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Prenatal and Perinatal Risk Factors for Eating Disorders in Women: A Population Cohort Study

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Abstract

Objective: The fetal programming model hypothesizes that developmental programming in utero and in early life induces adaptations that predetermine the adult phenotype. This study investigated whether prenatal/perinatal complications are associated with lifetime eating disorders in women.

Method: Participants included 46,373 adult women enrolled in the Norwegian Mother and Child Cohort Study [den norske Mor & barn-undersøkelsen (MoBa)]. MoBa mothers and their mothers (MoBa grandmothers) were the focus of the current study. MoBa mothers with lifetime eating disorders were compared to a referent group.

Results: MoBa mothers who weighed more at birth (birth weight, adj. OR=1.14, 95% CI 1.10, 1.19) or were born large-for-gestational-age (adj. OR=1.39, 95% CI 1.27, 1.52) were more likely to develop binge-eating disorder in later life. MoBa mothers who weighed less at birth were more likely to develop anorexia nervosa (birth weight, adj. OR=0.88, 95% CI: 0.81, 0.95). Bulimia nervosa and purging disorder were not significantly predicted by the prenatal and perinatal factors examined.

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Discussion: Results of this study, which include the first known investigation of prenatal and perinatal factors in binge-eating disorder and purging disorder, suggest that fetal programming may be relevant to the development of anorexia nervosa and binge-eating disorder. Future genetically informative research is needed to help disentangle whether these associations are a function of genetic influences or a true environmental fetal programming effect.

Keywords

anorexia nervosa; birth outcomes; binge-eating disorder; bulimia nervosa; eating disorder; MoBa; pregnancy

Prenatal and Perinatal Risk Factors for Eating Disorders in Women: A Population Cohort Study

Eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and OSFED (other specific feeding or eating disorders), affect ~8% of the population over the lifetime and confer risk for suicidality, medical complications, and functional impairment (Smink, van Hoeken, & Hoek, 2013). Given the limited success of existing treatments, understanding etiologies is essential for identifying prevention and treatment targets. A gene-environment diathesis is clear (Yilmaz, Hardaway, & Bulik, 2015), yet the role of particular environmental exposures such as prenatal (before birth) and perinatal (around birth) adversity is poorly understood. The fetal period has been conceptualized as a time of particular vulnerability for psychiatric risk later in life, given that brain development is at its greatest plasticity.

The “fetal programming hypothesis” is derived from Barker’s work on fetal undernutrition and heart disease. The model proposes that intrauterine factors and birth trauma permanently influence anatomical and functional neurobiology and epigenetic programming. In turn, these changes alter the risk of later life physical and psychiatric illnesses (Barker, Osmond, Winter, Margetts, & Simmonds, 1989). Prenatal and perinatal factors have been strongly implicated in schizophrenia and autism spectrum disorders (Cannon, Jones, & Murray, 2002; Rosenfeld, 2015). Prenatal and perinatal etiologies also have been implicated in affective disorders, attention-deficit hyperactivity disorder, psychosis, and bipolar disorder (Rosenfeld, 2015).

Our group has been investigating a transgenerational cycle of risk model proposed in Bulik et al. (2005) which implicates the perinatal period. The intent is to elucidate some of the factors in addition to genetics that account for eating disorder transmission in families from one generation to the next. In a previous work, we provided supporting evidence that exposure to maternal eating disorders increased the risk of negative perinatal outcomes in offspring (Watson, Zerwas, Torgersen, Gustavson, Diemer, Knudsen et al., 2017), and in the present study, we are evaluating whether exposure to specific perinatal events perpetuates risk of eating disorder onset in women.

Whether perinatal factors predict eating disorder onset is unclear. Conflicting findings and methodological heterogeneity challenge the interpretation of the evidence base (Goodman,

Heshmati, Malki, & Koupil, 2014; Krug, Taborelli, Sallis, Treasure, & Micali, 2013). Early studies with case-control designs and clinically ascertained cases tended to support a positive association but their methodology was limited by retrospective parental reports of birth outcomes (Foley, Thacker, Aggen, Neale, & Kendler, 2001; Kay, Schapira, & Brandon, 1967; Lewis & Murray, 1987; Råstam & Gillberg, 1992). In the 2000s, studies based on medical birth records using in some instances very large European samples revealed positive associations (Favaro, Tenconi, Ceschin, Zanetti, Bosello, & Santonastaso, 2011; Favaro, Tenconi, & Santonastaso, 2006). A systematic review covering obstetric risks (n=14 studies; Krug, Taborelli, Sallis, Treasure, & Micali, 2013) and a narrative review (n=22 studies; Raevuori, Linna, & Keski-Rahkonen, 2014) each concluded that the evidence was contradictory. The evidence for particular exposures is derived from single studies, and associations tested across multiple studies have failed to replicate. Results from Swedish birth and medical registers are noteworthy, because of their very large samples and standardized diagnoses from hospital records. The most recent (N~2 million) found that AN was associated with lower gestational age and BN with greater birth weight for gestational age, but revealed no association with delivery method, Apgar score, birth trauma, or premature rupture of membranes (Goodman, Heshmati, Malki, & Koupil, 2014). The research focus has been almost exclusively on AN, with no known studies of BED and purging disorder (PD) (Krug, Taborelli, Sallis, Treasure, & Micali, 2013; Raevuori, Linna, & Keski-Rahkonen, 2014). Findings are limited by case ascertainment predominantly through clinics with only a few studies of community-recruited individuals (Foley, Thacker, Aggen, Neale, & Kendler, 2001; Nicholls & Viner, 2009; Råstam & Gillberg, 1992). There is a need for both methods of inquiry, as clinical studies might contain high selection bias. The literature has also been compromised by small samples and a lack of correction for multiple hypothesis testing. In this study we tested the fetal programming model by examining whether prenatal and perinatal factors were associated with onset of lifetime eating disorders in a large, prospective pregnancy cohort study. The hypotheses in this paper test the fetal programming hypothesis, and will be supported by significant associations in the expected directions, and unsupported otherwise.

Method

Participants

This Norwegian Mother and Child Cohort Study [den norske Mor & barn-undersøkelsen (MoBa)] is a prospective population-based pregnancy-based cohort study conducted by the Norwegian Institute of Public Health (www.fhi.no/morogbarn) (Magnus, Birke, Vejrup, Haugan, Alsaker, Daltveit et al., 2016). Participants were recruited from 1999–2008 via a postal invitation in connection with a routine ultrasound examination offered to all pregnant women in Norway at 17–18 weeks' gestation. Informed consent to participate was obtained from 41% of pregnant women. The cohort now includes 95,200 recruited women (MoBa mothers). MoBa has a three-generational structure of MoBa mothers (who will be termed "mothers" in the present paper), their children (MoBa children), and their grandmothers (MoBa grandmothers) who will be called "grandmothers" in the current study to reflect the participation structure of the larger MoBa study. MoBa children were not included in the present study as they have not come of age for eating disorders. In the current study, MoBa

mothers with lifetime eating disorders were compared to a referent group on prenatal, postnatal, and parental exposures. MoBa follow-up surveys occur at regular intervals and linkages are available to national health registries including the Medical Birth Registry of Norway (MBRN) (Irgens, 2000), which includes all births in Norway since 1967. It is from this data source (MBRN) that grandmaternal data are accessible. The study was approved by The Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate, and the Institutional Review Board at the University of North Carolina at Chapel Hill.

This study is based on version 8 of the quality-assured data files released for research in 2015. The inclusion criteria were (i) non-missing eating disorder information from MoBa questionnaires for the mothers (n = 66,398), and (ii) a grandmother's record in the Medical Birth Registry of Norway for the mother's birth (n = 99,415) (total included = 58,851). The exclusion criteria were selected to minimize bias and maintain the assumption of independent observations. Exclusions for mothers were: (i) from a non-singleton birth (n = 951) (ii) congenital malformations at birth or in offspring (n = 3,782) (iii) invalid values for weight [<30 kg (67 lbs) or > 300 kg (661 lbs)] or height [< 100cm (3.3 feet)] (n = 162) (iv) if recruited into MoBa more than once (due to multiple pregnancies) only the last recruitment was kept (n = 7,895) and (v) invalid eating disorder classification (see Measures) (n = 751) (total excluded=12,478). The total number of individuals was 92,746 (n = 46,373 mothers, n = 46,373 grandmothers). Because AN was measured at a much later wave (8 years), the same criteria were used with total=14,798 (total included = 16,687, total excluded = 1,889).

Measures

Perinatal factors.—Pregnancy and birth-related characteristics that have been studied previously and/or might be anticipated to be associated with an increased risk for poor offspring health outcomes were chosen. Variables were obtained from the Medical Birth Registry of Norway which contains information on births from 1967 (Irgens, 2000). *Parental* factors included older maternal and paternal age (>40 years). *Pregnancy* factors included diabetes (gestational), pre-eclampsia, umbilical cord knot, bleeding during pregnancy, and hyperemesis gravidarum. *Delivery* factors were prolonged labor, instrument-assisted delivery (forceps, vacuum), caesarian delivery, induced delivery, and nonvertex presentation. *Neonatal* factors were birth weight (standardized), small-for-gestational-age (birth weight for age and sex < 10^{th} percentile), large-for-gestational-age (birth weight for age and sex > 90^{th} percentile), birth length (standardized), shorter birth length (birth length for age and sex < 10^{th} percentile), longer birth length (birth length for age and sex > 90^{th} percentile), gestational age (weeks), preterm birth (< 37 weeks), and postmature birth (≥ 42 weeks). Variables defined from percentiles were calculated using World Health Organization (WHO) references. Biologically implausible values defined by WHO were set to missing (WHO Multicentre Growth Reference Study Group, 2009). Variables were binary (0 = absent, 1 = present), except for gestational age, birth weight, and length.

Previous studies have used composite measures of perinatal complications (Krug, Taborelli, Sallis, Treasure, & Micali, 2013). We created composites by summing complications (binary variables above), then categorized these based on the frequency distributions to ensure

reasonable numbers per category. Composite factors were parental complications (0 = none, 1 = one or more), pregnancy complications (0 = none, 1 = one or more), delivery complications (0 = none, 1 = one, 2 = two or more), neonatal complications (0 = none, 1 = one, 2 = two or more), and total complications (0 = none, 1 = one, 2 = two, 3 = three or more).

Eating disorders.—Lifetime eating disorders were assessed with diagnostic algorithms constructed from the Diagnostic and Statistical Manual (DSM-5) (American Psychiatric Association, 2013), specifically the diagnoses of AN, BN, BED, and purging disorder (PD) from the other specified feeding or eating disorders category (OSFED). This method is used in our previous research (Watson, Torgersen, Zerwas, Reichborn-Kjennerud, Knoph, Stoltenberg et al., 2014; Watson, Zerwas, Torgersen, Gustavson, Diemer, Knudsen et al., 2017). Two differences from the DSM-5 are worth noting. The definition of BED is broad because MoBa survey items did not assess all DSM-5 elements of binge eating episodes (i.e., eating more rapidly, embarrassment, guilt, disgust, etc.). A threshold of "at least twice weekly" for recurrent objective binge eating and purging had to be adopted as the DSM-5 threshold ("at least once per week") was unavailable. Phenotyping information is fully provided in the Supplementary Text. Lifetime diagnoses were measured at two occasions, so this resulted in datasets (1) wave 18 months (BN, BED, and PD study) and (2) wave 8 years (AN study). Two datasets were used instead of one because lifetime AN was not assessed at wave 18 months (only at wave 8 years), and we wanted to make sure we included AN as a diagnosis in this study. The *N*s of the overall datasets were different because of follow-up attrition, so it made sense to analyze timepoint data separately. English language translations of the MoBa questionnaires are available for public download (18 months: https://www.fhi.no/globalassets/dokumenterfiler/studier/moba/dokumenter/questionnaire---18-months-after-birth.pdf, 8 years: https://www.fhi.no/globalassets/dokumenterfiler/studier/moba/dokumenter/moba-8-year-english-questionnaire.pdf).

Covariates.—MoBa mothers' household income, marital status, education, and age at assessment were included as covariates and obtained from the MoBa questionnaire administered at baseline. These covariates were included to address sociodemographic selection biases in the MoBa cohort (Magnus, Birke, Vejrup, Haugan, Alsaker, Daltveit et al., 2016; Nilsen, Vollset, Gjessing, Skjaerven, Melve, Schreuder et al., 2009).

Statistical Analysis

The crude relationship between perinatal outcomes and greater lifetime prevalence of eating disorders was assessed with regression methods. For BN, BED, and PD, a multinomial logistic regression was used, and the referent category was no eating disorder. For AN, a logistic regression model was used, and the referent category was no AN. A regression was run for each perinatal predictor. After the crude relationship was investigated, the model was adjusted for covariates. A false discovery rate (FDR)-corrected alpha level of $p < 0.05$ tested statistical significance. Missing data on composite factors and covariates were imputed with a maximum likelihood procedure solved by the expectation maximization algorithm. Analyses were done in SAS 9.4.

Results

Descriptive Statistics

The wave 18 months dataset included data from 92,746 individuals (n = 46,373 mothers, n = 46, 373 grandmothers). Approximately 2.7% of mothers were classified as BN (n = 1,244), 4.3% BED (n = 2,011), 0.6% PD (n = 292), and 92.3% no eating disorder (n = 42,826). Mothers had a mean age of 31 (SD = 4) years and the majority were married (96%), with a modal household income level of 200–500k Norwegian kroner (~30–75k USD) (47%). The modal education was technical college or a four-year university degree (43%). Complications from the birth record at the mother's birth are shown in Table 1. The most frequent were large-for-gestational-age (32.8%), long birth length (25.6%), postmature birth (24.3%), induced delivery (13.8%), prolonged labor (5.8%), anesthesia (5.5%), and instrumental delivery (4.7%).

The wave 8 year dataset included data from 29,596 individuals (n = 14,798 mothers, n = 14,798 grandmothers). The prevalence of lifetime AN in mothers was 2.5% (n = 369). This prevalence is within the range that has been reported for women in two-stage epidemiological studies in Nordic countries (0.2–2.9% with DSM-IV and 3.6% with DSM-5; Dahlgren, Stedal, & Wisting, 2018; Mustelin, Silén, Raevuori, Hoek, Kaprio, & Keski-Rahkonen, 2016). Mothers' mean age was 37 (SD = 4) years. This sample had a demographic profile equivalent to the first sample, and a similar prevalence of complications at birth (Table 1).

Association Between Prenatal and Perinatal Factors and Eating Disorders

Mothers with higher birth weight (adj. OR 1.14, 95% CI 1.10, 1.19) and born large-for-gestational-age (adj. OR 1.39, 95% CI 1.27, 1.52) were at an increased risk for BED (Figure 1). Grandmaternal diabetes during pregnancy (gestational and pregestational) was significantly associated with BED in the crude model, but attenuated to non-significant in the adjusted model (Figure 1). Post hoc Cochran-Mantel-Haenszel tests revealed that grandmaternal diabetes was no longer associated with BED after adjusting for education level (p=0.59) or household income (p=0.57). The composite total complications variable had a positive, significant association with BED but no dose-response pattern (adj. OR for 1 risk: 1.16, 95% CI 1.03, 1.31; adj. OR for 2 risks: 1.18, 95% CI 1.03, 1.34; adj. OR for ≥3 risks: 1.15 95% CI 1.01, 1.34). Composite neonatal complications (a variable constructed from small-for-gestational age, large-for-gestational-age, short birth length, large birth length, preterm birth, and postmature birth) was significantly associated with BED and a dose-response pattern was observed (adj. OR for 1 risk: 1.20, 95% CI 1.08, 1.33; adj. OR for ≥2 risks: 1.26, 95% CI 1.12, 1.42). No other variable was significant for BED. BN or PD were not significantly associated with any variables (Table 2; composite variables not shown).

Mothers at a lower birth weight were more likely to develop AN (adj. OR 0.88, 95% CI 0.81, 0.95). No other predictors were significantly associated with AN (Table 2; composite variables not shown).

Discussion

The fetal programming hypothesis proposes that in utero conditions can determine susceptibility to diseases later in life. Using data from a population-based sample of parous women (MoBa mothers) and their mothers (MoBa grandmothers), this study examined whether prenatal/perinatal factors prospectively predicted lifetime eating disorder risk. Higher birth weight and large-for-gestational-age in mothers were associated with BED in adjusted models. Mothers born at a lower birth weight were more likely to develop AN. In contrast to previous findings, lifetime BN was not associated with perinatal factors. In this first known investigation into birth characteristics and PD, no significant associations were found.

Prenatal and perinatal factors associated with maternal BED included higher birth weight and large-for-gestational-age. Individuals born large-for-gestational-age are more likely to develop obesity and negative cardiometabolic outcomes, and patterns of methylation associated with overnutrition in utero have been associated with altered adipocyte development (Chiavaroli, Derraik, Hofman, & Cutfield, 2016). The neurobiological effects of fetal overnutrition and higher birth weight have not been thoroughly examined, but possibly evoke metabolic risks for BED. This might include dopamine neurocircuitry underpinning appetite and motivation for food intake, proneness to overweight/obesity and overeating, and trajectories toward the cognitive risk factors of body dissatisfaction and dietary restraint (Davis, Levitan, Yilmaz, Kaplan, Carter, & Kennedy, 2012; Stice, Gau, Rohde, & Shaw, 2017). Alternatively, a genetically-mediated hypothesis is plausible such that mothers with greater risk for overweight and obesity are more likely to have large-for-gestational-age infants and diabetes and to pass these genes on to their children, and these genes might also increase risk for BED. The relationship between higher birth weight and BED may also be mediated by attendant social stressors to childhood obesity, which increase vulnerability to BED (Fairburn, Doll, Welch, Hay, Davies, & O'Connor, 1998).

Interestingly, MoBa mothers whose mothers had diabetes during pregnancy were more likely to have BED in the crude model. Although a large effect size was still apparent in the adjusted model, the association was non-significant after offspring education and household income were included. A recent study reported a positive association between gestational diabetes and eating disorders, though grouped all types of eating disorders together (Sacks, Friger, Shoham-Vardi, Abokaf, Spiegel, Sergienko et al., 2016). Maternal diabetes during pregnancy may dysregulate hormonal and appetitive traits, such as hypothalamic feeding circuitry and abnormal glucose homeostasis, that predispose to BED. Genetic confounding and shared risk factors for diabetes and BED, such as familial obesity, are possible explanations.

Lower birth weight was associated with AN onset. This is consistent with a prospective birth cohort finding that low premorbid BMI over the lifetime was associated with AN detected by community-based survey (Yilmaz, Gottfredson, Zerwas, Bulik, & Micali, 2019). However, prior studies on AN, including a population-based Swedish study of 2 million individuals, reported a null association with birth weight (Favaro, Tenconi, & Santonastaso, 2006; Favaro, Tenconi, & Santonastaso, 2010; Goodman, Heshmati, Malki, & Koupil, 2014;

Nicholls & Viner, 2009; Shoebridge & Gowers, 2000), and an association with higher birth weight (Wade, Treloar, Martin, Statham, & Heath, 2004). The present study might indicate a population association for AN detected in community samples, given other studies (except these studies; Nicholls & Viner, 2009; Yilmaz, Gottfredson, Zerwas, Bulik, & Micali, 2019) drew a considerable portion or all of their cases from clinical samples.

Several null associations in this study are concordant with previous research findings, including AN and breech delivery (Tenconi, Santonastaso, Monaco, & Favaro, 2015), preterm (Favaro, Tenconi, & Santonastaso, 2006; Nicholls & Viner, 2009) and small-for-gestational-age (Tenconi, Santonastaso, Monaco, & Favaro, 2015), as well as BN and maternal age (Goodman, Heshmati, Malki, & Koupil, 2014), paternal age (Goodman, Heshmati, Malki, & Koupil, 2014), diabetes during pregnancy (Favaro, Tenconi, & Santonastaso, 2006), pre-eclampsia (Favaro, Tenconi, & Santonastaso, 2006), delivery method (Favaro, Tenconi, & Santonastaso, 2006), gestational age (Goodman, Heshmati, Malki, & Koupil, 2014), and birth length (Favaro, Tenconi, & Santonastaso, 2006; Goodman, Heshmati, Malki, & Koupil, 2014; Nicholls & Viner, 2009; Tenconi, Santonastaso, Monaco, & Favaro, 2015). Previously identified significant and positive associations between AN and maternal age (Goodman, Heshmati, Malki, & Koupil, 2014), paternal age (Javaras, Rickert, Thornton, Peat, Baker, Birgegård et al., 2017), diabetes during pregnancy (Favaro, Tenconi, & Santonastaso, 2006), pre-eclampsia (Favaro, Tenconi, & Santonastaso, 2006), breech delivery (Lindberg & Hjern, 2003), instrumental delivery (Cnattingius, Hultman, Dahl, & Sparén, 1999), particular obstetric complications (Cnattingius, Hultman, Dahl, & Sparén, 1999; Favaro, Tenconi, & Santonastaso, 2006; Lewis & Murray, 1987; Tenconi, Santonastaso, Monaco, & Favaro, 2015), and preterm (Cnattingius, Hultman, Dahl, & Sparén, 1999; Lindberg & Hjern, 2003), and negative associations with gestational age (Cnattingius, Hultman, Dahl, & Sparén, 1999; Foley, Thacker, Aggen, Neale, & Kendler, 2001; Goodman, Heshmati, Malki, & Koupil, 2014) and postterm (Lindberg & Hjern, 2003) were not replicated in this study. Previously identified associations between prenatal and perinatal outcomes and AN and BN are drawn from single studies, which often fail to control for multiple testing. Inevitably, if enough variables and statistical tests are inspected, it will be possible to see significant associations, and thus, the real issue becomes the replicability of findings. Previously reported inverse associations between BN and birth weight and birth length (Favaro, Tenconi, & Santonastaso, 2006), and a positive association with BN and birth weight (Goodman, Heshmati, Malki, & Koupil, 2014) were also not observed in the present study. In contrast to AN and BED, a lack of support was found for a fetal programming model for BN or PD with the variables examined. PD was the smallest group size (n = 292) and it may be that the study lacked power to detect small effects. For some dichotomous outcomes (i.e., pre-eclampsia, preterm, placenta previa, umbilical cord knot), the lack of association could reflect the low incidence rate, which would require very large sample sizes to detect associations. Studies on the association between eating disorders and birth characteristics have typically yielded small effects when effects are noted, in clinical samples.

It is important to weigh the strengths and limitations of this study. Strengths are its very large sample size (>45,000) and the longitudinal prospective design. Such designs are rare in studies of this nature. This study was, to our knowledge, the first to investigate whether there

are fetal origins for BED and PD. Unlike many previous studies based on registry or clinical data, MoBa is population-based. Our findings are more generalizable to the broader population than clinical research (Favaro, Tenconi, & Santonastaso, 2006; Kay, Schapira, & Brandon, 1967; Shoebridge & Gowers, 2000; Tenconi, Santonastaso, Monaco, & Favaro, 2015). Another strength is the use of birth records, precluding the influence of recall bias, in contrast to other studies (Foley, Thacker, Aggen, Neale, & Kendler, 2001; Kay, Schapira, & Brandon, 1967; Wade, Treloar, Martin, Statham, & Heath, 2004). Since health registries are mandatory, the linkage between the participants to birth register data reduces selection bias (Magnus, Birke, Vejrup, Haugan, Alsaker, Daltveit et al., 2016). The rate of recruitment (41%) is a limitation, with recruited mothers (compared to all women giving birth in Norway) underrepresenting younger women (<25 years), mothers living alone, mothers with previous stillbirths, and smokers. This selection bias been evaluated and appears to have negligible influence on exposure-disease associations (Nilsen, Vollset, Gjessing, Skjaerven, Melve, Schreuder et al., 2009). Another limitation is the potential for misclassification bias, for instance, individuals being unable to be classified as having more than one eating disorder over the lifetime, which would reduce power to detect associations if the fetal programming hypothesis was true. Because of the differing structures of the MoBa Questionnaires at wave 18 months and wave 8 years, some individuals who were categorized as having no lifetime AN may have had other lifetime eating disorders. Although a strength of a measure like birth weight is that it is relatively easy and reliable to measure, birth weight correlates with many prenatal factors, and could be seen as a general index for the quality of the in utero environment rather than a specific risk correlate. Because MoBa is a large-scale study into the causes of many somatic and psychiatric conditions, it was not feasible for the MoBa project to assess all conditions by physician diagnosis or standardized interviews. Likewise, full validated screening instruments could not be included in surveys because of respondent burden. We applied DSM-based algorithms to the extent possible on survey items. This is better than relying on single-item self-report of disease as is common in large-scale studies, but was an unvalidated assessment and is unlikely to be as accurate as expert diagnosis or structured clinical interview. Another limitation is that because MoBa recruitment targeted pregnant women, data on birth complications in men and subsequent eating disorder onset were not available. This is a major study limitation and future studies are encouraged to include men. The specificity of the observed associations for eating disorders is not known and further research is needed to rule out the possibility that the associations are driven by alternative perinatal-disease ties, for example by associations between perinatal complications and psychiatric comorbidities.

A possibility is that shared causal risk factors for eating disorders and weight/metabolic status explain the observed associations. Associations between maternal eating disorder and anthropometric birth outcomes in offspring have been reported (Watson, Zerwas, Torgersen, Gustavson, Diemer, Knudsen et al., 2017), and recent genome-wide association studies have reported significant genetic correlations between AN and BMI and a range of metabolic factors (Duncan, Yilmaz, Gaspar, Walters, Goldstein, Anttila et al., 2017; Watson, Yilmaz, Thornton, Hübel, Coleman, Bryois et al., submitted manuscript). Future studies investigating the associations between perinatal phenotypes and eating disorders are encouraged to investigate genetic and familial factors, for example, do genetic variants passed down across

generations influence both perinatal and eating disorder phenotypes, or does the perinatal-eating disorder onset association reflect an environmentally-based fetal programming effect that is independent of genes? Genetically informative replication studies will be an important contribution to this literature.

Conclusions

The results of this study suggest that fetal programming may be relevant to the etiology of BED and AN. Adequately powered replication studies and cumulative meta-analysis will help to identify prenatal and perinatal factors consistently associated with the development of eating disorders. Additionally, genetically-sensitive designs will help to determine whether the associations are genetically or environmentally influenced, or both.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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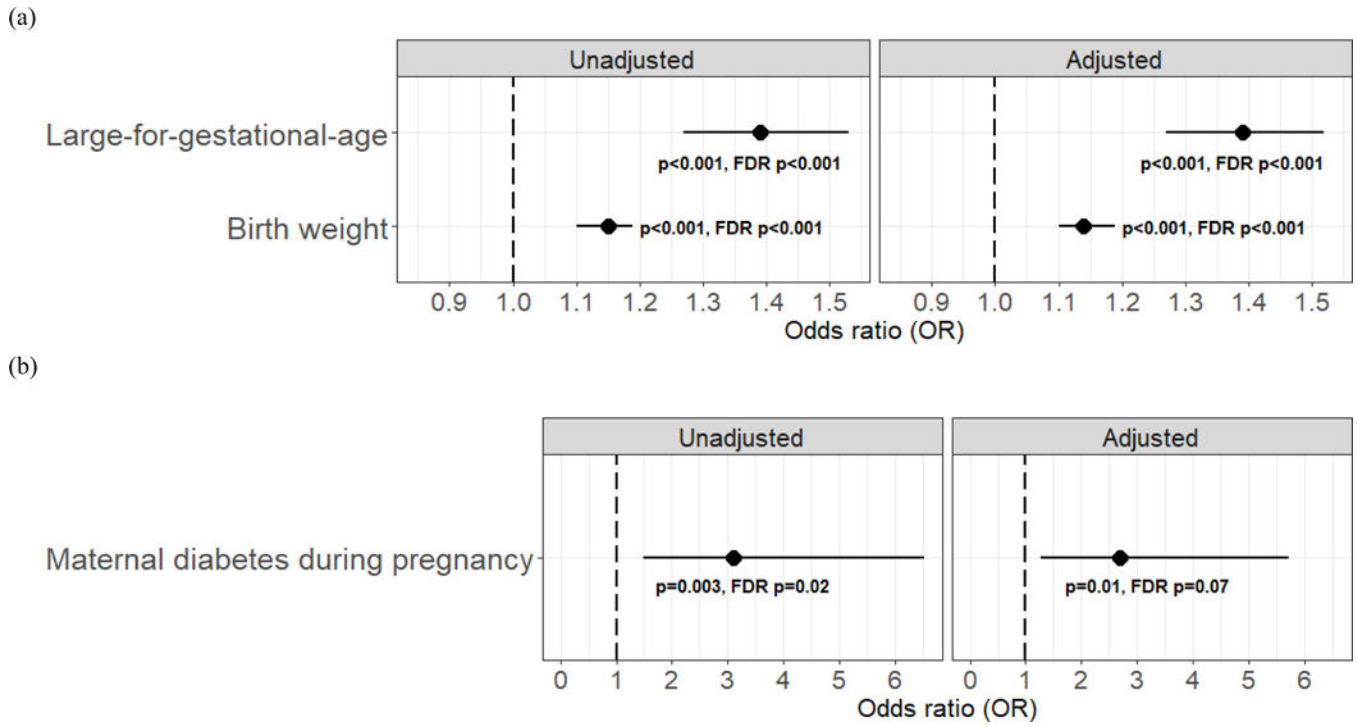

FIGURE 1. Association Between Prenatal and Perinatal Exposures and Binge-Eating Disorder.
Fig (a) depicts the association between large-for-gestational age, birth weight, and BED onset. Fig (b) depicts the association between maternal diabetes during pregnancy and BED onset. The figures contain nominal P values and false-discovery P values which are P values corrected for multiple hypothesis testing. The 95% CIs are shown.

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TABLE 1

Prenatal and Perinatal Exposure Variables of MoBa Mothers

.		Wave 18 months dataset				Wave 8 years dataset	
Predictor	**Characteristic**	**BN (*n* = 1,244)**	**BED (*n* =2,011)**	**PD (*n* = 292)**	**Control (*n* = 42,826)**	**AN (*n* = 369)**	**Control (*n* = 14,429)**
Parental	Paternal age > 40, % (*n*)	5.3 (66)	5.4 (109)	5.1 (15)	5.9 (2,524)	6.8 (25)	6.2 (901)
	Maternal age > 40, % (*n*)	1.4 (17)	1.2 (24)	0.3 (1)	1.4 (592)	1.1 (4)	1.6 (226)
Pregnancy	Diabetes, % (*n*)	0.1 (1)	0.4 (8)	-	0.1 (55)	0.3 (1)	0.1 (19)
	Pregestational	0.1 (1)	0.3 (6)	-	0.1 (48)	0.3 (1)	0.1 (16)
	Gestational	-	0.1 (2)	-	0.02 (7)	-	0.02 (3)
	Pre-eclampsia, % (*n*)	2.2 (28)	2.0 (41)	1.7 (5)	2.0 (846)	1.4 (5)	1.8 (267)
	Umbilical cord knot, % (*n*)	0.7 (9)	0.7 (14)	0.3 (1)	0.7 (288)	0.8 (3)	0.6 (90)
	Bleeding during pregnancy, % (*n*)	3.8 (4)	2.7 (54)	3.8 (11)	2.9 (1,199)	4.3 (16)	2.6 (375)
	Hyperemesis gravidarum, % (*n*)	0.4 (5)	0.6 (13)	0.7 (2)	0.6 (264)	1.4 (5)	0.7 (105)
Delivery	Prolonged labor, % (*n*)	4.2 (52)	5.1 (103)	6.2 (18)	5.9 (2,527)	5.1 (19)	5.2 (747)
	Instrument-assisted, % (*n*)	3.3 (41)	4.1 (83)	4.4 (13)	4.8 (2,045)	3.5 (13)	4.1 (587)
	Caesarian, % (*n*)	0.6 (8)	0.5 (10)	0.7 (2)	0.5 (218)	0.8 (3)	0.5 (66)
	Induced, % (*n*)	14.6 (181)	14.0 (282)	13.4 (39)	13.8 (5,906)	12.7 (47)	14.1 (2,041)
	Placenta previa, % (*n*)	0.3 (4)	0.1 (2)	0.7 (2)	0.2 (70)	0.3 (1)	0.2 (25)
	Nonvertex, % (*n*)	4.0 (50)	3.1 (63)	6.2 (18)	4.0 (1,730)	2.2 (8)	3.5 (507)
Neonatal	Birth weight (kg), *M* (*SD*)	3.6 (0.6)	3.7 (0.6)	3.6 (0.6)	3.6 (0.6)	3.5 (0.6)	3.6 (0.6)
	Small-for-gestational-age, % (*n*)	3.8 (47)	4.0 (80)	5.8 (17)	4.2 (1,792)	5.1 (19)	4.2 (613)
	Large-for-gestational-age, % (*n*)	31.0 (385)	40.1 (807)	32.2 (94)	32.5 (13,915)	27.6 (102)	34.5 (4,983)
	Birth length (cm), *M* (*SD*)	50.2 (2.2)	50.2 (2.2)	50.2 (1.9)	50.2 (2.2)	50.0 (2.5)	50.2 (2.2)
	Short birth length, % (*n*)	4.3 (53)	4.6 (93)	2.0 (6)	4.0 (1,698)	6.2 (23)	4.0 (575)
	Long birth length, % (*n*)	24.5 (305)	24.7 (496)	23.6 (69)	25.7 (11,007)	25.3 (93)	26.1 (3,770)
	Gestational age (weeks), *M* (*SD*)	40.4 (1.9)	40.5 (1.8)	40.4 (2.1)	40.4 (1.8)	40.4 (1.90)	40.4 (1.8)
	Preterm, % (*n*)	3.0 (37)	2.7 (55)	4.4 (13)	2.6 (1,137)	2.7 (10)	2.6 (379)
	Postmature, % (*n*)	24.0 (299)	25.0 (503)	25.7 (75)	24.3 (10,414)	25.2 (93)	24.2 (3,498)

Note.AN = anorexia nervosa; BED = binge-eating disorder; BN = bulimia nervosa; PD = purging disorder.

TABLE 2

Association Between Prenatal and Perinatal Exposures of MoBa Mothers and Subsequent Eating Disorder Onset

		AN			BN		
		OR (95% CI)	***p***	**FDR*p***	**OR (95% CI)**	***p***	**FDR*p***
Parental	Paternal age	1.10 (0.73, 1.67)	0.64	0.88	0.89 (0.69, 1.14)	0.37	0.80
	Maternal age	0.71 (0.26, 1.92)	0.50	0.86	1.00 (0.61, 1.62)	0.99	0.99
Pregnancy	Diabetes	1.82 (0.24, 13.8)	0.56	0.86	0.60 (0.08, 4.34)	0.61	0.80
	Pre-eclampsia	0.72 (0.30, 1.77)	0.48	0.86	1.14 (0.78, 1.67)	0.50	0.80
	Umbilical cord knot	1.24 (0.39, 3.93)	0.72	0.88	1.07 (0.55, 2.09)	0.84	0.92
	Bleeding	1.66 (0.99, 2.77)	0.05	0.31	**1.37 (1.02, 1.85)**	**0.04** *	0.28
	Hyperemesis gravidarum	1.90 (0.77, 4.71)	0.16	0.54	0.65 (0.27, 1.58)	0.34	0.80
Delivery	Prolonged labor	0.96 (0.60, 1.53)	0.85	0.89	**0.69 (0.52, 0.92)**	**0.01** *	0.19
	Anesthesia	1.23 (0.75, 2.04)	0.41	0.86	1.23 (0.98, 1.54)	0.07	0.39
	Instrument-assisted	0.84 (0.48, 1.47)	0.54	0.86	**0.68 (0.50, 0.93)**	**0.02** *	0.19
	Caesarian	1.73 (0.54, 5.55)	0.36	0.86	1.24 (0.61, 2.51)	0.56	0.80
	Induced	0.87 (0.64, 1.19)	0.39	0.86	1.06 (0.91, 1.25)	0.45	0.80
	Placenta previa	1.57 (0.21, 11.67)	0.66	0.88	2.03 (0.74, 5.57)	0.17	0.78
	Nonvertex	0.60 (0.30, 1.22)	0.16	0.54	1.01 (0.75, 1.34)	0.97	0.99
Neonatal	Birth weight	**0.88 (0.81, 0.95)**	**0.001** **	**0.03** *	1.01 (0.96, 1.06)	0.62	0.80
	Small-for-gestational-age	1.19 (0.75, 1.91)	0.46	0.86	0.88 (0.65, 1.18)	0.38	0.80
	Large-for-gestational-age	**0.74 (0.59, 0.94)**	**0.01** *	0.13	0.94 (0.83, 1.06)	0.32	0.80
	Birth length	0.94 (0.86, 1.02)	0.14	0.54	0.99 (0.94, 1.03)	0.59	0.80
	Short birth length	**1.56 (1.02, 2.41)**	**0.04** *	0.31	1.03 (0.78, 1.37)	0.81	0.92
	Long birth length	0.98 (0.77, 1.25)	0.89	0.89	0.96 (0.84, 1.10)	0.55	0.80
	Gestational age	1.00 (0.94, 1.05)	0.88	0.89	0.99 (0.96, 1.02)	0.53	0.80
	Preterm	1.06 (0.56, 2.00)	0.86	0.89	1.11 (0.79, 1.54)	0.55	0.80
	Postmature	1.04 (0.82, 1.32)	0.73	0.88	0.98 (0.86, 1.12)	0.73	0.89
		BED			**PD**		

		AN			BN		
		OR (95% CI)	***p***	**FDR*p***	**OR (95% CI)**	***p***	**FDR*p***
		OR (95% CI)	***p***	**FDR *p***	**OR (95% CI)**	***p***	**FDR*p***
Parental	Maternal age	0.92 (0.76, 1.12)	0.42	0.93	0.87 (0.52, 1.46)	0.59	0.93
	Paternal age	0.88 (0.58, 1.33)	0.55	0.93	0.25 (0.03, 1.78)	0.17	0.76
Pregnancy	Diabetes	**2.70 (1.27, 5.72)**	**0.01** **	0.07	0 (0, <0.01)	0.93	0.93
	Pre-eclampsia	1.03 (0.75, 1.41)	0.87	0.93	0.85 (0.35, 2.07)	0.73	0.93
	Umbilical cord knot	1.03 (0.60, 1.77)	0.92	0.93	0.52 (0.07, 3.72)	0.51	0.93
	Bleeding	0.98 (0.74, 1.30)	0.90	0.93	1.39 (0.76, 2.55)	0.28	0.85
	Hyperemesis gravidarum	1.07 (0.61, 1.88)	0.80	0.93	1.13 (0.28, 4.55)	0.87	0.93
Delivery	Prolonged labor	0.86 (0.71, 1.06)	0.16	0.61	1.06 (0.66, 1.71)	0.82	0.93
	Anesthesia	0.84 (0.69, 1.04)	0.11	0.51	1.11 (0.69, 1.79)	0.68	0.93
	Instrument-assisted	0.88 (0.70, 1.10)	0.27	0.79	0.95 (0.55, 1.67)	0.87	0.93
	Caesarian	0.89 (0.47, 1.68)	0.71	0.93	1.27 (0.31, 5.15)	0.74	0.93
	Induced	1.02 (0.89, 1.16)	0.80	0.93	0.97 (0.69, 1.36)	0.85	0.93
	Placenta previa	0.67 (0.16, 2.75)	0.58	0.93	**4.54 (1.11, 18.66)**	**0.04** *	0.45
	Nonvertex	**0.77 (0.60, 1.00)**	**0.04** *	0.28	1.58 (0.98, 2.56)	0.06	0.45
Neonatal	Birth weight	**1.14 (1.10, 1.19)**	**<0.001** ***	**<0.001** ***	0.95 (0.86, 1.05)	0.30	0.85
	Small-for-gestational-age	0.91 (0.72, 1.15)	0.42	0.93	1.35 (0.83, 2.21)	0.23	0.85
	Large-for-gestational-age	**1.39 (1.27, 1.52)**	**<0.001** ***	**<0.001** ***	0.99 (0.77, 1.27)	0.93	0.93
	Birth length	1.01 (0.97, 1.05)	0.54	0.93	1.03 (0.93, 1.14)	0.58	0.93
	Short birth length	1.07 (0.86, 1.32)	0.55	0.93	0.46 (0.21, 1.05)	0.06	0.45
	Long birth length	0.99 (0.90, 1.10)	0.91	0.93	0.94 (0.71, 1.23)	0.63	0.93
	Gestational age	1.02 (0.99, 1.04)	0.23	0.77	0.99 (0.93, 1.05)	0.69	0.93
	Preterm	0.99 (0.75, 1.30)	0.93	0.93	1.65 (0.94, 2.89)	0.08	0.45
	Postmature	1.02 (0.92, 1.13)	0.74	0.93	1.06 (0.81, 1.38)	0.66	0.93

*Note.*AN = anorexia nervosa; BED = binge-eating disorder; BN = bulimia nervosa; CI = confidence interval; FDR = false discovery rate; PD = purging disorder; OR = odds ratio.

* FDR $p < 0.05$

** FDR $p < 0.01$

***FDR $p < 0.001$.

Adjusted results are presented. Covariates were respondent characteristics of household income, marital status, education, and age. Age was not included as a covariate in the paternal and maternal age models.