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Association between Co-Twin Sex and Eating Disorders in Opposite Sex Twin Pairs: Evaluations in North American, Norwegian, and Swedish Samples

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Abstract

Objective—These three studies examined the hypothesis that prenatal exposure to sex hormones influences twins' risk for eating disorders based on co-twin sex, such that individuals with a female co-twin would be more likely than individuals with a male co-twin to meet diagnostic criteria for an eating disorder.

Methods—Male and female twins from the United States (*N*=2,607), Norway (*N*=2,796) and Sweden (*N*=16,458) with known co-twin sex and zygosity were assessed for eating disorders.

Results—In the U.S. and Swedish samples, sex was significantly associated with eating disorder diagnoses, and although co-twin sex was not associated with eating disorders overall, it was associated with broadly defined bulimia nervosa in the Swedish sample. The effects for bulimia

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were not sustained when monozygotic twins were excluded, suggesting that the effects of prenatal sex hormones play a minor role in influencing eating disorders. Sex and co-twin sex were not associated with eating disorders in the Norwegian sample.

Conclusion—The prenatal sex hormone hypothesis, which proposes that prenatal hormone exposure is associated with later eating disorder symptomatology, was not supported in these three population-based twin samples.

Keywords

eating disorders; estrogen; opposite sex twin pairs; prenatal hormone exposure; testosterone; twin study

Introduction

The significant preponderance of anorexia (AN) and bulimia nervosa (BN) in women compared with men suggests that sex is a significant risk factor for these disorders. In the United States, AN affects 0.9% of women and 0.3% of men; BN affects 1.5% of women and 0.5% of men (1). Both environmental (e.g., thin-ideal internalization) (2) and biological (e.g., estrogen gene activation) (3, 4) hypotheses have been proposed to explain this discrepancy. Exposure to sex hormones prenatally, including estrogen, testosterone and progesterone, might play an important role in the development of these conditions (3–9). These hormones might influence future behavior during prenatal development (i.e., organizational effect) (10), or elicit behaviors at the time of hormone exposure, such as puberty (i.e., activational effect) (11). Twin studies offer a unique opportunity to investigate organizational effects of prenatal sex hormones on eating behavior by estimating prenatal sex hormone exposure from twin pair sex composition. Specifically, it is hypothesized that individuals with a female co-twin are more vulnerable to eating disorders because of prenatal exposure to additional estrogen, whereas those with a male co-twin have lower risk for these conditions because of prenatal exposure to testosterone (12, 13).

In terms of organizational effects, direct research on prenatal levels of sex hormones and their relation to adult behavior presents ethical and practical challenges. Therefore, proxies for measuring prenatal exposure to hormones have been used in human studies. One proxy is the sex composition of a twin pair. Among human twins, females sharing a prenatal environment with male co-twins are more similar to males in cerebral lateralization (14), sensation seeking, rule-breaking (15), and social attitudes (15). These similarities provide evidence of the organizational effects of prenatal hormone exposure. Finger length ratio, also a proxy for prenatal testosterone exposure, is negatively associated with disordered eating (3, 9).

Evidence for activational effects of prenatal estrogen are seen in the association between developmental stage and age of eating disorder onset. The peak age of eating disorder onset is typically around puberty (3, 12), when estrogen and progesterone levels increase substantially in girls. For example, in female singletons, binge eating is positively related to increased progesterone and decreased estradiol associated with menstrual cycle timing (5, 7). Further, heritability of disordered eating characteristics (e.g., weight preoccupation, body dissatisfaction), which are minimal pre-pubertally, increase to account for approximately 50% of the variance observed post-pubertally (4).

Animal models support both organizational and activational effects of hormones. Studies on multiple births in rats, an animal model for prenatal sex hormone exposure, have found that uterine position influences the masculinization of behavior after birth (16), suggesting that intrauterine environment facilitates organizational effects of hormones. Further, in female

rats, perinatal testosterone exposure was positively related to increased caloric intake and higher body mass as adults (17), also suggesting organizational effects of testosterone. Evidence of activational effects comes from findings that adult female rats with higher circulating estrogen levels showed decreased caloric intake and increased exercise compared with female rats with lower estrogen levels (18, 19). Early exposure to androgens makes the brain less responsive to estrogen as it matures (10), indicating that organizational and activational effects are linked.

Several human studies have investigated the association between prenatal sex hormone exposure and disordered eating, with somewhat inconsistent results. Two recent investigations found no effect of co-twin sex on the likelihood that the other twin had an eating disorder (20, 21). Specifically, Raevuori and colleagues (21) found no difference in the prevalence of broadly defined AN or BN between opposite sex (OS) and same sex (SS) female twins in the Finnish Twin Registry. Results remained non-significant after grouping twins by zygosity and twin pair sex composition. Similar results were obtained in a study involving adolescents from the Swedish Twin Study of Child and Adolescent Development (20). However, three studies (3, 9, 13) did identify an association between prenatal hormone exposure and disordered eating, using finger length (3, 9) and co-twin sex (13) as proxies for prenatal hormone exposure. Of these, Culbert and colleagues (13) controlled for the effects of socialization by comparing disordered eating in OS female twins with female non-twins having at least one male sibling (13). OS female twins reported less disordered eating than female non-twins, suggesting the difference is not simply related to having a male sibling, but rather to prenatal sex hormone exposure. However, this result did not control for potential confounds such as sibling age, birth order, or the presence of other siblings of either sex, and did not include non-twins with sisters as a comparison group.

Zygosity is a confounding factor in studies using co-twin sex as a variable. Although OS twin pairs are exclusively dizygotic (DZ), SS twin pairs can be either DZ or monozygotic (MZ). The study that found significantly higher disordered eating in SS female twins (13) also investigated whether zygosity was associated with this risk. SS female twins remained at a higher risk for eating disorders, even when MZ twin pairs were excluded. However, more research is needed to establish whether twins with a female co-twin are at a higher risk independent of genetic effects, given that other studies (20, 21) have not found a link between co-twin sex and eating disorder symptomatology after excluding MZ twins from their analyses.

Another possible explanation for inconsistencies in earlier research is the use of different measures of disordered eating. The study that found a positive effect of co-twin sex on disordered eating (13) and the study that found a negative association of finger length with disordered eating (3) used the Minnesota Eating Behavior Survey (MEBS). The male study that found a negative association of finger length with disordered eating (9) used a male-specific measure and the Eating Disorder Examination Questionnaire, whereas studies that did not support the prenatal sex hormone hypothesis used eating disorder diagnostic status (21), or the Eating Disorder Inventory (EDI) (20, 21). Compared with other eating disorder measures, the MEBS places greater emphasis on compensatory behaviors and includes these behaviors on a subscale distinct from that measuring binge eating (22). Notably, continuous measures (3, 9, 13, 20) assessed symptomatology at the time of the study, whereas eating disorder diagnostic status was over the lifetime (21).

Inconsistencies might also be related to sample differences. Studies that found an effect of co-twin sex used samples from the Midwestern region of the United States, whereas those that did not used samples from Sweden (20) and Finland (21). The current paper includes three additional registries that include eating disorder diagnostic variables from three

independent samples of male and female twins—one from the Mid-Atlantic region of the United States (Study 1), one from Norway (Study 2), and one from Sweden (Study 3). Thus, these studies extend previous work examining the prenatal sex hormone exposure hypothesis by including new geographical regions and men.

Method

Study 1: Mid-Atlantic U.S. Sample

Participants—This sample comes from a project utilizing the population-based Virginia Twin Registry, now the Mid-Atlantic Twin Registry (MATR), which was approved by Virginia Commonwealth University's Institutional Review Board. A description of the sample and recruitment was published previously (23).

Participants were OS (n=481) and SS (n=1022) female twins (M_{age}=40.44, SD=8.34). Of the SS females, 614 were MZ, and 408 were DZ. OS (n=317) and SS (n=787) male twins were also included (M_{age}=42.33, SD=9.19). Of the SS males, 492 were MZ and 295 were DZ. Participants with more than one co-sibling were excluded because prenatal hormone exposure cannot be reliably estimated in higher-order multiples. Lifetime diagnoses of eating disorders by sex, co-twin sex (i.e., OS or SS) and zygosity, as well as percentages of all participants within that group, are included in Table 1.

Assessment of Eating Disorder Symptomatology

Self-Report Eating Disorder Items: Items assessing eating disorder diagnostic criteria were adapted from the Structured Clinical Interview for *DSM-IV* (SCID) (24) to be consistent with the self-report format of the questionnaire, and assessed all criteria from the *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)* (25) for AN, BN and binge eating disorder (BED) over the participant's lifetime. Several types of response options were used for the items: the majority were Likert-type, but free write-in (frequency of binges per month and duration of amenorrhea), and yes/no (ever having binged, binge characteristics, and lack of compensatory behaviors for BED) were also used. Because of the relative rarity of threshold ("narrow") eating disorders, we also included individuals meeting subthreshold ("broad") criteria. Diagnostic algorithms, described in detail elsewhere (26), were constructed for narrow and broad versions of each disorder from items associated with each criterion.

Study 2: Norway Sample

Participants—This sample comes from the Norwegian Institute of Public Health Twin Panel (NIPHTP). Study methods were approved by The Norwegian Data Inspectorate and the Regional Ethical Committee. A description of the sample and recruitment method was published previously (27).

This sample includes OS (n=345) and SS (n=1430) female twins (M_{age}=28.19, SD=3.89). Of the SS females, 900 were MZ, and 530 were DZ. OS (n=341) and SS (n=680) male twins (M_{age}=28.26, SD=3.82) were also included. Of the SS males, 445 were MZ and 235 were DZ. Higher-order multiples were not included in this sample. Frequencies of diagnoses by sex, co-twin sex and zygosity can be found in Table 1.

Assessment of Eating Disorder Diagnoses

Eating Disorder Items from Interview: Eating disorder items were included in the computerized Norwegian version of the Munich-Composite International Diagnostic Interview (28), a structured interview for the assessment of *DSM-IV* diagnoses. Interview

methods are described elsewhere (27). Response options to interview items were yes/no. AN and BN diagnoses were based on responses to these items.

Study 3: Sweden Sample

Participants—Participants in this sample are from the Swedish Twin study of Adults: Genes and Environment (STAGE) study of the Swedish Twin Registry (STR), a large population-based prospective sample of Swedish twins born 1959–1985 (29). Data were collected in 2005 using web-based questionnaires or telephone interviews. The Regional Ethics Committee at the Karolinksa Institutet and the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill approved this study. A detailed description of the study design is described elsewhere (30, 31), including algorithms for diagnostic variables (32).

This study includes OS (n=2433) and SS (n=7000) female twins (M_{age}=33.46, SD=7.71). Of the SS females, 4099 were MZ, and 2901 were DZ. OS (n=2423) and SS (n=4602) male twins (M_{age}=33.36, SD=7.69) were also included. Of the SS males, 2684 were MZ and 1918 were DZ. Frequencies of diagnoses within samples and grouped by sex, co-twin sex and zygosity can be found in Table 1. Higher-order multiples were not included in this sample.

Assessment of Eating Disorder Diagnoses—Lifetime history of narrowly and broadly defined AN and BN were assessed using an expanded, on-line SCID-based instrument. Response options were yes/no as well as Likert-type. *DSM-IV* criteria were used to develop algorithms for narrow and broad definitions of AN and BN based on whether they met full criteria (narrow) or subthreshold criteria (broad) (25, 32).

Statistical Analyses: All Samples

In all three samples, hierarchical linear modeling (HLM) compared SS and OS twins on eating disorder diagnoses. HLM is an ideal method for analyzing twin data because it allows for nested data analysis, accounting for the correlated nature of twin data. Models were estimated using the entire sample, and then excluding MZ twins, to be consistent with prior studies and to reduce potential genetic confounds, as MZ twins with an eating disorder are more likely to have a co-twin with an eating disorder (for a discussion of heritability of eating disorders, see 32). Within each sample, frequencies of AN, BN, and BED were similar in MZ and DZ groups (Table 1). Because subsamples of individuals meeting criteria for some specific eating disorders were small, consistent with low prevalence disorders (1), some models did not have sufficient power to run without MZ twins.

To analyze all three samples, we applied a two-level hierarchical model to assess the effects of sex, co-twin sex, sex by co-twin sex interaction, and age on disordered eating. Individual twins were the first-level unit, nested inside the “family” variable shared by co-twins. The interaction assesses whether co-twin sex matters differentially depending on the sex of the twin, such as whether having a male co-twin only matters when the twin is female. The prenatal hormone hypothesis would be supported if co-twin sex were associated with eating disorders, as co-twin sex is a proxy for prenatal sex hormone exposure. Age and sex were also included as predictors because of their known associations with disordered eating (1). Sex and co-twin sex were coded (*−1=males* and *1=females*), and age was centered prior to running HLM analyses. HLM was implemented through SAS NLMIXED, Version 9.1 (33). Samples were analyzed in the order presented.

Results

Study 1

Sex was the only significant main effect for BN Broad, BN Narrow, BED Broad, and BED Narrow in models estimating the impact of the independent variables on diagnostic outcomes in the Mid-Atlantic U.S. sample (see Table 2). Models of AN Broad and AN Narrow were not analyzed because so few participants met criteria for AN. When MZ twins were excluded from the model, sex remained significant for BED Broad (t=2.48, p=.01) and BED Narrow (t=2.25, p=.03). Because BN is also a low prevalence disorder, we were unable to model BN Broad and BN Narrow when MZ twins were excluded from analyses.

Study 2

Results for the Norwegian twin sample are also presented in Table 2. There were no significant main effects for BN Narrow. We were unable to estimate a model for AN Narrow because so few participants met criteria for this diagnosis. Further, power was insufficient to estimate a model of BN Narrow when MZ twins were excluded.

Study 3

HLM results for twins from Sweden are also presented in Table 2. A significant main effect for sex was observed for lifetime prevalence of AN Broad, BN Narrow, and BN Broad. Because of the low prevalence of AN Narrow, HLM could not be estimated for this diagnosis. For BN Broad, the interaction of sex and co-twin sex was significant. Thus, separate models were applied assessing the association between co-twin sex and BN Broad for men and women. Co-twin sex was not predictive of BN broad in women. No conclusive statement can be made about the relation between co-twin sex and BN broad in men because the model failed to run. Further, when analyses were applied excluding MZ twins, the main effect of co-twin sex (t=−0.95, p=.34) and the interaction effect of sex and co-twin sex were no longer significant (t=−0.84, p=.40). The initial significance of the interaction term observed in the full sample likely reflects that the model could be run in women, but not in men. Again, because of low prevalence, AN Narrow and BN Narrow models excluding MZ twins were unable to be estimated.

Discussion

The purpose of this study was to investigate the validity of the prenatal hormone hypothesis, which proposes that individuals with female co-twins are more likely to have eating disorder symptomatology than individuals with male co-twins because of prenatal exposure to additional estrogen (12, 13). Overall, results did not support the hypothesis that having a female co-twin increases eating disorder risk in either male or female twins. Specifically, no associations for diagnostic variables were found within the U.S., Norwegian, or Swedish samples for either men or women, when models were estimated with DZ twins only. Co-twin sex was initially significant before excluding MZ twins from BN Broad in the Swedish sample. The loss of significance when MZ twins were removed from the analysis is likely due to a loss of statistical power. These findings further highlight the importance of assessing DZ twins separately, whenever possible, to avoid potentially confounding genetic and environmental (i.e., prenatal hormone exposure) factors.

Three prior investigations (13, 20, 21) did analyze DZ twins separately, using the same methodology as the current paper. Only one of these studies (13) found support for the prenatal hormone hypothesis. Thus, the current study contributes to a growing body of research challenging this manifestation of the prenatal sex hormone exposure hypothesis. There are several possible reasons for the inconsistent results across studies.

First, the samples used in the current studies might have differed in some ways from samples used in prior research. For example, Culbert and colleagues' (13) participants were part of the Michigan State Twin Registry; participants were ethnically diverse young adults recruited through advertisements. The sample in the current Study 1 was from the Mid-Atlantic Twin Registry, was entirely White, and was contacted as part of a larger data collection. Participants from Studies 2 and 3 were part of the Norwegian Twin Registry and Swedish Twin Registry, respectively, and were also contacted as part of a larger data collection. Although the prevalence of eating disorders and extent of disordered eating symptoms may differ across countries, in our study eating disorder prevalence and presentation is similar in Swedish and American samples (see Table 1). The prevalence of AN in the Norwegian sample is higher, and prevalence of BN is lower than the other samples. This may have been due to population differences or measurement approaches, which suggests that these samples need to be assessed independently rather than as one group despite similarities. These differences further suggest that cross-cultural prevalence and presentation of eating disorders warrants additional study.

Age is both a limitation and a strength in this study. As the mean age of participants in all three registries is older than the average age at onset of eating disorders, and as diagnoses were at any point in participants' lifetime, we were unable to explore potential activational effects of prenatal estrogen exposure. Previous work has suggested that there may be two narrow windows from ages 12–14 and ages 21–23 when prenatal hormone exposure has an activational effect on the expression of eating disorder symptomatology (35) when an individual is exposed to an environmental insult (e.g., extreme dieting). Age is, however, a strength insofar as having participants past the peak age of eating disorder onset (1) suggests that participants would be less likely to develop eating pathology after participation in the study, allowing this study to examine potential organizational effects of prenatal hormone exposure. However, the mean age differences across samples, with participants in the U. S. sample being younger than the Scandinavian samples, necessitated the inclusion of age as a covariate in all models.

Despite the contribution this series of studies makes by investigating the prenatal hormone hypothesis in three distinct populations, it also has limitations. First, as stated above, all participants in both the Mid-Atlantic and Norwegian samples are White. Thus, it is unclear whether results obtained can be generalized to individuals from other ancestry groups. Second, the prevalence of AN, BN, and BED is low in North American and Scandinavian samples (e.g., 36), and these studies are no different. It is possible that an association between co-twin sex and eating disorder diagnosis was not detected due to low statistical power. Third, like other investigations of the prenatal hormone hypothesis (13, 20, 21), co-twin sex is an indirect measure of prenatal sex hormone exposure, and cannot provide information to differentiate between organizational and activational effects of hormones. Finally, measures used in the current as well as previous studies (e.g., 3, 13, 20, 21) included self-report questionnaires. This is a limitation, as self-reported data are susceptible to participants' perceptions and presentations of themselves. However, self-report formats are less intrusive than observational or interview methods, and this approach might be more likely to elicit honest responses among individuals with eating disorders, as these disorders are often associated with secrecy and shame (37).

Nonetheless, this series of studies extends prior research by investigating the prenatal hormone hypothesis to three novel populations, by including men and women, and by including narrowly and broadly defined diagnostic variables for three eating disorders: AN, BN, and BED. The overall lack of association suggests that future research, rather than considering co-twin sex as a risk factor for eating pathology because of its organizational effects, should focus on the interactions among biological, psychological, and social factors

in the development and maintenance of these disorders. Future research should also focus on whether there are possible activational effects of prenatal hormones, such as whether individuals who experience a known environmental insult during critical developmental periods such as puberty show a stronger association with prenatal exposure to female sex hormones. Future research would also benefit from investigation of the role that genetics and prenatal environment factors play in the development of disordered eating in adolescence and adulthood.

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Table 1

Lifetime Prevalence of Eating Disorder Diagnoses by Zygosity

	Mid-Atlantic Women			Mid-Atlantic Men			Norway Women			Norway Men			Sweden Women			Sweden Men		
Model	**MZ (%)**	**DZ SS (%)**	**DZ OS (%)**	**MZ (%)**	**DZ SS (%)**	**DZ OS (%)**	**MZ (%)**	**DZ SS (%)**	**DZ OS (%)**	**MZ (%)**	**DZ SS (%)**	**DZ OS (%)**	**MZ (%)**	**DZ SS (%)**	**DZ OS (%)**	**MZ (%)**	**DZ SS (%)**	**DZ OS (%)**
AN Narrow	2 (0.33)	0 (0)	5 (1.04)	0 (0)	0 (0)	0 (0)	20 (2.22)	9 (1.70)	5 (1.45)	1 (0.23)	0 (0)	2 (0.59)	29 (0.71)	12 (0.41)	19 (0.78)	0 (0)	0 (0)	0 (0)
AN Broad	19 (3.09)	9 (2.21)	22 (4.57)	1 (0.20)	0 (0)	3 (0.95)	-	-	-	-	-	-	147 (3.62)	90 (3.13)	84 (3.48)	3 (0.11)	2 (0.10)	3 (0.12)
BN Narrow	18 (2.93)	9 (2.21)	11 (2.29)	1 (0.20)	3 (1.02)	1 (0.32)	7 (0.78)	2 (0.75)	2 (0.58)	0 (0)	0 (0)	1 (0.29)	51 (1.24)	27 (0.93)	26 (1.07)	1 (0.04)	1 (0.05)	1 (0.04)
BN Broad	47 (7.65)	35 (8.58)	35 (7.28)	11 (2.24)	8 (2.71)	7 (2.21)	-	-	-	-	-	-	113 (2.76)	77 (2.65)	62 (2.55)	5 (0.19)	3 (0.16)	7 (0.29)
BED Narrow	19 (3.09)	13 (3.19)	11 (2.29)	2 (0.41)	4 (1.36)	1 (0.32)	-	-	-	-	-	-	-	-	-	-	-	-
BED Broad	27 (4.40)	18 (4.41)	16 (3.33)	2 (0.41)	6 (2.03)	3 (0.95)	-	-	-	-	-	-	-	-	-	-	-	-

Reported results are frequencies of the diagnosis and percentage of individuals within the same group who meet criteria. Mid- Atlantic *N*=2,607, Norway *N*=2,796, Sweden *N*=16,458; Abbreviations: MZ=monozygotic, DZ=dizygotic, SS=same sex, OS=opposite sex, AN=anorexia nervosa, BN=bulimia nervosa, BED=binge eating disorder

Table 2

Hierarchical Linear Modeling Results for Eating Disorder Diagnoses in Twins

	Mid-Atlantic			Norway			Sweden		
Model	**sex**	**co-twin sex**	**sex × co-twin sex**	**sex**	**co-twin sex**	**sex × co-twin sex**	**sex**	**co-twin sex**	**sex × co-twin sex**
AN Narrow	-	-	-	-	-	-	-	-	-
AN Broad	-	-	-	-	-	-	**9.31*****	0.16	−0.33
BN Narrow	**2.76***	−0.33	0.68	0.89	0.89	−0.54	**7.63*****	1.75	−1.75
BN Broad	**4.24*****	−0.16	0.8	-	-	-	**8.10*****	**3.88*****	**−3.96*****
BED Narrow	**2.74***	−0.6	1.01	-	-	-	-	-	-
BED Broad	**3.35****	0.09	0.4	-	-	-	-	-	-

* p<.01,

** p<.001,

*** p<.0001; Reported results are t-values of main effects in full samples (including MZ twins).

Mid- Atlantic N=2,607, Norway N=2,796, Sweden N=16,458; Abbreviations: AN=anorexia nervosa, BN=bulimia nervosa, BED=binge eating disorder

Table 3

Effect Sizes for Co-Twin Sex with and without MZ Twins

	Mid-Atlantic		Norway		Sweden	
Model	**MZ and DZ**	**DZ only**	**MZ and DZ**	**DZ only**	**MZ and DZ**	**DZ only**
AN Narrow	-	-	-	-	-	-
AN Broad	-	-	-	-	1.03 (0.72–1.49)	1.01 (0.64–1.60)
BN Narrow	2.94 (1.36–6.34)	-	2.98 (0.27–33.14)	-	4.06 (2.97–19.44)	-
BN Broad	2.12 (1.50–3.01)	-	-	-	3.34 (1.81–6.14)	1.18 (0.83–1.68)
BED Narrow	2.72 (1.33–5.58)	2.17 (1.10–4.30)	-	-	-	-
BED Broad	2.26 (1.40–1.54)	1.86 (1.14–3.05)	-	-	-	-

Reported results are odds ratios and 95% confidence intervals in full samples (MZ and DZ twins) and partial samples (DZ twins only). Odds ratios reflect the likelihood of having a diagnosis based on having a female co-twin. Mid- Atlantic *N*=2,607, Norway *N*=2,796, Sweden *N*=16,458; Abbreviations: MZ=monozygotic, DZ=dizygotic, AN=anorexia nervosa, BN=bulimia nervosa, BED=binge eating disorder