UNIVERSITY OF SKÖVDE

Sexual Distraction: The Sex-biased Influence of Estrogen on ADHD

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Abstract

Everyone gets frustrated over lack of motivation or focus sometimes, but people with ADHD have struggles of related character every single day in their lives. This struggle may be difficult for people to understand. Another factor not well understood is the large discrepancy in the ADHD prevalence between males and females. The most obvious way to study this sex biased male to female ratio of ADHD is by looking at the correlation between sex hormones and ADHD. Moreover, the biggest difference in hormonal profiles between the sexes is the menstrual cycle. Some research exists on testosterone and ADHD but research is limited on more female associated sex hormones such as estradiol. A systematic literature review is now conducted with search words relating to ADHD and estrogen. The results from this review imply that estrogen may mediate ADHD symptom presentation by interacting with other sex hormones. It is further indicated that estrogen receptors may affect ADHD symptom presentation, but this finding needs to be supported by replicating research.

Keywords: ADHD, estradiol, estrogen, sex differences, symptom presentation

Sexual Distraction: The Sex-biased Influence of Estrogen on ADHD

> "I do not know how you do something just enough. How you sleep just enough, drink just enough and study just enough. How you exercise just enough, love just enough, cry just enough, discuss just enough and eat just enough. I am not just enough."[1] (Karpathakis, p. 8, 2018)

Persons with attention-deficit/hyperactivity-disorder (ADHD) have behavioral inhibition deficits such as regulating their own motivation and keeping the energy up to do something they do not feel like doing (Barkley, 1997). ADHD is a neuropsychiatric disorder (Schatz & Rostain, 2006), with several possible subtypes as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (*DSM-V*; APA, 2013) (Chhabildas et al., 2001).

The global prevalence of ADHD is believed to be around 5 % (Polanczyk et al., 2007, 2014). The actual prevalence differs from country to country for reasons that are partly unclear (Faraone et al., 2003). But regardless of the country in question, one particularly notable feature of ADHD prevalence is the male to female ratio, which is estimated to be between 2:1 to 3:1 in general population samples (Bruchmüller et al., 2012; Gaub & Carlson, 1997; Willcutt, 2012). In clinical samples, the ratio is even higher, estimated to be somewhere between 2:1 and 9:1 (Nussbaum, 2012), but seemingly more towards the higher than the lower end (Derks et al., 2007; Gaub & Carlson, 1997; Levy et al., 2005). The question is *why* this difference in prevalence between the sexes occurs in the first place (Diamantopoulou et al., 2005; Mahone & Wodka, 2008; Quinn & Madhoo, 2014; Skogli et al., 2013).

Research indicates that sex hormones may regulate ADHD symptom presentation. For instance, the higher testosterone levels in males as compared to females may be a plausible explanation for the sex biased prevalence of ADHD (Li & Huang, 2006). Moreover,

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[1] Swedish original: "Jag vet inte hur man gör något lagom mycket. Hur man sover lagom, dricker lagom och pluggar lagom. Hur man tränar lagom, älskar lagom, gråter lagom, diskuterar lagom och äter lagom. Jag är inte lagom."

the interaction between testosterone and other hormones, such as estrogen, is mentioned in a review as a possible mediator in the development of ADHD (Budziszewska et al., 2010). Anyhow, even though females have some levels of testosterone, the major sex difference is the menstrual cycle with fluctuating sex hormones (Haimov-Kochman & Berger, 2014).

If estrogen, or other hormones fluctuating in the menstrual cycle, plays an important role in the female expression of ADHD symptoms, then an important aspect is the question of how it works and which age groups this should affect. This is complex. One study for instance shows that decreased levels of estrogen result in increased ADHD symptoms, but that this may be affected by interaction of other hormones, such as progesterone (Roberts, 2016). Additionally, if the menstrual cycle is mediating the estrogenic effect on ADHD this would imply that sexually immature children would not be affected or at least not in an equal sense. This is however just a note, since it is too complex to go into further detail. Strong scientific evidence and research dating back to the early 1980's state that the menstrual cycle, but also sex hormones in general such as estrogen, progesterone and testosterone, mediate neurological and cognitive capacities and performance (Broverman et al., 1981; Farage et al., 2008; Le et al., 2020; Sacher et al., 2013).

Even though looking at sex hormones in relation to ADHD would be a relatively obvious method to investigate the sex biased ADHD prevalence, the research is novel on this subject. Search words relating to testosterone and ADHD gave 103 respectively 114 hits on Scopus and Web of Science, whereas search words relating to estrogen and progesterone resulted in 87 and 80 hits, respectively 24 and 18 hits. These numbers indicate that the two most well-known "female" sex hormones are studied about as much as the most well-known "male" sex hormone. However, the vast majority of these articles are not actually investigating the relationship between ADHD and sex hormones, but rather coincidentally fit the search terms. The actual studies of relevance are fewer on estrogen or progesterone as compared to testosterone. It can further be noted that up until year 2000 the research

relating sex hormones to ADHD was almost exclusively on testosterone and there are still many issues for this kind of research to resolve, such as ways to conduct reliable and relevant measurements of the sex hormones.

No consensus exists regarding the relationship between testosterone and ADHD. A meta-analysis of finger-length ratios conclude that the right 2D:4D is the most reliable finger-length ratio to use as a measurement for prenatal testosterone (Hönekopp & Watson, 2010). Prenatal testosterone can also be predicted by studying twins, based on the hypothesis that the presence of a male co-twin will increase the prenatal testosterone exposure (Bütikofer et al., 2019; Cohen-Bendahan et al., 2005). Direct measure of prenatal testosterone is invasive and involves a risk for the fetus (Constantinescu & Hines, 2012; Kothari et al., 2014). Postnatal testosterone can be measured directly by taking saliva or blood samples of the subjects, (Vesper et al., 2014; Wang et al., 2017) which is referred to as serum testosterone levels.

Apart from testosterone, reviews have been made in the area claiming that estrogen and ADHD may be important to investigate, for instance due to the sex dependent hormonal profiles, girls greater tendency to both mask their ADHD symptoms and to get comorbid anxiety and depression (Haimov-Kochman & Berger, 2014; Quinn & Madhoo, 2014). Another review found that estradiol can affect the ADHD treatment depending on which phase females are in the menstrual cycle (Quinn, 2005) and also that estradiol treatment alters the effect of the ADHD medication. According to these reviews it is of interest to create sex-specific ADHD profiles. Regardless of these claimings, there are still few studies on estrogen and ADHD and the majority of the ones existing are on rats or mice.

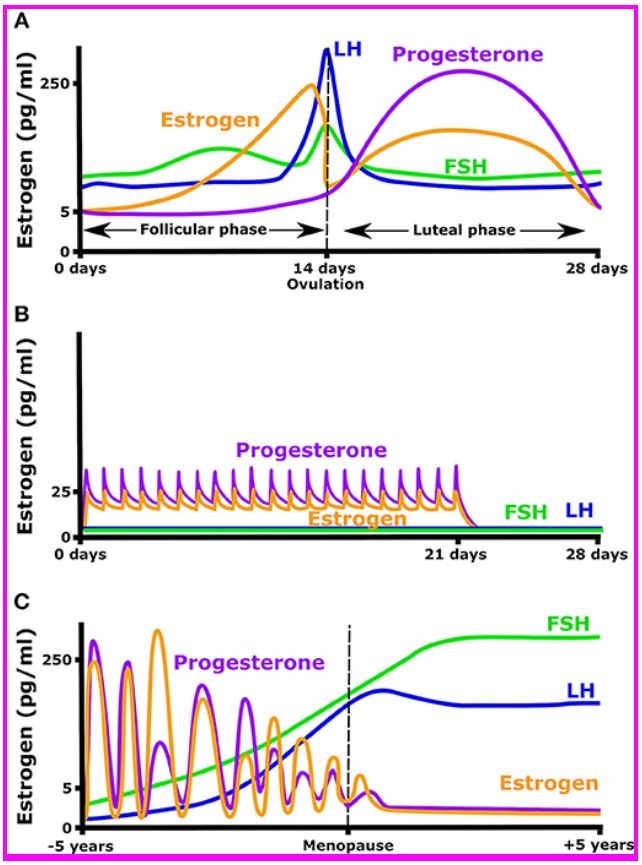
Estradiol is a sex hormone in the estrogen group most related to the menstrual cycle, but also existing in males. Estrogen for instance helps regulate the skeleton in both sexes (Khosla et al., 2002). It is important to note that estradiol is dependent on interactions with

other sex hormones, such as in different phases in the menstrual cycle. The effects of estradiol levels may for instance depend on the relative levels of progesterone (Klump et al., 2013; Puts et al., 2013; Quinn, 2005).

How estradiol is affecting individuals may differ both between and within sexes as well as within different age groups. It has been suggested that the sex hormones in the womb may be protective against ADHD for females that have a male co-twin instead of a female co-twin (Attermann et al., 2012; Eriksson et al., 2016). It is however a bit unclear what this means, which further strengthens the argument to do more research on this area. Figure 1 below shows how estrogen levels vary over the course of the menstrual cycle as well as five years before and after menopause. It is also relevant to further study estradiol in general since even the information here is difficult to retrieve. Therefore it is of interest to create a general overview of the field, to create a picture of just how much research that actually exists relating estrogen to ADHD.

Figure 1[2]

Chidi-Ogbolu & Baar 2019, p. 2 Hormonal fluctuation during (A) a normal menstrual cycle, (B) while taking an oral contraceptive (OC) containing both estrogen and progesterone, and (C) in the years before and after menopause



[2] FSH = follicle-stimulating hormone, LH = luteinizing hormone

Figure 2

Dimitrakakis & Bondy 2009, p. 6 Average estradiol (E2) and testosterone (T) levels across the female lifespan. Y-axis, level in picograms; X-axis, age in years. Dashed lines predict changes in T and E2 hormone levels resulting from estrogen replacement therapy (ERT) beginning at menopause

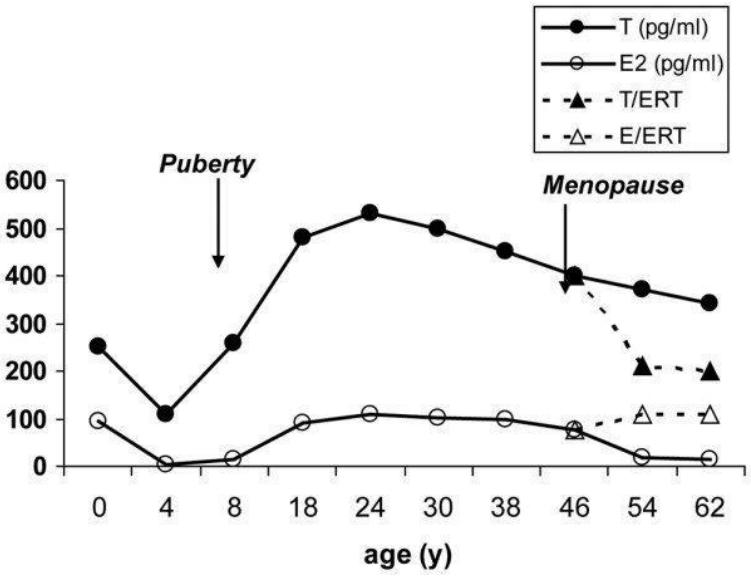
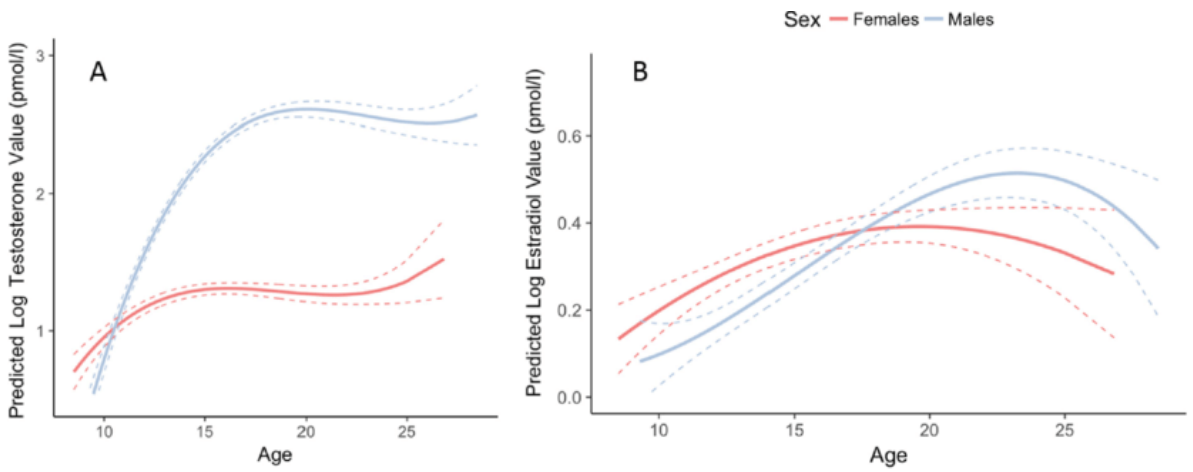


Figure 3[3]

Peper et al. 2018, p. 1896 Age-related change in testosterone (A) and estradiol (B) in males and females



[3] pmol/l = picomoles per litre

Figures 1 to 3 above depict how estradiol levels generally change depending on stage in the menstrual cycle, before and after menopause respectively in the developing years for females and males. The estradiol levels may of course be different within sexes as well. Despite what is generally assumed males have higher levels of estrogen from around 17 or 18 years of age.

In summary, consensus exists regarding that ADHD prevalence is biased towards males, but the reasons for this are unclear and not well understood. One possible explanation for the sex biased prevalence may be the concentrations of sex hormones, which vary both within and between sexes. It can be noted that factors such as brain maturation and social experiences or sex hormone interactions in different age groups (Schore, 2017) may be relevant for the estrogenic effect on ADHD symptom presentation. The ideal case would be to conduct a study investigating the interplay of such factors, as noted when discussing the menstrual cycle as the most prominent difference between the sexes. However, in order to be able to perform a relevant enquiry at all, the focus is restricted to estrogen and ADHD, hopingly leaving interesting openings for future investigations.

Therefore, this review investigates research into the possible link between ADHD symptom presentation and estrogen and estradiol, in order to try to establish if or how the two relate to each other. The aim of this review is to answer the question of what effect estrogen has on ADHD symptom presentation.

Here follows a final terminological clarification. There is a debate on the terminology of ADHD, in that some researchers state that it is not a *disease*, but rather a *disorder*, *diagnosis*, or a *collection of symptoms* (Furman, 2005). People are not chronically ill when having ADHD, even though the diagnosis in many cases persists (Biederman et al., 1996; Karam et al., 2015). If they receive treatment for their ADHD this may be because they feel a need to adapt to a society that is not fitting their cognitive profile, or to live an

ADHD-adjusted life since research emphasizes the importance of context and environment for living as ADHD optimally as possible (Delisle & Braun, 2011; Lasky et al., 2016). The above research creates an argument that ADHD does not need to be cured, but rather that life should be adjusted to adaptive circumstances and personal cognitive capabilities. This terminological clarification exists to underline this review's view on ADHD as a collection of neurological symptoms stable over time but with different outcomes depending on both the person having it and the circumstances of that person's life.

Methods

Search strategy

A systematic literature search on the potential link between estrogen and ADHD was carried out on Scopus and Web of Science on the 8 of June. The time frame was set from year 2000 until the date of search, which provided articles from a little more than 20 years of research. The keywords used for the literature search were: (TITLE-ABS-KEY (adhd OR "attention deficit hyperactivity disorder") AND TITLE-ABS-KEY (estrogen OR estradiol)).

The intended focus was to find explanations for the sex biased prevalence of ADHD by looking at the potential relationship between ADHD and estrogen. The original aim was, in other words, to study a more female-biased neurobiological contribution to ADHD in a context enabling comparisons between the sexes. The aim was thus also to provide an overview of how estrogen and estradiol may affect ADHD symptom presentation and the sex-biased prevalence of ADHD.

The search terms included estrogen respectively estradiol, the most well-known estrogen. Moreover, these studies provided material for specifically assessing the female side of ADHD, which is less studied compared to the male side of ADHD. Nevertheless, estrogen and estradiol are also present in males, which implies that the search terms enables a comparison between the sexes and may let us know what is female specific and what is more general and can be found in both sexes.

Therefore, this study provided an overview of how far research has come in the last 20 years regarding studies on estrogenic related effects on ADHD symptom presentation.

Inclusion & exclusion criteria

A superficial pre-analysis suggested that the field of ADHD and sex hormones is relatively novel and scattered in terms of hormone types included and research method,

which was one of the reasons for the consice search terms, and the choice to include estradiol since it is the major estrogen. The desire was to focus on studies of humans specifically, and so although there are several studies on estrogen and ADHD in rats and mice, these were excluded from this review. These studies were not removed already at the search-term stage, due to an abundance of precaution of not missing any potentially relevant studies; instead, all animal studies were excluded manually as part of the screening process. In other words, in the interest of focusing specifically on human subjects, the choice was therefore made to apply wider inclusion criteria in order to enable an overview of the field.

The inclusion criteria therefore merely required the articles to be original studies, include some form of empirical investigation into the link between ADHD and estrogen and / or estradiol, have human participants and be written in English. More specifically, the studies were required to have some form of measurement method for assessing the estrogen. Indirect measures were accepted, but studies merely using self-report scales as an indicator of sex hormonal presence were excluded since they were regarded as less reliable and were not aiming to specifically measure estrogen or estradiol.

As already noted, studies on animals were also excluded, as were book chapters, reviews and meta-analysis, since the articles for this overview were supposed to be original studies.

Data extraction

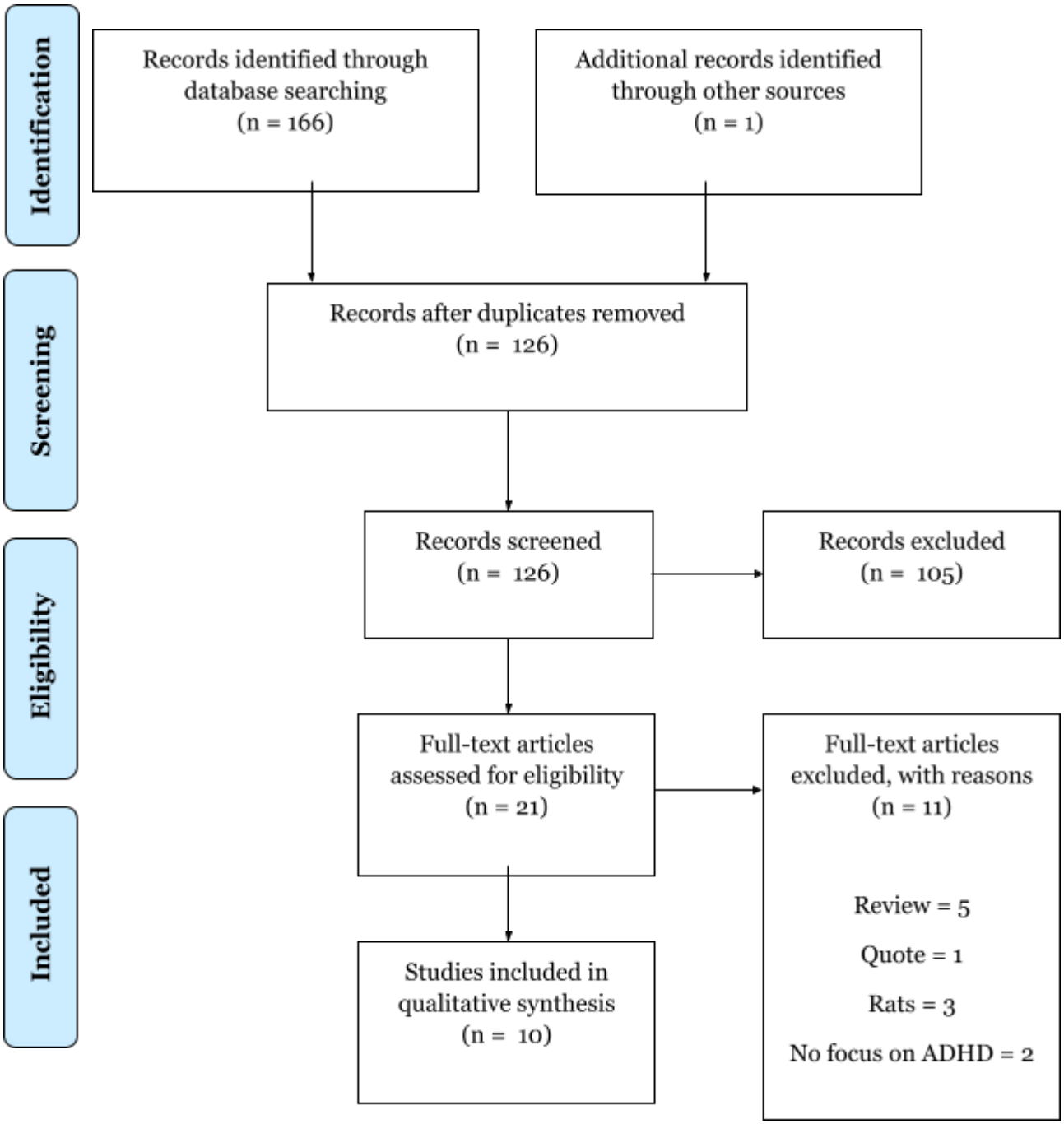
The data extracted from the studies and summarized in the results section are the measurements of estrogen levels in relation to ADHD symptom presentation or diagnosis. Information on the participants was also tracked, for instance age, sex or occupation.

The search terms resulted in 166 documents, of which 87 were from Scopus and 79 from Web of Science. A total of 41 documents were excluded after checking for duplicates, leaving 125 documents for screening. Some of the excluded articles included reviews and

meta-analyses – the bibliographies of these were searched, and an additional article of potential relevance was found and included, resulting in 126 articles in total after duplication-removal. The remaining 126 studies were first screened by reading their abstract and then included or excluded depending on whether the abstract seemed to contain a link investigation between ADHD and estrogen. 105 documents were excluded after the initial screening, leaving 21 documents for second assessment. The 21 documents passing the first screening were skimmed, with most focus on the method part. This resulted in the exclusion of eleven documents, resulting in a total of ten articles included in this systematic literature review.

Figure 4

Moher et al. 2009 PRISMA flow diagram used to document the literature search process



Results

RESULTS TABLE[4]

Article	Participants	Type of test	Hormonal aspects	Outcomes
De Water et al. (2017)	58 adolescents (age-range: 12-16) 31 females, 27 males	Saliva samples on two occasions. Female samples conducted with concern to their menstrual cycle.	**Estradiol**, testosterone	Overall: No sig. correlations between temporal discounting and estradiol. Note that temporal discounting is measured with fMRI as an ADHD related trait.
Epperson et al. (2015)	32 females (perimenopausal and early postmenopausal, age-range: 45-60)	Blood samples	**Estradiol**	No sig. effects reported. Prior hormone treatment reported to be irrelevant for EF.
Ergür et al. (2019)	M = 8,16 years. 4 females, 3 males	Blood samples	**Estradiol**, **estrogen**	No sig. correlations between estradiol and ADHD symptoms
Gokcen et al. (2019)	ADHD-group: 49 prepubertal males in (M = 6,9 +- 0,2 years). Controls: 30 age matched males	Blood samples	**Estradiol**, free and bioavailable testosterone	Less severe ADHD symptoms on all subscales due to less subscale scores after methylphenidate treatment. Furthermore, all the sex hormone levels where significantly lower and more alike the controls.
Hergüner et al. (2015)	PCOS group: 40 females (age-range: 18-35) Controls: 40 females (age-range: 18-35)	Self-reports on PCOS (non-clinical diagnosis of non-direct measure). Blood samples on PCOS-group in early follicular phase.	**Estradiol**, progesterone, testosterone	"ADHD"-females (PCOS): Hyperactivity-impulsivity score sig. higher than non-PCOS group. No sig. differences regarding inattention. No correlations found between sex hormone level in blood and ADHD symptoms. Control females (non-PCOS): Hyperactivity-impulsivity score significantly lower than PCOS group. No sig. differences regarding inattention.

[4] EF = executive function, GPER = G protein-coupled estrogen receptor 1, M = mean age, PCOS = polycystic ovary syndrome, SD = standard deviation, sig. = significant

Roberts et al. (2018)	32 females with natural cycles (age-range: 18-22. M = 19,43, SD = 1,38)	Saliva collection in the morning	**Estradiol**, progesterone, testosterone	Next day heightened ADHD symptoms when estradiol was decreased in combination with increased progesterone or testosterone.
Sahin et al. (2018)	ADHD group: 47 children (age-range: 6–12 years; males = 34, females = 13) Controls: 35 age-matched children (males = 19, females = 16)	Blood samples	**Estrogen**, GPER	Sig. finding: Seems like there could be a relationship between GPER and ADHD rather than the exact estrogen levels in themselves. Sig. lower GPER in ADHD group as compared to controls.
Tsai et al. (2020)	ADHD groups: 98 males (M = 8,5) and 32 females (M = 8,1). Controls: 42 males (M = 8,7) and 26 females (M = 9,2).	Blood samples in the morning.	**Estradiol**, testosterone, free testosterone, progesterone	No sig. differences in sex hormone levels between ADHD groups and control groups in either sex.
Wang et al. (2020)	ADHD group: 146 participants (M = 8,9 years, males = 76,7%) Controls: 70 participants (M = 9,2 years, males = 65,7%)	Blood samples in the morning	**Estradiol**, progesterone, testosterone, free testosterone	No sig. differences between ADHD group and controls in estradiol levels Changes in estradiol levels not associated with methylphenidate. No sig. correlations between serum estradiol levels and ADHD symptoms.
Zhuang et al. (2020)	53 healthy females (M = 22,77) divided into late follicular phase (28) and middle luteal phase (25)	Saliva sample	**Estradiol**, progesterone	Sig. increase in progesterone levels in mid luteal phase as compared to late follicular phase. No sig. correlations or changes in estradiol levels between the two groups.

General overview

The articles included in the systematic literature analysis all looked at estrogen in relation to ADHD symptom presentation. Ten articles were analyzed, and the results weakly contributed to the understanding of the impact of estrogen on ADHD symptom presentation. On the surface, it appears like estrogen levels or estrogen in itself does not impact ADHD symptom presentation, but rather that estrogen receptors or estrogen in interaction with other sex hormones may correlate with ADHD. It may for instance be that estrogen affects ADHD under some circumstances, but these ten articles provided only weak indications as to how or why.

These unclear and superficial results may be both due to a diverse set of studies in terms of the measured forms of sex hormones, the methods and the participants, but also due to the fact that this field is novel, causing the above to be the case. Nine of the analyzed articles measured estradiol, whereas one article measured estrogen and estrogen receptors (Sahin et al., 2018). Only one study throughout the complete set had single focus on estrogen (Sahin et al., 2018). Progesterone or testosterone was common to look at beside estradiol in the remaining studies.

Seven studies found no significant correlations between estradiol or estrogen levels and ADHD symptoms (Epperson et al., 2015; Ergür et al., 2019; Gokcen et al., 2019; Hergüner et al., 2015; Sahin et al., 2018; Tsai et al., 2020; Wang et al., 2020). One study showed that the interaction of estradiol with either progesterone or testosterone in the menstrual cycle may increase ADHD symptoms (Roberts et al., 2018). Another study found that estrogen receptors are significantly correlated with ADHD (Sahin et al., 2018).

Only one study excluded females (Gokcen et al., 2019) on the premise that they wanted to avoid menstrual-cycle changed patterns in the hormonal profile of the participants. Four studies excluded male participants (Epperson et al., 2015; Hergüner et al., 2015;

Roberts et al., 2018; Zhuang et al., 2020) since they examined questions related to menstrual cycle or specific female sex related conditions. These four studies had adult participants, minimum age 18. The number of participants was relatively small, and there were fewer controls than participants in ADHD groups amongst the entire category of studies, apart from one study with equal amount in the control group and the "ADHD" group (Hergüner et al., 2015). There were more males than females in all of the mixed-sex studies.

Two categories of studies could be identified from the set of studies shown in the above table. The first category (n=6) measured estrogen levels in children and/or adolescents, while the second category (n=4) measured estrogen levels in adults. The results are therefore reported according to these category divisions.

Children and adolescents

The category of studies that measured estrogen levels in children and/or adolescents consisted of six studies (De Water et al., 2017; Ergür et al., 2019; Gokcen et al., 2019; Sahin et al., 2018; Tsai et al., 2020; Wang et al., 2020).

Blood samples were used to assess the estradiol levels in five of the studies (Ergür et al., 2019; Gokcen et al., 2019; Sahin et al., 2018; Tsai et al., 2020; Wang et al., 2020). The remaining study used saliva samples (De Water et al., 2017). Five of the studies in this category had both female and male participants(De Water et al., 2017; Ergür et al., 2019; Sahin et al., 2018; Tsai et al., 2020; Wang et al., 2020), whereas one of the studies only had male participants (Gokcen et al., 2019).

These six studies had both similarities and differences in terms of ADHD measurement and classification for the ADHD group, but a majority of the studies did not need to measure ADHD traits since this was already a prerequisite for the ADHD groups respectively control groups. Parent and teacher ratings were used in five of the studies (De Water et al., 2017; Gokcen et al., 2019; Sahin et al., 2018; Tsai et al., 2020; Wang et al.,

2020). Five of the studies recruited people that already had a clinical ADHD diagnosis (Ergür et al., 2019; Gokcen et al., 2019; Sahin et al., 2018; Tsai et al., 2020; Wang et al., 2020). A questionnaire measuring ADHD related symptoms was used in one study (De Water et al., 2017), but this was not made in order to create an ADHD group but rather as an assessment for the whole set of participants.

One study examined the effect on ADHD symptoms of estradiol in combination with endocrine-disrupting chemicals (Tsai et al., 2020). Another study measured estradiol levels along with a brain scan (De Water et al., 2017) to investigate potential underlying neural connections between estradiol and the measured trait. Three studies examined the link between estradiol levels and sex hormone binding globulin (SHBG) and ADHD symptoms (Gokcen et al., 2019; Tsai et al., 2020; Wang et al., 2020). Three studies examined how ADHD treatment affects estradiol patterns in children with ADHD (Ergür et al., 2019; Gokcen et al., 2019; Wang et al., 2020). One study measured serum estrogen levels along with estrogen receptors (Sahin et al., 2018), more specifically G protein-coupled estrogen receptor 1 (GPER) levels. Five of the studies in this set measured estradiol together with other sex hormones (De Water et al., 2017; Ergür et al., 2019; Gokcen et al., 2019; Tsai et al., 2020; Wang et al., 2020). Testosterone was measured in all of these five. Only one study measured estrogen as a single hormone (Sahin et al., 2018).

No significant differences were found in estradiol or estrogen levels throughout the whole set of studies, even if one of the studies found an estradiol related significant group effect (Wang et al., 2020) this effect was not reported in more detail. Five studies found no significant interactions between estradiol or estrogen and ADHD symptom presentation (Ergür et al., 2019; Gokcen et al., 2019; Sahin et al., 2018; Tsai et al., 2020; Wang et al., 2020). The study investigating estradiol levels in relation to an ADHD symptom found no significant relations between estradiol and temporal discounting choices (De Water et al.,

2017), neither reported any significant results connecting estradiol to impulsivity nor to the underlying neurology behind the trait.

However, significant results were found between the ADHD group and control group in terms of GPER (Sahin et al., 2018). More specifically, the ADHD group was found to have significantly lower levels of GPER compared to the control group. No significant differences were found within the ADHD group, which indicates that at least in this isolated study there is no difference with regard to ADHD subtype. Moreover, GPER levels were found to be significantly related to ADHD symptom presentation, making this the only significant finding throughout the whole set of studies. It can further be noted that the study (Sahin et al., 2018) is the only found study on GPER and ADHD symptom presentation.

Altogether, the results from these seven studies gives a weak indication that estradiol maybe is not directly related to ADHD symptom presentation and that estradiol or estrogen levels in themselves might not affect the sex biased ADHD prevalence. It is however unclear since the field investigating estrogen and ADHD is novel at the very least. It is unclear how or if estrogen mediates ADHD, but the findings in one of these studies indicates that estrogen receptors may be of interest to further investigate in relation to ADHD symptom presentation or prevalence.

Adults

After the final analysis, the category of studies that measured estrogen levels in adults consisted of four studies (Epperson et al., 2015; Hergüner et al., 2015; Roberts et al., 2018; Zhuang et al., 2020). Blood samples were obtained from the participants in two of the studies as a way of assessing the estradiol levels (Epperson et al., 2015; Hergüner et al., 2015) and in two studies saliva collection was the chosen measurement method (Roberts et al., 2018; Zhuang et al., 2020). It was solely female participants in the entire set of articles in this category since the measurements were carried out with respect to their hormonal cycles.

There were some differences in terms of ADHD measurements between the studies, as was the case in the first category measuring estradiol levels in children and adolescents. One of the studies (Zhuang et al., 2020) did not explicitly measure ADHD, but measurement of the ADHD related trait impulsivity was conducted, and the authors stated that their study may contribute to insights in ADHD treatment. This study was included since it fits with the aim of the thesis but is interpreted and reported with caution since ADHD as a diagnosis is not measured; merely an ADHD-related trait (Zhuang et al., 2020). In three cases, an ADHD assessment was carried out within the study (Epperson et al., 2015; Hergüner et al., 2015; Roberts et al., 2018) and this assessment was in all cases done on a non-clinical "ADHD group" of females that were tested due to a prerequisite that was hypothesized to be correlated to ADHD. In one of the studies, a cut-off score of 20 was required in order to be included in the study (Epperson et al., 2015) together with the notion that the symptoms of EF decline should have started simultaneously as the menstrual cycle became irregular.

Female participants in the mid luteal phase respectively late follicular phase were included in one study (Zhuang et al., 2020). The progesterone levels were significantly higher in the participants in mid luteal phase, whereas the estradiol levels showed no significant differences, rather more similar levels (Zhuang et al., 2020). This however has an impact on the relative estradiol levels as compared to the progesterone levels. The effects of this study on ADHD symptoms were set aside since they were unspecific even in terms of the impulsivity measure.

One of the studies hypothesized about how ADHD could be affected by prenatal androgen exposure but called the findings tentative since the actual measured sex hormones were serum levels (Hergüner et al., 2015). The results of one study indicate that the interaction of testosterone or progesterone with estradiol may cause next day heightened ADHD symptoms (Roberts et al., 2018); this applies for increased progesterone or testosterone when the estradiol is decreased. Two studies found no significant interactions

between estradiol and ADHD symptom presentation (Epperson et al., 2015; Hergüner et al., 2015).

Altogether, the results from these four studies gives no clear indication of how estrogen mediates ADHD symptoms or affects the sex biased ADHD prevalence, other than it might be related to an interacting effect between estradiol and other circulating hormones such as progesterone or testosterone. However, conclusions cannot be drawn from these weak indications.

Final note

Some studies provide indications of possible impact of testosterone (eg. Gokcen et al., 2019; Roberts et al., 2018) and a majority in the studies included in this systematic literature review is measuring testosterone along with estradiol.

It can also be noted that even in the studies with child or adolescent participants, care was taken to the menstrual cycle (De Water et al., 2017) which in itself indicates that the female-specific hormone cycle is viewed as a possible mediator of ADHD symptom presentation.

Discussion

The aim of this review was to answer the question of what effect estrogen has on ADHD symptom presentation. The results emphasize a lack of research with a more female biased focus and method for investigating the sex differences in ADHD and how the ADHD symptom presentation may be affected by these differences. Several of the studies seem to be aware that a female-specific ADHD symptom presentation may exist, since some of the studies are adjusted to the menstrual cycle, by focusing exclusively on females with periods (Epperson et al., 2015; Hergüner et al., 2015; Roberts et al., 2018; Zhuang et al., 2020), or excluding females due to their menstrual cycles (Gokcen et al., 2019) or by conducting the measurements with concern to the cycle (De Water et al., 2017).

The menstrual cycle has per definition different phases of fluctuating sex hormones. Since these menstrual related fluctuations and inconstant interactions of sex hormones constitute the biggest difference between the female and the male sex hormone profiles, it is not sufficient to study isolated sex hormones, as already noted in the introduction. So, the reason for why the isolated estradiol or estrogen findings do not provide meaningful results in this context is probably at least partly because they do not study sex hormone interactions. Even if a majority of the studies measured several sex hormones and not exclusively focused on estrogen, the studies in most cases did not focus on the interactions, but rather saw no significant findings, changes or correlations in the single sex hormone levels, since they were observed and analyzed more as a single unit than with the intent to observe sex hormonal interactions.

The results are in line with the notion that estrogen is affected by the interactions of other sex hormones (Klump et al., 2013; Puts et al., 2013; Quinn, 2005). Furthermore, the results are as expected affected by the limited amount of research in the area. The studies on the correlation between ADHD and estrogen can hardly be mentioned as a field, since they

barely exist. The biggest finding in relation to other studies was made by Roberts (2016) where lower levels of estrogen is observed to increase ADHD symptoms when estradiol is in interaction with for instance progesterone. This finding is similar to the finding in this review (Roberts et al., 2018). It can be mentioned that the search terms resulted in 87 respectively 79 hits from Scopus and Web of Science when the time-frame was set from 2000-2021. The same search words with unlimited time-frame resulted in 87 respectively 80 hits on Scopus and Web of Science, indicating that barely a single study of relevance was conducted before year 2000 as mentioned in the introduction.

As noted in the final paragraph in the results section, even though the search terms for this systematic review were exclusively restricted to ADHD and estrogen, they resulted in more concrete information about testosterone than about estrogen. This may indicate that the study design in individual studies could benefit from a greater adjustion to the nature of estrogen and thus that the study method could be adjusted with caution to how dependent estrogen is to the fluctuations of other sex hormones such as progesterone. Since hormones are so complex it is unclear under which circumstances they may have importance or implications for ADHD symptom presentation and these results indicate that estrogen levels in themselves do not seem to be correlated to ADHD symptoms.

Therefore, it may be a better idea to study estrogen as a part of a larger system, in other words as a co-mediator in the menstrual cycle. This could for instance be done by comparing the estrogenic effects in the menstrual cycle in female participants with the estrogenic effects in male participants, but with the goal to observe and distinguish the menstrual cycle related effect on ADHD rather than the purely estrogenic one. This kind of research could potentially explain the more female biased tendency to mask ADHD symptoms, which in itself might be a reason for the male biased ADHD prevalence. However, this is just a side note since it is too complex to go into further detail.

Moreover, the results highlight that it may be relevant to look at the estrogen receptors (Sahin et al., 2018) as well, rather than simply measuring the estrogen levels. Conclusively, these results do not call for more research in estrogen and ADHD overall, but for specific research on menstrual cycle interactions and also on estrogen receptors in relation to ADHD symptom presentation. The single study on estrogen receptors may be a coincidental result or it may have found a setting in which estrogen indirectly affects ADHD symptom presentation, but since no previous studies have investigated the matter it is still worth studying due to the significant findings.

Even if estrogen or estradiol is studied in all of the ten articles, the results from this systematic literature review do not form a clear picture of estrogen in relation to ADHD. The unclear results may be due to the studies being diverse in multiple ways or it may be as reasoned above that estrogen levels in themselves lack direct relevance for ADHD symptoms. Sex and age of participants are similar in several cases, but there are solely females in some studies, and solely males in one, which may create different results in a set of merely ten studies. Maybe there is something here, in terms of correlation between estrogen or estradiol levels and ADHD symptom presentation, but individual studies mostly result in insignificant correlations, with the strongest support for a significant correlation when estradiol is interacting with other sex hormones or when estrogen receptors are involved in the observation.

More specifically, it would be of relevance to replicate the study conducted by Roberts et al. (2018) since that was the single isolated study that provided evidence of an interaction in the menstrual cycle. The study conducted by Sahin et al. (2018) would be relevant to replicate as well, due to the protruding focus and findings regarding estrogen receptors. The studies with female as well as male participants did not show significant effects, apart from the one by Sahin et al. (2018) but this may well be because the focus of those studies was not to examine the specific effects of estradiol or progesterone on ADHD symptom presentation

in females or at all. The study done by Zhuang et al. (2020) together with the results from Roberts et al. (2018) indicate that the menstrual cycle may indeed affect ADHD symptom presentation. The differences in estradiol and progesterone levels were relative during the menstrual cycle, and the results from these two studies suggest that the interaction between estradiol and progesterone may be mediating the sex-specific ADHD symptom presentation for females. Furthermore, no previous studies on the correlation between menstrual cycle and ADHD symptom presentation were found, which again emphasizes this gap of knowledge. Whether the two significant findings (Roberts et al., 2018; Sahin et al., 2018) can be interpreted as meaningful, or if the results are merely coincidental, require replication of the studies to answer, since the scientific support for these studies are unclear to say the least.

Altogether, the results indicate small but conflicting correlations between estrogen and ADHD symptoms. The results also emphasize the lack of knowledge regarding female-specific neurobiological contributions to ADHD and thus more sex biased ADHD profiles, but provide possible directions for research into the area such as investigating the correlation between ADHD and the menstrual cycle. The most simple conclusion to be drawn from these results is the relative lack of insight into the connection between ADHD and estrogen, which may be explained by various factors such as the male dominance in ADHD prevalence or the more commonly ADHD associated sex hormone testosterone.

When interpreting these results, it is important to keep in mind that they comprise the relationship between serum respectively saliva estradiol levels and ADHD symptom presentation, and thus not the actual or even general relationship between estrogen and ADHD. Because estrogen levels do not say everything about the actual relationship between ADHD and estrogen, something that Sahin et al. (2018) underlines. Caution is further

advised since the reviews and meta-analyses on the area are barely existing, which makes the results tentative.

Limitations

The search terms used for finding the articles reviewed here were a factor naturally limiting which papers that were available for screening. Estrogen and estradiol were used as search words apart from the ADHD terms, with the main thought that estradiol is the largest and most well-known estrogen, potentially increasing the chances of finding studies. Anyhow, when interpreting the results the study by Sahin et al. (2018) indicates that it might have been a good idea to include search terms relating to estrogen receptors as well. However, it is not likely that many studies were missed since Sahin et al. (2018) mentioned that no similar previous studies were found.

The final number of included studies was ten, which creates possible result or representation bias in terms of the actual scientific representation, but this seems like a minor problem since this field hardly exists in the first place, which may be a problem in itself or merely something acceptable due to the limited findings. The studies investigated also provided result limitations since they did not measure objective, true or even direct effects of estrogen on ADHD symptom presentation. It is not the same thing to directly assess blood or saliva levels as assessing the sex hormone production or function within the brain.

Sex hormones are present in living systems and their levels naturally fluctuate. Therefore, it is impossible to examine the entire picture, since estrogen and estradiol are affected by, and affect, different hormones and other entities in the endocrine system. Consequently, although it is necessary to focus on only small parts for the sake of conciseness and clarity of focus, it is important to keep in mind that they are merely an aspect of a larger system.

Societal and ethical aspects of enquiry

The relationship between estrogen and ADHD is barely studied in scientific settings, which is made clear in this review since merely ten relevant studies were found from the latest 20 years and almost not a single study was conducted before that. Consequently, the aim of this enquiry is at least partly controversial, even though the importance of studying more female specific contributions to ADHD such as the menstrual cycle induced sex hormonal interactions is mentioned in a few reviews (Haimov-Kochman & Berger, 2014; Quinn, 2005; Quinn & Madhoo, 2014). It can be argued from a societal point of view that much of the research is done from a male perspective. Even in this small set with studies derived from search terms exclusively focusing on estrogen and estradiol, females were excluded from one study because the researchers wanted to avoid confusions based on their hormonal cycles (Gokcen et al., 2019). Testosterone was studied in a majority of the articles along with estradiol or estrogen, which supports the notion that the research might be male biased, even in a "female biased" literature search.

It is an important question for society to consider why it is regarded as more relevant to conduct ADHD-related studies on testosterone than concrete menstrual cycle related studies. The original point of interest for this review was to study the menstrual cycle in relation to ADHD but this was impossible due to the limited amount of studies. Even if ADHD is more biased towards males, it is still important to investigate the female side of ADHD, maybe even more so since we do not know how common it is to let females go undiagnosed, suffering silently under various coping mechanisms. It should therefore be noticed that there is a need for studies examining the relationship between the menstrual cycle and ADHD. Many females may be suffering while unknowingly being in need of a cycle-adjusted ADHD treatment. If the results from this review can be replicated, they indicate that the menstrual cycle may regulate ADHD symptoms in a manner that potentially affects the sex biased ADHD prevalence. This is mostly indicated by the fact that the studies

on the correlation between menstrual cycle and ADHD were so few it was impossible to make out a meaningful review out of that material.

It can of course be argued that the studies made on testosterone are seemingly of equal amount as the studies on estrogen and progesterone, but this is a bit beside the point since there are still reviews claiming both that females have greater tendency to mask their symptoms, have more comorbid anxiety and depression and also that the menstrual cycle may be relevant for the found sex biased ADHD prevalence and differences. However, testosterone seems to be important for the male dominated ADHD prevalence and also for ADHD symptom presentation and it is surely of importance to investigate since there is still no consensus regarding its exact importance. Therefore it would be ethically and intellectually most strategic to keep on studying the effects of testosterone on ADHD and additionally starting to observe the menstrual cycle related effects on ADHD. Both of these perspectives seems relevant to research and there should be room for both testosterone and more female biased hormonal research, especially since it was concluded in the introduction that researchers ask for gender-specific neurobiological ADHD profiles, something that can only be acquired by comparing the difference between the female cycle in contrast to the lack of interchanging hormonal cycle in the male part of the population.

Apart from the above ethical considerations, it should also be noted that the present enquiry was conducted by reading and analyzing already existing studies. This way of investigating a question means no actual participants, which automatically means that no individual or sentient being was harmed or treated unethically in any kind of way. No informed consent was required due to the lack of participants. It can also be argued that a systematic literature review might be able to form a more objective and general answer to the question of interest as compared to an individual study.

Conclusion

This review investigated research into the possible link between ADHD symptom presentation and estrogen, in order to try to establish if or how the two relate to each other. Having performed a systematic review, the tentative conclusion that could be drawn here is that estrogen affects ADHD symptoms, but it is unclear exactly how and why. The menstrual cycle seems to be related to ADHD, but how much and why needs to be further investigated, suggestibly by starting to observe phase dependent estradiol and progesterone interactions with ADHD symptom presentation.

It is worth studying the interactions, where estradiol might be relevant, since there are reviews supporting the claim that menstrual cycle induced interactions may affect the ADHD symptoms along with the scientifically supported claim of a need of a gender-specific neurobiological ADHD profile. The results in this review does not directly support the menstrual cycle induced effect on ADHD symptom presentation, but that could easily be explained with the fact that most of the participants were children along with the fact that it was not possible to conduct such a review. The aim of these studies was not to investigate or even compare menstrual cycle related interactions to the male equivalent or rather lack of an interchanging hormonal cycle and that research actually is not existing in this area. Therefore, further research is not advised to focus exclusively on the correlation between estrogen and ADHD but rather on the sex hormonal interactions in which estrogen constitutes a part of an entity.

The most concrete findings implies that estrogen in interaction with progesterone or testosterone may increase ADHD symptoms, when estrogen is low in relation to the other sex hormones. It is also of interest to try and replicate the significant findings linking the estrogen receptor GPER to ADHD symptom presentation.

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