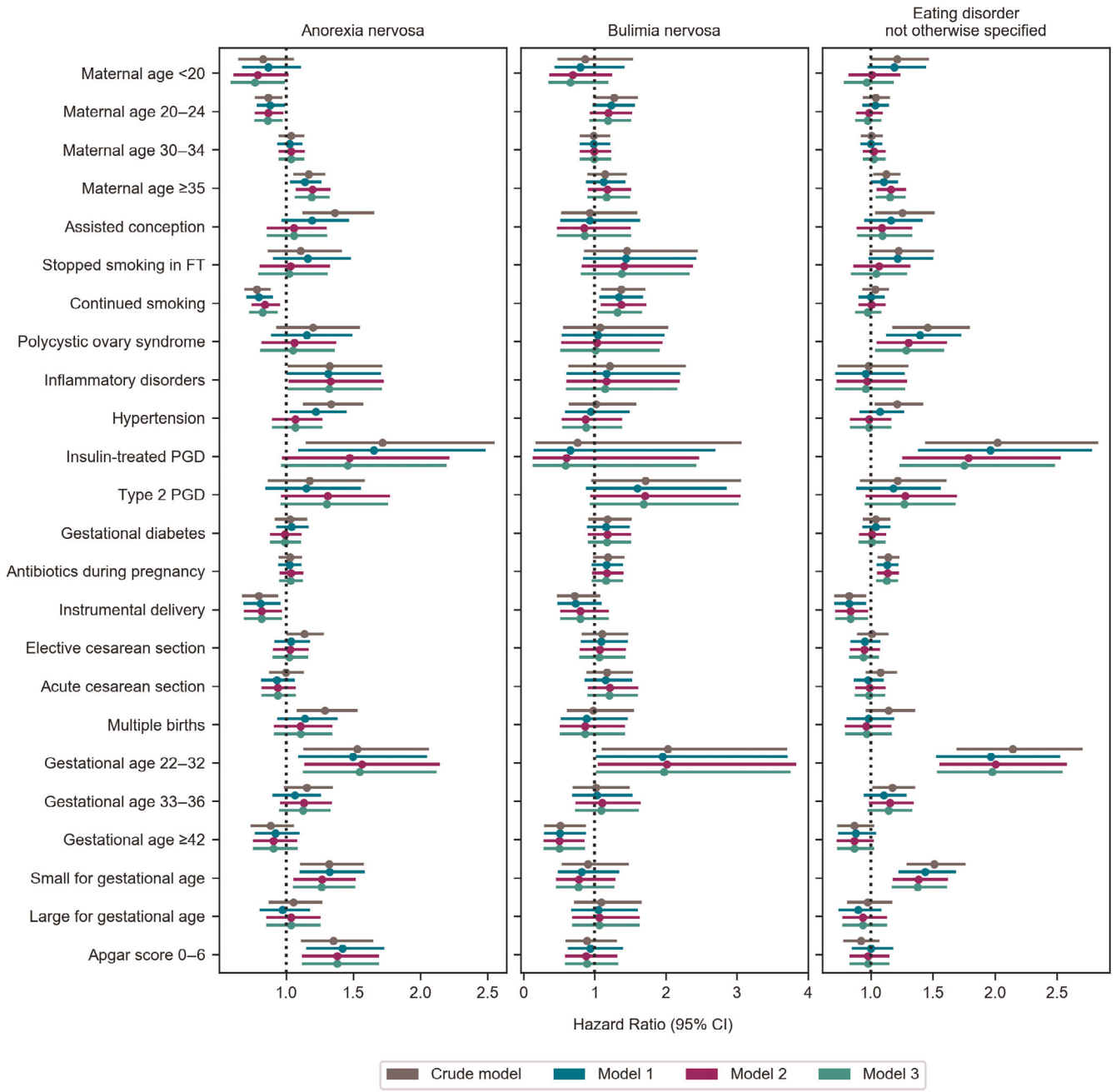

FIGURE 1 Associations between exposures during pregnancy and at birth and offspring eating disorders. The hazard ratio (HR) and 95% confidence interval (CI) estimates representing the contribution of the exposure variables to the risk of developing an eating disorder are displayed in a forest plot. The HRs are grouped by the eating disorder subgroups; anorexia nervosa ($N = 3668$), bulimia nervosa ($N = 666$), eating disorder not otherwise specified ($N = 4248$), and models; non-adjusted (crude) and adjusted (models 1–3). FT, first trimester; PGD, pregestational diabetes.

individuals with missing data as well as in the older cohort (born 1996–2008). Both associations remained for female offspring in the sex-stratified analysis; however, male offspring risk of BN was not analyzed separately due to the low number. Other studies have in agreement with our results observed a negative association between smoking and offspring AN with similar effect sizes (Goodman et al., 2014; Larsen et al., 2021), and a positive association between continuing, as well as ceasing smoking during pregnancy, compared to non-smoking mothers, and offspring BN (Montgomery et al., 2005). This latter study, however, found no association between smoking and offspring AN. Smoking during pregnancy has also been associated with preterm birth (Soneji & Beltran-Sanchez, 2019) and low birth weight (Ko et al., 2014), but since the associations remained statistically significant after adjusting for these factors, they are unlikely to contribute to the here detected associations with AN and BN. In rodents, maternal smoking results in prenatal ischemic–hypoxic brain

TABLE 3 Estimated hazard ratios (HRs) for offspring anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified after exposures during pregnancy and at birth in the cohort born 1996–2014 ($N = 1{,}097{,}753$) and followed until 2018.

Total, *N*	Anorexia nervosa 3668				Bulimia nervosa 666				Eating disorder not otherwise specified 4248			
Model, HR (95% CI)	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
Maternal preexisting and gestational conditions												
Maternal age												
<20	.83 (.65–1.05)	.87 (.68–1.10)	.79 (.62–1.01)	**.77 (.60–.98)**	.87 (.50–1.52)	.80 (.45–1.40)	.69 (.38–1.23)	.66 (.37–1.17)	**1.21 (1.01–1.46)**	1.19 (.99–1.43)	1.01 (.83–1.23)	.97 (.80–1.17)
20–24	**.86 (.78–.96)**	**.88 (.79–.98)**	**.87 (.78–.97)**	**.86 (.77–.96)**	**1.27 (1.02–1.59)**	1.24 (.99–1.54)	1.19 (.95–1.50)	1.18 (.94–1.49)	1.04 (.95–1.14)	1.03 (.94–1.14)	.99 (.90–1.08)	.98 (.89–1.07)
25–29	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
30–34	1.04 (.96–1.12)	1.02 (.94–1.11)	1.04 (.96–1.13)	1.04 (.95–1.13)	.98 (.81–1.20)	.98 (.81–1.20)	.99 (.81–1.21)	.99 (.81–1.21)	1.01 (.93–1.09)	1.00 (.93–1.08)	1.02 (.95–1.11)	1.03 (.95–1.11)
≥35	**1.17 (1.06–1.28)**	**1.14 (1.04–1.25)**	**1.20 (1.08–1.32)**	**1.19 (1.08–1.31)**	1.14 (.92–1.43)	1.13 (.90–1.41)	1.18 (.93–1.49)	1.16 (.92–1.48)	**1.12 (1.03–1.23)**	**1.11 (1.01–1.21)**	**1.16 (1.06–1.27)**	**1.16 (1.05–1.27)**
Mode of conception												
Natural	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Assisted	**1.36 (1.13–1.64)**	1.19 (.98–1.46)	1.06 (.87–1.29)	1.06 (.87–1.29)	.93 (.55–1.58)	.93 (.53–1.62)	.85 (.49–1.49)	.86 (.49–1.50)	**1.25 (1.05–1.50)**	1.16 (.96–1.41)	1.09 (.90–1.32)	1.09 (.90–1.32)
Smoking												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Stopped in first trimester	1.11 (.87–1.41)	1.16 (.91–1.47)	1.03 (.81–1.32)	1.02 (.80–1.30)	1.46 (.87–2.43)	1.44 (.86–2.41)	1.41 (.84–2.37)	1.38 (.82–2.32)	**1.22 (1.00–1.50)**	1.22 (.99–1.49)	1.07 (.87–1.31)	1.04 (.85–1.28)
Continued	**.78 (.7–.87)**	**.80 (.71–.89)**	**.84 (.75–.94)**	**.82 (.74–.92)**	**1.37 (1.11–1.69)**	**1.34 (1.08–1.66)**	**1.37 (1.1–1.71)**	**1.32 (1.06–1.64)**	1.04 (.95–1.14)	1.00 (.91–1.10)	1.01 (.92–1.11)	.98 (.89–1.07)
Polycystic ovary syndrome												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.20 (.94–1.54)	1.15 (.90–1.48)	1.06 (.83–1.36)	1.05 (.82–1.35)	1.08 (.58–2.02)	1.05 (.56–1.96)	1.03 (.55–1.94)	1.01 (.54–1.90)	**1.46 (1.19–1.79)**	**1.40 (1.14–1.72)**	**1.30 (1.06–1.60)**	**1.29 (1.05–1.58)**
Inflammatory disorders												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**1.32 (1.02–1.71)**	**1.31 (1.02–1.70)**	**1.33 (1.03–1.72)**	**1.32 (1.02–1.70)**	1.21 (.65–2.26)	1.17 (.62–2.18)	1.16 (.62–2.17)	1.15 (.61–2.14)	.98 (.74–1.29)	.96 (.73–1.26)	.97 (.74–1.28)	.96 (.73–1.26)
Hypertension												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**1.33 (1.14–1.56)**	**1.22 (1.04–1.44)**	1.07 (.90–1.26)	1.07 (.90–1.26)	1.01 (.66–1.57)	.94 (.60–1.47)	.87 (.56–1.36)	.88 (.56–1.37)	**1.21 (1.04–1.41)**	1.08 (.92–1.26)	.99 (.84–1.16)	.99 (.84–1.16)

TABLE 3 (Continued)

Total, *N*	Anorexia nervosa 3668				Bulimia nervosa 666				Eating disorder not otherwise specified 4248			
Model, HR (95% CI)	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
Diabetes												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Insulin-treated PG	**1.72 (1.16–2.54)**	**1.65 (1.10–2.47)**	1.47 (.98–2.20)	1.46 (.97–2.18)	.76 (.19–3.04)	.66 (.16–2.68)	.60 (.15–2.45)	.59 (.14–2.41)	**2.02 (1.45–2.82)**	**1.96 (1.39–2.77)**	**1.79 (1.27–2.52)**	**1.75 (1.24–2.47)**
Type 2 PG	1.17 (.88–1.58)	1.15 (.86–1.55)	1.31 (.97–1.76)	1.30 (.97–1.75)	1.71 (.97–3.04)	1.60 (.90–2.84)	1.70 (.96–3.03)	1.69 (.95–3.01)	1.22 (.92–1.60)	1.18 (.90–1.55)	1.28 (.97–1.68)	1.27 (.96–1.67)
Gestational	1.03 (.93–1.14)	1.04 (.94–1.16)	.99 (.89–1.10)	.99 (.89–1.10)	1.18 (.93–1.50)	1.16 (.91–1.47)	1.18 (.92–1.50)	1.17 (.92–1.50)	1.04 (.95–1.15)	1.04 (.95–1.15)	1.01 (.92–1.11)	1.01 (.92–1.11)
Antibacterial treatment during pregnancy												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.03 (.95–1.11)	1.03 (.95–1.10)	1.04 (.96–1.12)	1.03 (.96–1.11)	1.18 (1.00–1.40)	1.16 (.98–1.38)	1.17 (.99–1.39)	1.16 (.98–1.38)	**1.14 (1.06–1.22)**	**1.13 (1.06–1.21)**	**1.14 (1.06–1.22)**	**1.13 (1.06–1.21)**
Birth characteristics												
Mode of delivery												
Vaginal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Instrumental	**.80 (.68–.93)**	**.81 (.69–.95)**	**.82 (.70–.96)**	**.82 (.70–.96)**	.72 (.49–1.06)	.73 (.50–1.08)	.80 (.54–1.18)	.79 (.53–1.18)	**.83 (.72–.95)**	**.83 (.72–.95)**	**.84 (.72–.97)**	**.84 (.72–.97)**
Elective CS	**1.13 (1.01–1.27)**	1.04 (.92–1.17)	1.03 (.91–1.16)	1.02 (.91–1.15)	1.10 (.84–1.45)	1.09 (.83–1.45)	1.07 (.81–1.42)	1.06 (.80–1.41)	1.01 (.90–1.13)	.95 (.85–1.07)	.95 (.84–1.06)	.94 (.84–1.06)
Acute CS	1.00 (.89–1.12)	.93 (.82–1.05)	.94 (.83–1.06)	.94 (.83–1.06)	1.17 (.90–1.52)	1.15 (.88–1.51)	1.21 (.92–1.59)	1.21 (.92–1.59)	1.08 (.97–1.20)	.98 (.88–1.09)	.99 (.89–1.11)	.99 (.88–1.10)
Multiple births												
Singleton	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Multiples	**1.29 (1.09–1.52)**	1.14 (.94–1.37)	1.11 (.92–1.33)	1.11 (.92–1.34)	.98 (.63–1.53)	.89 (.55–1.44)	.86 (.53–1.40)	.86 (.53–1.40)	1.14 (.97–1.35)	.98 (.82–1.18)	.96 (.80–1.16)	.97 (.80–1.16)
Gestational age												
22–32	**1.53 (1.14–2.05)**	**1.50 (1.10–2.04)**	**1.56 (1.15–2.13)**	**1.55 (1.14–2.11)**	**2.03 (1.12–3.69)**	**1.96 (1.04–3.69)**	**2.02 (1.06–3.82)**	**1.97 (1.04–3.73)**	**2.14 (1.70–2.69)**	**1.97 (1.54–2.51)**	**2.00 (1.57–2.57)**	**1.98 (1.54–2.53)**
33–36	1.16 (1.00–1.34)	1.07 (.91–1.25)	1.13 (.97–1.33)	1.12 (.96–1.32)	1.02 (.71–1.47)	1.03 (.70–1.51)	1.11 (.75–1.62)	1.09 (.74–1.60)	**1.18 (1.02–1.35)**	1.10 (.96–1.28)	1.15 (1.00–1.33)	1.14 (.99–1.32)
37–41	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥42	.88 (.75–1.05)	.92 (.78–1.09)	.90 (.76–1.07)	.91 (.76–1.08)	**.51 (.31–.86)**	**.51 (.31–.85)**	**.50 (.30–.84)**	**.50 (.30–.84)**	.87 (.74–1.02)	.88 (.75–1.03)	.87 (.74–1.01)	.87 (.74–1.02)

(Continues)

TABLE 3 (Continued)

Total, *N*	Anorexia nervosa 3668				Bulimia nervosa 666				Eating disorder not otherwise specified 4248			
Model, HR (95% CI)	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**	**Crude model[a]**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
Birth weight for gestational age												
Small	**1.32 (1.11–1.57)**	**1.32 (1.11–1.57)**	**1.27 (1.06–1.51)**	**1.26 (1.06–1.50)**	.90 (.56–1.46)	.82 (.50–1.33)	.78 (.48–1.27)	.77 (.47–1.26)	**1.51 (1.30–1.75)**	**1.44 (1.24–1.68)**	**1.38 (1.19–1.61)**	**1.38 (1.18–1.60)**
Appropriate	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Large	1.05 (.88–1.26)	.97 (.81–1.17)	1.04 (.86–1.25)	1.04 (.86–1.25)	1.09 (.73–1.64)	1.05 (.69–1.59)	1.07 (.70–1.62)	1.06 (.70–1.61)	.98 (.82–1.16)	.90 (.75–1.07)	.94 (.78–1.12)	.94 (.78–1.12)
Apgar score												
0–6	**1.35 (1.12–1.64)**	**1.42 (1.16–1.72)**	**1.38 (1.13–1.68)**	**1.38 (1.13–1.68)**	.89 (.61–1.29)	.94 (.64–1.38)	.88 (.60–1.30)	.89 (.60–1.31)	.92 (.79–1.06)	1.00 (.86–1.17)	.98 (.84–1.14)	.98 (.84–1.14)
7–10	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Note: Statistically significant ($p < .05$) estimates are highlighted in bold.

Abbreviations: CI, confidence interval; CS, cesarean section; HR, hazard ratio; PG, pregestational; Ref, reference.

[a]Not adjusted.

[b]Model 1: Adjusted rate with all exposure variables.

[c]Model 2: The analysis was adjusted to the variables in model 1 plus offspring birth year, gender, parity, marital status, mother's country of birth, maternal socioeconomic status, and maternal eating disorder diagnosis.

[d]Model 3: The analysis was adjusted for the variables in model 1 plus maternal in- and outpatient psychiatric disorder diagnosis (excluding maternal eating disorder diagnosis).

injury (Li et al., 2012) and promotes alterations in the cholinergic system of the offspring brain (Nunes-Freitas et al., 2011). Another rodent study revealed abnormal dendritic morphology and synapse density in the cerebral cortex and nucleus accumbens, a brain region of relevance in ED (Berridge et al., 2010), after prenatal exposure to nicotine. Interestingly, they noted differences in both dendritic branching and spine density between female and male offspring (Mychasiuk et al., 2013) thus potentially relating to the sex differences found here. In humans, prenatal exposure to smoking has been linked to reduced growth of the fetal head (Roza et al., 2007), smaller size of total brain as well as cortical gray matter volumes, and cortical thinning (El Marroun et al., 2014). In addition, altered DNA methylation has been shown in offspring exposed prenatally to cigarette smoke (Chatterton et al., 2017; Philibert et al., 2008; Toledo-Rodriguez et al., 2010; Xu et al., 2010). Intriguingly, increased AN risk has been associated with monoamine oxidase A (Urwin et al., 2003; Urwin & Nunn, 2005) and catechol-o-methyltransferase (Mikolajczyk et al., 2006) genes and both these genes were reported hypermethylated after prenatal nicotine exposure (Philibert et al., 2008; Xu et al., 2010). Another speculative mechanism connecting offspring BN and maternal smoking is hypermethylation of *BDNF* promoter sites shown in bulimic eating syndromes (Thaler et al., 2014), and in offspring from smoking mothers (Toledo-Rodriguez et al., 2010). Lastly, a suggestive pathway is via the reported effects of smoking on offspring appetite control. A higher prevalence of poor appetite (Toschke et al., 2003) and rates of child overweight (Oken et al., 2008) have been reported with prenatal exposure to smoking. In animal models, fetal nicotine exposure resulted in alterations of dopaminergic (Dwyer et al., 2019) and serotonergic neurotransmitter systems (Xu et al., 2001), both involved in food intake behavior. In addition, maternal smoking, as well as other exposures such as maternal diabetes and inflammatory disorders, discussed below, are accompanied by immune activation which can result in long-lasting neurodevelopmental effects on the fetus (reviewed in Han et al., 2021) and thus play a role in offspring development of an ED. Lastly and importantly, it should be pointed out that a relation between smoking and body mass index (BMI)/body weight is evident even if too complex for the scope of this article, and sometimes results are contradictory (Audrain-McGovern & Benowitz, 2011). Since an association between maternal BMI and offspring risk of AN has also been reported (Goodman et al., 2014; Nicholls & Viner, 2009; Razaz & Cnattingius, 2018), and genetic correlations between AN and BMI have been established (Watson et al., 2019), we cannot exclude that the associations seen here are confounded by maternal BMI. We were, unfortunately, unable to control for maternal BMI in this cohort since the information was not collected into the Medical Birth Register before 2004: it was available only for a few children who received the diagnoses in early age. Future studies controlling for maternal BMI are needed to clarify the association.

Postmature birth was associated with an almost 50% lower risk of offspring BN, which remained in both sensitivity analyses. Male offspring EDNOS was also reduced with postmaturity. To our knowledge, this is the first study to describe such associations for BN and EDNOS. Larsen et al. (2021) described a reduced risk of offspring AN with postmature birth, not found here. A recent study investigating the relationship between gestational age and offspring neuropsychiatric disorders revealed that the risk of ED was reduced with postmature birth (Xia et al., 2021). Since higher maternal weight and BMI has been associated with postmature births (Halloran et al., 2012; Stotland et al., 2007), the associations may be confounded by maternal BMI.

Maternal age of 20–24 years was associated with a 14% reduced risk of offspring AN, in line with other reports (Larsen et al., 2021; Lindberg & Hjern, 2003), as well as with the increased risk (18%) found for high maternal age (see Supplementary Discussion). The associations remained in both sensitivity analyses. The sex-stratified analysis revealed a significant association only in female offspring. Furthermore, an association between very young maternal age (<20 years) and female offspring AN was detected only in the most adjusted model.

Insulin-treated PGD was associated with markedly increased risk of EDNOS, that is, 75% increase, seen for both female and male offspring. The effect size was increased somewhat when we excluded individuals with missing data, while reduced a bit in the older cohort. In addition, gestational diabetes increased the risk of EDNOS exclusively for male offspring. While previous studies have shown an association between maternal diabetes and several psychiatric disorders (Chen et al., 2021; Nahum Sacks et al., 2016; Nogueira Avelar et al., 2021), studies on ED have revealed conflicting results, and commonly focused on gestational diabetes (Cnattingius et al., 1999; Favaro et al., 2006; Kong, Nilsson, et al., 2020; Larsen et al., 2021; Nahum Sacks et al., 2016; Nicholls & Viner, 2009; Tenconi et al., 2015). To our knowledge, this is thus the first study to report an association between insulin-treated PGD and offspring EDNOS. Maternal diabetes has been linked to fetal developmental anomalies leading to potential neurological dysfunction, speculated to result from diabetes-induced oxidative stress, hypoxia, activation of apoptosis, and epigenetic alterations (Ornoy et al., 2015). Mechanisms that thus could play a role in the increased risk of offspring EDNOS with maternal diabetes. Insulin is a critical factor for the proper establishment of hypothalamic systems regulating food intake (Dearden et al., 2021), and in rodents, maternal diabetes leads to aberrant development of these systems and has long-term consequences on offspring metabolic regulation (Steculorum & Bouret, 2011). We speculate that this is involved in the association between maternal diabetes and offspring EDNOS. However, since weight is associated with the risk of type 2 (Yu et al., 2022) and gestational diabetes (Torloni et al., 2009) we cannot exclude that the association between diabetes and offspring EDNOS is confounded by maternal weight status. Future studies controlling for maternal weight status are needed to confirm the association.

Similarly, antibacterial treatment during pregnancy increased the risk of offspring EDNOS with around 13%. The association remained in both sensitivity analyses and for both female and male offspring. Prenatal antibiotic exposure has been associated with other psychiatric disorders in offspring (Lavebratt et al., 2019). To our knowledge,

however, we are the first to show an association with EDNOS, even if it needs to be stressed that the effect size is small. Animal studies have provided support for the importance of the maternal microbiome on fetal neurodevelopmental processes (Vuong et al., 2020). Antibacterial treatment during pregnancy, affecting the mother's microbial population and its metabolites potentially reaching the fetus, can possibly result in behavioral changes later in life (O'Connor et al., 2021; Vuong et al., 2020). Mueller et al. (2017) observed lower birth weight for gestational age with the administration of antibiotics during mid-pregnancy, while higher leptin levels in cord blood were seen with antibiotic administration during the third trimester, suggesting an interplay between antibiotics and different developmental processes. Leptin has also been shown to be important for the proper development of hypothalamic food intake regulating circuits (Bouret, 2010; Bouret et al., 2004), and hence this can be speculated to influence the risk to develop an ED.

A low Apgar score, indicative of lower neonatal vitality, significantly increased the risk of offspring AN with 30%–40% in the full cohort, and the sensitivity analyses. When stratifying for sex the association was significant only in female offspring. Associations between low Apgar and offspring AN (Lindberg & Hjern, 2003), as well as other psychiatric disorders, including ADHD (Grizenko et al., 2016; Li et al., 2011) and autism (Modabbernia et al., 2019), have been documented previously. Low Apgar is linked with maternal smoking (Garn et al., 1981), preterm birth (Svenvik et al., 2015), SGA (Cheng et al., 2020), and hypoxia (Hogan et al., 2007). We control for all these variables, except hypoxia, without loss of significance. Hypoxia has been associated with other psychiatric disorders including schizophrenia and other non-affective psychoses (Zornberg et al., 2000), but the exact mechanisms underlying this phenomenon are not clear. Altered epigenetic programming, endocrine axis dysfunction, and oxidative damage are hypothesized to be underlying mechanisms linking prenatal hypoxia with abnormal brain development and plasticity (reviewed in Wang et al., 2021). Thus, we cannot exclude that the link between low Apgar and offspring AN is hypoxia.

Multiple births were associated with an almost doubled risk of male offspring AN, exclusively. A general association between multiple births and AN has been reported previously (Goodman et al., 2014; Larsen et al., 2021). Previous results showed that same-sex female twins have the highest risk of disordered eating, followed by opposite-sex female twins, opposite-sex male twins and lastly, the lowest risk was seen for same-sex male twins (Culbert et al., 2008). Increased risk for complications such as growth abnormalities, preterm birth, and neurological deficits are seen with multiple births (Amorosa et al., 2017). Studies suggest increased vulnerability of male fetuses to prenatal insults, for example, gestational stress, maternal infection, and drug exposure, affecting the male's health long-term (Bale et al., 2010; DiPietro & Voegtline, 2017). Fetal development is dependent on normal placental function, with sex-specific differences carrying a female or male, such as the expression of different X- or Y-chromosome-linked epigenetic regulators (Nugent & Bale, 2015). The varying placental properties may hence lead to differences in resilience and vulnerability to prenatal insults in males and females (Nugent et al., 2018; Nugent & Bale, 2015). Additionally, a proinflammatory environment in women carrying males compared to females was reported (Nugent et al., 2018). Thus, the increased risk of pregnancy complications combined with the male fetus's increased vulnerability to prenatal insults may explain the increased risk of male offspring AN with multiple births.

Instrumental delivery, that is, the use of forceps or vacuum to deliver the baby, was, to our surprise, associated with a reduced risk of offspring AN and EDNOS in the full cohort as well as the older cohort. However, the effect size is rather small, and the association was not significant in the sensitivity analysis excluding individuals with missing data. In the sex-stratified analyses, the association reached significance only with female offspring AN. Nevertheless, previous studies have found conflicting results regarding instrumental delivery and ED outcome (reviewed in Krug et al., 2013). Indications for instrumental delivery are prolonged second stage of labor, maternal exhaustion, or non-reassuring fetal testing (Tsakiridis et al., 2020). Oxytocin which commonly is administered to stimulate labor when second-stage labor is prolonged (Jamal & Kalantari, 2004) has established roles in neurodevelopment, synaptic plasticity, milk ejection, parturition, and parenting (Rajamani et al., 2018), all factors that potentially could contribute to the association. One may though question if such a transient and short-term exposure can have this prominent effect. We also speculate that breast-feeding initiation is delayed for an exhausted mother, which potentially could contribute. Established risk factors for requiring instrumental delivery include advanced maternal age (Wang et al., 2011), epidural analgesia, high maternal BMI, and high birth weight (Schuit et al., 2012; Sharma et al., 2009). Of these, we controlled for maternal age and birth weight in the adjusted models with remaining significance, and thus these are unlikely contributors. We may speculate that the association between instrumental delivery and lower risk of offspring AN is mediated via maternal BMI, and future studies should control for this. Lastly, instrumental delivery not rarely results in head injuries such as hematoma/hemorrhage (Doumouchtsis & Arulkumaran, 2006) and painkillers might be provided to the newborn. Thus, the last speculation is that painkiller administration at birth could be a factor in the protective effect of instrumental delivery on offspring AN. That the statistically significant protective effect is not seen in the sex-stratified analysis for EDNOS and only in females with AN, could possibly be explained by small sample sizes.

Maternal inflammation, for example, inflammatory bowel disease and systemic lupus erythematosus, was associated with increased risk of offspring AN. However, in both the sensitivity analysis excluding individuals with missing data and the one including offspring followed until the age of 10 years or older, this association was no longer significant. In the sex-stratified analysis, the association was significant only for male offspring. Nevertheless, a previous study reported that parental history of autoimmune or autoinflammatory disorders significantly increased offspring risk of all three ED; AN, BN, and EDNOS (Zerwas et al., 2017) and a bidirectional relationship between ED and autoimmune disorders have previously been reported (Hedman et al., 2019). A potential underlying mechanism involves the transfer of autoantibodies, such as the N-methyl-D-aspartate receptor and

contacting-associated protein-like 2 autoantibodies, through the placenta. These may cross the underdeveloped blood–brain barrier of the fetus and target surface antigens affecting the cortical structure and function (Hansen et al., 2021; Lee et al., 2009; Palmeira et al., 2012).

PCOS was associated with an almost 30% increased risk of offspring EDNOS, in the sex-stratified analysis significant only for females. The association remained in the older cohort but not when we excluded individuals with missing information. Earlier studies have revealed an association between PCOS and ED, as well as, with other psychiatric disorders (Cesta et al., 2020; Chen et al., 2020). Increased levels of androgens as seen with PCOS (Rodriguez Paris & Bertoldo, 2019) are known to affect fetal neuronal system organization, for instance, the reward system, and influence later behavioral tendencies (Auyeung et al., 2013; Hatanaka et al., 2015; Lombardo et al., 2012). In general, we speculate that at least some sex differences seen in the present report are explained by the prenatal effects of sex hormones and their influence on fetal development in combination with a genetic predisposition. Previous studies described the influence of prenatal testosterone on the brain regions associated with reward later in life, which plays a critical role in ED as well as other neuropsychiatric disorders (Lombardo et al., 2012). PCOS is commonly associated with obesity/overweight (Barber & Franks, 2021), thus we cannot exclude that this association is confounded by maternal weight, and future studies need to take this into account.

We performed a sensitivity analysis by excluding the individuals with missing data on maternal SES and marital status. Most missing cases were in SES. It is difficult to define the SES of pregnant individuals since many are on maternity or childcaring leave or still in education (Gissler et al., 2003). Neither did we have information on their partners. While the most significant HRs remained, this analysis also revealed changes in statistical significance for associations that were originally very closely above the significance threshold. This emphasizes careful interpretation of such associations, that is, for offspring AN with preexisting maternal inflammatory disorders, and instrumental delivery, for BN with premature birth, and EDNOS with PCOS and instrumental delivery. In addition, a second sensitivity analysis including only offspring followed until the age of 10 years or longer, revealed minor changes in HR and loss of one single significant association, that is, offspring AN with maternal inflammatory disorders. No new association appeared in this cohort.

One may argue that multiple correction is required when analyzing as many exposures as here has been done. However, to aid in comparing our results with similar studies, for example, Larsen et al. (2021) that evaluated a similar-sized Danish cohort, we here present results with a significance level of $p < .05$ and discuss only those significant in the most adjusted model. Considering correcting for the 13 exposures would give a significance level of $p < .004$. As can be interpreted by looking at the p values for all associations presented in Table S3, the associations that would remain significant at such a stringent significance level in the non-sex stratified analysis are, offspring risk of AN with high maternal age, continued smoking, and low Apgar score, and offspring EDNOS with insulin-treated PGD, antibiotics during pregnancy, prematurity, and SGA.

A major strength of this study is the large cohort size, stemming from the usage of population-based Finnish registers. The Finnish health care system is based on a public system, providing equal access to health care. The results presented here should represent the Finnish population at large, even if some skewness in healthcare consumption cannot be excluded. Other strengths are the separate analyses of ED subdiagnosis; AN, BN, and EDNOS, and the sex-stratified analyses, even if we are underpowered to perform this for male offspring diagnosed with BN. This reflects that on average only 10% of those affected by an ED are male (Striegel-Moore & Bulik, 2007). A larger cohort is needed to further explore the associations between exposures prenatally and at birth and male offspring BN, in particular. A major limitation is the lack of information on maternal BMI, which likely contributes to some of the associations between exposures prenatally or at birth and the risk of offspring ED (Razaz & Cnattingius, 2018) (see discussion on specific exposures above), and further studies controlling for maternal BMI status are needed. Unfortunately, we neither have information on AN subtypes; restricting nor binge eating/purging. A future study analyzing the two subtypes separately would be very valuable. We are also limited by a relatively short follow-up time in relation to the average onset of ED, which may be one reason for the surprisingly low prevalence of BN seen here. We speculate that BN is more difficult to recognize in young children. Indeed, in the cohort, no offspring below the age of 12 years is diagnosed with BN, while both AN and EDNOS are diagnosed as early as 4 years of age. BN may for a longer time go unnoticed since BMI commonly is not low and we speculate that purging behaviors, included as a diagnostic criterion, may be difficult to detect in younger children (Schaumberg et al., 2017). EDNOS is a diagnosis encompassing a broad range of ED not completely fulfilling the diagnostic criteria of AN or BN. One may speculate that this is more frequently diagnosed in young children with eating- and weight concerns. The clinical meaning of associations with offspring EDNOS are thus difficult to interpret. In line with this, it is important to mention that not all cases of ED are detected here. In addition, the number of males in the sex-stratified analyses was low, and these results need to be interpreted with precaution. Next, we cannot exclude that we have adjusted for a mediator of an exposure effect pathway resulting in not detecting a true association. Lastly, even if we find it unlikely, we cannot disregard that some of our findings may reflect the genetics of psychiatric illness. Even if we control for maternal in- and out-patient psychiatric disorders, we may not catch those with milder psychiatric illnesses, since we do not have access to data from general practice, or non-diagnosed illnesses, alongside a possible paternal inheritance, not controlled for.

5 | CONCLUSION

In conclusion, we report several exposures during pregnancy and at birth that may influence the risk of offspring ED, however, we cannot exclude that the associations are confounded by maternal weight/BMI which as discussed above is related to several of the exposures as well as offspring risk of AN. Nevertheless, several associations are

specific for AN, BN, and/or EDNOS, and some are sex-specific. This strengthens the importance of analyzing the different ED separately, and when possible, in a sex-stratified manner. Offspring risk of AN was increased with prematurity, maternal inflammatory disorders, low Apgar, SGA, and high maternal age, while the risk was reduced when exposed to continued smoking during pregnancy and with instrumental delivery. The risk of offspring BN was contrary to AN, increased with continued smoking during pregnancy, and prematurity, while postmature birth reduced the risk. The risk of offspring EDNOS was increased with prematurity, insulin-treated PGD, SGA, maternal PCOS, high maternal age, and antibacterial treatment during pregnancy, while instrumental delivery reduced the risk.

AUTHOR CONTRIBUTIONS

Judit Ozsvar: Conceptualization; formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Mika Gissler:** Conceptualization; formal analysis; funding acquisition; methodology; resources; software; supervision; validation; writing – review and editing. **Catharina Lavebratt:** Conceptualization; formal analysis; funding acquisition; methodology; resources; supervision; validation; writing – review and editing. **Ida A. K. Nilsson:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to disclose.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the Finnish Institute for Health and Welfare. Restrictions apply to the availability of these data, which were used under license for this study. Similar data are available with the permission of the Finnish Social and Health Data Permit Authority Findata. Dr Gissler had full access to all of the data included in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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REFERENCES

Amorosa, J. M. H., Cleary-Goldman, J., & D'Alton, M. E. (2017). Physiologic effects of multiple pregnancy on mother and fetus. In *Fetal and neonatal physiology* (Vol. 1, 5th ed, pp. 167-176.e2). Elsevier, Amsterdam, The Netherlands.

Artama, M., Gissler, M., Malm, H., Ritvanen, A., & Drugs, & Pregnancy Study Group. (2011). Nationwide register-based surveillance system on drugs and pregnancy in Finland 1996-2006. *Pharmacoepidemiology and Drug Safety*, *20*(7), 729–738. https://doi.org/10.1002/pds.2159

Audrain-McGovern, J., & Benowitz, N. L. (2011). Cigarette smoking, nicotine, and body weight. *Clinical Pharmacology and Therapeutics*, *90*(1), 164–168. https://doi.org/10.1038/clpt.2011.105

Auyeung, B., Lombardo, M. V., & Baron-Cohen, S. (2013). Prenatal and postnatal hormone effects on the human brain and cognition. *Pflügers Archiv*, *465*(5), 557–571. https://doi.org/10.1007/s00424-013-1268-2

Bale, T. L., Baram, T. Z., Brown, A. S., Goldstein, J. M., Insel, T. R., McCarthy, M. M., Nemeroff, C. B., Reyes, T. M., Simerly, R. B., Susser, E. S., & Nestler, E. J. (2010). Early life programming and neurodevelopmental disorders. *Biological Psychiatry*, *68*(4), 314–319. https://doi.org/10.1016/j.biopsych.2010.05.028

Barber, T. M., & Franks, S. (2021). Obesity and polycystic ovary syndrome. *Clinical Endocrinology*, *95*(4), 531–541. https://doi.org/10.1111/cen.14421

Berridge, K. C., Ho, C. Y., Richard, J. M., & DiFeliceantonio, A. G. (2010). The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Research*, *1350*, 43–64. https://doi.org/10.1016/j.brainres.2010.04.003

Bouret, S. G. (2010). Development of hypothalamic neural networks controlling appetite. *Forum of Nutrition*, *63*, 84–93. https://doi.org/10.1159/000264396

Bouret, S. G., Draper, S. J., & Simerly, R. B. (2004). Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science*, *304*(5667), 108–110. https://doi.org/10.1126/science.1095004

Brainstorm, C., Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., … Murray, R. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, *360*(6395). https://doi.org/10.1126/science.aap8757

Cesta, C. E., Oberg, A. S., Ibrahimson, A., Yusuf, I., Larsson, H., Almqvist, C., D'Onofrio, B. M., Bulik, C. M., Fernandez de la Cruz, L., Mataix-Cols, D., Landen, M., & Rosenqvist, M. A. (2020). Maternal polycystic ovary syndrome and risk of neuropsychiatric disorders in offspring: Prenatal androgen exposure or genetic confounding? *Psychological Medicine*, *50*(4), 616–624. https://doi.org/10.1017/S0033291719000424

Chatterton, Z., Hartley, B. J., Seok, M. H., Mendelev, N., Chen, S., Milekic, M., Rosoklija, G., Stankov, A., Trencevsja-Ivanovska, I., Brennand, K., Ge, Y., Dwork, A. J., & Haghighi, F. (2017). In utero exposure to maternal smoking is associated with DNA methylation alterations and reduced neuronal content in the developing fetal brain. *Epigenetics & Chromatin*, *10*, 4. https://doi.org/10.1186/s13072-017-0111-y

Chen, S., Zhao, S., Dalman, C., Karlsson, H., & Gardner, R. (2021). Association of maternal diabetes with neurodevelopmental disorders: Autism spectrum disorders, attention-deficit/hyperactivity disorder and intellectual disability. *International Journal of Epidemiology*, *50*(2), 459–474. https://doi.org/10.1093/ije/dyaa212

Chen, X., Kong, L., Piltonen, T. T., Gissler, M., & Lavebratt, C. (2020). Association of polycystic ovary syndrome or anovulatory infertility with offspring psychiatric and mild neurodevelopmental disorders: A Finnish population-based cohort study. *Human Reproduction*, *35*(10), 2336–2347. https://doi.org/10.1093/humrep/deaa192

Cheng, J., Li, J., & Tang, X. (2020). Analysis of perinatal risk factors for small-for-gestational-age and appropriate-for-gestational-age late-term infants. *Experimental and Therapeutic Medicine*, *19*(3), 1719–1724. https://doi.org/10.3892/etm.2020.8417

Cnattingius, S., Hultman, C. M., Dahl, M., & Sparen, P. (1999). Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. *Archives of General Psychiatry*, *56*(7), 634–638. https://doi.org/10.1001/archpsyc.56.7.634

Culbert, K. M., Breedlove, S. M., Burt, S. A., & Klump, K. L. (2008). Prenatal hormone exposure and risk for eating disorders: A comparison of opposite-sex and same-sex twins. *Archives of General Psychiatry*, *65*(3), 329–336. https://doi.org/10.1001/archgenpsychiatry.2007.47

Culbert, K. M., Sisk, C. L., & Klump, K. L. (2021). A narrative review of sex differences in eating disorders: Is there a biological basis? *Clinical Therapeutics*, *43*(1), 95–111. https://doi.org/10.1016/j.clinthera.2020.12.003

Dearden, L., Bouret, S. G., & Ozanne, S. E. (2021). Nutritional and developmental programming effects of insulin. *Journal of Neuroendocrinology*, *33*(4), e12933. https://doi.org/10.1111/jne.12933

DiPietro, J. A., & Voegtline, K. M. (2017). The gestational foundation of sex differences in development and vulnerability. *Neuroscience*, *342*, 4–20. https://doi.org/10.1016/j.neuroscience.2015.07.068

Doumouchtsis, S. K., & Arulkumaran, S. (2006). Head injuries after instrumental vaginal deliveries. *Current Opinion in Obstetrics & Gynecology*, *18*(2), 129–134. https://doi.org/10.1097/01.gco.0000192983.76976.68

Dwyer, J. B., Cardenas, A., Franke, R. M., Chen, Y., Bai, Y., Belluzzi, J. D., Lotfipour, S., & Leslie, F. M. (2019). Prenatal nicotine sex-dependently alters adolescent dopamine system development. *Translational Psychiatry*, *9*(1), 304. https://doi.org/10.1038/s41398-019-0640-1

El Marroun, H., Schmidt, M. N., Franken, I. H., Jaddoe, V. W., Hofman, A., van der Lugt, A., Verhulst, F. C., Tiemeier, H., & White, T. (2014). Prenatal tobacco exposure and brain morphology: A prospective study in young children. *Neuropsychopharmacology*, *39*(4), 792–800. https://doi.org/10.1038/npp.2013.273

Favaro, A., Tenconi, E., & Santonastaso, P. (2006). Perinatal factors and the risk of developing anorexia nervosa and bulimia nervosa. *Archives of General Psychiatry*, *63*(1), 82–88. https://doi.org/10.1001/archpsyc.63.1.82

Florent, V., Baroncini, M., Jissendi-Tchofo, P., Lopes, R., Vanhoutte, M., Rasika, S., Pruvo, J. P., Vignau, J., Verdun, S., Johansen, J. E., Pigeyre, M., Bouret, S. G., Nilsson, I. A. K., & Prevot, V. (2020). Hypothalamic structural and functional imbalances in anorexia nervosa. *Neuroendocrinology*, *110*(6), 552–562. https://doi.org/10.1159/000503147

Foley, D. L., Thacker, L. R., 2nd, Aggen, S. H., Neale, M. C., & Kendler, K. S. (2001). Pregnancy and perinatal complications associated with risks for common psychiatric disorders in a population-based sample of female twins. *American Journal of Medical Genetics*, *105*(5), 426–431.

Frank, G. K., Shott, M. E., Hagman, J. O., & Mittal, V. A. (2013). Alterations in brain structures related to taste reward circuitry in ill and recovered anorexia nervosa and in bulimia nervosa. *The American Journal of Psychiatry*, *170*(10), 1152–1160. https://doi.org/10.1176/appi.ajp.2013.12101294

Frank, G. K., Shott, M. E., Riederer, J., & Pryor, T. L. (2016). Altered structural and effective connectivity in anorexia and bulimia nervosa in circuits that regulate energy and reward homeostasis. *Translational Psychiatry*, *6*(11), e932. https://doi.org/10.1038/tp.2016.199

Garn, S. M., Johnston, M., Ridella, S. A., & Petzold, A. S. (1981). Effect of maternal cigarette smoking on Apgar scores. *American Journal of Diseases of Children*, *135*(6), 503–506. https://doi.org/10.1001/archpedi.1981.02130300003003

Gissler, M., Merilainen, J., Vuori, E., & Hemminki, E. (2003). Register based monitoring shows decreasing socioeconomic differences in Finnish perinatal health. *Journal of Epidemiology and Community Health*, *57*(6), 433–439. https://doi.org/10.1136/jech.57.6.433

Goodman, A., Heshmati, A., Malki, N., & Koupil, I. (2014). Associations between birth characteristics and eating disorders across the life course: Findings from 2 million males and females born in Sweden, 1975-1998. *American Journal of Epidemiology*, *179*(7), 852–863. https://doi.org/10.1093/aje/kwt445

Grizenko, N., Eberle, M. L., Fortier, M. E., Cote-Corriveau, G., Jolicoeur, C., & Joober, R. (2016). Apgar scores are associated with attention-deficit/hyperactivity disorder symptom severity. *Canadian Journal of Psychiatry*, *61*(5), 283–290. https://doi.org/10.1177/0706743716635544

Halloran, D. R., Cheng, Y. W., Wall, T. C., Macones, G. A., & Caughey, A. B. (2012). Effect of maternal weight on postterm delivery. *Journal of Perinatology*, *32*(2), 85–90. https://doi.org/10.1038/jp.2011.63

Han, V. X., Patel, S., Jones, H. F., & Dale, R. C. (2021). Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. *Nature Reviews. Neurology*, *17*(9), 564–579. https://doi.org/10.1038/s41582-021-00530-8

Hansen, N., Luedecke, D., Malchow, B., Lipp, M., Vogelgsang, J., Timaus, C., Zindler, T., Gingele, S., Kuhn, S., Gallinat, J., Wiedemann, K., Denk, J., Moschny, N., Fiehler, J., Skripuletz, T., Riedel, C., Wattjes, M. P., Zerr, I., Esselmann, H., … Consortium, C. A. P. (2021). Autoantibody-associated psychiatric syndromes in children: Link to adult psychiatry. *Journal of Neural Transmission (Vienna)*, *128*(6), 735–747. https://doi.org/10.1007/s00702-021-02354-8

Hatanaka, Y., Wada, K., & Kabuta, T. (2015). Abnormal instability, excess density, and aberrant morphology of dendritic spines in prenatally testosterone-exposed mice. *Neurochemistry International*, *85–86*, 53–58. https://doi.org/10.1016/j.neuint.2015.04.008

Hedman, A., Breithaupt, L., Hubel, C., Thornton, L. M., Tillander, A., Norring, C., Birgegard, A., Larsson, H., Ludvigsson, J. F., Savendahl, L., Almqvist, C., & Bulik, C. M. (2019). Bidirectional relationship between eating disorders and autoimmune diseases. *Journal of Child Psychology and Psychiatry*, *60*(7), 803–812. https://doi.org/10.1111/jcpp.12958

Hogan, L., Ingemarsson, I., Thorngren-Jerneck, K., & Herbst, A. (2007). How often is a low 5-min Apgar score in term newborns due to asphyxia? *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *130*(2), 169–175. https://doi.org/10.1016/j.ejogrb.2006.03.002

Jamal, A., & Kalantari, R. (2004). High and low dose oxytocin in augmentation of labor. *International Journal of Gynaecology and Obstetrics*, *87*(1), 6–8. https://doi.org/10.1016/j.ijgo.2004.06.004

King, J. A., Frank, G. K. W., Thompson, P. M., & Ehrlich, S. (2017). Structural neuroimaging of anorexia nervosa: Future directions in the quest for mechanisms underlying dynamic alterations. *Biological Psychiatry*, *83*, 224–234. https://doi.org/10.1016/j.biopsych.2017.08.011

Klump, K. L., Bulik, C. M., Kaye, W. H., Treasure, J., & Tyson, E. (2009). Academy for eating disorders position paper: Eating disorders are serious mental illnesses. *The International Journal of Eating Disorders*, *42*(2), 97–103. https://doi.org/10.1002/eat.20589

Ko, T. J., Tsai, L. Y., Chu, L. C., Yeh, S. J., Leung, C., Chen, C. Y., Chou, H. C., Tsao, P. N., Chen, P. C., & Hsieh, W. S. (2014). Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: A birth cohort study. *Pediatrics and Neonatology*, *55*(1), 20–27. https://doi.org/10.1016/j.pedneo.2013.05.005

Koch, S. V., Larsen, J. T., Plessen, K. J., Thornton, L. M., Bulik, C. M., & Petersen, L. V. (2022). Associations between parental socioeconomic-, family-, and sibling status and risk of eating disorders in offspring in a

Danish national female cohort. *The International Journal of Eating Disorders*, *55*(8), 1130–1142. https://doi.org/10.1002/eat.23771

Kong, L., Chen, X., Gissler, M., & Lavebratt, C. (2020). Relationship of prenatal maternal obesity and diabetes to offspring neurodevelopmental and psychiatric disorders: A narrative review. *International Journal of Obesity*, *44*(10), 1981–2000. https://doi.org/10.1038/s41366-020-0609-4

Kong, L., Nilsson, I. A. K., Brismar, K., Gissler, M., & Lavebratt, C. (2020). Associations of different types of maternal diabetes and body mass index with offspring psychiatric disorders. *JAMA Network Open*, *3*(2), e1920787. https://doi.org/10.1001/jamanetworkopen.2019.20787

Kong, L., Norstedt, G., Schalling, M., Gissler, M., & Lavebratt, C. (2018). The risk of offspring psychiatric disorders in the setting of maternal obesity and diabetes. *Pediatrics*, *142*(3), e20180776. https://doi.org/10.1542/peds.2018-0776

Krug, I., Taborelli, E., Sallis, H., Treasure, J., & Micali, N. (2013). A systematic review of obstetric complications as risk factors for eating disorder and a meta-analysis of delivery method and prematurity. *Physiology & Behavior*, *109*, 51–62. https://doi.org/10.1016/j.physbeh.2012.11.003

Larsen, J. T., Bulik, C. M., Thornton, L. M., Koch, S. V., & Petersen, L. (2021). Prenatal and perinatal factors and risk of eating disorders. *Psychological Medicine*, *51*(5), 870–880. https://doi.org/10.1017/S0033291719003945

Lavebratt, C., Yang, L. L., Giacobini, M., Forsell, Y., Schalling, M., Partonen, T., & Gissler, M. (2019). Early exposure to antibiotic drugs and risk for psychiatric disorders: A population-based study. *Translational Psychiatry*, *9*(1), 317. https://doi.org/10.1038/s41398-019-0653-9

Lee, J. Y., Huerta, P. T., Zhang, J., Kowal, C., Bertini, E., Volpe, B. T., & Diamond, B. (2009). Neurotoxic autoantibodies mediate congenital cortical impairment of offspring in maternal lupus. *Nature Medicine*, *15*(1), 91–96. https://doi.org/10.1038/nm.1892

Li, J., Olsen, J., Vestergaard, M., & Obel, C. (2011). Low Apgar scores and risk of childhood attention deficit hyperactivity disorder. *The Journal of Pediatrics*, *158*(5), 775–779. https://doi.org/10.1016/j.jpeds.2010.10.041

Li, Y., Xiao, D., Dasgupta, C., Xiong, F., Tong, W., Yang, S., & Zhang, L. (2012). Perinatal nicotine exposure increases vulnerability of hypoxic-ischemic brain injury in neonatal rats: Role of angiotensin II receptors. *Stroke*, *43*(9), 2483–2490. https://doi.org/10.1161/STROKEAHA.112.664698

Lindberg, L., & Hjern, A. (2003). Risk factors for anorexia nervosa: A national cohort study. *The International Journal of Eating Disorders*, *34*(4), 397–408. https://doi.org/10.1002/eat.10221

Lombardo, M. V., Ashwin, E., Auyeung, B., Chakrabarti, B., Lai, M. C., Taylor, K., Hackett, G., Bullmore, E. T., & Baron-Cohen, S. (2012). Fetal programming effects of testosterone on the reward system and behavioral approach tendencies in humans. *Biological Psychiatry*, *72*(10), 839–847. https://doi.org/10.1016/j.biopsych.2012.05.027

Marzola, E., Cavallo, F., Panero, M., Porliod, A., Amodeo, L., & Abbate-Daga, G. (2021). The role of prenatal and perinatal factors in eating disorders: A systematic review. *Archives of Womens Mental Health*, *24*(2), 185–204. https://doi.org/10.1007/s00737-020-01057-5

Mikolajczyk, E., Smiarowska, M., Grzywacz, A., & Samochowiec, J. (2006). Association of eating disorders with catechol-o-methyltransferase gene functional polymorphism. *Neuropsychobiology*, *54*(1), 82–86. https://doi.org/10.1159/000096043

Modabbernia, A., Sandin, S., Gross, R., Leonard, H., Gissler, M., Parner, E. T., Francis, R., Carter, K., Bresnahan, M., Schendel, D., Hornig, M., & Reichenberg, A. (2019). Apgar score and risk of autism. *European Journal of Epidemiology*, *34*(2), 105–114. https://doi.org/10.1007/s10654-018-0445-1

Montgomery, S. M., Ehlin, A., & Ekbom, A. (2005). Smoking during pregnancy and bulimia nervosa in offspring. *Journal of Perinatal Medicine*, *33*(3), 206–211. https://doi.org/10.1515/JPM.2005.038

Mueller, N. T., Rifas-Shiman, S. L., Blaser, M. J., Gillman, M. W., & Hivert, M. F. (2017). Association of prenatal antibiotics with foetal size and cord blood leptin and adiponectin. *Pediatric Obesity*, *12*(2), 129–136. https://doi.org/10.1111/ijpo.12119

Mychasiuk, R., Muhammad, A., Gibb, R., & Kolb, B. (2013). Long-term alterations to dendritic morphology and spine density associated with prenatal exposure to nicotine. *Brain Research*, *1499*, 53–60. https://doi.org/10.1016/j.brainres.2012.12.021

Nahum Sacks, K., Friger, M., Shoham-Vardi, I., Abokaf, H., Spiegel, E., Sergienko, R., Landau, D., & Sheiner, E. (2016). Prenatal exposure to gestational diabetes mellitus as an independent risk factor for long-term neuropsychiatric morbidity of the offspring. *American Journal of Obstetrics and Gynecology*, *215*(3), 380.e1–380.e7. https://doi.org/10.1016/j.ajog.2016.03.030

Nicholls, D. E., & Viner, R. M. (2009). Childhood risk factors for lifetime anorexia nervosa by age 30 years in a national birth cohort. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(8), 791–799. https://doi.org/10.1097/CHI.0b013e3181ab8b75

Nogueira Avelar, E. S. R., Yu, Y., Liew, Z., Vested, A., Sorensen, H. T., & Li, J. (2021). Associations of maternal diabetes during pregnancy with psychiatric disorders in offspring during the first 4 decades of life in a population-based Danish birth cohort. *JAMA Network Open*, *4*(10), e2128005. https://doi.org/10.1001/jamanetworkopen.2021.28005

Nosarti, C., Reichenberg, A., Murray, R. M., Cnattingius, S., Lambe, M. P., Yin, L., MacCabe, J., Rifkin, L., & Hultman, C. M. (2012). Preterm birth and psychiatric disorders in young adult life. *Archives of General Psychiatry*, *69*(6), E1–E8. https://doi.org/10.1001/archgenpsychiatry.2011.1374

Nugent, B. M., & Bale, T. L. (2015). The omniscient placenta: Metabolic and epigenetic regulation of fetal programming. *Frontiers in Neuroendocrinology*, *39*, 28–37. https://doi.org/10.1016/j.yfrne.2015.09.001

Nugent, B. M., O'Donnell, C. M., Epperson, C. N., & Bale, T. L. (2018). Placental H3K27me3 establishes female resilience to prenatal insults. *Nature Communications*, *9*(1), 2555. https://doi.org/10.1038/s41467-018-04992-1

Nunes-Freitas, A. L., Ribeiro-Carvalho, A., Lima, C. S., Dutra-Tavares, A. C., Manhaes, A. C., Lisboa, P. C., Oliveira, E., Gaspar de Moura, E., Filgueiras, C. C., & Abreu-Villaca, Y. (2011). Nicotine exposure during the third trimester equivalent of human gestation: Time course of effects on the central cholinergic system of rats. *Toxicological Sciences*, *123*(1), 144–154. https://doi.org/10.1093/toxsci/kfr147

O'Connor, R., Moloney, G. M., Fulling, C., O'Riordan, K. J., Fitzgerald, P., Bastiaanssen, T. F. S., Schellekens, H., Dinan, T. G., & Cryan, J. F. (2021). Maternal antibiotic administration during a critical developmental window has enduring neurobehavioural effects in offspring mice. *Behavioural Brain Research*, *404*, 113156. https://doi.org/10.1016/j.bbr.2021.113156

Oken, E., Levitan, E. B., & Gillman, M. W. (2008). Maternal smoking during pregnancy and child overweight: Systematic review and meta-analysis. *International Journal of Obesity*, *32*(2), 201–210. https://doi.org/10.1038/sj.ijo.0803760

Ornoy, A., Reece, E. A., Pavlinkova, G., Kappen, C., & Miller, R. K. (2015). Effect of maternal diabetes on the embryo, fetus, and children: Congenital anomalies, genetic and epigenetic changes and developmental outcomes. *Birth Defects Research. Part C, Embryo Today*, *105*(1), 53–72. https://doi.org/10.1002/bdrc.21090

Palmeira, P., Quinello, C., Silveira-Lessa, A. L., Zago, C. A., & Carneiro-Sampaio, M. (2012). IgG placental transfer in healthy and pathological pregnancies. *Clinical & Developmental Immunology*, *2012*, 985646. https://doi.org/10.1155/2012/985646

Philibert, R. A., Gunter, T. D., Beach, S. R., Brody, G. H., & Madan, A. (2008). MAOA methylation is associated with nicotine and alcohol dependence in women. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *147B*(5), 565–570. https://doi.org/10.1002/ajmg.b.30778

Purper-Ouakil, D., Ramoz, N., Lepagnol-Bestel, A. M., Gorwood, P., & Simonneau, M. (2011). Neurobiology of attention deficit/hyperactivity disorder. *Pediatric Research*, *69*(5 Pt 2), 69R–76R. https://doi.org/10.1203/PDR.0b013e318212b40f

Raevuori, A., Linna, M. S., & Keski-Rahkonen, A. (2014). Prenatal and perinatal factors in eating disorders: A descriptive review. *The International Journal of Eating Disorders*, *47*(7), 676–685. https://doi.org/10.1002/eat.22323

Rajamani, K. T., Wagner, S., Grinevich, V., & Harony-Nicolas, H. (2018). Oxytocin as a modulator of synaptic plasticity: Implications for neurodevelopmental disorders. *Frontiers in Synaptic Neuroscience*, *10*, 17. https://doi.org/10.3389/fnsyn.2018.00017

Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: Update 2012. *Molecular Psychiatry*, *17*(12), 1228–1238. https://doi.org/10.1038/mp.2012.23

Razaz, N., & Cnattingius, S. (2018). Association between maternal body mass index in early pregnancy and anorexia nervosa in daughters. *The International Journal of Eating Disorders*, *51*(8), 906–913. https://doi.org/10.1002/eat.22921

Rodriguez Paris, V., & Bertoldo, M. J. (2019). The mechanism of androgen actions in PCOS etiology. *Medical Sciences (Basel)*, *7*(9), 89. https://doi.org/10.3390/medsci7090089

Roza, S. J., Verburg, B. O., Jaddoe, V. W., Hofman, A., Mackenbach, J. P., Steegers, E. A., Witteman, J. C., Verhulst, F. C., & Tiemeier, H. (2007). Effects of maternal smoking in pregnancy on prenatal brain development. The Generation R Study. *The European Journal of Neuroscience*, *25*(3), 611–617. https://doi.org/10.1111/j.1460-9568.2007.05393.x

Schaumberg, K., Welch, E., Breithaupt, L., Hubel, C., Baker, J. H., Munn-Chernoff, M. A., Yilmaz, Z., Ehrlich, S., Mustelin, L., Ghaderi, A., Hardaway, A. J., Bulik-Sullivan, E. C., Hedman, A. M., Jangmo, A., Nilsson, I. A. K., Wiklund, C., Yao, S., Seidel, M., & Bulik, C. M. (2017). The science behind the academy for eating disorders' nine truths about eating disorders. *European Eating Disorders Review*, *25*(6), 432–450. https://doi.org/10.1002/erv.2553

Schuit, E., Kwee, A., Westerhuis, M. E., Van Dessel, H. J., Graziosi, G. C., Van Lith, J. M., Nijhuis, J. G., Oei, S. G., Oosterbaan, H. P., Schuitemaker, N. W., Wouters, M. G., Visser, G. H., Mol, B. W., Moons, K. G., & Groenwold, R. H. (2012). A clinical prediction model to assess the risk of operative delivery. *BJOG*, *119*(8), 915–923. https://doi.org/10.1111/j.1471-0528.2012.03334.x

Sharma, V., Colleran, G., Dineen, B., Hession, M. B., Avalos, G., & Morrison, J. J. (2009). Factors influencing delivery mode for nulliparous women with a singleton pregnancy and cephalic presentation during a 17-year period. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *147*(2), 173–177. https://doi.org/10.1016/j.ejogrb.2009.08.015

Shott, M. E., Pryor, T. L., Yang, T. T., & Frank, G. K. (2016). Greater insula white matter fiber connectivity in women recovered from anorexia nervosa. *Neuropsychopharmacology*, *41*(2), 498–507. https://doi.org/10.1038/npp.2015.172

Soneji, S., & Beltran-Sanchez, H. (2019). Association of maternal cigarette smoking and smoking cessation with preterm birth. *JAMA Network Open*, *2*(4), e192514. https://doi.org/10.1001/jamanetworkopen.2019.2514

Steculorum, S. M., & Bouret, S. G. (2011). Maternal diabetes compromises the organization of hypothalamic feeding circuits and impairs leptin sensitivity in offspring. *Endocrinology*, *152*(11), 4171–4179. https://doi.org/10.1210/en.2011-1279

Stotland, N. E., Washington, A. E., & Caughey, A. B. (2007). Prepregnancy body mass index and the length of gestation at term. *American Journal of Obstetrics and Gynecology*, *197*(4), 378.e1–378.e5. https://doi.org/10.1016/j.ajog.2007.05.048

Striegel-Moore, R. H., & Bulik, C. M. (2007). Risk factors for eating disorders. *The American Psychologist*, *62*(3), 181–198. https://doi.org/10.1037/0003-066X.62.3.181

Svenvik, M., Brudin, L., & Blomberg, M. (2015). Preterm birth: A prominent risk factor for low Apgar scores. *BioMed Research International*, *2015*, 978079. https://doi.org/10.1155/2015/978079

Tenconi, E., Santonastaso, P., Monaco, F., & Favaro, A. (2015). Obstetric complications and eating disorders: A replication study. *The International Journal of Eating Disorders*, *48*(4), 424–430. https://doi.org/10.1002/eat.22304

Thaler, L., Gauvin, L., Joober, R., Groleau, P., de Guzman, R., Ambalavanan, A., Israel, M., Wilson, S., & Steiger, H. (2014). Methylation of BDNF in women with bulimic eating syndromes: Associations with childhood abuse and borderline personality disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *54*, 43–49. https://doi.org/10.1016/j.pnpbp.2014.04.010

Toledo-Rodriguez, M., Lotfipour, S., Leonard, G., Perron, M., Richer, L., Veillette, S., Pausova, Z., & Paus, T. (2010). Maternal smoking during pregnancy is associated with epigenetic modifications of the brain-derived neurotrophic factor-6 exon in adolescent offspring. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *153B*(7), 1350–1354. https://doi.org/10.1002/ajmg.b.31109

Torloni, M. R., Betran, A. P., Horta, B. L., Nakamura, M. U., Atallah, A. N., Moron, A. F., & Valente, O. (2009). Prepregnancy BMI and the risk of gestational diabetes: A systematic review of the literature with meta-analysis. *Obesity Reviews*, *10*(2), 194–203. https://doi.org/10.1111/j.1467-789X.2008.00541.x

Toschke, A. M., Ehlin, A. G., von Kries, R., Ekbom, A., & Montgomery, S. M. (2003). Maternal smoking during pregnancy and appetite control in offspring. *Journal of Perinatal Medicine*, *31*(3), 251–256. https://doi.org/10.1515/JPM.2003.034

Trace, S. E., Baker, J. H., Penas-Lledo, E., & Bulik, C. M. (2013). The genetics of eating disorders. *Annual Review of Clinical Psychology*, *9*, 589–620. https://doi.org/10.1146/annurev-clinpsy-050212-185546

Tsakiridis, I., Giouleka, S., Mamopoulos, A., Athanasiadis, A., Daniilidis, A., & Dagklis, T. (2020). Operative vaginal delivery: A review of four national guidelines. *Journal of Perinatal Medicine*, *48*(3), 189–198. https://doi.org/10.1515/jpm-2019-0433

Urwin, R. E., Bennetts, B. H., Wilcken, B., Lampropoulos, B., Beumont, P. J., Russell, J. D., Tanner, S. L., & Nunn, K. P. (2003). Gene-gene interaction between the monoamine oxidase A gene and solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2 gene in anorexia nervosa (restrictive subtype). *European Journal of Human Genetics*, *11*(12), 945–950. https://doi.org/10.1038/sj.ejhg.5201077

Urwin, R. E., & Nunn, K. P. (2005). Epistatic interaction between the monoamine oxidase A and serotonin transporter genes in anorexia nervosa. *European Journal of Human Genetics*, *13*(3), 370–375. https://doi.org/10.1038/sj.ejhg.5201328

Vuong, H. E., Pronovost, G. N., Williams, D. W., Coley, E. J. L., Siegler, E. L., Qiu, A., Kazantsev, M., Wilson, C. J., Rendon, T., & Hsiao, E. Y. (2020). The maternal microbiome modulates fetal neurodevelopment in mice. *Nature*, *586*(7828), 281–286. https://doi.org/10.1038/s41586-020-2745-3

Wang, B., Zeng, H., Liu, J., & Sun, M. (2021). Effects of prenatal hypoxia on nervous system development and related diseases. *Frontiers in Neuroscience*, *15*, 755554. https://doi.org/10.3389/fnins.2021.755554

Wang, Y., Tanbo, T., Abyholm, T., & Henriksen, T. (2011). The impact of advanced maternal age and parity on obstetric and perinatal outcomes in singleton gestations. *Archives of Gynecology and Obstetrics*, *284*(1), 31–37. https://doi.org/10.1007/s00404-010-1587-x

Watson, H. J., Yilmaz, Z., Thornton, L. M., Hubel, C., Coleman, J. R. I., Gaspar, H. A., Bryois, J., Hinney, A., Leppa, V. M., Mattheisen, M., Medland, S. E., Ripke, S., Yao, S., Giusti-Rodriguez, P., Anorexia Nervosa Genetics, I., Hanscombe, K. B., Purves, K. L., Eating Disorders Working Group of the Psychiatric Genomics Consortium, Adan, R. A. H., … Bulik, C. M. (2019). Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nature Genetics*, *51*(8), 1207–1214. https://doi.org/10.1038/s41588-019-0439-2

Xia, Y., Xiao, J., Yu, Y., Tseng, W. L., Lebowitz, E., DeWan, A. T., Pedersen, L. H., Olsen, J., Li, J., & Liew, Z. (2021). Rates of neuropsychiatric disorders and gestational age at birth in a Danish population. *JAMA Network Open*, *4*(6), e2114913. https://doi.org/10.1001/jamanetworkopen.2021.14913

Xu, Q., Ma, J. Z., Payne, T. J., & Li, M. D. (2010). Determination of methylated CpG sites in the promoter region of catechol-O-methyltransferase (COMT) and their involvement in the etiology of tobacco smoking. *Frontiers in Psychiatry*, *1*, 16. https://doi.org/10.3389/fpsyt.2010.00016

Xu, Z., Seidler, F. J., Ali, S. F., Slikker, W., Jr., & Slotkin, T. A. (2001). Fetal and adolescent nicotine administration: Effects on CNS serotonergic systems. *Brain Research*, *914*(1–2), 166–178. https://doi.org/10.1016/s0006-8993(01)02797-4

Yu, H. J., Ho, M., Liu, X., Yang, J., Chau, P. H., & Fong, D. Y. T. (2022). Association of weight status and the risks of diabetes in adults: A systematic review and meta-analysis of prospective cohort studies. *International Journal of Obesity*, *46*(6), 1101–1113. https://doi.org/10.1038/s41366-022-01096-1

Zerwas, S., Larsen, J. T., Petersen, L., Thornton, L. M., Quaranta, M., Koch, S. V., Pisetsky, D., Mortensen, P. B., & Bulik, C. M. (2017). Eating disorders, autoimmune, and autoinflammatory disease. *Pediatrics*, *140*(6), e20162089. https://doi.org/10.1542/peds.2016-2089

Zornberg, G. L., Buka, S. L., & Tsuang, M. T. (2000). Hypoxic-ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psychoses: A 19-year longitudinal study. *The American Journal of Psychiatry*, *157*(2), 196–202. https://doi.org/10.1176/appi.ajp.157.2.196

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