Therapeutic Advances in Endocrinology and Metabolism *Original Research*

The relationship between obstructive sleep apnoea and quality of life in women with polycystic ovary syndrome: a cross-sectional study

Ther Adv Endocrinol Metab

2020, Vol. 11: 1–12

DOI: 10.1177/2042018820906689

Hassan Kahal*, **Abd A. Tahrani***, **Ioannis Kyrou**, **Georgios K. Dimitriadis**, **Peter K. Kimani**, **Thomas M. Barber**, **Matthew Nicholls**, **Asad Ali**, **Martin O. Weickert#** and **Harpal S. Randeva#**

Correspondence to:
Harpal S. Randeva
Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM) and Human Metabolism Research Unit (HMRU), University Hospitals Coventry and Warwickshire NHS Trust, Coventry, CV2 2DX, UK

Division of Translational and Experimental Medicine, Warwick Medical School, University of Warwick, Coventry, UK

Aston Medical Research Institute, Aston Medical School, Aston University, Birmingham, UK

Centre of Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, UK
Harpal.Randeva@warwick.ac.uk

Hassan Kahal
Division of Translational and Experimental Medicine, Warwick Medical School, University of Warwick, Coventry, UK

Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM), University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Abd A. Tahrani
Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Centre of Endocrinology, Diabetes and Metabolism (CEDAM), Birmingham Health Partners, Birmingham, UK

Department of Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Abstract

Background: Obstructive sleep apnoea (OSA) and polycystic ovary syndrome (PCOS) are associated with significant comorbidities and commonly coexist. The primary aim of this study was to examine the relationship between OSA and quality of life (QoL) in women with PCOS.

Methods: We conducted an observational cross-sectional study. PCOS was diagnosed according to the Rotterdam criteria. Women with increased risk of OSA, based on the Berlin questionnaire or the Epworth Sleepiness Scale (ESS), had home-based polysomnography performed (ALICE PDx). Participants were divided into two groups: (a) PCOS only: women with normal ESS and low-risk Berlin questionnaire (no sleep studies performed), or women with normal sleep studies [oxygen desaturation index (ODI) <5 events/hour]; and (b) PCOS+OSA: women with PCOS and OSA ODI $\geqslant 5$. QoL was assessed using the World Health Organization QoL questionnaire (WHOQOL-BREF) and the PCOS health-related quality of life questionnaire (PCOSQ).

Results: A total of 39 women were included; age (mean $\pm$ SD) was 32.2 ± 8.9 years, weight 92.5 ± 23.7 kg and body mass index (BMI) 34.1 ± 7.9 kg/m^2; 38.5% ($n=15$) had OSA. Compared with women with PCOS only, women with PCOS+OSA had higher BMI, HbA1c, C-reactive protein and low-density lipoprotein. ODI was independently associated with impaired QoL. Excessive daytime sleepiness (EDS) was independently associated with anxiety, depression and impaired QoL.

Conclusions: OSA is highly prevalent and is associated with impaired QoL and worse metabolic profile in women with PCOS. Interventional studies are needed to examine the impact of OSA in women with PCOS.

ClinicalTrials.gov Identifier: NCT03065322

Keywords: obesity, obstructive sleep apnoea, polycystic ovary syndrome, quality of life

Received: 21 April 2019; revised manuscript accepted: 21 January 2020.

Introduction

Polycystic ovary syndrome (PCOS) and obstructive sleep apnoea (OSA) are associated with obesity and commonly coexist.[1,2] The underlying mechanisms that link PCOS and OSA include insulin resistance, hormonal disturbances, oxidative stress and sympathetic overactivity.[1] A recent systematic review and meta-analysis showed that around a third of women with PCOS may suffer from OSA,[3] while population-based cohort studies suggest higher incidence of OSA in women with PCOS compared with controls.[4,5] A better understanding of the relationship between PCOS and OSA is important, as OSA may contribute to

Ioannis Kyrou
Division of Translational and Experimental Medicine, Warwick Medical School, University of Warwick, Coventry, UK

Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM), University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Aston Medical Research Institute, Aston Medical School, Aston University, Birmingham, UK

Centre of Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, UK

Georgios K. Dimitriadis
Department of Endocrinology, King's College Hospital NHS Foundation Trust, Denmark Hill, London, UK

Peter K. Kimani
Statistics and Epidemiology, Warwick Medical School, University of Warwick, Coventry, UK

Thomas M. Barber
Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM), University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Warwickshire Institute for the Study of Diabetes, Endocrinology and Metabolism (WISDEM) and Human Metabolism Research Unit (HMRU), University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Division of Biomedical Sciences, Warwick Medical School, University of Warwick, Coventry, UK

Matthew Nicholls
Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Asad Ali
Department of Respiratory Medicine, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK

Martin O. Weickert
Division of Translational and Experimental Medicine, Warwick Medical School, University of Warwick, Coventry, UK

Warwickshire Institute for the Study of Diabetes, Endocrinology

the clinical phenotype of PCOS, which can be at least partly corrected by continuous positive airway pressure (CPAP) treatment.[1,6]

Excessive daytime sleepiness (EDS) is often seen in patients with OSA and is attributed to factors including intermittent night-time hypoxaemia, sleep fragmentation and changes in sleep architecture and quality.[7] However, many patients with OSA do not have EDS, and EDS is also commonly seen in the general population.[8] EDS has been independently associated with obesity, insulin resistance and components of the metabolic syndrome,[9] and has been linked to multiple comorbidities including cognitive impairment, mood disorders and road traffic accidents.[10] A small number of studies have suggested an increase of EDS in women with PCOS. However, it is not clear if the reported association between PCOS and EDS is independent of OSA and obesity, or what impact EDS has in women with PCOS. Similarly, the effects of OSA on important clinical outcomes in women with PCOS including QoL, risk of type 2 diabetes (T2DM) or cardiovascular disease (CVD) remain unknown.[6]

In this study, we hypothesized that women with PCOS and OSA have a more severe phenotype of PCOS and lower QoL compared with women with PCOS without OSA. Our primary aim was to examine the relationship between OSA and QoL in women with PCOS. Secondary outcomes included examining the associations of OSA with depression, anxiety and metabolic phenotype in women with PCOS, as well as the relationship between EDS, PCOS phenotype and QoL. This study was designed as preliminary exploratory proof of concept trial in order to inform the design of larger multicentre trial.

Methods

Study design

Observational cross-sectional study.

Study participants

PCOS was diagnosed according to the Rotterdam criteria.[11] Study participants were recruited consecutively from the PCOS, Weight Management and Reproductive Endocrinology clinics at the University Hospital Coventry, Coventry, United Kingdom. Participants were recruited regardless of symptoms suggestive of OSA. Invitation letters and study patient information sheets were also sent to patients who attended the PCOS clinic in the 12 months preceding the start of the study. In addition, a poster inviting women with a history of PCOS to take part in the study was displayed at different sites at University Hospital Coventry and an e-poster was displayed on the hospital intranet. Women who responded to the study advert and did not have a previously confirmed diagnosis of PCOS were booked into the PCOS clinic and only recruited to the study if the PCOS diagnosis was confirmed. Study exclusion criteria included women who were pregnant or breastfeeding; using CPAP for OSA treatment (as this may mask the effects of OSA on QoL); less than 18 years of age; unable to give consent or unable to adequately understand or speak English. The study was approved by the Cambridge South Research Ethics Committee (Reference: 16/EE/0469). All participants signed a written consent form before taking part in any study related activities.

Participants attended the study visit between 8 and 9 am after an overnight fast ($\geq$10 h). The study visit was performed at the follicular phase of the cycle in women with regular periods. Women with history of oligomenorrhoea were seen regardless of their stage of the cycle.

OSA assessment

Study participants were screened for OSA using the Berlin questionnaire[12] and Epworth Sleepiness Scale (ESS).[13] If both were normal (i.e. low-risk OSA on Berlin and ESS $<$ 11) then no further testing for OSA was performed. If the Berlin questionnaire showed high risk of OSA or the ESS was $\geq$11, then home-based sleep studies were arranged using a portable multichannel cardiorespiratory device (Alice PDx, Philips Respironics, USA) unless the participant already had a sleep study performed as part of routine care in the preceding year.

The scoring of the sleep studies was performed by a respiratory physician (A.A.) and a sleep technician (M.T.), and both assessors were blinded to participants' data. Any disagreements between the two examiners were resolved by consensus. Sleep studies with $<$4 h of adequate recordings were repeated and excluded if the quality remained poor. OSA was defined as an oxygen

desaturation index (ODI) ⩾ 5 events/hour.[14] The sleep studies were scored in accordance with the American Academy of Sleep Medicine guidelines 2017.[15] The hypopnea definition used in this study was a peak signal drop by ⩾30% for ⩾10 s when a ⩾3% desaturation was present.

Based on these assessments, the study population was divided into two groups. The PCOS only group, included women with ODI < 5 or women who had low risk of OSA using the Berlin questionnaire and ESS < 11. The PCOS+OSA group included women with ODI ⩾ 5 events/hour. The severity of OSA was defined as mild (ODI ⩾ 5 and <15 events/hour), moderate (ODI ⩾ 15 and <30 events/hour) and severe (ODI ⩾ 30 events/hour).[16]

Hirsutism

Hirsutism was assessed using the modified Ferriman–Gallwey score.[17] A total score of 8 or more on the modified Ferriman–Gallwey scoring system is considered suggestive of hirsutism.

Quality of life

QoL was assessed using the PCOS health-related quality of life questionnaire (PCOSQ) and the World Health Organization QoL questionnaire (WHOQOL-BREF).

The PCOSQ[18] is a validated method of assessing QoL in women with PCOS. The PCOSQ includes 26 items (questions) covering 5 domains that were found to be of most importance to women with PCOS: emotions (8 items), body hair (5 items), weight problems (5 items), menstrual problems (4 items) and infertility (4 items). Each item is scored on a scale of 1–7, in which a score of 7 denotes no problems or difficulties and a score of 1 indicates maximum impairment. Each domain score is calculated by dividing the total score of all items within a domain by the number of items in that domain.

The WHOQOL-BREF[19] is a validated generic measure of QoL. It includes 26 questions to assess four major domains (subscales): physical, psychological, social and environment. Scores are given out of 100, with higher scores indicating better QoL. WHOQOL-BREF provides a very good holistic assessment of QoL in the general population and its validation study included a group of women with PCOS, and a group of people with sleep disorders.[19]

Depression and anxiety

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS).[20] It consists of 14 items (questions), seven reflecting anxiety and seven reflecting depression. Each question answered will give the patient a four-point (0–3) response category with the possible total scores ranging from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0–7 in each subscale is regarded as normal, while a score of 11 or higher indicates the probable presence of a mood disorder.

Metabolic syndrome

The metabolic syndrome was assessed using the International Diabetes Federation criteria,[21] based on the presence of waist circumference >80 cm plus two of the following four factors: (i) triglycerides ⩾1.7 mmol/l or lipid lowering treatment; (ii) high-density lipoprotein (HDL) < 1.29 mmol/l or lipid lowering treatment; (iii) systolic blood pressure ⩾130 mmHg or diastolic blood pressure ⩾85 mmHg or on treatment for hypertension; (iv) fasting plasma glucose ⩾5.6 mmol/l or T2DM history.

Sample size calculation

QoL between the two groups was compared based on the PCOSQ and the WHOQOL-BREF questionnaires. The validation study for the WHOQOL-BREF[19] included a group of people with sleep disorders and a group of healthy controls. The mean difference between the two groups on the physical health component of the WHOQOL-BREF in this study was 17.8, and the pooled standard deviation (SD) was 18.2 (standardized difference of 0.98). Based on this study a total sample size of 38 participants would give us 80% power and 5% significance (two-tailed), to detect a large effect size (standardized difference of 0.98) on one item of the WHOQOL-BREF (physical health) between cases (PCOS+OSA) and controls (PCOS only). We used an allocation ratio for cases/controls of 0.67, 40% of participants in the PCOS+OSA group and 60% in the PCOS only group, based on previously published data.[1] Sample size was calculated using GPower 3.1.

and Metabolism (WISDEM), University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

Centre of Applied Biological & Exercise Sciences, Faculty of Health & Life Sciences, Coventry University, Coventry, UK

*These are joined first authors.

#These are joint senior authors.

This study was designed as preliminary exploratory proof of concept trial in order to inform the design of larger multicentre trial.

Statistical analysis

Data were checked for normality using the Shapiro–Wilk test.[22] Depending on data distribution, data were summarized using either the mean ± SD, median (interquartile range, IQR), or frequencies. Continuous variables were compared between the study groups using the independent t test or the Mann–Whitney U test, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. To adjust for baseline differences when comparing continuous variables, analysis of covariance was used. If the data were not normally distributed, data were log transformed.

Multiple linear regression was used to assess the associations between ODI and EDS, and QoL and psychological measurements. In the regression models, the dependent variables were the component of the PCOSQ, WHOQOL-BREF and HADS questionnaires. The independent variables were age, BMI, ODI and ESS. Log transformation was used for nonnormally distributed data. Linear regression statistical assumptions were adhered to including multicollinearity, singularity, outliers, normality, linearity and homoscedasticity. A two tailed p value of < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS statistics 25 package (SPSS Inc., Chicago, IL, USA).

Results

A total of 43 women were recruited and four were excluded as their sleep studies were not of good quality despite repeat testing, leaving 39 participants who were included in the analysis.

The study population age was 32.2 ± 8.9 years, weight 92.5 ± 23.7 kg and BMI 34.1 ± 7.9 kg/m^2. Of the 39 study participants, 7 (18.0%) had normal Berlin and ESS scores (no sleep studies performed), 13 (33.3%) had raised Berlin and ESS scores, 17 (43.6%) had raised Berlin but normal ESS and 2 (5.1%) had normal Berlin but raised ESS.

Sleep studies were performed in 32 participants (82.1%). Following sleep studies, 15 participants were found to have OSA (15/39, 38.5%). Of those women with PCOS and OSA, 9/15 (60%) had mild OSA, and 6/15 (40%) had moderate to severe OSA.

In women with a BMI < 30 kg/m^2 ($n = 14$), three were found to have OSA (21.4%); their corresponding BMIs were 24.5, 28.0 and 29.2 kg/m^2.

Baseline characteristics

Baseline characteristics for women with PCOS+OSA compared with those with PCOS only are summarized in Table 1. Women with OSA and PCOS were more obese than women with PCOS only. Women with PCOS and OSA were also numerically older, more likely to be White, had higher systolic BP, more hirsutism and more features of metabolic syndrome. Interestingly, the ESS was not different between patients with and without OSA.

Metabolic and hormonal profile

Women with PCOS and OSA had a more adverse CVD risk profile compared with women with PCOS only. Women with PCOS and OSA had higher low-density lipoprotein (LDL), HbA1c, Cholesterol/HDL and C-reactive protein (CRP) and lower HDL levels compared with PCOS only (Table 2). The OSA group also had higher haematocrit. The androgen profile was similar between groups but the free androgen index was numerically lower in the PCOS group. Only the difference in LDL remained significant after adjusting for age and BMI.

Psychological health and well-being

The PCOS+OSA group had worse scores on all the PCOSQ domains, but these differences were only statistically significant in the hirsutism domain. The PCOS+OSA group also had worse scores on the WHOQOL-BREF physical health and environment domains without reaching statistical significance. There were no differences between the two study groups in regard to the HADS (Table 3).

Relationship between ODI, ESS and QoL and psychological measurements

Examining the total study cohort, regardless of their OSA status, showed that higher ODI was

Table 1. Baseline characteristic for women with PCOS+OSA compared with women with PCOS only.

	PCOS+OSA ($n=15$)	PCOS only ($n=24$)	p value
Age (years)	33 (26–43)	29.5 (27–33)	0.43
Weight (kg)	101.8 ± 25.0	86.7 ± 21.3	0.052
BMI (kg/m^2)	37.3 ± 7.3	32.2 ± 7.8	0.046
Waist (cm)	116.9 ± 18.2	102.0 ± 18.1	0.017
Waist-to-hip ratio	0.93 ± 0.06	0.90 ± 0.09	0.27
Neck circumference (cm)	39.3 ± 4.1	36.8 ± 3.4	0.053
Systolic BP (mmHg)	124.5 (109–135)	115.3 (109.6–127.9)	0.50
Diastolic BP (mmHg)	75.5 (68–84)	78.5 (72.8–83)	0.45
PCOS phenotype			1.0
Hirsutism/hyperandrogenism + oligomenorrhoea	13 (86.7%)	21 (87.5%)	
Hirsutism/hyperandrogenism + PCO	0	1 (4.2%)	
Oligomenorrhoea + PCO	2 (13.3%)	2 (8.3%)	
Metabolic Syndrome	6 (40%)	5 (20.8%)	0.28
Modified Ferriman–Gallwey score	16.0 (11.0–20.0)	12.5 (10.0–17.5)	0.35
Amenorrhoea	4/12 (33.3%)	4/16 (25%)	0.81
Oxygen desaturation index (events/hour)	11.5 (7.3–18.7)	2.6 (1.6–3.7)	<0.001
ESS	9.1 ± 4.9	8.2 ± 4.7	0.57
EDS (ESS > 10)	13/15 (86.7%)	17/24 (70.8%)	0.24
Ethnicity			0.77
White	14 (93.3%)	19 (79.2%)	
Asian	1 (6.7%)	4 (16.6%)	
Other	0	1 (4.2%)	
Hormonal contraception			0.13
Combined OCP	0	5 (20.8%)	
Contraceptive implant	2 (13.3%)	1 (4.2%)	
Mirena coil	0	2 (8.3%)	
None	13 (86.7%)	16 (66.7%)	
Medications			
Metformin	9 (60%)	7 (29.2%)	0.12
Antidepressants	4 (26.7%)	4 (16.7%)	0.73

(Continued)

Table 1. (Continued)

	PCOS + OSA ($n = 15$)	PCOS only ($n = 24$)	p value
Levothyroxine	4 (26.7%)	3 (12.5%)	0.49
Spironolactone	2 (13.3%)	3 (12.5%)	1.0
Smokers	2 (13.3%)	3 (12.5%)	0.92
Marital status			0.78
Married	11 (73.3%)	15 (62.5%)	
Single	3 (20%)	7 (29.2%)	
Divorced	1 (6.7%)	2 (8.3%)	
Education			0.22
Tertiary	10 (66.7%)	21 (87.5%)	
Secondary school	5 (33.3%)	3 (12.5%)	

Amenorrhoea, defined as no periods in last 4 months; BMI, body mass index; BP, blood pressure; EDS, excessive daytime sleepiness; ESS, Epworth sleepiness scale; Hirsutism, defined as a modified Ferriman–Gallwey score ⩾8; Hyperandrogenism, defined as testosterone or androstenedione above the upper limit of normal in our lab (1.8 and 7.5 nmol/l, respectively) or a free androgen index >6.94[23]; Metabolic Syndrome, defined based on the IDF criteria; OCP, oral contraceptive pill; Oligomenorrhoea, defined as current or previous history of anovulation or ⩽9 periods per year; OSA, obstructive sleep apnoea; PCO, polycystic ovaries; PCOS, polycystic ovary syndrome.
Normally distributed data were presented as mean ± standard deviation, while nonnormally distributed data were presented as median (interquartile range). Frequencies were presented as numbers (percentages).

associated with lower QoL on the WHOQOL environment, PCOSQ infertility and PCOSQ menstruation domains independent of age, BMI and ESS. Higher ESS was independently associated with lower QoL on the PCOSQ weight, WHOQOL physical health and WHOQOL psychological health domains, and higher levels of depression and anxiety based on the HADS after adjustments for age, BMI and ODI. A summary of the linear regression analysis is presented in Table 4. Replacing BMI with the metabolic syndrome status or waist circumference in the regression model did not significantly improve the model performance (R^2) (data not presented).

Discussion

This is the first study to examine the relationship between symptomatic OSA, psychological health and general wellbeing in women with PCOS. We here show that symptomatic OSA is very common in women with PCOS and that OSA in women with PCOS was associated with lower QoL, higher HbA1c and a worse CVD risk profile. In addition, higher ODI was associated with lower QoL, and higher ESS was also associated with lower QoL and mental health independent of the ODI.

The prevalence of OSA in our study is in agreement with the findings of a recent systematic review and meta-analysis, which suggested a prevalence of 35% for OSA in women with PCOS.[3] However, the majority of studies in this meta-analysis included women with obesity, and had a high proportion of African American and Hispanic populations. Our study population included a wide range of BMIs and 21.4% of the women with PCOS and BMI $< 30\,kg/m^2$ in this study were found to have OSA. Women with PCOS might be at an increased risk of OSA through the association of PCOS with obesity, insulin resistance, hyperandrogenism, low progesterone levels, sympathetic overactivity, endothelial dysfunction and oxidative stress.[1] This high prevalence of OSA suggests that clinicians should have a high index of suspicion of OSA in women with PCOS even when the BMI is $<30\,kg/m^2$.

In this study there were fewer women prescribed the combined oral contraceptive pill (OCP) in the

Table 2. Metabolic and hormonal markers for the PCOS+OSA and PCOS only groups.

	PCOS+OSA ($n=15$)	PCOS only ($n=24$)	Unadjusted difference (95% CI)	*p*-value	
				Unadjusted	Adjusted[†]
CRP (mg/l)	5.0 (2.0–12.0)	2.0 (2.0–5.0)	3.9 (0.8–7.1)	**0.044**	0.058
Fasting plasma glucose (mmol/l)	5.0 ± 0.6	4.8 ± 0.4	0.24 (–0.11 to 0.58)	0.17	0.22
HbA1c (mmol/mol)	38.3 ± 5.7	35.0 ± 3.1	3.2 (0.26–6.2)	**0.034**	0.087
Cholesterol (mmol/l)	4.9 ± 0.8	4.5 ± 0.6	0.37 (–0.12 to 0.85)	0.13	0.17
LDL (mmol/l)	3.1 ± 0.7	2.4 ± 0.6	0.67 (0.24–1.1)	**0.003**	**0.014**
HDL (mmol/l)	1.1 ± 0.3	1.4 ± 0.4	–0.21 (–0.45 to 0.03)	0.089	0.35
Triglycerides (mmol/l)	1.4 ± 0.4	1.6 ± 0.7	–0.17 (–0.57 to 0.23)	0.39	0.21
Cholesterol/HDL	4.1 (3.9–5.2)	3.4 (2.7–4.6)	0.78 (0.04–1.5)	**0.015**	0.13
ALT (U/l)	18.0 (15.0–27.0)	15.0 (13.0–25.0)	–0.62 (–9.7 to 8.5)	0.3	0.98
Hb (g/l)	132.5 ± 9.1	127.7 ± 8.5	4.8 (–1.0 to 10.7)	0.10	0.35
Haematocrit (l/l)	0.41 ± 0.02	0.39 ± 0.02	0.02 (0.004–0.04)	**0.02**	0.13
Testosterone (nmol/l)	1.6 ± 0.9	1.4 ± 0.8	0.16 (–0.47 to 0.79)	0.60	0.29
FSH (IU/l)	6.4 ± 2.8	6.1 ± 2.4	0.31 (–1.7–2.3)	0.75	0.83
LH (IU/l)	9.7 ± 4.6	9.1 ± 5.2	0.61 (–3.2 to 4.5)	0.75	0.74
SHBG (nmol/l)	30.2 (21.5–48.8)	29.4 (21.8–59.3)	–5.8 (–20.5 to 8.9)	0.62	0.90
Free androgen index	5.2 (2.4–8.7)	3.9 (1.5–7.5)	0.61 (–2.5 to 3.7)	0.65	0.66
DHEAS (µmol/l)	7.6 ± 4.7	6.6 ± 3.2	0.98 (–1.9 to 3.8)	0.48	0.24
Androstenedione (nmol/l)	4.3 ± 2.1	4.3 ± 1.9	0.03 (–1.5 to 1.5)	0.97	0.70
Oestradiol (pmol/l)	185 (124.0–285.0)	170 (92.5–231)	7.1 (–151.3 to 165.3)	0.75	0.69
25-OH Vit D (nmol/l)	54.0 (40.0–69.0)	55.0 (37.3–76.8)	–5.5 (–24.9 to 13.9)	0.90	0.76

25-OH Vit D, 25-hydroxy vitamin D test; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; FSH, follicular stimulating hormone; Hb, haemoglobin; HbA1c, haemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinising hormone; OSA, obstructive sleep apnoea; PCOS, polycystic ovary syndrome; SHBG, sex hormone binding globulin.
Data presented as mean ± standard deviation, or median (interquartile range).
[†]Adjusted for age and BMI; nonnormally distributed data were log transformed before analysis.

PCOS+OSA group *versus* the PCOS only group. One explanation for this is that women in the PCOS+OSA group were heavier and subsequently less likely to receive the OCP because of the potential risk of venous thromboembolism.[24] However, the OCP might have played a protective role against developing OSA in the PCOS only group as progesterone lowers upper airway resistance;[25] OSA has been associated with lower progesterone levels,[26] and progesterone replacement lowered the risk of OSA in postmenopausal women.[27]

Evidence from systematic reviews and meta-analyses suggests that women with PCOS have worse mental health and impaired QoL compared with

Table 3. Quality of life, Depression and Anxiety scores for the PCOS+OSA and PCOS only groups.

	PCOS+OSA ($n=15$)	PCOS only ($n=24$)	Unadjusted difference (95% CI)	*p*-value	
				Unadjusted	Adjusted†
WHOQOL physical health	58.1 ± 18.3	68.3 ± 16.6	−10.2 (−21.8 to 1.4)	0.084	0.13
WHOQOL psychological health	51.9 ± 17.0	51.4 ± 16.7	0.4 (−10.9 to 11.8)	0.94	0.90
WHOQOL social health	75.0 (50.0–81.0)	75.0 (56.0–79.5)	2.9 (−8.9 to 14.7)	0.77	0.78
WHOQOL environment	64.9 ± 13.4	73.0 ± 12.4	−8.1 (−16.7 to 0.4)	0.061	0.079
PCOSQ emotions	3.7 ± 1.6	4.2 ± 1.3	−0.52 (−1.5 to 0.4)	0.27	0.23
PCOSQ hirsutism	2.5 ± 1.3	3.6 ± 1.7	**−1.2 (−2.2 to −0.1)**	**0.03**	0.17
PCOSQ weight	1.4 (1.0–2.2)	2.5 (1.2–4.4)	−0.8 (−1.8 to 0.3)	0.17	0.34
PCOSQ infertility	3.3 ± 2.1	4.3 ± 1.7	−1.0 (−2.2 to 0.3)	0.13	0.13
PCOSQ menstrual cycle	3.3 ± 1.3	3.8 ± 1.3	−0.56 (−1.4 to 0.3)	0.21	0.23
HAD anxiety	10.0 (6.0–12.0)	10.5 (7.0–13.0)	−0.6 (−3.6 to 2.4)	0.68	0.74
HAD depression	8.1 ± 4.1	7.0 ± 5.0	1.1 (−2.1 to 4.2)	0.49	0.51

BMI, body mass index; CI, confidence interval; HADS, Hospital Anxiety and Depression scale; OSA, obstructive sleep apnoea; PCOS, polycystic ovary syndrome; PCOSQ, PCOS health-related quality of life questionnaire; QoL, quality of life; WHOQOL, World Health Organization QoL-BREF questionnaire.
Data presented as mean (standard deviation).
†Adjusted for age and BMI; nonnormally distributed data were log transformed before analysis.

women without PCOS.[28] Our data suggests that there is an association between ODI and ESS and impaired QoL in women with PCOS, which was independent of weight and age. While an association between ODI and impaired QoL does not imply causality, this is an area of research that warrants further evaluation, particularly as OSA is a treatable condition.

OSA is associated with increased CVD[7] and while our study was not large enough to examine such a relationship, women with PCOS and OSA had higher cholesterol/HDL ratio, LDL and CRP levels compared with women with PCOS only. The difference in LDL levels between the two groups, in this study, remained significant after adjustment for BMI and age. In addition, women with PCOS and OSA had numerically, but not statistically, higher systolic blood pressure and more features of the metabolic syndrome compared with women with PCOS only. Hence, it is plausible that OSA might contribute to the increased CVD risk markers observed in women with PCOS.

Women with PCOS are approximately four times more likely to develop T2DM compared with weight-matched controls.[29] Women with PCOS and OSA in our study had higher HbA1c compared with women with PCOS only. OSA is associated with increased insulin resistance and glucose metabolism dysregulation.[7] In a small interventional study, 8 weeks of therapy with CPAP was associated with improvement in insulin sensitivity in women with PCOS and OSA.[30] Subsequently, OSA maybe a contributing factor to the increased risk of T2DM frequently observed in women with PCOS. Interventional studies are needed to examine the impact of OSA on T2DM risk in women with PCOS.

EDS, as measured by ESS in our study, was independently associated with impaired QoL, depression and anxiety. Studies suggest that obesity is a major risk factor for EDS, while weight loss is associated with its remission.[9,31] However, ESS in our study was not significantly associated with weight, BMI or waist-to-hip ratio. This suggests

Table 4. Predictors of QoL and psychological health outcomes in women with PCOS using linear regression.

Outcome measure†	Variable	Standardized beta value	*p*-value	
			Unadjusted	Adjusted
WHOQOL Physical health $R^2 = 0.242$	Age	−0.102	0.36	0.55
	BMI	0.102	0.98	0.56
	ODI	−0.327	0.17	0.063
	ESS	−0.527	**0.003**	**0.003**
WHOQOL Psychological health $R^2 = 0.133$	Age	0.264	0.17	0.16
	BMI	0.125	0.83	0.51
	ODI	−0.174	0.80	0.34
	ESS	−0.442	**0.009**	**0.017**
WHOQOL Environment $R^2 = 0.122$	Age	−0.032	0.45	0.86
	BMI	0.059	0.09	0.75
	ODI	−0.472	**0.006**	**0.013**
	ESS	0.061	0.41	0.73
PCOSQ weight $R^2 = 0.207$	Age	0.100	0.28	0.56
	BMI	−0.243	**0.034**	0.17
	ODI	−0.090	0.74	0.60
	ESS	−0.440	**0.003**	**0.012**
PCOSQ infertility $R^2 = 0.365$	Age	0.400	**0.012**	**0.014**
	BMI	−0.225	**0.006**	0.16
	ODI	−0.446	**0.018**	**0.007**
	ESS	−0.086	0.66	0.56
PCOSQ Menstruation $R^2 = 0.090$	Age	0.109	0.83	0.56
	BMI	0.048	0.58	0.80
	ODI	−0.457	**0.021**	**0.018**
	ESS	−0.185	0.46	0.30
HADS anxiety $R^2 = 0.116$	Age	−0.154	0.28	0.40
	BMI	−0.029	0.71	0.88
	ODI	−0.032	0.50	0.86
	ESS	0.443	**0.004**	**0.016**
HADS Depression $R^2 = 0.163$	Age	−0.191	0.24	0.29
	BMI	0.013	0.34	0.94
	ODI	0.179	0.64	0.31
	ESS	0.472	**0.003**	**0.009**

BMI, body mass index; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; ODI, oxygen desaturation index; PCOS, polycystic ovary syndrome; PCOSQ, PCOS health-related quality of life questionnaire; QoL, quality of life; WHOQOL, World Health Organization QoL-BREF questionnaire.
†R^2 given is for the adjusted model.

that obesity is not a major contributor to EDS in women with PCOS and that EDS might be driven by other metabolic or psychological abnormalities that are commonly observed in women with PCOS such as insulin resistance, metabolic syndrome, anxiety and depression. In a population-based longitudinal study of over 7000 women, insomnia, anxiety or depression and smoking were the most important factors for predicting incident EDS.[32] While depression and anxiety may cause EDS and impaired QoL, it is also possible that EDS may contribute to mental health problems and QoL. Further studies are needed to examine the relationship between EDS and mental health in women with PCOS.

OSA is a major risk factor for road traffic accidents that are caused by EDS and is amenable to treatment with CPAP.[33] Our study suggests that OSA is common in women with PCOS. Hence, clinicians should have a low threshold for investigating OSA in women with PCOS as they may benefit from CPAP treatment.

Recommendations for future research

This study highlights the need for (a) interventional studies examining the effect of CPAP on QoL and the risk of developing T2DM and CVD in women with PCOS and OSA; (b) large cohort studies examining the relationship between EDS and mental health in women with PCOS; and (c) interventional studies examining the impact of improving daytime sleepiness, for example through better night-time sleep hygiene or mindfulness, on anxiety and depression in women with PCOS.

Study limitations

The small sample size is a limitation of this study, but our findings will help inform the design of future larger multicentre studies. Another limitation was not performing sleep studies in all study participants. However, we have used validated questionnaires to assess the risk of OSA and only a small number of participants whose risk was low on both the Berlin and ESS questionnaires did not have a sleep study performed. Another limitation is that due to the cross-sectional study design, we cannot confirm causality or exclude other unmeasured confounders. The small sample size did not allow us to include too many variables in the regression model. Therefore, further cohort and interventional studies are needed to examine the impact of OSA on QoL in women with PCOS.

Study strengths

This is the first study to examine the relationship between OSA, QoL and psychological health in women with PCOS. Our cohort included women who were recruited from secondary care clinics and self-referred women from the community. It also included women with a wide range of BMI. Sleep studies were analysed by two experienced and independent operators who were blinded to participants other study data.

Conclusion

OSA is very common and is associated with impaired QoL and a worse metabolic profile in women with PCOS. Interventional studies examining the effects of CPAP on QoL, glucose metabolism and CVD risk in women with PCOS and OSA are needed.

Excessive daytime sleepiness, independent of OSA and obesity, is associated with worse QoL and mental health in women with PCOS. Further studies are needed to examine the relationship between EDS and mental health in women with PCOS.

Authors' note

HK, contributed to study design, collected data, analysed and interpreted data and wrote first draft of manuscript. AAT, research idea, contributed to study design and data interpretation and wrote first draft of manuscript. IK contributed to study design. GKD, contributed to participants' recruitment and data collection. TMB, provided sleep machines. PKK contributed to statistical analysis and power calculation. MN and AA, analysed sleep studies. AA contributed to study design. MOW and HSR, contributed to study design, data interpretation and the overall conduct of the study. All authors contributed to the writing of manuscript. HK and AAT contributed equally as first authors. MOW and HSR contributed equally as senior authors.

Acknowledgements

Alice PDx sleep machines used were a kind donation from Philips Respironics. We thank the World Health Organization for allowing us to use the WHOQOL-BREF. We thank the research nurses

at WISDEM centre (Diane Sambrook, Claire Hewins, Nilisha Nalawade and Allan Davasgaium) for their assistance in data collection. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Funding

No funding was received for doing this work.

Conflict of interest statement

The authors declare the following conflicts of interest: AAT is a Clinician Scientist supported by the National Institute for Health Research (NIHR). NIHR Clinical Lectureship supported HK. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

ORCID iDs

Hassan Kahal https://orcid.org/0000-0001-6258-1814

Thomas M Barber https://orcid.org/0000-0003-0689-9195

References

1. Kahal H, Kyrou I, Tahrani AA, *et al*. Obstructive sleep apnoea and polycystic ovary syndrome; a comprehensive review of clinical interactions and underlying pathophysiology. *Clin Endocrinol (Oxf)* 2017; 87: 313–319.
2. Fernandez RC, Moore VM, Van Ryswyk EM, *et al*. Sleep disturbances in women with polycystic ovary syndrome: prevalence, pathophysiology, impact and management strategies. *Nat Sci Sleep* 2018; 10: 45–64.
3. Kahal H, Kyrou I, Uthman OA, *et al*. The prevalence of obstructive sleep apnoea in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Sleep Breath*. Epub ahead of print 20 May 2019. DOI: 10.1007/s11325-019-01835-1.
4. Balachandran K, Sumilo D, O'Reilly MW, *et al*. Increased risk of obstructive sleep apnoea in women with polycystic ovary syndrome: a population-based cohort study. *Eur J Endocrinol* 2019; 180: 265–272.
5. Lin TY, Lin PY, Su TP, *et al*. Risk of developing obstructive sleep apnea among women with polycystic ovarian syndrome: a nationwide longitudinal follow-up study. *Sleep Med* 2017; 36: 165–169.
6. Kahal H, Kyrou I, Uthman O, *et al*. The association between obstructive sleep apnoea and metabolic abnormalities in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Sleep*. Epub ahead of print 1 July 2018. DOI: 10.1093/sleep/zsy085.
7. Tahrani AA. Diabetes and sleep apnea. In: DeFronzo RA, Ferrannini E and Alberti G (eds) *International textbook of diabetes mellitus*. 4th ed. Chichester, West Sussex: John Wiley & Sons, Ltd., 2015, pp. 316–336.
8. Pallesen S, Nordhus IH, Omvik S, *et al*. Prevalence and risk factors of subjective sleepiness in the general adult population. *Sleep* 2007; 30: 619–624.
9. Fernandez-Mendoza J, Vgontzas AN, Kritikou I, *et al*. Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity. *Sleep* 2015; 38: 351–360.
10. Shi L, Chen SJ, Ma MY, *et al*. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. *Sleep Med Rev*. Epub ahead of print 6 July 2017. DOI: 10.1016/j.smrv.2017.06.010.
11. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004; 81: 19–25.
12. Netzer NC, Stoohs RA, Netzer CM, *et al*. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999; 131: 485–491.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
14. Ling IT, James AL and Hillman DR. Interrelationships between body mass, oxygen desaturation, and apnea-hypopnea indices in a sleep clinic population. *Sleep* 2012; 35: 89–96.
15. Berry RB, Brooks R, Gamaldo C, *et al*. AASM scoring manual updates for 2017 (Version 2.4). *J Clin Sleep Med* 2017; 13: 665–666.
16. Chung F, Liao P, Elsaid H, *et al*. Oxygen desaturation index from nocturnal oximetry: a sensitive and specific tool to detect sleep-disordered breathing in surgical patients. *Anesth Analg* 2012; 114: 993–1000.
17. Hatch R, Rosenfield RL, Kim MH, *et al*. Hirsutism: implications, etiology, and management. *Am J Obstet Gynecol* 1981; 140: 815–830.
18. Cronin L, Guyatt G, Griffith L, *et al*. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary

syndrome (PCOS). *J Clin Endocrinol Metab* 1998; 83: 1976–1987.

19. Skevington SM and McCrate FM. Expecting a good quality of life in health: assessing people with diverse diseases and conditions using the WHOQOL-BREF. *Health Expect* 2012; 15: 49–62.
20. Herrmann C. International experiences with the hospital anxiety and depression scale–a review of validation data and clinical results. *J Psychosom Res* 1997; 42: 17–41.
21. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome, https://www.pitt.edu/~super1/Metabolic/IDF1.pdf (2006, accessed 7 July 2019).
22. Razali NM and Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. *J Stat Model Analytics* 2011; 2: 21–33.
23. Barber TM, Wass JA, McCarthy MI, *et al*. Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2007; 66: 513–517.
24. Reifsnider E, Mendias N, Davila Y, *et al*. Contraception and the obese woman. *J Am Assoc Nurse Pract* 2013; 25: 223–233.
25. Driver HS, McLean H, Kumar DV, *et al*. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. *Sleep* 2005; 28: 449–456.
26. Netzer NC, Eliasson AH and Strohl KP. Women with sleep apnea have lower levels of sex hormones. *Sleep Breath* 2003; 7: 25–29.
27. Shahar E, Redline S, Young T, *et al*. Hormone replacement therapy and sleep-disordered breathing. *Am J Respir Crit Care Med* 2003; 167: 1186–1192.
28. Li Y, Li Y, Yu Ng EH, *et al*. Polycystic ovary syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from a meta-analysis. *Fertil Steril* 2011; 96: 452–458.
29. Moran LJ, Misso ML, Wild RA, *et al*. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2010; 16: 347–363.
30. Tasali E, Chapotot F, Leproult R, *et al*. Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2011; 96: 365–374.
31. Ng WL, Stevenson CE, Wong E, *et al*. Does intentional weight loss improve daytime sleepiness? A systematic review and meta-analysis. *Obes Rev* 2017; 18: 460–475.
32. Theorell-Haglow J, Akerstedt T, Schwarz J, *et al*. Predictors for development of excessive daytime sleepiness in women: a population-based 10-year follow-up. *Sleep* 2015; 38: 1995–2003.
33. Strohl KP, Brown DB, Collop N, *et al*. An official American Thoracic Society Clinical Practice Guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. *Am J Respir Crit Care Med* 2013; 187: 1259–1266.