

# Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria

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**STUDY QUESTION:** What is the prevalence, phenotype and metabolic features of polycystic ovary syndrome (PCOS) in the same population according to three different diagnostic criteria?

**SUMMARY ANSWER:** The prevalence of PCOS under National Institutes of Health (NIH), Rotterdam and Androgen Excess and PCOS (AE-PCOS) Society criteria was 6.1, 19.9 and 15.3%, respectively. PCOS carried a 2-fold increased risk of metabolic syndrome regardless of the diagnostic criteria used.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS:** The prevalence rates of PCOS differ depending on the diagnostic criteria used to define the syndrome. The current paper gives the prevalence rates of the component and composite phenotypes of PCOS in the same population and reports similar rates of metabolic syndrome in women with PCOS under contrasting diagnostic criteria.

**DESIGN:** In this cross-sectional study, 392 women between the ages of 18 and 45 years were analyzed.

**PARTICIPANTS AND SETTING:** When the prevalence of PCOS according to NIH was set to 8% with a precision of 2.2% and confidence interval of 95%, the sample size required for a prevalence survey was found to be 400 subjects. The study was carried out in the General Directorate of Mineral Research and Exploration, a government-based institute, in which the largest number of female staff ( $n = 527$ ) are employed within a single institute in Ankara, Turkey. The study was performed between 7 December 2009 and 30 April 2010. All female subjects between the ages of 18 and 45 years were invited to participate. Women older than 45 or younger than 18 years, post-menopausal women, women with a history of hysterectomy or bilateral oophorectomy and pregnant women were excluded. Totally, 392 of the employees were recruited for the final analyses.

**MAIN RESULTS AND THE ROLE OF CHANCE:** The prevalence of PCOS under NIH, Rotterdam and AE-PCOS Society criteria were 6.1, 19.9 and 15.3%, respectively. While the prevalence of metabolic syndrome was 6.1% in the whole study group, within the patients diagnosed as PCOS according to NIH, Rotterdam and AE-PCOS Society criteria, it was 12.5, 10.3 and 10.0%, respectively.

**BIAS, CONFOUNDING AND OTHER REASONS FOR CAUTION:** Even though we have included women working at a single institution with a high response rate for the participation, we cannot exclude potential selection bias due to undetermined differences between our sample and background community. We might have underestimated actual prevalence of metabolic syndrome in PCOS due to lack of oral glucose tolerance test 2 h glucose data.

**GENERALIZABILITY TO OTHER POPULATIONS:** Current results can be generalized to Caucasian populations and may present variations in other populations according to race and ethnicity.

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## Introduction

The first description of the polycystic ovary syndrome (PCOS) dates back to the original report of seven cases by Stein and Leventhal in 1935. PCOS is now widely accepted as a syndrome, a constellation of clinically recognizable features, signs and symptoms. However, there remains a lack of consensus about how to define and diagnose this syndrome (Goodarzi and Azziz, 2006).

In the last two decades, three alternative definitions have been formulated for the diagnosis of PCOS. The most widely used 1990 National Institutes of Health (NIH) criteria (Zawadzki and Dunaif, 1992) include clinical and/or biochemical hyperandrogenism and chronic anovulation. The 2004 Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004) suggest PCOS should be diagnosed by two of the following three criteria: oligo-anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries (PCOs) on ultrasound (US). The most recent Androgen Excess and PCOS Society (AE-PCOS Society) criteria (Azziz et al., 2006) recommend that PCOS should be defined as clinical or biochemical hyperandrogenism associated with ovulatory dysfunction (OD) in the form of oligo-anovulation or PCOs. All three sets of criteria highlight exclusion of other related disorders before making a diagnosis of PCOS (Zawadzki and Dunaif, 1992; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Azziz et al., 2006).

Previous studies assessing the prevalence of PCOS in different populations reported rates between 4 and 8% using NIH criteria (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Michelmore et al., 1999; Asuncion et al., 2000; Azziz et al., 2004; March et al., 2010; Moran et al., 2010a,b), between 2.4 and 11.9% using Rotterdam criteria (Chen et al., 2008; Kumarapeli et al., 2008; March et al., 2010; Moran et al., 2010a,b) and between 2.2 and 10.2% using AE-PCOS Society criteria (Chen et al., 2008; March et al., 2010). Discrepancy even among the studies using the same diagnostic criteria might be due to differences in background study populations, difficulties in phenotypic definition and design limitations including biased sampling.

There is a paucity of data on the prevalence of PCOS and its component phenotypes in the same population using all available criteria. Similarly, limited information is available regarding metabolic features of women with PCOS in the same population, although several studies have reported increased prevalence of metabolic syndrome in PCOS patients presenting to the clinics, particularly in the NIH-PCOS phenotype (Moran and Teede, 2009; Moran et al., 2010a,b).

There is no available data regarding the prevalence or phenotypes of PCOS among the Turkish women. In the current study we aimed to determine the prevalence of PCOS according to NIH, Rotterdam, and the AE-PCOS Society sets of diagnostic criteria and associated metabolic syndrome among the same population.

## Materials and Methods

### Participants

This cross-sectional study was carried out in the General Directorate of Mineral Research and Exploration, a government-based institute, in which the largest number of female staff ( $n = 527$ ) are employed within

a single institute in Ankara, Turkey. The study was approved by the Institutional review Board of Hacettepe University and all participants gave informed consent for the trial.

The study was performed between 7 December 2009 and 30 April 2010. All female subjects between the ages of 18 and 45 years were invited to participate. Women older than 45 or younger than 18 years, post-menopausal women, women with a history of hysterectomy or bilateral oophorectomy and pregnant women were excluded ( $n = 38$ ). Patients using any form of medical treatment, including oral contraceptive pills, were not excluded to avoid treatment bias.

### Study protocol

A standardized interview-based medical form was used to obtain information regarding the age, obstetric history, last menstrual bleeding, and menstrual regularity, gynecological history, medical diseases, medications and family history. Height, weight, waist and hip circumferences were determined. Waist was measured at the point of midway between the lower rib margin and the iliac crest, and the hip was measured from a widest circumference over the great trochanters. The body mass index (BMI) was calculated as body weight (in kg)/height (in meters) squared.

The amount of terminal hair growth was assessed using a modified Ferriman–Gallwey (mF–G) method (Ferriman and Gallwey, 1961; Yildiz et al., 2010) in which the upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and upper arms were scored from 0 to 4 by a single physician (Z.Y.). Subjects with an mF–G score  $\geq 3$  were re-examined by another investigator (B.O.Y.). If a subject had epilation within the last 6 months, a color photo atlas was shown (Yildiz et al., 2010) and let her define the previous status of hair in the epilated area(s). The presence of acne and alopecia were also noted.

Blood samples from all the participants were collected on Days 2–7 of the menstrual bleeding between 08.00 and 10.00 a.m. after an overnight fast. In subjects using oral contraceptive pills, the samples were retrieved during the interval period. The blood samples were transferred to a central laboratory in the same morning; following centrifugation at 4°C for 20 min at 3000 rpm, the serum samples were transferred into polypropylene tubes and stored at  $-70^{\circ}\text{C}$  until final analysis.

All subjects underwent US during an early follicular phase for evaluation of the ovaries. Transvaginal or transabdominal US was performed according to marital status of the subjects.

### Defining PCOS

The individual criteria to diagnose the component phenotypes of the syndrome were as follows:

- (i) Clinical hyperandrogenism: an mF–G score of  $\geq 6$  regardless of the presence/absence of acne or alopecia.
- (ii) Biochemical hyperandrogenism (hyperandrogenemia): any androgen including total testosterone (tT), androstenedione, (A4), dehydroepiandrosterone sulfate (DHEAS) and/or free androgen index (FAI) level exceeding respective 95th percentile of healthy, non-hirsute, eumenorrhic women without PCO in this study ( $n = 216$ ). Specifically, the upper normal limits for tT, A4, DHEAS and FAI were 54.7 ng/dl (1.9 nmol/l, conversion factor: 0.0347), 2.97 ng/ml (10.4 nmol/l, conversion factor: 3.49), 3257.4 ng/ml (8840.6 nmol/l, conversion factor: 2.714) and 4.94, respectively.
- (iii) OD: menstrual cycles  $\geq 35$  or  $\leq 23$  days were defined as OD. In patients with hirsutism or PCO appearance who had apparently regular menstrual bleeding, luteal phase (Days 21–24) progesterone levels were determined and the threshold for the presence of ovulation was taken as  $>5$  ng/ml.

- (iv) PCOs on US (PCO): an antral follicle count (AFC) of  $\geq 12$  in 2–9 mm diameter and/or ovarian volume of  $\geq 10 \text{ cm}^3$  at least in a single ovary was defined as PCO. If a cyst or a follicle had persisted even in the second visit, than the ovarian volume of the current ovary was not calculated and just the ovarian volume of the contralateral ovary and the AFC of the both sites were considered for assignment.
- (v) Exclusion of related disorders: once oligo-amenorrhea was noticed, thyroid stimulating hormone (TSH) and prolactin levels were examined. Serum TSH levels were also checked in patients having clinical signs or symptoms of thyroid dysfunction. The 17-OH progesterone levels were tested in subjects with clinical or biochemical hyperandrogenism, and/or OD and/or PCO and adrenocorticotrophic hormone (ACTH) stimulation test was performed to exclude non-classical congenital adrenal hyperplasia (NCAH) when baseline early follicular levels exceeded 2 ng/dl.

Under the NIH criteria, PCOS was defined as clinical and/or biochemical hyperandrogenism associated with OD (Zawadzki and Dunaif, 1992). With reference to Rotterdam criteria, PCOS was defined as the presence of at least two of the criterion: (i) clinical and/or biochemical hyperandrogenism, (ii) OD, and (iii) PCO (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). According to AE-PCOS Society criteria, PCOS was diagnosed as clinical and/or biochemical hyperandrogenism associated with OD or PCO (Azziz et al., 2004, 2006). Other related disorders were excluded as described before making a diagnosis of PCOS under all three sets of diagnostic criteria (Zawadzki and Dunaif, 1992; Azziz et al., 2004, 2006; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

## Defining metabolic syndrome

Current ATP III criteria are used to define the metabolic syndrome as the presence of any three of the following five traits:

- abdominal obesity, defined as a waist circumference  $>88 \text{ cm}$  (35 in),
- serum triglycerides  $\geq 150 \text{ mg/dl}$  (1.7 mmol/l) or drug treatment for elevated triglycerides,
- serum HDL cholesterol  $<50 \text{ mg/dl}$  (1.3 mmol/l) or drug treatment for low HDL-C,
- blood pressure  $\geq 130/85 \text{ mmHg}$  or drug treatment for elevated blood pressure,
- fasting plasma glucose (FPG)  $\geq 100 \text{ mg/dl}$  (5.6 mmol/l) or drug treatment for elevated blood glucose.

Acanthosis nigricans was not taken into account in our evaluation.

## Hormonal and biochemical analyses

The hormonal analyses included follicular-stimulating hormone (FSH), luteinizing hormone (LH), tT, A4, DHEAS, sex hormone-binding globulin (SHBG), 17-OH progesterone, TSH and prolactin. tT was measured by electrochemiluminescence immunoassay after serum extraction (Cobas E601, Roche Diagnostics GmbH, D-68298 Mannheim, Germany) with an intra-assay coefficient of variation (CV) of 3.0%. DHEAS, SHBG, TSH and prolactin were also analyzed with the same method with CVs of 3.50, 2.91, 4.15 and 2.59%, respectively. FSH and LH were tested via chemiluminescence microparticle immunoassay (Architect i2000 SR, Abbott Laboratories, Abbott Park, IL 60064, USA) with a CV's of 3.67 and 3.70%, respectively. 17-OH progesterone (MP Biomedicals, Ankara, Turkey) and A4 (MP Medical, Ankara, Turkey) were measured with radioimmunoassay with CV's of 5.5 and 7.0%, respectively.

For the metabolic features, the blood glucose level both during fasting and 2 h, high-density lipoprotein cholesterol (HDL-C) and triglycerides were tested. The plasma glucose was analyzed via a colorimetric hexokinase technique with a CV of 1.6% (Cobas Integra 800, Roche Diagnostics GmbH). HDL cholesterol and triglyceride were analyzed by an enzymatic colorimetric method with the same device which presents CV's of 2.46 and 1.90%, respectively.

FAI was calculated from tT and SHBG levels:  $(\text{FAI} = \text{tT} \times 100/\text{SHBG})$ .

## Ultrasonography

All participants underwent US scanning on Days 2–7 of their menstrual bleeding employing Voluson e (GE Healthcare, Istanbul, Turkey). According to marital status, endocavitary (5–9 MHz) or abdominal (2–7 MHz) probe was preferred to calculate the estimated ovarian volume and AFC in which all procedures were performed by a single physician (Z.Y.). The ovarian volume was calculated with three available dimensions, namely maximal longitudinal (a), anteroposterior (b) and transverse diameters (c) ( $a \times b \times c \times 0.5$ ). The antral follicles were counted in a transverse section in each site. If any ovaries were bearing a follicle  $\geq 10 \text{ mm}$  in diameter or cyst having any degree of echogenicity under US, the woman was re-examined during Days 2–7 of the subsequent cycles to calculate the precise ovarian volume.

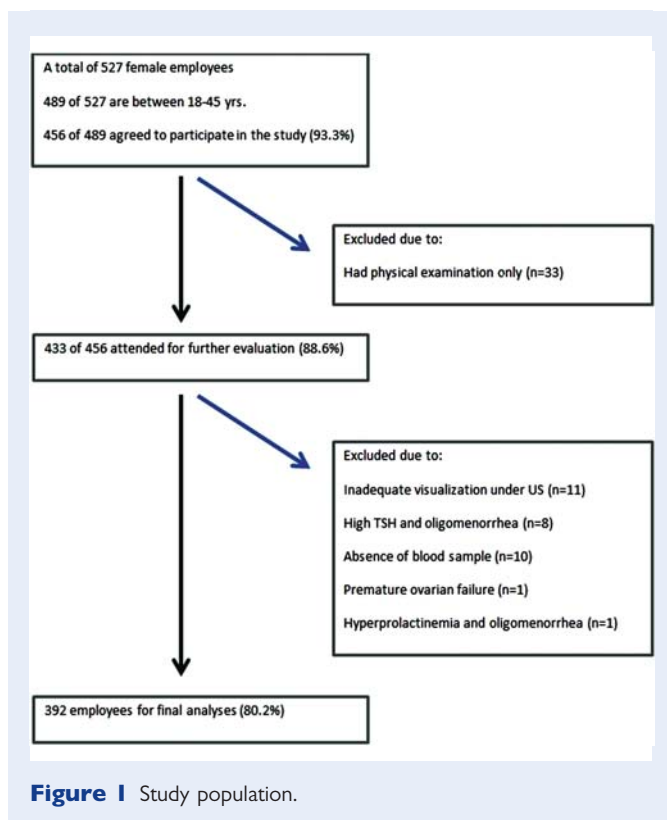
## Statistical analyses

When the prevalence of PCOS according to NIH was set to 8% with a precision of 2.2% and confidence interval (CI) of 95%, the sample size required for a prevalence survey was found to be 400 subjects. All parameters were given as mean  $\pm$  SD. Data analysis was performed using the SPSS 13.0 PC package (SPSS, Inc., Chicago, IL).

## Results

### Study population and baseline characteristics

Between 7 December 2009 and 30 April 2010 a total of 456 volunteers out of 489 female employees with ages of 18–45 years



**Figure 1** Study population.

agreed to participate in the study (Fig. 1). Thirty-three of them had physical examination only and did not come back for US and blood work-up. Thirty-one women were subsequently excluded due to various factors given in Fig. 1. Therefore, our study population consisted 392 of 489 subjects (80.2% of available women).

A total of 19 women were receiving thyroid hormones for hypothyroidism. Of these women, 11 with normal TSH values were included in the analysis, whereas 8 women who had high TSH levels and associated oligomenorrhea were excluded. Seventeen women were taking oral contraceptives all of which are included in the study. Among those, eight were on the pill for contraceptive purposes, whereas nine were taking the pill for gynecological problems.

Subjects having both oligomenorrhea and hyperprolactinemia were excluded from the final analyses ( $n = 8$ , Fig. 1). Two subjects with 17(OH) progesterone levels  $>2$  ng/dl are included in the study on which diagnosis of NCAH was excluded by the ACTH stimulation test.

The mean age was  $33.0 \pm 7.3$  years. The mean BMI was  $24.2 \pm 4.2$  kg/m<sup>2</sup>; the percentages of women who were overweight (BMI: 25.0–29.9 kg/m<sup>2</sup>) and obese (BMI  $\geq 30$  kg/m<sup>2</sup>) were 24.0 and 10.2%, respectively.

### Prevalence of hirsutism, hyperandrogenemia, OD and PCO

The overall proportion of subjects having clinical and/or biochemical hyperandrogenism was 24.8% (97/392; Table I). The prevalence rates for hirsutism and hyperandrogenemia were 10.2% (40/392) and 18.4% (72/392), respectively. Specifically, tT, A4, DHEAS and FAI were found to be above 95th percentile in 25, 37, 26 and 24 women, respectively. The rate of women suffering from OD was 15.3% (60/392), whereas 36.5% of women (143/392) had PCO (Table I). In the 143 patients having PCO, 59 had bilateral and 84 had unilateral PCO. Of note, the PCO was diagnosed according to the AFC, ovarian volume and AFC + ovarian volume in 95 (66.4%), 6 (4.2%) and 42 (29.4%) women, respectively.

**Table I** Prevalence of the component and composite phenotypes in PCOS.

Phenotype	n	%
All normal	190	48.5
PCO only	69	17.6
Hyperandrogenism only	37	9.4
Hirsutism only	6	1.5
Hyperandrogenemia only	26	6.6
Hirsutism and hyperandrogenemia	5	1.3
OD only	18	4.6
Hyperandrogenism + PCO	36	9.2
Hyperandrogenism + PCO + OD	20	5.1
OD + PCO	18	4.6
Hyperandrogenism + OD	4	1.0

The isolated presence of component phenotypes, namely PCO only, hyperandrogenism only and OD only were 17.6, 9.4 and 4.6%, respectively (Table I).

### Prevalence of PCOS according to NIH, Rotterdam and AE-PCOS Society criteria

The prevalence of PCOS according to NIH criteria was 6.1%. The prevalence rate of PCOS reached 19.9% with respect to Rotterdam criteria and the prevalence rate was in between according to AE-PCOS Society criteria with a figure of 15.3%. The distribution of subphenotypes is shown in Table I. The most common subphenotype was hyperandrogenism with PCO (9.2%).

### Prevalence of PCOS according to BMI

The prevalence of PCOS in non-obese (BMI  $<30$  kg/m<sup>2</sup>) women according to NIH, Rotterdam and AE-PCOS Society criteria were 5.1, 14.5 and 18.8%, respectively. Corresponding figures for obese women (BMI  $\geq 30$  kg/m<sup>2</sup>) were 15, 30 and 22.5%, respectively (Table II). The prevalence rates of obesity in women with PCOS according to NIH, Rotterdam and AE-PCOS criteria were 25, 15 and 15.4%, respectively (Table III).

### Prevalence and composition of metabolic syndrome in PCOS according to NIH, Rotterdam and AE-PCOS Society criteria

While the prevalence of metabolic syndrome in the whole study group was 6.1% (24/392), within the patients diagnosed as PCOS according to NIH, Rotterdam and AE-PCOS Society criteria, these rates were 12.5% (3/24), 10.3% (8/78) and 10.0% (6/60), respectively ( $P > 0.05$ ) (Table IV).

The respective odds ratios for metabolic syndrome in patients with PCOS having hyperandrogenism ( $n = 60$ ) is 1.13 (0.21–6.13) when compared with subjects without hyperandrogenism ( $n = 18$ ).

The distribution of components of the metabolic syndrome is also listed in Table IV.

In women having metabolic syndrome ( $n = 24$ ), the prevalence rates of PCOS were 12.5, 25.0 and 33.3% according to NIH, AE-PCOS and Rotterdam criteria, respectively. In women who did not have metabolic syndrome ( $n = 368$ ), these rates were 5.7, 14.7 and 19.0%, respectively.

**Table II** Prevalence of PCOS according to BMI.

	Whole group	NIH	Rotterdam	AE-PCOS
Total prevalence	392 (100)	24 (6.1)	78 (19.9)	60 (15.3)
Non-obese ( $<30$ kg/m <sup>2</sup> )	352 (89.8)	18 (5.1)	66 (18.8)	51 (14.5)
Obese ( $\geq 30$ kg/m <sup>2</sup> )	40 (10.2)	6 (15.0)	12 (30.0)	9 (22.5)

Percentages are given in parentheses.

**Table III** Prevalence of obesity in PCOS.

	Whole group (n = 392)	NIH (n = 24)	Rotterdam (n = 78)	AE-PCOS (n = 60)
Non-obese (<30 kg/m <sup>2</sup> )	352 (89.8)	18 (75.0)	66 (84.6)	51 (85.0)
Obese (≥30 kg/m <sup>2</sup> )	40 (10.2)	6 (25.0)	12 (15.4)	9 (15.0)

Percentages are given in parentheses.

## Discussion

We report here the prevalence of PCOS according to NIH, Rotterdam and AE-PCOS Society criteria as 6.1, 19.9 and 15.3%, respectively, among a relatively large Caucasian population. Although our results are in accordance with earlier studies giving prevalence rates between 4 and 8% using NIH criteria (Knochenhauer *et al.*, 1998; Diamanti-Kandarakis *et al.*, 1999; Michelmores *et al.*, 1999; Asuncion *et al.*, 2000; Azziz *et al.*, 2004; March *et al.*, 2010; Moran *et al.*, 2010a,b; Sanchon *et al.*, 2012), we found higher figures than previous studies using Rotterdam criteria (Chen *et al.*, 2008; Kumarapeli *et al.*, 2008; March *et al.*, 2010; Moran *et al.*, 2010a,b) and AE-PCOS Society criteria (Chen *et al.*, 2008; March *et al.*, 2010; Moran *et al.*, 2010a,b; Table V). However, a recent study (Boyle *et al.*, 2012) performed among indigenous women in Australia reported the prevalence of PCOS according to NIH and Rotterdam criteria as 15.3 and 20.9%, respectively. We also noted relatively higher prevalence of PCOS according to Rotterdam criteria, in concordance with Boyle *et al.* (Table V).

Rotterdam criteria broaden the spectrum of PCOS when compared with NIH criteria, adding two new phenotypic subgroups: hyperandrogenism and PCO so-called 'ovulatory PCOS', and OD and PCO (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The former is considered to be a phenotype of the syndrome by the AE-PCOS Society; however, the latter is not, since hyperandrogenism is considered to be a mandatory factor to make the diagnosis (Azziz *et al.*, 2006). Regardless of this controversy, it

comes as no surprise that the prevalence rates in our study as well as in previous studies are significantly higher under Rotterdam and AE-PCOS Society criteria compared with older NIH criteria.

The prevalence of the component phenotypes of PCOS, namely PCO, hyperandrogenism and OD significantly influence the overall prevalence of the syndrome. We were able to evaluate these three phenotypes in all the participants of our study. When prevalence studies of PCOS are considered, the presence of PCO has not usually been investigated in the initial evaluation of the participants. Among the volunteers from two universities and general practice surgery centers in Oxford, the prevalence of PCO was found to be 33% (74/224) defined by AFC criteria (Michelmores *et al.*, 1999). (Moran *et al.* (2010a,b) studying 132 hospital employees in Mexico reported 10.6% prevalence rate of PCO by AFC criteria. PCO prevalence by AFC or volume criteria was 38% among 108 women from a group of 277 women reporting menstrual irregularity and hirsutism in Australia (March *et al.*, 2010). In our study, the prevalence of PCO was 36.5% (143/392) in a relatively large and well-defined population. Interestingly, half of these women did not have associated

**Table IV** The composition of metabolic syndrome (ATP III) in patients with PCOS.

Variable	NIH (n = 24) n (%)	Rotterdam (n = 78) n (%)	AE-PCOS (n = 60) n (%)
Abdominal obesity	6 (25.0)	16 (20.5)	10 (16.7)
Hypertension	1 (4.1)	1 (1.3)	1 (1.7)
High triglyceride	4 (16.7)	7 (9.0)	6 (10.0)
Low HDL-C	6 (25.0)	21 (26.9)	15 (25.0)
High fasting glucose	0	3 (3.8)	1 (1.7)
Single component	6 (25.0)	17 (21.8)	13 (21.7)
Any two components	1 (4.1)	3 (3.9)	1 (1.7)
Any more than two components	3 (12.5)	8 (10.3)	6 (10.0)

**Table V** Prior studies evaluating the prevalence of PCOS.

Author, year (country)	NIH (%)	Rotterdam (%)	AE-PCOS (%)
Knochenhauer <i>et al.</i> , 1998 (USA)	4.0		
Diamanti-Kandarakis <i>et al.</i> , 1999 (Greece)	6.8		
Michelmores <i>et al.</i> , 1999 (UK)	8.0		
Asuncion <i>et al.</i> , 2000 (Spain)	6.5		
Azziz <i>et al.</i> , 2004 (USA)	6.6		
Chen <i>et al.</i> , 2008 (China)		2.4	2.2
Kumarapeli <i>et al.</i> , 2008 (Sri Lanka)		6.3	
March <i>et al.</i> , 2010 (Australia)	8.7 ± 2.0	11.9 ± 2.4	10.2 ± 2.2
Moran <i>et al.</i> , 2010a (Mexico)	6.0	6.6	6.0
Boyle <i>et al.</i> , 2012 (Australia)	15.3	20.9	
Sanchon <i>et al.</i> , 2012 (Spain and Italy)	5.4		
Our data (Turkey)	6.1	19.9	15.3

hyperandrogenism and/or OD questioning the significance of this very common finding in women of reproductive age. Besides, when the current data are analyzed in depth, among the all patients with PCOS, 6 of them were assigned to have PCO morphology due to increased ovarian volume only. Mostly, the definition of PCO was associated with increased AFC in the ovaries. The validity of ovarian volume in the absence of high AFC is not clear as mentioned before (Moran et al., 2010a,b) and not recognized as morphologic criteria for PCO in some of the previous published studies (Moran et al., 2010a,b). In this respect, anti-Mullerian hormone may be an alternative tool for the definition of PCOs (Dewailly et al., 2011) when compared with morphological criteria that are potentially dependent to observer.

Phenotypic definition of clinical and biochemical hyperandrogenism is fraught with difficulties due to lack of universally accepted, objective and reliable methods for clinical or laboratory diagnosis (Yildiz, 2006). In the prevalence studies of PCOS, hirsutism is the most commonly used diagnostic criterion of hyperandrogenism and has been reported in a wide range of 6.8–29% in Caucasian populations. The prevalence of hirsutism was 7.1% among 154 healthy blood donors from Spain (Asuncion et al., 2000), 29% in 192 women responding to a free medical examination in Greek island of Lesbos (Diamanti-Kandarakis et al., 1999), 7.6 and 6.8% in two cohorts of 277 and 400 women seeking pre-employment physical examination in Alabama, USA (Knochauer et al., 1998; Azziz et al., 2004). More recent studies showed 6% rate in employees of a hospital in Mexico (Moran et al., 2010a,b) and 21.2% rate of self-reported hirsutism in members of a retrospective birth cohort from Australia (March et al., 2010). The cut-off values chosen to diagnose hirsutism in these studies were between  $\geq 6$  and 8, and might have influenced the results along with differences in the study populations. The prevalence of hirsutism in our study was 10.2% similar to the rates in the USA, Mexico and Spain and much lower than those reported in Greek and Australian studies.

Importantly, race and ethnicity should be taken into account on clinical presentation of androgen excess. A survey assessing the prevalence of PCOS in South East Asia reported a hirsutism prevalence rate of 5% (Kumarapeli et al., 2008). A recent multicenter prevalence survey (Sancho et al., 2012) from Spain and Italy that included 592 consecutive premenopausal women reported that PCOS and idiopathic hirsutism were equally frequent (5.4% prevalence, 95% CI: 3.6–7.2) followed by idiopathic hyperandrogenism (3.9% prevalence, 95% CI: 2.3–5.4). Among the studies the hirsutism rates seem to be similar between Whites and Blacks in the USA (Azziz et al., 2004). However, Asian women usually do not represent with hirsutism. In a large study reporting 2.2% prevalence of PCOS from Southern China, there were no women with an mF–G score  $\geq 6$  (Chen et al., 2008). This finding highlights the importance of both clinical and biochemical evaluation of hyperandrogenism. Screening for clinical signs and symptoms of PCOS at first, and then measurement of serum androgens in selected probable cases might result in underestimation of the prevalence of hyperandrogenism in real life. Full blood work to the whole group in our study revealed biochemical hyperandrogenemia in 18.4% of women (72/392) which has not been reported in previous studies having such a large population. Overall, the prevalence of hyperandrogenism in the form of hirsutism and/or hyperandrogenemia was 24.8% in our study suggesting that one out of four

women in the general population does have a feature of androgen excess. It is noteworthy that only 6.6% of women had isolated hyperandrogenemia that is not associated with hirsutism, OD or PCO. However, consequences for health and clinical implications of idiopathic hirsutism/hyperandrogenism are not clear as mentioned earlier (Sancho et al., 2012).

OD has been defined as oligo-anovulation in the prevalence studies of PCOS, and determined applying cut-off values to number of menses per year or menstrual intervals. Among the available studies, the rate of OD seems to be most consistent compound phenotype of PCOS. The prevalence rates of reported OD were 14.6, 19.5, 20.3, 22.8 and 23.8% in Greece (Diamanti-Kandarakis et al., 1999), Spain (Asuncion et al., 2000), China (Chen et al., 2008), U.S. (Azziz et al., 2004) and Australia (March et al., 2010). This variation might be because OD was defined in different ways in the various studies (Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Azziz et al., 2004; Chen et al., 2008; March et al., 2010). For example, OD was taken as eight or less cycles per year in one trial (Diamanti-Kandarakis et al., 1999), whereas menstrual cycles  $< 26$  days were also included in others (Azziz et al., 2004) which might in part explain why the former and latter studies revealed 14.6 and 22.8% prevalence rates, respectively. We have defined OD by menstrual cycles of either  $\geq 35$  or  $\leq 23$  days, and revealed a rate of 15.3% in line with the results of previous studies. Of note, isolated OD was present only in 4.6% of participants suggesting that oligo-anovulation is strongly tied with other two features of the syndrome.

Obesity might influence both the prevalence and the severity of the phenotype in PCOS. We have reported previously in a large sample of US women whose obesity minimally increase the prevalence of PCOS according to NIH criteria (Yildiz et al., 2008). In the current study, we have observed that the prevalence rates of PCOS were 2-fold and 3-fold higher in obese women compared with non-obese according to NIH and Rotterdam criteria, respectively. Obesity resulted in a 20% increased prevalence rate of PCOS when AE-PCOS Society criteria applied. Different results in these two studies might in part be related to background prevalence rates of obesity. The prevalence of obesity was 10% in the current Turkish study, whereas 30% of the women were obese in the US study (Yildiz et al., 2008).

Increased prevalence of the metabolic syndrome and its individual components in PCOS has been consistently reported in the literature albeit with varying rates (Moran and Teede, 2009; Moran et al., 2010a,b). Hyperandrogenic PCOS defined by NIH criteria seems to have more adverse cardiometabolic risk profile mainly due to increased total and abdominal obesity (Moran and Teede, 2009). Available studies in the literature assessing the prevalence of metabolic syndrome in PCOS have included patients presenting to the clinics. Studying a large population, we report 12.5, 10.3 and 10.0% prevalence rates of metabolic syndrome in women with PCOS according to NIH, Rotterdam and AE-PCOS Society criteria. Considering the background prevalence rate of 6.1% for metabolic syndrome, our data suggest 80–100% increased risk in PCOS women regardless of the diagnostic criteria used. We should note however that we did not perform oral glucose tolerance test (OGTT) in our study which might have resulted in underestimation of the prevalence figures for metabolic syndrome.

Sampling methodology might be a limitation for our study. Even though we have included women working at a single institution with

a high response rate for the participation, we cannot exclude potential selection bias due to undetermined differences between our sample and background community. The strength of our study is evaluation of all three component phenotypes of PCOS, namely hyperandrogenism, OD and PCO, in a large, well-defined homogenous population accounting for the full range of signs and symptoms of the syndrome.

In conclusion, the prevalence of PCOS under NIH, Rotterdam and AE-PCOS Society criteria are 6.1, 19.9 and 15.3%, respectively. PCO is the most common component phenotype with a prevalence rate of 36.5%, whereas hyperandrogenism and OD are observed in 24.8 and 15.3%, respectively, of reproductive-aged women. The most common composite phenotype is hyperandrogenism with PCO (9.2%). The isolated presence of PCO, hyperandrogenism and OD are observed in 17.6, 9.4 and 4.6% of women, respectively. The prevalence of metabolic syndrome is increased 2-fold in PCOS regardless of the diagnostic criteria used. Future studies obtaining longitudinal data on phenotypes of the syndrome at different stages of reproductive age might contribute capturing the complex essence of the syndrome.

## Authors' roles

B.O.Y. and H.Y. were the principal investigators and they formulated the research question. G.B. contributed to acquisition and analysis of the data. Z.Y. and I.E. contributed to interpretation of the data. All authors contributed to the critical revision of intellectual content and approved the final version of the paper.

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## Conflict of interest

None declared.

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