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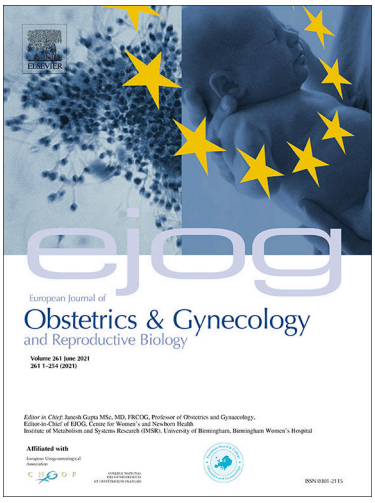


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PII: S0301-2115(22)00568-1
DOI: https://doi.org/10.1016/j.ejogrb.2022.10.020
Reference: EURO 12677

To appear in: *European Journal of Obstetrics & Gynecology and Reproductive Biology*

Received Date: 7 July 2022
Revised Date: 4 October 2022
Accepted Date: 25 October 2022

Please cite this article as: F. Chiaffarino, S. Cipriani, M. Dalmartello, E. Ricci, G. Esposito, F. Fedele, C. La Vecchia, E. Negri, F. Parazzini, Prevalence of Polycystic Ovary Syndrome in European countries and USA: a systematic review and meta-analysis, *European Journal of Obstetrics & Gynecology and Reproductive Biology* (2022), doi: https://doi.org/10.1016/j.ejogrb.2022.10.020

# Prevalence of Polycystic Ovary Syndrome in European countries and USA: a systematic review and meta-analysis.

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**Conflicts of interest**

The authors declare that they have no conflicts of interest.

# Prevalence of Polycystic Ovary Syndrome in European countries and USA: a systematic review and meta-analysis.

**ABSTRACT**

We conducted a systematic review and meta-analyses of the prevalence of Polycystic Ovary Syndrome (PCOS) and the frequency of its phenotypes in Europe and the USA, also focusing on temporal trends of the condition, to compare the PCOS prevalence among populations with a similar level of diagnostic resources availability and attitudes toward health problems, to improve comparability of estimates. We considered Europe and USA, two high-income areas with these characteristics.

The overall PCOS prevalence according to the NIH1990, ESHRE/ASRM 2003, AES-PCOS diagnostic criteria was respectively 6.2 % (95%CI 5.3-7.0), 19.5 % (95%CI 17.3-21.6), and 15.0 % (95%CI 12.9-17.1), with no appreciable heterogeneity across geographic areas. Phenotype A, the "complete PCOS", showed higher prevalence in all areas (44.8%, 95%CI 40.3-49.3), followed by phenotype D, called "non-hyperandrogenic PCOS" (19.5%), phenotype C termed as "ovulatory PCOS" (16.2%), and phenotype B, presenting as phenotype A but without polycystic ovarian morphology (14.9%). In all the studies analysing temporal trends of PCOS, an increase in prevalence of PCOS was reported, due, at least in part, to changing diagnostic criteria.

The prevalence of PCOS is similar in European countries and the USA. Interestingly, some differences in the frequency of PCOS phenotypes emerged between the two areas with a higher frequency of phenotype A and a lower one of phenotype C in the USA. Recognizing the factors which explain these differences would lead to a better understanding of the etiopathogenesis and the clinical expression of PCOS.

**Keywords**: Polycystic Ovary Syndrome, prevalence, PCOS phenotypes, high-income countries

**Abbreviations**

PCOS**:** Polycystic ovary syndrome

NIH**:** National Institutes of Health

ESHRE**:** European Society of Human Reproduction and Embryology

ASRM**:** American Society for Reproductive Medicine

AES**:** Androgen Excess Society

PCOM**:** polycystic ovarian morphology

**INTRODUCTION**

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age characterized by androgen excess, ovulatory dysfunction, and polycystic ovarian morphology (PCOM). Its diagnostic criteria have been repeatedly changing, thus creating uncertainty on the prevalence of PCOS. In 1990, the National Institutes of Health (NIH) first suggested diagnostic criteria for PCOS, where a combination of chronic anovulation and androgen excess were required for the diagnosis. In 2003, a consensus conference held in Rotterdam by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), proposed new diagnostic criteria (Rotterdam 2004) based on the presence of at least two of the followings criteria: the presence of hyperandrogenism, chronic ovulatory dysfunction and ultrasound characteristics of polycystic ovaries. In 2006 the Androgen Excess Society (AES) proposed a new definition of PCOS as a disorder predominantly of androgen excess (mandatory), characterized by the presence of clinical and/or biochemical hyperandrogenism in addition to ovulatory dysfunction, such as oligo-/anovulation or PCOM. To maximize the comparability in research, in 2012 the NIH Evidence-based Methodology Workshop Panel on PCOS proposed to maintain the broad inclusive diagnostic criteria of ESHRE/ASRM 2003 and to identify four subphenotypes[1]. Phenotypes A and B are often called “classic PCOS”: women with hyperandrogenism, ovulatory dysfunction, and with (phenotype A) or without (phenotype B) PCOM. Phenotype C, known as “ovulatory PCOS”, is characterized by hyperandrogenism and PCOM without ovulatory dysfunction. In phenotype D, termed “non-hyperandrogenic PCOS”, women have ovulatory dysfunction and PCOM without hyperandrogenism.

Finally, the 2018 International Guidelines for PCOS endorsed the ESHRE/ASRM criteria with one restatement: an ultrasound is not needed for diagnosis if the patient has irregular menstrual cycles and hyperandrogenism is present, but it is still recommended for phenotyping [2].

These changes in the diagnostic criteria have markedly affected estimates of PCOS prevalence in epidemiological studies. In 2016, in a systematic review and meta-analysis, Bozdag et al. analysed the PCOS prevalence estimates according to the three diagnostic criteria, NIH, ESHRE/ASRM, and AES guidelines [3]: the reported overall prevalence of PCOS according to the three diagnostic criteria was 6%, 10%, and 10%, respectively. In another systematic review and meta-analysis, the pooled prevalence of PCOS in studies that used NIH criteria was 7%, whereas with ESHRE/ASRM criteria was 12% and with AES criteria was 10% [4]

Some differences in the prevalence of PCOS were reported across geographic areas; high-income countries (e.g., Europe and North America) generally showed higher rates than Asian ones. However, a lower frequency of hirsutism was observed in studies conducted in the East Asian region [3,5]. Differences in lifestyle habits and in the prevalence of obesity and metabolic syndrome may explain, partially, this variability. Further, different access to healthcare in different geographic areas and availability of diagnostic resources, which are more frequently accessible in high-income countries, may also affect prevalence estimates. A way to reduce these biases is to compare the prevalence of PCOS among populations living in areas with a similar level of diagnostic resources availability and attitudes toward health problems. Europe and USA are two high-income areas with these characteristics.

In this perspective, we conducted a systematic review and meta-analysis of the prevalence of PCOS and the frequency of its phenotypes, also focusing on temporal trends of the condition, in different areas of Europe and the USA, not considered in previous published systematic reviews.

## METHODS

This report follows the PRISMA and MOOSE guidelines and was registered at PROSPERO (CRD42021237244).

### Search strategy

A systematic literature search was performed using the electronic databases MEDLINE and EMBASE on February 22, 2021. The search terms ("polycystic ovary syndrome" or "PCOS") and ("incidence" or "prevalence" or "trend") were used as Medical Subject Heading (MeSH PUBMED) or Embase subject headings (EMTREE EMBASE) terms or as a combination of free text. The search was limited to full-length articles, published in English from 1990, from the first diagnostic criteria. A PICOS (Patient, Intervention, Comparator, Outcome, Study) design structure was used to develop the study questions and the inclusion/exclusion criteria.

Two authors reviewed the papers and independently selected the articles eligible for the systematic review and discrepancies were resolved by discussion. If multiple reports from the same study were published, only the one with the most detailed information was included. Furthermore, they reviewed reference lists of the retrieved papers to identify any potential additional studies that could be included. All differences were discussed and resolved with a third reviewer.

### Inclusion criteria

Studies were selected if they met the following inclusion criteria:

- observational studies;

- studies with a defined diagnosis of PCOS, according to the NIH1990 and/or ESHRE/ASRM 2003 and/or AES-PCOS 2006 criteria or the International Classification of Disease-Ninth Revision (ICD-9) codes used in health databases;

- studies reporting prevalence of PCOS or data to calculate it, number of women with PCOS, and the total number of study population (for PCOS prevalence);

- studies reporting frequency of each phenotype on total cases of PCOS (for PCOS phenotypes frequency);

- studies reporting temporal trends of PCOS prevalence in unselected or referral populations;

- studies referred to the following geographic areas: Europe and USA.

**Exclusion criteria.**

Studies were excluded if they were:

- studies without a PCOS diagnosis according to the above-listed criteria;

- studies referred to other geographic areas.

**Data extraction.**

For each study, the following information was collected: first author's last name; year of publication; country of origin; study design; number of subjects; age of subjects; reported prevalence of PCOS according to the different diagnostic criteria, and information for the assessment of the risk of bias.

**Quality assessment.**

The methodological quality of the included studies was assessed using a critical appraisal checklist designed for prevalence studies, the Joanna Briggs Institute (JBI) Critical Appraisal tool [6]. It consists of 9 parameters and an overall rating of quality was assigned to each study, based on the number of yes answers to the checklist. Studies were rated as good quality when they have 7-9 yes answers; fair quality when the yes answers were 5-6; poor quality when yes answers were less than 5. We excluded studies rated as poor quality.

Two review authors independently evaluated and cross-checked the risk of bias. Discrepancies between review authors on the risk of bias were resolved through discussion with a third review author.

**Strategy for data synthesis.**

All analyses were performed using Metaprop, a command implemented in Stata to compute meta-analysis of proportions (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Freeman Tukey arcsine square root transformation was applied to the data

before pooling for meta-analysis [6]. Estimates of overall proportions and corresponding 95% confidence interval (CI) were calculated by using a random-effects model for all the analyses: in case of heterogeneity the random effects model is recommended and in the case of small heterogeneity, the fixed and the random effects models give similar results[7]. Thus, in order to standardize the analyses, the random model was applied to all the analyses. To evaluate heterogeneity across studies, heterogeneity $I^2$ value was also reported.

Analysis of studies according to different diagnostic criteria, geographic areas, and PCOS phenotypes were performed. Thus, for the meta-analysis of PCOS prevalence, we considered, separately, studies where the diagnosis of PCOS was according to the following criteria: NIH1990, ESHRE/ASRM 2003, AES-PCOS 2006, and ICD-9. Moreover, we compared findings of PCOS prevalence and PCOS phenotypes across specified geographic areas: USA, Europe divided in northern/central and southern Europe.

We conducted sensitivity analyses excluding: i) the studies conducted in unselected populations and ii) studies conducted in Turkey, considering that Turkey has also an Asiatic area.

**RESULTS**

Figure 1 showed the flowchart of the selection of studies. We identified 3559 records from Pubmed search and 3697 from Embase search. After removing duplicate records and excluding not relevant records, 181 reports were assessed for eligibility. We selected 21 studies on PCOS prevalence and 31 studies on the frequency of PCOS phenotypes.

1. **Prevalence of PCOS**

A total of 21 studies were included in the qualitative synthesis of the PCOS prevalence.

Their main characteristics are presented in Table 1 (notes are reported in Supplementary Table S1): 12 were cross-sectional studies[8–19], 3 were retrospective studies from health databases [20–22], 1 was a multicenter survey[23], 3 were cohort studies [24–26], 1 was a clinical series (unselected consecutive women)[27] and 1 was a paper based on the Global Burden of Diseases 2017 (GBD 2017) estimates [28]. A total of 8 studies were conducted in the USA, 3 in Denmark, 2 in the UK, Turkey, and Sweden, 1 in Greece, Italy-Spain, Spain, and Norway.

The most commonly used PCOS diagnostic criteria were NIH1990 (9 studies), followed by ESHRE/ASRM 2003 criteria (4 studies), and the AES-PCOS 2006 criteria (3 studies). Three American studies analysed data derived from health insurance claim databases [21,22], and from a health plan

ambulatory visit database [20], where PCOS patients were identified by ICD codes. Moreover, in a Sweden and in a Danish national register-based cohort studies, PCOS was diagnosed using ICD 7-10 codes [25,26] According to the JBI Critical Appraisal tool [6], 18 studies were of good quality, and 4 were evaluated as fair quality (Supplementary file S1).

Considering the studies that used the NIH1990 criteria, the prevalence of PCOS ranged from 4 % in a study conducted in the USA [15] to 8% in a study conducted in the UK [18].

The corresponding overall prevalence ranged from 16.6 % to 21.4 % for studies using the ESHRE/ASRM 2003 criteria and from 13.9 % to 16.8 % for studies using the AES-PCOS 2006 criteria. The prevalence estimates were markedly lower in the studies that used the ICD-9 codes to identify women with PCOS (range from 1.0 to 2.2).

In a Swedish register-based cohort study of 681,123 singleton births, 3738 (0.54%) girls (≥ 15 years of age) were diagnosed with PCOS [26]. In this study, only women who requested hospital medical care (as outpatients or inpatients) for PCOS were included.

We identified 2 studies using other diagnostic criteria. A Turkish cross-sectional study on female university students reported a physician-diagnosed PCOS prevalence of 3.5%. In the same study, the rate of young women without a diagnosis by a physician but reporting PCOS symptoms was 13% [8].

A study including 156 unselected consecutive women of reproductive age with a family history of coronary artery disease from the UCLA/Cedars-Sinai Mexican-American Coronary Artery Disease (MACAD) Project, analysed the prevalence of PCOS using a questionnaire for self-reporting PCOS symptoms [27], which was defined by authors as a reliable method of detecting PCOS. Overall, 13% of women met the criteria for PCOS (self-reporting of irregular menses and clinical hyperandrogenism).

*1.1 Meta-analysis of prevalence data*

A total of 15 studies reported relevant information to be included in the meta-analysis.

Six studies were excluded. In one, PCOS was diagnosed by physicians [8]; in the study by Goodarzi, PCOS diagnosis was self-reported [27]. In a Swedish study and in a Danish register-based cohort study [25,26], only data on PCOS prevalence overall follow-up period were available. In a British historic cohort study, PCOS prevalence in 2014 was reported but we excluded it from the meta-analysis because the total number of women was not published [24]. Lastly, data from the GBD 2017

Injuries and Risk Factors Study provided model-based estimates of incidence and age-standardized rate for PCOS based on various primary sources, not relevant for our meta-analysis [28].

The estimated overall PCOS prevalence according to the NIH1990, ESHRE/ASRM 2003, AES-PCOS diagnostic criteria was respectively 6.2 % (95%CI 5.3-7.0), 19.5 % (95%CI 17.3-21.6), 15.0 % (95%CI 12.9-17.1) (Fig. 2) with no appreciable heterogeneity across geographic areas.

Considering the studies conducted in the USA in which PCOS patients were identified by ICD-9 codes, the overall prevalence was 1.6 % (95%CI 1.1-2.1) (Fig. 2).

2. **PCOS phenotypes frequency.**

Table 2 shows the characteristics of the 31 studies reporting the frequency of the four PCOS phenotypes (notes are reported in Supplementary Table S2). Two studies were conducted in the USA, 9 in northern-central Europe, and 20 in southern Europe. The diagnosis of PCOS was based on ESHRE/ASRM 2003 criteria and then classified into four phenotypes.

In 29 studies women were referred to the hospital for PCOS symptoms or with PCOS diagnosis [12,29–56]; one study involved healthcare workers [16] and another study involved volunteers employed in a government-based institute [19]. The age of the women ranged from 17 to 45 years. The smallest study had 89 women [51] and the largest had 2288 women [34] for a total of 12,074 women included.

*2.1 Meta-analysis of proportional frequency of PCOS phenotypes*

All the studies listed in Table 2 were included in the meta-analysis.

Phenotype A, the “complete PCOS”, showed a higher prevalence in all the considered areas (44.9%) (95%CI, 41.3-48.5) (Fig. 3), followed by phenotype D (18.2%), C (16.2%), and B (14.9%). Prevalence of phenotype A was different between the USA, northern/central Europe, and southern Europe (p=0.004), with statistically significant heterogeneity. The higher frequency was observed in the USA: 55.0% (95% CI 50.0-59.9) though this finding is based only on 2 studies.

Concerning phenotype B, the overall prevalence estimate was 14.9 % (95%CI 10.6-19.7) without significant heterogeneity across different geographic areas (Fig. 4).

The overall pooled estimated prevalence of phenotype C was 16.2 % (95%CI 12.3-20.5) with statistically significant heterogeneity across areas and with lower values in the USA (Fig.5).

The prevalence of phenotype D tended to be higher in northern/central Europe than in other regions (without significant heterogeneity) and the overall pooled estimated prevalence was 18.2% (95%CI 12.8-24.3) (Fig.6).

In the sensitivity analysis excluding the 2 studies conducted in unselected populations [16,19] the heterogeneity, among areas regarding phenotypes A and C, remained significant (Supplementary file S2).

Considering that Turkey includes also an Asiatic area, we performed another sensitivity analysis. Excluding Turkish studies, phenotype A showed a higher estimate (49.5, 95% CI 45.3-53.7), whereas phenotypes B, C and D showed both lower overall estimates (13.2, 95% CI 7.9-19.6; 13.2, 95% CI 8.8-18.3 and 16.2, 95% CI 9.3-24.4, respectively) in comparison with previous analysis (Supplementary files S3).

### 3. Temporal trend of PCOS

Three studies analysed the temporal trend of PCOS [24,25,28] (see Table 1).

In a historic cohort study conducted in the UK in the primary care setting, Ding et al. estimated the prevalence of PCOS between 2004 and 2014 [24]. PCOS diagnosed cases were selected using a hierarchical clinical coding system, the Read code, for “polycystic ovary syndrome” to identify women with a clinical diagnosis of PCOS, whereas women with two or more Read codes indicative of PCOS symptoms were considered as “probable cases”. The incidence of PCOS increased from 1.67 per 1000 person-years in 2004 to 20.00 per 1000 person-years in 2010, after which the rate remained relatively constant. This increase could be due at least in part to the difference in diagnostic criteria (publication of new diagnostic criteria, ESHRE/ASRM, in 2003).

In a Danish cohort study, including 523,757 female singleton children born between 1973 and 1991, a total of 3204 PCOS diagnoses occurred during the follow-up period: from age 15 years until the end of 2006 [25]. A linear increase in the incidence of PCOS of 11% every year was detected during the study period (1988 to 2006).

Very recently, GBD 2017 Injuries and Risk Factors Study published estimates of PCOS incidence at the global, regional, and national levels [28]. The estimated age-standardized PCOS incidence rates from 2007 to 2017 increased in all European and North-American countries, except for Austria (-5.68%) and Greece (-1.13%). UK and Turkey showed the larger increase in PCOS incidence with a percentage change of 2.48% and 2.61% respectively.

**DISCUSSION**

This study indicates that PCOS prevalence in European countries and USA is about 6%, 20%, and 15% according respectively to the NIH1990, ESHRE/ASRM 2003, and AES-PCOS diagnostic criteria. The prevalence across areas was similar when using the same diagnostic criteria, thus supporting the validity of the estimates and indicating that in high-income European countries and USA the prevalence of PCOS is similar.

In previous reviews, the estimate of the worldwide prevalence of PCOS according to the NIH1990 criteria was consistent with our estimate (6% -7%) [3,4]. However, lower worldwide estimates were reported considering the Rotterdam (ESHRE/ASRM 2003) or AES-PCOS criteria. These differences may be due, at least in part, to the different geographic areas considered. Along this line, the estimates reported for the European countries are consistent with our results [3].

Three studies from the USA analysed data derived from health insurance claim databases [21,22] and health plan ambulatory visit database [20], where PCOS patients were identified by ICD-9 codes: the overall prevalence of PCOS was much lower than that reported in other studies using the more specific diagnostic criteria. A reason for the lower prevalence rate is that these estimates were based on electronic databases and on claim data, where an under-coding may be possible due to a limited number of diagnoses on a claim, and where PCOS symptoms could not be recognized and thus underreported. Therefore, PCOS prevalence in these studies is likely underestimated. Moreover, the validity of the ICD-9 codes used to identify PCOS diagnoses has not been yet established [21].

A low rate of physician-diagnosed PCOS prevalence was also reported in a study conducted in Turkey, but the prevalence of PCOS could be underestimated because in Turkey gynaecological visits are less frequent than in the USA or in other European countries [8].

A major interest of the present study was the analysis of the proportional frequency of the different PCOS phenotypes in different countries of the same geographic area.

Phenotype A, the “complete PCOS”, showed a higher prevalence in all the considered areas, followed by phenotypes D, C, and B. The prevalence of phenotype A was higher and that of C was lower in the USA than in Europe.

The presentation of PCOS does also not appear homogenous among European and USA populations. These differences are likely an interplay between genetic and environmental factors that affect the pathogenesis of PCOS and it can be expressed differently across different populations. For example,

obesity is more frequent in USA women than in European ones and in turn, obesity is associated with insulin resistance which is a determinant of polycystic ovarian morphology [57].

In our meta-analysis, the majority of studies reporting phenotype distribution were mainly based on women identified in a clinical setting and two studies only considered women in the general population [16,19]. Women with PCOS identified in the clinical settings tend to have a higher prevalence of the most severe PCOS phenotype A, suggesting that patients seeking medical attention had a more complete disorder [58].

Women from Turkey showed a higher proportion of phenotypes C and D (ovulatory and non-hyperandrogenic PCOS) and a lower proportion of so-called "classic" phenotypes in comparison to other populations from Southern Europe. These differences could be influenced by ethnicity, considering that Turkey also covers an Asiatic area, it could be also attributed to the lack of consensus on thresholds of phenotype definitions [59]. Moreover, the interaction between genetic and environmental factors could influence PCOS phenotypes distribution in different populations.

Some studies reported a relationship between phenotype distribution and socioeconomic factors: in an Italian cohort study, a higher prevalence of the "ovulatory" phenotype was related to a higher socioeconomic status [60]. However, we did not find marked differences in the frequency of phenotype C cases across countries.

We also considered the available data on the trend of the prevalence of PCOS over time. A general increase in PCOS prevalence was observed. Increasing clinical awareness of PCOS followed by more careful registration may have played a role. The strength of the national register-based study design lies in a large birth cohort, which reduces the risk of selection bias [25]. However, in this large database, the prevalence of PCOS tends to be underestimated. Moreover, a proportion of women with PCOS have fertility problems, thus they were not included in the population analysed [25].

Although the role of changing diagnostic criteria and increased clinical awareness of PCOS cannot be ruled out, these findings are consistent with the estimates of the analysis of the GBD 2017 [28] which suggested that the greatest increase in the age-standardized PCOS rates were observed in the areas with a high-middle socio-demographic index.

1. **Potential limitations and risk of bias.**

Among the potential limitations of our study, we have to take into account, due to the long period of many studies, not only changes in diagnostic criteria but also changes in laboratory assays for endocrine and metabolic assessment of PCOS diagnosis. The application of different clinical cut-offs in the diagnostic criteria could be a likely source of bias causing both over and under-diagnosis of

PCOS. In the systematic review, Skiba et al. underlined the broad clinical spectrum of PCOS and the lack of standardization of the parameters within each diagnostic criteria[4]

Previous studies suggested that PCOS prevalence, as well as phenotypes distribution, was different according to whether PCOS patients were identified in the referral population or in a more unselected setting [58], thus selection bias could have played a role in our meta-analysis. It should be underlined that the quality of the studies, assessed using the checklist of JBI Critical Appraisal tool [6], was good for most of the studies.

Moreover, when considering the prevalence of PCOS, the role of sex hormones should be considered: some studies included also women taking hormonal therapy, whereas in others the information was not checked. Lifestyle factors and differences in body composition also play a role in the estimates of PCOS prevalence.

A clear evaluation of the differences in the frequency of PCOS and its phenotypes may be important to understanding the impact of different lifestyles in genetically susceptible women on the development of this complex metabolic disorder. Since it is now recognised that PCOS phenotypes are derived from a mismatch between ancient susceptible genomic traits and modern lifestyle factors[61,62], describing the international differences is the basis for quantifying the impact of environmental exposures in different populations.

**CONCLUSION**

In conclusion, our results show that the prevalence of PCOS is similar in European countries and the USA, two high-income areas with similar availability of gynaecological health services. Interestingly, some differences in the frequency of the PCOS phenotypes emerged with a higher frequency of phenotype A and a lower one of phenotype C in the USA, but these findings are based on two studies only and need confirmation. Identifying the factors explaining these differences would lead to a better understanding of the etiopathogenesis and the clinical expression of PCOS.

**Acknowledgments**

This work was funded under CEFIC Long Range Research Initiative Contract number EMSG60. CEFIC was not involved in the preparation or approval of the manuscript. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the views of CEFIC.

## DATA AVAILABILITY

All data relevant to the study are included in the article or uploaded as supplementary information.

## References


[1] NATIONAL INSTITUTES OF HEALTH Evidence-based Methodology Workshop on Polycystic Ovary Syndrome. Final Report. Executive Summary 2012. https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/evidence-based-methodology-workshop-polycystic-ovary-syndrome-pcos

[2] Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human Reproduction 2018;33:1602–18. https://doi.org/10.1093/humrep/dey256.

[3] Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: A systematic review and meta-Analysis. Human Reproduction 2016;31:2841–55. https://doi.org/10.1093/humrep/dew218.

[4] Skiba MA, Islam RM, Bell RJ, Davis SR. Understanding variation in prevalence estimates of polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update 2018;24:694–709. https://doi.org/10.1093/humupd/dmy022.

[5] Sendur SN, Yildiz BO. Influence of ethnicity on different aspects of polycystic ovary syndrome: a systematic review. . Reprod Biomed Online 2021;42:799–818.

[6] Munn Z, MClinSc SM, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 2015;13:147–53. https://doi.org/10.1097/XEB.0000000000000054.

[7] Nikolakopoulou A, Mavridis D, Salanti G. Demystifying fixed and random effects meta-analysis. Evidence Based Mental Health 2014;17:53 LP – 57. https://doi.org/10.1136/eb-2014-101795.

[8] Akarsu RH, Alsac SY. Risks with gynaecological problems on the health of university students. Pak J Med Sci 2019;35:758–63. https://doi.org/10.12669/pjms.35.3.834.

[9] Asuncion Miryam, Calvo Rosa M, San Millan Jose L, Sancho Jose, Avila Sergio, Escobar-Morreale Hector F. A Prospective Study of the Prevalence of the Polycystic Ovary Syndrome in Unselected Caucasian Women from Spain. The Journal of Clinical Endocrinology & Metabolism 2000;85:2434–8.

[10] Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. Journal of Clinical Endocrinology and Metabolism, vol. 89, 2004, p. 2745–9. https://doi.org/10.1210/jc.2003-032046.

[11] Chang AY, Ayers C, Minhajuddin A, et al. Polycystic ovarian syndrome and subclinical atherosclerosis among women of reproductive age in the Dallas heart study. Clin Endocrinol (Oxf) 2011;74:89–96. https://doi.org/10.1111/j.1365-2265.2010.03907.x.

[12] Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al. A Survey of the Polycystic Ovary Syndrome in the Greek Island of Lesbos: Hormonal and Metabolic Profile. 1999.

[13] Eilertsen TB, Vanky E, Carlsen SM. Anti-Mullerian hormone in the diagnosis of polycystic ovary syndrome: Can morphologic description be replaced. Human Reproduction 2012;27:2494–502. https://doi.org/10.1093/humrep/des213.

[14] Greenwood EA, Yaffe K, Wellons MF, Cedars MI, Huddleston HG. Depression over the Lifespan in a Population-Based Cohort of Women with Polycystic Ovary Syndrome: Longitudinal Analysis. Journal of Clinical Endocrinology and Metabolism 2019;104:2809–19. https://doi.org/10.1210/jc.2019-00234.

[15] Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the Southeastern United States: A prospective study. Journal of Clinical Endocrinology and Metabolism 1998;83:3078–82. https://doi.org/10.1210/jc.83.9.3078.

[16] Lauritsen MP, Bentzen JG, Pinborg A, et al. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Müllerian hormone. Human Reproduction 2014;29:791–801. https://doi.org/10.1093/humrep/det469.

[17] Lindholm Å, Andersson L, Eliasson M, Bixo M, Sundström-Poromaa I. Prevalence of symptoms associated with polycystic ovary syndrome. International Journal of Gynecology and Obstetrics 2008;102:39–43. https://doi.org/10.1016/j.ijgo.2008.01.023.

[18] Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. vol. 51. 1999.

[19] Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Human Reproduction 2012;27:3067–73. https://doi.org/10.1093/humrep/des232.

[20] Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby J v., Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. Journal of Clinical Endocrinology and Metabolism 2006;91:1357–63. https://doi.org/10.1210/jc.2005-2430.

[21] Okoroh EM, Hooper WC, Atrash HK, Yusuf HR, Boulet SL. Prevalence of polycystic ovary syndrome among the privately insured, United States, 2003-2008. Am J Obstet Gynecol 2012;207:299.e1-299.e7. https://doi.org/10.1016/j.ajog.2012.07.023.

[22] Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 2013;6:1–13. https://doi.org/10.2147/clep.s37559.

[23] Sanchón R, Gambineri A, Alpañés M, Martínez-Garca MÁ, Pasquali R, Escobar-Morreale HF. Prevalence of functional disorders of androgen excess in unselected premenopausal women: A study in blood donors. Human Reproduction 2012;27:1209–16. https://doi.org/10.1093/humrep/des028.

[24] Ding T, Baio G, Hardiman PJ, Petersen I, Sammon C. Diagnosis and management of polycystic ovary syndrome in the UK: a retrospective cohort study. BMJ Open 2016;6:12461. https://doi.org/10.1136/bmjopen-2016.

[25] Mumm H, Kamper-Jørgensen M, Nybo Andersen AM, Glintborg D, Andersen M. Birth weight and polycystic ovary syndrome in adult life: A register-based study on 523,757 Danish women born 1973-1991. Fertil Steril 2013;99:777–82. https://doi.org/10.1016/j.fertnstert.2012.11.004.

[26] Valgeirsdottir H, Vanky E, Sundström-Poromaa I, et al. Prenatal exposures and birth indices, and subsequent risk of polycystic ovary syndrome: a national registry-based cohort study. BJOG 2019;126:244–51. https://doi.org/10.1111/1471-0528.15245.

[27] Goodarzi MO, Quiñones MJ, Azziz R, Rotter JI, Hsueh WA, Yang H. Polycystic ovary syndrome in Mexican-Americans: Prevalence and association with the severity of insulin resistance. Fertil Steril 2005;84:766–9. https://doi.org/10.1016/j.fertnstert.2005.03.051.

[28] Liu J, Wu Q, Hao Y, et al. Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. Hum Reprod 2021;36:1108–19. https://doi.org/10.1093/humrep/deaa371.

[29] Shroff R, Syrop CH, Davis W, van Voorhis BJ, Dokras A. Risk of metabolic complications in the new PCOS phenotypes based on the Rotterdam criteria. Fertil Steril 2007;88:1389–95. https://doi.org/10.1016/j.fertnstert.2007.01.032.

[30] Davis EM, Peck JD, Hansen KR, Neas BR, Craig LTB. Associations between vitamin Dlevels and polycystic ovary syndrome phenotypes. Minerva Endocrinol 2019;44:176–84. https://doi.org/10.23736/S0391-1977.18.02824-9.

[31] Adamska A, Łebkowska A, Krentowska A, et al. Ovarian Reserve and Serum Concentration of Thyroid Peroxidase Antibodies in Euthyroid Women With Different Polycystic Ovary Syndrome Phenotypes. Front Endocrinol (Lausanne) 2020;11. https://doi.org/10.3389/fendo.2020.00440.

[32] Aziz M, Sidelmann JJ, Faber J, et al. Polycystic ovary syndrome: Cardiovascular risk factors according to specific phenotypes. Acta Obstet Gynecol Scand 2015;94:1082–9. https://doi.org/10.1111/aogs.12706.

[33] Mumm H, Jensen DM, Sørensen JA, et al. Hyperandrogenism and phenotypes of polycystic ovary syndrome are not associated with differences in obstetric outcomes. Acta Obstet Gynecol Scand 2015;94:204–11. https://doi.org/10.1111/aogs.12545.

[34] Daan NMP, Louwers Y v., Koster MPH, et al. Cardiovascular and metabolic profiles amongst different polycystic ovary syndrome phenotypes: Who is really at risk? Fertil Steril 2014;102:1444-1451.e3. https://doi.org/10.1016/j.fertnstert.2014.08.001.

[35] Huijgen NA, Laven JSE, Labee CT, Louwers Y v., Willemsen SP, Steegers-Theunissen RPM. Are dieting and dietary inadequacy a second hit in the association with polycystic ovary syndrome severity? PLoS One 2015;10. https://doi.org/10.1371/journal.pone.0142772.

[36] MacKens S, Pareyn S, Drakopoulos P, et al. Outcome of in-vitro oocyte maturation in patients with PCOS: Does phenotype have an impact? Human Reproduction 2020;35:2272–9. https://doi.org/10.1093/humrep/deaa190.

[37] Cupisti S, Haeberle L, Schell C, et al. The different phenotypes of polycystic ovary syndrome: No advantages for identifying women with aggravated insulin resistance or impaired lipids. Experimental and Clinical Endocrinology and Diabetes 2011;119:502–8. https://doi.org/10.1055/s-0031-1277136.

[38] Dewailly D, Catteau-Jonard S, Reyss AC, Leroy M, Pigny P. Oligoanovulation with polycystic ovaries but not overt hyperandrogenism. Journal of Clinical Endocrinology and Metabolism 2006;91:3922–7. https://doi.org/10.1210/jc.2006-1054.

[39] Belosi C, Selvaggi L, Apa R, et al. Is the PCOS diagnosis solved by ESHRE/ASRM 2003 consensus or could it include ultrasound examination of the ovarian stroma? Human Reproduction 2006;21:3108–15. https://doi.org/10.1093/humrep/del306.

[40] Guastella E, Longo RA, Carmina E. Clinical and endocrine characteristics of the main polycystic ovary syndrome phenotypes. Fertil Steril 2010;94:2197–201. https://doi.org/10.1016/j.fertnstert.2010.02.014.

[41] Carmina E, Campagna AM, Lobo RA. A 20-year follow-up of young women with polycystic ovary syndrome. Obstetrics and Gynecology 2012;119:263–9. https://doi.org/10.1097/AOG.0b013e31823f7135.

[42] Moro F, Morciano A, Tropea A, et al. CD4+CD28null T lymphocyte frequency, a new marker of cardiovascular risk: Relationship with polycystic ovary syndrome phenotypes. Fertil Steril 2012;98:1609–15. https://doi.org/10.1016/j.fertnstert.2012.08.015.

[43] Romualdi D, di Florio C, Tagliaferri V, et al. The Role of Anti-Müllerian Hormone in the Characterization of the Different Polycystic Ovary Syndrome Phenotypes. Reproductive Sciences 2016;23:655–61. https://doi.org/10.1177/1933719115611751.

[44] Carmina E, Nasrallah MP, Guastella E, Lobo RA. Characterization of metabolic changes in the phenotypes of women with polycystic ovary syndrome in a large Mediterranean population from Sicily. Clin Endocrinol (Oxf) 2019;91:553–60. https://doi.org/10.1111/cen.14063.

[45] Panidis D, Tziomalos K, Misichronis G, et al. Insulin resistance and endocrine characteristics of the different phenotypes of polycystic ovary syndrome: A prospective study. Human Reproduction 2012;27:541–9. https://doi.org/10.1093/humrep/der418.

[46] Yilmaz M, Isaoglu U, Delibas IB, Kadanali S. Anthropometric, clinical and laboratory comparison of four phenotypes of polycystic ovary syndrome based on Rotterdam criteria. Journal of Obstetrics and Gynaecology Research 2011;37:1020–6. https://doi.org/10.1111/j.1447-0756.2010.01478.x.

[47] Cinar N, Harmanci A, Aksoy DY, Aydin K, Yildiz BO. Adrenocortical steroid response to ACTH in different phenotypes of non-obese polycystic ovary syndrome. J Ovarian Res 2012;5. https://doi.org/10.1186/1757-2215-5-42.

[48] Ozkaya E, Cakir E, Cinar M, et al. Is hyperandrogenemia protective for fibrocystic breast disease in PCOS. Gynecological Endocrinology 2012;28:468–71. https://doi.org/10.3109/09513590.2011.633658.

[49] Ates S, Sevket O, Sudolmus S, et al. Different phenotypes of polycystic ovary syndrome in Turkish women: Clinical and endocrine characteristics. Gynecological Endocrinology 2013;29:931–5. https://doi.org/10.3109/09513590.2013.819082.

[50] Sahmay S, Atakul N, Oncul M, Tuten A, Aydogan B, Seyisoglu H. Serum anti-mullerian hormone levels in the main phenotypes of polycystic ovary syndrome. European Journal of Obstetrics and Gynecology and Reproductive Biology 2013;170:157–61. https://doi.org/10.1016/j.ejogrb.2013.05.019.

[51] Bagir GS, Bakiner OS, Bozkirli E, Cavlak G, Serinsoz H, Ertorer ME. Body Mass Index below Obesity Threshold Implies Similar Cardiovascular Risk among Various Polycystic Ovary Syndrome Phenotypes. Medical Principles and Practice 2016;25:61–6. https://doi.org/10.1159/000440810.

[52] Bil E, Dilbaz B, Cirik DA, Ozelci R, Ozkaya E, Dilbaz S. Metabolic syndrome and metabolic risk profile according to polycystic ovary syndrome phenotype. Journal of Obstetrics and Gynaecology Research 2016;42:837–43. https://doi.org/10.1111/jog.12985.

[53] Çelik E, Türkçüoğlu I, Ata B, et al. Metabolic and carbohydrate characteristics of different phenotypes of polycystic ovary syndrome. Journal of the Turkish German Gynecology Association 2016;17:201–8. https://doi.org/10.5152/jtgga.2016.16133.

[54] Yıldırım E, Karabulut O, Yuksel UÇ, et al. Echocardiographic evaluation of diastolic functions in patients with polycystic ovary syndrome: A comperative study of diastolic functions in sub-phenotypes of polycystic ovary syndrome. Cardiol J 2017;24:364–73. https://doi.org/10.5603/CJ.a2017.0032.

[55] Işık Y, Telatar GY, Neşelioğlu S, Biçer C, Gürlek B. Evaluation of periodontal status in different phenotypes of polycystic ovary syndrome in untreated patients of early reproductive age: A case–control study. Journal of Obstetrics and Gynaecology Research 2020;46:459–65. https://doi.org/10.1111/jog.14179.

[56] Georgopoulos NA, Papadakis E, Armeni AK, Katsikis I, Roupas ND, Panidis D. Elevated serum androstenedione is associated with a more severe phenotype in women with polycystic ovary syndrome (PCOS). Hormones (Athens) 2014;13:213–21. https://doi.org/10.1007/BF03401335.

[57] Reid SP, Kao C-N, Pasch L, Shinkai K, Cedars MI, Huddleston HG. Ovarian morphology is associated with insulin resistance in women with polycystic ovary syndrome: a cross sectional study. Fertil Res Pract 2017;3. https://doi.org/10.1186/s40738-017-0035-z.

[58] Lizneva D, Kirubakaran R, Mykhalchenko K, al. Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis. Fertil Steril 2016;106:1510-1520.e2. https://doi.org/10.1016/j.fertnstert.2016.07.1121.

[59] Zhao Y, Qiao J. Ethnic differences in the phenotypic expression of polycystic ovary syndrome. Steroids 2013;78:755–60. https://doi.org/10.1016/j.steroids.2013.04.006.

[60] di Fede G, Mansueto P, Longo RA, Rini GB, Carmina E. Influence of sociocultural factors on the ovulatory status of polycystic ovary syndrome. Fertil Steril 2009;91:1853–6. https://doi.org/10.1016/j.fertnstert.2008.02.161.

[61] Parker J, O'brien C, Hawrelak J, Gersh FL. Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment. Int J Environ Res Public Health 2022;19. https://doi.org/10.3390/ijerph19031336.

[62] Escobar-Morreale HF, Luque-Ramírez M, San Millán JL. The Molecular-Genetic Basis of Functional Hyperandrogenism and the Polycystic Ovary Syndrome. Endocr Rev 2005;26:251–82. https://doi.org/10.1210/er.2004-0004.

**Figures Legends**

Figure 1. 2020 flow diagram for study selection.

Figure 2. Study-specific and pooled estimates (ES) for prevalence of PCOS, and corresponding 95% confidence intervals (CI), by geographic area according to different diagnostic criteria.

NIH 1990: National Institutes of Health
ESHRE/ASRM 2003: European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM)
AES-PCOS 2006: Androgen Excess Society (AES)
ICD-9: International Classification of Disease-Ninth Revision

Figure 3. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype A, and corresponding 95% confidence intervals (CI), by geographic area.

Figure 4. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype B, and corresponding 95% confidence intervals (CI), by geographic area.

Figure 5. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype C, and corresponding 95% confidence intervals (CI), by geographic area.

Figure 6. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype D, and corresponding 95% confidence intervals (CI), by geographic area.

**Tables Legends**

Table 1. Main characteristic of the selected studies on PCOS prevalence

Table 2. Characteristics of studies included in the meta-analysis on PCOS phenotypes frequency

# Prevalence of Polycystic Ovary Syndrome in European countries and USA: a systematic review and meta-analysis.

**ABSTRACT**

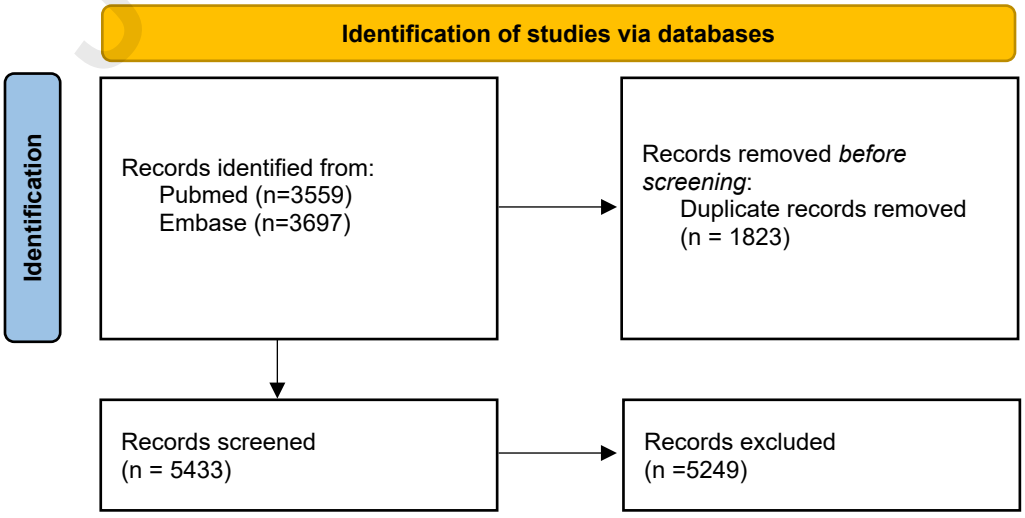
We conducted a systematic review and meta-analyses of the prevalence of Polycystic Ovary Syndrome (PCOS) and the frequency of its phenotypes in Europe and the USA, also focusing on temporal trends of the condition, to compare the PCOS prevalence among populations with a similar level of diagnostic resources availability and attitudes toward health problems, to improve

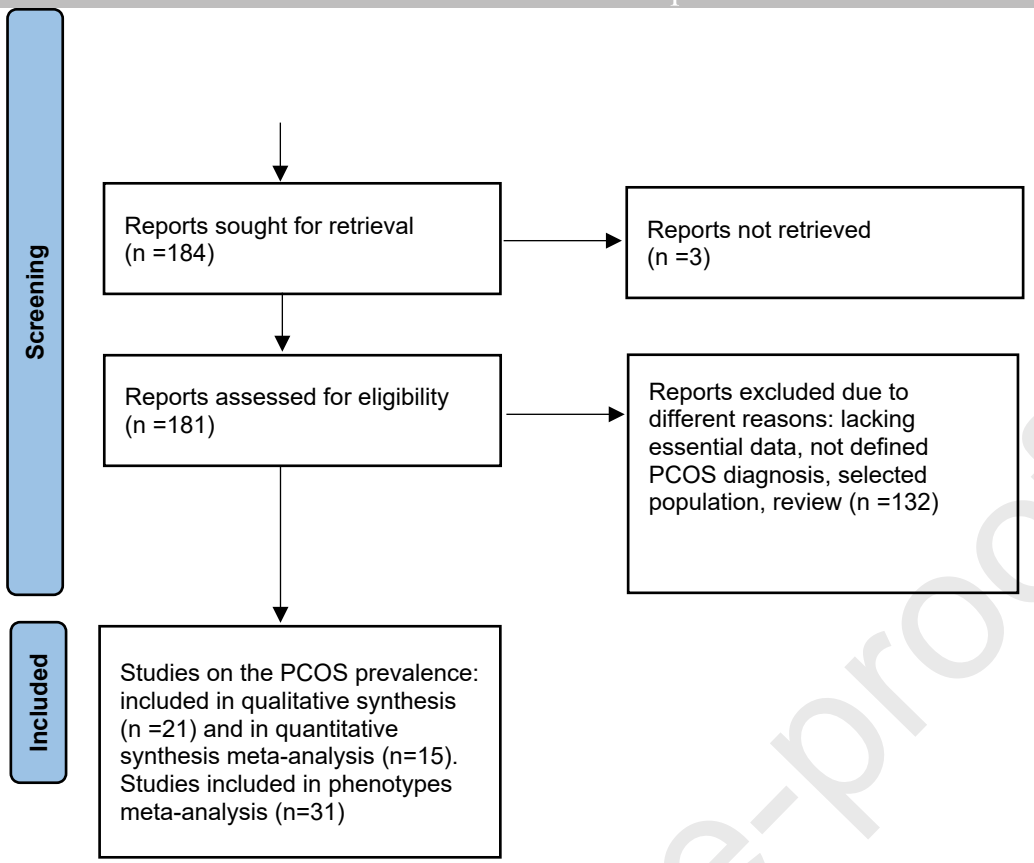
comparability of estimates. We considered Europe and USA, two high-income areas with these characteristics.

The overall PCOS prevalence according to the NIH1990, ESHRE/ASRM 2003, AES-PCOS diagnostic criteria was respectively 6.2 % (95%CI 5.3-7.0), 19.5 % (95%CI 17.3-21.6), and 15.0 % (95%CI 12.9-17.1), with no appreciable heterogeneity across geographic areas. Phenotype A, the "complete PCOS", showed higher prevalence in all areas (44.8%, 95%CI 40.3-49.3), followed by phenotype D, called "non-hyperandrogenic PCOS" (19.5%), phenotype C termed as "ovulatory PCOS" (16.2%), and phenotype B, presenting as phenotype A but without polycystic ovarian morphology (14.9%). In all the studies analysing temporal trends of PCOS, an increase in prevalence of PCOS was reported, due, at least in part, to changing diagnostic criteria.

The prevalence of PCOS is similar in European countries and the USA. Interestingly, some differences in the frequency of PCOS phenotypes emerged between the two areas with a higher frequency of phenotype A and a lower one of phenotype C in the USA. Recognizing the factors which explain these differences would lead to a better understanding of the etiopathogenesis and the clinical expression of PCOS.

Figure 1. 2020 flow diagram for study selection.



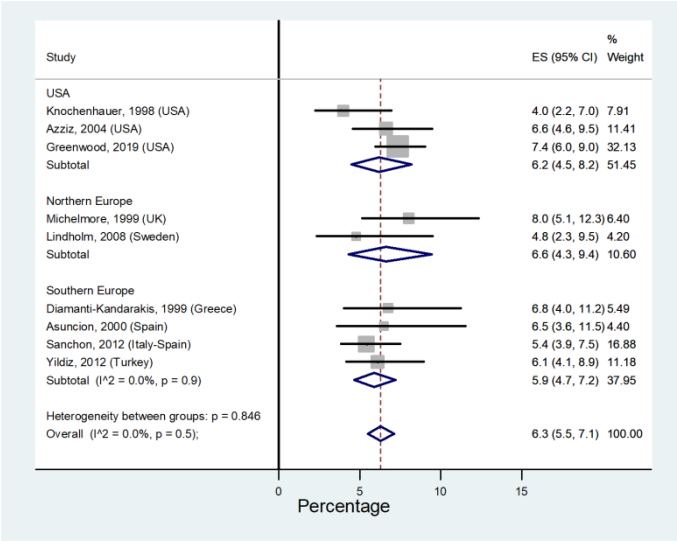


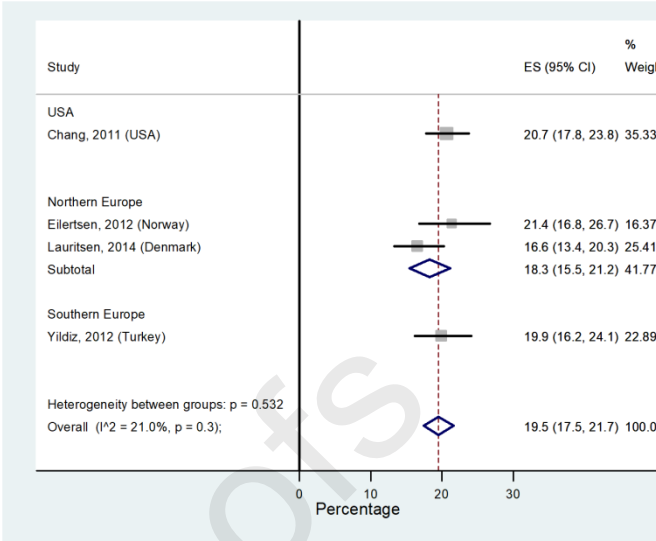

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

**Figure 2. Study-specific and pooled estimates (ES) for prevalence of PCOS, and corresponding 95% confidence intervals (CI), by geographic area according to different diagnostic criteria**

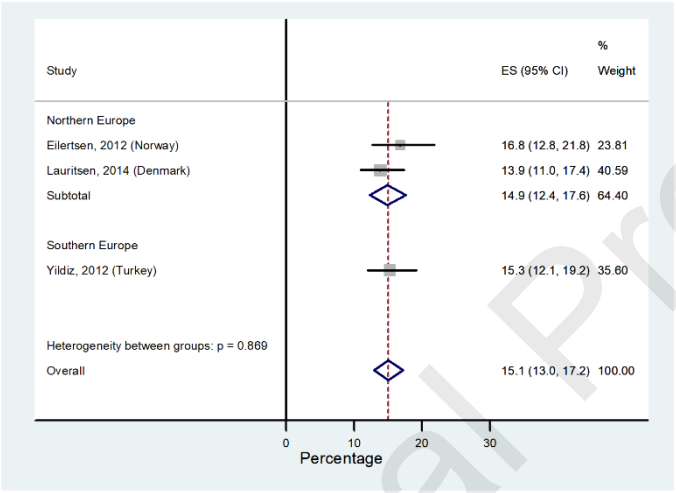
NIH1990 ESHRE/ASRM 2003

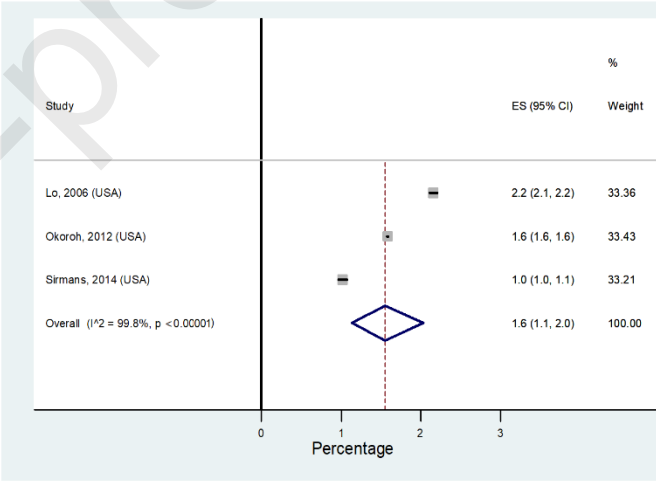



AES-PCOS 2006

ICD-9




NIH 1990: National Institutes of Health
ESHRE/ASRM 2003**:** European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM)
AES-PCOS 2006: Androgen Excess Society (AES)
ICD-9: International Classification of Disease-Ninth Revision

**Figure 3. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype A, and corresponding 95% confidence intervals (CI), by geographic area.**

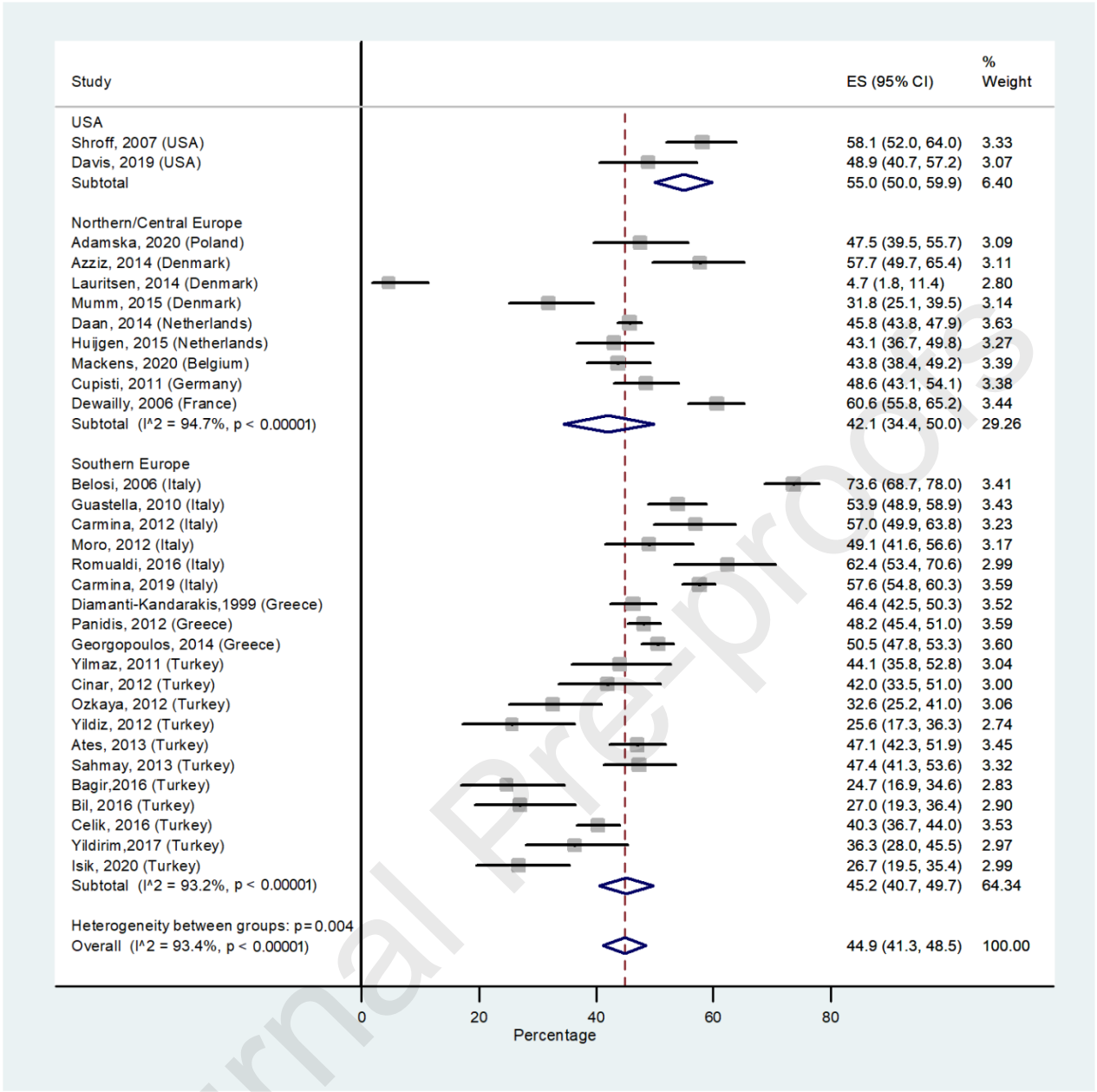



**Figure 4. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype B, and corresponding 95% confidence intervals (CI), by geographic area.**

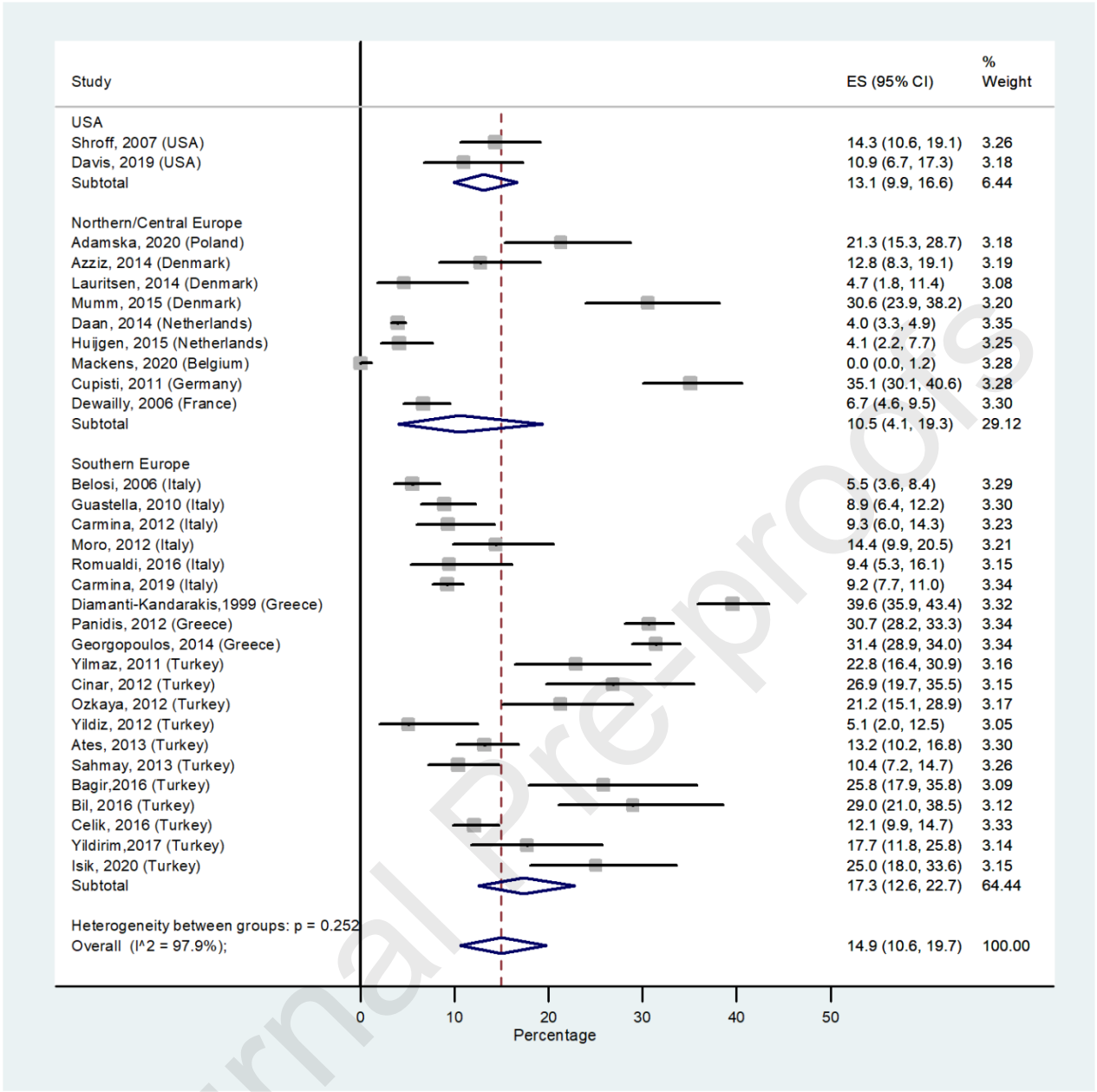



**Figure 5. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype C, and corresponding 95% confidence intervals (CI), by geographic area.**

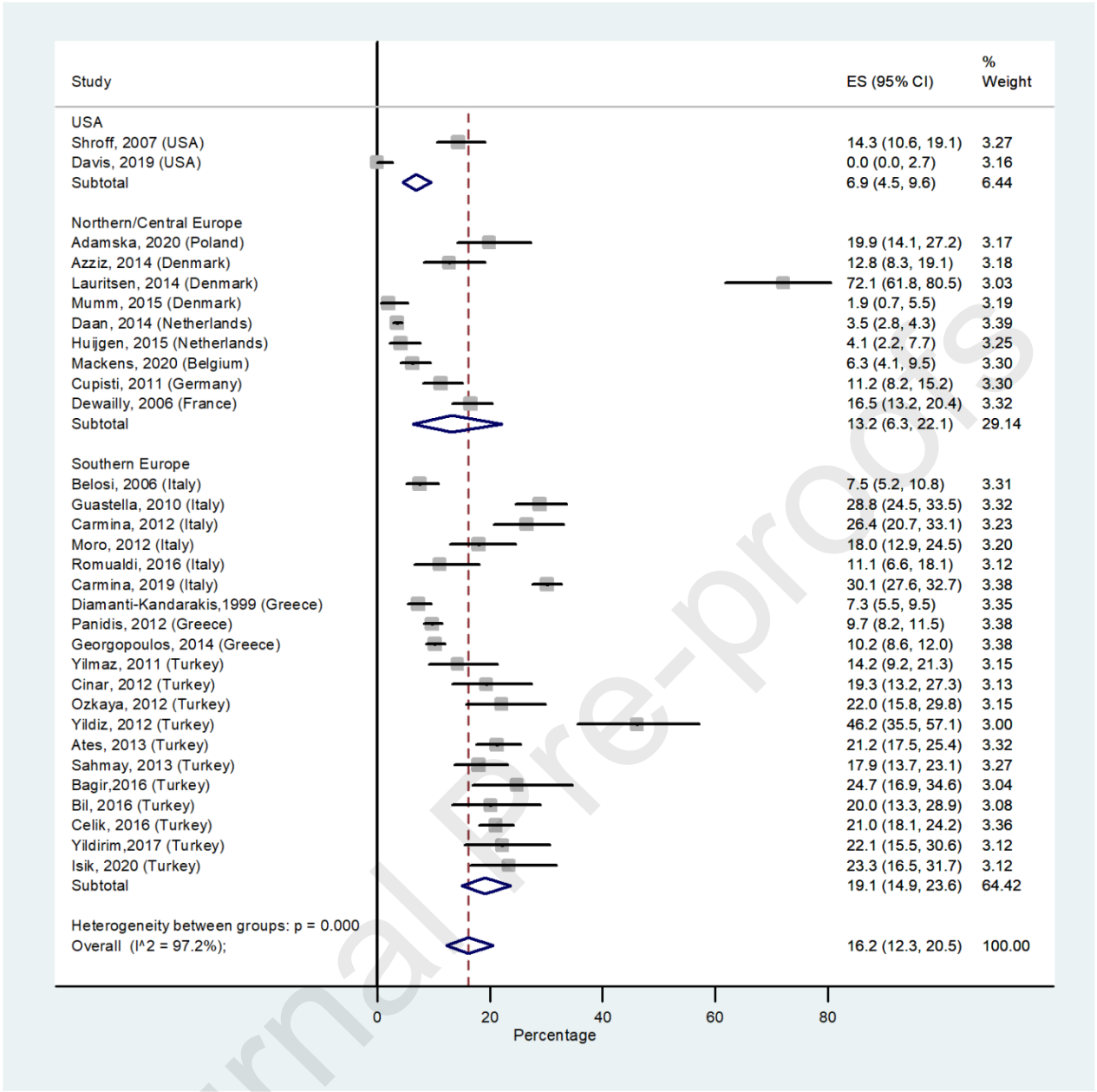
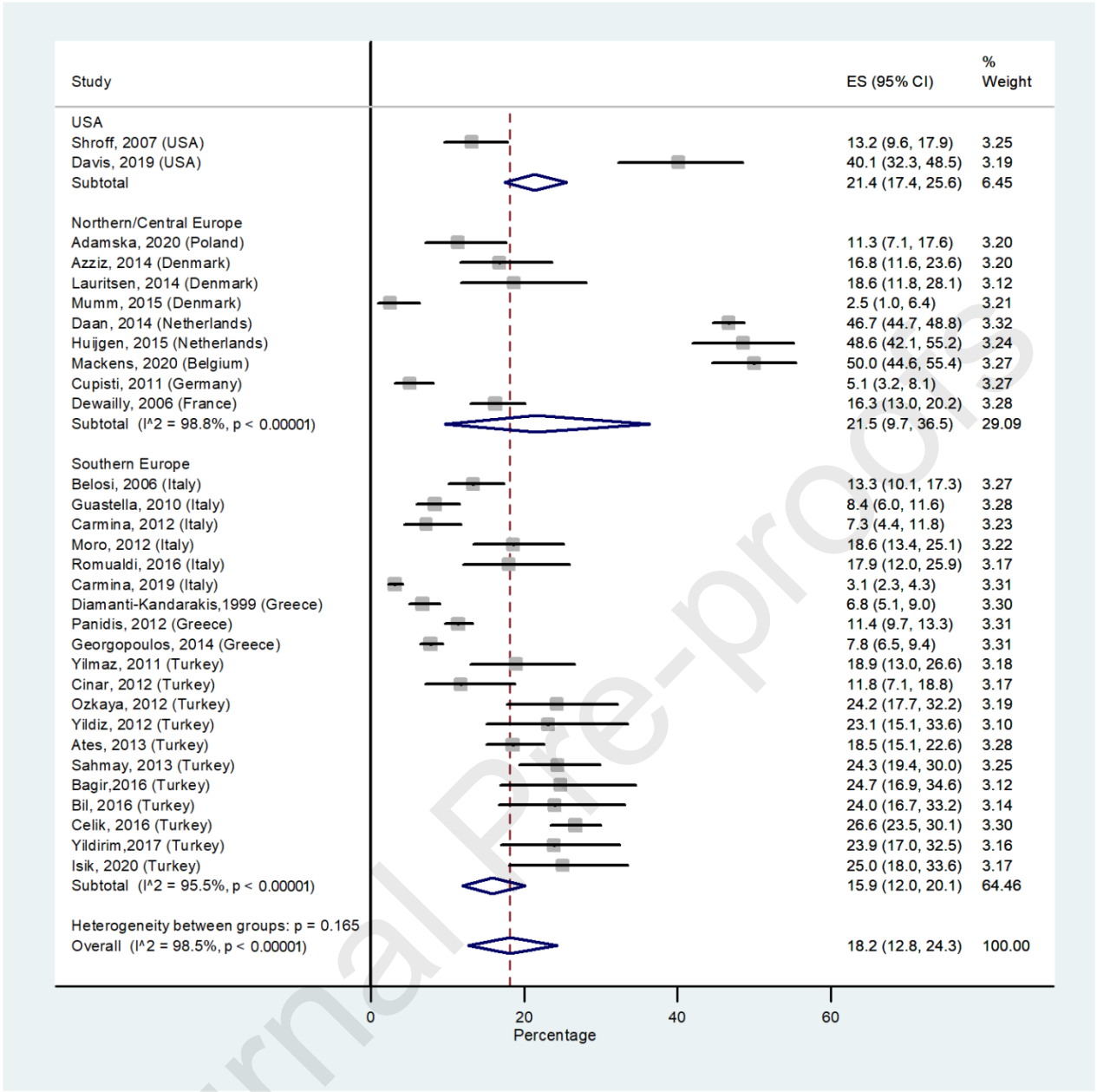



**Figure 6. Study-specific and pooled estimates (ES) for frequency of PCOS phenotype D, and corresponding 95% confidence intervals (CI), by geographic area.**




**Highlights**

- PCOS prevalence is similar in European countries and in the USA, two high-income areas with similar availability of gynaecological health services.
- A major interest of the present study was the analysis of the proportional frequency of the different PCOS phenotypes in different countries of the same geographic area.
- Phenotype A, the “complete PCOS”, showed the higher prevalence in all the considered areas, followed by phenotype D, C, and B. The prevalence of phenotype A was higher and that of C was lower in the USA than in Europe.

Table 1. Main characteristic of the selected studies on PCOS prevalence

| Author, year | Study design | Population | N | N PCOS | Age | PCOS prevalence ( | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | NIH1990 | ESHRE/ASRM 2003 | AES-PCO 2006 |
| mm, 2013 | National register-based cohort study | Female singleton children born 1973-1991 | 523757 | 3204 | | | | |
| itsen, 2014 | Cross-sectional study | Employees at Copenaghen Un. Hospital | 447 | 4/74/62 | 20-40 | | 16.6 | 13.9 |
| iu, 2021 | GBD 2017 | data from GBD study 2007-2017 | | | 15-49 | | | |
| nti-Kandarakis, 1999 | Cross-sectional study | Women invited for free medical examination | 192 | 13 | 17-45 | 6.8 | | |
| chón, 2012 | Multicenter survey | Blood donors from Spain and Italy | 592 | 32 | 18-49 | 5.4 | - | - |
| nción, 2000 | Cross-sectional study | Female blood donors | 154 | 10 | 33.1 ± 9.1 (18-45) | 6.5 | - | - |
| tsen, 2012B | Cross-sectional study | Women with prior preterm birth | 262 | -/56/44 | 34.9 | - | 21.4 | 16.8 |
| holm,2008 | Cross-sectional study | Women from population based survey (MONICA) | 147 | 7 | 25-39 | 4.8 | | |
| rsdottir, 2019 | National register-based cohort study | Female singleton children born 1982-1995 | 681123 | 3738 | | | | |
| diz, 2012 | Cross sectional study | Employed women | 392 | 24/78/60 | 18-45 | 6.1 | 19.9 | 15.3 |
| arsu, 2019 | Cross-sectional study | Female university students | 1305 | 46 | 19.7± 0.5 | | | |
| elmore, 1999 | Cross-sectional study | Volunteers * | 224 | -/18/- | 18-25 | 8 | | - |
| ng, 2016 | Retrospective cohort study | Cohort in primary care database (2004-2014) | 2087107 | 14290 | 15-45 | | | |
| enhauer,1998 | Cross-sectional study | Pre-employment medical assessment | 277 | 11 | 18-45 | 4 | - | - |
| zziz, 2004 | Cross-sectional study | Pre-employment medical assessment | 400 | 27 | 18-45 | 6.6 | - | - |
| darzi, 2005 | unseleceted consecutive women | Mexican American coronary Artery Disease (MACAD Project) | 156 | 20 | 34 ±8.6 | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Lo, 2006 | Retrospective study | Women receiving ambulatory care | 414298 | 8948 | 20-39 | | | |
| ang, 2011 | Cross-sectional study | Women of cohort of the Dallas Heart study(2000-2002) | 697 | 144 | 35-49 | | 19.6/20.7 | - |
| oroh, 2012 | Retrospective study | Women from Reuters Healthcare database (2003-2008) | 12171830 | 192936 | 18-45 | | | |
| hans, 2014 | Retrospective study | Louisiana Medicaid claims data | 143413 | 1689 | 15-45 | | | |
| nwood, 2019 | Cross-sectional study | Coronary artery risk development in young adult (CARDIA study) | 1127 | 83 | 20-32 | 7.4 | | |

NIH 1990: National Institutes of Health
ESHRE/ASRM 2003: European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM)
AES-PCOS 2006: Androgen Excess Society (AES)
ICD-9: International Classification of Disease-Ninth Revision

Table 2. Characteristics of studies included in the meta-analysis on PCOS phenotypes frequency

| Country | Author,Year | Period of recruitment | Setting | |
|---|---|---|---|---|
| USA | Shroff, 2007 | 2002-2005 | Department of Reproductive Endocrinology of the University | Re-eva |
| USA | Davis, 2019 | January 2008-June 2012 | Fertility clinic of the University | Wome |
| **Northern/Central Europe** | | | | |
| Poland | Adamska, 2020 | January 2016 - May 2019 | Department of Endocrinology, Diabetology of the University | Wome |
| Denmark | Lauritsen, 2014 | 2008-2010 | Fertility clinic of the University Hospital | Emplo |
| Denmark | Aziz, 2015 | April 2010 - February 2012 | Three University hospitals | Wome gineco |
| Denmark | Mumm, 2015 | 2003-2011 | Department of Obstetrics and Gynaecology of the University | Wome |
| Netherlands | Daan,2014 | January 2004 - May 2013 | Reproductive outpatient clinic of the University | Wome |
| Netherlands | Huijgen, 2015 | October 2007- March 2011 | Department of Obstetrics and Gynaecology of the University | Wome referre |
| Belgium | Mackens, 2020 | April 2014- January 2018 | ART patients | Wome matura |
| Germany | Cupisti, 2011 | January 2007 - December 2008 | Obstetrics and Gynaecological department of the University | Wome |

| | | | | |
|---|---|---|---|---|
| France | Dewailly, 2006 | 2000-2005 | Outpatient Department of reproductive endocrinology of the University | Wome hypera disorde |
| **Southern Europe** | | | | |
| Italy | Belosi, 2006 | n.a. | Department of Obstetrics and Gynecology of the University | All wor and/or hirsuti |
| Italy | Guastella, 2010 | 2004-2009 | Endocrine Unit, Department of Medicine of the University | Wome |
| Italy | Carmina, 2012 | 1985 - 1990 | Endocrinology Unit of the University | Wome hypera |
| Italy | Moro, 2012 | January 2006- Sptember 2011 | Unit of Human Reproductive pathophysiology of the University | Wome for hyp menstr |
| Italy | Romualdi, 2016 | January 2011-Sptember 2012 | Gynaecological outpatients | Wome clinical |
| Italy | Carmina, 2019* | July 2008 - June 2018 | Department of Mother and Children care of the University | Wome hypera disorde |
| Greece | Diamanti-Kandarakis, 1999 | 2003-2005 | Outpatient Department of reproductive endocrinology of two Universities | Wome hypera disorde |
| Greece | Panidis, 2012 | May 2004-May 2011 | Gynaecological Endocrinology Department of the University | Wome |
| Greece | Georgopoulos, 2014 | n.a. | Department of reproductive endocrinology of two Universities | Wome |
| Turkey | Yilmaz, 2011 | January 2007- August 2008 | Gynaecological department of the University | Wome |
| Turkey | Cinar, 2012 | January 2006 - December 2010 | Outpatient Endocrinology Clinic of the University | Wome sympto |
| Turkey | Ozkaya,2012 | May 2010-December 2010 | Department of Obstetrics and Gynaecology of the Hospital | Wome (oligom |
| Turkey | Yildiz, 2012 | December 2009- April 2010 | General Directorate of Mineral Research | Volunt based |
| Turkey | Ates,2013 | 2010 - 2012 | Department of Infertility and Endocrinology of the University | Wome |
| Turkey | Sahmay, 2013 | January 2008-November 2011 | Department of Reproductive Endocrinology of the University | Wome |
| Turkey | Bagir,2016 | February 2010 - June 2011 | Outpatient Endocrinology clinic of the University | Newly |
| Turkey | Bil, 2016 | September 2013 - July 2014 | Outpatient clinic of the Reproductive Endocrinology Division of the Hospital | Wome or hirsu |
| Turkey | Celik,2016 | April 2011 - August 2012 | Gynaecology Clinic of the University | Wome |
| Turkey | Yildirim,2017 | n.a. | Department of Cardiology and Department of Obstetrics and Gynecology of the Hospital | Wome |
| Turkey | Isik, 2020 | April 2018-December 2018 | **G**ynaecology polyclinic of the University | Newly |