INVITED PAPER

Prenatal and Perinatal Factors in Eating Disorders: A Descriptive Review

Anu Raevuori, MD, PhD[1,2,3,4]*
Milla S. Linna, MD[1]
Anna Keski-Rahkonen, MD, PhD, MPH[1]

ABSTRACT

Objective: The objective of this descriptive review is to summarize the current scientific evidence on various prenatal and perinatal exposures affecting later development of eating disorders among offspring.

Method: Studies were searched from PubMed database with the following keywords: eating disorders and disordered eating and anorexia nervosa and bulimia nervosa and binge eating disorder and prenatal exposure delayed effects and maternal exposure and perinatology. A comprehensive manual search, including search from the reference list of included articles, was also performed.

Results: The attributable risk for prenatal and perinatal factors in anorexia nervosa (AN) is 3.6%. Numerous prenatal and perinatal factors have been associated with offspring AN, but only prematurity has been replicated in different samples. The risk of bulimia nervosa (BN) in offspring has attracted less study, and despite varying positive associations, there are no replicated findings. Higher prenatal testosterone may protect against the development of a range of disordered eating symptoms, although studies are not consistent.

Discussion: Evidence in support of an effect of prenatal and perinatal factors on eating disorders or disordered eating in offspring is conflicting. If present, the overall effect appears to be relatively small, and it is likely that the early risk factors operate in conjunction with other biological, genetic, and/or environmental risk factors to bring on eating pathology. Genetically sensitive designs, such as sibling and twin studies, are needed to disentangle the different types of risk factors and ensure that prenatal/perinatal effects are "causal" rather than indications of genetic risk. © 2014 Wiley Periodicals, Inc.

Keywords: eating disorders; prenatal exposure delayed effects; maternal exposure; perinatology; review; disordered eating; anorexia nervosa; bulimia nervosa; binge eating disorder

(Int J Eat Disord 2014; 47:676–685)

Introduction

Accumulating evidence suggests that various exposures early in the development affect neural development and can play a role in the development of psychopathologies, including eating disorders, in later life.[1–5] Early development can be defined in diverse ways. In this descriptive review, we include prenatal and perinatal periods. Prenatal development refers to the process in which an embryo or fetus gestates during pregnancy, from fertilization until birth. The partially overlapping term "perinatal period" includes the time immediately before and after birth (from the 20th or 28th week of gestation to 4 weeks after birth). By definition, prenatal and perinatal periods exhibit some overlap.[6]

In anorexia nervosa (AN), the research in prenatal and perinatal factors, such as obstetric complications, began in the 1960s.[7] However, only a few studies provide prevalence estimates for prenatal and perinatal risk factors in individuals with eating disorders vs. control individuals. In one study,[5] just 16% of individuals with AN, 19% of those with bulimia nervosa (BN), and 27% of control participants were free of obstetric complications, demonstrating how common these complications are. In a register-based study,[8] 1.8% of the hospital treated cases with AN and 0.6% of the controls were born

Accepted 9 June 2014
Additional Supporting Information may be found in the online version of this article.
Supported by 259764 from Academy of Finland.
*Correspondence to: Dr. Anu Raevuori, PO Box 41,00014 University of Helsinki, Finland. E-mail: anu.raevuori@helsinki.fi
[1] Department of Public Health, Hjelt Institute, University of Helsinki, Finland
[2] Child Psychiatry Research Center, Institute of Clinical Medicine, University of Turku, Turku, Finland
[3] Department of Adolescent Psychiatry, Helsinki University Central Hospital, Helsinki, Finland
[4] Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland
Published online 19 June 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/eat.22323

very pre-term (≤32nd week of gestation) and 2.4% of cases and 1.1% of controls had a cephalhematoma (a hemorrhage between the skull and the membrane that covers the skull), meaning that severe individual complications are fortunately relatively rare. In both studies, these differences between individuals with and without eating disorders were statistically significant. Another register study[9] estimated the attributable risk fraction for pre- and perinatal factors in AN to be 3.6%. Although this is much smaller than the risk attributed to factors like sex (89.4%) and psychosocial factors (7.6%), it implies that up to 4% of eating disorders could be prevented by optimizing perinatal health care and preventing birth traumas.

Prenatal and perinatal risk factors can also provide clues for etiological mechanisms and increase understanding about the pathways that lead to eating disorders. For example, evidence of prenatal infection and immune dysfunction as risk factors for autism[10] suggests that the maternal immune response and inflammation alter the development of the fetal central nervous system and may represent a pathway by which infectious insults give rise to neurodevelopmental disorders. Respective cerebellar abnormalities have been demonstrated in the brains of individuals with autism.[11]

To our knowledge, two previous reviews coupled with meta-analyses of early risk factors for disordered eating and eating disorders exist so far. The study by Lydecker et al.[12] examined the hypothesis that prenatal exposure to sex hormones influences twins' risk for eating disorders based on co-twin sex by combining three different twin samples.

Krug et al.[13] reviewed the role of perinatal or obstetric factors for a subsequent eating disorders and performed a meta-analysis of case-control studies of AN and obstetric complications. The current descriptive review is the first one to cover the entire prenatal and perinatal period. We aimed to summarize the literature on prenatal and perinatal factors and explore their role in the development of subsequent AN, BN, binge eating disorder (BED), or disordered eating symptoms.

Method

Studies were searched from PubMed database with the following keywords: eating disorders and disordered eating and anorexia nervosa and bulimia nervosa and binge eating disorder and prenatal exposure delayed effects and maternal exposure and perinatology. A comprehensive manual search, including search from the reference list of included articles, was also performed. All reviewed studies are described in the Supporting Information Table 1.

Prenatal Risk Factors of Eating Disorders

Prenatal Sex-hormone Effects

Research on the organizational role of sex hormones in disordered eating has been very active in recent years. Organizational effects refer to permanent effects during development, such as lateralization of the brain or development of sex organs before birth and during puberty. In terms of eating behavior, prenatal testosterone exposure increases food intake in male mammals, while females, in the absence of testosterone, do not develop male characteristics and eat less.[14] Prenatal organizational effects of sex hormones have been investigated using two indirect methods. First, when opposite-sex twins share the womb, masculinization of the female fetus and feminization of the male fetus may occur.[15–17] Girls from opposite-sex twin pairs exhibit more masculine patterns of brain lateralization[15] and visuo-spatial cognitive skills,[18] and are more likely to engage in risky behaviors[16] than girls from same-sex twin pairs. Second, organizational effects of sex hormones have been studied by using the ratio of the length of the 2nd and 4th fingers (2D:4D) as a proxy measure of fetal testosterone levels.[19] In both sexes, lower 2D:4D ratios are associated with increased prenatal testosterone exposure.[20] In general, the 4th digit tend to be longer than the 2nd in males (i.e. the mean 2D:4D ratio is less than one), whereas in females the 2nd and 4th digits tend to be of equal length (i.e. the mean 2D:4D ratio is approximately one).[19]

Lower levels of prenatal testosterone exposure have been associated with increased eating disorder symptoms (body dissatisfaction, weight preoccupation, binge eating, and compensatory behaviors) in women,[21] and it has been suggested[21] that the relatively low level of testosterone before birth in females permits their brains to respond to estrogens at puberty, when the hormones activate the genes contributing to disordered eating in vulnerable girls. Among men, positive correlations between 2D:4D ratio and disordered eating and drive for leanness, and negative correlation between 2D:4D and drive for muscularity have also been reported. These findings imply that greater prenatal testosterone exposure in males is associated with less disordered eating, less drive for leanness, but increased drive for muscularity.[22]

By contrast, some studies have shown opposite effects of prenatal testosterone exposure on eating

disorder risk. For example, lower 2D:4D ratios were observed among daughters of women with lifetime BN compared to daughters of unaffected mothers.[23] No significant differences were observed in sons. Another study[24] found lower 2D:4D ratios (i.e., higher prenatal testosterone) in women with AN compared to women with BN, with control individuals intermediary.

Studies of opposite-sex twins have been more contradictory than those of 2D:4D. In a twin study by Culbert et al.,[25] the highest levels of disordered eating were observed for same-sex female twins, followed by opposite-sex female twins, opposite-sex male twins, and same-sex male twins. The authors suggested that the prenatal organizational effects of testosterone might protect female offspring from opposite-sex twin pairs from future disordered eating. These findings on disordered eating were unlikely to be due to socialization effects of opposite-sex sibling alone, since the analyses in females controlled for the effects of growing up with a brother near one's age. In another study by the same group, no differences in levels of disordered eating attitudes between opposite-sex and same-sex twins were observed in pre-early puberty; yet during later phases of puberty, females from opposite-sex twin pairs exhibited more masculinized (i.e., lower) disordered eating attitudes than females from same-sex twin pairs.[26] The authors concluded that prenatal testosterone exposure decreases disordered eating and contributes to the sex differences of disordered eating after mid-puberty.

Studies in other twin samples have generally not replicated these findings.[12,27,28] In a meta-analysis of three different twin samples,[12] lifetime prevalence of eating disorders (AN, AN broad, BN, BN broad, BED) and binge eating behaviors did not differ between same-sex and opposite-sex twins. Although broadly defined BN was more common among same-sex than opposite-sex twins in the Swedish sample, the result did not stand after monozygotic twins were excluded from analyses, implying either loss of statistical power (as suggested by the authors) or that the difference between same-sex and opposite-sex twins (prevalence 2.55%) were due to higher prevalence of broadly defined BN in monozygotic twins (2.76%) compared to same-sex dizygotic twins (2.65%). By contrast, in the study by Culbert et al.,[25] the effect of being from an opposite-sex pair on disorder eating did remain when controlling for zygosity. In the Finnish twin cohort study,[28] the overall results were also negative. However, women from opposite-sex twin pairs had a marginally decreased risk of developing AN and engaging in recurrent weight loss attempts, which is in accordance with the findings of Culbert et al.[25,26] In the Finnish study,[28] the lifetime prevalence of DSM-IV narrow and broad AN was 1.6–3.3% in women from opposite-sex twin pairs (95% Confidence Interval [CI] 0.8–2.5), while it was 2.9–5.1% (95% CI 1.7–4.1) in women from same-sex pairs.

The Effects of the Maternal Physical States

Maternal physical states (e.g., under-eating, anemia, pre-eclampsia) during pregnancy may increase the risk of AN in their offspring, for example through chronic insufficient supply of oxygen and/or nutrients, which may damage fetal central nervous system development. An Italian community-based study[5] that also included patients from a local eating disorder clinic found increased rates of maternal anemia, diabetes, and pre-eclampsia in offspring with AN. In a partially overlapping, Italian eco-epidemiological study,[29] exposure to epidemics of chickenpox (OR 1.6, 95% CI 1.2–2.0) and rubella (OR 1.5, 95% CI 1.1–2.0) during the sixth month of pregnancy were associated with an increased risk of developing AN, even after controlling for socio-economic status, urbanization and month of birth.

The Italian authors also found weak evidence in support of a previously reported season-of-birth[30] bias that showed a higher risk of eating disorders among those born in the spring as opposed to other months. A season of birth bias provides indirect evidence of the role of infections in eating disorder risk, since the occurrence of many infections tends to follow a seasonal pattern.[31] However, not all studies have found an increased rate of spring births in women with eating disorders.[32,33]

Finally, a lower cumulative incidence of AN in children of younger mothers ($\leq$24 years of age at birth) was reported in a Swedish register study,[9] whereas in another Swedish register study,[34] higher maternal and paternal age were related to an increased risk of AN. In the latter study, the finding was mostly explained by parental characteristics (e.g., education), which might be the case also in the former study, where AN was more common in daughters from families of higher socioeconomic position. In the latter study, maternal smoking during pregnancy had an inverse association with child's AN, but this effect was also attenuated when controlling for parental characteristics.

The risk of eating disorders (a composite including AN, BN, BED, and purging disorder) in female adolescents was recently reported to be predicted

by low maternal vitamin D level at 18 weeks pregnancy.[35] Vitamin D levels at the lowest quartile were associated with a 1.8-fold increase in eating disorder risk relative to the levels in the highest quartile, even after controlling for sociodemographic factors, body mass index and depressive symptoms (the latter is associated with lower vitamin D levels in adults[36]). However, BN was the only individual disorder in which the risk remained significantly increased when eating disorders were assessed separately.

In general, prenatal maternal risk factors in BN have attracted less study than those of AN. Of these, only maternal smoking,[37] in addition to low vitamin D levels mentioned above, has been shown to increase the risk of offspring BN. In terms of maternal smoking, neither offspring BMI in adulthood, nor variation between childhood and adult BMI, explained the association. In the same study, smoking during pregnancy was not associated with AN in offspring. By contrast, in a recent Swedish register study,[34] smoking had no association with BN.

Markers of Prenatal Risks in Children

Child related markers of prenatal risks associated with future AN include prematurity[9,34,38] and in a single study, smaller than expected birth size (low weight for gestational age) in very preterm (i.e., born $\leq$32 weeks of gestation) female infants.[8] The association between shorter gestational or premature age and AN has been observed both in more severe hospital-treated cases and in outpatient cases derived from Swedish registers[8,9,34] as well as in the population-based Virginian twin sample.[38] Importantly, in the latest Swedish register-study with a large sample size,[34] there was clear dose-response pattern between lower gestational age and higher risk for AN, with a gradient even observed within term (i.e., births at $\geq$37 weeks of gestation). In the twin sample, shorter gestational age was associated with DSM-III AN, but not with broadly defined AN, suggesting that the association may vary as a function of severity.[38] However, twins are generally born earlier than singletons, and the mechanisms underlying prematurity may differ in multiple vs. singleton pregnancies; therefore this information derived from twin samples might not be generalizable to non-twins. In addition, in the latest Swedish register study[34] including both outpatients and inpatients, AN was independently predicted by twin or triplet birth (Hazard Ratio 1.33, 95% CIs 1.15–1.53). On the other hand, in the same study, lower gestational age and prematurity were shown to predict AN also in singletons. An earlier meta-analysis by Krug et al.,[13] which included six studies conducted in non-twin samples, showed a non-significant (OR 1.17, 95% CI 0.91–1.52) association between prematurity and offspring AN risk.

Child related markers of prenatal problems, such as retarded growth[5] and prenatal complications,[38] were associated with higher risk of offspring BN. In the former study,[5] retarded growth was defined as birth weight, birth length and head circumference all below 10th percentile at birth. In the latter twin study,[38] a composite measure of prenatal complications included premature contractions, swelling, high blood pressure, vaginal bleeding, seizures/toxemia, German measles, labor lasting more than 24 h, serious physical injury, other serious illness, any other complication, and any prenatal complication. Birth weight was also examined in the latter study, but no association was observed with BN. Conversely, higher, not lower birth weight for gestational age showed an independent, dose-response association (the higher the weight, the higher the risk) with BN in females in the latest Swedish register study.[34] In contrast to previous findings, prematurity and very low birth weight appeared protective of eating disorder symptoms in a study that tracked prematurely born babies into adulthood.[39]

The Prenatal Effects of Maternal Eating Disorders

Women who suffer from eating disorders during pregnancy have been shown to be at increased risk for prenatal complications (e.g., slow fetal growth and low birth weight in the offspring of females with AN).[40,41] These complications could, in turn, further increase the risk of eating disorders among offspring. Maternal stress has been hypothesized to be one of the key mediating factors (for a comprehensive review, see Micali et al.[42]) by directly influencing fetal behavior and neurodevelopment. The programming of fetal metabolism and the stress regulating system might take place through epigenetic[43] or other routes. The effects of maternal eating disorder are also thought to be mediated through nutritional factors, including undernutrition in women with past or current AN, and alterations in glucose metabolism in women with BN.[42] However, it should be noted that genetic vulnerability can confound the association between maternal prenatal eating disorders and fetal outcomes, as genetic influences[34,44] or maternal eating

disorder diagnosis[34] have usually not been controlled in the studies.

Summary of Prenatal Risk Factors for Eating Disorders

A substantial body of evidence suggests that higher prenatal testosterone exposure increases food intake and masculinizes behavior in offspring. Higher prenatal testosterone might also protect against the development of disordered eating symptoms, although studies are not fully consistent. Studies of 2D:4D ratios have yielded more positive evidence than those examining females from opposite-sex twin pairs. Direct positive evidence for prenatal testosterone effects in twins from opposite-sex pairs is scarce from sources other than the Michigan State University Twin Registry. Ethnic diversity (more common in the Michigan twin study than in other samples) might account for some of the observed differences. On the other hand, supporting data of prenatal testosterone effects (for both 2D:4D and opposite-sex twins) has for the greater part been based on disordered eating symptoms rather than eating disorder diagnoses. It is therefore possible, although perhaps not very likely (because disordered eating and diagnostic eating disorders should be part of the same continuum), that prenatal hormone effects are only important for disordered eating symptoms. More likely, low statistical power contribute to the inconsistent results—studies with broader diagnostic definitions are able to recruit far more participants than those with narrow criteria and this translates into better ability to detect between-group differences. The same is true for dimensional vs. categorical symptom measurements. Even in the meta-analysis,[12] which combined three twin samples, inadequate statistical power might explain negative findings.

Evidence linking prenatal maternal physical states to future eating disorders in the offspring is also conflicting. The association between maternal anemia, diabetes, and pre-eclampsia and offspring AN was shown in one study,[5] but has not been replicated in others.[8,34,45] Utilization of composite measures instead of examination of individual prenatal factors[38,46] has complicated interpretations of results (see also Supporting Information Table 1). Likewise, there is suggestive evidence for the potential importance of maternal infections and maternal vitamin D levels, but replications are lacking. The season of birth effect, shown in some studies of AN and BN, but not replicated in others, may also provide indirect evidence of the significance of infection susceptibility and vitamin D levels in eating disorders. Finally, prematurity has been found to predict later AN in several studies[8,9,34,38]; the effect has been observed in both outpatients and inpatients, and in twins. However, evidence has been somewhat conflicting, with a meta-analysis not supporting an association, and the three Swedish register studies[8,9,34] that did show a prematurity effect were based on partly overlapping samples.

Evidence of maternal smoking as a risk factor for BN is based on one study[37] that failed to control for maternal eating disorders, and was not replicated in another one[34] that had a significantly larger sample, more reliable register-based prospective measures, and control for maternal vulnerability to eating disorders. This latter point is important, since maternal eating disorder symptoms may be associated with smoking and explain the association through genetic transmission mechanisms, as has been shown in maternal smoking/alcohol use and externalizing disorders.[47–49]

Smaller birth size as a risk factor for BN also appears to be based on one study[5] only. Opposite findings, i.e. higher birth weight and increased risk for BN,[34] and fewer eating disorder symptoms among prematurely born very low birth weight ($\leq$1500 g) individuals assessed in adulthood,[39] have been reported. On the other hand, the metabolic programming in prematurely born individuals with very low birth weight may be completely different compared to those with slightly lower birth weights.[39] Research also shows that a neonate's small size for gestational age, i.e., a "thrifty phenotype,"[50] predisposes to depression,[51] higher neuroticism[52] and early metabolic programming for a tendency toward weight gain, impaired glucose tolerance and type 2 diabetes.[53,54] All of these factors have been associated with BN and BED in the past,[55–57] suggesting that the "thrifty phenotype" hypothesis might be important to investigate in BN and BED. Importantly, infant's higher birth weight is shown to be associated with risk similar to those pertaining to thrifty phenotype,[58] which might explain some of the seemingly contrasting findings.

Perinatal Risk Factors for Eating Disorders

Markers of Perinatal Risks in Children

Child related perinatal problems associated with increased risk of later AN include placental infarctions, early cardiac problems (such as congenital

cardiomyopathy), neonatal hyporeactivity and hypotonia, hypothermia, tremors, and need of oxygen administration immediately after the birth.[5] These findings were based on data including both patients from The Eating Disorders Unit of Padua, Italy and a population-based sample from the same area. In Swedish register data that included only inpatients, cephalhematoma, mediated through forceps delivery or vacuum extraction, was associated with future AN[8,9]; however, in a reanalysis in a significantly larger, extended sample,[34] cephalhaematoma was no longer associated with AN or any other eating disorder, even in a separate analysis of inpatients and outpatients. Infant feeding problems (defined as frequent feeding/gastroenterological problems at age $\leq$6 months) were associated with increased risk of AN in the 1970s British Cohort Study.[45] The same study found no association between AN and the need for oxygen administration or ventilation following birth.

Of perinatal child related risk indicators for BN, placental infarction, neonate hyporeactivity, and early feeding problems[5] have been implicated, but two other studies[34,38] have failed to replicate these findings.

The Effects of Obstetric Complications

An increasing number of obstetric complications (1–5 complications: OR 1.8, 95% CI 1.1–3.2; $>$5 complications: OR 3.3, 95% CI 1.6–6.6) has been reported to increase the risk of AN.[5] An increasing number of complications also predicted lower age of onset of AN in the same study. Single obstetric complications associated with AN included umbilical cord wrapped around the neck,[5] premature rupture of membranes, and breech delivery.[9] In a recent Swedish register study[34] including outpatients and inpatients, "other birth trauma" (involving head/neck/central nervous system, but not cephalhaematoma) and Cesarian section, but not premature rupture of membranes, were associated with later AN. However, in the same study, within-family analyses suggested that the associations could at least partly be explained by maternal vulnerability, and not by the independent effects of birth trauma or Cesarian section. Nonetheless, in a recent review and meta-analysis,[13] the authors could not confirm an association between these and other obstetric complications and AN, BN or disordered eating symptoms. In the same review paper, a separate meta-analysis of a vaginal instrumental delivery and offspring AN yielded nonsignificant results (OR 1.6, 95% CI 0.7–1.7). No obstetric complications have been associated with BN, although the definition of "obstetric complications" has varied between the studies, e.g., placental infarction, hyporeactivity or composite of perinatal complications including obstetric factors were defined as obstetric complications in the studies by Favaro et al.[5] and Foley et al.[38] (reviewed above).

The Perinatal Effects of Maternal Eating Disorders

As noted previously, the offspring of mothers with eating disorders may be exposed to a double disadvantage, wherein they may have inherited genes that increase risk for eating disorders as well as the environments (in part shaped by the parental genotype) that increase the likelihood of expression of the underlying risk genotype in the child ("cycle of risk").[59] A parent who suffers from an eating disorder may extend the excessive eating restrictions to a child; some reports suggest that mothers suffering from AN may not recognize the child's hunger and may also excessively restrict child's eating.[60] In a case-control study of feeding practices of women with past or present eating disorders, female infants at 2 and 4 weeks of age had higher rates of suckling and were weaned from the bottle later and with more difficulties compared to controls.[61] Women with high body shape and weight concerns were also found to be less likely to breastfeed their infants,[62] which has been associated with adverse child outcomes.[63, 64]

Summary of Perinatal Risk Factors for Eating Disorders

Of the studies with positive findings of perinatal factors and eating disorders, two were based on largely overlapping Swedish register data that included only inpatients with AN, whereas the third and most recent register study included both inpatients and outpatients from several eating disorder groups (and had partly overlapping data with the two former studies). The study by Favaro et al.[5] included a diverse sample with both outpatients and general population participants, whereas the 1970 British Cohort Study[45] comprised a population-based sample and examined quite different prenatal/perinatal variables, rendering comparisons difficult. However, for variables strictly comparable across studies (such as the need for oxygen and ventilation at birth), no associations were found. A lack of association with perinatal factors has also been shown in several other studies. For example, in the twin study by Foley et al.,[38] no significant association was found between a composite measure of perinatal risk factors and

AN, BN or their broad forms. Feingold et al.[46] also failed to observe associations between a composite measure of perinatal complications and eating disorder symptoms (assessed with the eating disorder inventory and eating attitude test) in a cohort born prematurily. Finally, a meta-analysis by Krug et al.[13] found no association between instrumental delivery and risk for AN.

Of the above mentioned studies, only the most recent Swedish register study controlled for the genetic effects, although genetic liability for eating disorders is significant,[65] and women with eating disorders tend to have increased risk for prenatal and perinatal complications.[40–42] In the Swedish study, evidence for maternal-level confounding for AN was found for several factors including maternal smoking, Caesarian delivery, a composite of other birth trauma, and the protective effects of higher maternal weight. By contrast, using a discordant sibling design that examined healthy sisters of women with AN, Favaro et al.[44] found no evidence for confounding by familial risk. These authors explored whether the risk for a composite of perinatal/obstetric complications was a consequence of the genetic vulnerability for AN, or whether obstetric complications increase the risk of AN independently of, or in interaction with, the disorder's genetic liability. Elevated rates of complications in unaffected sisters of patients with AN was not found, suggesting that perinatal complications are an independent risk factor that may interact with, but are not caused by, familial risk factors for AN.

Discussion

Based on the existing evidence, the overall effect of prenatal/perinatal factors to the total risk of eating disorders and disordered eating appears to be relatively small. One study reported an attributable risk of prenatal or perinatal factors to the total risk of AN in hospital treated cases as 3.6%. If there are early prenatal/perinatal risk factors, it is likely that they operate in conjunction with other individual or environmental factors, and depending on the combination of the risk factors, the outcome varies. For example, hypoxia during pregnancy or delivery can damage fetal brain tissue and predispose to several different neuropsychological disorders besides AN.[66,67] Maternal smoking, low vitamin D, and retarded or accelerated fetal growth shown sporadically in BN also appear to be associated with multiple other psychiatric and somatic outcomes in offspring.[68–70]

The small effects of prenatal sex-hormones may be hard to detect when examining low base rate disorders such as AN and BN, which may explain the lack of association. Nevertheless, the small effect sizes question how much clinical significance prenatal sex hormone have on disordered eating and highlight the need to further establish the effect size. Future studies should also examine whether the effects are larger when interacting with other risk factors.

Evidence derived from a few independent data sets[8,29] suggest that early insults to the central nervous system and subsequent subtle brain damage may contribute to the onset of AN at least in a subpopulation of individuals. Italian data[44] further support an independent role of perinatal factors (including composite measure of clearly harmful pregnancy and delivery complications, hypoxia-related neonatal complications, and dysmaturity, i.e./signs of retarded fetal growth), and the latest Swedish register data[34] supports an independent role of multiple births and lower gestational age as risk factors for AN. In both of these studies, the elevated risk for these specific factors was not caused by genetic risk factors for AN shared by the mother and the offspring.

Negative findings, particularly from the meta-analysis,[13] should also be taken into account. However, negative findings might reflect power issues[5,45] overall small effect sizes of these risk factors, or varying definitions of prenatal/perinatal factors. Furthermore, it is possible that early risk factors pertain only to a sub-population of individuals with AN.

Prenatal/perinatal risk factors of BN have attracted less study.[5,34,35,37] In addition to the study by Favaro et al.,[5] where restricted growth and smaller birth size predicted later BN, another line of research suggests that the newborn's slightly smaller than normal size for gestational age[71] predisposes to early metabolic programming towards range of vulnerabilities[72,73] relevant in BN. A seemingly contrary finding of the higher birth weight predicting BN from the Swedish data,[34] may reflect the significance of the early metabolic programming towards tendency to weight gain,[58] which is also relevant in BN. These factors' role in BN should be investigated further in the future.

To overcome the major obstacle related to statistical power in earlier studies, it would be important to use large data sets, perhaps by combining different samples. With large combined data sets, future

studies in the field could also focus on interactions between early risks, protective factors, and various environmental and genetic influences. Research on potential sex-specific exposures in males with eating disorders could provide hints for general mechanisms of these disorders, since males appear to demand more risk factors than females in order to develop eating disorders.[74] Different risks between sexes, such as the effect of maternal weight in the Swedish register study,[34] provide intriguing clues about future lines of research. Because psychiatric disorders tend to overlap and share part of their underlying etiology,[75, 76] evidence from several other disorders such as ADHD, major depression, autism and schizophrenia[1,3,77] suggest that research on prenatal infections and maternal immune response would be worth pursuing in eating disorders.

When planning future studies, it should be noted that prenatal risk factors are not necessarily causal.[2,34,47,78,79] Risks such as maternal stress and poorer overall health are also associated with adverse postnatal factors, like parental psychological problems. It is therefore important that prenatal and postnatal developmental effects could be teased out with future study designs.

Another central caveat is the genetic liability for eating disorders that ranges from 30% up to 80%.[65] Genetic influences can confound the outcomes if maternal vulnerability is left uncontrolled, and so far, only two studies[38,44] in eating disorders have taken genetic confounding into account. Another type of approach would be to control for maternal eating disorder diagnosis or other parental psychopathology and social factors,[37] which is obviously useful. Nevertheless, these methods do not tackle unknown and unmeasured confounding. It is likely that only a fraction of those with higher vulnerability for eating disorders have prominent symptoms and have been diagnosed with an eating disorder. Consequently, simply controlling for eating disorder diagnoses is likely to address only the tip of the iceberg. Moreover, studies of other psychiatric disorders have shown that statistical methods are not necessarily able to sufficiently address genetic confounding. As an example, when investigating the effects of maternal smoking on offspring ADHD, Thapar et al.[47] separated prenatal environmental effects from inherited ones with a design based on assisted reproductive technologies with offspring both genetically unrelated and related to the mother; i.e., the sample included mothers who had been pregnant with their biological offspring as well as with offspring conceived with donated egg cells. The authors found that for ADHD symptoms, the magnitude of association was significantly higher in the genetically related mothers and offspring than in the genetically unrelated ones. Likewise, using a co-twin control method, Maughan et al.[69] examined the effects of prenatal smoking on early childhood conduct problems and found that around half of the association was attributable to correlated genetic effects, which means that the same genes contributing to maternal smoking during pregnancy are also related to increased conduct problem risk. Therefore the studies that do not control for genetic risk are inflating the degree of effect from the smoking alone. Given these findings, most association between prenatal and perinatal factors and later eating disorders in offspring should be interpreted with caution in terms of causality. Limitations of traditional studies could be avoided by using genetically sensitive designs, such as sibling designs, twin designs such as the co-twin control method,[80] and novel designs including mothers with genetically unrelated offspring. These designs are difficult to implement, but would yield stronger data that can speak to the independent effects of prenatal and perinatal factors on eating disorder risk.

The authors thank Dr. Klump for extremely valuable comments concerning this manuscript.

References

1. Ratnayake U, Quinn T, Walker DW, Dickinson H. Cytokines and the neurodevelopmental basis of mental illness. Front Neurosci 2013;7:180.
2. Gaysina D, Fergusson DM, Leve LD, Horwood J, Reiss D, Shaw DS, et al. Maternal smoking during pregnancy and offspring conduct problems: Evidence from 3 independent genetically sensitive research designs. JAMA Psychiatry 2013;70:956–963.
3. Rana SA, Aavani T, Pittman QJ. Sex effects on neurodevelopmental outcomes of innate immune activation during prenatal and neonatal life. Horm Behav 2012;62:228–236.
4. Suvisaari J, Mantere O. Inflammation theories in psychotic disorders: A critical review. Infect Disord Drug Targets 2013;13:59–70.
5. Favaro A, Tenconi E, Santonastaso P. Perinatal factors and the risk of developing anorexia nervosa and bulimia nervosa. Arch Gen Psychiatry 2006;63:82–88.
6. Webster's New World™ Medical Dictionary, 3rd ed. Wiley, 2008.
7. Kay DW, Schapira K, Brandon S. Early factors in anorexia nervosa compared with non-anorexic groups. A preliminary report with a discussion of methodology. J Psychosom Res 1967;11:133–139.
8. Cnattingius S, Hultman CM, Dahl M, Sparén P. Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. Arch Gen Psychiatry 1999;56:634–638.
9. Lindberg L, Hjern A. Risk factors for anorexia nervosa: A national cohort study. Int J Eat Disord 2003;34:397–408.
10. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, McKeague IW, Sundvall J, Surcel HM. Elevated maternal C-reactive protein and autism in a national birth cohort. Mol Psychiatry 2014;19:259–264.
11. DiCicco-Bloom E, Lord C, Zwaigenbaum L, Courchesne E, Dager SR, Schmitz C, et al. The developmental neurobiology of autism spectrum disorders. J Neurosci 2006;26:6897–6906.

12. Lydecker JA, Pisetsky EM, Mitchell KS, Thornton LM, Kendler KS, Reichborn-Kjennerud T, et al. Association between co-twin sex and eating disorders in opposite sex twin pairs: Evaluations in North American, Norwegian, and Swedish samples. J Psychosom Res 2012;72:73–77.
13. Krug I, Taborelli E, Sallis H, Treasure J, Micali N. A systematic review of obstetric complications as risk factors for eating disorder and a meta-analysis of delivery method and prematurity. Physiol Behav 2013;109:51–62.
14. Wade GN. Gonadal hormones and behavioral regulation of body weight. Physiol Behav 1972;8:523–534.
15. Cohen-Bendahan CC, Buitelaar JK, van Goozen SH, Cohen-Kettenis PT. Prenatal exposure to testosterone and functional cerebral lateralization: A study in same-sex and opposite-sex twin girls. Psychoneuroendocrinology 2004;29:911–916.
16. Cohen-Bendahan CC, Buitelaar JK, van Goozen SH, Orlebeke JF, Cohen-Kettenis PT. Is there an effect of prenatal testosterone on aggression and other behavioural traits? A study comparing same-sex and opposite-sex twin girls. Horm Behav 2005;47:230–237.
17. Resnick SM, Gottesman II, McGue M. Sensation seeking in opposite-sex twins: An effect of prenatal hormones? Behav Genet 1993;23:323–329.
18. Vuoksimaa E, Kaprio J, Kremen WS, Hokkanen L, Viken RJ, Tuulio-Henriksson A, et al. Having a male co-twin masculinizes mental rotation performance in females. Psychol Sci 2010;21:1069–1071.
19. Berenbaum SA, Bryk KK, Nowak N, Quigley CA, Moffat S. Fingers as a marker of prenatal androgen exposure. Endocrinology 2009;150:5119–5124.
20. Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: A predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 1998;13:3000–3004.
21. Klump KL, Gobrogge KL, Perkins PS, Thorne D, Sisk CL, Breedlove SM. Preliminary evidence that gonadal hormones organize and activate disordered eating. Psychol Med 2006;36:539–546.
22. Smith AR, Hawkeswood SE, Joiner TE. The measure of a man: Associations between digit ratio and disordered eating in males. Int J Eat Disord 2010; 43:543–548.
23. Kothari R, Gafton J, Treasure J, Micali N. 2D:4D Ratio in children at familial high-risk for eating disorders: The role of prenatal testosterone exposure. Am J Hum Biol 2014;26:176–182.
24. Quinton SJ, Smith AR, Joiner T. The 2 to 4 digit ratio (2D:4D) and eating disorder diagnosis in women. Pers Individ Dif 2011;51:402–405.
25. Culbert KM, Breedlove SM, Burt SA, Klump KL. Prenatal hormone exposure and risk for eating disorders: A comparison of opposite-sex and same-sex twins. Arch Gen Psychiatry 2008;65:329–336.
26. Culbert KM, Breedlove SM, Sisk CL, Burt SA, Klump KL. The emergence of sex differences in risk for disordered eating attitudes during puberty: A role for prenatal testosterone exposure. J Abnorm Psychol 2013;122:420–432.
27. Baker JH, Lichtenstein P, Kendler KS. Intrauterine testosterone exposure and risk for disordered eating. Br J Psychiatry 2009;194:375–376.
28. Raevuori A, Kaprio J, Hoek HW, Sihvola E, Rissanen A, Keski-Rahkonen A. Anorexia and bulimia nervosa in same-sex and opposite-sex twins: Lack of association with twin type in a nationwide study of Finnish twins. Am J Psychiatry 2008;165:1604–1610.
29. Favaro A, Tenconi E, Ceschin L, Zanetti T, Bosello R, Santonastaso P. In utero exposure to virus infections and the risk of developing anorexia nervosa. Psychol Med 2011;41:2193–2199.
30. Winje E, Willoughby K, Lask B. Season of birth bias in eating disorders—Fact or fiction? Int J Eat Disord 2008;41:479–490.
31. Silva DR, Viana VP, Müller AM, Livi FP, Dalcin Pde T. Respiratory viral infections and effects of meteorological parameters and air pollution in adults with respiratory symptoms admitted to the emergency room. Influenza Other Respir Viruses 2014;8:42–52.
32. Winje E, Torgalsbøen AK, Brunborg C, Lask B. Season of birth bias and anorexia nervosa: Results from an international collaboration. Int J Eat Disord 2013;46:340–345.
33. Winje E, Torgalsbøen AK, Brunborg C, Lask B. Season of birth bias and bulimia nervosa—Results from a multi-centre collaboration. Eur Eat Disord Rev 2013;21:170–174.
34. Goodman A, Heshmati A, Malki N, Koupil I. Associations between birth characteristics and eating disorders across the life course: Findings from 2 million males and females born in Sweden, 1975–1998. Am J Epidemiol 2014; 179:852–863.
35. Allen KL, Byrne SM, Kusel MM, Hart PH, Whitehouse AJ. Maternal vitamin D levels during pregnancy and offspring eating disorder risk in adolescence. Int J Eat Disord 2013;46:669–676.
36. Ju SY, Lee YJ, Jeong SN. Serum 25-hydroxyvitamin D levels and the risk of depression: A systematic review and meta-analysis. J Nutr Health Aging 2013;17:447–455.
37. Montgomery SM, Ehlin A, Ekbom A. Smoking during pregnancy and bulimia nervosa in offspring. J Perinat Med 2005;33:206–211.
38. Foley DL, Thacker LR II, Aggen SH, Neale MC, Kendler KS. Pregnancy and perinatal complications associated with risks for common psychiatric disorders in a population-based sample of female twins. Am J Med Genet 2001; 105:426–431.
39. Wehkalampi K, Hovi P, Strang-Karlsson S, Räikkönen K, Pesonen AK, Heinonen K, et al. Reduced body size and shape-related symptoms in young adults born preterm with very low birth weight: Helsinki study of very low birth weight adults. J Pediatr 2010;157:421–427.
40. Linna MS, Raevuori A, Haukka J, Suvisaari JM, Suokas JT, Gissler M. Pregnancy, obstetric and perinatal health outcomes in eating disorders. Am J Obstet Gynecol 2014, Apr 3. [Epub ahead of print].
41. Solmi F, Sallis H, Stahl D, Treasure J, Micali N. Low birth weight in the offspring of women with anorexia nervosa. Epidemiol Rev 2014;36:49–56.
42. Micali N, Treasure J. Biological effects of a maternal ED on pregnancy and foetal development: A review. Eur Eat Disord Rev 2009;17:448–454.
43. Pjetri E, Schmidt U, Kas MJ, Campbell IC. Epigenetics and eating disorders. Curr Opin Clin Nutr Metab Care 2012;15:330–335.
44. Favaro A, Tenconi E, Bosello R, Degortes D, Santonastaso P. Perinatal complications in unaffected sisters of anorexia nervosa patients: Testing a covariation model between genetic and environmental factors. Eur Arch Psychiatry Clin Neurosci 2011;261:391–396.
45. Nicholls DE, Viner RM. Childhood risk factors for lifetime anorexia nervosa by age 30 years in a national birth cohort. J Am Acad Child Adolesc Psychiatry 2009;48:791–799.
46. Feingold E, Sheir-Neiss G, Melnychuk J, Bachrach S, Paul D. Eating disorder symptomatology is not associated with pregnancy and perinatal complications in a cohort of adolescents who were born preterm. Int J Eat Disord 2002;31:202–209.
47. Thapar A, Rice F, Hay D, Boivin J, Langley K, van den Bree M, et al. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: Evidence from a novel design. Biol Psychiatry 2009;66:722–727.
48. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, et al. Smoking during pregnancy and offspring externalizing problems: An exploration of genetic and environmental confounds. Dev Psychopathol 2008;20:139–164.
49. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, et al. Maternal alcohol use disorder and offspring ADHD: Disentangling genetic and environmental effects using a children-of-twins design. Psychol Med 2006;36:1461–1471.
50. Barker DJ, Lampl M. Commentary: The meaning of thrift. Int J Epidemiol 2013;42:1229–1230.
51. Räikkönen K, Pesonen AK, Heinonen K, Kajantie E, Hovi P, Järvenpää AL, et al. Depression in young adults with very low birth weight: The Helsinki study of very low-birth-weight adults. Arch Gen Psychiatry 2008;65:290–296.
52. Lahti M, Räikkönen K, Lemola S, Lahti J, Heinonen K, Kajantie E, et al. Trajectories of physical growth and personality dimensions of the Five-Factor Model. J Pers Soc Psychol 2013;105:154–169.
53. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005;353:1802–1809.
54. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. Int J Epidemiol 2013;42:1215–1222.

55. Fairburn CG, Welch SL, Doll HA, Davies B, O'Connor ME. Risk factors for bulimia nervosa: A community-based case-control study. Arch Gen Psychiatry 1997;54:509–517.
56. Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. Risk factors for binge eating disorder: A community-based, case-control study. Arch Gen Psychiatry 1998;55:425–432.
57. de Jonge P, Alonso J, Stein DJ, Kiejna A, Aguilar-Gaxiola S, Viana MC, et al. Associations between DSM-IV mental disorders and diabetes mellitus: A role for impulse control disorders and depression. Diabetologia 2014;57:699–709.
58. Skilton MR, Siitonen N, Würtz P, Viikari JS, Juonala M, Seppälä I, et al. High birth weight is associated with obesity and increased carotid wall thickness in young adults: The cardiovascular risk in young Finns study. Arterioscler Thromb Vasc Biol 2014;34:1064–1068.
59. Bulik CM, Reba L, Siega-Riz AM, Reichborn-Kjennerud T. Anorexia nervosa: Definition, epidemiology, and cycle of risk. Int J Eat Disord 2005;37: S2–S9.
60. Park RJ, Senior R, Stein A. The offspring of mothers with eating disorders. Eur Child Adolesc Psychiatry 2003;12 (Suppl 1):I110–I119.
61. Agras S, Hammer L, McNicholas F. A prospective study of the influence of eating-disordered mothers on their children. Int J Eat Disord 1999;25:253–262.
62. Foster SF, Slade P, Wilson K. Body image, maternal fetal attachment and breastfeeding. J Psychosom Res 1996;4:181–184.
63. Liu J, Leung P, Yang A. Breastfeeding and active bonding protects against children's internalizing behavior problems. Nutrients 2013;6:76–89.
64. Saki Malehi A, Hajizadeh E, Ahmadi K, Kholdi N. Modeling the recurrent failure to thrive in less than two-year children: Recurrent events survival analysis. J Res Health Sci 2014;14:96–99.
65. Thornton LM, Mazzeo SE, Bulik CM. The heritability of eating disorders: Methods and current findings. Curr Top Behav Neurosci 2011;6:141–156.
66. Goldstein JM, Seidman LJ, Buka SL, Horton NJ, Donatelli JL, Rieder RO, et al. Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. Schizophr Bull 2000;26:323–334.
67. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: Comprehensive meta-analysis. Br J Psychiatry 2009;195:7–14.
68. Zosky GR, Hart PH, Whitehouse AJ, Kusel MM, Ang W, Foong RE, et al. Vitamin D deficiency at 16–20 weeks gestation is associated with impaired lung function and asthma at 6 years of age. Ann Am Thorac Soc 2014;11:571–577.
69. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal smoking and early childhood conduct problems: Testing genetic and environmental explanations of the association. Arch Gen Psychiatry 2004;61:836–843.
70. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005;353:1802–1809.
71. Barker DJ, Lampl M. Commentary: The meaning of thrift. Int J Epidemiol 2013;42:1229–1230.
72. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005;353:1802–1809.
73. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. Int J Epidemiol 2013;42:1215–1222.
74. Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Males with anorexia nervosa: A controlled study of eating disorders in first-degree relatives. Int J Eat Disord 2001;29:263–269.
75. Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington HL, Israeli S, et al. The p Factor: One general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2013;14:1–19.
76. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 2013;45:984–994.
77. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev Neurobiol 2012;72:1272–1276.
78. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, et al. Smoking during pregnancy and offspring externalizing problems: An exploration of genetic and environmental confounds. Dev Psychopathol 2008;20:139–164.
79. Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, et al. Maternal alcohol use disorder and offspring ADHD: Disentangling genetic and environmental effects using a children-of-twins design. Psychol Med 2006;36:1461–1471.
80. Kendler KS, Myers J, Damaj MI, Chen X. Early smoking onset and risk for subsequent nicotine dependence: A monozygotic co-twin control study. Am J Psychiatry 2013;170:408–413.