



# MYTH OR SCIENCE? MISSING: GIRLS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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I volunteer at two organisations where I teach children between the ages of six and eleven years old weekly. Somehow, at both of these organisations, there are many children (and volunteers) with neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD). One of the intriguing aspects of this disorder is the difference in prevalence between boys and girls; ADHD is more prevalent in boys than in girls. Where does this difference in diagnoses between boys and girls come from? Are the girls who are bouncing around missed ADHD cases? Are dreamy girls who cannot remember what you just said displaying different characteristics of the same disorder? Or are there just more boys affected by ADHD than girls?

**A**ttention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder, meaning that the disorder has its origins in the development of the brain. Typical symptoms of ADHD include inattention, hyperactivity, and impulsivity [1]. In order to be diagnosed with ADHD, symptoms should have their onset before the age of 12 and should cause significant impairment in at least two areas of daily life, e.g. at school and at home [1]. About five per cent of children are diagnosed with ADHD, as opposed to two to three per cent of adults [2,3].

If I ask you to imagine someone with ADHD, the chances are that the first person that comes to your mind is a ten-year-old boy. This might be a stereotypical image; however, the representation is based upon truth, as ADHD is more often diagnosed in boys than in girls [4]. A European study found that the sex ratio (boys:girls) of ADHD diagnoses ranges from 3:1 to 16:1 in Europe [4]. Where do these differences come from? Are boys more susceptible to ADHD than girls? Are we missing girls in our diagnoses, or do girls have a different presentation of ADHD than boys? In this article, we will try to answer whether ADHD is genuinely more prevalent in boys than in girls or if there is another reason for this underrepresentation of girls.

## History and symptoms of ADHD

Let us take a look at the history of ADHD. One of the first described ADHD cases is "Fidgety Philipp". He appeared in a children's book in 1864, written by Dr. Heinrich Hoffmann, a German psychiatrist [5]. This male fictional character displays all ADHD symptoms, predominantly hyperactivity [5]. Dr. Hoffmann also described two other characters, Johnny-Head-In-The-Air, who is very inattentive, and Flying Robert, who is impulsive [5]. Together, Johnny, Philipp, and Robert display all the ADHD symptoms. Other researchers describing ADHD at the beginning of the previous century found that more boys than girls had the symptoms they were focusing on, such as hyperactivity and impulsivity [6]. Currently, ADHD is seen as one disorder with three different presentations: the mainly inattentive presentation, the mainly hyperactive/impulsive presentation, and the combined presentation [1].

## Underdiagnosis: sex-specific presentations

ADHD can be more difficult to diagnose in girls due to differences in the presentation of the disorder, and this underdiagnosis might be the cause of underrepresentation [7,8]. When we look at Johnny, Philipp, and Robert, it is evident that these boys present with very different symptoms and behaviours, although these boys have the same disorder. In a community sample, girls presented more often with internalising behaviour, such as inattentive symptoms and comorbid disorders, in comparison to boys [9]. Boys often display more externalising behaviour, such as hyperactivity and impulsivity [8,9]. Externalising behaviour is more easily picked up by parents and teachers than internalising behaviour, such as inattentiveness [7]. This leads to a phenomenon called referral bias, where boys are more easily referred to physicians than girls because the problems children with ADHD experience are less visible in girls than in boys [10]. One study by Mowlem *et al.* investigated which factors influence ADHD diagnosis in boys and girls [8]. The researchers interviewed a group of children with more severe ADHD symptoms than the general ADHD population and found that emotional problems most often determined if a girl with more severe ADHD symptoms was diagnosed with ADHD or not, an effect that was weaker in boys [8]. Moreover, parents rated impairments, such as conduct and peer problems, for diagnosed boys higher than for undiagnosed boys with severe symptoms of ADHD, but the same pattern did not show for girls [8]. Additionally, parents overestimated hyperactive/impulsive symptoms for boys in comparison with clinical interview data but underestimated these symptoms for girls [8]. This study shows how important the perception of parents and teachers is in order to make sure girls receive an appropriate ADHD diagnosis and get the help they need.

## Perception of girls with ADHD

It is crucial to know how disorders, including ADHD, are perceived in society, as the perception of a disorder by society influences the acceptance of the disorder [11]. An interview with a representative population consisting of randomly selected adults, parents of children with ADHD, teachers, and adolescents, found that the majority of the included adults and teachers believe that ADHD is more prevalent in boys than in girls [12]. Moreover, the adults and teachers think that girls more often present with the inattentive presentation

instead of the hyperactive or combined presentation [12]. The most important result of this interview is the finding that 85% of the teachers and half of the general population and parents think that ADHD is underdiagnosed in girls [12]. Thus, underdiagnosis of girls is not only visible in research but also recognised by society.

## The female protective effect

However, can underdiagnosis truly explain the underrepresentation of girls with ADHD? Recently, a new hypothesis, called the female protective effect, was formed to explain the differences in ADHD prevalence between boys and girls [15]. This theory assumes that there is a certain aspect of being female that protects you from developing ADHD. In other words, as a girl, you need more risk factors or a higher etiological load before you display symptoms of ADHD than boys do [15].

The female protective effect hypothesis is not completely new. Much more research on this theory has been done for autism spectrum disorders (ASD). In ASD, we see, just like in ADHD, more diagnoses for boys than for girls [13]. For ASD without an intellectual disability, the ratio (boys: girls) is 6-16:1, and with an intellectual disability, it is 1-2:1 [13]. Moreover, studies found that females with ASD often have more genetic mutations than males with ASD [13]. Furthermore, siblings of affected girls have higher ASD symptom scores and a higher risk of having ASD themselves than siblings of affected boys [14]. Additionally, the mutations that girls carry often have a higher impact considering that these are more closely related to the functionality of the gene network, meaning that the mutations have a higher impact on the biological pathways associated with ASD [13].

Following this line of thought, researchers wanted to investigate if they could find evidence for a female protective effect in ADHD. The first study to investigate this effect used a twin sample [15]. As ADHD symptoms vary with age, using twins was advantageous since they have the same age at the time of measurement. If being female is a protective factor, you would need to have more risk factors to develop a symptomatic disorder. If you are a twin of a female (sharing 50% of the genetic load), you are, therefore, likely to also carry more risk factors if you have a female twin with full symptomatic ADHD. A total of 10,759 dizygotic twin pairs from two cohorts were included and filled out a questionnaire about the presence and severity of ADHD symptoms. One twin from each pair was randomly selected as the index-twin, the other twin was the co-twin. The highest-scoring 5% and 10% on the questionnaire from the index-twins were selected. The researchers found that the co-twins of girls in the highest-scoring 5% and 10% cut-off groups had higher ADHD symptom scores than co-twins of boys in the corresponding highest-scoring groups [15]. This outcome was independent of the gender of the co-twin [15]. The effect is visible for total ADHD symptom scores, inattentiveness, and hyperactivity/impulsivity. Moreover, co-twins of affected girls were more likely to be affected themselves [15].

In conclusion, if you have a female co-twin diagnosed with ADHD or high ADHD symptom questionnaire scores, you are more likely to have ADHD or high ADHD symptom questionnaire scores yourself than when you have a male co-twin with ADHD or high ADHD scores. This study shows evidence that there might be a female protective effect. However, with one twin study, we have not nearly enough data to completely accept this hypothesis. Is this effect also visible for healthy siblings? Can we find a neural or even genetic basis to base our hypothesis on?

## Finding further evidence

A recent study investigated the risk of developing a neurodevelopmental disorder in siblings of boys and girls with ADHD [16]. The study found that siblings of female subjects with ADHD had a higher risk of developing any psychiatric or neurodevelopmental disorder in comparison to siblings of male probands with ADHD. ADHD was the neurodevelopmental disorder that was most often diagnosed in siblings of the probands. Again, higher percentages of girls with ADHD were found to have a sibling with ADHD than boys with ADHD [16]. These results are interesting because we see evidence for the female protective effect both in a twin sample as in siblings. However, these findings still need to be supported by biological findings, such as molecular genetics or brain imaging, to fully explain the female protective effect.

If we look at the relationship between genetics and the risk of developing ADHD, the results differ between studies [17,18]. There is some evidence that siblings of girls with ADHD have a higher polygenic risk score than siblings of boys with ADHD. This finding indicates that siblings of girls have more low risk and more high-frequency genetic variants associated with ADHD than siblings of boys. However, in the diagnosed siblings, no difference in polygenic risk score was found for boys and girls. Overall, this means that girls have a higher familial genetic burden for ADHD than boys but do not necessarily have more genetic variants than boys [17]. Martin *et al.* suggest that ADHD in females could be more often associated with larger, more rare genetic mutations, which are associated with a worse clinical phenotype [17].

Considering that ADHD is a brain disorder, it would also be interesting to see if there are differences in brain structure and connectivity between siblings of boys and girls with ADHD. If the female protective effect on the risk of developing ADHD exists, we would expect that the brains of siblings from girls with ADHD are more similar to the brains of ADHD cases than the brains of siblings from boys with ADHD. Unfortunately, no research investigating this has been performed yet; nevertheless, it is a hot topic. In conclusion, there is evidence for a female protective effect on ADHD, but there is too little evidence to completely accept the hypothesis. This female protective effect would not be able to explain all of the differences in ADHD prevalence between boys and girls, but it can bring us one or a few steps closer.

## Conclusion

Two theories might explain why ADHD is more often diagnosed in boys than in girls. The first theory concerns an underdiagnosis of ADHD in girls due to a different presentation of the disorder. This theory implies that the actual difference in the prevalence between boys and girls is much smaller than we now see or even non-existent. The second theory encompasses the female protective effect on the risk of developing ADHD. This theory implies that there truly is a difference in the prevalence of ADHD between boys and girls and that aspects of being female are protective for developing ADHD.

Which theory is true? Is there truly a difference in ADHD prevalence between boys and girls? We should keep in mind that the theories are not mutually exclusive. We are missing many girls in the ADHD diagnoses, and we should do better to give them the help they need. However, from the second theory, it seems plausible that females are protected, even though it is not yet clear how; much more research needs to be done to strengthen this hypothesis. When combining the two theories, there probably is an actual difference in ADHD prevalence between boys and girls due to the female protective effect, but this gap is not as large as it currently seems because of missed

diagnoses in females. Future research should, on the one hand, look into how we can recognise and diagnose ADHD better in girls and, on the other hand, look into the mechanisms behind the female protective effect.

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## CORRECT ANSWERS TO THE EXAM QUESTIONS

### Answer question 1:

A. Cytokines released by macrophages

During the start of an infection, macrophages release the cytokines IL-1, IL-6, and TNF- $\alpha$ , which stimulate the liver to produce acute-phase proteins. One of these proteins is C-reactive protein (CRP). CRP can bind to bacteria, yeasts, fungi, and several parasites, functioning as an opsonin and starting the classical route of activation of the complement system. Its serum concentration peaks within hours after the start of an infection. Therefore, the serum concentration of CRP is a relatively reliable biomarker for infections.

For further reading:

Parham, P. Chapter 3: Innate Immunity: the Induced Response to Infection in *The Immune System*, 4th edition. (Garland Science, New York, 2015).

During the exam, 85% of the participants answered this question correctly.

The exam questions can be found back on page 20 in this journal.

### Answer question 2:

A. APO lipoprotein allele epsilon 4 is necessary for fat metabolism at a younger age, whereas it increases the rate of developing Alzheimer's disease at an older age

Antagonistic pleiotropy is one of the proposed theories of ageing, stating that certain genes that promote our fitness during reproductive age can cause health problems at a later age, contributing to ageing. An example of this phenomenon is APO lipoprotein allele epsilon 4 that contributes to our health (fat metabolism) during our reproductive years but increases the risk of developing Alzheimer's disease later in life.

For further reading:

Stater, S., Saffitz, J., Rubin, E. Chapter 10: Aging in Rubin's *Pathology: Mechanisms of Human Disease*, 8th edition. (Wolters Kluwer, Philadelphia, 2020)

During the exam, 87% of the participants answered this question correctly.