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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Sex Differences in Adolescent Anorexia and Bulimia Nervosa: Beyond the Signs and Symptoms

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Abstract

Purpose of Review We review research related to sex differences in eating disorders (EDs) in adolescents. Prior work has explored clinical differences; thus, we examine literature in areas identified as playing an etiological or maintenance role in EDs including: genetics, hormones, neurocognitive inefficiencies, and reward circuitry.

Recent Findings Sex steroids appear to a play role in the unmasking of genetic risk for development of EDs and puberty may be a heightened period of risk for females. While neurocognitive differences have been well studied in adults with ED, research with adolescents has been less conclusive. Recent work suggests that neural circuitry involved in reward and punishment may play role in development and maintenance of EDs in females. Males are underrepresented in these areas of research.

Summary Given known sex differences in healthy adolescents, it is likely there are sex differences in the putative biological etiology/maintenance of EDs. Males should be included in future research.

Keywords Eating disorders · Anorexia nervosa · Bulimia nervosa · Sex differences · Adolescents · Neurobiology · Reward circuitry · Gonadal hormones

Introduction

Prior to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1], the two primary eating disorders (EDs) were anorexia nervosa (AN) and bulimia nervosa (BN). By definition, both are characterized by an over-concern of weight and shape and attempts to control weight. Individuals with AN are underweight for their age, sex, and developmental history and can engage in behaviors to avoid weight gain or not recognize the severity of their illness. Those with BN have multiple episodes of binge eating a week followed by some form of inappropriate weight compensatory behavior (e.g., diuretic misuse, self-induced vomiting, fasting, laxative misuse, and excessive exercise). While often considered to be primarily female disorders, a considerable proportion of sufferers are male [2, 3]. To reflect this, the recent changes to the DSM-5 have broadened the criteria for EDs attempting to make them less sex specific (e.g., elimination of amenorrhea as a diagnostic criterion for AN). In turn, there has been a 28.9% increase in lifetime prevalence of any ED for male and female adolescents combined under DSM-5 [2]. In the last 10 years, there has been an increasing amount of attention paid to males diagnosed with EDs. The vast majority of this work has focused on sex differences in the epidemiology of EDs, as well as symptom presentation of the different disorders; however, only a minority of studies has directly compared males to females. This

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review examines significant aspects of EDs that may have relevance for understanding potential sex differences in the etiology and maintenance of EDs in adolescents.

EDs, particularly AN, have been identified as severe, biologically based mental illnesses [4], which are often considered difficult to treat. As such, there is an increased interest in understanding the genetic basis, neurobiology, and other putative endophenotypes of EDs in order to inform new or targeted treatment. Much of this work has focused on adults and women, foci that limit our understanding of these illnesses.

By only studying females, we largely ignore potentially important differences in the development and maintenance of EDs in males—differences that could impact treatment development and effectiveness. Although males and females are more similar than different in terms of presentation of ED symptoms (see below), it is important to bear in mind that we have not established whether or not any observed differences represent a true difference in symptom presentation and severity or if observed differences between males and females are side effects of using measures that were developed using a female centric model of EDs and normed on females [5]. That is, measures may not have measurement invariance (i.e., the instrument functions may not similarly and equivalently measure the underlying construct(s)) of ED features across sexes. Establishing the validity of current assessment tools for both males and females or developing new ones is vital to further study and understand sex differences in the presentation of EDs. Research on sex differences indicates that even if males and females display the same signs and symptoms of an ED (see below), the pathway to its development could be different between sexes [6•].

By only studying adults, we focus on individuals who have been ill longer and who likely represent only a sub-sample of individuals ever diagnosed with an ED. EDs typically begin in adolescence, a key period of psychosocial development and significant brain development [7–11]. Caloric restriction and malnutrition have the potential to significantly impact development and could, hypothetically, impact girls and boys differently. The role of puberty in the onset of EDs has been studied primarily in girls. While data for females with AN are mixed, girls with BN are more likely to have more severe symptoms with early onset and later pubertal status [12••]. Research on males is equivocal, leading some researchers to conclude that puberty may play a more significant role for females than males [12••].

In order to truly understand the underlying biology of EDs, it is essential that we focus our efforts during adolescence and that we include males whenever possible. This review aims to highlight current research related to sex differences found in EDs in pediatric and adolescent populations. While other EDs exist (e.g., binge-eating disorder, other specified feeding or eating disorders), we limit our review to AN and BN as this where most of the work has taken place. We identified three primary areas where a focus on sex differences may be particularly salient: genetic risk, neurocognition, and reward circuitry. These three areas have received the most research attention and likely play a role in the etiology and/or maintenance of AN and/or BN. As gonadal hormones impact all three of these areas, we have also highlighted where a deeper understanding of the role of sex hormones in EDs is needed.

Symptom Presentation

While it is generally assumed that males present less frequently and have a different symptom profile than females, the rates of EDs in males is much higher than previously thought—with female to male ratios ranging from 1:1 to 1:10 [2, 13]. A smaller female-to-male ratio appears much more common in samples of children and adolescents [14, 15]. Eating Disorder Not Otherwise Specified (EDNOS) has traditionally been the most common ED diagnosed in males [16•, 17]. However, recent studies (using DSM-5 criteria) have shown a decrease in the prevalence of unspecified EDs (e.g., EDNOS), along with an increase in AN and BED for both sexes [18]. Compared to females, males are more likely to present with avoidant/restrictive food intake disorder (ARFID) or subthreshold binge-eating disorder [19–21]. Few differences have been found between sexes with regard to core ED symptoms, including patterns of restriction, binging, vomiting, or laxative abuse [22, 23]. Males do, however, appear to engage in more over-exercising as compensatory behavior [24–26]. Differences in other features such as age of onset [22, 23, 27] and psychiatric comorbidity [28, 29] are less clear (particularly in adults). In adolescents, there is some evidence that females have higher rates of comorbidities [16•, 26]. Males and females appear to differ in their motives for restriction and disordered eating. For example, males tend to show less concern about body image or drive for thinness [30, 31] but increased concern with muscularity and shape (consistent with their higher use of exercise in order to increase muscle definition) [32, 33]. On the other hand, females more consistently endorse a desire to be thinner [34]. Males not only are more likely to have a history of higher weight prior to ED onset but also are less likely to receive an eating disorder consult [35]. Males and females report similar levels of overall psychological distress and impaired quality of life associated with disordered eating behaviors. However, females report elevated levels of distress associated with subjective binge eating episodes compared to males [36]. Of note, the muscularity-oriented eating and exercise behaviors observed in adult males appears to be comparable in terms of disability and distress to weight controlling behaviors often observed in females [37]. Eating disorders have a high mortality rate; research in adults indicates that the mortality rate for males and females may be similar, though males with AN

who have a comorbid disorder may be at greater risk for death due to suicide [38•]. In adolescents, extreme weight control behaviors are associated with suicidal thoughts and plans in females and with suicide attempts in males [39].

For a review of recent studies related to characteristics of males with EDs, see Raevuoir and colleagues [40] and Murray and colleagues [41••]. Table 1 provides a summary.

Genetic Risk

The vast majority of the research examining the genetic components of EDs focuses on adult women with either AN or BN. EDs seem highly heritable, with heritability estimates ranging between 0.48 and 0.74 for AN [42] and between 0.55 and 0.62 for BN [43]. Over the years, researchers have conducted linkage studies, searched for candidate genes, attempted to understand shared genetic risk for EDs and other, comorbid psychiatric disorders, and have recently begun to study the epigenetics of EDs [44–46]. The majority of this work has used samples of adult women, most is underpowered, and replications are rare [47]. The few studies that have included men have had such a small sample that sex differences cannot be examined [48]. What the research does tell us is that EDs, particularly AN, are highly heritable and have a genetic component.

The research that does include males highlights the importance of the consideration of sex differences in research on EDs in order to fully understand their development in both males and females. There appears to be sex differences in genetic risk for EDs. Specifically, sex steroids may play an important role (as moderators and/or mediators) in the expression of ED behaviors. Prior to puberty, genetic influence on risk of developing an ED is 0% in females and 50% in males. After puberty onset, risk stays stable in males but increases to 50% in females [49]. This stark increase in risk for females (which is stable until puberty [12••]) points to an activation of genetic risk, most likely related to the onset of puberty and highlights the potential role of estrogen in activating risk [50].

In a sample of monozygotic twin females with normal body mass index, those with higher levels of estrogen had more disordered eating symptoms [50]. In females, there appears to be shared genetic predisposition for early menarche and the onset of disordered eating [51]. Genes responsible for estrogen and food intake also account for some of the shared genetic factors for early menarche [52]. Estrogen plays role in regulating the genes responsible for brain derived neurotropic factor and the serotonin system, both of which are associated with ED symptoms [53, 54]. Importantly, the activation of genetic risk for females during puberty appears to be independent of environmental factors. While the vast majority of research on sex hormones and EDs has focused on the role of estrogen, testosterone exposure during prenatal development may protect against risk for the development of EDs [55, 56] particularly in early adolescence and young adulthood [57•]. It may also be a protective factor for males vis-a-vis binge eating [58]. One study has found that males with a female twin are at greater risk for developing an ED than males with a male twin [59]. Genetic data, therefore, highlight the importance of puberty in the development of EDs in females and point to sex hormones, especially estrogen, as playing a significant role in this process.

Table 1 Summary of sex differences (how males differ from females) in eating disorders

Domain	Documented differences and similarities
Signs and symptoms	• Males are more likely to present with ARFID or sub-threshold BED
	• Mortality rates comprable between sexes
	• Males engage in high rates of physical activity as compensatory method
	• Females demonstrate increased drive for thiness, while males have increased concern with muscularity and shape
	• Males are more likely to have a history of higher weight prior to ED onset
	• Males may have fewer psychiatric co-morbidities
	• Levels of distress are comprable between sexes
	• Males with comorbidities are at greater risk for suicide attempts
Genetics	• Genetic influence on risk for males is constant (50%), whereas female risk jumps from 0 to 50% at puberty
Sex hormones	• Testosterone exposure during prenatal development may protect against risk for the development of eating disorders
	• Testosterone may be a protective factor for males vis-a-vis binge eating
Neurocogntive differences	• Common areas of study in adults include central coherence and set-shifting
	• Rarely examined in adolescence, sample sizes are small and generalizaations cannot be made regarding sex differences
Reward circuitry	• No research examining sex differences in EDs

While there is growing evidence that sex hormones play a role in the onset of EDs, it is also possible that the onset of an ED (or, more specifically, the malnutrition that accompanies it) could alter the expression of genes. For example, in AN, there is evidence that early onset or a longer course of illness is associated with differential DNA methylation in gene pathways associated with social awareness, anxiety, and serotonin receptor genes [60], all of which are known to be associated with AN [61–63]. Thus, multiple pathways may exist to explain certain endophenotypes observed in EDs. Little is known about these various factors that may differentially impact the development of ED symptoms between males and females.

Overall, it appears as if puberty is a sensitive period for development of eating disorders and the risk of developing an eating disorder during this period is different from males and females. Gonadal hormones likely play a significant role, with fluctuations that occur during puberty potentially unmasking genetic risk; this may be truer for females as there is evidence that estradiol may organize/activate genetic risk. Our understanding of this process is limited by sample size and statistical power. More in-depth work is needed to understand the genetics of eating disorders, particular vis-a-vis sex differences. Increased research with sufficient male samples are needed to examine the role of genetics and hormones in the etiology and maintenance of AN and BN [64].

Neurocognitive Inefficiencies

In the past 15 years, the putative endophenotypes of difficulties in set-shifting (i.e., inflexibility when moving from one task to another) and weak central coherence (i.e., processing bias toward feature or local information, at expense of gestalt) have garnered significant attention as potential risk factors for the development of EDs [65–67] and/or specific core features (i.e., body image disturbance) of EDs [68]. There have been a number of meta-analyses [66, 69–71] examining differences between individuals with EDs, healthy controls, and individuals with EDs pre-and post-treatment. Overall, findings in adults have been fairly robust—with inefficiencies present when ill, when recovered, and in the family members of probands [72]. The majority of this work has been in AN; however, there are few studies suggesting similar neurocognitive inefficiencies in adults with BN [73].

Although there is sufficient evidence that neurocognitive inefficiencies are present in adults, it is unknown whether these inefficiencies are an actual endophenotype, a "scar" of the illness, or a marker of a longer course of illness. Expanding the study of neurocognitive inefficiencies to adolescents is necessary to shed light on whether or not observed difficulties in set shifting and weak central coherence are truly endophenotypes. Overall, evidence points to the set-shifting deficits found in adults with AN being less pronounced in youth [74•], with some studies failing to find inefficiencies in set-shifting and weak central coherence in adolescent samples [67]. The lack of replication in adolescent samples points to neurocognitive inefficiencies being either a scar of the illness or a marker for a longer course of illness.

Not surprisingly, there is a dearth of research examining potential sex differences in cognitive flexibility and central coherence in EDs. Of the four studies, we found that included adolescent males with EDs [75–78] all were hampered by small sample sizes limiting power to investigate sex differences. Allen and colleagues [75] conducted an exploratory investigation suggesting that males made more perseverative errors on a set-shifting task than females. However, the authors note that males' scores were likely skewed due to three males' particularly poor performance on the task. No further studies have included analysis on sex differences in set shifting abilities for youth with BN.

What is often missing from research on neurocognition in the context of adolescent EDs is an incorporation of developmental framework. Hormonal changes during puberty are hypothesized to differentially impact structural changes in the brain during adolescence and changes in gray and white matter are different in males and females. These sexually dimorphic changes are hypothesized to relate to sex differences in the development of executive functioning [7]. We know that in early adolescence, females tend to display more cognitive flexibility than males (though males can catch up in late adolescence) [79]. Furthermore, the development of set-shifting ability tends to reach adult levels by age 15 [79]. The median age of onset for AN and BN is 12 years of age; thus, adolescents who develop EDs during this time may have not yet fully developed their shifting abilities. It is plausible that the developmental trajectory of executive functioning could be impacted by malnutrition and that the impact could differ by sex. More work needs to be done in this area.

The role of sex hormones in both set-shifting and central coherence has been largely unexplored in the context of EDs. This is in contrast to a larger literature exploring the impact of menopause (and therefore reduced estrogen) on women. Estrogen therapy for women and testosterone therapy for men has been demonstrated to improve cognitive functioning when started during critical periods [80, 81]. In one of the only studies to explore executive functioning and sex hormones in AN, Chui and colleagues found that continued neurocognitive inefficiencies were associated with disruptions in menses [82]. This is an area that needs further exploration to determine what unique impact sex hormones may have on executive functioning in adolescents with EDs.

Reward Circuitry

The neural circuitry involved in reward and punishment has been implicated in the motivational processes of abnormal

eating behaviors [83]. There are a number of different reward centered models for EDs, the majority of which focus on AN. Broadly speaking, reward centered models of AN suggest that persistent weight loss can lead to negative appraisal of food and taste stimuli; in turn, individuals are rewarded for aberrant cognitions and illness related cues [84]. Key to these models is a focus on altered reward sensitive regions of the brain including the anterior cingulate cortex, orbito-frontal cortex, insular-striatal regions, as well as mesolimbic dopamine systems [85–88]. AN, in particular, appears to be associated with heightened responsiveness in brain reward circuits, which may relate to hypersensitive dopamine systems [89, 90]. It has also been postulated that abnormalities in reward/punishment sensitivity may contribute to an increased risk of binge eating and purging behaviors [91]. Specifically, greater reward sensitivity may contribute to binge eating, while increased punishment sensitivity may contribute to compensatory behaviors [87]. The vast majority of the research on reward circuitry in AN has focused on adult samples and has used symptom-eliciting stimuli (e.g., food or taste). To date, the small body of research in adolescents with AN has mirrored that of the adult findings. No studies that have investigated reward circuitry in adolescents with AN or BN included males.

The development of reward circuitry in healthy adolescents has received a great deal of attention in the literature. While research has indicated both hypo- and hyper responsiveness to reward, the majority of research has supported the latter view [92]. Adolescents tend to have greater activation of the ventral striatum and nucleus accumbens, as well as increased engagement of higher order cortical regions in reward processing compared to adults [92]. Adolescents may engage the reward system differently than adults at different stages of reward tasks (e.g., anticipation) [92], respond to reward paradigms differently [93•], and find different stimuli rewarding than adults. In attempting to understand how reward systems may be different in individuals with EDs compared to those without, it is necessary to take developmental differences into consideration—particularly because it is unknown how malnutrition or dietary restriction may impact the development and responsiveness of the reward system.

The lack of inclusion of males in studies is striking as we know that there are sex differences in reward. As noted, the vast majority of previous research on the reward system in adults with AN has employed food or taste related stimuli. In a systematic review of sex differences in response to food stimuli in adults, women were found to be more reactive than men to visual stimuli, particularly in the striatal/limbic and frontal and cortical systems [94•]. Whether or not this would occur at the low end of the weight spectrum or in adolescents is unknown. Estrogen levels in women can impact response to food stimuli, with responses to food stimuli higher when estrogen is high [94•]. How responsiveness changes due to low levels of sex hormones secondary to malnutrition (as opposed to an ED) is unknown. Sex differences in response to rewarding stimuli are found in other domains as well: males tend to respond faster to monetary reward than social reward, whereas females have stronger anticipation of social reward compared to males [95].

Gonadal hormones impact both the development of the reward system during adolescence and are believed to play a large role in both sensation seeking behavior and reward sensitivity in adolescence. The vast majority of this work has focused on the role of testosterone. Broadly speaking, higher levels of testosterone are associated with reward sensitivity and reward driven behavior in healthy adolescent females and males [96•]. For example, higher testosterone levels are associated with greater activation in the ventral striatum during a monetary reward task in healthy male and female adolescents [97]. Research on the role of estrogen in reward is mixed, but it appears as if estradiol is negatively associated with both reward sensitivity and reward driven behavior in adolescents [96•].

The clear differences that exist in activation of the reward system in adults versus adolescents combined with sex differences in response to reward stimuli (in particular food) highlight the need to focus our research on reward circuity in EDs in adolescents and to, whenever possible, include males in research. It is unlikely that research on reward circuitry in adult women with EDs is generalizable to adolescents and/or males. Of note, sex differences in neural circuitry are implicated as contributing factors in adolescent vulnerability to substance use, which has many similar features to EDs. See Hammerslag & Gulley [98] for review of sex differences in behavior and neural development as it relates to substance use.

Conclusion

Historically, researchers were able to justify excluding males from studies on EDs in part because prevalence was considered rare. It is now known that all EDs occur in males, EDs in males are not as rare as previously thought, and that there are subtle sex differences in the presenting signs and symptoms of EDs. With increased focus on understanding the etiology and maintenance of EDs and using a greater understanding of the underlying neurobiology to develop new or targeted treatments, it is essential that males be included in research. Likewise, research into both the neurobiology of EDs and sex differences in the neurobiology of EDs should be focused on adolescence, as this is the critical period in which EDs typically develop. Research with females indicates that a percentage of individuals with EDs will recover, while others will have symptom crossover or continue to experience sub clinical symptoms [99]. Focusing on adults by default focuses on those who have had a longer course of illness. Similarly, there

are clear sex differences in development during adolescence (e.g., brain development, hormonal changes) and it is unclear how malnutrition may impact sexes differently. As research on the neurobiology of eating disorders continues, it is important that males be included in order inform treatment development and refinement. In order to do this, concerted effort should be made to recruit males with EDs for clinical studies. Collaboration across multiple sites may be necessary in order to fully explore questions of sex differences in adolescents with EDs.

Compliance with Ethical Standards

Conflict of Interest Levi DeFilipp and Antonios Dakanalis declare no conflict of interest. C. Alix Timko is supported by 5K12HD085848 (PI: N. Epperson).

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