

## Examining Sex and Gender Differences in Anxiety Disorders

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# Examining Sex and Gender Differences in Anxiety Disorders

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## Abstract

Several studies have examined sex differences in different anxiety disorders. Females are repeatedly found to be more likely than males to suffer from anxiety in general and to be diagnosed with most anxiety disorders, including agoraphobia (AG), panic disorder (PD), separation anxiety (SA), specific phobia (SP), social anxiety disorder (SAD), generalised anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and acute and posttraumatic stress disorder (ASD and PTSD), although the latter three are technically no longer categorised as anxiety disorders according to DSM-5. This chapter provides an overview of research on sex and gender differences in anxiety disorders ranging from the well-established female preponderance in prevalence and severity to possible sex differences in the risk and protective factors associated with anxiety, sex differences in the clinical presentation of anxiety disorders, and potential sex differences in the effectiveness of different treatments. The chapter contains suggestions for future research, including important questions that remain to be answered.

**Keywords:** Sex differences, Gender differences, Anxiety disorders, OCD, PTSD, Acute stress disorder

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## 1. Introduction

Anxiety disorders are the most prevalent group of psychiatric disorders [1]. It is well-documented that females are more likely than males to develop an anxiety disorder with lifetime

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and past-year rates of anxiety disorders being 1.5–2 times higher among females than males [2]. The increased prevalence of anxiety disorders in females has persisted independently of changes in the diagnostic criteria from DSM-III-R to DSM-IV [3, 4]. Sex differences in different anxiety disorders do not emerge at the same time, but sex differences in general anxiety levels emerge before the age of 4, and by age 6, anxiety levels in girls are about twice as high as in boys [5]. Once they have emerged, sex differences in DSM-IV anxiety disorders generally remain stable across age groups ranging from 18 years to 60+ years [6].

In spite of a few studies failing to find significant sex differences in the prevalence of anxiety disorders, clinical and community studies have generally reported higher rates of panic disorder (PD), agoraphobia (AG), specific phobias (SP), generalised anxiety disorder (GAD), separation anxiety (SA), and both acute and posttraumatic stress disorder (ASD and PTSD) in females compared to males [2, 3, 7, 8]. Sex differences are less pronounced for social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD), and sex differences in the prevalence rates of these two disorders are not always significant [7, 9]. As can be seen in Table 1, lifetime prevalence rates of DSM-IV anxiety disorders range from 1.1% AG to 11.1% SAD in males and from 1.6% AG to 15.8% SP in females [3]. The three most prevalent anxiety disorders in males are SAD followed by SP and GAD [3]. In comparison, the three top-ranging anxiety disorders in females are SP, SAD, and PTSD. In spite of these widely reported sex differences in the prevalence and severity of anxiety disorders, sex differences in anxiety have been largely neglected compared to depression [10].

In the most recent edition of the diagnostic and statistical manual of mental disorders (DSM-5) [12], some of the anxiety disorders were re-arranged. As a consequence, ASD, PTSD, and OCD are no longer characterised as anxiety disorders. ASD and PTSD were moved to the new category trauma- and stressor-related disorders and OCD was relocated to the newly created category of obsessive-compulsive and related disorders. However, because these changes are still relatively recent, a limited amount of research has been published based on these categories of disorders. Furthermore, as a substantial amount of research has been conducted on these disorders in combination with other traditional anxiety disorders, it was considered expedient to include ASD, PTSD, and OCD in this chapter.

The inclusion of these three disorders further provides an opportunity to compare sex differences in ASD, PTSD, and OCD with sex differences in the disorders that have remained classified as anxiety disorders. Whereas ASD, PTSD, and OCD are no longer considered anxiety disorders, two new disorders have taken their place. In DSM-IV, selective mutism and SA were classified under the category of “Disorders usually first diagnosed in infancy, childhood, or adolescence” [13] but with the revisions carried out in the DSM-5, they were re-categorised as anxiety disorders [12]. Unfortunately, studies focusing specifically on sex differences in selective mutism are non-existing perhaps because the disorder is so rare that sex differences are rarely detected. Furthermore, this chapter will focus primarily on sex differences in adults, and research on selective mutism in adults is as hard to come by as research on sex differences. Thus, this chapter will examine the current status of research on sex differences in AG, ASD, GAD, OCD, PD, PTSD, SA, SAD, and SP.

Diagnosis	Males % <sup>1</sup>	Females % <sup>1</sup>	F:M ratio <sup>2</sup>	Classification <sup>3</sup>
AG	1.1	1.6	4:1	Substantial
ASD	-	-	-	-
GAD	4.2	7.1	3:1	Moderate
OCD	-	-	1:1	Moderate
PD	3.1	6.2	2:1 / 3:1 <sup>4</sup>	Substantial
PTSD	3.6	9.7	2:1	Substantial
SA	-	-	OR = 1.4 <sup>5</sup>	Substantial
SAD	11.1	13.0	1:1	Moderate
SP	8.9	15.8	2:1	Moderate
Any anxiety disorder	22.4	32.4	OR = 1.76 <sup>1</sup>	-

Notes: GAD: generalised anxiety disorder; SAD: social anxiety disorder; PD: panic disorder; AG: agoraphobia; SP: specific phobia; PTSD: posttraumatic stress disorder; ASD: acute stress disorder; SA: separation anxiety; OR: Odds ratio for sex differences, OD >1 reflects higher prevalence in females.

<sup>1</sup>DSM-IV prevalence rates (and OR for any anxiety disorder) based on the NCS-R and published by Gum et al. [3].

<sup>2</sup>DSM-IV-TR female-to-male ratios published by Bekker et al. [7] (except for SA and any anxiety disorder).

<sup>3</sup>Classifications presented by Mackinaw-Koons & Vasey [11].

Substantial differences: females exceed males by at least 100%

Moderate differences: females exceed males by 33–99%

<sup>4</sup>PD with AG/PD without AG

<sup>5</sup>Prevalence for males and females combined is 6.6%. Prevalence and OR published by Shear et al. [8].

**Table 1.** Lifetime prevalence of DSM-IV anxiety disorders in adult males and females

### 1.1. Overview of relevant studies on sex differences in anxiety disorders since 2010

A search of studies on sex or gender differences in the different anxiety disorders published and indexed in PsycINFO and/or PubMed from 2010 until the end of 2014 was conducted. Search criteria can be seen in Table 2.

The literature search only included articles identified through the searches in PsycINFO and PubMed, even though articles published in the same period but not identified in these searches, may have been included in this chapter. The reasoning behind this is that the searches were intended to give an overview of the amount of sex/gender research published in relation to the different disorders over a period of 5 years. In addition, studies were excluded that did not focus primarily on anxiety disorders, focused on animals, focused primarily on children and younger adolescents, were not written in English, or were published as book chapters or dissertations. Articles were categorised as either relevant or not relevant based on whether their focus was on sex differences in the specific disorders. Furthermore, articles were classified as uniquely relevant to a specific anxiety disorder if that disorder was the sole focus of the article. Because many studies report sex differences in the prevalence or severity of anxiety without mentioning this in the abstract, only studies that examined sex differences beyond this level (i.e., tried to explain these differences – or absence thereof – or examined moderation effects or sex differences in specific symptoms etc.) were categorised as relevant. In addition,

studies that did not focus on specific anxiety disorders and studies that examined specific subsamples of limited general relevance (e.g., sex differences in anxiety in patients undergoing treatment for substance dependence) were not categorised as relevant. Finally, articles that did not present original research or conduct thorough reviews or meta-analyses were not included.

An overview of articles identified in the searches can be seen in Table 3. Several of the studies were indexed in both of the databases. Such overlap was taken into account, which reduced the number of total articles identified somewhat. As can be seen in Table 3, more studies have been published on sex differences in PTSD than in any other anxiety disorder within the past 5 years.

	<b>Keywords</b>
Abstract	"General anxiety disorder" OR "generalised anxiety disorder" OR "generalized anxiety disorder" "Obsessive compulsive disorder" OR "obsessive-compulsive disorder" OR OCD "Specific phobia" "PTSD" OR "post-traumatic stress disorder" OR "posttraumatic stress disorder" "Acute stress disorder" "Panic disorder" "Agoraphobia" "Social phobia" OR "social anxiety disorder" "Separation anxiety"
Abstract	"Sex differences" OR "Gender differences"
Publication date	2010–2014

Note: At least one keyword from each row had to be present in the title/abstract for articles to be identified in the search

**Table 2.** Search criteria for sex/gender differences in anxiety studies published 2010–2015

Between 1 and 11 relevant studies were identified on sex differences in AG, GAD, OCD, PD, and SAD, whereas no relevant studies were identified on sex differences in ASD, SA, and PD. Quite a few of the studies published examined sex differences in several disorders, resulting in substantial overlap between the articles identified in the different searches. As a result of this, the number of unique articles identified in the searches of each disorder was substantially reduced for most of the disorders. The two exceptions to this were OCD where 5 of the 7 articles identified were unique and PTSD where a full 95.6% of the articles were unique. For the remaining diagnoses, between 0 and 5 articles were identified that were unique to each disorder. This overview of studies published within the past 5 years highlights the need for more research examining sex differences in anxiety. With the exception of PTSD, the number of published articles identified including sex or gender differences in the abstract is very low, and this number is reduced even further, when results are limited to those specifically focusing on sex or gender differences in relation to each disorder. The difference in numbers between the studies originally identified and the studies categorised as relevant suggests that future research on sex differences in anxiety should be much more focused. For this reason, the

purpose of this chapter is to give an overview of what is presently known about sex differences in anxiety disorders and what still remains to be examined. Thus, this chapter may be read as a guide to research on sex and gender differences in anxiety disorders, summarising what is currently known and posing relevant questions for future research to answer.

Diagnosis	PubMed total	PsycINFO total	Total	Relevant	Uniquely relevant
AG	3	4	5	1	0
ASD	1	1	2	0	0
GAD	15	20	24	6	1
OCD	18	23	27	7	5
PD	23	21	27	9	4
PTSD	111	115	15	91	87
SA	6	6	9	0	0
SAD	23	28	21	11	5
SP	6	6	6	0	0

Note: AG: agoraphobia; ASD: acute stress disorder; GAD: generalised anxiety disorder; OCD: obsessive-compulsive disorder; PD: panic disorder; PTSD: posttraumatic stress disorder; SA: separation anxiety; SAD: social anxiety disorder; SP: specific phobia

**Table 3.** Results from literature search on sex/gender differences in the different anxiety disorders

## 2. Sex and gender differences in anxiety research

### 2.1. Sex differences in anxiety

A vast amount of research has documented sex differences in brain regions involved in cognition, memory, and affect [14]. In spite of important sex differences in the structure and function of the brain, most research on the brain's involvement in learning, memory, fear conditioning, and fear extinction has been conducted on male populations, as less than 2% of studies in these areas have focused on females [14]. However, what little research has been conducted has uncovered both structural and functional sex differences in brain regions relevant to anxiety, including the prefrontal cortex, hippocampus, and the extended amygdala complex. For example, significant genetic differences between males and females with OCD have been reported, although findings are sometimes contradictory and replication is needed [15, 16]. Furthermore, blood pressure and pulse have been reported to be more reactive to anxiety in females compared to males [17]. As a result of such sex differences, females appear to be more easily conditioned than males [7, 18], and males and females have also been found to differ in fear extinction [18]. One way through which biological sex differences can affect anxiety disorders is through gonadal hormones.

Important sex differences have been reported in several brain and bodily functions associated with anxiety [14]. Female gonadal hormones, such as oestrogen and progesterone appear to

have substantial effects on the functions of anxiety-related neurotransmitter systems and affect fear extinction [14, 19]. Similarly, among the male gonadal hormones, testosterone has been found to have anxiolytic effects [20], possibly by reducing responsiveness to stress and suppressing activity of the hypothalamic pituitary adrenal (HPA) axis [20]. For this reason, gonadal hormones are likely to account for at least part of the increased prevalence and severity of anxiety disorders in females. Fluctuations in oestrogen and progesterone throughout the female menstrual cycle appear to affect HPA axis reactivity, glucocorticoid feedback sensitivity, and brain GABA connections, causing the homeostatic system to become less stable in females compared to males [17]. Such fluctuations may cause both short-term instability in females and be responsible for more long-term changes in the severity of anxiety symptoms occurring in relation to puberty, pregnancy, lactation, and menopause [17, 19, 20]. Support for the effects of monthly and major lifetime hormone fluctuations on anxiety in females comes from findings that self-reported changes in OCD and PD symptoms related to the female reproductive cycle and the occurrence of pregnancy and menopause have been found [10, 16, 17, 19]. The importance of gonadal hormones is further supported by findings that manipulating them can have consequences. For example, prolonged use of oral contraceptives appears to alter the reactivity of the HPA axis to psychological stress [21], thereby affecting the prevalence and severity of anxiety symptoms in females.

Altemus has made an interesting point in arguing that there may have been an evolutionary advantage in both the HPA axis and the catecholamine stress response system being suppressed during pregnancy and lactation, as it is a very recent development in evolutionary terms that females no longer spend the majority of the years between puberty and menopause being either pregnant or lactating [17]. Thus, the increased prevalence of depression and anxiety in females may be a recent development, as the primary female defence against these disorders is made ineffective in modern human society.

## 2.2. Gender differences in anxiety

It has been suggested, that sex differences in the development of internalising and externalising disorders may be partly attributable to differences in socialisation processes that are intensified during adolescence and activate concepts of masculinity and femininity [22]. Such gender-roles are likely to affect sex differences in anxiety. For example, there are some indications that sex differences in PTSD are smaller or even non-existing in male-dominated professions where females assume more masculine gender-roles [23]. Whereas femininity and masculinity were originally considered opposite ends of a continuum, they are now most commonly believed to exist independently of each other [24]. Masculinity/femininity measured on a single scale has been found to correlate negatively with manifest anxiety, indicating that males and females with high femininity scores report more anxiety [25]. However, when measured separately, femininity has been reported to be unassociated with AG and related measures, whereas masculinity is negatively associated with AG severity, trait anxiety, social anxiety, and avoidance behaviour in general [7, 24]. Furthermore, masculinity scores for both male and female patients with AG were found to be significantly lower than in community samples [26]. The protective function of masculinity is equally strong in males and females and has been

found both in adults and in children suffering from various anxiety disorders [7, 24]. One study reported that sex was no longer associated with avoidance in patients with AG when masculinity was controlled for [26]. These findings suggest that the lower levels of masculinity in females compared to males may at least partly account for sex differences in anxiety. In contrast to masculinity, masculine gender-role stress, defined as stress resulting from rigid commitment to gender-roles in combination with dysfunctional coping, has been reported to be associated with certain characteristics of OCD as well as increased fears related to AG, blood, and social situations [7].

Gender-roles may affect sex differences in anxiety reports in at least two ways [27]. Identification with a masculine gender-role may cause a person to underreport anxiety symptoms [7, 27], resulting in a reporting bias. Some support for an underreporting of fear and anxiety in males has been found in a study that reported an increase in fear reports in males, but not in females, when their physiological fear reactions were being monitored and participants believed that lying would be detected [27]. However, other studies have found that sex differences in anxiety are not simply a result of sex differences in social desirability [10, 28]. In addition, it is possible for socialisation processes to result in actual sex differences in anxiety levels. From childhood, males are generally encouraged to confront feared objects, resulting in a greater exposure and extinction of fear responses in males compared to females, for whom avoidance and fearful behaviour is less likely to be dissuaded [9]. Furthermore, as females are more likely to ruminate than males [9], sex differences in recall bias may cause females to report more prior symptoms of anxiety. In accordance with this, depression research comparing baseline and follow-up reports of depressive episodes have found that females are more likely to recall new depressive episodes at follow-up, whereas males are more likely to forget previously reported episodes [22]. Finally, gender differences in the division of work status, socioeconomic status, and social roles may leave females more vulnerable to anxiety disorders than males [7], as males and females are exposed to different types of environmental stressors, which is likely to affect their susceptibility to anxiety disorders. For example, females are more at risk of being exposed to certain potentially traumatic events, such as sexual trauma and domestic abuse, as well as relationship stressors [9].

### *2.2.1. Summary and discussion of sex and gender influences in anxiety*

Sex differences in anxiety have been reported universally and such consistencies in sex differences across cultures suggest a biological component. However, whereas sex differences in PTSD have been found to be culturally persistent, variations have been reported in the strength of these sex differences across cultures, suggesting that both biological sex and cultural gender play a role in differences between male and female PTSD severity [23]. Similarly, examining the lifetime prevalence of different DSM-III-R anxiety disorders, the National Comorbidity Survey (NCS) reported a significant interaction between sex and ethnic group on lifetime prevalence of anxiety disorders [29], suggesting that some inter-cultural variation in the extent of sex differences in anxiety disorders does occur. Also, in spite of their general presence, gender differences in anxiety symptoms are often non-significant in college

students [28], suggesting that the strength of sex differences in anxiety may also differ between subcultures.

Unfortunately, potential interaction effects for specific anxiety disorders in the NCS were not examined, and thus it is unknown whether sex differences in the severity and prevalence of certain anxiety disorders are more stable than others across different ethnic groups and cultures. It has been suggested that PD may be more strongly related to physiological factors than the other anxiety disorders [30]. It is thus possible that differences between males and females with PD have more to do with sex and less to do with gender than what may be the case for the other anxiety disorders. Furthermore, the relative importance of sex and gender may differ for specific symptoms or groups of symptoms. There are some indications in PTSD research that sex differences in arousal are related primarily to biological sex differences, whereas sex differences in avoidance and re-experiencing are relatively more affected by social gender differences [23]. It is highly likely that similar variation can be found in other anxiety disorders, causing sex differences in certain symptoms, gender differences in others, and similarities between males and females in yet other symptoms.

Both sex and gender influences appear to contribute to the development of sex differences in anxiety, and telling them apart can be quite difficult. Whereas the changes in sex differences associated with the onset of puberty and menopause are often interpreted as support of the importance of gonadal hormones, such developments may equally well be explained by changes in gender-related variables, such as relationship and family status, social status, and gender-role identification [31]. Influences of sex and gender are likely to work together both at the societal and the individual level. Several gender differences in society are likely to build on pre-existing sex differences, such as those related to brain structure and functioning, physiological stress response, and influences of gonadal hormones. For example, features associated with femininity were probably originally based on sex differences and shaped by evolution. The increased prevalence of such traits in females is likely to have caused society to expect such traits in women, allowing socialisation processes to further strengthen the association between femininity and being female. Similarly, it is possible that if the same traits have been preferred in women by society for long enough for evolutionary processes to come into play, such traits may over time become biologically based, even if this was not originally the case. A similar process may take place at the individual level, where it has been argued that articulated traits are likely to reflect a complex, bidirectional process between inherent genetic vulnerabilities and socialisation experiences [2, 22].

Although sex differences in anxiety disorders are generally well-documented, the degree to which such differences can be accounted for by biological sex or cultural gender differences is unclear. More studies are needed to examine whether the impact of sex and gender influences are equal for different anxiety disorders. In spite of the fact that the female brain has been largely ignored in research on the brain processes behind fear and anxiety, sex differences have been reported in relevant areas of the brain, and gonadal hormones appear to be heavily involved in anxiety. These results are very promising and point strongly to the importance of more studies being conducted on the female brain. Such studies should include the impact of gonadal hormones, the female menstrual cycle, oral contraceptives, and HRT on anxiety

symptoms as well as sex differences in fear networks and HPA axis reactivity. Also gender differences need to be more thoroughly studied in future research. Important gender-related concepts that invite further scrutiny include gender-roles, gender-role stress, and sexual identity. Another way to further examine the influences of gender on anxiety is to conduct more studies that examine cultural and subcultural influences on sex differences in anxiety. As previously mentioned, sex differences in trait anxiety were found to be more pronounced in Israeli compared to American college students [28]. However, although the American and Israeli college populations are likely to differ on a number of parameters, other cultures may differ even more, and these cultures will need to be included in future studies on cultural variations in sex differences in anxiety.

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- Sex differences in anxiety are universally reported but their strength may vary across cultures, suggesting that both sex and gender influences are important.
  - The relative importance of sex versus gender may vary for different disorders and specific symptoms or groups of symptoms.
  - Biological sex can affect anxiety through differences in brain structuring and organisation and through gonadal hormones, and female hormonal fluctuations caused by the menstrual cycle and major lifetime hormonal influences (e.g., puberty, oral contraceptives, pregnancy, lactation, menopause).
  - Sex differences in reactivity to stress associated with differences in HPA axis activation, increased fear conditioning in females, and a less stable female homeostatic system have been reported.
  - Gender influences may be based on socialisation processes that activate gender-roles associated with masculinity and femininity.
  - Masculinity is associated with decreased anxiety reports in both males and females, whereas femininity is unassociated with anxiety. Gender-role stress has been reported to increase anxiety.
  - Socialisation processes may result in reporting bias, memory bias, and actual differences in anxiety levels.
  - The latter may be affected by gender differences in work status, socioeconomic status, social roles, and exposure to different stressors (e.g., sexual assault, domestic abuse, relationship stressors).
  - Future research should focus on gonadal hormones, the female menstrual cycle, oral contraceptives, HRT, HPA axis reactivity, fear networks, gender-roles, gender-role stress, sexual identity, and cultural/sub-cultural variations in sex differences in anxiety.
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**Table 4.** Summary points for sex and gender influences in anxiety

### **2.3. Accounting for sex differences in anxiety severity**

As both biological influences of sex and cultural influences of gender appear to be involved in the genesis of sex differences in anxiety, any model attempting to account for such differences must take both these types of influences into account. A thorough discussion of the different theories that have been used to explain different aspects of sex differences in anxiety is beyond the scope of this chapter. Furthermore, instead of simply explaining sex differences in the prevalence and severity of anxiety, a good theory should also be able to predict and explain differences between males and females once an anxiety disorder is present as well as sex differences between anxiety and associated variables and potential sex differences in the

outcome of different approaches to treatment. As will be made clear later in this chapter, sex differences in these other areas of anxiety research are nowhere near as well-established as those in relation to the prevalence and severity of anxiety. Thus, rather than attempting to explain sex differences in anxiety, it is worth looking into how far research has come in its endeavours to account for sex differences in anxiety severity.

The mediation hypothesis suggests that sex differences in anxiety severity may be explained by the fact that several risk factors of anxiety are more prevalent in females than in males [10, 32]. Several such individual risk factors have been examined. In particular, prior sexual assault and abuse have been put forward as possible explanations for why females develop more anxiety, and specifically more PTSD, than males. However, sex differences in PTSD exist across all trauma types [33] and even prior sexual trauma has been found to account for only a small part of the association between sex and PTSD [32, 34]. In general, most studies have found that when examined individually, even the most promising potential mediators cannot fully account for sex differences in anxiety. Instead, several potential mediators are likely to work together.

A recent study found that a combination of 10 pre-, peri-, and posttraumatic risk factors could account for 83% of the association between sex and PTSD severity in bank employees exposed to robbery [32]. The strongest mediators in this mediation model were peritraumatic emotional responses and posttraumatic cognitions, although the authors argued that it was the combined effect of mediators, rather than the few uniquely significant variables, that were responsible for accounting for such a large proportion of sex differences in PTSD severity. Similarly, Leach and colleagues tested a multivariate mediation model consisting of 35 socio-demographic, psychological, and social mediators in three age groups [31]. Sex differences were most pronounced in the youngest age group (20–24 years) but were also significant in the other two (40–44 years and 60–64 years). Although several of these potential mediators contributed significantly to sex differences in anxiety, sex remained a significant predictor of anxiety in the youngest age group. In contrast, the combination of mediators fully accounted for sex differences in anxiety in the two older age groups. Adding rumination and neuroticism improved all three models, but sex still remained significant in the youngest age group [31]. The total and direct effects found in this study were obtained from the first author (Liana Leach, personal communication, January 2015). These were used to calculate how much of the association between sex and anxiety could be accounted for by the mediators. In the two older age groups, the mediators accounted for a similar amount of the association whether or not rumination and neuroticism were included (92–97%). Although this does look impressive, it is important to bear in mind that the total effects were very small in these two age groups (both  $c$ 's  $< 0.095$ ), suggesting that the impact of sex on anxiety, though significant, was negligible. Thus, although mediation did occur in the two older age groups, this was not clinically relevant. However, in the younger population, sex had a much larger direct effect on anxiety ( $c = 0.233$ ). In this population, the first mediation model accounted for 43.5% of the association between sex and anxiety. When rumination and neuroticism were included, the model accounted for 56.1% of the impact of sex on anxiety. Finally, Lewinsohn and colleagues used an ANOVA and logistic regression analysis to examine whether 10 psychosocial variables

could account for sex differences in anxiety levels in high school students [10]. The impact of sex on diagnostic status remained largely unaltered after controlling for the impact of the 10 variables [10]. Together, results from these three studies suggest that several potential mediators are needed to fully account for sex differences in anxiety and particularly strong risk factors, such as neuroticism, emotional response, and subsequent negative cognitions and rumination, are necessary to include in such models. Interestingly, these variables appear to represent the presence of both biological and environmental influences on sex differences in anxiety. Whereas neuroticism appears to have a large hereditary component, emotional responses are more likely to be affected by socialisation processes [9]. Thus, it is most likely that any model attempting to account for sex differences in anxiety must include both sex-related and gender-related components.

One way in which gender and sex may work together to cause sex differences in anxiety is through a diathesis-stress model. Inspired by the arguments presented by Parker and Brotchie [22], the diathesis component of such a model may represent an inherent preparedness in females towards readily responding with anxiety when faced with a stressor. This inherent preparedness most likely consists of biologically grounded traits, such as neuroticism, anxiety sensitivity, and trait anxiety, along with HPA axis reactivity, limbic system hyperactivation, and similar biologically based systems. In accordance with this, it has been suggested that sex differences in anxiety may largely correspond with a larger genetic predisposition to anxiety and to general vulnerability traits in females compared to males [9]. Whereas biological sex differences result in an inherent vulnerability towards anxiety in females, cultural gender may further increase sex differences in the development of specific anxiety disorders through the stress component of the diathesis-stress model. The different roles that males and females hold in society are associated with exposure to different daily and traumatic stressors that can trigger the development of specific anxiety disorders and further increase sex differences in such disorders [20, 23]. Among the stressors that are most prevalent in females are sexual trauma, domestic abuse, and low socioeconomic status. In addition, it has been suggested that the social and environmental influences experienced by females may support the genetic predisposition, whereas experiences in males may be more likely to counteract such predispositions [9]. Some support has been offered for the possibility that the impact of genetic factors may be greater in females compared to males even in the absence of sex differences in the distribution of such genetic factors [9].

### *2.3.1. Summary and discussion of mediation studies*

Mediation studies show great promise in helping researchers account for sex differences in the prevalence and severity of anxiety. However, very little is known about how different mediators may work together to account for sex differences. Furthermore, several potential mediators remain unstudied. For example, Bekker and Mens-Verhulst suggest that future studies examine sex/gender differences in the meanings being contributed to feared and avoided situations [7]. For example, although an interpersonal assault, such as a robbery, may not contain any element of sexual assault, it is still likely to be differently interpreted by a female compared to a male victim, as the whole experience is more likely to be shaped by fear

of the assault becoming sexual in the female's case. The studies reviewed here suggest in accordance with the diathesis-stress model that both variables associated with biological sex and variables associated with cultural gender will need to be included as potential mediators for such mediation models to account for a substantial amount of sex differences in the prevalence and severity of anxiety. It is important that such future mediation studies are designed properly. In addition to being theoretically driven and including as many relevant potential mediators as possible, it is important that future studies build on prior research and include mediators that have previously been found to be among the strongest mediators of sex differences in anxiety. Neuroticism, rumination, emotional response, and negative cognitions have been found to be strong candidates to be included in future studies. Furthermore, potential mediators should represent both pre-existing risk and protective factors, stressor-related factors that appear to be involved in triggering the development of specific anxiety disorders, and maintaining factors involved in the continued presence or worsening of anxiety symptoms. Finally, future mediation studies should use statistical analyses designed specifically for testing multivariate mediation models [35].

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- The mediation hypothesis suggests that the higher prevalence of anxiety symptoms in females can be accounted for by a higher female prevalence of related risk factors and a higher male prevalence of protective factors.
  - Although several such variables have been proposed and examined, it appears that no single risk factor can sufficiently account for the increased anxiety in females. Instead, a combination of risk factors is needed.
  - Multivariate mediation models show great promise helping researchers account for the preponderance of females in anxiety disorders.
  - The diathesis-stress theory suggests that both an increased inherent vulnerability towards anxiety in females and different exposure to stressors contribute to sex differences in anxiety.
  - The diathesis part of the model may manifest as a psychological (e.g., neuroticism, anxiety sensitivity, trait anxiety) and/or a physiological (HPA axis reactivity, limbic system hyperactivation) preparedness to respond to stressors with anxiety.
  - The stress part of the model concerns different environmental factors that are associated with the development of anxiety (e.g., socioeconomic status, socialisation, minority status, everyday stressors, and traumatic exposure).
  - The diathesis-stress theory is a great example of how influences of sex and gender can work together to affect the development of anxiety and increase prevalence rates in females compared to males.
  - The diathesis-stress theory can be used to guide future mediation studies, as it suggests that both the diathesis and the stress component should be represented in multivariate mediation models.
  - Future studies should include multiple mediators, including variables that have not previously been studied and variables found to be important in previous studies (e.g., neuroticism, rumination, emotional response, negative cognitions), as well as pre-existing, stressor-related, and maintaining factors.
  - Future studies should use statistical methods developed specifically for testing multivariate mediation models.
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**Table 5.** Summary points for accounting for sex differences in anxiety severity

The mediation hypothesis is neither a theory of sex differences in anxiety nor can it replace such theories. Rather, it may represent a way for sex differences in associated variables to affect sex differences in anxiety disorders. Which specific variables are relevant and why they affect

anxiety levels are among the questions that we need good theories of sex differences in anxiety to answer. Furthermore, even if future mediation studies can fully account for sex differences in different anxiety disorders, this does not get us any closer to understanding these sex differences, if we still do not know why sex differences exist in the mediators [32]. In addition, sex differences in anxiety disorders appear to go beyond a higher prevalence and symptom severity in females. Even if a combination of different risk factors can fully account for why females report more anxiety symptoms than males, we still do not know whether these risk factors predict anxiety equally well in males and females. As has previously been suggested specifically for PTSD [23, 32], sex differences in anxiety are likely to involve both mediation and moderation effects. The association between anxiety symptoms and other variables, such as risk and protective factors, comorbidity, and treatment efficacy, may differ in males and females and may ultimately cause the two sexes to follow separate pathways to the different anxiety disorders.

#### **2.4. Sex as a moderator in anxiety research**

Doing a systematic review of moderation effects of sex in anxiety disorders is made extremely difficult by the fact that such moderation effects are rarely mentioned in the abstracts of the articles reporting them. Very often such moderation analyses appear to be conducted on little more than an afterthought and are rarely given much attention. For this reason, the results presented in this section do not represent a thorough or systematic discussion of how sex moderates important associations in anxiety research. Rather, the results presented here are meant as an appetizer, highlighting the importance of conducting such research – both within the field of anxiety and in relation to other mental disorders.

Some moderation effects may affect detection and self-reporting of anxiety in males and females. One study reported that primary care physicians detected ICD-10 GAD, panic disorder, and agoraphobia equally well in males and females, suggesting that sex differences in the prevalence rates of these disorders are not caused by detection bias [36]. However, the same study found that females were slightly more likely than males to be falsely diagnosed with an ICD-10 affective or anxiety disorder, suggesting that prevalence rates may be artificially inflated in females compared to males, although the impact of this on sex differences in prevalence rates are most likely negligible. Furthermore, whereas social desirability cannot account for sex differences in anxiety, males may be more likely than females to be biased by social desirability. One study reported that social desirability was only significantly correlated with state anxiety in males, and that the correlation between social desirability and trait anxiety, although significant in both males and females, was stronger in males [28]. However, the original study did not test whether these sex differences were significant. For the purpose of this chapter, the correlation coefficients and male and female population sizes reported in the original study were used to conduct a Z-test to examine the significance of the reported sex differences in the associations. This test revealed that sex did not significantly moderate the associations between social desirability and trait or state anxiety (both  $Z$ 's  $< 1.75$ ; two-tailed tests).

In addition to such moderation effects relevant to the prevalence and severity of anxiety disorders, moderation effects may be of tremendous theoretical and clinical importance when

they affect associations between risk factors and the development of different anxiety disorders. The presence of such moderation effects may cause males and females to primarily follow different pathways to these disorders. For example, sex differences in the initial response to a traumatic event and subsequent moderation effects of sex on associations between PTSD and multiple correlates have been combined in a preliminary model suggesting sex-specific pathways to PTSD [23]. Although the existence of such sex-specific pathways have not been identified in adults, it is possible that they exist both in PTSD and other anxiety disorders where certain risk or protective factors are found to be predictive of symptoms only in males or females.

A study on SAD severity in graduate students found that the impact of independence and interdependence on social anxiety was moderated by sex. Whereas the association between social anxiety severity and independence was negative in males, it was positive in females [24]. The authors suggest that in accordance with self-discrepancy theory, social anxiety arises in individuals who perceive their social role and behaviour to be inconsistent with the expectations of others, causing social anxiety to arise in different situations for males and females. Similarly, another study found that there was a trend ( $p = 0.07$ ) towards submissive behaviour being more strongly and positively associated with social anxiety in males compared to females [37]. These analyses were conducted in a relatively small sample, suggesting that submissive behaviour may prove in future studies to be more relevant to social anxiety, and possibly other types of anxiety, in males if examined in larger populations. Finally, more complicated analyses have found a significantly stronger association between submissive behaviours and shame in males compared to females with SAD [37]. This illustrates that sex is also an important variable to consider in future studies when examining the interactions between different variables and their impact on anxiety disorders.

Sex differences may also exist in the association between exposure to different stressors and the development of anxiety disorders. One study found that the occurrence of childhood trauma in patients with OCD differed between males and females, with sexual abuse being more common in females and emotional neglect being more common in males [16]. It is likely that such sex differences in prior traumatic events in clinical samples merely represent sex differences in the general exposure to such events. However, another possibility is that childhood trauma and severe stressors may play a stronger role in the development of OCD in males than in females. For example, it has been suggested that early brain trauma may be particularly involved in the early development of OCD in males [16, 38], whereas other stressful events are more likely to precipitate OCD in females [16]. It is further possible that sex differences exist in the associations between specific or general stressful and traumatic events and the development of different anxiety disorders. In addition to the possibility that different traumatic or stressful events may precipitate anxiety in males and females, it is possible that males and females may differ in the degree to which anxiety is associated with hereditary or environmental factors.

In general, the heritability of anxiety-related vulnerability factors, such as neuroticism, anxiety sensitivity, and trait anxiety have been found to be greater in females compared to males, and higher heritability estimates for fears and phobias have similarly been found in females in both

child and adolescent samples [9]. In accordance with this, an Australian twin study found that 41% of SA in females was attributable to hereditary/genetic factors, whereas 58% was attributable to unique environmental factors, and only 2% to shared environmental factors [39]. In contrast, hereditary factors made no contribution to male SA, which could in turn be contributed to 73% unique environmental factors and 27% shared environmental factors. Two other studies have also reported sex differences in the influence of hereditary and environmental factors in SA. These studies found that the genetic contribution to SA was 50–75% in females but only 0–14% in males [11]. In accordance with a stronger environmental component to male SA, two studies have found that separation from fathers and overprotective parenting are associated with increased early separation anxiety symptoms in males only [39].

In contrast to the findings in SA, a study examining the heritability of OCD in children separately for males and females found that two out of three OCD dimensions were significantly inheritable in males with 60–65% of the variance in these two dimensions being attributable to genetic factors [28]. In contrast, none of the three dimensions were found to be inheritable in females. In addition, another study found a higher correlation between state and trait anxiety in males (0.456) compared to females (0.385). The authors deduced that situational factors may exert a greater impact on anxiety symptoms in females compared to males. However, they did not test whether this moderation effect was significant. For the purpose of this chapter, a Z-score was calculated using the information provided by the authors relating to the number of male and female participants and the two correlation coefficients [28]. This analysis provided a Z-score of 0.81, implying that although the correlation between state and trait anxiety appears to be stronger for males than females, this difference was not significant at the  $p < 0.05$  level.

#### *2.4.1. Summary and discussion of moderation effects*

Research on moderation effects of sex on associations between anxiety and associated variables is very scarce. The few studies presented here are evidence that sex may have the potential to moderate important associations in anxiety research. In accordance with this, several researchers have called for more studies examining the impact of sex/gender on the epidemiology of anxiety disorders [2, 23]. Future research on moderation effects may involve any associations thought to be relevant in anxiety research. Whereas studies on mediation effects should focus on risk factors more prevalent in females and protective factors more prevalent in males, any variable thought to be associated with anxiety may be moderated by sex. Moderation effects are highly relevant to examine when studying risk and protective factors of anxiety disorders, as they may help researchers make sense of inconsistent findings. If a risk factor is only sometimes found to predict anxiety, this may be due to sex differences in its predictive value.

At this early stage, research may be guided by preliminary research hypotheses. For example, Christiansen and Elklit have presented a preliminary model of potential sex-specific pathways to PTSD based on sex differences in the physiological stress response [23]. This model suggests that variables such as dissociation, social support, and emotion-focused coping may be particularly involved in the development and maintenance of PTSD, and possibly other anxiety disorders, in females compared to males. In contrast, physiological arousal, anxiety,

avoidant coping, and problem-focused coping may be more strongly associated with PTSD in males.

Another hypothesis used to guide moderation research could be based on the results regarding the apparently stronger genetic component in SA in females compared to males. It is possible that this moderation effect is specific to SA, perhaps because SA has represented an evolutionary advantage in females but not in males [39]. However, another possibility is that the increased hereditary effect in females is generalised to other anxiety disorders, with the likely exception of OCD. If that is the case, then biological risk and protective factors may prove more important in female compared to male anxiety disorders. Furthermore, this would suggest that personality traits with a high degree of heritability, such as neuroticism, trait anxiety, and similar variables are likely to be more strongly associated with SA in females compared to males. In contrast, variables associated with upbringing, personal experience, and environmental factors, such as employment status, socioeconomic status, and recent stressors, may be more important to male anxiety. In accordance with this, Silove and colleagues suggested that unless specifically challenged by distinctive environmental stressors, males are less likely to develop high levels of SA in childhood and adolescence [39]. If a similar hereditary component exists for females in other anxiety disorders, making females genetically more vulnerable to developing symptoms of anxiety, males may only develop such disorders if they are exposed to certain environmental stressors associated with each disorder.

Finally, the diathesis-stress model may be used to guide research on moderation effects of sex in anxiety. Because this model would suggest an inherent vulnerability to anxiety that is stronger in females compared to males, this would also result in hypotheses of physiological variables and hereditary traits being more important to anxiety in females compared to males. However, this model would not necessarily lead to hypotheses stating that environmental factors would be more strongly associated with anxiety in males. Rather, environmental factors could be expected to be equally important to anxiety in males and females, or certain variables could be particularly important in males and others in females. Regardless of the hypotheses used to guide moderation research, it is important that more such research is carried out. If sex differences exist in the ability of different risk and protective factors to predict anxiety disorders, this may point to the existence of sex-specific pathways to different anxiety disorders. Furthermore, if different risk factors dominate in males and females, this may result in sex differences once an anxiety disorder exists. Such sex differences may affect the age of onset, course, comorbidity, and general clinical presentation of different anxiety disorders in males and females.

There are different ways of examining moderation effects. One way is by examining interaction effects in ANOVA or regression analyses. These analyses make it easy to test for moderation effects while simultaneously controlling for other variables. However, the number of associations that can be examined in this way is limited. A different way of testing moderation is to conduct correlation or regression analyses separately in males and females. The benefit of this approach is that it presents an easy way of comparing multiple associations between males and females. An important limitation, however, is that the power of the analyses conducted is reduced, as the population sample is divided into two. Furthermore, there is a potential

problem with these kinds of analyses. A number of studies have conducted correlation or regression analyses separately for males and females and have reported the results of such analyses without testing whether sex differences are significant. Even though the association between two variables is significant in males, but not in females, or is even positive in males and negative in females, such differences are not necessarily significant. Thus, in order to avoid reporting sex differences that are not significant, Z-tests should always be conducted to establish the significance levels of moderation effects in this type of analyses. There are several examples in the literature of authors who have based their conclusions on apparent moderation effects that are not actually significant. In addition, it is easy to overlook significant moderation effects if an association is significant in both males and females. In such cases, a Z-test can reveal that the association is significantly stronger in one sex, even though the main effect is significant in both. Thus, conducting Z-tests can reduce the risk of both type I and type II errors.

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- Both mediation and moderation are likely to be involved in sex differences in anxiety.
  - Whereas mediation effects can help account for sex differences in the severity and prevalence of anxiety, the presence of moderation effects would mean that the association between anxiety and certain variables are not equally strong in males and females.
  - Moderation effects in the associations between anxiety and associated risk and protective factors may ultimately point to males and females primarily following different pathways to anxiety, which may result in sex differences in the expression and treatment of anxiety disorders.
  - Moderation effects have been reported for both factors related to reporting and classification of anxiety (e.g., social desirability), genetic versus societal contributions to anxiety, and risk and protective factors (e.g., independence).
  - Research is very scarce, non-significant moderation effects are likely to remain unreported, and all reported moderation effects should be replicated in other studies.
  - Future studies could examine moderation effects for any associations in anxiety. However, associations that may be particularly relevant to examine in a moderation context include hereditary traits versus societal influences.
  - There are different ways of examining moderation effects in anxiety research. Multivariate models can examine potential interaction effects or separate male and female correlation or regression analyses can be compared to each other. If the latter approach is used, the significance of potential moderation effects should always be examined in order to avoid both type I and type II errors.
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**Table 6.** Summary points for sex as a moderator in anxiety research

## **2.5. Sex differences in clinical characteristics of anxiety disorders**

Whereas it is well-established that females are more likely than males to develop most anxiety disorders, it is more uncertain whether sex differences exist once the disorder has developed. Several researchers have found that males and females do not differ in mean age of onset for anxiety disorders in general, nor for any specific anxiety disorder [2, 10]. However, other studies have reported a later onset of PD, GAD, and especially OCD in females compared to males [16, 30, 40, 41]. Only one disorder appears to have a later onset in males than in females. Although the vast majority of childhood cases of separation anxiety (SA) remit before adulthood, new as well as persisting cases of SA do exist in adults [8]. The odds ratio for females

compared to males is 2.2 in childhood and 1.4 in adulthood [8]. Analyses have revealed that the higher female:male odds ratio in children compared to adults is caused by the fact that males are more likely than females to have a first onset of SA in adulthood [8].

In spite of a later onset for some of these disorders in females, PD and PTSD have both been found to be more chronic or recurrent in females compared to males [5, 9, 30, 11, 42, 43] although findings are inconsistent [30]. In contrast, OCD appears to take a more chronic course in males, as early onset OCD is often particularly severe [9]. Finally, studies have reported similar chronicity in males and females with SP, AG, SAD, and GAD [30]. Taking the high degree of comorbidity into account, one study found that females with a lifetime prevalence of any anxiety disorder were more likely than males to have met criteria for any anxiety disorder within the past year [2]. This suggests that females with anxiety disorders either have more re-occurrences or more onsets of different anxiety disorders than males.

Some sex differences have been reported in comorbidity. Overall, females who are diagnosed with one mental disorder are more likely than males to have three or more comorbid disorders [4]. Across different anxiety disorders, females appear to be more likely than males to report comorbid affective disorders, eating disorders, impulse control disorders, self-injurious behaviour, and other anxiety disorders [2, 10, 16, 38]. In contrast, males are more likely to report comorbid ADHD, intermittent explosive disorder, and substance use disorders [2, 16, 38]. Furthermore, males are more likely than females to have met criteria for hypersexual disorder and pyromania at an earlier time in their life [16], and specifically for OCD, comorbidity with Tourette syndrome and tics are much more pronounced in males compared to females [38, 44]. Finally, although the presence of any anxiety disorder is associated with high blood pressure and vascular disease in both males and females, the risk of suffering from vascular disease is more pronounced in males even after controlling for socio-demographic variables and risk factors for vascular disease [45].

The higher rates of comorbid disorders in females compared to males are likely to affect both symptom severity and clinical presentation. Some studies have reported comparable symptom levels in males and females suffering from GAD, PD (with or without agoraphobia), or SAD [24, 30, 37]. Similarly, in the NCS-R, no interaction effects were found between sex and disability on DSM-IV anxiety disorders when assessed together [3]. In contrast, other studies have found that females with PD, AG, GAD, SP, SAD, and PTSD report higher symptom levels than males with these disorders [7, 46]. Furthermore, sex differences in the clinical presentation of different anxiety disorders have been reported. For example, males and females with SP tend to differ in the specific content of their phobias [11]. Furthermore, whereas some studies have found that males and females with SAD report similar fears of social situations [24], others have found sex differences in regards to which specific social situations are most fear-provoking [37, 11]. Similar sex differences have been reported for OCD where obsessions and compulsions related to cleaning, contamination, and aggression are more prevalent in females, whereas those related to sexual content, exactness, ordering, repeating, hoarding, touching, and especially symmetry and checking, are more prevalent in males [9, 16, 38]. In PD, equal rates of panic attacks are generally reported by males and females, but physical panic symptoms, such as shortness of breath, faintness, and smothering sensations are more likely to be

among the primary panic symptoms in females compared to males [9]. Furthermore, PD is more likely to be associated with AG in females than in males [42]. In AG, males are more likely than females to report fear of bodily illness and of the heart stopping, whereas females report more fears related to going into the street and into crowded shops and also appear to be more dependent on a companion when going out [26].

The generally higher symptom severity and more pronounced comorbidity in females may result a higher degree of functional impairment compared to males [41]. In contrast, it has been suggested that the earlier age of OCD onset in males may result in a higher impact on several areas of daily life in males, including both social adjustment and interpersonal relationships [38]. In accordance with this, sex differences have been reported specifically for OCD with several studies reporting better overall quality of life in females compared to males [47]. For anxiety disorders other than OCD, the degree of impairment tends to be similar for males and females. The clinical presentation of PD has been reported to be very similar in the two sexes [41], and males and females with an anxiety disorder are equally likely to miss work and to seek help for emotional and substance abuse issues [2]. In accordance with these findings, the symptom profiles of males and females with PTSD appear to be very similar [23].

### *2.5.1. Summary and discussion of sex differences in clinical characteristics*

All in all, some sex differences occur in onset of anxiety with early onset of most disorders being more common in males. The one exception to this general rule appears to be SA, which may have a higher prevalence of adult onset in males compared to females. However, research on sex differences in adults with SA is practically non-existing, so this finding needs to be replicated. The most widely reported sex differences in the clinical presentation of anxiety disorders are those related to comorbidity. Females are more likely than males to report comorbid conditions, especially other anxiety disorders. In general, these findings regarding sex differences in comorbidity are hardly surprising, as they reflect the sex differences generally reported for these disorders, with males reporting higher degree of comorbidity with externalising disorders and females reporting higher degree of comorbidity with internalising disorders. In fact, a lack of sex differences in comorbid disorders would be a more interesting finding than the sex differences described here, as that would imply that males and females with anxiety disorders differ less on the prevalence of other disorders compared to the general population. That said, expected sex differences in comorbidity are not completely uninteresting, as the presence of comorbidity reduces the likelihood of remission and offers additional problems for the patient that are likely to affect everyday functioning and quality of life [5].

Males and females do appear to differ somewhat in the symptom profiles of different disorders. However, sex differences are generally not substantial and are mostly limited to the specific contents of phobias, social fears, obsessions, and compulsions. Furthermore, the general impairment related to the different disorders appears to be mostly comparable between males and females, although females generally report higher symptom levels. All in all, these results suggest that in spite of the substantial impact of sex on the prevalence and severity of anxiety in the general population, there appear to be more similarities than differences once an anxiety disorder has developed.

The biggest exception to this rule is OCD. Early onset OCD is significantly more prevalent in males compared with females. Furthermore, OCD in males is more likely to be associated with tics, and possibly also with early brain injury, compared to females. OCD is also the only disorder that is sometimes found to be associated with a higher degree of impairment in males. In fact, the differences between male and female OCD are so substantial that researchers have suggested they are etiologically different from one another [15]. This hypothesis is supported by findings that male OCD patients show distinct patterns of neuropsychological dysfunction [15]. Perhaps it is not surprising that sex differences in OCD appear to be more substantial compared to sex differences in the other anxiety disorders, as OCD is no longer considered an anxiety disorder. In contrast, sex differences in PTSD appear to be more similar to those found in other anxiety disorders. Although sex differences in ASD have been less extensively studied, the influence of sex in ASD is likely to be comparable to that in PTSD because of the general similarities and partial symptom overlap between the two disorders. However, whereas sex differences in PTSD, and presumably also ASD, are similar to those found in conditions still categorised as anxiety disorders, the unique requirement of traumatic exposure in ASD and PTSD sets them aside from the other disorders discussed in this chapter.

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- Whereas it is clear that females have a higher risk of developing anxiety disorders than males, it is less clear whether differences exist once the disorders have developed.
  - Whereas findings are inconsistent, there is some support for sex differences related to age of onset, chronicity, comorbidity, severity, and clinical presentation.
  - Females may have later onset of PD, GAD, and OCD but earlier onset of SA compared to males.
  - OCD may be more chronic in males, but females appear to have more chronic and/or more recurrent anxiety disorders in general.
  - Males and females appear to differ in their patterns of comorbid disorders. These sex differences generally follow the common clinical pattern of more external disorders in males and more internal disorders in females.
  - Females with anxiety disorders tend to have higher symptom levels than their male counterparts.
  - Sex differences in the clinical presentation of anxiety disorders are generally not substantial and have mostly been reported in relation to the specific content of phobias, social fears, obsessions, and compulsions.
  - The degree of impairment and reduced quality of life associated with having an anxiety disorder is generally similar for males and females. The exception is OCD, as male OCD patients tend to be more negatively affected than their female counterparts.
  - In general, there appear at present to be more similarities than differences between males and females diagnosed with an anxiety disorder.
  - Only for OCD do sex differences appear to be so substantial that it has been suggested that male and female OCD are etiologically distinct disorders.
  - More research is needed to further examine sex differences and similarities in patients suffering from different anxiety disorders.
  - Future research should among other things examine the temporal association between anxiety and comorbid disorders along with the potential impact of sex on such associations.
  - Even minor sex differences once an anxiety disorder has developed can potentially affect impairment, quality of life, and treatment response.
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**Table 7.** Summary points for sex differences in clinical characteristics of anxiety disorders

McLean and colleagues have suggested that future research move beyond documenting sex differences in the differential patterns of comorbidity to examine how sex affects the sequential association between anxiety diagnoses and comorbidity [2]. As suggested by Christiansen and Elklit, gonadal hormones are likely to affect male and female stress responses over long periods of time [23]. Thus, it is possible that such stress response patterns may affect both the development of a first anxiety disorder and the development of comorbidity over time. If more is learned about how one anxiety disorder affects the development of other anxiety disorders along with depression and other types of comorbidity, we may be able to do more to prevent the generalisation of fears and anxiety. Such research should account for sex as a potential moderator from the very beginning to increase our understanding of interaction effects and to better help males and females suffering from anxiety and other disorders. In addition, more research should examine how sex affects other aspects of anxiety disorders once they have developed. Although such research is unlikely to find anxiety disorders, other than OCD, to be etiologically different in males and females, even minor sex differences are relevant to identify, as they may have the potential to affect both impairment and quality of life. Finally, such differences may affect how males and females respond to both pharmacotherapy and psychotherapy.

## **2.6. Sex differences in treatments of anxiety disorders**

Males are generally significantly less likely to seek and receive mental health services compared to females [48], and females suffering from anxiety disorders have a significantly higher health care usage compared to their male counterparts [2]. This general tendency has been confirmed in a study of GAD [49] but disconfirmed in a study of SAD [24]. In the latter study, males were more likely than females to seek treatment, which may explain why sex differences are not always found in clinical populations of SAD [9]. Finally, one study examined help-seeking behaviour across the life span separately in males and females with different anxiety and mood disorders. They found that females were more likely than males to seek help for all the anxiety disorders that were examined [48]. According to this study, 25–32% of males suffering from GAD, PTSD, PD, SAD, or SP sought treatment, whereas the numbers for females were 68–75%. However, it is possible that a large proportion of the increased help-seeking behaviour in females is due to the higher prevalence of comorbid disorders in females.

In addition to sex differences in treatment-seeking behaviour, sex differences in anxiety have the potential to greatly influence treatment outcomes. Variables that are found to be moderated by sex in their effects on anxiety are particularly relevant to sex differences in treatment outcome, as they may be targeted in therapy aimed specifically at male or female patients. In addition, sex differences have been reported in the physiological stress response involving both the HPA axis and the serotonergic system [23, 50]. Such sex differences are likely to affect treatment outcomes and possibly cause sex differences in response to psychotropic medication. Several researchers have suggested that knowledge about sex and gender should be implemented in research on treatment of anxiety disorders [7, 23]. Furthermore, both sex and gender influences may affect how males and females respond to different treatments, including how well they tolerate them and how different aspects of treatment affect different symptoms.

Unfortunately, sex and gender differences are very rarely examined in studies of treatment effects on different anxiety disorders. Bekker and Mens-Verhulst conducted a literature search for empirical studies of the influence of sex on outcomes in treatment studies [7]. Although this search initially resulted in the identification of 33 studies, only four reported the results of sex-specific analyses, two studies on pharmacotherapy and two studies on psychotherapy. For the remaining studies, it was unclear whether no such results were reported because no significant interaction effects were found or because sex-specific analyses were not conducted. Finally, the authors identified a meta-analysis that had divided 33 treatment studies into studies based primarily on male or female populations and found no significant differences in treatment efficacy between the two groups [7]. A review of sex differences specifically in PTSD treatment efficacy published in 2010 identified only nine randomised controlled trials that had analysed sex differences in PTSD treatment [51].

### 2.6.1. Pharmacotherapy

There are several reasons to expect that sex differences in the impact of different psychopharmacological treatments on different anxiety symptoms may exist. Although research in this area is very scarce, the existence of some sex differences have been reported for the metabolism, and side-effects of benzodiazepines, tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs) [5, 19]. Sex differences may further depend on age as well as reproductive status, use of oral contraceptives, and HRT in females. For example, lower concentrations of benzodiazepines may be expected in premenopausal females, but not postmenopausal females, compared to males [19]. Furthermore, use of oral contraceptives and HRT appear to affect the impact of benzodiazepines, TCAs, and SSRIs [19, 41], and probably also other types of anxiolytic and psychotropic medication. However, whereas significant sex differences have been identified in both the pharmacokinetics and pharmacodynamics of antidepressants [52], the clinical implications of these sex differences have not been properly examined [19]. In spite of the fact that such sex differences may result in more adverse effects occurring in females compared to males when receiving the same dose of anxiolytic medications [19], such clinically relevant sex differences are rarely examined in research on pharmacotherapy in patients with different anxiety disorders.

Whereas several studies have found an increased effect of SSRIs on depression in females compared to males [52, 53], only few studies have examined the effects of SSRIs on anxiety separately in males and females. One study found that there were no sex differences in the efficacy of sertraline over placebo in the treatment of GAD [49]. In contrast, another study found that female patients with PD benefitted more from sertraline treatment than males on some of the outcome measures [41]. It is possible that the lack of significant sex differences in the former study is related to the finding that a significantly greater proportion of females had prior experience with psychotropic medication, thereby suggesting that a greater proportion of female compared to male patients may have been particularly difficult to treat. Furthermore, although males and females had similar scores on most pre-treatment measures, females did score significantly higher on a few, including overall clinical severity. Thus, any potentially stronger effect of sertraline in female patients may have been cancelled out by a higher severity

level and more treatment-resistant symptoms in females. Finally, in spite of a very small sample size, one study found that females with GAD had a significantly worse response to 6 weeks of treatment with the SSRI fluoxetine compared to males [53]. In this study, patients with current comorbid anxious or affective disorders were not excluded from the study, whereas patients with alcohol or substance abuse/dependence were. However, this is unlikely to explain the differences in treatment outcome, as there were no significant sex differences in comorbid mood or anxiety disorders, and comorbidity did not predict treatment outcome.

In contrast to the apparently greater effect of SSRIs in females, results from research on depression suggest that both TCAs and tetracyclic antidepressants (TeCAs) may result in better outcomes in males [52]. A study of OCD patients found that females responded better to treatment with either the TCA clomipramine or the SSRI fluvoxamine than males [54]. However, due to an already small sample size and high drop-out rates, it is unclear whether these differences were equal for the two drugs and whether interactions between treatment and response to a prior symptom-provoking agent differed for males and females. In addition to these studies of antidepressives, a pilot study examining the effects of propranolol found promising results that this beta-blocker decreases PTSD severity in males, but may actually increase symptom levels in females [55].

Finally, one of the treatment studies examined sex differences in tolerance levels for males and females undergoing sertraline treatment for GAD. It was reported that sertraline was generally tolerated equally well by males and females with comparable reports of side-effects and similar dropout rates [49]. The exceptions were nausea for which a larger placebo versus treatment effect was found in males and increased sweating which was more commonly reported by females in the sertraline group. In accordance with these minor sex differences, other studies have reported that males and females differ in the specific side effects associated with different antidepressives [52]. This may cause sex differences in the attrition rates associated with different drugs used for treating anxiety. In accordance with this, there is some support that females are more likely to drop out from TCA treatment, whereas males are more likely to drop out from SSRI treatment [52]. One study treating male and female OCD patients with either a TCA or an SSRI found no significant sex differences in drop-out rates [54]. However, as 46% of males compared to 29% of females failed to complete the treatment, it is possible that the lack of significant sex differences were due to low power. Furthermore, because of the low power, a sex by treatment interaction effect could not be examined for attrition rates.

### 2.6.2. *Psychotherapy*

Males and females may also differ in how they respond to psychotherapy. Possibly because of oestrogen effects, sex differences have been reported in both fear conditioning and extinction [18]. As exposure therapy is commonly used to treat anxiety disorders, it is very likely that sex differences may exist in the effectiveness of such therapies. A review of sex differences in PTSD treatment identified a few studies that in spite of low sample sizes reported that females responded significantly better to trauma-focused therapy than males [51]. In contrast, a more recent study comparing the effects of exposure therapy given alone to exposure therapy combined with cognitive restructuring reported similar outcomes for males and females with

PTSD [56]. However, although the combined treatment was superior to exposure given alone for both sexes, females maintained their gains from exposure therapy significantly better than males, suggesting that the difference between the two treatments was greater for males than for females.

Studies examining the impact of behavioural therapy for other anxiety disorders have reported inconsistent findings. One study on cognitive behavioural therapy (CBT) combined with acceptance and commitment therapy (ACT) reported that the treatment was equally effective in males and females with different anxiety disorders [57]. Another study examined the effects of intensive behavioural therapy in severely affected treatment-resistant OCD patients and reported greater symptom decrease in females than in males [58]. Sex differences in treatment outcome remained even after controlling for initial OCD severity and psychosocial functioning. Finally, a study on cognitive processing therapy in patients with PTSD found that males and females did not differ significantly on the primary outcomes of PTSD and depression [59]. This was found both following the last session and at 3 months follow-up in spite of medium effect sizes favouring females. In contrast, females did score significantly higher than males on the secondary outcomes of guilt, anger, and dissociation with medium-to-large effect sizes. Furthermore, the improvement on these measures occurred at a significantly higher rate in females compared to males.

Finally, there are some indications that males and females may differ in their tolerance of different aspects of psychotherapy, although results are inconsistent. One study reported comparable attrition rates and treatment length for males and females undergoing cognitive processing therapy for PTSD [59]. Other studies have found that males are more likely than females to drop out of treatments including aspects of exposure [26, 51, 57]. Similarly, females appear to be more compliant in CBT compared to males [58]. It is possible that these differences in compliance and attrition are at least partly responsible for the superior response rates in females that have sometimes been reported.

### *2.6.3. Summary and discussion of sex differences in treatment*

In general, very little research exists that has examined sex differences in the effectiveness of anxiety treatment. Most such research is designed to have adequate statistical power for detecting treatment differences, rather than gender by treatment interactions, and is often limited by small sample sizes, resulting in higher risk of type II errors. Sex differences are rarely a primary focus in treatment research, and even when significant moderation effects are found, this may not even be mentioned in the abstract. In addition, studies that do examine the impact of sex on treatment outcomes are often characterised by a failure to examine other potential moderators, such as comorbidity. In fact, patients with comorbid disorders are often excluded from treatment studies, which is likely to result in the exclusion of the worst-functioning females who are likely to benefit less from treatment. Whereas such studies may better reflect the direct impact of sex, they may prevent the identification of actual sex differences likely to be present in clinical populations. Whereas it is indeed relevant to examine whether potential sex differences in treatment effects are caused by a higher degree of comorbidity in females, such associations should be examined in mediation and moderation analyses, rather than by

individuals with comorbidity being excluded from the study. Furthermore, most studies examining sex differences in the effects of pharmacological treatment are of relatively short duration (8–12 weeks) and do not assess whether the presence or absence of sex differences remain over time. Finally, sex-specific analyses are often limited to the primary outcome measures. Sex differences in treatment effects may be more likely to be found for secondary outcomes, as these may be related to differences in comorbidity.

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- Overall, females are more likely than males to seek and receive mental health services.
  - Although knowledge of sex and gender ought to be routinely implicated in research on treatment outcomes, this is very rarely done.
  - Sex differences in gonadal hormones, metabolism, fear conditioning, and extinction are likely to cause males and females to respond differently to both pharmacotherapy and psychotherapy.
  - Although evidence stems mainly from research on depression, there is some support that females respond better to SSRIs than males, whereas males respond better to TCAs and TeCAs.
  - Results from research on psychotherapy are even more inconsistent, but may suggest that females benefit more from CBT (particularly exposure) than males.
  - Sex differences in secondary outcomes (e.g., guilt, anger, dissociation) may be found even in the absence of sex differences in primary outcome.
  - Although results are inconsistent, sex differences may exist in treatment tolerance, side effects, compliance, and drop-out rates. However, the impact of such sex differences on treatment outcome remains unexplored.
  - Research on sex differences in treatment response is often limited by small populations, inadequate statistical power, failure to take potential moderators and mediators into account, and short follow-up range. Furthermore, sex differences are rarely a primary focus, non-significant sex differences often go unreported, and even significant sex differences may not be mentioned in the abstracts of the studies reporting them.
  - In addition to avoiding these limitations, future studies should examine whether the effects of specific elements of psychotherapy are moderated by sex and whether female use of oral contraceptives, HRT, reproductive status, and menstrual cycle affect the outcomes of pharmacotherapy and psychotherapy.
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**Table 8.** Summary points for sex differences in treatments of anxiety disorders

In addition to more research examining sex differences in the general efficacy of different treatments, future studies should also begin to examine the unique role of different treatment elements in male and female treatment outcomes. For example, even if CBT is found to work equally well in males and females, it is possible that certain features (e.g., exposure) are particularly beneficial for males, if they can tolerate it, whereas others (e.g., cognitive elements) are particularly beneficial for females. Identifying sex differences in the effects of different treatment elements may help improve interventions offered to males and females. It is possible that future research will teach us that males and females benefit from the same pharmacotherapeutic and psychotherapeutic interventions, in which case they can continue to be offered the same treatments. However, another possibility is that future research may identify specific interventions and specific elements of psychotherapy or anxiolytic medications that are substantially more beneficial to one sex compared to the other, and that this will call for sex-specific interventions tailored specifically to males or to females with general or specific

symptom profiles. Whatever the answer may be, it is highly important that we begin to ask the necessary questions.

Future studies on sex differences in treatment outcomes should make an effort to include more variables that may contribute to sex differences. This is especially true for psychotropic treatment trials where a great gap exists in knowledge on hormonal influences on treatment outcomes, particularly in females. Despite the fact that data from the United States suggest that one in four females between the ages of 15 and 44 years receive oral contraceptives, and one in three females between the ages of 50 and 65 years receive some kind of HRT [19], the effects of oral contraceptives and HRT on anxiety levels remain largely unexamined. Future research should also examine whether it is beneficial, when prescribing psychotropic therapy to females, to adjust for phase of the menstrual cycle [50]. Future studies should examine the impact of gonadal hormones on the effectiveness of both pharmacotherapy and psychotherapy, as both appear to be affected by oestrogen.

### 3. Conclusion

The chapter examined the current status of research on sex differences in agoraphobia, general anxiety disorder, panic disorder, separation anxiety, social anxiety disorder, acute stress disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Although the extent of sex differences across the different anxiety disorders varies, a higher symptom severity in females compared to males has been reported for all these disorders. Studies using multivariate mediation models to examine whether the influence of sex on the severity and prevalence of anxiety can be accounted for by sex differences in associated variables show some promise, especially if a combination of several variables are taken into account and if these represent both biological and environmental risk and protective factors. However, mediation analyses can only account for a small part of the contribution of sex to anxiety, as sex differences in anxiety appear to go beyond sex differences in the prevalence and severity of the different anxiety disorders. Although studies on sex as a moderator in anxiety research are few and far between certain risk factors have been reported to be significantly more strongly associated with anxiety in one sex compared to the other. Thus, much more research is needed to examine the extent of such moderation effects. Future studies should strive to conduct proper moderation analyses, making sure to report not just sex differences in relevant associations, but also report whether such sex differences are significant. Furthermore, moderation effects of sex should be confirmed in more than one study, and it should be examined whether the same moderation effects exist across different anxiety disorders. At the present time, so little research has been conducted on moderation effects in anxiety disorders, that a lack of significant sex differences in such associations will be as interesting a finding as the identification of significant differences. As has been suggested for PTSD [23], even small sex differences in associations between anxiety and related variables may point to the involvement of different mechanisms in the development of anxiety disorders in males and females. Sex differences in the association between anxiety and important risk and protective factors have the potential to affect the clinical expression of such anxiety disorders. However, although

some sex differences have been reported in relation to age of onset, specific symptoms, and comorbidity, more similarities than differences appear to exist between the clinical profiles of males and females with anxiety disorders. Finally, very little research has examined whether different approaches to treat anxiety are equally effective in males and females. Although findings are inconsistent, there are some indications that SSRIs may be more effective in females, TCAs may be more effective in males, and males may be more likely to drop out of exposure-based psychotherapy than females. The fact that no studies were published during the past 5 years examining sex differences specifically in AG, ASD, SA, and SP suggests that research on sex differences in these disorders is particularly warranted. However, the generally low numbers found for all anxiety disorders, except for PTSD, highlight the importance for much more research focusing on sex differences in anxiety disorders in general.

The present review of sex differences in diagnoses previously or currently classified as anxiety disorders has generally found many similarities across the different disorders. Thus, although ASD and PTSD are no longer categorised as anxiety disorders, it remains defensible to compare findings to those reported in relation to anxiety disorders. As much more research has been conducted on sex differences in PTSD compared to any of the other disorders, there may be some benefit to letting the design of future studies on other anxiety disorders be inspired by research on sex differences in PTSD. For example, moderation effects reported in PTSD research are likely to also be found in relation to other anxiety disorders. Whereas more similarities than differences exist in the clinical profiles of males and females with most anxiety disorders, once the disorder has developed, this does not appear to be the case with OCD. OCD in males have been found to be more genetically based, have an earlier onset, be associated with tics and Tourette syndrome, and be associated with a lower quality of life compared to OCD in females. All these findings support the possibility of OCD in males being etiologically distinct from OCD in females, which is further consistent with the removal of OCD from the anxiety disorder category. When it comes to sex differences, at least, OCD does not appear to have much in common with other traditional anxiety disorders.

## Nomenclature

Diagnoses:

- AG: agoraphobia
- ASD: acute stress disorder
- GAD: generalised anxiety disorder
- OCD: obsessive-compulsive disorder
- PD: panic disorder
- PTSD: posttraumatic stress disorder
- SA: separation anxiety

- SAD: social anxiety disorder
- SP: specific phobia

Other abbreviations:

- ACT: acceptance and commitment therapy
- DSM-III-R: diagnostic and statistical manual of mental disorders 3rd edition revised
- DSM-IV: diagnostic and statistical manual of mental disorders 4th edition
- DSM-IV-TR: diagnostic and statistical manual of mental disorders 4th edition – text revision
- DSM-5: diagnostic and statistical manual of mental disorders 5th edition
- HPA axis: hypothalamic-pituitary-adrenal axis
- NCS: national comorbidity survey
- NCS-R: national comorbidity survey-replication
- SSRI: selective serotonin re-uptake inhibitors
- TCA: tricyclic antidepressives
- TeCA: tetracyclic antidepressives

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