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ORIGINAL ARTICLE

Association between maternal body mass index in early pregnancy and anorexia nervosa in daughters

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Abstract

Background: The etiology of anorexia nervosa is poorly understood. Although genetic factors play a major role, maternal factors, and obstetric complications are possible environmental causes. We investigated the association between maternal overweight and obesity in early pregnancy and risk of anorexia nervosa in daughters.

Methods: A retrospective cohort study including all live singleton females born in Sweden from 1992 through 2002. Anorexia nervosa diagnosis was identified by using the nation-wide Swedish Patient and Cause of Death Registers. Multivariable Cox hazards regression was used to estimate adjusted hazard ratios (aHRs) and 95% CIs, adjusting for confounders. Stratified Cox regressions were applied to data on siblings to adjust for unmeasured familial confounding.

Results: Among 486,688 live singleton females, 2,414 (0.50%) were diagnosed with anorexia nervosa through 2012. The aHR of anorexia nervosa decreased linearly by maternal BMI (*p*-value for trend < .001). When compared with daughters of normal weight mothers (body mass index [BMI] 18.5–24.9), aHRs (95%CI) of anorexia nervosa were 0.74 (0.65–0.84) in daughters of overweight mothers (BMI 25–29.9) and 0.61 (0.47–0.78) in daughters of mothers with obesity Grade I (BMI 30–34.9). In sibling control analysis, no associations were observed between maternal BMI and aHRs of anorexia nervosa in offspring.

Conclusions: The rate of anorexia nervosa decreased with maternal overweight and obesity in a dose–response manner. However, the sibling control analysis suggests that these findings are not consistent with causals effects of maternal BMI on anorexia nervosa in offspring.

KEYWORDS

anorexia nervosa, body mass index, prepregnancy weight, sibling design

1 | INTRODUCTION

Anorexia nervosa is most common among adolescent and young adult females, and it has the highest mortality rate of all psychiatric disorders (Chesney, Goodwin, & Fazel, 2014; Stice, Marti, & Rohde, 2013). The etiology of anorexia nervosa is poorly understood, with more than 30 identified genetic and environmental risk factors (Jones, Pearce, Barrera, & Mummert, 2017; Mazzeo & Bulik, 2009). A recent genome-wide association study (GWAS) demonstrated a negative genetic correlation between anorexia nervosa and body mass index (BMI), suggesting that the same markers that increase the risk of anorexia nervosa also predict lower BMI in adulthood (Duncan et al., 2017).

While genetic factors play a major role, there are also a number of environmental risk factors for anorexia nervosa including, maternal factors, obstetric, and neonatal complications (Goodman, Heshmati, Malki, & Koupil, 2014; Krug, Taborelli, Sallis, Treasure, & Micali, 2013; Tenconi, Santonastaso, Monaco, & Favaro, 2015). Preeclampsia, placental infarction, preterm birth, multiple birth, birth trauma, and early feeding difficulties have been suggested to be predictors of anorexia nervosa in adolescence (Cnattingius, Hultman, Dahl, & Sparén, 1999; Goodman et al., 2014; Tenconi et al., 2015).

Obesity during pregnancy and obesity-related diseases and pregnancy complications influence prenatal environment. Obesity in pregnancy has been linked to an increased risk of systematic inflammation, altered endocrine responses, insulin resistance, and risk of neural tube

defects in offspring (Denison, Roberts, Barr, & Norman, 2010; Heerwagen, Miller, Barbour, & Friedman, 2010; Rasmussen, Chu, Kim, Schmid, & Lau, 2008). Recent evidence indicates that prenatal exposure to maternal obesity and metabolic diseases may have a long term impact on offspring psychiatric conditions, such as attention deficit hyperactive disorder, autism, and schizophrenia (Rivera, Christiansen, & Sullivan, 2015). However, the association between putative environmental risk factors, such as maternal prepregnancy BMI and risk of anorexia nervosa in offspring has not been fully explored and findings are inconsistent. Some report that higher maternal BMI and weight gain during pregnancy reduces the risk of anorexia nervosa (Goodman et al., 2014; Nicholls & Viner, 2009), whereas others report an increased risk (Favaro, Tenconi, & Santonastaso, 2006).

Any possible association between maternal BMI and risk of anorexia nervosa in offspring may be due to effects of BMI per se or due to confounding by genetics (Duncan et al., 2017). In this large nation-wide Swedish study, we investigated the association between maternal early pregnancy BMI and anorexia nervosa in daughters, while adjusting for measured covariates that relates to the offspring and their mothers. Further, we also used a sibling control design to assess whether a possible association could be ascribed to direct intrauterine effects or to familial (genetic and environmental) factors. We hypothesized that maternal prepregnancy over-weight and/or obesity are associated with a decreased risk of anorexia in offspring, and such an association may be explained by familial factors.

2 | METHODS

2.1 | Study design and population

We designed a population based cohort study of all singleton live-born girls in Sweden between January 1, 1992 and December 31, 2002, recorded in the Swedish Medical Birth Register. We cross-linked this cohort using the person-unique national registration numbers with several Swedish research registries (Ludvigsson et al., 2016). The linked data included: the Medical Birth Register, that contains prospectively recorded population-based information on antenatal, obstetrical, and neonatal care on >98% of all births in Sweden (Swedish National Board of Health and Welfare, 2003a); the nationwide Patient Register, including diagnostic codes for hospital in-patient care from 1987 and hospital out-patient care from 2001 (Ludvigsson et al., 2011; Swedish National Board of Health and Welfare, 2013); the Cause of Death Register, including information of all deaths in Sweden (Swedish National Board of Health and Welfare, 2013); the Education and the Total Population Registers, which provide information on maternal education and country of origin, respectively (Ludvigsson et al., 2016; Statistics Sweden, 2006). In the Medical Birth-, Patient-, and Cause of Death Registers diseases are coded according to the International Classification of Diseases (ICD). Sweden used the ninth Revision (ICD-9) from 1987 through 1996, and the tenth revision (ICD-10) has been used since 1997. The study was approved by the Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden (No. 2012/1813-31/4).

Of 1,047,105 live singleton children born between January 1, 1992 and December 31, 2002, we excluded 9,582 (0.9%) children with missing data on maternal or child identification, 596 (0.06%) children with malformations of the digestive system, 4,749 (0.4%) children who died before their tenth birthdays, and 31,731 (3%) children who emigrated before the study follow-up time. We further excluded children with anorexia nervosa who at the same time also had a cancer diagnosis (n = 15) or bulimia (n = 55). Given that the rate of anorexia nervosa is 15–20 times higher in females than in males (Goodman et al., 2014), this study was restricted to females, providing a study population of 486,688 girls. Data on BMI were available in 415,523 (85.3%) of mothers.

2.2 | Exposure

Maternal BMI in early pregnancy was calculated from self-reported height and weight measured in light indoor clothing without shoes at the first prenatal visit, which occurs within the first 14 weeks of gestation (i.e., first trimester) for 90% of pregnant women in Sweden since 1992 (Swedish National Board of Health and Welfare, 2003b). The correlation of height values between consecutive pregnancies by the same mother is 0.98 (Villamor & Cnattingius, 2016). Therefore, we computed the median height across pregnancies for multiparous women to reduce measurement error (Villamor & Bosch, 2015). Maternal BMI in the first pregnancy was categorized as underweight (BMI < 18.5), normal weight (18.5–24.9), overweight (25–29.9), obesity Grade I (30–34.9), or obesity Grades II–III (≥35) (World Health Organization, 2006). We also considered BMI as a continuous exposure. Gestational age in completed weeks was estimated using either the date of early second trimester ultrasound (which is offered to all women) in 87.7% (Hogberg & Larsson, 1997), the date of the last menstrual period in 7.4%, or a postnatal assessment in 4.9%.

Maternal age at delivery was calculated as date of delivery minus mother's birth date. Smoking habits during pregnancy was obtained from self-reported data at the first prenatal visit and the third trimester. We defined women as smokers who stated that they were daily smokers in early and/or late pregnancy, whereas women who only stated that they were nonsmokers were classified as nonsmokers. Information on selfreported smoking during pregnancy in Sweden has previously been validated, using cotinine markers (George, Granath, Johansson, & Cnattingius, 2006). Birth weight-for-gestational age was categorized as: small- (<10th percentile), appropriate- (10th-90th percentile) and large- (>90th percentile) for-gestational age and sex, using the current Swedish standard for normal fetal growth Maršál el al., 1996). Categorizations of covariates are provided in Table 1.

2.3 | Outcome

We identified cases as individuals with anorexia nervosa diagnosis (ICD-9 code 307B and ICD-10 codes F500, F501) in the Swedish Patient or Cause of Death Registers. Diagnosis of anorexia nervosa was restricted to the period after the girl's 10th birthday.

TABLE 1 Incidence of anorexia nervosa according to maternal and birth characteristics

	Anorexia nervosa				
				Hazard ratios (95% CI)	
Characteristic	Number of children	n	Rate per 10,000 child-years	Unadjusted	Adjusted[a]
Maternal age (years)					
≤19	10,085	39	6.34	0.96 (0.68–1.33)	1.00 (0.69–1.44)
20–24	82,554	353	6.74	1.00	1.00
25–29	176,566	896	8.45	1.28 (1.13–1.45)	1.21 (1.06–1.38)
30–34	146,710	734	9.14	1.44 (1.27–1.63)	1.38 (1.20–1.59)
≥35	70,773	392	10.38	1.64 (1.42–1.90)	1.61 (1.36–1.90)
Country of birth					
Nordic	423,427	2,248	9.03	1.00	1.00
NonNordic	60,705	155	4.91	0.57 (0.49–0.67)	0.63 (0.52–0.76)
Data missing	2,556	11	5.1		
Education (years)					
≤9	45,781	135	5.00	1.00	1.00
10–11	133,526	603	7.10	1.38 (1.15–1.67)	1.20 (0.97–1.48)
12	103,736	441	7.76	1.59 (1.31–1.93)	1.40 (1.12–1.73)
13–14	79,062	468	10.09	2.02 (1.67–2.45)	1.64 (1.32–2.04)
≥15	121,800	757	11.49	2.37 (1.97–2.84)	1.90 (1.54–2.35)
Data missing	2,783	10	6.33		
Mother cohabits with partner					
Yes	431,693	2,120	8.53	1.00	1.00
No	23,036	103	7.82	0.92 (0.75–1.12)	1.12 (0.91–1.38)
Data missing	31,959	191	9.18		
Parity					
1	202,992	1,024	8.89	1.00	1.00
2	180,124	924	8.77	0.98 (0.90–1.01)	0.93 (0.84–1.02)
3	72,268	342	7.91	0.87 (0.77–0.98)	0.80 (0.70–0.92)
≥4	31,304	124	6.59	0.73 (0.60–0.88)	0.69 (0.56–0.86)
Maternal height (cm)					
≤159	61,082	251	7.17	0.83 (0.71–0.95)	1.00 (0.85–1.17)
160–164	122,716	576	8.09	0.93 (0.83–1.04)	0.98 (0.87–1.1)
165–169	140,656	709	8.72	1.00	1.00
≥170	146,456	772	9.22	1.06 (0.96–1.18)	1.02 (0.92–1.14)
Data missing	15,778	106	9.30		
Smoking					
No	388,846	1990	9.03	1.00	1.00
Yes	76,289	317	6.32	0.66 (0.59–0.75)	0.75 (0.66–0.85)
Data missing	21,553	107	8.94		
Year of delivery					
1992–1995	204,120	1,761	9.58	1.00	1.00
1996–1999	159,765	612	7.60	1.18 (1.07–1.31)	1.12 (1.01–1.25)
2000–2002	122,803	41	2.24	1.52 (1.07–2.16)	1.19 (0.81–1.75)
Mode of delivery					
Vaginal noninstrumental	399,861	1971	8.36	1.00	1.00
Vaginal instrumental	28,907	137	8.54	1.04 (0.88–1.24)	0.97 (0.81–1.17)
Elective cesarean section	27,322	155	10.83	1.35 (1.15–1.60)	1.24 (1.03–1.49)
Emergency cesarean section	26,485	110	7.83	0.98 (0.81–1.19)	0.96 (0.78–1.18)
Ata missing	4,113	41	16.02		
Gestational age at delivery (weeks)					
Term (≥37)	461,942	2,274	8.47	1.00	1.00
Moderately preterm (32–36)	19,559	117	10.21	1.20 (1.00–1.45)	1.26 (1.04–1.55)

(Continues)

TABLE 1 (Continued)

Characteristic	Anorexia nervosa				
	Number of children	n	Rate per 10,000 child-years	Hazard ratios (95% CI)	
				Unadjusted	Adjusted[a]
Very preterm (22–31)	2,543	15	10.47	1.25 (0.75–2.07)	1.54 (0.91–2.61)
Data missing	2,644	8	5.89		
Birth weight for gestational age					
Small	31,540	134	7.17	0.82 (0.69–0.98)	0.88 (0.72–1.06)
Appropriate	390,749	1968	8.65	1.00	1.00
Large	61,755	304	8.65	1.01 (0.90–1.14)	1.00 (0.88–1.14)
Data missing	2,644	8	5.89		

Note. Live-born singleton females in Sweden 1992–2002.
[a] From a Cox proportional hazards model adjusted for all other variables in the table.

2.4 | Statistics

Incidence rates of anorexia nervosa were quantified by dividing the number of individuals with anorexia nervosa by the total follow-up time in person-years. Girls were followed from their 10th birthday until the first diagnoses of anorexia nervosa, death, emigration, or end of follow up (December 31, 2012), whichever came first. Confounders were included in the final models based on the literature (Favaro et al., 2006; Goodman et al., 2014 or statistical significance (p-value < .10). We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% *CI*s to compare the HRs of anorexia nervosa between BMI categories, adjusting for maternal age, country of origin, education level, cohabitation with partner, parity, height, smoking, and year of delivery. Variables were categorized according to Table 1. We specified the robust sandwich estimate of the covariance matrix to account for the correlations of sequential births to the same mother in the study. A linear trend in the association of BMI with offspring's anorexia nervosa was assessed by introducing a variable representing ordinal categories of BMI as a continuous predictor into the models. In addition, we performed Cox regression for BMI as a continuous predictor. We also tested the cross-product interaction terms between BMI and length of gestation (five and two categories, respectively) with the use of a Wald χ^2 test.

To investigate the potential confounding from shared family related factors, we conducted full sibling control analyses (sisters only). If there is an association between maternal BMI and anorexia nervosa in offspring, the use of sibling controls enables clarification of whether this association is consistent with a causal hypothesis or due to residual confounding, including genetic and early environmental factors shared by siblings. Paired t-testing was used to examine the mean and the *SD* of differences in maternal BMI between discordantly exposed siblings. Matched full sibling control analyses were carried out using stratified Cox proportional hazard regression with robust variance estimates, grouped on maternal identification number and adjusted for smoking, birth year, sibling birth order, parity, and maternal age at the time of birth. The stratified Cox regression model is an extension of the paired binomial model, taking into account the differences in follow-up time. Thus, only sibling pairs discordant for maternal prepregnancy overweight/obesity as well as anorexia nervosa were "informative" to the estimates. To be informative, the sibling without anorexia nervosa should have at least as long a follow-up time as the sibling with anorexia nervosa. No adjustment was made for multiple comparisons in this explanatory study. All analyses were carried out with the use of Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Of 486,688 females born between 1992 and 2002, 2,414 (0.50%) were diagnosed with anorexia nervosa through 2012. The overall incidence rate of anorexia nervosa was 8.54 per 10,000 person-years. The median age at follow-up was 15 years (range: 10–20.5 years).

The incidence rates and HRs of anorexia nervosa in offspring increased with increasing maternal age and education level in a dose–response pattern (p values for trend < .0001, respectively; Table 1). Daughters of mothers who were multiparous (≥3 births), born in non-Nordic countries, and smokers had lower HRs of anorexia nervosa. The vast majority of girls who developed anorexia nervosa were born at term, but moderately preterm birth (32–36 weeks) was associated with 1.26-fold increased HR (HR 1.26, 95% CI 1.04–1.55), and elective cesarean delivery was associated with 1.24-fold increased HR (HR 1.24, 95% CI 1.03–1.49).

Early pregnancy BMI was negatively associated with hazard ratio of anorexia nervosa (Table 2). When compared with daughters of normal weight mothers, HRs of anorexia nervosa decreased by 26% in overweight mothers and obesity grade I was associated with 39% decrease in HR (Table 2). Gestational length modified the association between maternal BMI and HR of anorexia nervosa (p value, test for interaction .0004). In term births, the HRs of anorexia nervosa decreased with maternal overweight and obesity, while severe obesity (BMI ≥ 35) was associated with increased HR of anorexia nervosa in preterm births (aHR 2.52, 95% CI 1.02–6.22; Table 3). However, given that power was limited in the analysis of preterm born girls, we further analyzed risks of anorexia nervosa in term and preterm born daughters of overweight or obese mothers (BMI ≥ 25) compared with daughters of normal weight mothers (BMI 18.5–24.9). When compared with daughters of normal weight mothers, term born girls of overweight or obese mothers (BMI ≥ 25) had a reduced risk of anorexia (aHR 0.69, 95% CI 0.61–0.77), while preterm born girls of overweight or obese mothers had no such reduced risk (aHR 1.24, 95% CI 0.83–1.86; data not shown).

TABLE 2 The association between early pregnancy body-mass index and rates of anorexia nervosa in offspring

Maternal BMI (kg/m^2)	Number of births (486,688)	Number with outcome (2,414)	Child-years of follow-up (2,826,367)	Rate/10,000 person-years (8.54)	Unadjusted HR (95% CI)	aHR (95% CI)[a]
<18.5	12,088	73	74,775	9.76	1.01 (0.80–1.28)	1.13 (0.89–1.45)
18.5–24.9	273,829	1,528	1,611,645	9.48	1.00	1.00
25.0–29.9	94,861	332	515,418	6.44	0.70 (0.62–0.79)	0.74 (0.65–0.84)
30.0–34.9	26,052	68	135,592	5.02	0.56 (0.44–0.71)	0.61 (0.47–0.78)
≥35.0	8,693	26	42,240	6.16	0.70 (0.48–1.03)	0.82 (0.55–1.21)
Missing	71,165	387	446,699	8.66		
p, trend[b]					<0.001	<0.001
Per unit BMI					0.95 (0.94–0.97)	0.96 (0.95–0.97)

Note. Live-born singleton females in Sweden, 1992–2002.
[a] From a Cox proportional hazards model adjusted for maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy and year of delivery.
[b] Wald test when a variable representing ordinal categories of BMI was introduced into the model as a continuous predictor.

In the sibling sample, the complete case cohort included a total of 117,951 siblings born to 56,872 distinct mothers. Of these families, 615 (0.11%) were discordant on anorexia nervosa. The mean difference in maternal BMI between pregnancies was 0.80 (*SD* = 1.92, *t* = 81.7, *p* = .001). In the sibling control analyses, maternal overweight and obesity severity were not associated with reduced risks of anorexia nervosa (Table 4). However, the confidence intervals were wider in the sibling control analyses than in the population-based analyses, and power was limited in girls prenatally exposed to maternal underweight or obesity. Nevertheless, the null effect within full siblings was replicated when continuous BMI was used as exposure (aHR 1.04, 95% CI 0.96–1.13; Table 4), highlighting the robustness of our results.

4 | DISCUSSION

4.1 | Principal findings

In this population-based study, we found that the risks of anorexia nervosa in girls born at term decreased with maternal overweight and obesity in a dose–response manner. However, we found no evidence of an association in the sibling control analyses, suggesting that the association between maternal prepregnancy BMI and offspring anorexia nervosa is not consistent with a causal interpretation, but rather could be explained by familial (genetic or shared environmental) factors not accounted for in the population-based analyses. Factors increasing the risk of anorexia nervosa in offspring included older maternal age, higher maternal education, nulliparity, elective cesarean section, and preterm birth.

4.2 | Comparison to other studies

Some (Goodman et al., 2014; Nicholls & Viner, 2009) but not all (Favaro et al., 2006) studies have found a progressive association between higher prepregnancy weight status in the mothers and a lower risk of anorexia nervosa in daughters. However, consistent with our findings, adjustment for measured parental covariates and unmeasured familial confounding, largely attenuated this association (Goodman et al., 2014). Furthermore, a recent GWAS study has shown a significant negative correlations between anorexia nervosa and BMI-related and anthropometric measures (Duncan et al., 2017). Taken together, this suggests that previously reported positive associations between maternal BMI and increased risk of anorexia nervosa in offspring may reflect residual confounding rather than a casual effect of prenatal exposure to maternal BMI. This highlights the value of family-based approaches that use kinship to preclude gene–environment correlations.

We confirmed the earlier described associations between multiparity (Goodman et al., 2014), and preterm birth (Cnattingius et al., 1999; Favaro et al., 2006; Goodman et al., 2014) and risk of anorexia nervosa. However, a few studies have shown no association between preterm birth (Favaro et al., 2006; Nicholls & Viner, 2009;

TABLE 3 The association between early pregnancy BMI and rates of anorexia nervosa in offspring stratified by gestational age at delivery

	Term delivery (≥37 weeks) *n* = 461,942			Preterm delivery (22–36 weeks) *n* = 22,102		
Maternal BMI (kg/m^2)	Number with outcome	Rate/10,000 child-years	Adjusted HR (95% CI)[a]	Number with outcome	Rate/10,000 child-years	Adjusted HR (95% CI)[a]
<18.5	70	9.99	1.16 (0.90–1.45)	3	6.71	0.80 (0.25–2.58)
18.5–24.9	1,453	9.45	1.00	70	10.15	1.00
25.0–29.9	305	9.21	0.71 (0.63–0.81)	26	11.57	1.26 (0.80–1.97)
30.0–34.9	64	4.99	0.61 (0.47–0.79)	4	6.02	0.72 (0.26–1.95)
≥35.0	21	5.33	0.70 (0.45–1.09)	5	19.79	2.52 (1.02–6.22)
Missing	361	8.63		24	10.06	

Note. Live-born singleton females in Sweden, 1992–2002.
[a] From a Cox proportional hazards model adjusted for maternal age, country of origin, education level, cohabitation with a partner, parity, height, smoking during pregnancy and year of delivery.

TABLE 4 The association between early pregnancy BMI and rates of anorexia nervosa in offspring using sibling control analysis

Maternal BMI (kg/m^2)	Number of births (117,951)	Number with outcome (628)	Rate/10,000 person-years (9.35)	HR (95% CI)	
				Crude	Sibling control adjusted[a]
<18.5	3,386	16	7.40	0.30 (0.08–1.09)	0.34 (0.10–1.20)
18.5–24.9	77,227	491	10.76	1.00	1.00
25.0–29.9	27,339	95	6.56	0.95 (0.52–1.71)	0.97 (0.52–1.81)
30.0–34.9	7,554	20	5.27	1.78 (0.41–7.65)	1.86 (0.41–8.42)
≥35.0	2,445	6	5.30	1.50 (0.14–15.80)	1.75 (0.14–21.68)
p, trend[b]				0.33	0.31
Per unit BMI				1.07 (0.99–1.16)	1.04 (0.96–1.13)

Note. Live-born singleton female children in Sweden, 1992–2002.
[a] From a Cox proportional hazards model adjusted for maternal age, parity, smoking during pregnancy and year of delivery.
[b] Wald test when a variable representing ordinal categories of BMI was introduced into the model as a continuous predictor.

Shoebridge & Gowers, 2000) and anorexia nervosa. Our findings that risks of anorexia nervosa increase with increasing maternal age and maternal education are also consistent with previous studies (Ahrén et al., 2013; Duncan et al., 2017; Goodman et al., 2014). Anorexia nervosa has been shown to be positive genetically correlated with higher levels of educational attainment that could reflect greater internal and external demands for academic success in higher educated families (Duncan et al., 2017).

It has been suggested that the adoption of the so-called western lifestyle, including thin ideal internalization (Zipfel, Giel, Bulik, Hay, & Schmidt, 2015) and the cultural values and orientations of high socioeconomic status families (e.g., valuing healthy food, self-restraint and high achievement) may lead to the development of eating disorder in offspring (Ahrén et al., 2013; Darmon, 2009). Our findings add to a growing literature suggesting that anorexia nervosa may be a distinct eating disorder with different risk factors to bulimia nervosa or binge eating disorder. Future studies should replicate our findings across diagnostic groups.

The protective effect of maternal obesity and anorexia nervosa in daughters may be partly explained by the clear link between higher maternal prepregnancy BMI and increased risk of childhood obesity and offspring adiposity outcomes later in life (Catalano & Ehrenberg, 2006; Oken, Rifas-Shiman, Field, Frazier, & Gillman, 2008; Reilly et al., 2005). Specifically, childhood obesity has been shown to have a protective effect for development of anorexia (Nicholls & Viner, 2009). Another possible explanation is that anorexia nervosa is strongly familial, and heritability estimates range from 28 to 74% (Zipfel et al., 2015). Shared familial environmental factors influence eating behaviour through parental role modeling of nutritional habits and cultural emphasis on diet and appearance (Bulik, 2005; Mazzeo & Bulik, 2009).

In preterm born girls, we found that severe obesity (BMI ≥ 35) was associated with increased rate of anorexia nervosa. Nevertheless, power was limited, but preterm born girls of overweight or obese mothers did not (unlike term born girls) have a reduced risk of anorexia nervosa. The association between preterm birth and risk of anorexia nervosa is well established in the literature (Jones et al., 2017); yet, in our study, over 90% of all cases of anorexia nervosa occurred in children born at term. Recent evidence has shown that the risk relationship between maternal overweight and obesity and adverse childhood outcomes are mainly pertaining to children born at term (Razaz, Tedroff, Villamor, & Cnattingius, 2017; Villamor et al., 2017).

4.3 | Strengths and limitations of study

Key strengths of this study include the total-population design, and the use of multiple comprehensive population-based data sources. Data on exposures and the outcome were prospectively collected using nation-wide Swedish health care registries. Maternal BMI was calculated based on information of measured weight and self-reported height in early pregnancy, which limits the risks of recall and selection bias. Using data from several national registries increased the probability that we identified the vast majority of individuals diagnosed with anorexia nervosa. Furthermore, in addition to the population-based analyses, sibling control analyses were performed which allowed us to adjust for unmeasured factors shared by siblings, such as family environment, diet, lifestyle, maternal characteristics, and genetic factors.

This study is also subject to some limitations. First, although the cohort analyses were based on a very large cohort of girls, using sibling analysis for a rare outcome like anorexia nervosa reduced power, possibly obscuring true associations. However, the continuous analyses are better powered and more reliable. Only those mother/child groups that are discordant on the exposure will contribute to the risk estimates that could lead to confounding from unmeasured factors that make siblings different from one another. Information for anorexia was collected from the nation-wide Swedish Patient Register, including hospital in- and out-patient care which does not include cases treated in private practices or by general practitioners. Also our samples may not be generalizable to milder community cases or to men. In addition, cases may have been incorrectly coded and/or missed. However, diagnoses of anorexia nervosa were based on ICD-10 codes, which have shown to have validity (Bould et al., 2015). Finally, we did not adjust for maternal mental disorders or eating disorder, which may mediate some of the observed association with eating disorders in offspring.

5 | CONCLUSION

In summary, we found that risk of anorexia nervosa in offspring progressively decreases with maternal overweight and obesity severity.

Nevertheless, results from the sibling control analyses suggested that this association is not consistent with casual hypothesis and may to a large extend be ascribed to unmeasured environmental or genetic factors.

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CONFLICT OF INTEREST

The authors declared that they have no potential conflicts of interest.

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