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Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression

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BACKGROUND: Our prior meta-analyses demonstrated an increased prevalence of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) with polycystic ovary syndrome (PCOS), but with substantial clinical heterogeneity.

OBJECTIVE AND RATIONALE: We aimed to update our previous review to quantify the prevalence of IGT and T2DM in PCOS with only quality studies (good and fair quality). We also aimed to examine the contribution of parameters including ethnicity, obesity and method of diagnosing T2DM in explaining the observed heterogeneity in IGT and T2DM prevalence in PCOS.

SEARCH METHODS: We conducted a literature search (MEDLINE, CINAHL, EMBASE, clinical trial registries and hand-searching) up to June 2016 to identify studies reporting the prevalence of dysglycemia (IGT and T2DM) in women with and without PCOS. We included

studies where women with PCOS (defined according to original National Institute of Health) were compared to women without PCOS for the end-points of the prevalence of IGT or T2DM. We excluded case reports, case series, editorials, and narrative reviews. Studies where PCOS was diagnosed by self-report, or where IGT or T2DM were measured by fasting glucose, only were excluded. We assessed the methodological quality of the included studies using a priori criteria based on the Newcastle–Ottawa Scaling (NOS) for non-randomized studies. Data are presented as odds ratio (OR) (95% CI) with random-effects meta-analysis by Mantel–Haenszel methods. We assessed the contribution of demographic and clinical factors to heterogeneity using subgroup and meta-regression analysis.

OUTCOMES: We reviewed 4530 studies and included 40 eligible studies in the final analysis. On meta-analysis of quality studies, women with PCOS had an increased prevalence of IGT (OR = 3.26, 95% CI: 2.17–4.90) and T2DM (OR = 2.87, 95% CI: 1.44–5.72), which differed by ethnicity (for IGT, Asia: 5-fold, the Americas: 4-fold and Europe: 3-fold), was higher with obesity, and doubled among studies using self-report or administrative data for diagnosing diabetes. The ethnicity-related difference retained its significance for Asia and Europe in BMI-matched subgroups. Clear contributors to heterogeneity did not emerge in meta-regression.

WIDER IMPLICATIONS: Our findings underscore the importance of PCOS as a cause of dysglycemia with a higher prevalence of IGT and T2DM. They support the relevance of ethnicity and obesity and emphasize the need for accurate diagnostic methods for diabetes.

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Key words: polycystic ovary syndrome / impaired glucose tolerance / type 2 diabetes mellitus / meta-analysis / meta-regression

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder which can affect up to 18% women of reproductive age depending on the diagnostic criteria and population studied (March *et al.*, 2010). It is associated with a range of reproductive (hyperandrogenism, oligo or anovulation, infertility); metabolic (gestational diabetes mellitus (GDM), impaired glucose tolerance (IGT), type 2 diabetes (T2DM), cardiovascular disease (CVD), cardiovascular risk factors); and psychological (depression, anxiety, poor self-esteem, disordered eating, psychosexual dysfunction) features (Deeks *et al.*, 2010; Teede *et al.*, 2011a, 2011b; Palomba *et al.*, 2015; Zhao *et al.*, 2016; Moran *et al.*, 2010). Women with PCOS frequently demonstrate intrinsic insulin resistance (IR) which is inherent to PCOS (Diamanti-Kandarakis and Papavassiliou, 2006; Teede *et al.*, 2007; Stepto *et al.*, 2013; Cassar *et al.*, 2016). IR is suggested as one of the main pathophysiological features contributing to both reproductive and metabolic disturbances in PCOS. IR increases hyperandrogenism, through insulin increasing ovarian androgen production, either in isolation or synergistically with luteinizing hormone (Barbieri *et al.*, 1986), and reduces hepatic sex hormone-binding globulin (SHBG) production (Plymate *et al.*, 1988). Women with PCOS may also have an elevated prevalence of overweight and obesity (Lim *et al.*, 2012), which then confers extrinsic or lifestyle-related IR (Stepto *et al.*, 2013) and in turn worsens the reproductive, metabolic, and psychological features of the condition. While there is a recognized role of IR in contributing to the aetiology of PCOS, the complete etiology surrounding PCOS is not yet entirely understood.

PCOS and IR are associated with dysglycemia (American Diabetes, 2004; Alberti *et al.*, 2007; Joham *et al.*, 2014). PCOS may also contribute to worsened cardiovascular risk-profiles (Zhao *et al.*, 2016). Economic evaluations in the United States estimate that 40% of the economic costs of PCOS can be to attributed to T2DM (Azziz *et al.*, 2005). This rise in the adverse cardio-metabolic health of women underscores the considerable impact of PCOS on health outcomes and health care costs.

In 2010, our previous systematic review and meta-analysis compared the prevalence of IGT and T2DM among women with and without PCOS (Moran *et al.*, 2010). The meta-analysis reported a 4-fold increased prevalence of type 2 diabetes among women with PCOS which was independent, and additive to obesity. However, the study reported substantial clinical heterogeneity on pooled analysis. Given that there are significant ethnic variations in the frequency of obesity and insulin resistance among women with PCOS, it is likely that the prevalence of diabetes would also differ among women of distinct ethnic background. Moreover, there are demographic and clinical parameters, such as age, BMI, body composition, ethnicity, diagnostic criteria, markers of insulin resistance and reproductive hormones, which could confound or modify the association between PCOS and dysglycemia. The impact of these factors on the heterogeneity between studies in dysglycemia in PCOS is as yet unclear. The aim of this review was, therefore, to update the previous meta-analysis with a focus on quality studies and examine the contribution of demographic and clinical parameters, especially ethnicity and obesity, in explaining the observed heterogeneity in the prevalence of IGT and T2DM among women with and without PCOS.

Methods

Search strategy

This systematic review is an update and expansion of a previously published review (Moran *et al.*, 2010). We searched the following electronic databases to identify relevant published literature: Medline (1950–June 2016), Medline in-process, and other non-indexed citations: CINAHL (1937–June 2016), EMBASE (1980–June 2016), all EBM Reviews, including Cochrane Database of Systematic Reviews, American College of Physician (ACP) Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment and National Health Services (NHS) Economic Evaluation Database. We hand searched the bibliographies of relevant studies identified by the search strategy for identification of additional research. We also searched the International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/), which provides access to a central database containing the trial registration data sets provided by 16 different international registries, using the term PCOS

Table I MeSH terms.

- exp Polycystic Ovary Syndrome/
- Polycystic Ovar$.tw
- pco.tw or pcos.tw
- (sclerocystic adj3 ovar$).tw
- stein leventhal.tw
- or/1–5
- animals/not (animals/and humans/)
- 6 not 7
- diabet$.tw
- NIDDM.tw
- exp Diabetes Mellitus, Type 2/
- exp glucose intolerance/
- glucose intoleran$.tw
- impaired glucose toleran$.tw
- (obes$ adj diabet$).tw
- dm2.tw
- (non insulin$ depend$ or noninsulin$ depend$ or noninsulin? depend$ or non insulin?depend$).tw
- ((typ$ 2 or typ$II or typ$ ii) adj diabet$).tw
- ((keto?resist$ or non?keto$) adj diabet$).tw
- ((adult$ or matur$ or late or slow or stabl$) adj diabet$).tw
- (insulin$ defic$ adj relativ$).tw
- (exp obesity/or obes$.mp) and (exp diabetes mellitus/or Diabet$.mp)
- or/9–22
- exp Diabetes Insipidus/
- diabet$ insipidus.tw
- 24 or 25
- 23 not 26
- (insulin$ resistan$ adj3 syndrome$).tw
- metabolic$ syndrom$.tw or exp metabolic syndrome X/
- (pluri metabolic$ syndrom$ or plurimetabolic$ syndrom$).tw
- (syndrome$ adj x).tw
- or/28–31
- 8 and (27 or 32)

Unless otherwise stated, search terms were free text terms. MeSH, Medical Subject Heading for Medline; Exp, exploded; mp, title, original title, abstract, name of substance word, subject heading word; tx, text word; adj, adjacency; $, any character; *, substitute one or no characters.

to identify ongoing trials. A systematic search outlined in Table I, combining MeSH terms and text words, were developed using the OVID platform and translated to other databases as appropriate. This search is relevant for both this current review and an additional review on the prevalence of the metabolic syndrome in women with and without PCOS. The search strategy was limited to English language papers.

Inclusion criteria

According to a priori selection criteria, we included studies where women with PCOS were compared with women without PCOS for the end-points of the prevalence of IGT or T2DM. We included articles where PCOS was defined under the original National Institute of Health (NIH) criteria, as the presence of chronic anovulation and clinical 'and' 'or' biochemical signs of hyperandrogenism (with exclusion of other aetiologies, e.g. congenital adrenal hyperplasia) or the ESHRE/ASRM diagnostic features (Rotterdam ASRM/ESHRE-Sponsored PCOS Consensus Workshop Group, 2004). IGT and T2DM were defined by physician diagnosis, current treatment, history of T2DM (self-report) or oral glucose tolerance test (OGTT) measures.

Exclusion criteria

We excluded case reports, case series, editorials and narrative reviews. We also excluded studies where PCOS was self-reported or studies where IGT or T2DM were measured by fasting glucose only. To avoid selection bias, two reviewers (from N.S.K., C.L.H., L.J.M. and M.B.K) identified and selected articles that met the inclusion criteria. Disagreements between them were discussed and resolved by consensus or discussion with a third reviewer (L.J.M.).

Data extraction

We extracted data on the number of cases of IGT and T2DM and general study and demographic characteristics including ethnicity, weight, waist-hip ratio (WHR), waist circumference (WC), BMI, BMI-matching and WHR/WC matching, diagnostic criteria used for PCOS, IGT or T2DM, location, year of publication, method of diagnosis, selection criteria and age of participants. As most of the studies did not accurately report on ethnicity of the study population, the country in which the study was conducted was used as a proxy for ethnic origin. We used the listing of countries of the United Nations prepared by the Department of General Assembly Affairs and Conference Services of the United Nations Secretariat as a guide to classifying countries into ethnic groups. For the eligible studies in this review, Asia included China, India, Iran, Thailand, Taiwan and Turkey; the Americas included Brazil, Chile and United States of America (USA); Australia and New Zealand included Australia; and Europe included Austria, Czech Republic, Denmark, Greece, Italy, Norway, Poland, Romania, Spain, Sweden and United Kingdom (UK). We also extracted data on clinical parameters including reproductive hormones (total testosterone and free androgen index (FAI)), surrogate markers of insulin resistance (fasting insulin, fasting glucose, homoeostasis model assessment (HOMA), post OGTT insulin response), SHBG, lipid profile (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG)), blood pressure (systolic and diastolic) and C-reactive protein (CRP). Two reviewers (from L.J.M., N.S.K., C.L.H. and M.B.K.) independently extracted the data from all included studies and a third reviewer (S.D.C.) re-checked the extracted data. Any disagreements between them were discussed and resolved by consensus or discussion with a fourth reviewer (L.J.M.).

Critical appraisal

Two reviewers (from L.J.M., C.L.H., N.S.K. and M.B.K.) independently assessed the methodological quality of the included studies using a priori criteria based on the Newcastle–Ottawa Scaling (NOS) for nonrandomized studies (Wells et al., 2011) (Supplementary Table SI). The criteria assessed the representativeness of participants within the PCOS and control groups, comparability of participants by BMI and age, validity of diagnostic criteria and outcome measurement, withdrawals and losses to follow-up and the presence of selective reporting. Each item within the NOS assessment criteria was assigned a point each. We categorized studies as either good quality or fair quality if they scored greater than one in all assessment domains and low or poor quality if they scored a one or zero in the selection or outcome domain or a zero in the comparability domain (Supplementary Table SI). Disagreements in scoring between individual reviewers were discussed and resolved by consensus and discussion with a third reviewer (L.J.M.). We considered good and fair quality studies as methodologically higher quality studies. A meta-analysis conducted to evaluate differences in impact size by analytical methods showed that results significantly varied when using poor quality studies in a meta-analysis (Stroup *et al.*, 2000; Dechartres *et al.*, 2014). We therefore included all eligible studies in the systematic review,

whereas we included only good quality and fair quality studies in the meta-analysis and meta-regression to provide a robust quantitative assessment.

Outcomes of interest

The primary a priori end-point was odds of the prevalence of IGT or T2DM in women with PCOS compared with women without PCOS. The secondary a priori end-point was to explore the influence of demographic and clinical variables in explaining heterogeneity for the prevalence of IGT and T2DM in women with and without PCOS. These were explored through subgroup analysis for the variables of ethnicity, BMI-matching, BMI and WHR/WC matching, lean-matching, and method of diagnosis of IGT/T2DM. We explored the effect of continuous variables, such as age, weight, BMI, WC, WHR, lipids including total cholesterol, HDL, LDL, TG, CRP, surrogate markers of insulin resistance (fasting insulin, fasting glucose, HOMA, FAI, post OGTT insulin response) and reproductive hormones (total testosterone, SHBG) SBP (systolic blood pressure), and DBP (diastolic blood pressure), through meta-regression.

Statistical analysis

The dichotomous outcome measure was the proportion (prevalence) of patients with IGT or T2DM. Data are presented as odds ratio (OR) (95% CI). I^2 was used to assess heterogeneity with significance set at $I^2 \geq 50\%$. We conducted random-effects meta-analyses modelling (Mantel–Haenszel methods) to calculate a pooled estimate of IGT and T2DM prevalence. We then subgrouped after stratification of studies into relevant categories. For meta-regression, the relative difference in continuous variables was expressed by the ratio of their mean value in women with PCOS compared to women without PCOS for each study. We assessed the effect of these variables in explaining heterogeneity for the prevalence of IGT or T2DM through restricted maximum likelihood (REML)-based random-effects meta-regression. We performed univariable meta-regression analyses first. Variables that were significant at ≤ 0.05 level were considered significant confounders. We estimated the percentage of between-study variance explained by the model (tau^2) with Knapp-Hartung modification. We could not perform multivariable meta-regression as there were insufficient studies reporting outcomes of interest. We used STATA (TX, 14.0) for conducting all analyses.

Results

Characteristics of included studies

The search yielded 4530 citations. We removed 270 duplicate articles, with 4260 articles screened. Using a priori selection criteria, we excluded 4010 studies based on screening of title and abstract and identified 250 for assessment of full text. We excluded 164 articles based on the full-text assessment: 25 articles based on selective selection of controls; 47 based on exclusion criteria for IGT or T2DM; 40 based on lack of complete reporting on IGT 'and' 'or' T2DM; 18 based on no comparison with a healthy control group, 17 based on article type; 15 based on PCOS diagnosis not being consistent with ESHRE/ASRM/NIH criteria; one based on language of the report being non-English; and one based on the use of a non-standard diagnostic method for classifying IGT/T2DM (Fig. 1).

We included 86 full-text eligible studies in our final analysis. We report on 40 studies for the current meta-analysis of IGT and T2DM. Characteristics of included studies are reported in Table II and Supplemental Table SII. All included studies were observational employing a cross-sectional ($n = 31$), case–control ($n = 1$) and cohort ($n = 8$) study design. Of the included studies, 24 used a diagnosis of PCOS consistent with the NIH criteria and 16 with the ESHRE/ASRM criteria. All studies assessed post-menarcheal and pre-menopausal women except six which assessed adolescents (Sawathiparnich *et al.*, 2005; Coviello *et al.*, 2006; Leibel *et al.*, 2006; Fulghesu *et al.*, 2010; Angioni *et al.*, 2011; Huang *et al.*, 2010). Most of the studies assessed overweight and obese women with PCOS except six studies which also assessed lean sub groups (Ciampelli *et al.*, 1998; Dos Reis *et al.*, 1995; Liang *et al.*, 2012; Faloia *et al.*, 2004; Attaoua *et al.*, 2008; Vrbikova *et al.*, 2009). The majority of the studies included in the update were out-patient based except for one which was conducted in a community setting (Boyle *et al.*, 2015). A similar number of studies were conducted from the Americas ($N = 15$) and Europe ($N = 14$), with nine studies from Asia and two studies from Australia and New Zealand.

Study quality

Out of 40 studies included in the systematic review, 14 studies were of good quality, 7 were of fair quality, and 19 studies were of poor quality. Furthermore, eight studies in this review were found to have a high risk of detection bias, 10 studies had a high risk of selection bias, and 10 studies had poor comparability among cases and controls (Supplementary Table SI).

Prevalence of IGT

For IGT, 15 studies provided data for the combined analysis. Women with PCOS had an increased prevalence of IGT compared to women without PCOS (OR = 3.26, 95% CI: 2.17–4.90) with minimal statistical heterogeneity ($I^2 = 11.3\%$, $P = 0.327$) (Fig. 2A).

Subgroup analysis for IGT by demographic variables and study quality is reported in Table III. All ethnic groups including women from Asia, the Americas, and Europe, showed an increased prevalence of IGT among women with PCOS. Women from the Asian sub-continent and the Americas showing the highest risk (5.2-fold and 4.4-fold, respectively) whereas European women had a 2.6-fold increased prevalence of IGT. When the analysis was limited to BMI-matched studies, the significantly increased risk of IGT among women was retained for Europe (1.8-fold 95% CI (1.09, 3.05)) and Asia (3.2-fold, 95% CI: 1.27, 7.87), but lost for women from the Americas (5.3-fold, 95% CI: 0.63, 44.0).

Subgroup matching based on anthropometry (BMI, WC and WHR) showed an increased prevalence of IGT among women with PCOS in BMI-matched (2.1-fold), non-BMI matched (4.8-fold), lean-matched (4.4-fold), overweight or obese matched (2.5-fold) and WHR/WC matched subgroups (1.3-fold; non-significant). We could not conduct any subgroup analysis by the method of IGT diagnosis as only one study reported use of retrospective review of administrative medical code as a means of diagnosing IGT.

Meta-regression analyses were conducted to further explore the impact of continuous demographic and clinical variables in explaining heterogeneity for IGT prevalence (Table IV). For IGT, the REML estimate of the between-study variance (t^2) when no covariates were present in the model was 0.21. The regression coefficient for total cholesterol was borderline significant ($P = 0.06$) on univariable analysis. The REML estimate for the between-study variance was reduced from 0.21 to 0.02 indicating the percentage of between-study heterogeneity

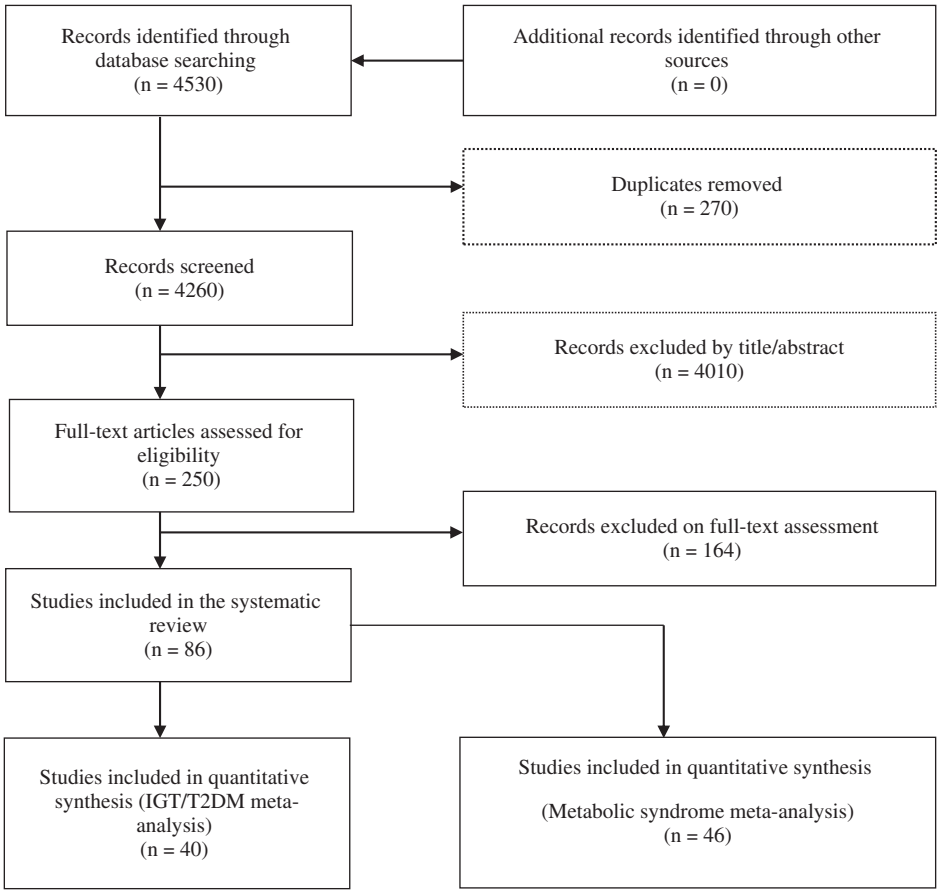

Figure 1 Flow chart for systematic review and meta-analysis.

explained by total cholesterol to be 92.6%. As none of the clinical or demographic variables was significant, we could not conduct multivariable meta-regression analysis.

Prevalence of type 2 diabetes

For T2DM, 12 studies of women generally aged around 30 years, provided data for the combined analysis. Overall, in quality studies women with PCOS had an increased prevalence of T2DM compared to women without PCOS (OR 2.87; 95% CI: 1.44–5.72) on combined meta-analysis (Fig. 2B). There was substantial statistical heterogeneity present (I^2 = 85.9%; $P < 0.001$) among the studies.

Subgroup analysis for T2DM is reported in Table III. Women from Asia and the Americas presented with a 4.4- and 4.7-fold increased prevalence of T2DM among women with PCOS compared to women without, while there were no significant differences in the prevalence of T2DM among European women with and without PCOS, although the numbers were small (4 studies) (63/650 vs 259/1930, respectively). When we restricted the analysis to BMI-matched studies, we no longer observed significant differences in the risk for T2DM among women with PCOS from Asia, the Americas and Europe, although numbers affected by T2DM in these subgroups was relatively small.

There was an increased risk of T2DM in non-BMI matched studies (4.7-fold), non-BMI and non-WHR/WC matched studies (3.1-fold) and non-lean (obese/overweight matched) populations (2.8-fold). There were no significant differences in the risk of T2DM among women with compared to without PCOS among subgroups matched by BMI or BMI and WHR/WC, although participant numbers in this subgroup analysis were relatively small (n = 73/1023 and n = 259/2098 (7 studies) for BMI matched and n = 1/62 and n = 3/102 (two studies) for WHR/WC matched respectively). No subgroup analysis could be conducted for studies by lean participants as there was only one study meeting this criterion. Studies that diagnosed T2DM prospectively by a blood-based technique had a 2.4-fold increased prevalence compared to a 4.7-fold increased prevalence among studies that identified diabetes by self-report/by review of medical or administrative records.

Meta-regression analyses to determine sources of heterogeneity for T2DM are reported in Table IV. For T2DM, the REML estimate of the between-study variance (t^2) when no covariates were present in the model was 0.34. None of the variables, including BMI and WHR/WC examined on univariable analysis, explained the between-study heterogeneity observed on pooled analysis.

Discussion

We report an update and expansion of our previous systematic review and meta-analysis examining the prevalence of IGT and T2DM in women with and without PCOS (Moran *et al.*, 2010). The

Table II Characteristics of included studies assessing IGT and T2DM in women with and without PCOS.

Study	PCOS	Controls	Location	Study quality	IGT/T2DM definition
Alvarez-Blasco et al. (2006)	N = 32; NIH; age = 26.0 years; BMI = 34.8 kg/m^2	N = 72; age = 32.0 years; BMI = 35.2 kg/m^2	Europe	Good quality	Not stated
Apridonidze et al. (2005)	N = 106; NIH; age = (29.1–31.0) years; BMI = 33.7-39.2 kg/m^2	NHANES III, age/BMI; details not given	Americas	Low quality	Retrospective from medical records
Attuoua et al. (2008)	N = 207; ESHRE; age = (23.1–26.3) years; BMI = 23.0-34.9 kg/m^2	N = 100; age = 34.1 years; BMI = 22.2 kg/m^2	Europe	Good quality	ADA (2006)
Bhattacharya (2009)	N = 264; NIH; age = 23.1 years; BMI = 26.8 kg/m^2	N = 116; age = 25.7 years; BMI = 24.6 kg/m^2	Asia	Low quality	WHO
Boudreaux et al. (2006)	N = 97; NIH; age = 38.0 years; BMI = 31.6 kg/m^2	N = 95; age = 40.0 years; BMI = 26.2 kg/m^2	Americas	Low quality	Fasting glucose ≥7 mmol/L or doctor diagnosis
Ciampelli et al. (1998)	N = 35; NIH; age = (21–36) years; BMI not stated	N = 11; age = (28–30) years; BMI = not stated	Europe	Low quality	NDG
Cibula et al. (2000)	N = 28; NIH; age = 51.9 years; BMI = 28.0 kg/m^2	N = 752; age = 51 years; BMI = 28.2 kg/m^2	Europe	Low quality	Fasting glucose ≥7 mmol/L, current medical treatment
Diamanti-Kandarakis et al. (2005)	N = 29; NIH; age = 25.8 years; BMI = 27.2 kg/m^2	N = 22; age = 28.1 years; BMI = 23.3 kg/m^2	Europe	Fair quality	OGTT, not stated
Dos Reis (1995)	N = 29; NIH; age = (18–37) years; BMI = not mentioned; N = 14 lean, N = 15 obese	N = 19; age = (18–37) years; BMI = not mentioned; N = 10 lean, N = 9 obese	Americas	Low quality	NDG, WHO
Dunaif et al. (2001)	N = 14; NIH; age = 29 years; BMI = 40.5 kg/m^2	N = 12; age = 30 years; BMI = 40.5 kg/m^2	Americas	Good quality	WHO
Echiburu et al. (2008)	N = 159; NIH; age = 24.3 years; BMI = 28.7 kg/m^2	N = 93; age = 24.6 years; BMI = 25.5 kg/m^2	Americas	Good quality	WHO
Faloia et al. (2004)	N = 50; NIH; age = 22.0 years; BMI N = 23 lean 22.0 kg/m^2, N = 27 overweight 32.0 kg/m^2	N = 20; age = 26.0 years; BMI N = 12 lean 20.0 kg/m^2, N = 8 overweight 37.0 kg/m^2	Europe	Low quality	WHO
Legro et al. (2005)	N = 71; NIH; age = (27.0–29.6) years; BMI = (35.7-38.7) kg/m^2	N = 23; age = 36.2 years; BMI = 29.3 kg/m^2	Americas	Low quality	ADA/WHO
Leibel et al. (2006)	N = 36; ESHRE/ASRM; age = 16.0 years; BMI = (30.3-37.9) kg/m^2	N = 21; age = 15.2 years; BMI = 24.9 kg/m^2	Americas	Low quality	ADA
Lo et al. (2006)	N = 11, 035; NIH; age = 30.7 years; BMI = 67% obese	N = 55, 175; age = 30.8 years; BMI = 31.4 kg/m^2	Americas	Fair quality	Outpatient visits
Marquez et al. (2008)	N = 50; NIH; age = 28.8 years; BMI = 33.3 kg/m^2	N = 70; age = 28.6 years; BMI = 23.4 kg/m^2	Americas	Fair quality	Fasting glucose ≥7 mmol/L or history of T2DM
Moini and Eslami (2009)	N = 273; ESHRE/ASRM; age = 27.9; BMI = 27.9 kg/m^2	N = 276; age = 31.1 years; BMI = 25.6 kg/m^2	Asia	Fair quality	Self-report
Phy et al. (2004)	N = 7; NIH; age = 30.9 years; BMI = 30.9 kg/m^2	N = 18; age = 31.1 years; BMI = 25.0 kg/m^2	Americas	Low quality	ADA
Rajkhowa et al. (1996)	N = 72; ESHRE/ASRM; age = 26.0 years; BMI = 31.6 kg/m^2	N = 39; age = 30.0 years; BMI = 25.9 kg/m^2	Europe	Fair quality	WHO
Sawathiparnich (2005)	N = 6; NIH; age = 14.1 years; BMI = 37.4 kg/m^2	N = 6; age = 14.5 years; BMI = 34.2 kg/m^2	Asia	Low quality	Medical records
Shaw et al. (2008)	N = 104; NIH; age = 62.5 years; BMI = 31.1 kg/m^2	N = 286; age = 65.8 years; BMI = 28.4 kg/m^2	Americas	Low quality	Retrospective from medical records/prior history/ medication use
Sir-Petermann et al. (2004)	N = 146; NIH; age = 22.0 years; BMI = 29.0 kg/m^2	N = 97; age = 24.0 years; BMI = 24.8 kg/m^2	Americas	Low quality	WHO
Yarali et al. (2001)	N = 30; NIH; age = 27.9 years; BMI = 27.3 kg/m^2	N = 30; age = 31.4 years; BMI = 25.0 kg/m^2	Asia	Fair quality	WHO
Valderhaug et al. (2015)	N = 312; NIH; age = (33-36) years; BMI = (42.8–44.8) kg/m^2	N = 1588; age = (35-39) years; BMI = (43.2–44.4) kg/m^2	Europe	Good quality	Prior history, fasting plasma glucose ≥7.0 mmol/L or an HbA1c ≥6.5%

Continued

Table II *Continued*

Study	PCOS	Controls	Location	Study quality	IGT/T2DM definition
Zhao *et al.* (2010)	*N* = 818; ESHRE/ASRM; age = 25.7 years; BMI = not reported	*N* = 717 age = 30.5 years; BMI = not reported	Asia	Good quality	ADA
Ozegowska and Pawelczyk (2015)	*N* = 168; ESHRE/ASRM; age = 27.0 years; BMI = 24.2 kg/m^2	*N* = 110; age = 28.5 years; BMI = 20.5 kg/m^2	Europe	Low quality	ADA
Li *et al.* (2012)	*N* = 56; ESHRE/ASRM; age = 17.6 years; BMI = 22.0 kg/m^2	*N* = 26; age = 17.4 years; BMI = 19.7 kg/m^2	Asia	Fair quality	ADA
Hudecova *et al.* (2011)	*N* = 84; ESHRE/ASRM; age = 43.0 years; BMI = 26.2–29.2 kg/m^2	*N* = 87; age = 43.7 years; BMI = 25.6 kg/m^2	Europe	Good quality	WHO
Lerchbaum *et al.* (2011)	*N* = 611; NIH; age = 27.0 years; BMI = 24.5 kg/m^2	*N* = 139; age = 30 years; BMI = 24.2 kg/m^2	Europe	Good quality	ADA
Nur *et al.* (2009)	*N* = 101; ESHRE/ASRM; age = 15.3 years; BMI = 33.2 kg/m^2	*N* = 40; age = 14.6 years; BMI = 32.4 kg/m^2	Americas	Good quality	Medical records
Huang *et al.* (2010)	*N* = 128; ESHRE/ASRM; age = 18.0 years; BMI = 20.0 kg/m^2	*N* = 40; age = 19.0 years; BMI = 19.6 kg/m^2	Asia	Good quality	ADA
Glintborg *et al.* (2015)	*N* = 1217; ESHRE/ASRM; age = 29.3 years; BMI = 27.3 kg/m^2	*N* = 57, 483; age = 30.6 years; BMI = not stated	Europe	Low quality	Self-reports and use of medications
Hossain *et al.* (2011)	*N* = 34; NIH: Standard clinical definitions; age = 38.6 years; BMI = 45.4 kg/m^2	*N* = 32; age = 38.4 years; BMI = 44.6 kg/m^2	Americas	Low quality	WHO
Liang *et al.* (2012)	*N* = 220; ESHRE/ASRM; age = 26.9 years; BMI = 25.3 kg/m^2	*N* = 70; age = 28.5 years; BMI = 24.9 kg/m^2	Asia	Good quality	NDDG
Fulghesu *et al.* (2010)	*N* = 71; ESHRE/ASRM; age = 18.6 years; BMI = 24.0 kg/m^2	*N* = 94; age = 18.1 years; BMI = 22.6 kg/m^2	Europe	Good quality	NDDG
Boyle *et al.* (2015)	*N* = 35; NIH; age = 32.0 years; BMI = 33.4 kg/m^2	*N* = 74; age = 33.0 years; BMI = 23.8 kg/m^2	Australia and New Zealand	Good quality	2-h plasma glucose 11.1 mmol/L
Hart and Doherty (2015)	*N* = 2566; NIH: Hospital administrative codes; age = 27.9 years; BMI = not stated	*N* = 25, 660; age/BMI = not stated	Australia and New Zealan	Low quality	Hospital codes assigned by physicians: ICD-9
Okoroh *et al.* (2012)	*N* = 192, 936; ESHRE/ASRM/NIH; age = 31.4 years; BMI = not stated	*N* = 11,978,894; age = 32.2 years; BMI = not stated	America	Low quality	Hospital administrative data
Celik *et al.* (2014)	*N* = 84; ESHRE/ASRM; age = 24.7 years; BMI = 27.2 kg/m^2	*N* = 45; age = 27.4 years; BMI = 24.5 kg/m^2	Asia	Low quality	NDG
Angioni *et al.* (2011)	*N* = 79; ESHRE/ASRM; age = 16.4 years; BMI = 20.8 kg/m^2	*N* = 50; age = 16.9 years; BMI = 20.8 kg/m^2	Europe	Good quality	OGTT

ADA, American Diabetes Association; T2DM, type 2 diabetes mellitus; ASRM/ESHRE, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; IGT, impaired glucose tolerance; ICD, International Classification of disease. NDG, National Diabetes Group; NDGG, National Diabetes Data Group; NHANES, National Health and Nutrition Examination Survey; NIH, National Institute of Health; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; WHO, World Health Organization.

current update focussed on meta-analysis of quality studies and also explored the effect of different ethnicities, different anthropometric groups and different methods of T2DM diagnosis on the observed heterogeneity in the prevalence of dysglycaemia in women with and without PCOS. We observed a greater prevalence of both IGT and T2DM in women with PCOS which differed by ethnicity, appeared higher with obesity, and doubled among studies that diagnosed diabetes through self-report or by review of existing administrative records. Meta-regression did not reveal clear drivers of heterogeneity (e.g. BMI) between studies in the assessment of the prevalence of T2DM in PCOS.

We confirm findings from our original review (Moran *et al.*, 2010) of an increased prevalence of IGT and T2DM among women with PCOS compared to women without PCOS. However, the overall risk for T2DM presented with substantial clinical heterogeneity. Risk appeared to differ across different ethnic groups. There was a higher risk of IGT among women from Asia and the Americas and moderate risk among women with PCOS from Europe. This ethnic difference retained its significance in the BMI matched subgroups among Asians and Europeans but not Americans. This may indicate the smaller sample size and the wide confidence interval within the Americas subgroup, indicating that further research in larger community based studies may be needed to confirm our findings. This may also indicate a differential genetic underpinning in the risk for abnormal glucose tolerance. PCOS is commonly thought to be a multifaceted syndrome

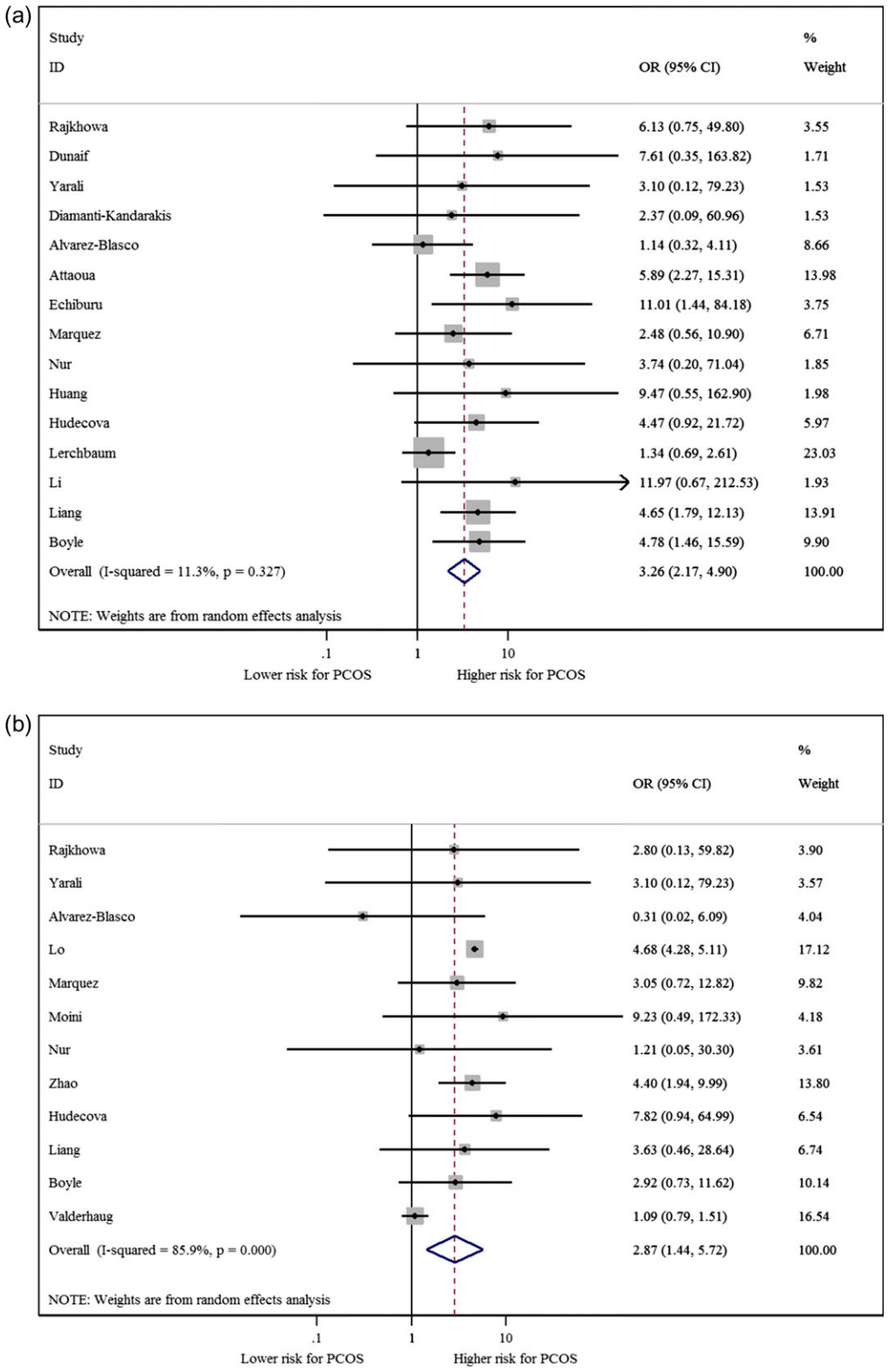

Figure 2 (**a**) IGT prevalence in women with and without PCOS. Meta-analyses were conducted using random-effects modelling (Mantel–Haenszel methods). OR, odds ratio. (**b**) T2DM prevalence in women with and without PCOS. Meta-analyses were conducted using random-effects modelling (Mantel–Haenszel methods). OR, odds ratio.

Table III Subgroup analysis of IGT and T2DM according to ethnicity, anthropometry and method of diagnosing diabetes.

		IGT						T2DM					
	Subgroup	Tot (*N*)	#	# cases	OR, 95% CI	*P*-value	I^2 (%)	Tot (*N*)	#	# Cases	OR, 95% CI	*P*-value	I^2 (%)
Ethnicity	Europe	1494	6	162	2.59 (1.25, 5.36)	0.010	45.30	2286	4	322	1.48 (0.53, 4.14)	0.451	30.90
	Europe, BMI matched	1189	5	121	1.83 (1.09, 3.05)	0.022	3.50	2081	3	314	1.09 (0.79, 1.49)	0.612	0.00
	Americas	539	4	33	4.40 (1.55, 12.48)	0.005	0.00	66 471	3	2134	4.67 (4.27, 5.09)	<0.001	0.00
	Americas, BMI matched	167	2	7	5.26 (0.63, 44.00)	0.126	0.00	141	1	1	NA		
	Asia	600	4	87	5.22 (2.26, 12.04)	<0.001	0.00	2434	4	58	4.42 (2.15, 9.07)	<0.001	0.00
	Asia, BMI matched	518	3	77	3.16 (1.27, 7.87)	0.014	0.00	899	3	17	2.60 (0.60, 11.34)	0.203	0.00
	Australia and New Zealand	109	1	14	NA			109	1	9	NA		
	Australia and New Zealand, BMI matched		0		NA				0	0	NA		
Anthropometry	Lean participants only	367	2	34	4.37 (1.66, 11.54)	0.003	0.00	160	1	2	NA		
	Non-lean participants	2034	12	168	2.47 (1.56, 3.91)	<0.001	3.80	71 029	11	2519	2.88 (1.40, 5.91)	0.004	87.20
	BMI matched	1874	10	205	2.13 (1.39, 3.25)	0.001	0.00	3121	7	332	1.13 (0.83, 1.54)	0.406	0.00
	Non-BMI matched/ overweight/obese	734	5	60	4.75 (2.31, 9.74)	<0.001	0.00	68 397	5	2191	4.66 (4.27, 5.09)	<0.001	0.00
	BMI and WHR/WC matched	164	2	13	1.31 (0.40, 4.30)	0.659	0.00	164	2	4	0.89 (0.09, 8.66)	0.922	6.3
	Non-BMI/WHR/WC matched	2444	13	252	3.06 (2.09, 4.48)	<0.001	0.00	71 102	10	2519	3.12 (1.53, 6.39)	<0.002	88.00
Method of diagnosing diabetes	Prospectively using blood	2601	14	292	3.33 (2.16, 5.14)	<0.001	17.60	4400	9	394	2.43 (1.24, 4.79)	0.010	52.40
	Self-report/historical	141	1		NA			66 900	3	2129	4.68 (4.28, 5.11)	<0.001	0.00

#, number of studies; # of cases, number of cases of T2DM; IGT, impaired glucose tolerance; NA, not-applicable; OR, odds ratio; T2DM, type 2 diabetes mellitus; Tot, total number of participants; WC, waist circumference; WHR, waist-hip ratio.

that manifests in different ways among ethnic subpopulations (Wang and Alvero, 2013; Dumesic *et al.*, 2015), with Asian women expressing a higher metabolic risk (Zhao *et al.*, 2010; Zhao and Qiao, 2013). Genome-wide association studies in Chinese, Korean and European populations have aided in elucidating some of the genetic components and novel susceptibility loci for PCOS and reported single nucleotide polymorphism which vary slightly among different racial and ethnical groups (Dumesic *et al.*, 2015). However, we are still a long way from fully understanding the genetic variants implicated in the development and pathophysiology of PCOS which may also explain ethnicity related differences in glucose abnormality observed among women with PCOS. In an analysis of ethnic variation in PCOS, Casarini and Brigante (2014) reported Asians and Americans to more often be represented by the metabolic phenotype of PCOS (characterized by insulin resistance, high BMI or central obesity and increased risk of T2DM); whereas Europeans and Middle Eastern women were characterized by the hyperandrogenic phenotype (defined by hirsutism, androgenic alopecia and hyperandrogenism). Given our ethnicity-related differences in the prevalence of IGT in all women, and particularly among BMI-matched subgroups of Asian and European women, we believe a genetic contribution could underpin glucose abnormalities among the different ethnicities of women with PCOS. The risks of T2DM independent of BMI, across the ethnic groups, also needs more research. We recommend considering ethnicity in screening recommendations, aligned with diabetes screening guidelines in the general population to facilitate early detection of dysglycemia.

Previous studies have demonstrated IR to be an intrinsic feature among women with PCOS (Diamanti-Kandarakis and Papavassiliou, 2006; Stepto *et al.*, 2013; Teede *et al.*, 2007). The presence of intrinsic IR among women with PCOS is also supported by a recent systematic review reporting a 27% reduction in insulin sensitivity among women with PCOS independent of BMI and age (Cassar *et al.*, 2016). One of the inherent problems associated with complex obesity-related conditions such as PCOS and T2DM is the contribution of PCOS status per se versus obesity-related risk. It is likely that it is the intrinsic IR inherent to PCOS that is the main contributor to dysglycaemia which develops in this condition. Although we did not observe an impact of surrogate markers of insulin resistance (HOMA, OGTT induced insulin response, SHBG, and fasting insulin) on heterogeneity in our meta-regression, we cannot assess the independent contribution of these factors to dysglycaemia in PCOS. While reduced SHBG, as a surrogate marker of insulin resistance (Plymate *et al.*, 1988), has been reported to be associated with T2DM in the general population (Ding *et al.*, 2006; Brand *et al.*, 2011), prior research in PCOS reports no independent association

Table IV Univariate meta-regression analysis of demographic and clinical variables on IGT and T2DM among women with and without PCOS.

IGT					T2DM				
Characteristics	**# studies**	**Coefficient, 95% CI**	***P*-value**	**tau^2**	**Characteristics**	**# studies**	**Coefficient, 95% CI**	***P*-value**	**tau^2**
Age (years)	15	1.22 (−4.83, 7.26)	0.671	0.26	Age	12	2.62 (−7.62, 12.85)	0.581	0.37
BMI (kg/m^2)	15	1.63 (−1.48, 4.74)	0.278	0.15	BMI	10	2.35 (−1.06, 5.76)	0.150	0.07
WC (cm)	6	4.35 (−7.64, 16.34)	0.371	0.36	WC	4	4.20 (−8.83, 17.23)	0.300	0
WHR	9	5.38 (−3.06, 13.82)	0.176	0.18	WHR	7	15.62 (−30.68, 61.92)	0.425	0.29
Weight (kg)	Insufficient observation				Weight	3	18.10 (−488.0, 524.1)	0.729	0.03
SBP (mm of Hg)	5	11.83 (−5.95, 29.62)	0.125	0	SBP	3	18.84 (−150.24, 187.81)	0.392	0
DBP (mm of Hg)	5	8.70 (−11.06, 28.46)	0.256	0.12	DBP	3	18.35 (−150.11, 186.81)	0.398	0
Total cholesterol (mmol/L)	8	7.41 (−0.49, 15.31)	0.062	0.02	Total cholesterol	5	3.28 (−19.6, 26.20)	0.679	0
HDL (mmol/L)	7	3.80 (−8.62, 16.21)	0.467	0.21	HDL	5	−1.39 (−19.81, 17.03)	0.826	0
LDL (mmol/L)	7	2.35 (−7.46, 12.15)	0.565	0.22	LDL	5	1.99 (−11.89, 15.86)	0.680	0
TG (mmol/L)	8	1.30 (−1.75, 4.35)	0.338	0.17	TG	5	1.10 (−4.65, 6.86)	0.585	0
Fasting insulin (pmol/L)	13	0.60 (−0.63, 1.83)	0.308	0.2	Fasting insulin	7	1.03 (0.49, 2.56)	0.141	0.01
Fasting glucose (mmol/L)	12	5.77 (−3.53, 15.06)	0.197	0.15	Fasting glucose	5	4.22 (−16.65, 25.09)	0.566	0
HOMA	10	0.63 (−0.41, 1.67)	0.198	0.18	HOMA	7	0.95 (−1.10, 3.00)	0.287	0.21
2 h GTT (mmol/L)	8	2.28 (−4.98, 9.54)	0.471	0.21	2 h GTT	4	−0.34 (−23.00, 22.32)	0.955	0
Total testosterone (nmol/L)	13	0.71 (−1.13, 2.55)	0.416	0.16	Total testosterone	7	1.19 (−0.41, 2.80)	0.113	0
SHBG (nmol/L)	7	−1.46 (−10.21, 7.29)	0.686	0.46	SHBG	4	−2.21 (−8.84, 4.41)	0.287	0

*Proportion of between-study variance explained with Knapp-Hartung modification; DBP, diastolic blood pressure; 2 h GTT, 2 h glucose tolerance test; HOMA, homoeostasis model assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SHBG, sex-hormone binding globulin; TG, triglyceride; WC, waist-circumference; WHR, waist-hip ratio.

between SHBG and dysglycemia (Moran *et al.*, 2013). In addition, hyperandrogenism among women with PCOS has been reported to increase insulin resistance through the chronic inflammation pathway which can contribute to hyperglycaemia (Shorakae *et al.*, 2015). We also did not find any contribution of testosterone to heterogeneity in dysglycemia in our systematic review. It is important to note that the meta-regression had a minimal number of studies reporting biochemical or hormonal variables. These markers should be reported more widely in future studies to provide further insights on potential markers for early identification of dysglycemia among women with PCOS in a clinical setting.

It is recognized that obesity worsens the severity of outcomes among women with PCOS (Lim *et al.*, 2013; Diamanti-Kandarakis, 2007). In line with this, we also demonstrated in the current review that the risk of IGT was doubled among studies conducted with overweight/obese women compared to lean women with PCOS. However, in the BMI and WHR/ WC matched subgroup, we did not show an increased prevalence of T2DM in PCOS. This is likely due to the young age of the participants overall, the limitations in meta-analysis of aggregate data and relatively small sample size of T2DM cases. Meta-analysis of aggregate data is limited as linear regression models to explore independent relationships cannot be performed and meta-analyses in subgroups cannot account for other confounding factors. Ultimately an individual patient data meta-analysis with original data is needed to allow multiple linear regression to be performed to explore the independent relationships between obesity, T2DM and PCOS. We also note here that anthropometric variables did not emerge as key contributors to heterogeneity between studies on meta-regression. Prior evidence has indicated a greater pathophysiological role of adiposity distribution (WC) rather than total adiposity (BMI) in contributing to metabolic aberrations and this should be explored in future large scale studies and in individual patient data meta-analysis among the different ethnicities to gain a better insight into the pathophysiologic process underlying the development of diabetes.

We did observe differences in the prevalence of T2DM according to the method used to diagnose diabetes. We observed a higher prevalence of diabetes among the subset of studies where women self-reported as having diabetes or in situations where diabetes was confirmed through the review of administrative records, compared to studies that used a prospective blood-based method of diagnosing new cases. Our finding may be related to differences in populations across these types of studies but also likely represent misclassification of diabetes, which is a form of bias that could inflate the risk of disease. Our recommendation would be to exercise caution when interpreting the findings from studies that use self-report or make use of routine administrative or medical codes as a method of diagnosing medical conditions including diabetes.

There remain some confounders in the association of PCOS with dysglycemia that we could not confirm in our review, such as clinical markers of IR, reproductive hormones, participant source, and family history of diabetes. Few PCOS studies reported broad clinical or

biochemical variables including markers of insulin resistance, anthropometric measures such as WC or WHR or family history of T2DM. Future studies need to clearly document clinical and biochemical parameters when reporting on dysglycemia in PCOS. Additionally, there are likely to be unobserved factors that could differ significantly between individual studies, the impact of which, cannot be addressed in a meta-analysis. These could then be analysed in a large scale individual patient data meta-analysis to provide insights on the independent influence of clinical and biochemical factors on dysglycemia in PCOS. Finally, while PCOS guidelines recommended an OGTT as the test of choice, there are limitations to this test with poor reproducibility including false positive cases observed based on the carbohydrate diet preparation within the general population (Ko *et al.*, 1998). We do not have sufficient data to evaluate the impact of this on our results, which warrants assessment in future research.

The strengths of our meta-analysis are the extensive and comprehensive literature search, the focus on studies of higher methodological quality for meta-analysis and meta-regression and a thorough assessment of the impact of demographic and clinical factors thought to confound the association between PCOS and dysglycemia on heterogeneity between studies. Limitations include that we have used the country in which the study was conducted as a proxy indicator of ethnicity. Most of the studies in our review did not include an accurate description of the study population by race or ethnicity. However, the few studies that did include a detailed description of study population by ethnicity, suggest ethnicity for the majority of the study population to come from the country in which the study was conducted, supporting our classification. Furthermore, as with all meta-analyses of aggregate data from observational studies, we cannot eliminate bias due to confounding, nor assume a causal relationship. In our subgroup analyses, numbers of women was lower, which will have impacted the significant relationships observed. There is a need for a longitudinal cohort of women with PCOS documenting epidemiological data as well as biochemical markers of disease progression over the life course and a role for individual patient data meta-analysis. These would enable us to examine the incidence and explore relationship and confounders as well as explore causality in PCOS.

In conclusion, we report an increased prevalence of IGT and T2DM among women with PCOS. We observed differences in the risk for IGT among women from Asia and Europe, which retained significance in BMI-matched subgroups. We also observed an increased prevalence of IGT among all women with PCOS, which was sustained in the BMI-matched subgroup, and worsened by obesity. Subgroup meta-analysis matching for anthropometric variables did not indicate an independent relationship between PCOS and T2DM, however this requires further exploration with larger T2DM samples and with individual patient data meta-analysis. The prevalence of T2DM was doubled among studies using self-report or review of administrative codes as a method of diagnosis. Our findings, highlight the consideration of ethnic background, obesity and method of diabetes diagnosis, when studying PCOS and dysglycemia in addition to other predictors. A considerable challenge for future research in this field is to gain a better understanding of the independent impact of PCOS on dysglycemia including understanding the role of genetic predisposition, and body composition, the source of participants, as well as the impact of clinical and biochemical markers. Understanding their role on dysglycemia will help in developing optimal screening guidelines while informing and targeting preventive interventions for women with PCOS.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Authors' roles

N.S.K. contributed to the study design, execution and analysis, article drafting and critical review of article. M.B.K., C.L.H. and S.D.C. contributed to execution of the study and revision of the article. A.E.J., M.L.M., R.J.N. and H.J.T. contributed to critical discussion and revision of the article. S.R. contributed to the analysis and critical revision of the article. L.J.M. contributed to the study design, execution and analysis and critical review of article.

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Conflicts of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership or other equity interest, expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this article.

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