Department of clinical neuroscience
Karolinska Institutet, Stockholm, Sweden

MENTAL HEALTH IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

Mattias Månsson

Stockholm 2022

MENTAL HEALTH IN WOMEN WITH POLYCYSTIC OVARY SYNDROME
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Mattias Månsson

The thesis will be defended in public at Hjärtat, Danderyds Sjukhus, Stockholm, 2022 06 03 at 13.00

Principal Supervisor:
Professor Mikael Landén
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Co-supervisor(s):
Dr Anna Lena Nordström
Formerly at Karolinska Institutet
Department of clinical neuroscience

Opponent:
Professor Åsa Westrin
Lund University
Department of Psychiatry

Examination Board:
Docent Stefan Arver
Karolinska Institutet
Department of Medicine

Docent XinXin Guo
University of Gothenburg
Department of Neuroscience and Physiology

Professor Mats Hammar
Linköping University
Department of Biomedical and Clinical Sciences

POPULAR SCIENCE SUMMARY OF THE THESIS

The young successful female athlete, who after retiring discovers that it is more difficult to conceive a child than she believed, and finds that the extra weight she has gained after reducing physical activity is hard to get rid of, could be seen as the archetype of Polycystic Ovary Syndrome (PCOS). PCOS is the most common hyperandrogenic condition among women, affecting up to ten percent of women of childbearing age. The high levels of androgens (male sex hormones) might cause infertility as well as the gain of unwanted weight. Given that there are differences between women and men with respect to the prevalence of many major psychiatric disorders, as well as sex differences in personality, the overarching question in this thesis was whether women with PCOS differ from other women in the rate of psychiatric disorders, sexual health, and personality.

We first performed psychiatric interviews with a group of women with PCOS and women without PCOS who were born on the same day. Self-rated questionnaires were administered to assess personality, quality of life, and sexual health. We found that a history of depression, anxiety disorders, and suicide attempts were more common among women with PCOS. We also found that women with PCOS reported lower psychological well-being than women without PCOS. Further, women with PCOS were less satisfied with their sex life, including having difficulties getting aroused and not wanting physical contact with their partner.

We then conducted a register-based study. The aim was threefold. First, to test whether our finding of increased prevalence of depressive and anxiety disorder in women with PCOS could be replicated in a national sample. Second, to investigate whether less common psychiatric disorder might also differ between women with and without PCOS. Third, to test if any such finding was due to common genetic factors or due to an association with PCOS. Using a linkage of several nationwide registers in Sweden, we estimated the prevalence of psychiatric disorders in women diagnosed with PCOS, in the siblings of women with PCOS, and in age-matched controls. We found again that depression and anxiety disorders were more common in women with PCOS compared with other women. In addition, several rarer psychiatric disorders were more common in women with PCOS: bipolar disorder, schizophrenia spectrum disorders, bulimia nervosa, personality disorders, gender identity disorder, and autism spectrum disorder. The increased occurrence of psychiatric disorders in women with PCOS was generally modest with odds ratios ranging from one to two. After adjusting for comorbid conditions, the prevalence of depression, anxiety, and schizophrenia spectrum disorders was also higher in sisters of women with PCOS than in sisters of women without PCOS. Among brothers of women with PCOS, only the prevalence of autism spectrum disorder was higher than among brothers of women without PCOS. The latter is interesting given that autism spectrum disorders are more common among men than

women, and there is evidence to suggest that increased cerebral lateralization due to high foetal testosterone concentrations might be a contributing factor to autism.

Last, we investigated personality traits in PCOS. We used data from our clinical study together with another similarly sized sample of women with PCOS and controls who had been recruited by advertisement in local newspapers in Gothenburg, Sweden. We found that in both study cohorts, anxious personality traits were on average higher, whereas scores on the trait 'socialization' were lower, in women with PCOS compared with controls.

In conclusion, women with PCOS have an increased prevalence of a wide range of psychiatric disorders and have more anxious personality traits than women without PCOS. The increased frequency of autism spectrum disorders in both women with PCOS and their siblings lends support to the notion that androgens play a role in the development of autism.

ABSTRACT

Polycystic Ovary Syndrome (PCOS) is the most common hyperandrogenic condition in women. It is associated with several adverse health outcomes as subfertility, obesity, the metabolic syndrome, and skin issues. PCOS can be viewed as a naturally occurring model of the activating effect of androgens on women. There are significant differences in mental disorders and behaviour between men and women. The effects of androgens are a potential contributor to those differences. The overarching question in this thesis is whether women with PCOS differ from women without PCOS in terms of quality of life, psychiatric morbidity, personality, and sexual health.

We first conducted a clinical study of women with PCOS and age-matched controls who were thoroughly examined using structured interviews, biochemical analyses, and questionnaires (study I, II and IV). In study IV, we also used an independent cohort of women with PCOS and controls matched for age and BMI. Second, we used a register linkage of several nationwide Swedish registers (study III).

In study I, we found that depressive disorder, anxiety disorders, and eating disorders were more common in PCOS than controls. In women with PCOS, recurrent depression and social phobia were associated with higher Body Mass Index (BMI). In study III, we confirmed that depressive and anxiety disorders are more common among women with PCOS, and furthermore found increased prevalence of almost all studied diagnoses with the exception of alcoholism and anorexia nervosa. In a sibling analysis, both brothers and sisters of PCOS probands had more autism spectrum disorders than controls, and sisters had more anxiety, depression, and schizophrenia spectrum disorders.

In study II, we found that a larger proportion of women with PCOS are dissatisfied with their sex life than controls, and that arousal and lubrication are special areas of concern. Total sexuality correlated with testosterone in women with PCOS, but not in controls. In controls total sexuality correlated with higher psychological wellbeing, which it didn't do in PCOS. Total psychological wellbeing was lower in women with PCOS compared to controls.

In study IV, we found that women with PCOS scored higher on several anxious personality traits are higher, and lower on the personality trait 'socialization', than controls regardless of whether they were matched on BMI or not.

Taken together, we found that PCOS has significant effects on mental health including increased risks of several psychiatric disorders, psychological wellbeing, personality, and also sexual health. Some of these differences might be due to a direct or indirect effect of androgens, while other might be due to secondary effects such as subfertility, and comorbid conditions.

LIST OF SCIENTIFIC PAPERS

I. Mattias Månsson, Jan Holte, Kerstin Landin-Wilhelmsen, Eva Dahlgren, Anette Johansson, Mikael Landén, 2008
Women with polycystic ovary syndrome are often depressed or anxious – A case control study.
Psychoneuroendocrinology 33, 1132-1138

II. Mattias Månsson, Kajsa Norström, Jan Holte, Kerstin Landin-Wilhemsen, Eva Dahlgren, Mikael Landén. 2010
Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls.
European Journal of Obstetrics & Gynecology and Reproductive Biology 155, 161-165

III. Carolyn E. Cesta, Mattias Månsson, Camilla Palm, Paul Lichtenstein, Anastasia N. Iliadou, Mikael Landén. 2016
Polycystic Ovary syndrome and psychiatric disorders: Co-morbidity and heritability in a nationwide Swedish cohort.
Psychoneuroendocrinology 73, 196-203

IV. Mattias Månsson, Kerstin Landin-Wilhelmsen, Eva Dahlgren, Elisabet Stener-Victorin, Mikael Landén. 2022
Personality traits in women with polycystic ovary syndrome in two Swedish cohorts
(Submitted)

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit and Hyperactivity Disorder
BMI	Body Mass Index
CDR	Cause of Death Register
FAI	Free Androgen Index
ICD	International Classification of Diseases
KSP	Karolinska Scales of Personality
MGR	Multi Generation Register
MINI	Mini International Neuropsychiatric Interview
NIH	National Institute of Health
NOS	Not otherwise specified
NPR	National Patient Register
OR	Odds Ratio
PCOS	Polycystic Ovary Syndrome
PGWB	Psychological General Wellbeing
SHBG	Steroid Hormone Binding Globulin

1   BACKGROUND

A brief history of Polycystic Ovary Syndrome

In the mid-1930s, a pair of American gynaecologists, Irving Stein and Michael Leventhal, found an association between amenorrhea and polycystic ovaries. The condition was therefore originally known as Stein Leventhal's syndrome. Today, the condition is called Polycystic Ovary Syndrome and generally abbreviated PCOS. The proposed treatment of wedge resection of the ovaries restored menstruation and fertility in the Stein Leventhal sample. Over time, surgical treatment was replaced by medical treatment of infertility and amenorrhea.

Hyperandrogenism was recognized in the original paper (Szydlarska, 2017). As more advanced methods of investigation became available, several hormonal abnormalities were found in women with PCOS, among them increased levels of luteinizing hormone and testosterone. During the 1950s to 1970s, different biochemical methods of diagnosing PCOS were proposed. With the advent of ultrasonography in medical diagnostics and laparoscopic surgeries, focus returned to the surgical treatment and morphology of polycystic ovaries for making the diagnosis (Szydlarska, 2017).

The first widely recognized formal diagnostic criteria for PCOS were put forward by the National Institute of Health (NIH) in the early 1990s as unexplained hyperandrogenic anovulation (Dunaif et al., 1992). In 2004, a new set of criteria were adopted following an expert workshop in Rotterdam (Rotterdam, 2004). These became known as the Rotterdam criteria, where the diagnosis of PCOS requires the presence of two out of three of the following criteria: amenorrhea / oligomenorrhea, hyperandrogenism, and polycystic ovaries on ultrasound examination after excluding other pathologies.

An overview of PCOS

As defined with the Rotterdam criteria, about 5–15 percent of all women of fertile age meet the diagnostic threshold of PCOS (Lizneva et al., 2016). Hyperandrogenism is one of the core features and the main endocrinological disturbance of the syndrome together with insulin resistance (Moghetti and Tosi, 2021; Zacur, 2001). The most common presentation in health care is either one of irregular menses or difficulties getting pregnant (Ovesen et al., 1998). The diagnosis of PCOS is usually made at young adulthood because of reproductive concerns. In older age, the clinical picture changes with increasing metabolic risks associated with obesity and insulin resistance that can lead to type 2 diabetes (Teede et al., 2018). There is an interplay between high levels of androgens and insulin resistance exacerbating each other. Androgens decrease glucose transporter activity, inhibit insulin break down in the liver, and induce male pattern obesity, which causes insulin resistance. Insulin resistance leads to higher circulating

levels of insulin, which in turn stimulates androgen production in the ovaries and decreases the production of Steroid Hormone Binding Globulin (SHBG) (Wang et al., 2019).

Aetiology of PCOS

Despite that PCOS has been recognized as a distinct disorder for nearly a century, the specific aetiology remains elusive (Escobar-Morreale, 2018). PCOS is a common condition despite being associated with subfertility and considerable risks for secondary morbidity. Given that PCOS is at least partly hereditary, it stands to reason that there might be evolutionary benefits associated with the condition. One hypothesis is that PCOS is the result of a genotype adapted for strength and being able to utilize scarce supplies of food and conserve energy during periods of starvation. That would confer significant advantages during harsh conditions common in earlier history of mankind, but entails disadvantages during times of sedentary living and unlimited supplies of food (Azziz et al., 2011; Holte, 1998). Interestingly, significantly higher frequencies of PCOS than expected by chance have been shown in female endurance and power athletes (Hagmar et al., 2009; La Vignera et al., 2018).

There does not seem to be a simple single pathway leading to the development of PCOS. Twin studies have estimated the hereditability of PCOS to roughly 70 percent, but the condition is highly polygenic where a large number of genes involved in ovarian androgen synthesis and function have been associated with PCOS (Ajmal et al., 2019; Khan et al., 2019). There is some evidence to suggest that high levels of androgens during pregnancy confer changes in ovarian function and increase the odds of PCOS during adulthood. This means that women with PCOS might increase the risk of PCOS in their offspring in a nongenetic way (Dumesic et al., 2014; Stener-Victorin and Deng, 2021). Dysfunction in ovarian androgen producing cells, inflammatory processes, an interplay between high levels of androgens and insulin resistance mutually increasing each other have all been proposed as causes, but also as effects, of PCOS. In summary, the specific aetiology of PCOS has not yet been clarified (Teede et al., 2018).

PCOS and mental health

General measures of quality of life have shown that women with PCOS on average report lower quality of life than other women (Behboodi Moghadam et al., 2018; de Lima Nunes et al., 2019). Further, compared with other women, women with PCOS have higher risks for a wide range of clinical psychiatric disorders (Brutocao et al., 2018; Cesta et al., 2016; Månsson et al., 2008). As of this date, few studies have tried to disentangle whether this is an effect of PCOS per se, or due to secondary effects such as obesity, hirsutism, and unwanted childlessness (Teede et al., 2018). Studies on sexual health among women with PCOS have generally reported lower overall satisfaction with the sex life, but there are exceptions (Yin et al., 2021). In regard to the known effect of androgens to stimulate certain aspects of sexuality, there are some intriguing studies

that have shown a lower age of sexual debut among women with PCOS, higher number of sexual partners (Tzalazidis and Oinonen, 2021), and that women with PCOS are more likely to take the initiative to sex more often than other women (Månsson et al., 2011). A few studies have examined personality traits among women with PCOS. Generally, anxious and depressive personality traits have been found to be more common among women with PCOS (Cesta et al., 2017; Ozcan Dag et al., 2015; Scaruffi et al., 2019; Urban et al., 2022), and two studies found increased hyperthymic and hypomanic traits (Ozcan Dag et al., 2015), respectively.

The androgen connection

PCOS is the most common hyperandrogenic condition among women (Goodarzi et al., 2011). The fact that androgen have significant effects on the development of the nervous system as well as on behaviour is well known from animal studies (Domonkos et al., 2018; Filová et al., 2013) . In humans, androgens affect the developing brain. Supraphysiological doses of androgens affect human behaviour in both sexes. (Durdiakova et al., 2011; Roselli, 2018).

There are well known sex differences in the frequencies and expression of many psychiatric disorders. For example, major depressive disorder and anxiety disorders are more common among women than men (Faravelli et al., 2013; Kuehner, 2017), while autism spectrum disorders and learning disorders are more common in men (May et al., 2019; Zablotsky et al., 2019). Aberrations in androgen function have been linked to several psychiatric disorders, including schizophrenia, depression, and bipolar disorder (Rubinow and Schmidt, 1996). Androgens have also been suggested to play a role in the pathophysiology of Tourette´s disorder, autism spectrum disorders, and obsessive-compulsive disorder (Knickmeyer and Baron-Cohen, 2006; Martino et al., 2013). Although testosterone and other androgens have profound effects on the nervous system, research on mammals with less complex nervous systems often yields conflicting and confusing results. In a seemingly similar situation, the response might be the opposite: As when male apes are confronted with a stressor and a dominant male reacts with increased testosterone while a non-dominant male reacts with decreased levels (Sapolsky, 1986).

Obesity and mental health in the context of PCOS

Overweight and obesity is both a contributing cause of PCOS and a common complication (Naderpoor et al., 2015). About half of all women with PCOS suffer from obesity (Sam, 2007). Conversely, about a quarter of among women with severe obesity have PCOS (Kataoka et al., 2019). Obesity is known to be associated with worse mental wellbeing, and decreased quality of life (Kolotkin et al., 2001). Obesity is also associated increased frequency of major depressive disorder (Rajan and Menon, 2017), bipolar disorder (Girela-Serrano et al., 2022), and schizophrenia (Wirshing, 2004) in both men and women. Thus, obesity have been proposed as a possible pathway that might partly

explain why women with PCOS suffers from more depression, anxiety, and lower quality of life than other women (Panico et al., 2017; Teede et al., 2018). In a large genomic analysis, only a weak association was found for depression and PCOS that did not remain after adjusting for BMI. No genetic association was found for any other psychiatric disorder and PCOS (Jiang et al., 2021).

The metabolic syndrome, psychiatric disorders, and PCOS

The metabolic syndrome is a cluster of obesity, high blood pressure, high circulating triglycerides, low levels of high-density cholesterol, and insulin resistance (Huang, 2009). It has for long been known that there is an association between the metabolic syndrome and major depressive disorder, but also for bipolar disorder and schizophrenia (Penninx and Lange, 2018). PCOS shares many features of the metabolic syndrome and consequently women with PCOS have a high frequency of metabolic syndrome (Lim et al., 2019). Hyperandrogenism in women have distinct causal pathways leading to, or increasing the risks for, many of the components of the metabolic syndrome (Ali, 2015). It has been proposed that the metabolic syndrome is partly caused or made worse by disturbances in circadian rhythm, which in turn is linked to increased inflammatory markers including neuroinflammation, which might be a possible way in which the metabolic syndrome impacts mental health (Zimmet et al., 2019). Conversely, several psychiatric disorders are interacting with stress hormones as well as affecting behaviour in a way that might cause or increase the components of the metabolic syndrome (Goh and Agius, 2010; Maripuu et al., 2016; Penninx and Lange, 2018).

Does subfertility affect mental health adversely?

PCOS is the most common reason for anovulatory amenorrhea and one of the most common causes of subfertility and for seeking fertility treatment to get pregnant (Thurston et al., 2019). In Sweden, women with PCOS are not childless to a greater degree than other women, but they get children later in life and often have only one child (Persson et al., 2019). Given the similarities in health care system and culture, this is probably true for other western welfare states as well.

It has been recognized that failing to conceive is associated with reduced quality of life for women (Chachamovich et al., 2010; Kitchen et al., 2017; Massarotti et al., 2019). A Swedish study showed good long-term outcome in anxiety and depression for women who had successfully received a child either through pregnancy or adoption, while women who had not received a child had significantly more depressive symptoms (Vikström et al., 2015). There have been some research showing that mental health is worse in infertile women with PCOS compared with infertile women with other conditions (Angin et al., 2019; Naumova et al., 2021).

2 RESEARCH AIMS

The idea of this thesis was born out of the knowledge of significant sex differences in the epidemiology of many psychiatric illnesses. Sex hormones are a potential contributor to those differences. PCOS is the most common hyperandrogenic syndrome among women and could be viewed as a natural occurring model of the activating effect of androgens on women. The overarching question in this thesis is whether women with PCOS differ from women without PCOS in terms of quality of life, psychiatric morbidity, personality, and sexual health.

The specific aims were

1 – to examine if the rates of common psychiatric disorders differ between women with PCOS and other women in a clinical sample.

2 –to examine if sexual satisfaction, functioning, and psychological well-being differ between women with PCOS and other women in a clinical sample.

3 –to compare the rates of psychiatric disorders in PCOS women with i) their non-affected siblings of both sexes, and ii) non-affected other women in a nationwide register study.

4 –to examine if personality factors differ between women with PCOS compared with other women in two independent clinical samples.

3 MATERIALS AND METHODS

For study I, II, and IV, a total of 49 women with PCOS were recruited from the Carl von Linné clinic in Uppsala, Sweden, and from the Department of obstetrics and gynaecology, as well as the Department of medicine at Sahlgrenska University hospital, Gothenburg, Sweden. The women had been diagnosed using the Rotterdam criteria (Rotterdam, 2004) at their respective clinic. Age-matched control women born on the same day were identified using the telephone registry. Known psychiatric disorders and use of psychotropic drugs were not exclusion criteria.

For study IV, we used the case-control population above together with an independent sample of women with PCOS and controls that had been recruited by advertisement in the major newspaper in Gothenburg, Sweden. Here, diagnosis of PCOS was made using Rotterdam criteria (Rotterdam, 2004) during the inclusion process by trained gynaecologists. The women with PCOS and controls were matched on age and BMI. Known psychiatric disorders and use of psychotropic drugs were exclusion criteria in both subjects and controls.

In study III, patients and controls were identified using a linkage of several nationwide registers. Women with PCOS were identified by International Classification of Diseases (ICD) codes in the Swedish national patient register (NPR) during 1990–2013. A total of 26,314 patients with PCOS were identified. A small number (N=813) were excluded as they also had a condition that might cause symptoms similar to PCOS, most notably pituitary gland disorders, adrenal gland disorders, and Turner´s syndrome. In addition, 103 patients were excluded due to a prepubertal diagnosis of PCOS that did not re-occur after 13 years of age. A further 953 women were excluded due to migration and diagnosis date conflicts. Siblings to the women with PCOS were identified using the Swedish multigeneration register (MGR). Controls were chosen by selecting 10 random women matched by birth year and county for every woman with PCOS for most diagnoses, but 100 for the rarer diagnoses, i.e., schizophrenia, tics, gender dysphoria, autism, cluster A and C personality disorders, and suicide. Further data sources used to collect information about these persons were the Migration register, the Prescribed drug register (PDR) and the Cause of death register (CDR).

Clinical interviews and assessments

In the clinical cohort used in study I, II, and part of study IV, patients and controls were interviewed by physicians trained in psychiatry as well as a research nurse supervised by a board-certified psychiatrist. Background data were collected, the MINI International Neuropsychiatric Interview (Sheehan et al., 1998) was performed to assess DSM-IV psychiatric disorders. The MINI interview was modified to assess whether the patient or control had had any disorder covered by MINI during their life in addition to potential current disorders. Sexual health was examined partly by

interviewing using a structured interview, and partly by administering the 9-question version of the McCoy female sexual rating scale, which has been used in numerous studies of female sexuality (Nathorst-Böös et al., 2006; Valtysdottir et al., 2003). Psychological wellbeing was measured using the Psychological General Well Being index (PGWB), which is a self-report inventory that is commonly used in research on quality of life in both psychiatric and somatic health conditions (Lundgren-Nilsson et al., 2013). Personality traits were examined using the Karolinska Scale of personality (KSP)(Ortet-Fabregat et al., 2002), which is a self-report inventory developed on theoretical assumptions with the purpose of connecting neurobiology and personality traits predisposing to mental disorders. The KSP was also administrated in the second case-control sample used in study IV.

Biochemical analyses

Testosterone concentrations and Steroid hormone binding globulin concentrations were analysed at accredited clinical laboratories using immune-assay techniques.

Statistical analyses

The main analyses for study I, II, and IV were done using Student´s t-test for continuous data, and Chi Square test for cross tabulations. Fisher´s exact test was used when expected cases were fewer than five in study I and II. In study II, ordinal scales were analysed using Wilcoxon´s ranked pair test as well as Spearman´s correlation matrices. Linear regression analyses were used for relationships between multiple factors. A two tailed p-value of 0.05 or less were considered statistically significant. Instead of correcting for multiple analyses in study IV, we opted to require that a trait had to differ from controls in both independent populations of PCOS women. Statistica 8.0 were used as software.

In study III, conditional logistic regression was used to calculate odds ratios for risks for psychiatric disorders in cases compared with controls. Pairs of sisters are included in the analysis and those observations are not independent on each other, thus confidence intervals had to be adjusted for not being independent. To this end, a robust sandwich estimator function was used. Odds ratios (OR) were adjusted for comorbidity with other psychiatric disorders. SAS version 9.4 was used for the calculations.

Ethical considerations

The studies followed Swedish national standards and the Helsinki declaration for medical research on human subjects and was approved by the ethical committees of the Gothenburg University and Karolinska Institutet, Sweden. The participants in study I, II, and IV consented orally and in writing to participate in the studies. Some of the included patients were clinical patients to some of the co-authors, but the researchers conducting the clinical interviews had no patient-clinician relationship. All study participants were

informed that whether they opted to participate or not in the study would not affect future or current care. There is nevertheless a slight risk that such a relation might affect the decision to participate or not. The interviews contained question about mental health, suicidality, and sexual behaviour, which is considered sensitive information. The study participants were informed in advance about the topics being studied and the possibility not to answer individual questions or not continue in the study. Drawing blood samples involve some minor discomfort but no risks. These factors together with time spent constituted the cost side of the ethical equation. There was some possible individual benefit in participating in the study, most notably getting a thorough health examination and time to share their experience.

The register study involves the use of sensitive information gathered without active consent in ordinary healthcare, without any serious risk of individual information being made public nor known to the researchers. Using such information in a benign way to gather new knowledge about health conditions and advance medical knowledge is within a utilitarian frame likely to result in larger benefits than harm. Using information gathered in healthcare to improve knowledge in medicine cannot be considered a totalitarian misuse of state power.

4 RESULTS

Study I

We found that women with PCOS were more likely to had suffered from a major depressive episode, recurrent depression, social phobia, general anxiety disorder, or any eating disorder than age matched women without PCOS. A previous suicide attempt was seven times more common among women with PCOS. Almost half of the women with PCOS had used antidepressant medication compared with a fifth of the controls. Marital status and education level were similar between the groups, and notably, the number of children did not differ either. Employment status were comparable, but a significantly higher percentage of women with PCOS were on sick benefits compared with controls. In a post hoc analysis, we found that among women with PCOS, those with recurrent depression had higher BMI and were more often experiencing perspiration odour than those without recurrent depression. Similarly, within the PCOS group, social phobia was associated with higher BMI, higher free androgen index (FAI), and experiencing perspiration odour. Finally, eating disorder was associated with not having children within the PCOS group, but no other variable.

Study II

Compared with controls, women with PCOS did not differ significantly from controls in regard to having a current sexual partner, being able to talk with their partner about sex, being interested in sex, having an orgasm most of the time while having sex, sexual orientation, number of lifetime partners, age at first intercourse, or intercourse frequency. However, a significantly larger proportion of women with PCOS reported not being interested in physical contact with their partner, being the one taking the initiative to sex, not at all being satisfied with their sex life, and finding it difficult to get aroused.

The McCoy total score did not significantly differ between women with or without PCOS. With respect to individual items, however, women with PCOS reported significantly more often having insufficient lubrication and not being satisfied with their partners as friends.

Among women with PCOS, the total McCoy score significantly correlated with higher serum testosterone concentration and was borderline significantly correlated with Free Androgen Index (FAI) (p=0.06). Within the PCOS group, women with experience of assisted fertility treatment had higher McCoy total scores than those who did not have that experience. There was no association between McCoy total score and having or not having children in the PCOS group.

Psychological wellbeing as measured by the PGWB was significantly lower among women with PCOS compared with controls. Among women with PCOS, there were no

significant association between to PGWB score and McCoy score. By contrast, higher psychological wellbeing was associated with higher sexual satisfaction among controls.

Study III

Using a linkage of Swedish nationwide registers, we found that of women with a diagnosis of PCOS, 22,4 percent had received at least one psychiatric diagnosis. Among other women, 15,7 had received at least one psychiatric diagnosis (OR 1,56 (1.51-1.61)). The unadjusted risks were increased for almost all psychiatric disorders surveyed with the notable exceptions of alcoholism and anorexia nervosa. Of notice, after adjusting for comorbidity, cluster A and C personality disorders, autism spectrum disorders and tics were the most overrepresented conditions in women with PCOS compared with other women, while anorexia nervosa were less common in women with PCOS compared with other women.

We also included 11,981 non-affected sisters and 13,940 brothers of the women with PCOS in a sibling analysis. Both brothers [OR 1.16 (1.09–1.24)] and sisters [OR 1.18 (1.12–1.25)] of women with PCOS were more likely to have any psychiatric diagnosis compared with siblings of other women. Of note, siblings of both sexes had higher adjusted risks for autism spectrum disorders. Sisters of women with PCOS had higher risks for anxiety, depression, and schizophrenia spectrum disorders.

The diagnoses of included women with PCOS were made 1990–2013. During this time period, the criteria for making a diagnosis of PCOS was broadened with the Rotterdam criteria in 2004. Moreover, only inpatient diagnoses were registered in the NPR prior to 2001. This means that the later time-period might on average contain less severe PCOS cases. We therefore investigated the if these changes affected the frequency of psychiatric disorders. Generally, frequencies of psychiatric disorders were slightly lower after the broader criteria had been introduced and after the inclusion of outpatient diagnoses in the NPR.

Study IV

We compared personality traits in PCOS women with controls by administering the KSP self-rated questionnaire in two independent case-control cohorts. In both cohorts, women with PCOS scored higher than controls on the anxiety personality traits 'somatic anxiety', 'muscular tension', and 'psychic anxiety', and scored lower than controls on the 'socialization' subscale.

In the second study cohort—where psychiatric disorders had served as an exclusion criterion in both cases and controls, and controls had been matched by BMI—women with PCOS scored lower than controls on 'psychasthenia', 'guilt', and 'inhibition of aggression'. In the first study cohort—where psychiatric disorders were allowed, and

14

controls were not matched by BMI—women with PCOS scored higher than controls on 'monotony avoidance'.

5 DISCUSSION

The studies included in this thesis were conducted during a protracted period of time. During this period, the questions explored in this thesis went from being novel and unexplored to an area of significant interest. Thus, knowledge about mental health and wellbeing in women with PCOS has grown rapidly. Study I was the first study using formal psychiatric diagnostic interviews in women with PCOS and aged matched controls (Mansson et al., 2008), and also the first study examining other psychiatric diagnoses than major depressive disorder. Before that there had been surveys of quality of health, general questionnaires about well-being and depressive symptoms suggesting that depressive symptoms were more common than chance in women with PCOS (Elsenbruch et al., 2003; Hollinrake et al., 2007; Rasgon et al., 2003). There had also been reports that PCOS were more common than chance in women with either bipolar disorder or schizophrenia (Pethö et al., 1982; Rasgon et al., 2005).

Despite the modest sample size in our clinical study, we could demonstrate that major depression, recurrent depression, social phobia, generalized anxiety disorder, and eating disorders NOS were more common in women with PCOS than controls. The seriousness of the mental health issues women with PCOS might experience was evident from the seven-fold higher rate of previous suicide attempts compared with the controls.

Following our study, systematic reviews and meta-analyses have confirmed high prevalence of depressive and anxiety symptoms in PCOS (Cooney et al., 2017; Wang et al., 2021) including studies from India (Chaudhari et al., 2018; Joshi et al., 2022), Iran (Ahmadi et al., 2020),Turkey (Annagür et al., 2015), South Korea (Lee et al., 2021), and China (Lin et al., 2021).

Study III is the hitherto largest study that estimate the frequencies of psychiatric disorders in women with PCOS and age-matched controls (Cesta et al., 2016). We replicated the finding that major depression, anxiety disorders, eating disorders, and suicide attempts were more common in women with PCOS. But given the large statistical power in a nationwide sample, we could also demonstrate an increased frequency of less common psychiatric disorders in PCOS, e.g., bipolar disorder, schizophrenia, autism spectrum disorder, obsessive-compulsive disorder, and personality disorders. Psychiatric comorbidity is common with our current diagnostic systems, and after adjusting for this the odds were no longer significant for social phobia, obsessive compulsive disorder, ADHD, or suicide attempts.

Following the publication of study I, there has been some studies using a clinical case control design investigating psychiatric disorders, and at least one large register study investigating some psychiatric disorders, though not as comprehensive as study III (Ahmadi et al., 2020; Başar Gökcen et al., 2020; Hung et al., 2014). A meta-analysis summarized the current evidence and concluded that PCOS is associated with increased

risks of depression, bipolar disorder, anxiety disorders, and obsessive-compulsive disorder (Brutocao et al., 2018).

In study III, the finding of increased rates of autism spectrum disorders in both women with PCOS and their unaffected sisters and brothers is of particular interest. Intrauterine exposure to increased levels of androgens have been suggested to be important in the pathogenesis of both PCOS (Dumesic et al., 2014) and autism spectrum disorders (James, 2012). Our data fits these hypotheses well. Subsequent research has further strengthened this notion with a large register study from UK finding a significantly higher rate of autism in children to women with PCOS, also after adjusting for psychiatric comorbidities (Cherskov et al., 2018). A large meta-analysis confirmed that women with PCOS had more children with autism spectrum disorder than other women (Katsigianni et al., 2019). Another meta-analysis confirmed the association between PCOS in mothers and neurodevelopmental disorders in the offspring, but were not able to find an association between the degree of androgen exposure during gestation and outcome, thereby questioning whether intrauterine exposure of androgens is the relevant mechanism of action (Dubey et al., 2021).

We found a higher proportion of schizophrenia not only in women with PCOS but also in their sisters, compared with controls. Subsequent research has confirmed a higher risk of schizophrenia in PCOS (Chen et al., 2021). A possible mechanism of action for a protective effect of metformin could be through decreased androgen synthesis and decreased systematic inflammation (Carvalho et al., 2018). A protein network analysis has concluded that there is a close association between proteins involved in both schizophrenia and PCOS (Ramly et al., 2019).

In study I, we did not study the impact of obesity per se on psychiatric morbidity, but we found that among women with PCOS, BMI was on average higher in those with recurrent depression as well as in those with social phobia. Obesity has been recognized as a possible pathway of psychiatric morbidity in PCOS, especially for depression (Jiang et al., 2021; Kolhe et al., 2021). Although depression is more common in obese women with PCOS, lean women with PCOS still have more depression than other women (Cooney and Dokras, 2017)

Weight loss in general does not have a positive effect on depression and might even have a detrimental effect. In obese persons with depression, it does seem to have a beneficial effect on depressive symptoms though (Patsalos et al., 2021). Why this is so is not clear, though both normalization of endocrinological function as well as decreased neuroimmune reactions are possible mechanisms (Ambrósio et al., 2018).

That physical activity and exercise have both protective and curative effect for anxiety and depression has been increasingly recognized during the last decade (Carek et al., 2011). Testosterone is an anabolic hormone. It is possible that resistance training or other physical exercise have a greater impact in women with PCOS compared with

18

other women or require less effort. There is some research on the effects of physical exercise in PCOS that shows promising results on both depression and anxiety. Comparisons with women without PCOS is lacking though, as well as research on whether any particular kind of training is more suited to women with PCOS (Patten et al., 2021).

There are also some pharmacological treatments available for the primary symptoms of PCOS (Bednarska and Siejka, 2017). This begs the question whether treatment with those compounds ameliorate depression or other psychiatric disorders in women with PCOS. In a placebo-controlled study, the combination of metformin and pioglitazone—but not metformin alone—reduced anxiety and depression (Guo et al., 2020). Another study reported positive effects on quality of life from treatment for hirsutism and acne with the combination of cyproterone and ethinylestradiol (Ruan et al., 2017). Of note, neither of those studies were targeted at treatment for clinical depression disorders or anxiety disorders.

Sexuality in PCOS

In study III, we examined sexuality in PCOS. Highlighting normalcy, it could be stressed that on average using our main method of measurement the McCoy short scale, there were no significant difference between women with and without PCOS. Nor did we find differences in the number of partners, self-identified sexual orientation, age at sexual debut, or frequency of intercourse. This is somewhat surprising given that testosterone is known to increase sexual function and behavior in both men and women (Davis and Wahlin-Jacobsen, 2015; Hutchinson, 1995) On specific items of the McCoy scale and on interview questions, we did see some differences in women with and without PCOS. In women with PCOS, sexuality was not associated with psychological wellbeing, but positively correlated with s-testosterone, while the opposite was found in the controls. A Polish study also found a disparate pattern in women with and without PCOS regarding how their sexuality correlated with testosterone. In line with our study, they found no difference on the average score. Interestingly, they also found that frequency of masturbation correlated positively with depressive and anxious symptoms in women with PCOS, while the opposite was true for women without PCOS (Glowinska et al., 2020). A Canadian study found a correlation between the number and severity of PCOS symptoms—that can be seen as a proxy for testosterone activation—and being more positive to noncommitted sex, having a higher frequency of sexual fantasies, masturbating more, and being more interested in sex with other women.

We did find a larger proportion of women with PCOS being dissatisfied with their sex life, which is in line with a recent review and meta-analysis that found a small but significant negative effect of PCOS on sexual satisfaction (Firmino Murgel et al., 2019). For improving sexual functioning and satisfaction in women with PCOS, physical exercise seems a promising way (Lopes et al., 2018), and one study showed that resistance training, i.e., lifting heavy weights had a significantly more positive effect on

sexual desire and function in women with PCOS compared with controls (Lara et al., 2015)

Personality in PCOS

In study IV, we found that women with PCOS scored higher on several anxious personality traits and lower on socialization, regardless of whether they were matched on BMI, or whether psychiatric disorders served as exclusion criteria or not. Several other studies have shown higher anxious or neurotic personality traits compared with women without PCOS (Urban et al., 2022). Neuroticism is a major personality traits that indicates proneness to experiencing negative emotions as worrying, feeling low, and feeling anxious (Eysenck, 1990). It has been shown that neuroticism is a risk factor for major depressive disorder and is, not surprisingly, higher in persons with anxiety disorders (Clark et al., 1994). Furthermore, neuroticism is a very strong candidate for being an intermediate link between genes and clinical depression, i.e., an endophenotype (Goldstein and Klein, 2014). Lower scores on socialization have been found in binge eating disorders, but to what degree those patients had comorbid PCOS is not known (Edwards and Nagelberg, 1986).

A factor to consider is the strong correlation between PCOS and obesity (Glueck and Goldenberg, 2018). Obesity and higher BMI has been found to be associated with higher scores on neurotic personality traits (Faith et al., 2001; Ryden et al., 2003; Vainik et al., 2019). Most research on personality and obesity has not controlled for PCOS. As our study included a group matched for BMI just obesity cant explain the differences in personality between women with PCOS and other women.

The hypothesis that prenatal androgen exposure is a cause of PCOS (Abbott et al., 2005) might have bearing on anxiety as well. Androgen exposure during pregnancy have been shown to alter the limbic system and increase anxiety in mice (Manti et al., 2018). In addition, unaffected daughters to women with PCOS have a higher incidence of anxiety disorders than daughters to women without PCOS (Risal et al., 2021). An organizational effect of androgens is therefore a potential contributor to the neurotic personality traits seen in women with PCOS.

Does testosterone affect mental health in women?

The rationale for this thesis was to study PCOS as a naturally occurring model for the activating effect of testosterone on mental health in women. (In reality, however, things are not that simple. For one, a likely cause of PCOS is an organizing effect of testosterone at least intrauterine and possibly during adolescence as well.) A simplistic prediction of the results that we would find is that the sex dependent pattern of psychiatric illnesses would in women with PCOS have tilted towards a pattern more resembling a male psychiatric panorama. But that is not what we found.

For autism spectrum and schizophrenia spectrum disorders, our results were in line with a more male pattern of illness and for autism supporting the theory that hyperandrogenism during pregnancy changes the neurodevelopment of the brain to a more lateral pattern. But anxiety and depression are more common in women than in men in the general population. Here, we found that PCOS made this difference even larger. It thus seems that increased testosterone levels have a generally negative effect on mental health in women with PCOS.

Methodological considerations

In this thesis we have been using two different approaches to address a similar question. The first approach was using a clinical sample that was thoroughly examined by us. The other approach was using nationwide data collected over a long period of years of all women who had received a diagnosis of PCOS in Sweden.

Both approaches are, however, based on clinical samples. When studying PCOS, it is important to acknowledge that it is possible to meet the criteria for PCOS without knowing it or seeking help for it. Therefore, it is likely that a clinical PCOS sample have a more severe kind of the condition, or give rise to certain symptoms that prompts the woman to seek health care, for example acne, obesity, or hirsutism. It is also known that failing to conceive is a factor that disproportionately leads to a clinical diagnosis of PCOS. A more concerning source of bias with respect to our studies is the possibility that women with certain combinations of the comorbidities we are examining are more prone to seeking clinical care. A known example of this is that persons suffering from anxiety disorders generally are more prone to seeking medical care than other persons. It can thus not be excluded that those women with PCOS that also suffer from a psychiatric condition are more likely to seek healthcare, and thus more likely to be diagnosed with PCOS. If so, we would overestimate the prevalence of psychiatric disorders in the PCOS population.

The first clinical approach has the benefit of securing the validity of the psychiatric disorders, the possibility to select which data to collect by adding investigations for the specific questions, and to collect a wealth of collateral data from the individual subject. The disadvantage is that time and resources are limited and as a consequence it is hard to include large samples. Therefore, power to detect rare conditions is often lacking and even though there are a lot of data on possible confounders, creating models incorporating these possible confounders decreases the power to detect significant differences even more, making it necessary to choose such prudently.

The second register-based approach give the possibility to include massive numbers of both subjects and controls, but studies are limited to data collected for other purposes and with the possible risk that certain clinical diagnoses are not registered in a way that is proportional to how common they are in the population. A likely example in this context is obesity, which is probably registered in a far smaller proportion in health

care than the number of patients suffering from it. Including massive numbers of subjects gives the possibility to discover rare conditions, as well as to retain power when adjusting for confounders. Something you do need to consider when using large sample sizes is that there is a distinct possibility of finding significant associations that —although statistically significant — are too small to matter in any clinical sense.

The cross-sectional case control design is appropriate when the aim is to discover potential differences between two groups, in this case women with PCOS and women from the general population. But a cross-sectional is not able to answer questions about what causes those differences; it can at best hint at possible pathways. When we planned these studies, it was still unclear whether women with PCOS suffered from more clinical psychiatric disorders than other women, and if so, which disorders were more or less common. Therefore, we opted for an inclusive design generally not adjusting ad hoc for possible contributing co morbidities.

6   CONCLUSIONS

Most importantly, we found that women with PCOS had significantly higher rates of several psychiatric disorders during their life. With a case-control design in a clinical sample, we first found more major depressive episodes, recurrent depression, generalized anxiety disorder, and suicide attempts. Using a nationwide register study, we once again found that women with PCOS had a higher frequency of depression, anxiety disorders, and suicide attempts. Furthermore, we found that most studied psychiatric disorders were more common in PCOS than in controls. Adjusting for psychiatric comorbidity, the highest odds were found for cluster A and C personality disorders, tics, and autism spectrum disorder. In the siblings analysis, we found that sisters of women with PCOS had increased odds for anxiety, depression, and schizophrenia, while both brothers and sisters had increased odds for autism spectrum disorder compared with controls. The increased risk for autism in both PCOS women and their non affected sisters and brothers is of particular interest in the context of a possible effect of androgens.

Expanding beyond psychiatric disorders, we found no difference in total McCoy score between women with and without PCOS, though a higher proportion of women with PCOS reported being very dissatisfied with their sex life and not being interested in physical contact with their partner. A curious finding was that in women with PCOS, there was no correlation between general psychological wellbeing and sexual health, but there was a correlation between total McCoy and serum testosterone, while the opposite was true in controls.

Finally, we explored differences in personality traits as measured by KSP in one cohort of women with PCOS and controls without psychiatric disorders and who were matched for BMI, and in one cohort that allowed psychiatric disorders were not matched for weight or height. We found in both cohorts that women with PCOS women had higher psychic anxiety, muscular tension, somatic anxiety, and scored lower on socialization, than controls.

7 POINTS OF PERSPECTIVE

It has by now clearly been shown that women with PCOS suffer from a higher frequency of several psychiatric disorders including affective disorders, several anxiety disorders, schizophrenia spectrum disorders, and autism spectrum disorder. Whether and to what degree PCOS in and by itself is causative to the higher frequency or if a large part of the increased psychiatric morbidity is due to comorbidity with obesity or a common genetic or epigenetic liability is largely unknown. Studies designed to find causative mechanism are warranted.

It has been proposed that women with PCOS should be screened for psychiatric illness, but given the mostly modest increased odds, it is by no means certain that the benefits of doing this outweighs the costs. Therefore, trying to find contexts in which screening for psychiatric disorders in women is beneficial is warranted.

PCOS is a hyperandrogenic condition. It is possible that the pattern of treatment response for some psychiatric disorders differ between women with and without PCOS. Studies examining treatment response in women with and without PCOS are warranted.

Research on sexuality in PCOS is still scarce and our and other findings centre on two diverging pathways. One is that several aspects of sexuality is decreased in women with PCOS compared with controls and that the women themselves think that PCOS is to blame for that. Finding out why this is so and trying to find treatments to improve sexual health is needed. The other pathway is the intriguing findings that certain aspects of sexuality might be improved or increased in women with PCOS compared with other women in a way expected of the action of testosterone. Further investigation of this might yield pathways to improve sexuality in women with PCOS.

8 ACKNOWLEDGEMENTS

First and foremost, I am grateful and in debt to the women who participated as subjects and controls in this thesis

Further I want to thank

My principal supervisor, Mikael Landén, for a great sense of humor, introducing me to the scientific community, a great intellect, daring to ask even difficult questions and having more patience than is humanly possible when I prioritized everything in life but my research.

My assistant supervisor, Anna-Lena Nordström, who gave me a much-needed push to get on track with my research in Stockholm and introduced me to the PET lab at Karolinska. Always positive and filled with energy.

My co-authors without whom this work wouldn't have been possible, with special thanks to Anette Johansson, longtime colleague and once clinical supervisor, that time after time remind me of the merit of hard work, scholarship and moral virtue.

My little sister, Teresia Månsson, who finished her thesis aeons before me in a field I hardly understand a word in, but has always inspired with intelligence and curiosity.

My brother, Lukas Månsson, for showing that patience and hard work pays off

My family, Monica Conrad and my sons Markus and Erik who reminds me what life is all about with joy and love.

9 REFERENCES

Abbott, D.H., Barnett, D.K., Bruns, C.M., Dumesic, D.A., 2005. Androgen excess fetal programming of female reproduction: a developmental aetiology for polycystic ovary syndrome? Hum Reprod Update 11, 357-374.

Ahmadi, M., Faramarzi, M., Basirat, Z., Kheirkhah, F., Chehrazi, M., Ashabi, F., 2020. Mental and personality disorders in infertile women with polycystic ovary: a case-control study. Afr Health Sci 20, 1241-1249.

Ajmal, N., Khan, S.Z., Shaikh, R., 2019. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. Eur J Obstet Gynecol Reprod Biol X 3, 100060.

Ali, A.T., 2015. Polycystic ovary syndrome and metabolic syndrome. Ceska Gynekol 80, 279-289.

Ambrósio, G., Kaufmann, F.N., Manosso, L., Platt, N., Ghisleni, G., Rodrigues, A.L.S., Rieger, D.K., Kaster, M.P., 2018. Depression and peripheral inflammatory profile of patients with obesity. Psychoneuroendocrinology 91, 132-141.

Angin, P., Yoldemir, T., Atasayan, K., 2019. Quality of life among infertile PCOS patients. Arch Gynecol Obstet 300, 461-467.

Annagür, B.B., Kerimoglu Ö, S., Tazegül, A., Gündüz, Ş., Gençoglu, B.B., 2015. Psychiatric comorbidity in women with polycystic ovary syndrome. J Obstet Gynaecol Res 41, 1229-1233.

Azziz, R., Dumesic, D.A., Goodarzi, M.O., 2011. Polycystic ovary syndrome: an ancient disorder? Fertil Steril 95, 1544-1548.

Başar Gökcen, B., Akdevelioğlu, Y., Canan, S., Bozkurt, N., 2020. Increased risk of eating disorders in women with polycystic ovary syndrome: a case-control study. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 36, 764-767.

Bednarska, S., Siejka, A., 2017. The pathogenesis and treatment of polycystic ovary syndrome: What's new? Adv Clin Exp Med 26, 359-367.

Behboodi Moghadam, Z., Fereidooni, B., Saffari, M., Montazeri, A., 2018. Measures of health-related quality of life in PCOS women: a systematic review. Int J Womens Health 10, 397-408.

Brutocao, C., Zaiem, F., Alsawas, M., Morrow, A.S., Murad, M.H., Javed, A., 2018. Psychiatric disorders in women with polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine 62, 318-325.

Carek, P.J., Laibstain, S.E., Carek, S.M., 2011. Exercise for the treatment of depression and anxiety. Int J Psychiatry Med 41, 15-28.

Carvalho, L.M.L., Dos Reis, F.M., Candido, A.L., Nunes, F.F.C., Ferreira, C.N., Gomes, K.B., 2018. Polycystic Ovary Syndrome as a systemic disease with multiple molecular pathways: a narrative review. Endocr Regul 52, 208-221.

Cesta, C.E., Kuja-Halkola, R., Lehto, K., Iliadou, A.N., Landén, M., 2017. Polycystic ovary syndrome, personality, and depression: A twin study. Psychoneuroendocrinology 85, 63-68.

Cesta, C.E., Månsson, M., Palm, C., Lichtenstein, P., Iliadou, A.N., Landén, M., 2016. Polycystic ovary syndrome and psychiatric disorders: Co-morbidity and heritability in a nationwide Swedish cohort. Psychoneuroendocrinology 73, 196-203.

Chachamovich, J.R., Chachamovich, E., Ezer, H., Fleck, M.P., Knauth, D., Passos, E.P., 2010. Investigating quality of life and health-related quality of life in infertility: a systematic review. Journal of psychosomatic obstetrics and gynaecology 31, 101-110.

Chaudhari, A.P., Mazumdar, K., Mehta, P.D., 2018. Anxiety, Depression, and Quality of Life in Women with Polycystic Ovarian Syndrome. Indian J Psychol Med 40, 239-246.

Chen, S.F., Yang, Y.C., Hsu, C.Y., Shen, Y.C., 2021. Risk of schizophrenia in patients with polycystic ovary syndrome: a nationwide population-based cohort study from Taiwan. Journal of psychosomatic obstetrics and gynaecology 42, 272-278.

Cherskov, A., Pohl, A., Allison, C., Zhang, H., Payne, R.A., Baron-Cohen, S., 2018. Polycystic ovary syndrome and autism: A test of the prenatal sex steroid theory. Transl Psychiatry 8, 136.

Clark, L.A., Watson, D., Mineka, S., 1994. Temperament, personality, and the mood and anxiety disorders. Journal of abnormal psychology 103, 103-116.

Cooney, L.G., Dokras, A., 2017. Depression and Anxiety in Polycystic Ovary Syndrome: Etiology and Treatment. Curr Psychiatry Rep 19, 83.

Cooney, L.G., Lee, I., Sammel, M.D., Dokras, A., 2017. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 32, 1075-1091.

Davis, S.R., Wahlin-Jacobsen, S., 2015. Testosterone in women--the clinical significance. Lancet Diabetes Endocrinol 3, 980-992.

de Lima Nunes, R., Dos Santos, I.K., Cobucci, R.N., Pichini, G.S., Soares, G.M., de Oliveira Maranhão, T.M., Dantas, P.M.S., 2019. Lifestyle interventions and quality of life for women with polycystic ovary syndrome: A systematic review and meta-analysis protocol. Medicine (Baltimore) 98, e18323.

Domonkos, E., Hodosy, J., Ostatníková, D., Celec, P., 2018. On the Role of Testosterone in Anxiety-Like Behavior Across Life in Experimental Rodents. Front Endocrinol (Lausanne) 9, 441.

Dubey, P., Thakur, B., Rodriguez, S., Cox, J., Sanchez, S., Fonseca, A., Reddy, S., Clegg, D., Dwivedi, A.K., 2021. A systematic review and meta-analysis of the association between maternal polycystic ovary syndrome and neuropsychiatric disorders in children. Transl Psychiatry 11, 569.

Dumesic, D.A., Goodarzi, M.O., Chazenbalk, G.D., Abbott, D.H., 2014. Intrauterine environment and polycystic ovary syndrome. Semin Reprod Med 32, 159-165.

Dunaif, A., Given, J., Haseltine, F., 1992. Diagnostic criteria for Polycystic ovary syndrome: towards a rational apporoach. polycystic ovary syndrome, Boston, 377-384.

Durdiakova, J., Ostatnikova, D., Celec, P., 2011. Testosterone and its metabolites--modulators of brain functions. Acta Neurobiol Exp (Wars) 71, 434-454.

Edwards, F.E., Nagelberg, D.B., 1986. Personality characteristics of restrained/binge eaters versus unrestrained/nonbinge eaters. Addictive behaviors 11, 207-211.

Elsenbruch, S., Hahn, S., Kowalsky, D., Offner, A.H., Schedlowski, M., Mann, K., Janssen, O.E., 2003. Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88, 5801-5807.

Escobar-Morreale, H.F., 2018. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol 14, 270-284.

Eysenck, H.J., 1990. Genetic and environmental contributions to individual differences: the three major dimensions of personality. Journal of personality 58, 245-261.

Faith, M.S., Flint, J., Fairburn, C.G., Goodwin, G.M., Allison, D.B., 2001. Gender differences in the relationship between personality dimensions and relative body weight. Obes Res 647-650.

Faravelli, C., Alessandra Scarpato, M., Castellini, G., Lo Sauro, C., 2013. Gender differences in depression and anxiety: the role of age. Psychiatry Res 210, 1301-1303.

Filová, B., Ostatníková, D., Celec, P., Hodosy, J., 2013. The effect of testosterone on the formation of brain structures. Cells Tissues Organs 197, 169-177.

Firmino Murgel, A.C., Santos Simões, R., Maciel, G.A.R., Soares, J.M., Jr., Baracat, E.C., 2019. Sexual Dysfunction in Women With Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. J Sex Med 16, 542-550.

Girela-Serrano, B.M., Guerrero-Jiménez, M., Spiers, A.D.V., Gutiérrez-Rojas, L., 2022. Obesity and overweight among children and adolescents with bipolar disorder from the general population: A review of the scientific literature and a meta-analysis. Early Interv Psychiatry 16, 113-125.

Glowinska, A., Duleba, A.J., Zielona-Jenek, M., Siakowska, M., Pawelczyk, L., Banaszewska, B., 2020. Disparate Relationship of Sexual Satisfaction, Self-Esteem, Anxiety, and Depression with Endocrine Profiles of Women With or Without PCOS. Reprod Sci 27, 432-442.

Glueck, C.J., Goldenberg, N., 2018. Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. Metabolism: clinical and experimental.

Goh, C., Agius, M., 2010. The stress-vulnerability model how does stress impact on mental illness at the level of the brain and what are the consequences? Psychiatr Danub 22, 198-202.

Goldstein, B.L., Klein, D.N., 2014. A review of selected candidate endophenotypes for depression. Clinical psychology review 34, 417-427.

Goodarzi, M.O., Dumesic, D.A., Chazenbalk, G., Azziz, R., 2011. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 7, 219-231.

Guo, Q.J., Shan, J., Xu, Y.F., Hu, Y.Y., Huo, C.L., Song, J.Y., Wang, C.Q., Zhou, H., Yu, C.Q., Huang, Q., 2020. Pioglitazone Metformin Complex Improves Polycystic Ovary Syndrome Comorbid Psychological Distress via Inhibiting NLRP3 Inflammasome Activation: A Prospective Clinical Study. Mediators Inflamm 2020, 3050487.

Hagmar, M., Berglund, B., Brismar, K., Hirschberg, A.L., 2009. Hyperandrogenism may explain reproductive dysfunction in olympic athletes. Med Sci Sports Exerc 41, 1241-1248.

Hollinrake, E., Abreu, A., Maifeld, M., Van Voorhis, B.J., Dokras, A., 2007. Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertil Steril 87, 1369-1376.

Holte, J., 1998. Polycystic ovary syndrome and insulin resistance: thrifty genes struggling with over-feeding and sedentary life style? J Endocrinol Invest 21, 589-601.

Huang, P.L., 2009. A comprehensive definition for metabolic syndrome. Dis Model Mech 2, 231-237.

Hung, J.H., Hu, L.Y., Tsai, S.J., Yang, A.C., Huang, M.W., Chen, P.M., Wang, S.L., Lu, T., Shen, C.C., 2014. Risk of psychiatric disorders following polycystic ovary syndrome: a nationwide population-based cohort study. PLoS One 9, e97041.

Hutchinson, K.A., 1995. Androgens and sexuality. Am J Med 98, 111s-115s.

James, W.H., 2012. A potential explanation of some established major risk factors for autism. Dev Med Child Neurol 54, 301-305.

Jiang, X., Deng, Q., Stener-Victorin, E., 2021. Is there a shared genetic basis and causal relationship between polycystic ovary syndrome and psychiatric disorders: evidence from a comprehensive genetic analysis. Hum Reprod 36, 2382-2391.

Joshi, R.D., Sawant, N., Mayadeo, N.M., 2022. How Common are Depressive-Anxiety States, Body Image Concerns and Low Self-Esteem in Patients of PCOS? J Obstet Gynaecol India 72, 72-77.

Kataoka, J., Larsson, I., Björkman, S., Eliasson, B., Schmidt, J., Stener-Victorin, E., 2019. Prevalence of polycystic ovary syndrome in women with severe obesity - Effects of a structured weight loss programme. Clin Endocrinol (Oxf) 91, 750-758.

Katsigianni, M., Karageorgiou, V., Lambrinoudaki, I., Siristatidis, C., 2019. Maternal polycystic ovarian syndrome in autism spectrum disorder: a systematic review and meta-analysis. Mol Psychiatry 24, 1787-1797.

Khan, M.J., Ullah, A., Basit, S., 2019. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. Appl Clin Genet 12, 249-260.

Kitchen, H., Aldhouse, N., Trigg, A., Palencia, R., Mitchell, S., 2017. A review of patient-reported outcome measures to assess female infertility-related quality of life. Health Qual Life Outcomes 15, 86.

Knickmeyer, R.C., Baron-Cohen, S., 2006. Fetal testosterone and sex differences in typical social development and in autism. J Child Neurol 21, 825-845.

Kolhe, J.V., Chhipa, A.S., Butani, S., Chavda, V., Patel, S.S., 2021. PCOS and Depression: Common Links and Potential Targets. Reprod Sci.

Kolotkin, R.L., Meter, K., Williams, G.R., 2001. Quality of life and obesity. Obes Rev 2, 219-229.

Kuehner, C., 2017. Why is depression more common among women than among men? Lancet Psychiatry 4, 146-158.

La Vignera, S., Condorelli, R.A., Cannarella, R., Duca, Y., Calogero, A.E., 2018. Sport, doping and female fertility. Reprod Biol Endocrinol 16, 108.

Lara, L.A., Ramos, F.K., Kogure, G.S., Costa, R.S., Silva de Sá, M.F., Ferriani, R.A., dos Reis, R.M., 2015. Impact of Physical Resistance Training on the Sexual Function of Women with Polycystic Ovary Syndrome. J Sex Med 12, 1584-1590.

Lee, I.O., Kim, J.C., Seo, J.W., Pak, H.Y., Chung, J.E., 2021. Risk of developing major depressive disorder in polycystic ovary syndrome: a retrospective cohort study. J Obstet Gynaecol 41, 1157-1161.

Lim, S.S., Kakoly, N.S., Tan, J.W.J., Fitzgerald, G., Bahri Khomami, M., Joham, A.E., Cooray, S.D., Misso, M.L., Norman, R.J., Harrison, C.L., Ranasinha, S., Teede, H.J., Moran, L.J., 2019. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. Obes Rev 20, 339-352.

Lin, H., Liu, M., Zhong, D., Ng, E.H.Y., Liu, J., Li, J., Shi, Y., Zhang, C., Wen, X., Mai, Z., Ou, M., Ma, H., 2021. The Prevalence and Factors Associated With Anxiety-Like and Depression-Like Behaviors in Women With Polycystic Ovary Syndrome. Front Psychiatry 12, 709674.

Lizneva, D., Suturina, L., Walker, W., Brakta, S., Gavrilova-Jordan, L., Azziz, R., 2016. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 106, 6-15.

Lopes, I.P., Ribeiro, V.B., Reis, R.M., Silva, R.C., Dutra de Souza, H.C., Kogure, G.S., Ferriani, R.A., Silva Lara, L.A.D., 2018. Comparison of the Effect of Intermittent and Continuous Aerobic Physical Training on Sexual Function of Women With Polycystic Ovary Syndrome: Randomized Controlled Trial. J Sex Med 15, 1609-1619.

Lundgren-Nilsson, Å., Jonsdottir, I.H., Ahlborg, G., Jr., Tennant, A., 2013. Construct validity of the Psychological General Well Being Index (PGWBI) in a sample of patients undergoing treatment for stress-related exhaustion: a Rasch analysis. Health Qual Life Outcomes 11, 2.

Mansson, M., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E., Johansson, A., Landen, M., 2008. Women with polycystic ovary syndrome are often depressed or anxious-A case control study. Psychoneuroendocrinology 33, 1132-1138.

Manti, M., Fornes, R., Qi, X., Folmerz, E., Linden Hirschberg, A., de Castro Barbosa, T., Maliqueo, M., Benrick, A., Stener-Victorin, E., 2018. Maternal androgen excess and obesity induce sexually dimorphic anxiety-like behavior in the offspring. FASEB J 32, 4158-4171.

Maripuu, M., Wikgren, M., Karling, P., Adolfsson, R., Norrback, K.F., 2016. Relative hypocortisolism is associated with obesity and the metabolic syndrome in recurrent affective disorders. J Affect Disord 204, 187-196.

Martino, D., Macerollo, A., Leckman, J.F., 2013. Neuroendocrine aspects of Tourette syndrome. Int Rev Neurobiol 112, 239-279.

Massarotti, C., Gentile, G., Ferreccio, C., Scaruffi, P., Remorgida, V., Anserini, P., 2019. Impact of infertility and infertility treatments on quality of life and levels of anxiety and depression in women undergoing in vitro fertilization. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 35, 485-489.

May, T., Adesina, I., McGillivray, J., Rinehart, N.J., 2019. Sex differences in neurodevelopmental disorders. Curr Opin Neurol 32, 622-626.

Moghetti, P., Tosi, F., 2021. Insulin resistance and PCOS: chicken or egg? J Endocrinol Invest 44, 233-244.

Månsson, M., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E., Johansson, A., Landén, M., 2008. Women with polycystic ovary syndrome are often depressed or anxious--a case control study. Psychoneuroendocrinology 33, 1132-1138.

Månsson, M., Norström, K., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E., Landén, M., 2011. Sexuality and psychological wellbeing in women with polycystic ovary syndrome

compared with healthy controls. European journal of obstetrics, gynecology, and reproductive biology 155, 161-165.

Naderpoor, N., Shorakae, S., Joham, A., Boyle, J., De Courten, B., Teede, H.J., 2015. Obesity and polycystic ovary syndrome. Minerva Endocrinol 40, 37-51.

Nathorst-Böös, J., Flöter, A., Jarkander-Rolff, M., Carlström, K., Schoultz, B., 2006. Treatment with percutanous testosterone gel in postmenopausal women with decreased libido--effects on sexuality and psychological general well-being. Maturitas 53, 11-18.

Naumova, I., Castelo-Branco, C., Kasterina, I., Casals, G., 2021. Quality of Life in Infertile Women with Polycystic Ovary Syndrome: a Comparative Study. Reprod Sci 28, 1901-1909.

Ortet-Fabregat, G., Ibáñez, M., Llerena, A., Torrubia, R., 2002. The Underlying Traits of the Karolinska Scales of Personality (KSP). European Journal of Psychological Assessment.

Ovesen, P.G., Moller, N., Greisen, S., Ingerslev, H.J., 1998. [Polycystic ovary syndrome I. Clinical presentation and treatment]. Ugeskr Laeger 160, 260-264.

Ozcan Dag, Z., Oguzturk, O., Isik, Y., Turkel, Y., Bulcun, E., 2015. Personality profile in patients with polycystic ovary syndrome. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 31, 540-542.

Panico, A., Messina, G., Lupoli, G.A., Lupoli, R., Cacciapuoti, M., Moscatelli, F., Esposito, T., Villano, I., Valenzano, A., Monda, V., Messina, A., Precenzano, F., Cibelli, G., Monda, M., Lupoli, G., 2017. Quality of life in overweight (obese) and normal-weight women with polycystic ovary syndrome. Patient Prefer Adherence 11, 423-429.

Patsalos, O., Keeler, J., Schmidt, U., Penninx, B., Young, A.H., Himmerich, H., 2021. Diet, Obesity, and Depression: A Systematic Review. J Pers Med 11.

Patten, R.K., Pascoe, M.C., Moreno-Asso, A., Boyle, R.A., Stepto, N.K., Parker, A.G., 2021. Effectiveness of exercise interventions on mental health and health-related quality of life in women with polycystic ovary syndrome: a systematic review. BMC Public Health 21, 2310.

Penninx, B., Lange, S.M.M., 2018. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci 20, 63-73.

Persson, S., Elenis, E., Turkmen, S., Kramer, M.S., Yong, E.L., Sundström-Poromaa, I., 2019. Fecundity among women with polycystic ovary syndrome (PCOS)-a population-based study. Hum Reprod 34, 2052-2060.

Pethö, B., Karczag, I., Czeizel, A., 1982. Familially accumulated schizophrenia (folie à cinq) in association with Stein-Leventhal syndrome. Psychiatr Clin (Basel) 15, 206-211.

Rajan, T.M., Menon, V., 2017. Psychiatric disorders and obesity: A review of association studies. J Postgrad Med 63, 182-190.

Ramly, B., Afiqah-Aleng, N., Mohamed-Hussein, Z.A., 2019. Protein-Protein Interaction Network Analysis Reveals Several Diseases Highly Associated with Polycystic Ovarian Syndrome. Int J Mol Sci 20.

Rasgon, N.L., Altshuler, L.L., Fairbanks, L., Elman, S., Bitran, J., Labarca, R., Saad, M., Kupka, R., Nolen, W.A., Frye, M.A., Suppes, T., McElroy, S.L., Keck, P.E., Jr., Leverich, G., Grunze, H., Walden, J., Post, R., Mintz, J., 2005. Reproductive function and risk for PCOS in women treated for bipolar disorder. Bipolar Disord 7, 246-259.

Rasgon, N.L., Rao, R.C., Hwang, S., Altshuler, L.L., Elman, S., Zuckerbrow-Miller, J., Korenman, S.G., 2003. Depression in women with polycystic ovary syndrome: clinical and biochemical correlates. J Affect Disord 74, 299-304.

Risal, S., Manti, M., Lu, H., Fornes, R., Larsson, H., Benrick, A., Deng, Q., Cesta, C.E., Rosenqvist, M.A., Stener-Victorin, E., 2021. Prenatal androgen exposure causes a sexually dimorphic transgenerational increase in offspring susceptibility to anxiety disorders. Transl Psychiatry 11, 45.

Roselli, C.E., 2018. Neurobiology of gender identity and sexual orientation. J Neuroendocrinol 30, e12562.

Rotterdam, E.A.-S.P.C.W.G., 2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 81, 19-25.

Ruan, X., Kubba, A., Aguilar, A., Mueck, A.O., 2017. Use of cyproterone acetate/ethinylestradiol in polycystic ovary syndrome: rationale and practical aspects. The European Journal of Contraception & Reproductive Health Care 22, 183-190.

Rubinow, D.R., Schmidt, P.J., 1996. Androgens, brain, and behavior. Am J Psychiatry 153, 974-984.

Ryden, A., Sullivan, M., Torgerson, J.S., Karlsson, J., Lindroos, A.K., Taft, C., 2003. Severe obesity and personality: a comparative controlled study of personality traits. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 27, 1534-1540.

Sam, S., 2007. Obesity and Polycystic Ovary Syndrome. Obes Manag 3, 69-73.

Sapolsky, R.M., 1986. Stress-induced elevation of testosterone concentration in high ranking baboons: role of catecholamines. Endocrinology 118, 1630-1635.

Scaruffi, E., Franzoi, I.G., Civilotti, C., Guglielmucci, F., La Marca, L., Tomelini, M., Veglia, F., Granieri, A., 2019. Body image, personality profiles and alexithymia in patients with polycystic ovary syndrome (PCOS). Journal of psychosomatic obstetrics and gynaecology 40, 294-303.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20, 22-33;quiz 34-57.

Stener-Victorin, E., Deng, Q., 2021. Epigenetic inheritance of polycystic ovary syndrome - challenges and opportunities for treatment. Nat Rev Endocrinol 17, 521-533.

Szydlarska, 2017. History of discovery of polycystic ovary syndrome. Adv Clin Exp Med 26, 555-558.

Teede, H.J., Misso, M.L., Costello, M.F., Dokras, A., Laven, J., Moran, L., Piltonen, T., Norman, R.J., International, P.N., 2018. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod 33, 1602-1618.

Thurston, L., Abbara, A., Dhillo, W.S., 2019. Investigation and management of subfertility. J Clin Pathol 72, 579-587.

Tzalazidis, R., Oinonen, K.A., 2021. Continuum of Symptoms in Polycystic Ovary Syndrome (PCOS): Links with Sexual Behavior and Unrestricted Sociosexuality. J Sex Res 58, 532-544.

Urban, W., Nizioł, A., Pytlewski, A., Zaborowska, Ł., Dadański, E., Rutkowski, K., Klasa, K., Kacalska-Janssen, O., Jach, R., Mielimąka, M., 2022. Polycystic Ovary Syndrome - personality and temperamental characteristics. J Obstet Gynaecol Can.

Vainik, U., Dagher, A., Realo, A., Colodro-Conde, L., Mortensen, E.L., Jang, K., Juko, A., Kandler, C., Sørensen, T.I.A., Mõttus, R., 2019. Personality-obesity associations are driven by narrow traits: A meta-analysis. Obes Rev 20, 1121-1131.

Valtysdottir, S.T., Wide, L., Hallgren, R., 2003. Mental wellbeing and quality of sexual life in women with primary Sjögren's syndrome are related to circulating dehydroepiandrosterone sulphate. Ann Rheum Dis 62, 875-879.

Vikström, J., Josefsson, A., Bladh, M., Sydsjö, G., 2015. Mental health in women 20-23 years after IVF treatment: a Swedish cross-sectional study. BMJ Open 5, e009426.

Wang, J., Wu, D., Guo, H., Li, M., 2019. Hyperandrogenemia and insulin resistance: The chief culprit of polycystic ovary syndrome. Life Sci 236, 116940.

Wang, Y., Ni, Z., Li, K., 2021. The prevalence of anxiety and depression of different severity in women with polycystic ovary syndrome: a meta-analysis. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 37, 1072-1078.

Wirshing, D.A., 2004. Schizophrenia and obesity: impact of antipsychotic medications. J Clin Psychiatry 65 Suppl 18, 13-26.

Yin, X., Ji, Y., Chan, C.L.W., Chan, C.H.Y., 2021. The mental health of women with polycystic ovary syndrome: a systematic review and meta-analysis. Arch Womens Ment Health 24, 11-27.

Zablotsky, B., Black, L.I., Maenner, M.J., Schieve, L.A., Danielson, M.L., Bitsko, R.H., Blumberg, S.J., Kogan, M.D., Boyle, C.A., 2019. Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. Pediatrics 144.

Zacur, H.A., 2001. Polycystic ovary syndrome, hyperandrogenism, and insulin resistance. Obstet Gynecol Clin North Am 28, 21-33.

Zimmet, P., Alberti, K., Stern, N., Bilu, C., El-Osta, A., Einat, H., Kronfeld-Schor, N., 2019. The Circadian Syndrome: is the Metabolic Syndrome and much more! J Intern Med 286, 181-191.