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The Cyprus Women's Health Research Initiative: Characterisation, prevalence and quality of life of polycystic ovary syndrome patients in Northern Cyprus.

8,428 Words

Acknowledgments

This thesis is dedicated to women affected by polycystic ovary syndrome everywhere, with particular acknowledgement of the participants in Northern Cyprus who took part in this study.

Abstract

Background. Polycystic Ovary Syndrome (PCOS) is a complex multifactorial endocrine women's health disorder, with genetic and environmental components. PCOS is characterised by combination of hyperandrogenism, polycystic ovarian morphology, ovulatory dysfunction, and reduced fertility. There has been limited research on prevalence and patient characteristics of PCOS from the Eastern Mediterranean region, which this study aims to address.

Methods. The Cyprus Women's Health (COHERE) Initiative study is the largest population-based cross-sectional analysis of women's health conditions in Northern Cyprus and within the Eastern Mediterranean region. 7,646 participants completed an adapted version of the World Endometriosis Research Foundation Endometriosis and Phenome Biobanking Harmonisation Project (WERF-EPHect) questionnaire which included questions to capture common women's health conditions and the Short-Form 36 version 2 (SF-36v2) to measure health-related quality of life. 668 women also attended a clinical visit involving an ultrasound scan. PCOS cases were ascertained from self-report and the ultrasound scan visits. Descriptive statistical analysis and logistic regression modelling were performed to describe and compare demographic, lifestyle, clinical, health-related quality of life, and pain between the PCOS cases and the control group.

Results. PCOS prevalence was estimated to be 6.5% in this population. Compared to the control group PCOS cases had significantly; younger mean age, higher BMI, and had a higher level of education. Infertility, hyperandrogenism symptoms, and irregular periods were significantly more prevalent in the PCOS group compared to controls. Pelvic pain symptoms including dysmenorrhea and dyspareunia were also more prevalent in the PCOS group compared to controls. All dimensions of the SF-36-v2 including physical and mental component scores, PCOS cases showed significantly reduced scores compared to controls. Controlling for pelvic pain symptoms made the relationship between PCOS and increased bodily pain insignificant.

Discussion. This is the first assessment of PCOS patient characteristics, prevalence estimates, and burden for Northern Cyprus. Prevalence findings are in line with those from the Republic of Cyprus. The significant effect of PCOS on clinical associations, lower health-related quality of life, and pain experiences underline the burden of PCOS and points to the need for future research and funding to address these issues.

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List of Abbreviations

AE-PCOS ..... Androgen Excess & PCOS Societ

ASRM ..... American Society of Reproductive Medicine

BMI ..... Body Mass Index

CI ..... Confidence Interval

COHERE ..... Cyprus Women's Health Research

CoHERS ..... Cyprus Women's Health Research Society

EMU ..... Eastern Mediterranean University

EPHect ..... Endometriosis and Phenome Biobanking Harmonisation Project

ESHRE ..... European Society of Human Reproduction and Embryology

GnRH ..... Gonadotrophin Releasing Hormone

GWAS ..... Genome Wide Association Studies

MCS ..... Mental Component Summary

NICE ..... National Institute for Health and Care Excellence

NIH ..... National Institutes of Health

OR ..... Odds Ratio

PCOS ..... Polycystic Ovary Syndrome

PCS ..... Physical Component Summary

QoL ..... Quality of Life

UK ..... United Kingdom

US ..... United States of America

USS ..... Ultrasound scan

WERF ..... World Endometriosis Research Foundation

1 Introduction

1.1 Polycystic Ovary Syndrome (PCOS)

1.1.1 The history, nomenclature, and diagnostic criteria of Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) receives its name from one of its key features which is the development of small cysts on the ovaries. These were first observed in 1721 by Antonio Vallisneri, in 1893 the clinical overview was described by Kronid Fedorovich Slavyansky [Kiryushkina, 2019, Szydlarska et al., 2017, Speca et al., 2007, Tsvelev and Kalchenko, 1997]. Sergei Kuzmich Lesnoy described the features as "sclerocystic ovaries" in 1928, and when in 1935 it was described by Stein and Leventhal it received another earlier name of "Stein-Leventhal syndrome" [Kiryushkina, 2019, Stein and Leventhal, 1935]. It was later referred to as "polycystic ovary disease" but as this complex disorder is not a specific disease this changed to "polycystic ovary syndrome" [Rodgers et al., 2019, Azziz, 2014, Insler and Lunenfeld, 1990]. The debate around the name and evolution of the diagnostic criteria offers a lens for looking at the characteristics of PCOS. "Hyperandrogenic chronic anovulation", "estrogenic ovulatory dysfunction", and "functional female hyperandrogenism" are alternative names proposed by Lobo and Behera et al. which all place more of a focus on the hormonal cause of the condition with the effect on ovulation [Rodgers et al., 2019, Azziz, 2014, Behera et al., 2006, Lobo, 1995]. It is possible that in the future the name will better reflect the complex condition with "Hyperandrogenic Persistent Ovulatory Dysfunction Syndrome (HA-PODS)" or "Hyperandrogenic Polycystic Ovary Spectrum Syndrome (H-POSS)" [Khadilkar, 2016].

The diagnostic criteria has had four iterations [Smet and McLennan, 2018, Azziz et al., 2016, Lizneva et al., 2016], these being;

1. The 1990 National Institutes of Health (NIH) focused on the occurrence of both (i) hyperandrogenism, and (ii-a) oligo-anovulation
2. The 2003 European Society for Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) also referred to as the 2003 Rotterdam criteria, required two out of the following (i) hyperandrogenism, (ii-b) ovulatory dysfunction, and (iii) polycystic ovarian morphology (PCOM).
3. The 2006 Androgen Excess & PCOS Society (AE-PCOS) required both (i) hyperandrogenism, and (ii-b) Ovarian dysfunction (which included (iii) polycystic ovarian morphology in their definition).

4. The 2012 NIH extension of the 2003 Rotterdam criteria again requiring two out of the following (i) hyperandrogenism, (ii-b) ovulatory dysfunction, and (iii) polycystic ovarian morphology, with the addition of four phenotypes;

   A (i) Hyperandrogenism, (ii-b) ovulatory dysfunction and (iii) polycystic ovarian morphology.

   B (i) Hyperandrogenism, and (ii-b) ovulatory dysfunction

   C (i) Hyperandrogenism, and (iii) polycystic ovarian morphology

   D (ii-b) ovulatory dysfunction, and (iii) polycystic ovarian morphology

1.1.2 Polycystic Ovary Syndrome Symptoms and Diagnosis

The symptoms and diagnosis of PCOS involves the presentation and evaluation of the aforementioned key features [Sirmans and Pate, 2013]. Hyperandrogenism physically presents, as the the Greek origin of the word suggests, as male characteristics [Sharma and Welt, 2021]. This includes; hirsutism, alopecia, adult acne, darkening of the skin, oligomenorrhea, and amenorrhea, for which the prevalence among PCOS cases are that affects 65-75%, 30-42.5%, 30-48%, 30%, 75-80%, and 30-40% respectively [Carmina et al., 2022, Abusailik et al., 2021, Barber et al., 2019, Keen et al., 2017, Bhate and Williams, 2013, Kelekci et al., 2010, Maluki, 2010, Bunker et al., 1989]. Hyperandrogenism can be assessed biochemically by assessing the levels of total or free testosterone or calculating the indices of free testosterone using the free androgen index (FAI) or bioavailable testosterone (BioT). It is argued that total testosterone may be more reliable than free due to difficulties seen with many of the assays. Most PCOS patients will have testosterone elevated to around 150 ng/dL ($\leq$5.2 nmol/L). If it is greater than 200ng/dL ($\geq$6.9nmol/L this may indicate an adrenal or ovarian tumor. Excess androgens can also be diagnosed via clinical measures. The most reliable clinical indicator of hyperadrogenism is hirsutism [Escobar-Morreale et al., 2011], since presence of acne unaccompanied by excess androgens is not associated with menstrual irregularities and has no reproductive implications for women [Schmidt et al., 2016, Sanchon et al., 2012].

Ovulatory dysfunction in terms of diagnosis for PCOS can present as amenorrhea but is often oligomenorrhea which is characterized and clinically determined by menstrual cycles which are either more than 35 days apart or less than eight per year. If menstruation is normal in a patient presenting with PCOS it is advisable to also assess serum progesterone or luteinizing hormone. Polycystic ovarian morphology in the case of PCOS is typically evaluated using transvaginal ultrasonography and determined by the presence of $\geq$20 follicles per ovary in either ovary and an ovarian volume of $\geq$10cm^3 [Cho et al., 2007]. However, assessing ovarian morphology through ultrasonography might not be necessary for diagnosing women

who already show clinical signs of hyperandrogenism and ovulatory dysfunction [Escobar-Morreale, 2010, Balen et al., 2003]. Epidemiological studies have illustrated that hirsutism, acne and oligomenorrhea are good markers of PCOS in the general population [Franks and McCarthy, 2004].

There is ongoing debate about whether pain is part of the clinical expression of PCOS, although PCOS has commonly been found to be associated with the bodily pain dimension on health-related quality of life measures [Lu et al., 2022]. In terms of co-morbidities, PCOS patients often experience metabolic disruptions such as insulin resistance and disturbances in regulating glucose levels [Diamanti-Kandarakis and Dunaif, 2012]. Moreover, depression and anxiety disorders are observed at a higher prevalence in PCOS cases compared to health controls [Cooney et al., 2017].

1.1.3 The Pathophysiology of Polycystic Ovary Syndrome

PCOS is an endocrine disorder of women within the reproductive ages. It is a multifactorial disorder caused by presence of multiple genetic and environmental factor. Family studies have estimated the heritable component, disease risk due to genetic factors, of PCOS to be between 60-72% in different populations [Vink et al., 2006, Kahsar-Miller et al., 2001]. Large scale genome-wide association studies (GWAS) have started to identify the common genetic variant contributing to the genetic component of PCOS mainly in European ancestry populations [Day et al., 2018]. There are also important environmental factors including diet, environmental exposures, and lifestyle factors, that contribute to disease risk which may vary between populations. Both the genetic factors and environmental factors could be influenced by population-specific differences hence it is vital to investigate these factors in diverse populations to better understand the causal factors [Escobar-Morreale, 2018].

Genetic variants associated with PCOS so far include variants related to genes involved in androgen biosynthesis, androgen action, insulin signaling, metabolism, folliculogenesis, and inflammation [Day et al., 2018]. Dysfunction in these genes cause disturbed release of pulsatile gonadotropin hormone (GnRH) from the hypothalamus, resulting in increased pulse frequency. Which then causes hypersecretion of luteinizing hormone (LH) by the pituitary gland leading to ovulatory dysfunction and hyperandrogenism. However, follicle-stimulating hormone (FSH) levels are generally normal, leading to increased circulating ratio between LH and FSH, which is more common in lean women. The sensitivity to FSH seems to be reduced in women with PCOS, resulting in oligomenorrhea or amenorrhea. This may be due to increased levels of intra-ovarian anti-Mullerian hormone (AMH), which can result in reduced sensitivity to FSH sensitivity and contribute to hyperandrogenism [Dewailly et al., 2016]. Moreover, exposure to environmental toxins such as endocrine-disruptors and advanced glycation end products,

may influence programming of reproductive and metabolic functions that my contribute to PCOS and associated metabolic functions in particular if happens over a long period of time during prenatal stages and childhood [Rutkowska and Diamanti-Kandarakis, 2016].

1.2 The Epidemiology of Polycystic Ovary Syndrome

1.2.1 The Prevalence and phenotypic ratio of Polycystic Ovary Syndrome

Prevalence of PCOS ranges between 6%, using more restrictive diagnostic criteria and 20%, using more current and inclusive diagnostic criteria, in reproductive age women [Yildiz et al., 2012, Azziz et al., 2004, Asunción et al., 2000, Diamanti-Kandarakis et al., 1999]. It is the most common endocrine disorder among reproductive-age women [Carmina and Lobo, 1999]. Prevalence varies widely depending on; region, cohort, and PCOS criteria used. For instance a study using the NIH 1990 criteria during routine physical examination of 915 women in Southern China gave a prevalence as low as 2.2% while three other studies in China with sample sizes between from 1,645 to 15,924 using differing criteria gave a prevalence from 5.6-11.2%. But the highest prevalence figures come from a 2012 study where PCOS prevalence in 248 Indigenous women in Australia reached 15.3% and 21.3% while using the NIH 1990, and ESHRE/ASRM 2003 criteria, respectively. For Greece a 1999 study of 192 white women recruited through free medical evaluation gave a prevalence of 6.8%. While a 2012 study of 392 women in Turkey from data collected during pre-employment assessment gave a prevalence of 6.1%, 19.9% or 15.3% using the NIH 1990, ESHRE/ASRM 2003, and AE-PCOS 2006 criteria. The prevalence by phenotype on this same Turkish population with 78 PCOS cases was 25.6% A, 5.1% B, 46.2% C, and 23.1% D. However the proportion of these vary greatly depending on the study and setting.

1.2.2 Quality of life

Past research has highlighted that PCOS is associated with reduced health-related quality of life (HRQoL) more broadly [Teede et al., 2011]. HRQoL is a multi-faceted concept. In one common standardized tool for measuring HRQoL, the Short Form 36 (SF-36)[Ware et al., 1993], a version of which is also used in this study, HRQoL is divided into a physical health component summary score (made up of; general health, bodily pain, role limitations due to physical health, and physical function), and a mental health component summary score (comprising; vitality, social functioning, role limitations due to emotional problems, and mental health). The clinical issues associated with PCOS of hormonal disruption, hirsutism, acne, alopecia, infertility, and obesity can lead to reduced self-image, and self-esteem, and through this and other pathways have noticeable effects on health-related quality of life [Jones et al., 2007]. Gilbert

et al (2018) conducted an overview of 23 systematic reviews on the comorbidities and complications of PCOS. Three of these systematic reviews reviewed looked at the association of PCOS with anxiety and depression. They found that PCOS was reliably associated with higher anxiety and higher depression [Gilbert et al., 2018]. Four of the systematic reviews looked at the effect of PCOS on HRQoL, finding a reliable and consistent negative effect of PCOS on HRQoL.

1.2.3 Risk factors

PCOS has diverse risk factors, and understanding them is important in disease detection and management [Roos et al., 2011]. Genetic associations from GWAS are illustrating various genes involved in androgen biosynthesis, androgen action, insulin signaling, metabolism, folliculogenesis and inflammation [Day et al., 2018]. Various lifestyle factors have been suggested as potential risk factors including poor eating habits, such as consuming diet with high saturated fats and low fibres, and a sedentary lifestyle, smoking and alcohol consumption [Escobar-Morreale, 2018]. As multiple studies in multiple countries report 28-40% of women with PCOS are current or past smokers these issues can often be exacerbated by smoking, in terms of increased insulin resistance (affecting 50-70%) with worsening lipid and metabolic profiles, with all the issues known to be associated with smoking. Smoking cessation is recommended, and the first-line therapy for PCOS is weight and lifestyle management, across multiple evidence based-guidelines. Weight loss of 2-5% can restore ovulation and cyclicity, with 5-15% producing stronger effects as well as a long list of various comorbidities including but not limited to; glycemic improvement, triglyceride reduction, HDL increase, quality of life, depression, urinary incontinence, sexual function, healthcare costs, mobility and mortality. This can be comforting to patients as a seemingly more manageable reduction can have proven health benefits without the possibly large task of reducing to a healthy BMI of $<25 kg/m^2$ [Rababa'h et al., 2022].

1.2.4 Infertility, adverse pregnancy and birth outcomes

Oligo-anovulation presents links with infertility with PCOS contributing between 70-80% of oligo-anovulatory infertility cases [Balen et al., 2016, Joham et al., 2015]. Infertility categorisation varies from country to country, with the American Society for Reproductive Medicine recommending evaluation for infertility should an individual not achieve pregnancy after 6 months of intercourse 2 to 3 times a week without contraception. While the UK recommendation is 12 months, as per National Institute of Health and Care Excellence (NICE) guidelines, and evidence on the cumulative probability of conceiving a clinical pregnancy after 12 or 24 cycles show that women aged 30-34 are 86% or 94% respectively. The adverse pregnancy and birth outcomes are more prevalent in women with PCOS which cannot be

explained by assisted reproductive technology, and include a strong association with preeclampsia, and very preterm birth. PCOS patients are also two times more likely to have gestational diabetes and their infants have increased risk of; being large for gestational age, requiring meconium aspiration, and having a low Apgar score at five minutes, which predicts neonatal encephalopathy and neurological outcomes giving indicators for cerebral palsy and epilepsy risk [Roos et al., 2011].

1.3 Study setting

Cyprus is the third largest island in the Mediterranean and is home to approximately 300 000 Turkish-speaking Cypriots and 700 000 Greek-speaking Cypriots. Due to unresolved political circumstances, Northern Cyprus, home to Turkish Cypriots, has been isolated from Europe for the past 45 years [Bryant, 2014]. Although Cyprus is a member of the European Union since May 1, 2004, the acquis communautaire is suspended in the northern part of the island [Central Intelligence Agency, 2017]. There is no collaboration between north and south administrations and as a results no population-level health data from Northern Cyprus have been included in health statistics reported from Cyprus [Rahmioglu et al., 2012]. Furthermore, there is no population-level data on common benign women's health conditions such as PCOS, endometriosis and uterine fibroids and related co-morbidities generally from the Eastern Mediterranean regions.

Resident of Northern Cyprus can access healthcare services from multiple streams; the public and private healthcare systems in Northern Cyprus, Turkey and Republic of Cyprus [Rahmioglu et al., 2012]. None of which are synced creating an issue for accurate healthcare data, furthermore there are broad issues around views of ownership of such data, where it does exist dividing healthcare professionals and academics which may ultimately harm research and patients. The Cyprus Women's Health Research (COHERE) Initiative, a cross-sectional study of women between the ages of 18-55 residing in Northern Cyprus, was established to determine the burden of women's benign health conditions and related co-morbidities in Northern Cyprus [Hocaoglu et al., 2019]. It is the first large-scale cross-sectional population-based study of the Northern Cyprus based on a household/workplace sampling method utilising the World Endometriosis Research Foundation's (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) questionnaire [Mis et al., 2021, Vitonis et al., 2014] that includes validated instruments used in previous studies. The study targeted to recruit 10% of women aged 18-55 living in Northern Cyprus. The participants completing the extensive questionnaires were able to also (1) provide a saliva sample for genotyping to understand the genetic landscape of this population (10%), (2) participate in a clinical follow-up to a women's health clinic including a transvaginal or transabdominal pelvic ultra-sound

scan that provides additional clinical data (10%) [Hocaoglu et al., 2019]. The study recruited 7,646 women between January 2018 and February 2020.

1.4 Aims

As evidenced from varied results from both genetic and epidemiological studies, it is important to investigate diseases symptomatology, presentation and its effects on quality of life in diverse populations to determine population-specific the burden of PCOS. Here, I will utilise COHERE Initiative data from this under-investigated Turkish Cypriot population in the Eastern Mediterranean region. The study we will make use of the self-reported questionnaire-based data from all participants, supplemented by clinical data on 10% of the participants. The specific aims of my project are as following:

Aim 1 - Determine the prevalence of polycystic ovary syndrome and baseline demographic and health characteristics of the sample.

Aim 2 - Investigate the clinical associations of infertility, hyperandrogenism, menstrual irregularity, and pain prevalence within the defined PCOS cases groups.

Aim 3 - Assess the quality of life impact of PCOS cases compared to population controls utilising the standardised SF36v2 scale reported as part of the questionnaire.

2 Methods

2.1 Study sample: The COHERE Initiative

The data for this study came from the COHERE Initiative, which is a population based cross-sectional study that determine the burden of underserved women's health conditions in Northern Cyprus. The initiative aimed to sample 10% of the women between the ages of 18-55, who had been residing in Northern Cyprus for at least 5 years across the 6 main districts; Famagusta, Kyrenia, Lefke, Morphou, Nicosia, Trikomo, and 12 sub-districts, with targets for each area being adjusted for population density. Individuals who did not meet these criteria were excluded. Recruitment took place between 31st January 2018 - 31st January 2020 through face-to-face (85%) and online (15%) recruitment, at homes and workplaces, culminating in the aforementioned sample population of 7,646 making it the largest population-based cross-sectional study focused women's health issues in this region to date. The sample representativeness was demonstrated by Swift et al (2022) by comparing the sample to census data [Swift et al., 2022].

2.2 The COHERE Initiative Questionnaire

Before completing the questionnaire, respondents gave their informed consent (see Appendix I for the consent form). The questionnaire was an expanded version of the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect) questionnaire [Vitonis et al., 2014, Mis et al., 2021]. The WERF-EPhect questionnaire components included questions on medical history, menstrual characteristics, pelvic pain, fertility and pregnancy history, hormone use and other medication use. In addition, (1) the standardised SF-36v2 health survey designed to give an overview of an individuals physical and mental health conditions [Ware Jr et al., 2000], (2) the Pain Catastrophizing Scale [Sullivan et al., 1995], (3) McGill Pain questionnaire [Melzack, 1975]. These scales had validated in Turkish version. Moreover, the remaining parts of questionnaire were translated and culturally adapted for the Turkish Cypriot population [Mis et al., 2021]. The full survey can be seen in Appendix II. In addition to the questionnaire, anthropometric measurements such as height, weight, and waist to hip ratio and blood pressure were measured in all participants.

2.3 Clinical Follow-up

As part of this study, all women were invited to take part in an optional clinical visit including a transvaginal or transabdominal pelvic ultrasound scan (USS). The ultrasound scan was performed by three different experienced gynaecologists in three different clinics, with 2 being based in Nicosia and

1 being based in Kyrenia. In total 686 individuals participated in pelvic ultrasound scan (8.7% of the study participants). Highest clinical visit rate was observed in Nicosia (12%, n=395) and Kyrenia (12.3%, n=155) with rates being lower in other areas (Range: 2.1% (n=13) in Trikomo and 8.8% (n=23) in Lefke) [Swift, 2022]. When comparing demographics between women who did and did not have a pelvic scan, women attending the scan tended to be older (39.8 vs 36.6, p<0.001). Comparing education, women attending the scan were more likely to have an undergraduate (35.8% vs 33.6%) or postgraduate (17.7% vs 16.7%) degree compared to women without a pelvic scan, and this was significant after adjustment for age. There was no significant difference in civil status between the two groups after adjustment for age.

2.4 PCOS case ascertainment

PCOS cases were women who self reported to have PCOS and/or were found to have evidence of polycystic ovarian morphology during the USS and received a diagnosis of PCOS from the doctor at their clinical visit during the ultrasound scans. Self-report of PCOS was evaluated using the following questions in the questionnaire; (Question B4) What are/were your reasons for using hormones?, (Question D4) Have you or your partner ever had any tests/investigations to find out why you were not getting pregnant? What were the results of these tests?, and (Question F1) tick if you have any of the following medical conditions.

2.5 Definition of clinical variables

Infertility was classified by those who self-reported the inability to conceive after 6 months unprotected regular intercourse (Question D3). Hyperandrogenism was determined by asking respondents to report whether they experienced excessive hair growth on your face or body that is not a side effect of a medication (Question F5), adult acne (Question F6), hair thinning or loss (Question F7), and darkening skin around your neck, under arms, hands, or groin (Question F8). Two variables were constructed - a binary variable (if the respondent experienced any of the symptoms versus not) and a variable that captured the total number of hyperandrogenism symptoms they experienced (scale of 0 to 4).

Respondents answered several questions regarding their menstruation (Questions B2). These were used to construct a variable capturing menstruation regularity with three categories (3) amenorrhea (no periods), (2) irregular periods, and (1) regular periods. In question B2, respondents first reported whether they had periods in the last 3 months. If they responded no to this they were categorised as having amenorrhea (3), provided they did not have excluding reasons for not having their periods such as menopause, pregnancy/breastfeeding and hormone use. If respondents, reported that they had

periods, they were asked about the regularity or irregularity of them in 5 categories (Question B2.9): Irregular (periods more than 20 days before/after expected), slightly irregular (periods 8-20 days before or after it is expected), regular (periods 5-7 days before or after expected), very regular (periods 3-4 days before or after expected), extremely regular (periods 1-2 days before or after expected). These responses for those menstruating were then classified as follows: (1) regular, made up of those reporting regular, very regular, extremely regular periods, and (2) irregular, consisting of those reporting irregular or slightly irregular periods. The variable excluded individuals who did not have periods due to menopause, pregnancy/breastfeeding and hormone use.

2.6 Definition of demographic and life-style variables

In the final section (H) of the survey, respondents completed a series of demographic questions and question on their lifestyle. Respondents were asked about their age (H1), ethnicity (H2), residence type (H3), residence (H3), employment status (H26), highest level of education level (H9), civil status (H6), displacement status (H3), and migrant status (H3-H6). Respondents who reported being born in the Republic of Cyprus where categorised as displaced (vs. not displaced). Respondents who reported not being born in Northern Cyprus or who were born there but did not have parents born in Northern Cyprus were categorised as migrants (vs. not migrants). Respondents also reported how much total alcohol they drank in a week (H25) and whether they smoked or not (H24). Those that responded "yes" to having smoked over 100 cigarettes during their lifetime were categorised as "smoking", those that responded "no" to this question or did not answer the question where categorised as "not smoking". Body Mass Index (BMI) was both self reported, where respondents answered height (H11) and weight (H12) questions, and for some respondents, measured at a clinical appointment. These clinical appointment measurements were preferred if available. The BMI was calculated and categorised into underweight, healthy weight, overweight, and obese using World Health Organization guidelines. The waist to hip ratio was measured at a clinical appointment for some of the respondents. The levels of each of the variables constructed can be seen in Table 1 and Table 2.

2.7 Quality of Life variables

The standardized tool for measuring health-related quality of life (HRQoL) used in this survey was the Short Form 36 version 2 (SF-36v2) which is a self-reported measure of overall well-being, quality of life, and functional health. It encompasses 36 items categorized into eight scaled scores, giving two summary measures of physical and mental health [Ware et al., 1993, Ware Jr, 2000]. The physical health

component summary score (PCS) is made up of; general health (GH), bodily pain (BP), role limitations due to physical health (RP), and physical function (PF), with the mental health component summary score (MCS) comprising; vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The SF-36v2 questions were included as the first part of the questionnaire including 11 questions (Questions A1-A11, see the Appendix II for a copy of the full survey). How the 11 questions correspond to the 8 dimensions can be found in the SF-36 Survey Manual and Interpretation Guide [Ware et al., 1993].

Health scores from SF-36v2 convey each health domain, mentioned above, on a scale from 0 to 100 representing the lowest and best health respectively, and were calculated and published using the standard SF-36 methods [Ware, 1994, Ware et al., 1993] for the overall cohort by Dr. Bethan Swift as part of her DPhil [Swift, 2022, Swift et al., 2022]. She utilised factor analysis and T-score transformation against UK values on these subscores to derive the Physical and Mental component health scores, with the mean being set to 50 and standard deviation being set to 10 [Jenkinson, 1999]. For further methodological details on how these were constructed please reference Swift et al. 2022 [Swift et al., 2022]. Both the computed PCS and MCS component scores as well as the 8 sub-scale to test will be used to test for statistical differences in the PCOS case group and controls.

Respondents self-reported whether they experienced pelvic pain (Question E27), period pain (Question E2), and pain during or after intercourse (Questions E15, E17). For period pain, individuals that reported no or mild pain were categorised as no pain (0) and those that reported moderate or severe pain were categorised as having period pain. The question for pelvic pain (acyclical pain unrelated to the respondent's cycle) was a simple binary yes (1) and no (0) question. Respondents reported in questions E15 and E27 whether they had pain during, after or both during and after intercourse, these were then coded as two variables with pain (1) and no pain (0) levels.

2.8 Data entry, storage, and computation

Researchers at the Eastern Mediterranean University uploaded the questionnaire data (10% of the data was double-entered and checked for data entry error rates which were all below 5%), the final storage, maintenance, and computation uses the Oxford Biomedical Research Computing (BMRC) facility. This is a joint development between the Big Data Institute and the Wellcome Centre for Human Genetics supported by the NIHR Oxford Biomedical Research Centre and Health Data Research UK.

2.9 Statistical analysis

Logistic regressions were performed for each of the demographic clinical and health variables, where these were categorical and ordered these were done as a factor with the reference stated. The logistic regression analysis comparing cases vs. controls were computed crude and then adjusted for age and education level adjusted. All statistical analysis was performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) [R Core Team, 2023].

2.10 Ethics and consent

Only those who were able to give informed consent were recruited, verbal and written consent was obtained from all participants. Ethical approval was given by the Oxford Tropical Research Ethics Committee (OxTREC) (Reference # 37-17), and a local Ethics committee (ETK00-2017-0240) of the University of Oxford and the Eastern Mediterranean University respectively.

2.11 Funding

The majority of funding came from crowdfunding led by Dr Nilufer Rahmioglu, Oxford University, UK, Professor Mustafa Bahceci M.D., Bahceci Health Group, Turkey, also donated funds. The Cyprus Women's Health Research Society (CoHERS) gave local support which facilitated promotion and information for potential participants through the European Union Civic Space. Finally, funds for local data collection, communications were received from the Eastern Mediterranean University and Vodafone Mobile Operation Ltd respectively. The research was supported by the Wellcome Trust Core Award Grant Number 203141/Z/16/Z with additional support from the NIHR Oxford BRC.

3 Results

3.1 PCOS Prevalence

3.1.1 Self reported and ultrasound scan PCOS prevalence

The prevalence of PCOS in this population of 7,646 was 6.5% (n=499). Of the 499 PCOS cases 228, 62, and 417, were declared as their reason for hormone use (B4), as the reason after testing as to why they were not getting pregnant (D4), and as a known medical condition (F1), respectively.

The prevalence of PCOS in the 662 who had an ultrasound scan was 6.6% (n=44) had active polycystic ovarian morphology, these were approximately evenly divided between the 21 who had previously self reported as having PCOS, and the 23 incident cases who had not. Of the self-reported PCOS cases attending the ultrasound scan (N=662), 5.0% (n=33) did not identify to have active polycystic ovarian morphology. This group of self-reported PCOS cases without polycystic ovarian morphology (mean age = 37.7) were significantly older than the PCOS cases identified with polycystic ovarian morphology (mean age = 29.9 at the scan (p<0.000)).

3.1.2 Demographic and lifestyle baseline characteristics

Logistic regressions were completed for each variable separately on PCOS cases (n=499) against the control group, those without PCOS diagnosis (n=7,147). Table 1 (Demographics) and 2 (Lifestyle) show the means (M), standard deviations (SD), counts, percentages, and p-values of the logistic regressions.

The PCOS group had a significantly younger mean age (M = 33.7 years SD = 8.0) compared to the control group (M = 37.1 years SD = 9.7, p = 0.004). The odds ratio indicates that for each year decrease in age there is a 3.78% (0.96, 95% CI (0.95, 0.97)) decrease chance of PCOS. The 46-55 age group had significantly higher representation in the control group than in the case group when using the 18-25 age group the reference group (p = 0.042). The PCOS case group and control group also significantly differed in education at the Undergraduate level when using primary/middle school educated individuals as the reference group (p = 0.020). No significant difference was found in any of the other measured demographic characteristics.

Table 1: Demographic characteristics and comparisons of polycystic ovary syndrome case group and control groups

	PCOS (n = 499)	Control (n = 7,147)	p-value
Demographics			
Age, mean (SD)	33.7 (8.0)	37.1 (9.7)	**0.004**
Age, n (%)			
18-25	81 (16.2)	1027 (14.4)	Reference
26-35	222 (44.5)	2161 (30.2)	0.510
36-45	157 (31.5)	2290 (32.0)	0.323
46-55	39 (7.8)	1669 (23.4)	**0.042**
Ethnicity, n (%)			
Turkish Cypriot	385 (77.2)	4993 (69.9)	Reference
Turkish	66 (13.2)	1459 (20.4)	0.700
Other/Mixed	30 (6.0)	358 (5.0)	0.764
Residence type, n (%)			
City	264 (52.9)	3788 (53.0)	Reference
Village	235 (47.1)	3359 (47.0)	0.0869
Residence, n (%)			
Famagusta	93 (18.6)	1518 (21.2)	Reference
Kyrenia	98 (19.6)	1165 (16.3)	0.718
Lefke	13 (2.6)	248 (3.5)	0.631
Morphou	23 (4.6)	562 (7.9)	0.385
Nicosia	240 (48.1)	3061 (42.8)	0.382
Trikomo	32 (6.4)	353 (4.9)	0.560
Employment, n (%)			
In employment	410 (82.1)	5510 (77.1)	Reference
Unemployed	72 (14.4)	1311 (18.3)	0.430
Education, n (%)			
Primary/Middle school	22 (4.4)	823 (11.5)	Reference
High school/Post-secondary	107 (21.4)	2450 (34.3)	0.139
Undergraduate	228 (44.7)	2360 (33.0)	**0.020**
Postgraduate	127 (25.5)	1077 (15.1)	0.113
Civil status			
Single	163 (32.7)	1590 (22.2)	Reference
Divorced/ Separated	42 (8.4)	642 (9.0)	0.371
Married	277 (55.1)	4562 (63.8)	0.623
Displaced, n (%)			
No	490 (98.2)	6822 (95.5)	
Yes	9 (1.8)	325 (4.5)	0.982
Migrant status			
Non-migrant	378 (75.8)	5058 (70.8)	Reference
Migrant	103 (20.6)	1751 (24.5)	0.727

[a] PCOS: Polycystic Ovary Syndrome, Age in years.
[b] P-values are from logistic regressions run on each demographic variable predicting PCOS individually.
[c] Values are reported as mean (standard error) or proportions, see methods (2.6) for more information on demographic variable description.

The PCOS case group and control group differed significantly in BMI ($B = 0.024$, $SE = 0.009$, $Wald = 2.76$, $p = 0.006$). The PCOS group had a significantly higher BMI ($M = 25.7$ kg/m^2 $SD = 5.3$) compared to the control group ($M = 25.0$ kg/m^2 $SD = 5.1$, $p = 0.015$). The odds ratio indicates that one unit increase in BMI is associated with a 2.4% (1.02, 95% CI (1.01, 1.04) increased chance of PCOS. No significant difference was found in any of the other measured lifestyle characteristics until adjusted for age. After adjusting for age, it was found that individuals with PCOS consumed significantly higher total alcohol than controls.

Table 2: Lifestyle characteristics and comparisons of polycystic ovary syndrome case group and two control groups

	PCOS (n = 499)	Control (n = 7,147)	Unadjusted p-value	Age adjusted p-value
BMI, mean (SD)	25.7 (5.3)	25.0 (5.1)	**0.006**	**<0.000**
BMI, n (%)				
Underweight	14 (2.8)	280 (3.9)	Reference	Reference
Healthy weight	239 (47.9)	3571 (50.0)	0.301	0.060
Overweight	118 (23.6)	1814 (25.4)	0.364	**0.016**
Obese	104 (20.8)	995 (13.9)	**0.012**	**<0.000**
Waist to hip ratio, mean (SD)	0.9 (0.1)	0.9 (0.3)	0.18905	0.249
Smoking, n (%)				
Smoking	40 (8.0)	510 (7.1)	Reference	Reference
Not Smoking	123 (24.6)	1677 (23.5)	0.933	0.321
Total Alcohol (ml), mean (SD)	36.8 (98.9)	24.5 (66.9)	0.06911	**0.002**

[a] PCOS: Polycystic Ovary Syndrome, Age in years. BMI: Body Mass Index (categories calculated using WHO guidelines).
[b] P-values are from logistic regressions run on each health variable predicting PCOS individually.
[c] Values are reported as mean (standard error) or proportions, see methods (2.6) for more information on demographic variable description.

3.2 Clinical associations with PCOS

Logistic regressions were completed for each variable separately on PCOS cases (n=499) against the control group (n=7,147). Figure 1 shows the counts and percentages of each clinical association for the PCOS case and control groups. Table 3 (unadjusted) and 4 (age and education adjusted) show the same counts and percentages, with the addition of the; estimate, standard error, p-values and odds ratios with 95% confidence intervals of the logistic regressions.

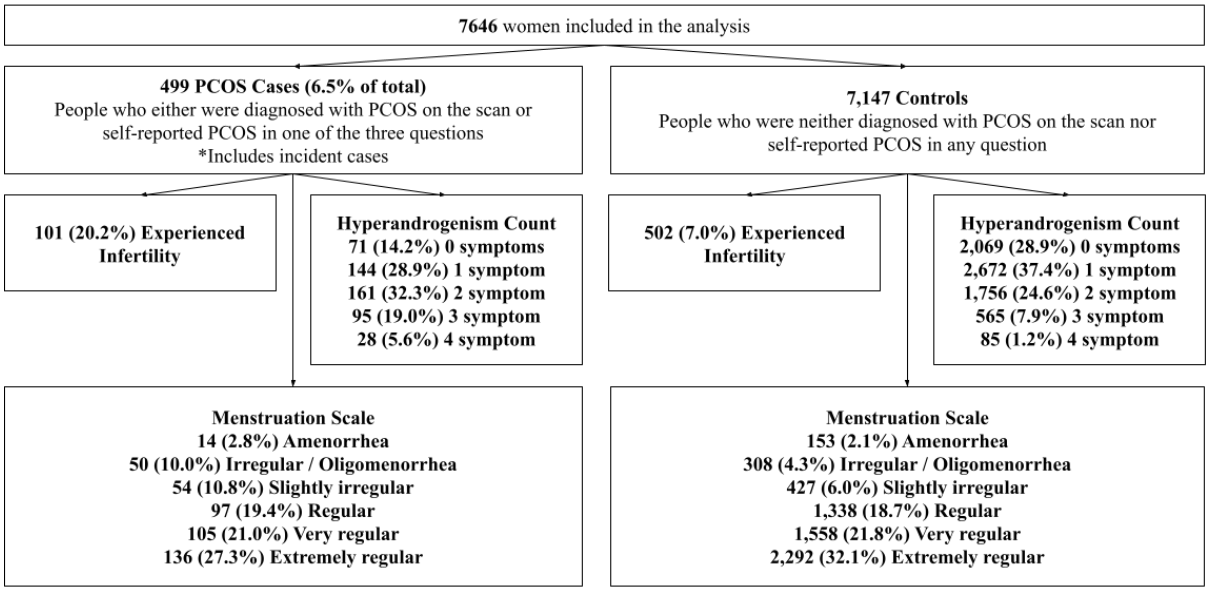

Figure 1: A diagram to show the clinical counts and percentages within the PCOS case and control groups.

Infertility was significantly more prevalent in the PCOS case group compared to the control group at 20.2% (n=101) and 7.0% (n=502) respectively ($B = 1.19$, $SE = 0.131$, $Wald = 9.11$, $p = <0.000$) with an odds ratio of 3.29 (95% CI:2.55 -4.25). This higher prevalence of infertility remained when adjusted for age and education ($B = 1.28$, $SE = 0.143$, $Wald = 9.437$, $p = <0.000$) with an odds ratio of 3.611 (2.73-4.78).

The PCOS group displayed significantly increasing hyperandrogenism symptoms when compared to controls ($B = 0.55$, $SE = 0.04$, $Wald = 12.36$, $p = <0.000$). PCOS cases were also more likely to report any hyperandrogenism symptoms at all ($B = 0.90$, $SE = 0.13$, $Wald = 6.87$, $p = <0.000$). Both of these effects remained significant after controlling for age and education (see Table 4). Compared to having no hyperandrogenism symptoms, there was a significantly higher proportion of individuals with fewer hyperandrogenism symptoms in the control group than the PCOS group. 28.9% (n=2,069) of the control group had no symptoms, compared to 14.2% (n=71) of the PCOS cases. The no symptoms category

served as a reference group for the other comparisons. 37.4% (n=2,672) of the control group had one symptom, which is significantly greater than the PCOS groups 28.9% (n=144) ($B = 0.45$, $SE = 0.15$, $Wald = 3.05$, $p = 0.002$) with an odds ratio of 1.57 (1.18-2.10). This is not the case for the higher end of hyperandrogeism symptoms where the PCOS group had a significantly higher proportion compared to controls. 32.3% (n=161) of the PCOS group having two symptoms, being significantly greater than the control group's 24.6% (n=1,756) ($B = 0.98$, $SE = 0.15$, $Wald = 6.73$, $p = <0.000$) with an odds ratio of 2.67 (2.01-3.56). 19.0% (n=95) of the PCOS group had three symptoms, which is significantly greater than the control group's 7.9% (n=565) ($B = 1.59$, $SE = 0.16$, $Wald = 6.73$, $p = <0.000$) with an odds ratio of 4.9 (3.55-6.76). 5.6% (n=28) of the PCOS group had four symptoms, which is significantly greater than the control group's 1.2% (n=85) ($B = 2.261$, $SE = 0.25$, $Wald = 9.08$, $p = <0.000$) with an odds ratio of 9.60 (5.89-15.64). As seen in Table 4, of these hyperandrogenism symptom analyses remained to be significant when adjusted for age and education.

PCOS was associated with increasingly irregular periods compared to controls ($M = 1.289$ $SD = 0.52$ vs $M = 1.17$ $SD = 0.44$, $p = <0.000$). The odds ratio may show that having irregular periods is associated with a 129% (2.23, 95% CI (1.84, 2.70) chance of PCOS. A total of 20.8% (n=104) of respondents with PCOS reported that they have irregular periods, whilst 10.3% (n=735) of respondents without PCOS had irregular periods. 2.8% (n=14) of respondents with PCOS reported that they had no periods (amenorrhea), whilst 2.14% (n=153) of respondents without PCOS had amenorrhea. Compared to those with regular periods, those with PCOS were significantly more likely to have oligomenorrhea ($B = 0.78$, $SE = 0.12$, $Wald = 6.53$, $p = <0.000$, 2.17 (1.72 - 2.74)) but not amenorrhea ($B = 0.34$, $SE = 0.28$, $Wald = 1.19$, $p = 0.233$, 1.40 (0.80 - 2.45)). Upon doing a logistic regression adjusted for age and education on menstration regularity it showed that compared to those with regular periods, those with PCOS were significantly more likely to have oligomenorrhea ($B = 1.00$, $SE = 0.13$, $Wald = 7.96$, $p = <0.000$, 2.72 (2.13 - 3.48)) as well as significantly more likely to have amenorrhea ($B = 1.13$, $SE = 0.30$, $Wald = 3.74$, $p = <0.000$, 3.08 (1.71 - 5.56)).

Table 3: Unadjusted clinical comparisons of polycystic ovary syndrome case group and control group

	(A) PCOS Cases (n = 499)	(B) Controls (n = 7,147)	Estimate (SE)	p-value	Odds ratio (95%CI)
Infertility, n (%)	101 (20.2%)	502 (7.0%)	1.190 (0.131)	**0.000**	3.29 (2.55 - 4.25)
Hyperandrogenism binary, n (%)	423 (85.8%)	5078 (71.1%)	0.899 (0.131)	**0.000**	2.46 (1.90 - 3.17)
Hyperandrogenism symptom count, Mean (SD)	0.858 (0.350)	0.711 (0.454)	0.550 (0.044)	**0.000**	1.73 (1.59 - 1.89)
0 symptoms, n (%)	71 (14.2%)	2,069 (28.9%)	Reference	Reference	Reference
1 symptoms, n (%)	144 (28.9%)	2,672 (37.4%)	0.451 (0.148)	**0.002**	1.57 (1.18 - 2.10)
2 symptoms, n (%)	161 (32.3%)	1,756 (24.6%)	0.983 (0.146)	**0.000**	2.67 (2.01 - 3.56)
3 symptoms, n (%)	95 (19.0%)	565 (7.9%)	1.589 (0.164)	**0.000**	4.90 (3.55 - 6.76)
4 symptoms, n (%)	28 (5.6%)	85 (1.2%)	2.262 (0.249)	**0.000**	9.60 (5.89 - 15.64)
Menstruation regularity, Mean (SD)	1.289 (0.517)	1.171 (0.439)	-3.175 (0.123)	**0.000**	0.04 (0.03 - 0.05)
Regular (1), n (%)	338 (67.7%)	5188 (32.1%)	Reference	Reference	Reference
Irregular (2), n (%)	104 (20.8%)	735 (10.3%)	0.776 (0.119)	**0.000**	2.17 (1.72 - 2.74)
Amenorrhea (3), n (%)	14 (2.8%)	153 (2.14%)	0.340 (0.285)	0.233	1.40 (0.80 - 2.45)
NA or excluding reasons, n (%)	43 (8.6%)	615 (8.6%)	-	-	-

[a] PCOS: Polycystic Ovary Syndrome.
[b] Estimate, standard error (SE), p-values, and odds ration with confidence intervals (CI) are from logistic regressions run on each clinical variable comparing PCOS group against control group individually.
[c] Values are reported as mean (standard error) or proportions.
[d] Infertility is defined as > 6 months of regular unprotected intercourse without conception.
[e] hyperandrogenism symptoms are counts from 0 to 4 where individuals self-reported; (a) excessive hair growth on face or body that is not a side effect of a medication, (b) adult acne, (c) hair thinning or loss, and/or (d) darkening skin around neck, underarms, hands, or groin.
[f] Menstruation regularity is defined as those who self reported to have regular periods (period starts 1-7 days before or after is expected), Irregular periods (period starts $8 \geq 20$ days before or after is expected), or amenorrhea (no periods in the last 3 months). In the amenorrhea category individuals who had excluding reasons (taking hormones which prevent periods, pregnant/breastfeeding, or due to menopause), or did not respond to the question (NA) were included here.

Table 4: Age and education adjusted clinical comparisons of polycystic ovary syndrome case group and control group

	(A) PCOS Cases (n = 499)	(B) Controls (n = 7,147)	Estimate (SE)	p-value	Odds ratio (CI)
Infertility, n (%)	101 (20.2%)	502 (7.0%)	1.318 (0.14)	**0.000**	3.74 (2.84 - 4.91)
Hyperandrogenism binary, n (%)	423 (85.8%)	5078 (71.1%)	0.792 (0.143)	**0.000**	2.21 (1.67 - 2.93)
Hyperandrogenism symptom count,					
Mean (SD)	0.858 (0.350)	0.711 (0.454)	0.462 (0.048)	**0.000**	1.59 (1.44 - 1.75)
0 symptoms, n (%)	71 (14.2%)	2,069 (28.9%)	Reference	Reference	Reference
1 symptoms, n (%)	144 (28.9%)	2,672 (37.4%)	0.401 (0.159)	**0.012**	1.49 (1.09 - 2.04)
2 symptoms, n (%)	161 (32.3%)	1,756 (24.6%)	0.867 (0.158)	**0.000**	2.38 (1.74 - 3.24)
3 symptoms, n (%)	95 (19.0%)	565 (7.9%)	1.410 (0.176)	**0.000**	4.10 (2.90 - 5.79)
4 symptoms, n (%)	28 (5.6%)	85 (1.2%)	2.090 (0.265)	**0.000**	8.08 (4.81 - 13.59)
Menstruation regularity,					
Mean (SD)	1.289 (0.517)	1.171 (0.439)	0.802 (0.098)	**0.000**	2.23 (1.84 - 2.70)
Regular (1), n (%)	338 (67.7%)	5188 (72.6%)	Reference	Reference	Reference
Irregular (2), n (%)	104 (20.8%)	735 (10.3%)	1.001 (0.126)	**0.000**	2.72 (2.13 - 3.48)
Amenorrhea (3), n (%)	14 (2.8%)	153 (2.14%)	1.125 (0.301)	**0.000**	3.08 (1.71 - 5.56)
NA or excluding reasons, n (%)	43 (8.6%)	615 (8.6%)	-	-	-

[a] PCOS: Polycystic Ovary Syndrome.
[b] Estimate, standard error (SE), p-values, and odds ration with confidence intervals (CI) are from logistic regressions run on each clinical variable comparing PCOS group against control group individually.
[c] Values are reported as mean (standard error) or proportions.
[d] Infertility is defined as > 6 months of regular unprotected intercourse without conception.
[e] hyperandrogenism symptoms are counts from 0 to 4 where individuals self-reported; (a) excessive hair growth on face or body that is not a side effect of a medication, (b) adult acne, (c) hair thinning or loss, and/or (d) darkening skin around neck, underarms, hands, or groin.
[f] Menstruation regularity is defined as those who self reported to have regular periods (period starts 1-7 days before or after is expected), Irregular periods (period starts 8$\geq$20 days before or after is expected), or amenorrhea (no periods in the last 3 months). In the amenorrhea category individuals who had excluding reasons (taking hormones which prevent periods, pregnant/breastfeeding, or due to menopause), or did not respond to the question (NA) were included here.

3.2.1 Pain associations with PCOS

The PCOS case group displayed significantly higher prevalence of pelvic pain at 10.0% compared to the 6.2% in control group (p=0.001) with an odds ratio of 1.69 (1.25-2.30). Period pain prevalence was also more prevalent at 50.5% compared to the 37.7% prevalence in the control group (p =<0.000) with an odds ratio of 1.69 (1.41-2.02). Pain during and after intercourse were each significantly raised at 6.8% vs 3.4% (p =<0.000) with an odds ratio of 2.09 (1.44-3.02) and 5.2% vs 2.5% (p =<0.000) with an odds ratio of 2.17 (1.42-3.30) when compared to controls. All these remained significant after adjusting for age and education. Pain during and after intercourse was approximately twice as common in PCOS patient than in controls, and around half of the PCOS patients complained of period pain, compared to the controls proportion of just over one third.

Table 5: Pain comparisons of PCOS cases and controls

		(A) PCOS (n = 499)	(B) Control (n = 7,147)	p-value	Odds ratio (95% CI)	Adjusted p-value	Adjusted odds ratio (95% CI)
Pelvic pain	Yes	50 (10.0%)	441 (6.2%)	**0.001**	1.69 (1.25 - 2.30)	**0.007**	1.55 (1.13 - 2.13)
	No	449 (90%)	6706 (93.8%)				
Period pain	Yes	252 (50.5%)	2694 (37.7%)	<**0.000**	1.69 (1.41 - 2.02)	**0.006**	1.32 (1.08 - 1.61)
	No	247 (49.5%)	4453 (62.3%)				
Pain during intercourse	Yes	34 (6.8%)	242 (3.4%)	<**0.000**	2.09 (1.44 - 3.02)	<**0.000**	2.01 (1.37 - 2.95)
	No	465 (93.1%)	6905 (96.6%)				
Pain after intercourse	Yes	26 (5.2%)	117 (2.5%)	<**0.000**	2.17 (1.42 - 3.30)	**0.001**	2.17 (1.39 - 3.36)
	No	473 (94.8%)	6970 (97.5%)				

[a] Adjusted for age in years (continuous) and education status (in categories).
[b] PCOS: Polycystic Ovary Syndrome, Age in years.
[c] Values from logistic regressions run on each health variable predicting comparing PCOS group and control groups individually.
[d] Values are reported as proportions.
[e] Pelvic pain is self-reported acyclical pain (unrelated to the respondent's cycle).
[f] Period pain is self reported moderate or severe pain.
[g] Pain during or after intercourse is self reported as the binary, yes, no presented.

3.3 Health-related quality of life

3.3.1 Health-related quality of life associations with PCOS

Following adjustment for age and education, both physical component score (PCS) and metal health component score were significantly lower in PCOS cases compared to controls (Table 5). All the physical and mental-health subscales were also significantly lower in PCOS cases compared to controls (Table 5) showing PCOS is a condition that affecting women's physical and mental wellbeing significantly in this population. When controlling for all four pain variables, scores on all dimensions except bodily pain remained significant when comparing PCOS cases with controls.

Table 6: Health-related quality of life Comparisons of PCOS Cases and Controls

	(A) PCOS (n = 499)	(B) Control (n = 7,147)	Unadjusted p-value	Age and education level adjusted p-value	Age, education level & pain adjusted p-value
Physical functioning (PF)	88.2 (16.3)	88.3 (15.8)	0.938	**<0.000**	**0.003**
Role Physical (RP)	78.5 (23.3)	80.8 (15.8)	**0.032**	**<0.000**	**0.002**
Bodily pain (BP)	67.2 (23.7)	68.3 (24.4)	0.314	**0.007**	0.074
General health (GH)	60.1 (23.7)	64.0 (19.7)	**<0.000**	**<0.000**	**<0.000**
Vitality (VT)	54.7 (19.6)	57.7 (20.8)	**0.002**	**<0.000**	**0.002**
Social functioning (SF)	72.8 (24.5)	77.7 (23.1)	**<0.000**	**<0.000**	**<0.000**
Role emotional (RE)	72.7 (24.4)	77.4 (23.8)	**<0.000**	**<0.000**	**0.001**
Mental health (MH)	60.9 (19.4)	64.3 (19.8)	**<0.000**	**<0.000**	**0.002**
PCS	48.3 (9.4)	48.3 (8.8)	0.870	**0.003**	**0.006**
MCS	44.6 (11.1)	46.9 (10.9)	**<0.000**	**<0.000**	**0.018**

[a] PCOS: Polycystic Ovary Syndrome.
[b] P-values are from logistic regressions run on each health-related quality of life variable predicting PCOS individually.
[c] Values are scores reported as mean score (standard deviation).
[d] PCS represents the Physical (Component) Summary score, which summarizes physical health-related quality of life, benchmarked against UK values. This is made up of; (1) Physical functioning (PF) measures the ability to perform everyday physical activities, (2) Role Physical (RP) assesses the extent to which physical health affects daily activities, (3) Bodily pain (BP) evaluates the presence and impact of bodily pain, and (4) General health (GH) reflects overall self-rated health.
[e] MCSrepresents the Mental (Component) Summary score, which summarizes mental health-related quality of life, benchmarked against UK values. (1) Vitality (VT) assesses the level of energy and fatigue, (2) Social functioning (SF) evaluates the impact of physical health on social activities, (3) Role emotional (RE) measures the extent to which emotional health affects daily activities, and (4) Mental health (MH) assesses overall mental well-being.

4 Discussion

4.1 PCOS Prevalence

The COHERE Initiative aimed to fill the gap in understanding the burden of underserved womens health conditions in Northern Cyprus. Before this, there was no data on PCOS prevalence, clinical symptoms, and related health and quality of life indictators in Northern Cyprus. Past research has found that PCOS phenotype can vary across different ethnicities [Guo et al., 2012], increasing the importance of filling such gaps when trying to build an understanding of PCOS.

In the one study that does exist of the Cypriot population, a study of 642 women from the Republic of Cyprus, the estimated self-report PCOS prevalence was 6.1% [Kyprianidou et al., 2020]. This is in line with the prevalence finding in the present study of 6.5% in Northern Cyprus in a sample of 7646 women. However, the study lacked any clinical, symptoms descriptions as well as quality of life descriptors for the Greek-Cypriot PCOS cases. Whilst the prevalence rates look similar, it remains to be determined whether there are differences in patient characteristics and the impact of the condition on women from both communities.

6.5% is towards the lower end of the 5-20% that is generally quoted [Azziz et al., 2016]. As previously mentioned, the recruitment strategy of the COHERE initiative reduced the issue of lacking representativeness as shown through the sample of the population accurately matching census data [Swift et al., 2022]. The higher end of this spectrum may misrepresent/exaggerate the issue of PCOS through recruiting at clinics or other over representative locations [Lizneva et al., 2016].

4.2 Baseline and Lifestyle Characteristics

The study found that in comparison to controls, women with PCOS had a significantly lower mean age and lower representation in the 46-55 age group (in comparison to the 18-25 age group). The PCOS case group and control group also significantly differed in education. When using primary/middle school educated individuals as the reference group, women with PCOS were significantly more likely to have an undergraduate degree (44.7%) than controls (33.0%). There were no significant difference found in any of the other measured demographic characteristics including ethnicity, residence, employment, civil status, displacement status, or migrant status.

Women with PCOS were found to have significantly higher BMI than controls. Specifically, they were more likely to be clinically considered obese (20.8%) than controls (13.9%) when underweight was taken

as the reference group in the logistic regression. When adjusting for age PCOS cases were also more likely to be considered overweight than controls. No significant differences in waist to hip ratio, smoking status or alcohol consumption were found between women with PCOS and the controls when not controlling for age. When controlling for age, it was found that those with PCOS consumed significantly more total alcohol than controls. Escobar-Morreale (2018) found that increased alcohol consumption is a risk factor for PCOS, along with other lifestyle factors [Escobar-Morreale, 2018]. Longitudinal research would be needed to determine whether there are effects of having PCOS on alcohol consumption separate from baseline characteristics and risk factors that could account for this effect.

These age and BMI findings are common in observational studies of PCOS [Fakhoury et al., 2012]. Selection biases can contribute to demographic and lifestyle differences between PCOS cases and controls. However, in regard to age and BMI other factors may be at play. The lower mean age could be due to age-related differences in PCOS phenotype, such as the reduction in serum androgens in older age and resulting reduction in hyperandrogenism symptoms [Hsu, 2013, Bili et al., 2001]. Past systematic reviews and meta-analyses have also found that women with PCOS were more likely to have a higher BMI and were more at risk of being obese, which has long been established [Lim et al., 2012b, De Groot et al., 2011, Hopkinson et al., 1998]. Obesity is likely to affect the endocrine, metabolic, reproductive, and psychological features of PCOS [Barber and Franks, 2021, Li et al., 2017], and in turn, some research suggests PCOS may increase the likelihood of obesity [Lim et al., 2012a, Lim et al., 2009, Georgopoulos et al., 2009, Himelein and Thatcher, 2006a].

The higher representation of those with undergraduate degrees, was found in previous work on this data set with endometriosis [Swift, 2022] and supports the previously indicated issue that socioeconomic factors influence PCOS identification and health outcomes [Hochberg et al., 2023, Merkin et al., 2011, Di Fede et al., 2009].

4.3 Clinical associations with PCOS

The study found that in comparison to controls, women with PCOS had a significantly higher rates of infertility, menstrual irregularity , and hyperandrogenism. These associations remained significant when controlling for age and education. In terms of rates of infertility, women with PCOS were more than double as likely to report or be diagnosed with inferility (20.2%) than controls (7.0%). The prevalence of reporting irregular menstruation was also twice as high in those with PCOS (20.8%) than in controls (10.4%). Women with PCOS were more likely to report any of the symptoms of hyperandrogenism (85.8%) in comparison to controls (71.1%).

It is generally well established that hyperandrogenism, menstrual irregularities, and infertility form part of the interlinked clinical symptoms of PCOS [Alshammary et al., 2023, Haddad-Filho et al., 2023, Kicińska et al., 2023]. Hyperandrogenism has been linked to menstrual irregularities [Kim et al., 2014, Gordon, 1999]. In turn, menstrual irregularities cause infertility through the absence of an ovum to fertilise and early detection can mean better prevention and harm reduction [West et al., 2014]. The previously mentioned pathogenosis of PCOS explains these clinical symptoms with genetic variants associated with PCOS causing issues with the release of pulsatile gonadotropin hormone (GnRH). This subsequently causes hypersecretion of luteinizing hormone (LH) by the pituitary gland leading to hyperandrogenism and ovulatory dysfunction. The menstrual irregularity may be exacerbated by increased levels of intra-ovarian anti-Mullerian hormone (AMH) resulting in the reduced sensitivity to FSH. Because of this association between PCOS and infertility, there have been previous efforts to diagnose PCOS at infertility clinics as a result [Hanson et al., 2016, Brassard et al., 2008].

These clinical symptoms can have significant effects on the lived experiences and quality of life of those with PCOS. Infertility has been linked to decreased quality of life [Tabassum et al., 2021]. Some biochemical markers of hyperandrogenism have been found to be associated with psychological well-being outcomes such as social anxiety and self-esteem [Besenek and Gurlek, 2021]. Menstruation irregularity has been found to be associated with quality of life indicators, pain, sleep quality, fatigue, and premature mortality [Kennedy et al., 2021, Wang et al., 2020, Kwan et al., 2022].

Pain experiences appear to form part of the clinical expression of PCOS in the current sample. In the current study, those with PCOS were significantly more likely to report experiencing pelvic pain (10.0%), period pain (50.5%), pain during intercourse (6.8%), and pain after intercourse (5.2%), in comparison to controls (6.2%, 37.7%, 3.4%, and 2.5%, respectively). Double the number of respondents reported experiencing pain during and after intercourse in comparison to those without PCOS. These associations between pain reports and PCOS remained significant after controlling for age and education.

The evidence for this association with pain is somewhat mixed in the previous literature and a topic of ongoing debate [Lu et al., 2022, Martin et al., 2017, Mantzou et al., 2021]. The findings are in line with the current study and literature that PCOS is associated with the bodily pain dimension on the SF-36 [Li et al., 2011]. However, some studies do not find that PCOS is reliably associated with increased experiences of pain. One study, for example, found that the pain dimension scores on the Female Sexual Function Index were not significantly different between the 76 young women and 133 matched controls [Mantzou et al., 2021]. In addition, when used as controlling variables in looking at the effect of PCOS on HRQoL in the present analysis, the addition of the four pain variables resulted in the bodily pain

dimension no longer being a significant predictor differentiating between PCOS cases and controls. This suggests that it may be these experiences of pelvic pain, period pain, and pain during and after intercourse that contribute to higher scores on the bodily pain dimension on the SF-36v2. However, further analysis and research will be needed to explore this relationship.

4.4 Quality of life

Previous literature has generally found that PCOS has a negative effect on physical and mental HRQoL. PCOS has been found to be associated with lower HRQoL, decreased mental health outcomes, such as increased anxiety and depression, and lower sexual function [Li et al., 2011, Himelein and Thatcher, 2006b, Gilbert et al., 2018, Pastoor et al., 2018]. This is in line with the current findings for the population of Northern Cyprus, where women with PCOS were found to score significantly lower on all dimensions and component summary scores of the SF-36 when controlling for age and education. This points to PCOS being associated with a significant burden on the physical, emotional, and social quality of life of those living with PCOS. Four of the reviews evaluated the effects of PCOS onHRQoL and all found PCOS to have a significant negative effect. The one review that examined the effect of PCOS on physical, social, and emotional HRQoL using the SF-36 questionnaire also used in the present study found that women with PCOS had significantly lower scores on all dimensions of the SF-36, which include physical function, physical role function, bodily pain, general health, vitality, social functioning, role emotional function, and mental health [Li et al., 2011]. As such, the findings of the present study on the effects of PCOS on HRQoL are in line with the previous literature. It should be noted that the association between one dimension of the SF-36 (bodily pain) and PCOS became insignificant after controlling for age, education, and all four pain variables. This highlights that for this population, the reduction in HRQoL associated with PCOS cannot simply be explained by the higher levels of pain experienced by those with PCOS compared to controls.

4.5 Limitations and future directions for research

There are a number of limitations to the current study. Only 8.7% of the total respondents were given an ultra-sound scan, meaning the majority of the PCOS cases relied on self-report. In addition, the existence of clinical symptoms - hyperandrogenism, infertility, and irregular menstruation - all relied on self-report. This means there is a risk of information and recall bias in reporting symptoms which were not further verified by other means of clinically diagnosing such symptoms. The gold standard for hyperandrogenism diagnosis, and subsequent PCOS diagnosis, is a blood test which was

not performed in this study. When not done through clinical markers hyperandrogenism can also be determined by a modified Ferriman-Gallwey assessment which is an evaluation of body hair used to evaluate hirsutism of $\geq$4 to $\geq$8 [Cook et al., 2011]. The threshold level for hyperandrogenism criteria for PCOS in the modified Ferriman-Gallwey assessment is dependent on the context of patient ethnicity [Cebeci Kahraman and Savaş Erdoğan, 2022, Khan et al., 2019, Lumezi et al., 2018]. Future efforts to create large-scale datasets of PCOS cases may wish to incorporate this into their evaluation where blood tests are not available, for example, in low resource environments.

The study is also a cross-sectional study, where the survey was taken at a different time than the ultra-sound scan was performed. This temporality issue complicates interpretation of the result since the time lag means that whether someone had active PCOS (i.e. with PCOM) at the time of the survey cannot be determined. Future studies should consider conducting the survey at the same time as any medical procedures.

It appears that like previous studies of PCOS selection bias is hard to overcome. Women more interested or aware of women's health issues may have self-selected into the COHERE study. For example, it may be the case that those who are younger or have higher educational levels are more aware of such issues, leading to an over representation of such populations in the current study. This issue, however, is difficult to disentangle in the case of age from differences in the presentation of PCOS across the lifespan.

The reasons and precise mechanisms for why PCOS cases could have increased pain perceptions remain unclear. Based on a review of 14 studies, it has been suggested that both infertility and obesity may contribute to the development of such pain symptoms and that the association could be linked to pro-inflammatory factors [Lu et al., 2022, Regidor et al., 2022]. To further examine the relationship between pelvic pain experiences, the bodily pain dimension on HRQoL measures, and PCOS, future research and analysis of the COHERE dataset could look at the role that such additional clinical and health-related symptoms may play in the relationship. Additionally, more research will be needed that compares PCOS cases and controls on both the bodily pain dimension and other measures of pain experiences such as dysmenorrhea and dyspareunia to understand the findings. This will require wider use of survey designs with more comprehensive sets of pain-related questions to better evaluate this association with PCOS [Lu et al., 2022].

Further analysis and research exploring the effect of BMI as a factor in the relationship between PCOS and HRQoL should be conducted, since there is mixed evidence and inconclusive evidence of the role it plays [Jones et al., 2007, Kaczmarek et al., 2016]. A systematic review of seven studies found that across the board PCOS was related to lower HRQoL in patients adolescents and young adults aged 13 to

24 [Kaczmarek et al., 2016]. The review found that this appears to mediated in part by higher amount of bodyweight issues and higher Body Mass Index (BMI) in PCOS patients, with some studies finding the effect disappears when controlling for BMI. However, a systematic review of 19 studies found that the evidence was inconclusive for the role BMI plays in the relationship of PCOS and lower HRQoL [Jones et al., 2007].

Another issue is the benchmarking of the SF-36v2 component scores. The physical health component score (PCS) and mental health component scores were benchmarked against a UK population since it was identified as the most relevant comparison population due the Northern Cypriot lifestyle being most similar to the UK compared to the other US option. The COHERE dataset is however large enough to be a reliable representation of Northern Cypriot lifestyle in and of itself. Hence the scores can be also calculated using the general population normative values from Northern Cyprus [Swift, 2022] in future studies.

Finally, future research should be done for PCOS that takes a comprehensive look at the co-morbidities, treatments utilised and their cost, quality of life, economic burden, and work productivity impairment, similar to the work of Dr. Bethan Swift on endometriosis [Swift, 2022]. This will allow for more accurate prioritising when considering condition intervention policy.

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