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META-ANALYSIS ***Reproductive epidemiology***

The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis

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STUDY QUESTION: What is the reported overall prevalence of polycystic ovary syndrome (PCOS) according to the criteria of the National Institutes of Health (NIH), Rotterdam or the Androgen Excess and PCOS Society (AE-PCOS Society)?

SUMMARY ANSWER: The reported overall prevalence of PCOS (95% CI) according to diagnostic criteria of the NIH, Rotterdam and the AE-PCOS Society is 6% (5–8%, *n* = 18 trials), 10% (8–13%, *n* = 15 trials) and 10% (7–13%, *n* = 10 trials), respectively.

WHAT IS ALREADY KNOWN: PCOS is the most common endocrine disorder among women of reproductive age. Although many studies have investigated the prevalence of PCOS, there are discrepancies in their results, in part due to the use of various definitions of the syndrome and its subphenotypes, differences between study cohorts, ethnicities, and types of recruitment and sampling.

STUDY DESIGN, SIZE, DURATION: A systematic review and meta-analysis were performed on all published studies that have reported the prevalence of PCOS according to at least one subset of diagnostic criteria.

PARTICIPANTS/MATERIALS, SETTING, METHODS: To identify relevant studies based on the PRISMA statement, PubMed and Ovid databases were searched up to September 2015 by two blind investigators using the terms 'PCOS', 'polycystic ovarian disease', 'Stein Leventhal syndrome', 'Androgen Excess Society', 'National Institute of Health', 'Rotterdam', 'ESHRE/ASRM', 'criteria' and 'prevalence'. Articles that represented the prevalence of PCOS according to at least one subset of diagnostic criteria were included. Exclusion criteria were a focus on adolescent subjects, an absence of data on prevalence, inappropriate design or non-English reporting. An appraisal tool to evaluate the methodological quality of the available studies was generated by the authors.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 55 reports remained following screening of the abstracts and text for the subject of the study. Of these, 24 articles were eligible and evaluated for qualitative and quantitative synthesis. Since heterogeneity was observed among studies, a random-effects model was used to estimate the prevalence and its 95% CI. The proportions of PCOS prevalence (95% CI) according to the diagnostic criteria of NIH, Rotterdam and AE-PCOS Society were 6% (5–8%, *n* = 18 trials), 10% (8–13%, *n* = 15 trials) and 10% (7–13%, *n* = 10 trials), respectively. When only unselected population studies were included, the given rates were 6% (5–8%, *n* = 3 trials), 9% (7–12%, *n* = 6 trials) and 10% (7–14%, *n* = 3 trials). The respective proportions for hirsutism, hyperandrogenaemia, polycystic ovaries (PCO) and oligo-anovulation were 13% (8–20%, *n* = 14 trials), 11% (8–15%, *n* = 9 trials), 28% (22–35%, *n* = 12 trials) and 15% (12–18%, *n* = 19 trials), respectively.

LIMITATIONS, REASONS FOR CAUTION: The effects of ethnic differences, particularly, on the presence or severity of hirsutism cannot be ruled out in any way. In addition, there was a lack of standardization in defining phenotypes of the syndrome and selection bias was evident in most of the studies regarding recruitment of the cohorts.

WIDER IMPLICATIONS OF THE FINDINGS: Geographical differences in frequencies of the components of the syndrome, such as oligo-anovulation and clinical/biochemical androgen excess, must be taken into account in the development and implementation of regional

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diagnostic and precision treatment strategies. Further efforts and resources are required to increase standardization of the methods and comparability of the study results on prevalence and phenotypic characterization of PCOS around the globe.

STUDY FUNDING/COMPETING INTEREST(S): No funding to declare. The authors have no conflicts of interest to declare.

REGISTRATION NUMBER: None.

Key words: polycystic ovary syndrome / androgen excess / oligo-anovulation / phenotype / prevalence

Introduction

In the last three decades, three attempts have been made to standardize the diagnosis of polycystic ovary syndrome (PCOS). Initially, a subset of criteria was suggested at a 1990 meeting of the National Institutes of Health (NIH) (Zawadzki and Dunaif, 1992) in which both clinical/biochemical hyperandrogenism and chronic anovulation were required for the diagnosis. Following this, a consensus workshop group, sponsored by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine, proposed that at least two of the following three criteria were mandatory: oligo-anovulation, clinical/biochemical hyperandrogenism and polycystic ovary (PCO) appearance on ultrasonography (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). Most recently, the Androgen Excess and PCOS (AE-PCOS) Society (Azziz *et al.*, 2006) recommended that clinical or biochemical hyperandrogenism should be essential for diagnosis, but also ovulatory dysfunction was required in the form of oligo-anovulation or PCO.

Even using the same subset of diagnostic criteria, the epidemiological studies present significant variation in the reported prevalence due to differences in study populations, limitations within the sampling and protocols applied and a lack of standardized definitions for the phenotypes. The effects of race and ethnicity, particularly, on the clinical presentation of androgen excess (Chen *et al.*, 2008) and enhancement in the visibility of antral follicles over time with ultrasonography (Dewailly *et al.*, 2011) might also contribute to the inconsistencies between prevalence studies.

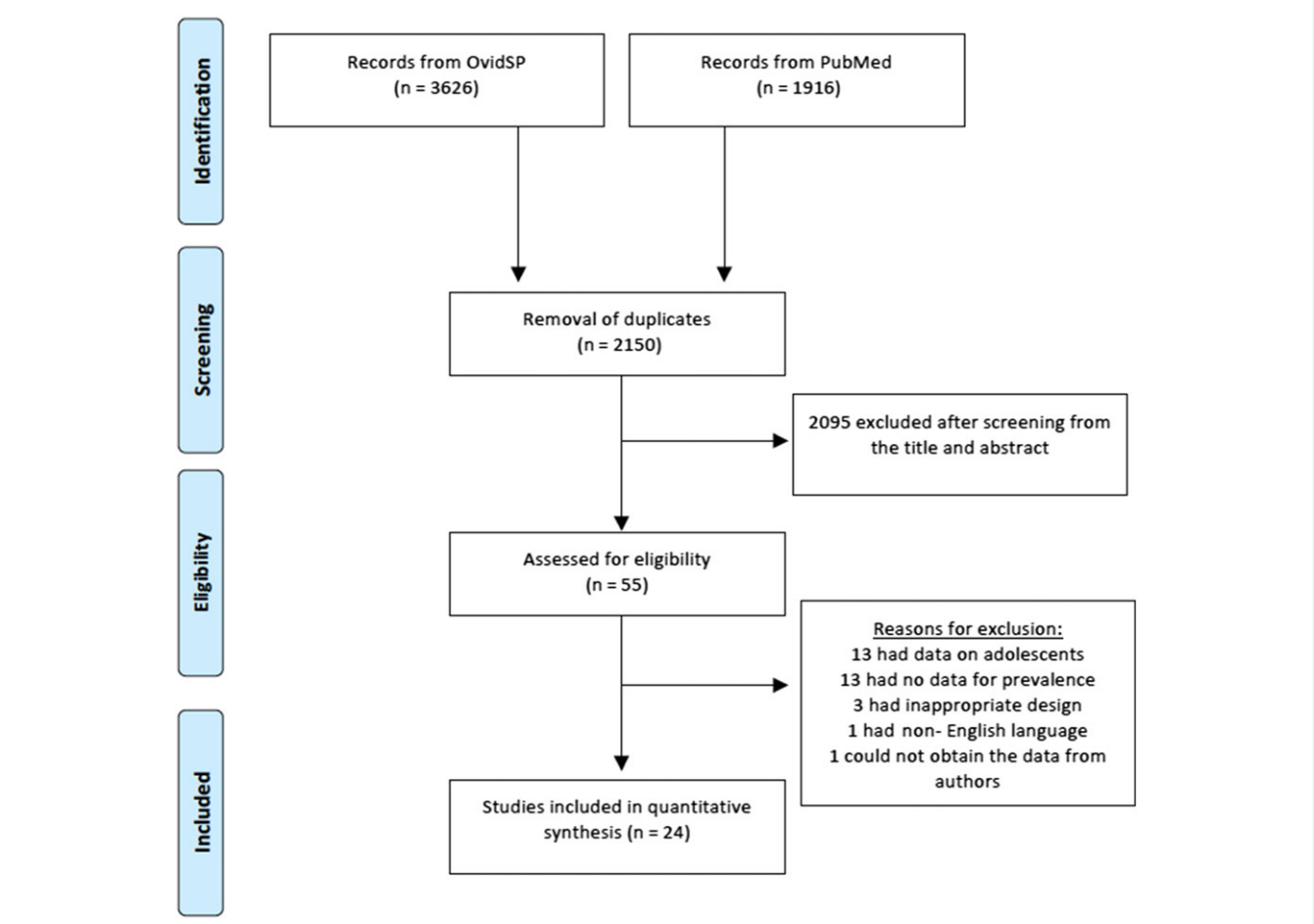

Figure 1 PRISMA flow diagram depicting the study selection.

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Table I Studies included in the meta-analysis of polycystic ovary syndrome (PCOS) prevalence.

Author, year	Country	Study population selection	*n* (Age)	HS a/b, (≥mF–G)	HA a/b, (biomarkers)	OA a/b, (diagnosis)	PCO a/b, (AFC, OV)	PCOS prevalence, *n* (NIH/ Rotterdam/ AE-PCOS)
Knochenhauer (1998)	US	At the time of preemployment	277 (18–45)	39/277, (≥6)	NA, (TT, fT)	35/277, (MH)	NA, (NA)	11/NA/NA
Diamanti-Kandarakis (1999)	Greece	Participants from Greek island Lesbos	192 (17–45)	70/192, (≥6)	19/84, (fT)	28/192, (MH)	NA, (NA)	13/NA/NA
Michelmore (1999)	England	Volunteers from 2 universities and 2 general practice surgeries in Oxford	224 (18–25)	NA, (≥8)	NA, (TT, fT, A, DHEAS, FAI)	NA, (MH)	74/224, (≥10, NA)	18/17/NA
Asuncion (2000)	Spain	Female blood donors at Hospital Ramon	154 (18–45)	11/154, (≥8)	19/145, (TT, DHEAS, FAI)	30/154, (MH)	NA, (NA)	10/NA/NA
Azziz (2004)	US	At the time of preemployment in Birmingham	400 (18–45)	27/400, (≥6)	NA, (TT, fT, A, DHEAS)	91/400, (MH, P)	NA, (NA)	27/NA/NA
Taponen (2004)	Finland	Northern Finland Birth Cohort in 1966	3077 (31)	NA, (NA)	NA, (TT, FAI)	NA, (MH)	81/251, (≥10, NA)	NA/NA/NA
Kumarapeli *et al.* (2008)	Sri Lanka	4 out of 13 areas at Gampaha	2915 (15–39)	160/495, (≥8)	26/495, (TT)	209, (MH)	NA, (≥12, >10 cm^3)	NA/183/NA
Chen *et al.* (2008)	China	Patients undergoing routine physical examination	915 (20–45)	0/915, (≥6)	88/915, (TT, fT, DHEAS, FAI)	190, (MH)	NA, (NA)	NA/22/20
Ma *et al.* (2010)	China	Stratified sample of 2111 residents in Beijing	2111 (19–45)	NA, (≥6)	NA, (TT, A)	401, (MH)	NA, (≥12, >10 cm^3)	NA/129/NA
Moran *et al.* (2010)	Mexico	Employees of a hospital	150 (20–45)	NA, (≥8)	16/130, (TT, fT, A, DHEAS)	NA, (MH)	14/132, (≥12, NA)	9/10/NA
March *et al.* (2010)	Australia	Birth records from 1973–1975 in Queen Elizabeth Hospital	728 (35–37)	154/728, (≥8)	NA, (TT, fT)	173/728, (MH)	41/108, (≥12, >10 cm^3)	63/87/74
Mehrabian *et al.* (2011)	Iran	Females attending pre-marriage clinic in Isfahan	820 (17–34)	58/820, (≥8)	NA, (TT, fT)	105/820, (MH, P)	65/122, (≥12, >10 cm^3)	57.7/124.6/ 67.7
Tehrani (2011)	Iran	From 4 randomly selected regions	929 (18–45)	NA, (≥8)	NA, (TT, FAI, A, DHEAS)	170/929, (MH)	156/929, (≥12, >10 cm^3)	170/66/136
Gabrielli and Aquino (2012)	Brazil	Women attending for cervical cancer screening	859 (18–45)	108/859, (≥6)	25/98, (TT)	99/859, (MH)	10/56, (≥12, >10 cm^3)	69/73/72
Yildiz *et al.* (2012)	Turkey	Employees of an institute	392 (18–45)	40/392, (≥6)	72/392 (TT, A, DHEAS, FAI)	60/392, (MH, P)	143/392, (≥12, >10 cm^3)	24/78/60
Sanchon *et al.* (2012)	Italy–Spain	Blood donors from Madrid and Bologna	592 (18–49)	72/592, (≥8)	44/444, (TT, FT, A, DHEAS, FAI)	25/592, (MH)	NA, (NA)	32/NA/NA
Eilertsen *et al.* (2012)	Norway	Women with prior preterm birth and controls	262 (NA)	58/262, (≥8)	18/262, (TT, A, FAI)	32/262, (MH)	113/262, (≥12, >10 cm^3)	NA/56/44
Gill *et al.* (2012)	India	College students	1520 (NA)	NA, (NA)	NA, (TT, FAI)	175/1520, (MH)	NA, (NA)	56/NA/NA
Boyle *et al.* (2012)	Australia	Indigenous women from DRUID study	248 (15–44)	NA, (NA)	NA, (TT, fT, FAI, DHEAS)	NA, (MH)	NA, (NA)	38/53/NA

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Table I *Continued*

Author, year	Country	Study population selection	*n* (Age)	HS a/b, (≥mF–G)	HA a/b, (biomarkers)	OA a/b, (diagnosis)	PCO a/b, (AFC, OV)	PCOS prevalence, *n* (NIH/ Rotterdam/ AE-PCOS)
Li *et al.* (2013)	China	Residents from 10 provinces	15924 (19-45)	NA, (≥6)	NA, (TT, fT, FAI, A)	748/3565, (MH)	1014/3565 (≥12, >10 cm^3)	NA/894/NA
Musmar *et al.* (2013)	Palestine	University students	137 (18–24)	38/137, (≥8)	NA, (fT)	35/137, (MH)	NA, (NA)	10/NA/NA
Lauritsen *et al.* (2014)	Denmark	Employees at Copenhagen University	447 (20–40)	30/447, (≥8)	NA, (TT, fT, A, DHEAS)	20/447, (MH)	239/447, (≥12, NA)	NA/74/62
Rashidi *et al.* (2014)	Iran	Women selected with cluster sampling	602 (18–45)	NA, (≥8)	NA, (TT, fT, A, DHEAS, FAI)	80/602, (MH)	125/602, (≥12, NA)	29/85/72
Zhuang *et al.* (2014)	China	Resident in Chengdu and some adolescent girls	1645 (12–44)	NA, (≥6)	NA, (fT)	116/1645, (MH)	NA, (≥12, >10 cm^3)	116/184/182

AFC, antral follicle count; HS, hirsutism; HA, hyperandrogenemia; NIH, National Institutes of Health; OA, oligo-anovulation; PCO, polycystic ovary; OV, ovarian volume.
a/b, found/examined; TT, total testosterone; fT, free testosterone; A, androstenedione; DHEAS, dehidroepiandrostenedione sulphate; FAI, free androgen index; mF-G, modified Ferriman-Gallwey scoring.
NA, not available or not applicable; MH, based on menstrual history; P, based on progesterone level.
DRUID, Darwin Region Urban Indigenous Diabetes.

Table II Number of studies scored as 'yes' by the senior author (B.O.Y.) using the risk of bias appraisal tool and kappa values to define the inter-rater agreement with two other authors (G.B. and S.M.). The total number of studies = 24.

Items	No. of studies scored as 'yes' by B.O.Y.	Kappa for B.O.Y. and G.B. (95% CI)	Kappa for B.O.Y. and S.M. (95% CI)
Q1. Was the sample representative of the target population?	6	0.89 (0.81–0.96)	0.72 (0.61–0.84)
Q2. Were study participants recruited in an appropriate way?	15	0.83 (0.73–0.93)	0.91 (0.83–0.98)
Q3. Was the sample size adequate?	16	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Q4. Were the study subjects and setting described in detail?	21	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Q5. Is the data analysis conducted with sufficient coverage of the identified sample?	16	0.82 (0.72–0.93)	0.82 (0.72–0.93)
Q6. Was the same mode of data collection used for all subjects?	14	1.00 (1.00–1.00)	0.91 (0.84–0.98)
Q7. Was the hirsutism scoring and definition performed with standard and objective criteria based on population characteristics?	21	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Q8. Were reliable hyperandrogenemia measurement methods used?	19	0.90 (0.81–0.99)	0.78 (0.66–0.91)
Q9. Was oligo-anovulation defined according to correct terminology, not merely patients' own reports?	3	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Q10. Was the ultrasonography performed on whole target population by measuring both antral follicle count and ovarian volume to identify PCO?	12	1.00 (1.00–1.00)	0.91 (0.84–0.98)
Overall[a]	24	0.97 (0.96–0.98)	0.95 (0.93–0.96)

[a]Intra-class correlation coefficient (ICC) was used.

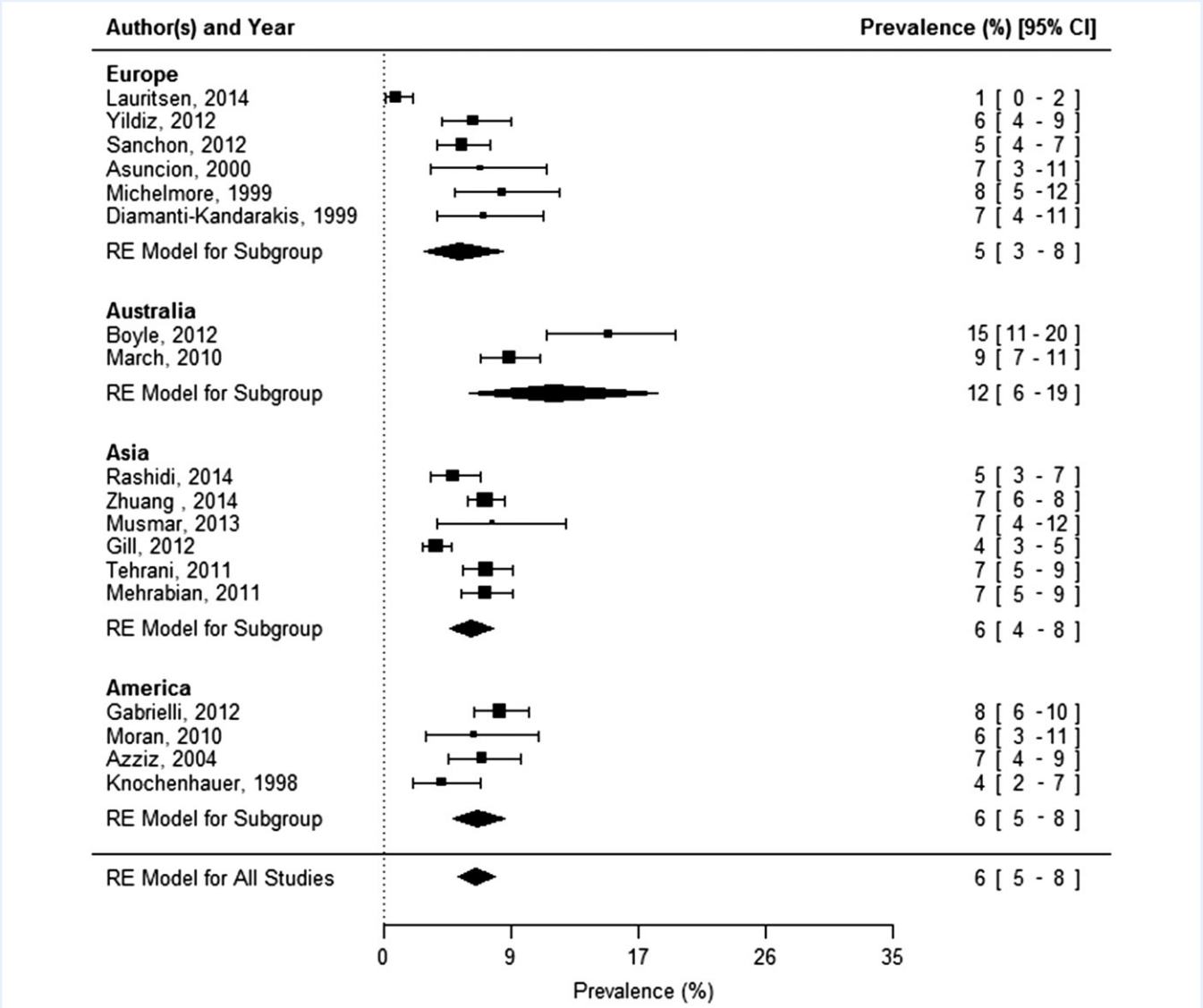

Figure 2 Polycystic ovary syndrome (PCOS) prevalence (95% CI) according to National Institutes of Health (NIH) criteria.

In the current study, we aimed to construct a systematic review and meta-analysis of all available studies to document the reported overall prevalence and phenotypic features of PCOS according to all three diagnostic criteria.

Material and methods

Study design

The current study was conducted as a systematic review and meta-analysis of the existing literature to determine the overall prevalence of PCOS according to NIH, Rotterdam and AE-PCOS Society criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines were used and, hence, all aspects of the current review were decided before the literature search; no post hoc change was performed.

Search method and data sources

An extensive literature search was performed up to September 2015 in PubMed and OvidSP by two blind investigators (S.M. and D.Z.) to generate the meta-analyses. The search strategy is given in Supplementary File I.

Study selection

Criteria for inclusion in the current study were established in advance of the literature search. Articles that represent the prevalence of PCOS according to at least one subset of diagnostic criteria were included. Two investigators (G.B. and S.M.) screened independently and a senior author (B.O.Y.) decided whether the study would be included or not, if there was a disagreement.

The search strategy yielded a total of 3626 and 1916 references from PubMed and OvidSP, respectively (Fig. 1). Following duplication removal, 2150 references remained. We did not identify any references that had not been covered by search engines. As depicted in detail in Fig. 1, after

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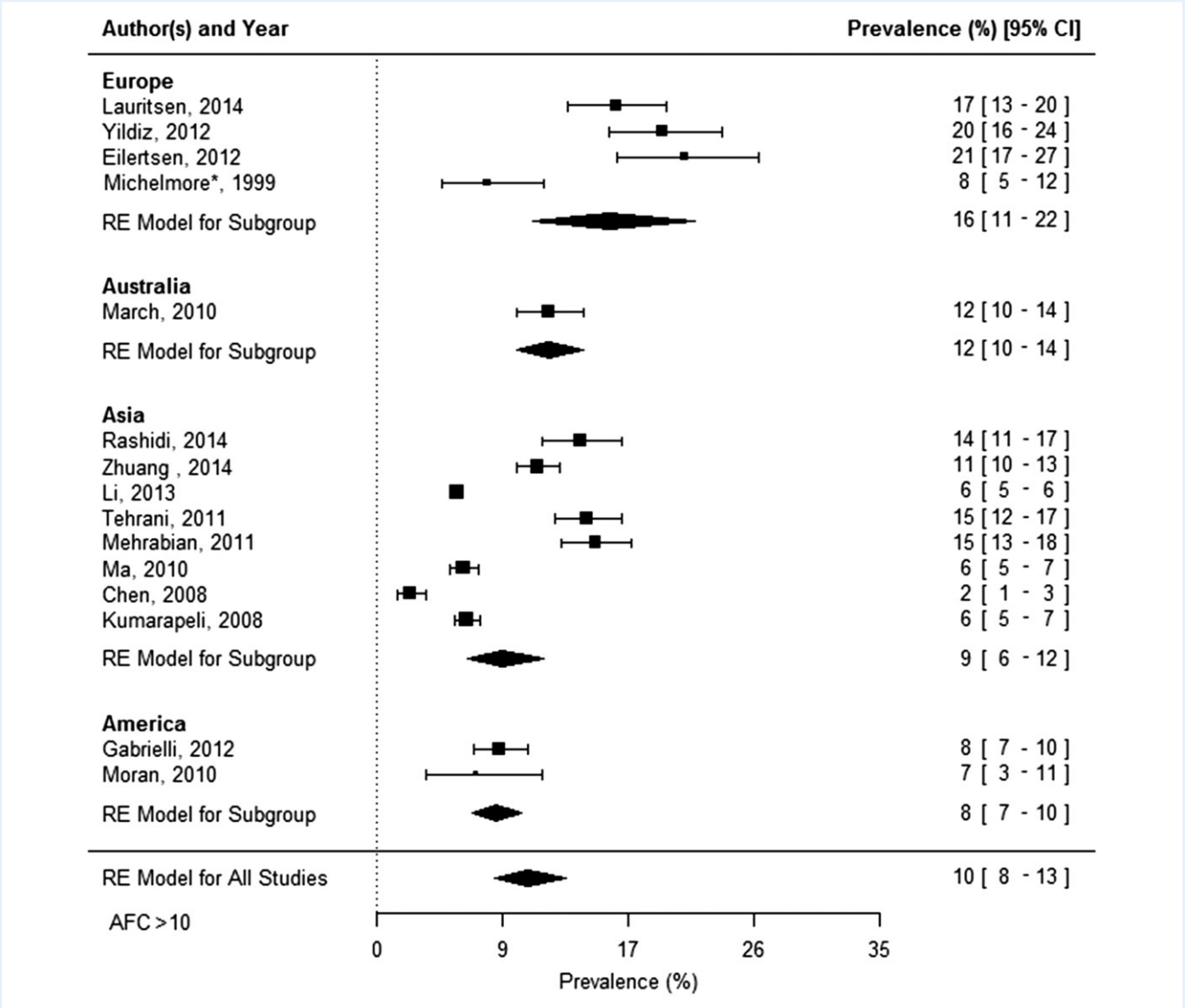

Figure 3 PCOS prevalence (95% CI) according to Rotterdam criteria (AFC, antral follicle count).

screening from the abstracts and titles, 55 articles remained and 31 articles were further excluded for various reasons (Supplementary File II). The remaining 24 articles were included in quantitative synthesis (Table I).

For the methodological aspect, the term 'unselected population' was used to denote when a multi-layered, stratified sampling method was preferred to determine the sample frame.

Data extraction

For the data extraction process, two authors (G.B. and S.M.) generated a data table form that was pilot tested to create consensus among the authors. After identifying data that were missing from the form or likely to be superfluous, we modified the table to avoid any misunderstandings or later disagreements. While initial abstraction was performed independently (G.B. and S.M.), another experienced author (B.O.Y.) was responsible for resolution of disagreements. The author, publication year, country, sample size, setting, selection of study population, subset criteria of diagnostic used, prevalence of PCOS and subgroup of phenotypes were noted (Table I). The primary outcome was the prevalence of PCOS according to NIH, Rotterdam and AE-PCOS criteria. A secondary outcome was the prevalence of hirsutism, hyperandrogenism, PCO appearance and oligo-anovulation. We contacted corresponding authors via email for any information missing from the table.

Risk of bias appraisal

Since there was no appropriate method by which to assess the risk of bias of the included studies, an appraisal tool to evaluate the methodological quality was generated by the authors (B.O.Y. and E.K.) (Supplementary File III). This appraisal tool was inspired by recent protocols produced by Munn *et al.* (2014) and Hoy *et al.* (2012). Since 5 out of 10 questions (Q1–Q5) were similar between those protocols to assess external validity, we kept the versions as in the original tool from Munn *et al.* For the assessment of internal validity, since Q6 was not defined in Munn *et al.*, we instead used the question found in the latter tool (Hoy *et al.*, 2012) to evaluate the mode of data collection used for all subjects. To evaluate the standard criteria for the measurement of the condition, the reliability of a given method and the identification of subpopulations using objective criteria, we modified available questions for each phenotype including

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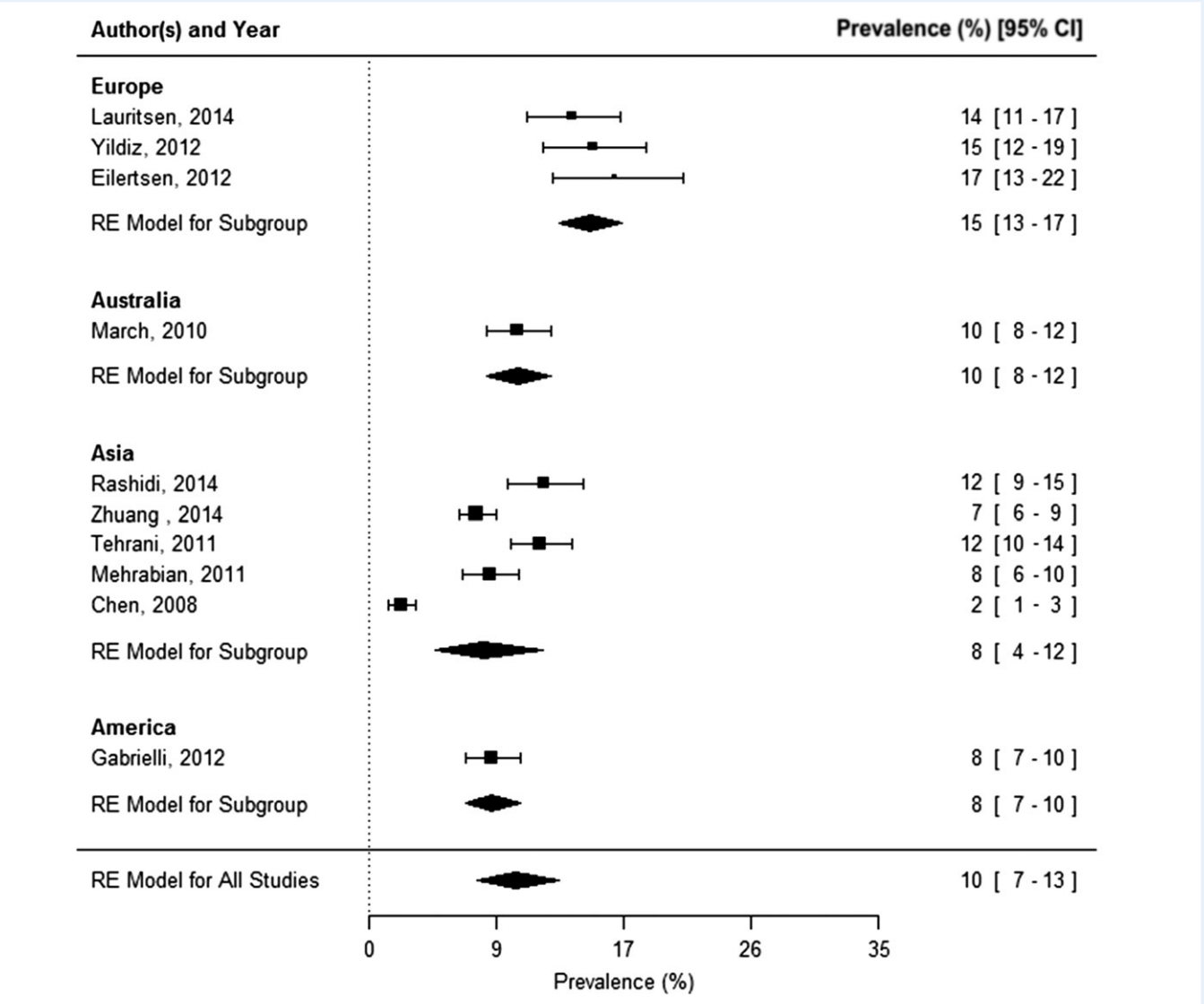

Figure 4 PCOS prevalence (95% CI) according to Androgen Excess and PCOS (AE-PCOS) Society criteria.

hirsutism (Q7) hyperandrogenaemia (Q8), oligo-anovulation (Q9) and PCO appearance (Q10) (Supplementary File III). Those questions were answered either with a 'yes', 'no', 'unclear' or 'not applicable'. Questions that were answered as 'yes' were scored 1 point, whereas all other answers were assigned 0 points, as done previously (Shea *et al.*, 2009). Overall scores were used to weight each study. Three researchers (B.O. Y., G.B. and S.M.) independently tested the risk of bias to calculate inter-rater agreement of the individual item (Table II).

Data synthesis and meta-analysis

Meta-analysis was performed using metafor package version 1.9–5 in R 3.0.0 software. The Freeman–Tukey double arcsine transformation was applied for normalizing and variance stabilizing of the proportions sampling distribution. This transformation also provided confidence limits of proportions between zero and one. Cochran's *Q*-test and Higgins' I^2 statistics were used to assess the heterogeneity among studies. Since heterogeneity was observed among studies, the random-effects model of DerSimonian and Laird was used to estimate the pooled prevalence and its 95% CI. The risk of bias assessment of the prevalence studies was modified according to PCOS features (Supplementary File III) and the obtained scores were used in meta-regression to evaluate the potential source of heterogeneity. Sensitivity analyses were also performed by estimating the combined prevalence in the absence of each study to assess the influence of each study on the pooled prevalence.

Results

Studies included for meta-analysis

A total of 55 articles remained after screening titles, abstracts or manuscripts and 24 were finally chosen for qualitative and quantitative synthesis. Detailed descriptions of the studies included in the meta-analysis are provided in Table I. Among the chosen studies, 6 of the 24 were deemed 'unselected' (Kumarapeli *et al.*, 2008; Ma *et al.*, 2010; Li *et al.*, 2013; Rashidi *et al.*, 2014; Tehrani *et al.*, 2014; Zhuang *et al.*, 2014).

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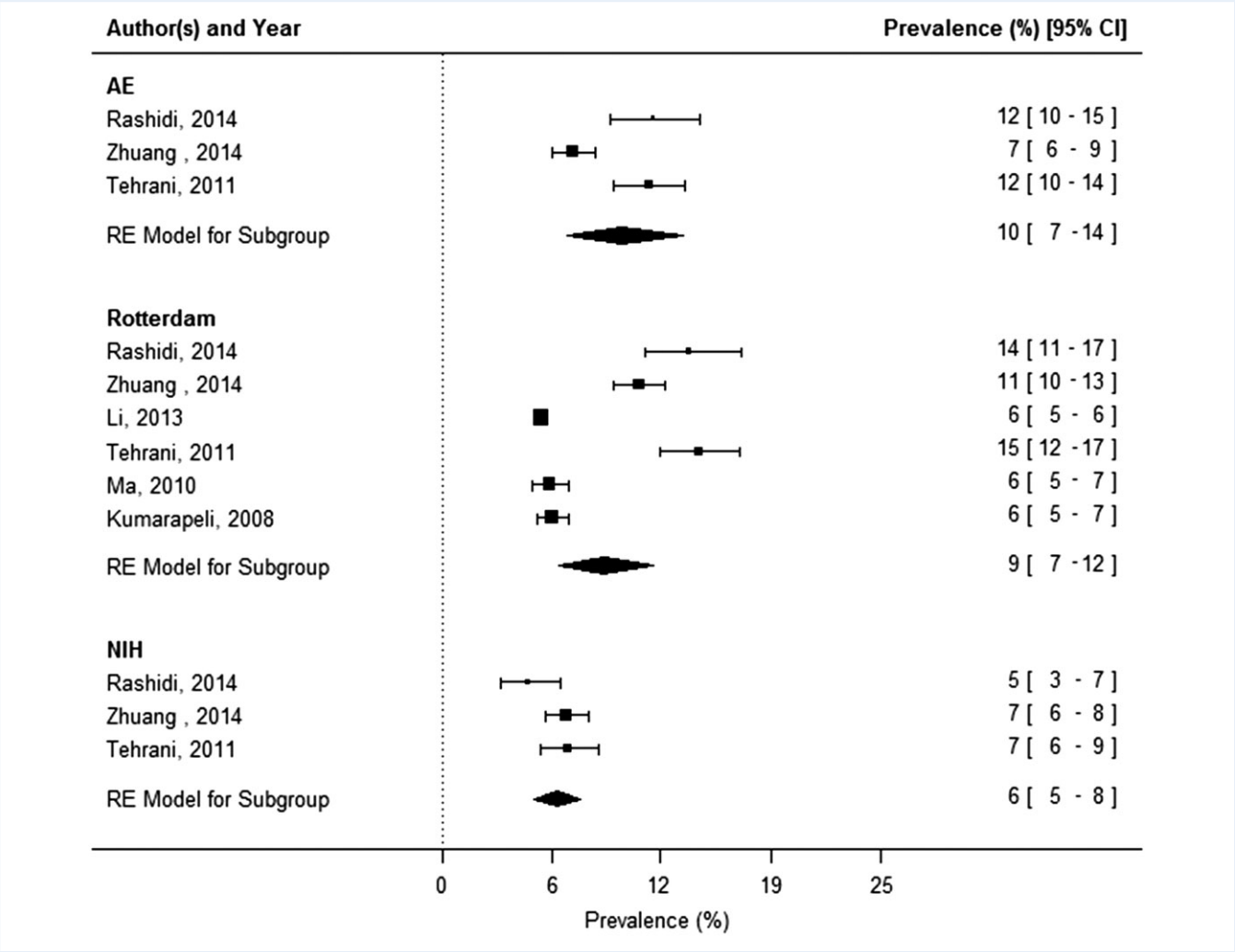

Figure 5 PCOS prevalence (95% CI) rates according to unselected population studies.

Clinical hyperandrogenism was defined by a modified Ferriman–Gallwey (mF–G) score of ≥6 or ≥8 (Table I). However, data on the proportion of hirsutism were available in 14 out of the 24 trials. The presence or feature of acne or alopecia was not taken into consideration in the current meta-analysis for defining clinical hyperandrogenism, but these data are provided to note the reported overall proportion. The definition of biochemical hyperandrogenism was based on any androgen hormone level exceeding its respective 95th percentile in healthy, non-hirsute, eumenorrheic women without PCO in 17 trials (Supplementary Table I). The remaining seven trials used upper limits established by the assay manufacturer (Supplementary Table I). We were able to obtain the prevalence of biochemical hyperandrogenism from 9 out of the 24 trials (Table I).

To detect PCO, only antral follicles were counted in each ovary in some studies (Table I), whereas the others also estimated ovarian volume. However, the prevalence of polycystic ovaries was reported in only 12 out of the 24 trials (Table I).

The majority of the studies preferred to rely on menstrual intervals to define ovulatory dysfunction (Table I). Three studies confirmed ovulation by measuring progesterone (P) levels, even in women with regular bleeding but presenting hirsutism or PCO appearance (Table I). However, the prevalence of oligo-anovulation was reported in only 20 out of 24 trials.

For the exclusion of related disorders, thyroid stimulating hormone and prolactin levels were checked in 17 trials, if oligo- anovulation was noticed (Supplementary Table I). In women with clinical or biochemical hyperandrogenism, the assessment of 17-hydroxyprogesterone levels and utilization of an ACTH stimulation test were clearly mentioned in 12 trials (Supplementary Table I).

Of note, two corresponding authors (Gabrielli and Aquino, 2012; Sanchon *et al.*, 2012) responded to our request for missing data.

Assessment of bias risk

Three researchers (B.O.Y., G.B. and S.M.) independently tested the risk of bias to calculate inter-rater agreement of the individual item (Supplementary File III). While one author had been involved in the tool development (B.O.Y.), the remaining two raters (G.B. and S.M.) had not. Nevertheless, to assess the validity of generated risk of bias tool, individual and overall kappa values (95% CI) for inter-rater agreement were analysed and given in Table II.

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Primary outcomes

PCOS prevalence (95% CI) according to the diagnostic subsets of NIH, Rotterdam and AE-PCOS Society criteria was 6% (5–8%, $n = 18$ trials), 10% (8–13%, $n = 15$ trials) and 10% (7–13%, $n = 10$ trials), respectively (Figs 2–4). When only unselected population studies were included, the given rates were 6% (5–8%, $n = 3$ trials), 9% (7–12%, $n = 6$ trials) and 10% (7–14%, $n = 3$ trials), respectively (Fig. 5).

A sensitivity analysis was generated by estimating the combined prevalence in the absence of each study, in order to assess its influence (Fig. 6). As depicted in Fig. 6, when we exclude either of two Asian

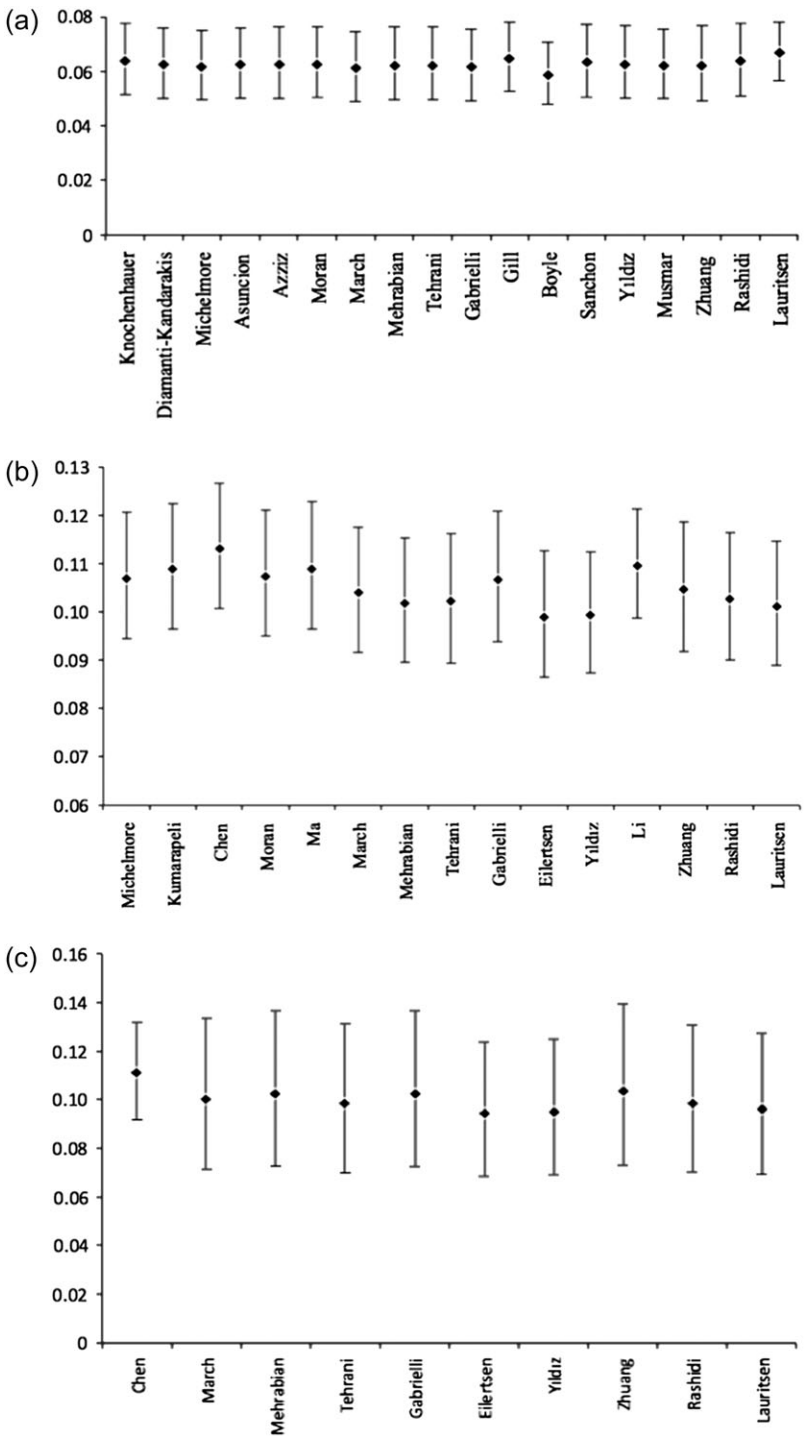

Figure 6 Sensitivity analysis, generated by estimating the combined proportion in the absence of each study according to NIH (a), Rotterdam (b) and AE-PCOS Society (c) criteria.

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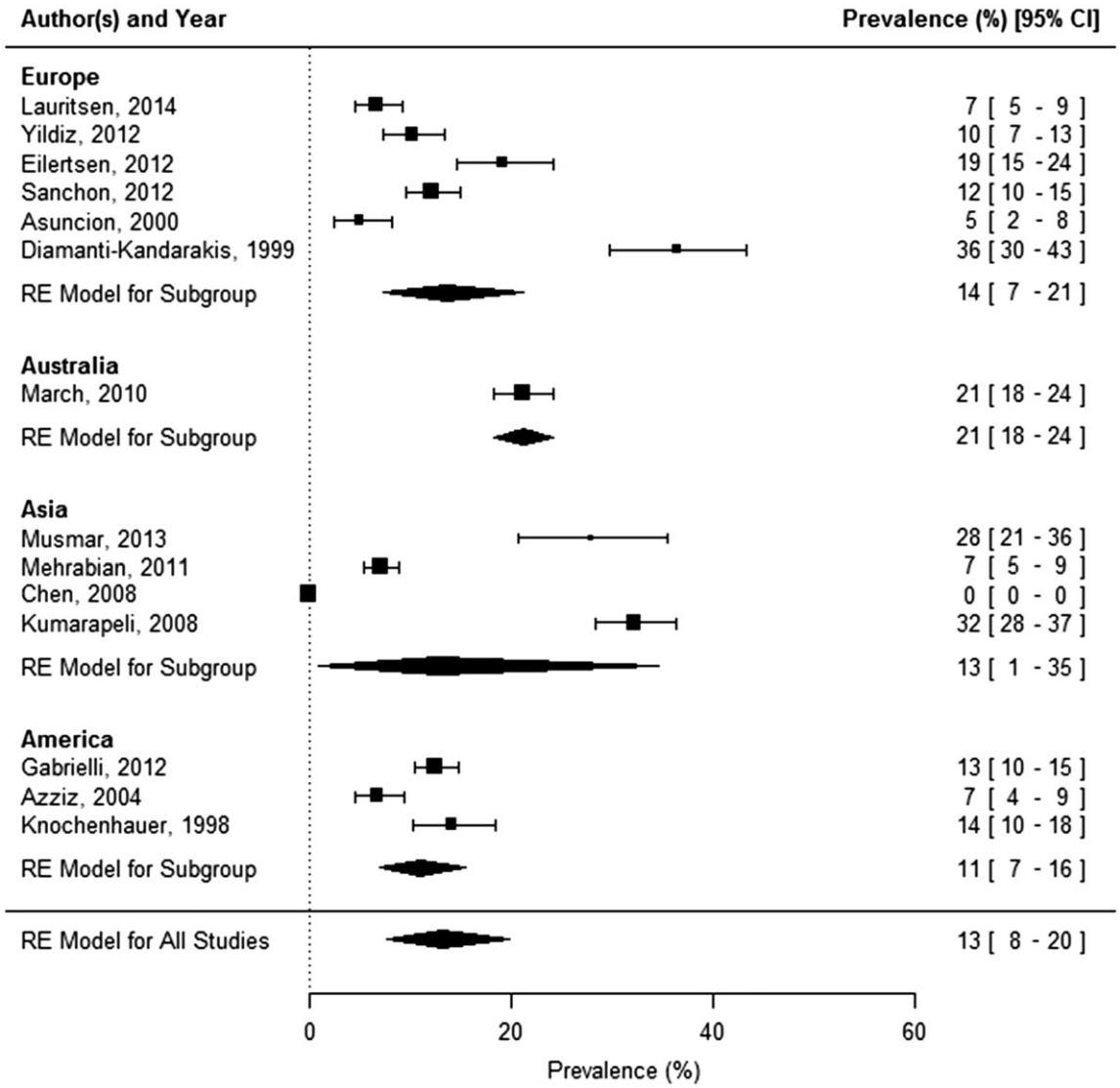

Figure 7 Prevalence of hirsutism (95% CI) in PCOS studies across continents.

studies (Chen *et al.*, 2008; Li *et al.*, 2013), the prevalence increases to 12% according to Rotterdam or AE-PCOS Society criteria.

Secondary outcomes

The respective prevalence rates for hirsutism, hyperandrogenaemia, PCO and oligo-anovulation were 13% (8–20%, $n = 14$ trials), 11% (8–15%, $n = 9$ trials), 28% (22–35%, $n = 12$ trials) and 15% (12–18%, $n = 19$ trials) (Figs 7–10).

As presented in Supplementary Figs I and II, the prevalence of acne and androgenetic alopecia were 16% (8–26%, $n = 12$ trials) and 2% (0–5%, $n = 5$ trials), respectively.

Discussion

Our findings indicate that the overall prevalence of PCOS according to NIH criteria is 6%, while this prevalence is 10% when subsets of Rotterdam or AE-PCOS Society criteria are applied. These results are similar to those generated when only unselected population studies were included. To our knowledge, the current report presents the first meta-data analysis on the overall reported prevalence of PCOS according to all three different subsets of criteria.

When the studies evaluating prevalence using NIH criteria were considered alone, similar prevalence rates were found for most geographical regions (Fig. 2). However, the data generated for Australia suggested a doubled risk for PCOS, which may have been due to the relative dearth of studies for this region (March *et al.*, 2010; Boyle *et al.*, 2012) and a relatively higher reported frequency of hirsutism in the phenotype (Fig. 7).

Although the mean prevalence of PCOS according to Rotterdam and AE-PCOS Society criteria were similar, one could speculate that the absolute prevalence might be higher according to Rotterdam for two reasons. Firstly, when ratios that had been generated within the same setting and population were compared (Figs 3 and 4), most

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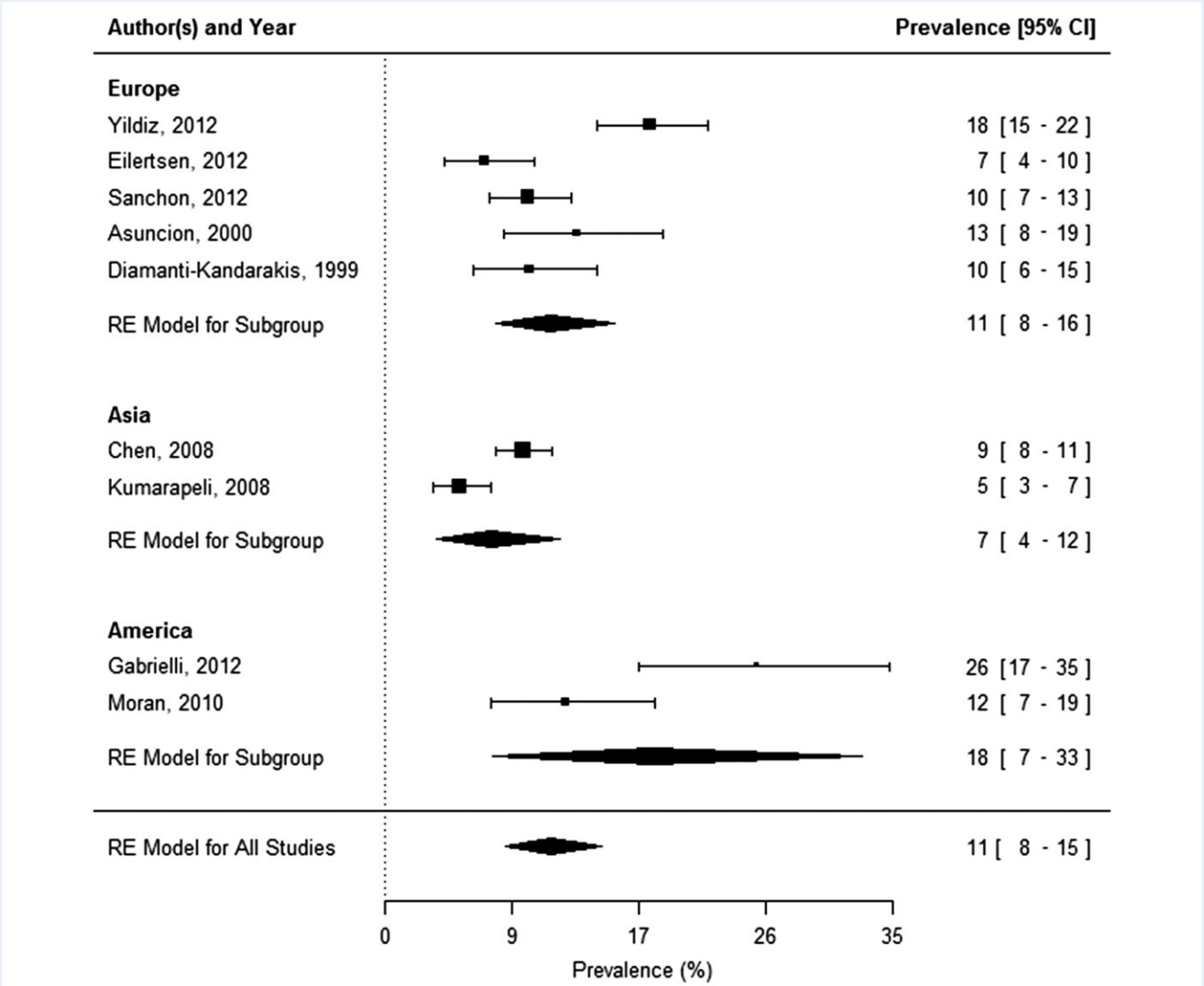

Figure 8 Prevalence of hyperandrogenaemia (95% CI) in PCOS studies across continents.

presented higher prevalence with Rotterdam (March *et al.*, 2010; Mehrabian *et al.*, 2011; Eilertsen *et al.*, 2012; Yildiz *et al.*, 2012; Lauritsen *et al.*, 2014; Rashidi *et al.*, 2014; Tehrani *et al.*, 2014; Zhuang *et al.*, 2014). This might be related to a lower frequency of hirsutism, particularly for those conducted in the Asian region (Chen *et al.*, 2008; Gill *et al.*, 2012). Secondly, studies with large sample sizes presented low prevalence rates according to Rotterdam but there were no data available for AE-PCOS Society criteria (Kumarapeli *et al.*, 2008; Ma *et al.*, 2010; Li *et al.*, 2013). Nevertheless, we performed sensitivity analysis to estimate the combined prevalence in the absence of each study (Fig. 6b). Accordingly, the absence of either of the two Chinese studies (Chen *et al.*, 2008; Li *et al.*, 2013) clearly increased the overall prevalence according to Rotterdam or AE-PCOS society criteria. This finding once again highlights the importance of ethnic variation among the available studies.

For the view of hyperandrogenism, neither the cut-off score of mF–G used for hirsutism nor the list of hormones employed for hyperandrogenaemia was standardized (Table I). In addition, 14 out of the 24 studies preferred to measure free testosterone, which is not currently recommended (Wierman *et al.*, 2007). Notably, the overall reported CI was quite wide for acne, once again pointing to the complexity of its association with PCOS. Although the prevalence rates of androgenic alopecia were very low according to the limited amount of data, it is worth noting that studies reporting high prevalence rates for acne also exhibited remarkable rates for androgenic alopecia (Musmar *et al.*, 2013; Lauritsen *et al.*, 2014). While one of these studies reported a higher proportion of hirsutism than the mean overall prevalence (Musmar *et al.*, 2013), the other study failed to identify such a connection (Lauritsen *et al.*, 2014). Unfortunately, we have no data regarding the rate of hyperandrogenemia in those studies.

For the definition of PCO morphology, the selected threshold for antral follicle count (AFC), the application of ovarian volume and the frequency of the transducer might contribute to the differences in prevalence rates (Table I). Whereas the lowest prevalence of PCO

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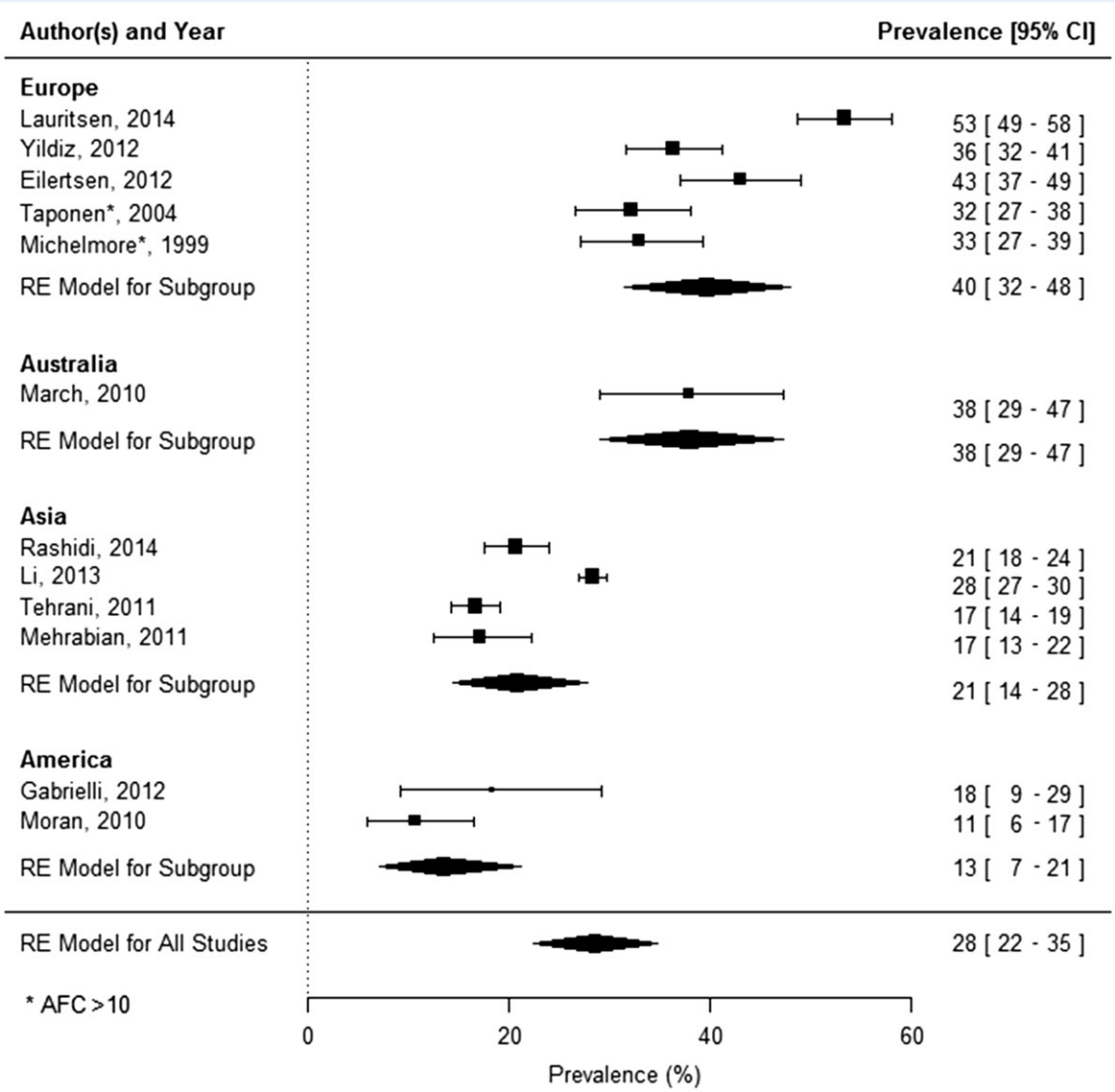

Figure 9 Prevalence of polycystic ovaries (95% CI) in PCOS studies across continents.

was obtained with a 5 mHz probe (Moran *et al.*, 2010), a recent paper with a 7.9 mHz device produced one of the highest rates (Lauritsen *et al.*, 2014).

With regard to available studies, the definition of oligo-anovulation infrequently included the documentation of low *P* levels ($n = 3$ studies) (Table I). Nevertheless, heterogeneity regarding rates of oligo-anovulation was obvious among the regions. From the perspective of methodology, this finding may once again be seen to underline the importance of screening an unselected population, rather than acquiring the selected cohort of women depending on menstrual history and subsequently performing blood work and/or scanning with ultrasonography.

Among systematic reviews and meta-analyses, the assessment of the methodological quality of the included studies should be understood as a prerequisite to interpretation of the findings. Although critical appraisal tools exist to evaluate the bias risk of the prevalence studies, none of these was eligible for the assessment of a 'syndrome', which includes more than one outcome. During the development of the tool used in our analysis, we modified existing questions and scored them to employ an overall score. Notably, the overall agreement between observers was good.

In the current meta-analysis, the potential effect of selection bias cannot be ruled out. Previous reports mentioned that the phenotype of PCOS, including the ethnic spectrum, severity of presentation and rate of obesity, was significantly affected by whether the PCOS subject was ascertained from a referral population or through unselected screening (Ezeh *et al.*, 2013). Referral PCOS patients appear to have greater body mass indices, higher hirsutism scores and androgen levels when compared with unselected cohorts (Luque-Ramirez *et al.*, 2015). Similarly, obesity itself might also influence the reported prevalence of the syndrome, with higher reported proportions among overweight and obese women than lean subjects (Alvarez-Blasco *et al.*, 2006). To avoid referral bias, we aimed to determine prevalence rates according to unselected populations in which the

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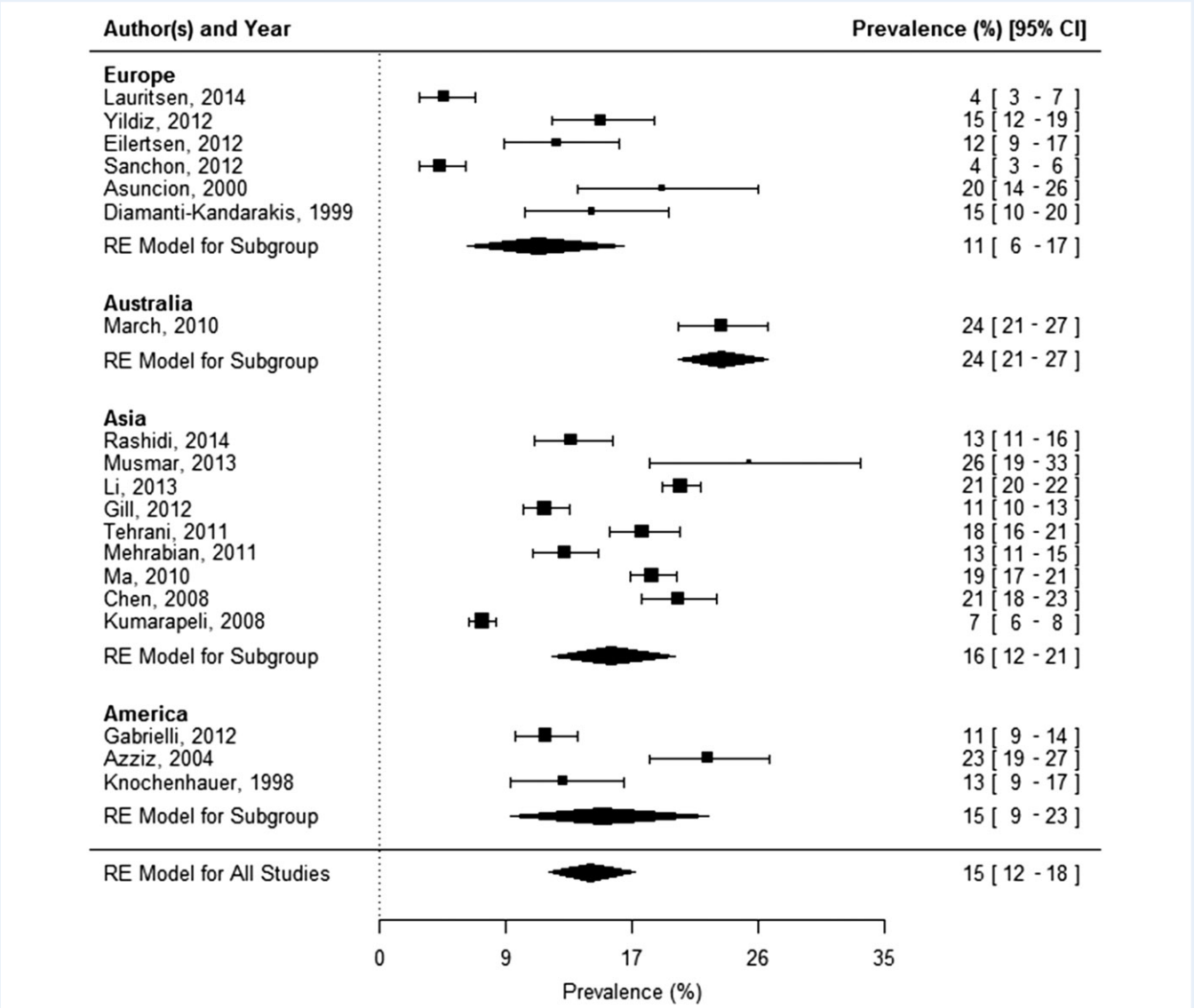

Figure 10 Prevalence of oligo-anovulation (95% CI) in PCOS studies across continents.

sample frame was close to the target population and true representation. However, we noticed similar proportions when analysed according to all studies or only for unselected populations. These results suggest that the 'true' prevalence of PCOS is close to the rates found in the current study.

In terms of drawbacks, the prevalence of PCOS presented significant heterogeneity across geographical regions. Mainly, this result has been attributed to the lack of consensus on phenotype definitions. Secondly, some phenotypes, such as hirsutism, might also be influenced by ethnic differences. Thirdly, since there has not yet been a study generated for Africa, we were unable to produce its prevalence rate to incorporate into the meta-analysis. Finally, although the assessment of the methodological quality of the included studies was the main strength of our analysis, it is worth considering that the use of overall scores, instead of individual component scores, may potentially obscure important strengths or weaknesses. Of note, the exclusion of non-English articles might also have influenced the reported proportions and result in underrepresentation of some populations.

In conclusion, the reported overall prevalence rates of PCOS according to Rotterdam and AE-PCOS Society criteria were similar, and were twice as high as those according to NIH criteria. Whereas the lowest rates for oligo-anovulation were in Europe, hirsutism and hyperandrogenaemia were found to be uncommon in Asia. These findings might guide the local use of different diagnostic criteria and adoption of treatment approaches according to geographical region. The reported frequency of PCO morphology was over 40% in many studies, and the overall rate of 28% once again stresses the need for revisions of the relevant definitions and perhaps exploration of the use of objective biochemical findings, such as anti-Müllerian hormone measurements.

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Supplementary Data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors' Roles

B.O.Y. and G.B. were the principal investigators. They formulated the meta-analysis and wrote the manuscript. S.M. contributed to the acquisition of the data and the manuscript writing process. D.Z. helped in the acquisition of the data. E.K. created the statistical analysis. All authors also contributed to the critical revision of the intellectual content and approved the final version of the paper.

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Conflict of Interest

None declared.

References

Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. *Arch Intern Med* 2006;**166**:2081–2086.

Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE *et al*. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab* 2006;**91**:4237–4245.

Boyle JA, Cunningham J, O'dea K, Dunbar T, Norman RJ. Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin, Australia. *Med J Aust* 2012;**196**:62–66.

Chen X, Yang D, Mo Y, Li L, Chen Y, Huang Y. Prevalence of polycystic ovary syndrome in unselected women from southern China. *Eur J Obstet Gynecol Reprod Biol* 2008;**139**:59–64.

Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, Duhamel A, Catteau-Jonard S. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. *Hum Reprod* 2011;**26**:3123–3129.

Eilertsen TB, Vanky E, Carlsen SM. Anti-Mullerian hormone in the diagnosis of polycystic ovary syndrome: can morphologic description be replaced? *Hum Reprod* 2012;**27**:2494–2502.

Ezeh U, Yildiz BO, Azziz R. Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2013;**98**:E1088–E1096.

Gabrielli L, Aquino EM. Polycystic ovary syndrome in Salvador, Brazil: a prevalence study in primary healthcare. *Reprod Biol Endocrinol* 2012;**10**:96.

Gill H, Tiwari P, Dabadghao P. Prevalence of polycystic ovary syndrome in young women from North India: a community-based study. *Indian J Endocrinol Metab* 2012;**16**:S389–S392.

Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, Baker P, Smith E, Buchbinder R. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;**65**:934–939.

Kumarapeli V, Seneviratne Rde A, Wijeyaratne CN, Yapa RM, Dodampahala SH. A simple screening approach for assessing community prevalence and phenotype of polycystic ovary syndrome in a semi-urban population in Sri Lanka. *Am J Epidemiol* 2008;**168**:321–328.

Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, Cohen A, Hougaard DM, Nyboe Andersen A. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone. *Hum Reprod* 2014;**29**:791–801.

Li R, Zhang Q, Yang D, Li S, Lu S, Wu X, Wei Z, Song X, Wang X, Fu S *et al*. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. *Hum Reprod* 2013;**28**:2562–2569.

Luque-Ramirez M, Alpanes M, Sanchon R, Fernandez-Duran E, Ortiz-Flores AE, Escobar-Morreale HF. Referral bias in female functional hyperandrogenism and polycystic ovary syndrome. *Eur J Endocrinol* 2015;**173**:603–610.

Ma YM, Li R, Qiao J, Zhang XW, Wang SY, Zhang QF, Li L, Tu BB, Zhang X. Characteristics of abnormal menstrual cycle and polycystic ovary syndrome in community and hospital populations. *Chin Med J (Engl)* 2010;**123**:2185–2189.

March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* 2010;**25**:544–551.

Mehrabian F, Khani B, Kelishadi R, Ghanbari E. The prevalence of polycystic ovary syndrome in Iranian women based on different diagnostic criteria. *Endokrynol Pol* 2011;**62**:238–242.

Moran C, Tena G, Moran S, Ruiz P, Reyna R, Duque X. Prevalence of polycystic ovary syndrome and related disorders in mexican women. *Gynecol Obstet Invest* 2010;**69**:274–280.

Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag* 2014;**3**:123–128.

Musmar S, Afaneh A, Mo'alla H. Epidemiology of polycystic ovary syndrome: a cross sectional study of university students at An-Najah national university—Palestine. *Reprod Biol Endocrinol* 2013;**11**:47.

Rashidi H, Ramezani Tehrani F, Bahri Khomami M, Tohidi M, Azizi F. To what extent does the use of the Rotterdam criteria affect the prevalence of polycystic ovary syndrome? A community-based study from the Southwest of Iran. *Eur J Obstet Gynecol Reprod Biol* 2014;**174**:100–105.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41–47.

Sanchon R, Gambineri A, Alpanes M, Martinez-Garcia MA, Pasquali R, Escobar-Morreale HF. Prevalence of functional disorders of androgen excess in unselected premenopausal women: a study in blood donors. *Hum Reprod* 2012;**27**:1209–1216.

Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol* 2009;**62**:1013–1020.

Tehrani FR, Rashidi H, Khomami MB, Tohidi M, Azizi F. The prevalence of metabolic disorders in various phenotypes of polycystic ovary syndrome: a community based study in Southwest of Iran. *Reprod Biol Endocrinol* 2014;**12**:89.

Wierman M, Basson R, Davis S, Khosla S, Miller K, Rosner W, Santoro N. Are the endocrine society's clinical practice guidelines on androgen therapy in women misguided? A commentary-response. *J Sex Med* 2007;**4**:1782–1783; author reply 1784–1785.

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Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. *Hum Reprod* 2012;**27**:3067–3073.

Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif AGJ, Haseltine F (eds). *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific, 1992: 377–384.

Zhuang J, Liu Y, Xu L, Liu X, Zhou L, Tang L, Kang D, Guo W, He M, Yang F *et al*. Prevalence of the polycystic ovary syndrome in female residents of Chengdu, China. *Gynecol Obstet Invest* 2014;**77**:217–223.

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