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Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis

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BACKGROUND: Polycystic ovary syndrome (PCOS) is associated with cardiometabolic disease, but recent systematic reviews and meta-analyses of longitudinal studies that quantify these associations are lacking.

OBJECTIVE AND RATIONALE: Is PCOS a risk factor for cardiometabolic disease?

SEARCH METHODS: We searched from inception to September 2019 in MEDLINE and EMBASE using controlled terms (e.g. MESH) and text words for PCOS and cardiometabolic outcomes, including cardiovascular disease (CVD), stroke, myocardial infarction, hypertension (HT), type 2 diabetes (T2D), metabolic syndrome and dyslipidaemia. Cohort studies and case–control studies comparing the prevalence of T2D, HT, fatal or non-fatal CVD and/or lipid concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) between women with and without PCOS of ≥18 years of

age were eligible for this systematic review and meta-analysis. Studies were eligible regardless of the degree to which they adjusted for confounders including obesity. Articles had to be written in English, German or Dutch. Intervention studies, animal studies, conference abstracts, studies with a follow-up duration less than 3 years and studies with less than 10 PCOS cases were excluded. Study selection, quality assessment (Newcastle–Ottawa Scale) and data extraction were performed by two independent researchers.

OUTCOMES: Of the 5971 identified records, 23 cohort studies were included in the current systematic review. Women with PCOS had increased risks of HT (risk ratio (RR): 1.75, 95% CI 1.42 to 2.15), T2D (RR: 3.00, 95% CI 2.56 to 3.51), a higher serum concentration of TC (mean difference (MD): 7.14 95% CI 1.58 to 12.70 mg/dl), a lower serum concentration of HDL-C (MD: −2.45 95% CI −4.51 to −0.38 mg/dl) and increased risks of non-fatal cerebrovascular disease events (RR: 1.41, 95% CI 1.02 to 1.94) compared to women without PCOS. No differences were found for LDL-C (MD: 3.32 95% CI −4.11 to 10.75 mg/dl), TG (MD 18.53 95% CI −0.58 to 37.64 mg/dl) or coronary disease events (RR: 1.78, 95% CI 0.99 to 3.23). No meta-analyses could be performed for fatal CVD events due to the paucity of mortality data.

WIDER IMPLICATIONS: Women with PCOS are at increased risk of cardiometabolic disease. This review quantifies this risk, which is important for clinicians to inform patients and to take into account in the cardiovascular risk assessment of women with PCOS. Future clinical trials are needed to assess the ability of cardiometabolic screening and management in women with PCOS to reduce future CVD morbidity.

Key words: cardiometabolic health / polycystic ovary syndrome / hypertension / type two diabetes mellitus / dyslipidaemia / systematic review / meta-analysis / long term

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine condition in women of reproductive age and has been suggested as a risk factor for cardiometabolic disease. Depending on which diagnostic criteria are applied, approximately 6–10% of the women of reproductive age are affected by PCOS. PCOS is diagnosed based on the presence of a combination of clinical signs of menstrual irregularities or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries. It is often diagnosed in the reproductive phase of life when women with PCOS are confronted with infertility, or because of symptoms of hyperandrogenism, including acne, alopecia androgenica and hirsutism (McLuskie and Newth, 2017).

PCOS has been suggested to be a specific female reproductive risk factor for cardiometabolic diseases such as type 2 diabetes (T2D), myocardial infarction and stroke, which are the leading causes of death in women (Dokras, 2013; Harvey *et al.*, 2015). Obesity, one of the major modifiable risk factors for cardiometabolic disease, frequently co-occurs with PCOS: approximately half of the women with PCOS are obese (Figure 1) (Glueck *et al.*, 2005; Rojas *et al.*, 2014). However, there is no evidence that PCOS is caused by obesity (Legro, 2012). Both obesity and PCOS are linked to a higher metabolic and cardiovascular disease (CVD) risk, but there is conflicting evidence whether these are independent associations (Moran *et al.*, 2010; Karabulut *et al.*, 2012). Insulin clamp studies have shown that women with PCOS also have intrinsic insulin resistance, independent of weight, suggesting a higher T2D risk, even in the absence of obesity (Stepto *et al.*, 2013; Cassar *et al.*, 2016).

Current evidence regarding PCOS and cardiometabolic risk is mostly extracted from cross-sectional studies, comparing cardiometabolic risk factors, such as elevated blood pressure, hyperglycaemia and dyslipidaemia, between women with and without PCOS, providing information about associations (Moran *et al.*, 2010; Wild *et al.*, 2011). The current systematic review and meta-analysis evaluates all evidence from observational longitudinal studies comparing cardiometabolic risk factors, and fatal and non-fatal CVD events in women with and without PCOS.

Methods

Study design

This systematic review and meta-analysis is conducted following the PRISMA guidelines and recommendations of the Cochrane collaboration (Moher *et al.*, 2009; Higgins, 2011). The study protocol was published in PROSPERO on 15 July 2015 (Registration number: PROSPERO 2015 CRD42015023765).

Data sources

A medical information specialist (J.L.) performed a systematic search in OVID MEDLINE and OVID EMBASE from inception to 2 September 2019, to identify studies that reported the longitudinal association between PCOS and hypertension (HT), T2D and serum concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs), as well as (non)fatal cardiovascular events (myocardial infarction, stroke). The search consisted of controlled terms (e.g. MESH) and text words for PCOS, and cardiometabolic outcomes, including CVD, stroke, myocardial infarction, HT, T2D, metabolic syndrome and dyslipidaemia. The retrieved records were imported in ENDNOTE X7.5 and duplicate records were removed. Cited and citing references of the included studies were screened for additional relevant publications. The complete search is presented in Supplementary Data A.

Study selection

Cohort studies and case–control studies comparing the prevalence of HT, T2D, fatal or non-fatal cardiovascular events and/or lipid concentrations (TC, HDL-C, LDL-C and TG) between a group of women with, and a control group without, PCOS of ≥18 years of age were eligible for this systematic review and meta-analysis. The identification of PCOS cases could be based on: the National Institutes of Health (NIH) 1990 (Zawadzki and Dunaif, 1992), androgen excess (AE)-PCOS (Azziz *et al.*, 2009) and Rotterdam 2003 criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004);

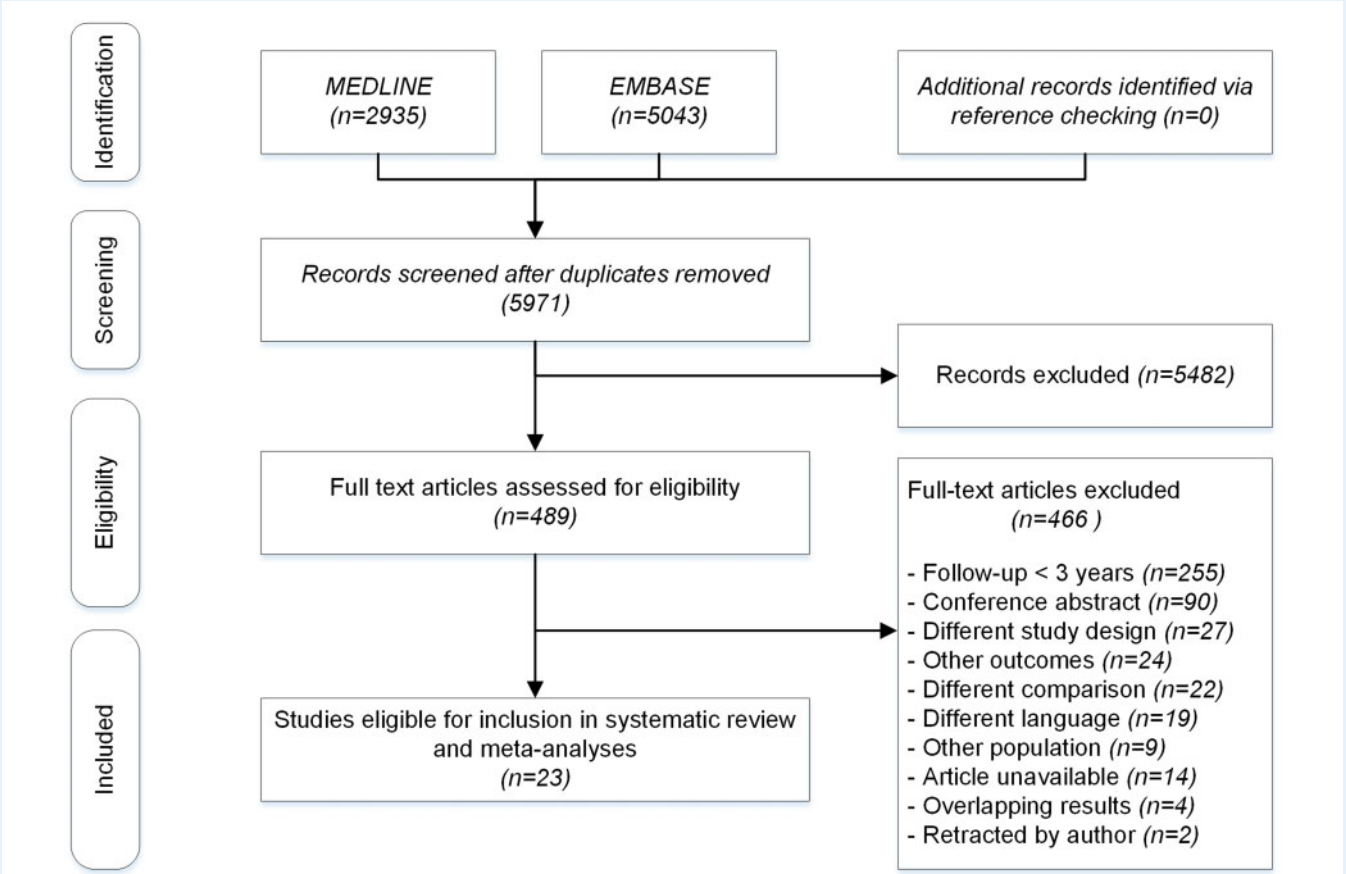

Figure 1. Flow chart of study inclusion for a systematic review and meta-analysis of long-term cardiometabolic disease risk in women with polycystic ovary syndrome.

The International Classification of Diseases (ICD)-9/ICD-10 codes, READ codes; or a combination of at least two of the following symptoms: menstrual irregularities or anovulation, hyperandrogenism and polycystic ovaries. Intervention studies, animal studies, conference abstracts, studies in languages other than English, German and Dutch, studies with less than 3 years between PCOS diagnosis and outcome assessment, and studies with less than 10 PCOS cases were excluded. Two authors (V.W. and L.v.D.) independently screened all potential studies on title and abstract with the use of COVIDENCE®. Disagreements were solved by discussion. The same authors performed the full-text screening to determine the final selection.

Data extraction and quality assessment

The data extraction and quality assessment was performed by A.K. and independently cross-checked (by V.W.), using a standardized extraction form (Supplementary Data B). Disagreements were resolved by discussion and inspection of the original data. The prespecified outcomes of interest were rates of HT, T2D, (non)fatal CVD events (myocardial infarction, stroke) and serum concentrations of TC, LDL-C, HDL-C and TG. To include the data of studies that reported on a composite outcome of CVD events, including myocardial infarction, stroke or other vascular events, two additional meta-analyses were performed. The outcomes could be self-reported, based on medical records, physical examination or be based on ICD codes. In case of overlapping outcomes in the same study, population was reported in multiple publications, the data on the outcome was extracted from the publication with the longest follow-up duration or largest number of participants. If data on prespecified outcomes were not reported in a way that allowed aggregation, corresponding authors were contacted via institutional e-mail, or the e-mail address published in the article. The Newcastle–Ottawa Scale for quality assessment of cohort studies was used for both prospective as retrospective cohort studies (Wells *et al.*, 2012). This scale assesses the risk of selection bias, the comparability of the groups and ascertainment of exposure and results in a graphical overview of potential types of bias across the included studies. A higher number of stars represents a higher study quality. Summary scores for low ($\leq$4), moderate (4–7) and high-quality studies ($\geq$7) were assigned (Yarmolinsky *et al.*, 2016). However, studies were not excluded based on the quality assessment.

Statistical analysis

All statistical analyses were performed with Review Manager (RevMan 5.3) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Meta-analyses of dichotomous outcomes (HT,

Table I Characteristics of the included prospective cohort studies.

First author, year of publication	Title	Journal, country of publication. Country of study, study period	Population Number Age (years) BMI (kg/m^2)	PCOS criteria	Selection of controls	Follow-up duration	Outcomes	Matching criteria/ adjusted
Carmina *et al.* (2013)	Emergence of ovulatory cycles with aging in women with PCOS alters the trajectory of cardiovascular and metabolic risk factors	*Human Reproduction*, UK Italy, 1985–1990	n PCOS: 118 n Control: 35 Age PCOS: 21.8 ± 2 Age Control: 21.8 ± 2 (at baseline) BMI PCOS: 27.5 ± 6 BMI Control: 21.5 ± 5	Rotterdam 2003	At the end of the study with normal body weight, normal ovulatory cycles and with no clinical or biochemical signs of hyperandrogenism	20 years	LDL-C, HDL-C, TC, TG	Matched: Age, weight
Kazemi Jaliseh *et al.* (2017)	PCOS is a risk factor for diabetes and prediabetes in middle-aged but not elderly women: a long-term population-based follow-up study	*Fertility and Sterility*, USA Iran, 1998–2010	n PCOS: 178 n Control: 1524 Age PCOS: 26.4 (8.5) Age Control: 28.9 (8.6) BMI PCOS: 26.1 (5.1) BMI Control: 25.4 (4.7)	NIH 1990	Healthy, eumenorrhoeic, non-hirsute women from the same prospective study (Tehran Lipid and Glucose Study)	Median 12.9 years (IQR 1.98–15.79)	T2D (fasting plasma glucose ≥126 mg/dl or 2 h plasma glucose ≥200 mg/dl, medication for previous diagnosis)	Adjusted: Baseline fasting blood sugar, BMI, physical activity, family history of diabetes
Merz *et al.* (2016)	Cardiovascular disease and 10-year mortality in postmenopausal women with clinical features of PCOS	*Journal of Women's Health*, USA USA, 1997–(unknown end year)	n PCOS: 25 n Control: 270 Age PCOS: 62.6 (11.6) Age Control: 64.8 (9.6) BMI PCOS: 28.7 (5.9) BMI Control: 30.0 (6.7)	Biochemical evidence of hyperandrogenemia (top quartile of androstenedione (≥701 pg/ml), or testosterone (≥30.9 ng/dl) or free testosterone (≥4.5 pg/ml) for the population) and self-reported history of irregular menses.	Women without PCOS participating in the Women's Ischaemia Syndrome Evaluation study who underwent a clinically indicated coronary angiogram for suspected ischaemia, yet with stable cardiac symptoms	Median 9.3 years (IQR 8.4–10.3)	Fatal cardiovascular event (sudden cardiac death, end stage congestive heart failure, acute MI, peripheral arterial disease, cerebrovascular accident)	Adjusted: CRP
Meun *et al.* (2018)	High androgens in postmenopausal women and the risk for atherosclerosis and cardiovascular disease: the Rotterdam study	*Journal of Clinical Endocrinology & Metabolism*, USA Netherlands, 1997–2001	n PCOS: 106 n Control: 171 Age PCOS: 69.6 (8.7) Age Control: 69.2 (8.6) BMI PCOS: 27.9 (4.5) BMI Control: 26.8 (3.8)	Irregular cycles and test or FAI in highest quartile	Women with no history of cycle irregularities and hormone levels in the reference range (P25–P50) who also participated in the Rotterdam study	Median 11.4 years	Non-fatal cerebrovascular disease (neurologic symptoms, diagnosed with CT/MRI within 4 weeks)	Adjusted: Age, years since menopause, cohort TC, HDL-C, Lipid lowering drugs, smoking, SBP, HT, DM, WHR, use of hormones
Ollila *et al.* (2016)	Overweight and obese but not normal weight women with PCOS are at increased risk of type 2 diabetes mellitus—a prospective population-based cohort study	*Human Reproduction*, UK Finland, 1966–2012	n PCOS: 279 n Control: 1577 Age PCOS: 46 Age Control: 46 BMI PCOS: 28.6 (6.3) BMI Control: 26.3 (5.3)	Long cycle and excessive body hair or PCOS diagnosis (self-reported)	Women who had no long cycle and excessive body hair or PCOS diagnosis who also participated in the Northern Finland Birth Cohort	15 years	T2D (OGTT or self-reported, cross-checked with hospital discharge and national drug registers)	Matched: Age Adjusted: Education level, alcohol consumption, smoking and current use of combined contraceptives and of cholesterol-lowering drugs

(continued)

Table I Continued

First author, year of publication	Title	Journal, country of publication. Country of study, study period	Population Number Age (years) BMI (kg/m^2)	PCOS criteria	Selection of controls	Follow-up duration	Outcomes	Matching criteria/ adjusted
Schmidt *et al.* (2011)	Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21 year follow-up study	*Journal of Clinical Endocrinology and Metabolism*, USA Sweden, 1987–2008	n PCOS: 32 n Control: 95 Age PCOS: 70.4 ± 5 Age Control: 70.7 ± 5.6 BMI PCOS: 27.1 ± 5 BMI Control: 26.4 ± 4.8	Rotterdam 2003	Women were randomly allocated from the population of the Gothenburg World Health Organization (WHO) monitoring of trends and determinants for cardiovascular disease (MONICA) study	21 years	Fatal cardiovascular events, non-fatal coronary heart disease, non-fatal cerebrovascular disease, T2D, HT (ICD codes and self-reported) TC, LDL-C, HDL-C, TG	Matched: Age
Ramezani Tehrani *et al.* (2015)	Trend of cardio-metabolic risk factors in PCOS: a population-based prospective cohort study	*PLOS ONE*, USA Iran, 1999–2011	n PCOS: 85 n Control: 552 Age PCOS: 29.8 (9.2) Age Control: 29.3 (9.0) BMI PCOS: 27.2 (5.3) BMI Control: 25.6 (5.0)	NIH 1990	Women without hirsutism or ovulatory dysfunction by history, physical examination, and hormonal profile who also participated in the Tehran Lipid and Glucose Study (TLGS)	12 years	TC, LDL-C, HDL-C	NA
Udesen *et al.* (2019)	Levels of circulating insulin cell-free DNA in women with PCOS—a longitudinal cohort study	*Reproductive Biology and Endocrinology*, UK Denmark, unknown	n PCOS: 40 n Control: 8 Age PCOS: 34.7 (4.2) Age Control: 35.6 (6.0) BMI PCOS: 27.7 (6.1) BMI Control: 27.0 (4.3)	Rotterdam 2003	Healthy age-match women, who were recruited at the Fertility Clinic at Holbæk Hospital, Denmark, as a part of the PICOLO cohort	Mean 5.8 years (SD 0.8) Median 6.1 years (4.0–7.1)	TC, LDL-C, HDL-C	NA
Wang *et al.* (2011)	PCOS and risk for long-term diabetes and dyslipidaemia	*Obstetrics & Gynecology*, USA USA, 1985–2000	n PCOS: 53 n Control: 1074 Age PCOS: 26.8 ± 3.7 Age Control: 27.3 ± 3.6 (at baseline) BMI not reported	NIH 1990	Women who did not fulfil the NIH 1990 criteria for PCOS who also participated in the Coronary Artery Risk Development In young Adults (CARDIA) cohort	15 years	T2D (fasting plasma glucose ≥126 mg/dl or use of antidiabetic), HT (blood pressure ≥140/90 mmHg or use or antihypertensive medication)	Adjusted: Age, Race, BMI baseline, Education, Parity, Family history DM; 2) 1 + BMI follow-up

CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; ICD, International Classification of Diseases; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MRI, magnetic resonance imaging; NIH, National Institutes of Health; n, number; NA, not applicable; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; T2D, type 2 diabetes, WHR, wait–hip ratio; TC, total cholesterol; TG, triglycerides.

T2D and CVD events) were performed with the inverse variance method and a random effects model because the included trials were expected to differ clinically and methodologically at least to some extent. The results were reported as risk ratios (RRs) including a 95% CI. Meta-analyses of continuous outcomes (TC, LDL-C, HDL-C and TG) were reported as mean differences (MDs) in mg/dl including 95% CI. If a study compared groups of women with different phenotypes of PCOS to a control group, then the data of the PCOS groups were pooled in review manager (Higgins, 2011). Meta-analyses were also reported in forest plots, including subgroups for study design. Heterogeneity between studies included in one meta-analysis was evaluated using the χ^2 (significance level: <0.1) and I^2 statistic, which assesses the appropriateness of pooling the individual study results. In case of considerable heterogeneity (I^2 > 70%), sensitivity analyses were performed excluding studies of which the CI of the study and summary CI do not overlap (outliers) (Moher *et al.*, 2009; Higgins, 2011). Funnel plot asymmetry was used to detect publication bias if more than 10 studies were included in one meta-analysis (Higgins, 2011).

Subgroup analyses

All meta-analyses were reported including subgroups for prospective and retrospective study designs. Sensitivity analyses including high-quality studies and based on the diagnostic criteria for PCOS (NIH 1990 criteria (Zawadzki and Dunaif, 1992), AE-PCOS criteria (Azziz *et al.*, 2009) or Rotterdam 2003 criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004)) were performed if three or more studies used the same diagnostic criteria.

Results

Study selection

In the selection process, a total of 23 cohort studies were identified to be eligible for this systematic review. The 23 studies consist of nine prospective and 14 retrospective cohort studies, and no case-control studies. In the prospective cohort studies, a total of 945 women with PCOS were compared to 5293 women without PCOS. In the retrospective cohort studies, a total of 54 894 women with PCOS were compared to 225 622 women without PCOS. (The study characteristics of the included prospective studies are presented in Table I and of the retrospective studies in Table II.)

Follow-up duration ranged from approximately 5–31 years. Fourteen studies were performed in Europe (Cibula *et al.*, 2000; Wild *et al.*, 2000; Lunde and Tanbo, 2007; Schmidt *et al.*, 2011; Hudecova *et al.*, 2011a,b, 2010; Morgan *et al.*, 2012; Carmina *et al.*, 2013; Ollila *et al.*, 2017; Rubin *et al.*, 2017; Glintborg *et al.*, 2018; Meun *et al.*, 2018; Udesen *et al.*, 2019), six in North America (Talbott *et al.*, 1995; Lo *et al.*, 2006; Talbott *et al.*, 2007; Wang *et al.*, 2011; Iftikhar *et al.*, 2012; Merz *et al.*, 2016), two in the Middle East (Ramezani Tehrani *et al.*, 2015; Kazemi Jaliseh *et al.*, 2017) and one in Oceania (Hart and Doherty, 2015). The criteria used to diagnose PCOS were the Rotterdam criteria in seven studies (Schmidt *et al.*, 2011; Hudecova *et al.*, 2011a,b, 2010; Iftikhar *et al.*, 2012; Carmina *et al.*, 2013; Udesen *et al.*, 2019), three studies the NIH criteria (Wang *et al.*, 2011; Ramezani Tehrani *et al.*, 2015; Kazemi Jaliseh *et al.*, 2017), five studies used ICD codes (Lo *et al.*, 2006; Morgan *et al.*, 2012; Hart and Doherty, 2015; Rubin *et al.*, 2017; Glintborg *et al.*, 2018) and eight used a definition based on the presence of either hyperandrogenism, hirsutism or menstrual irregularities/anovulation (Talbott *et al.*, 1995; Cibula *et al.*, 2000; Wild *et al.*, 2000; Lunde and Tanbo, 2007; Talbott *et al.*, 2007; Merz *et al.*, 2016; Ollila *et al.*, 2017; Meun *et al.*, 2018) (Tables I and II). The risk of bias varied from moderate to high quality between the studies. On average, the included studies scored seven out of nine stars. Four studies scored low risk of bias on all eight criteria (nine stars), indicating these studies were of the highest quality (Table III) (Morgan *et al.*, 2012; Kazemi Jaliseh *et al.*, 2017; Rubin *et al.*, 2017; Glintborg *et al.*, 2018). The most prevalent high risk of bias was because of studies not indicating whether the outcome of interest, such as HT and diabetes, was already present at the start of the study.

Outcomes

Supplementary Tables SI–SXII show the results according to outcome and include the definition of the outcome as used in the study, the number of participants and frequency of the outcomes or, for metabolic outcomes, concentrations in mg/dl. The risk comparisons as reported by the studies as well as the confounders used in the analysis for the outcome of interest and factors used to match the populations are reported in these tables.

Cardiometabolic risk factors

Hypertension. Ten studies (Talbott *et al.*, 1995; Cibula *et al.*, 2000; Wild *et al.*, 2000; Lo *et al.*, 2006; Lunde and Tanbo, 2007; Schmidt *et al.*, 2011; Wang *et al.*, 2011; Iftikhar *et al.*, 2012; Hart and Doherty, 2015; Glintborg *et al.*, 2018) were included in the meta-analysis for HT. Five studies showed a higher rate of HT among women with PCOS compared to those without PCOS. The meta-analysis showed a higher rate of HT among women with PCOS compared to women without PCOS (13.1% vs 6.6%; RR: 1.75, 95% CI 1.42 to 2.15; I^2 = 93%) (Fig. 2a). Subgroup analyses by study design showed no higher rate in the two prospective studies (RR: 1.35, 95% CI 0.85 to 2.16); I^2 = 63%); but a higher rate of HT among women with PCOS based on the findings of eight retrospective studies (RR: 1.86, 95% CI 1.48 to 2.33; I^2 = 94%). Exclusion of three outliers in the meta-analysis for HT (Lo *et al.*, 2006; Hart and Doherty, 2015; Glintborg *et al.*, 2018), led to a decrease in the I^2 statistic from 94% to 10%, and a smaller point estimate for HT among women with PCOS compared to women without PCOS (RR: 1.28, 95% CI 1.11 to 1.48). Visual inspection of the funnel plot for the meta-analysis of HT among women with PCOS compared to women without PCOS did not indicate publication bias (Fig. 2b). Sensitivity meta-analysis including five high-quality studies also showed a higher rate of HT among women with PCOS compared to women without PCOS (12.9% vs 6.3%; RR: 2.07, 95% CI 1.61 to 2.65; I^2 = 95%) (Supplementary Table SXIII).

Type 2 diabetes. Thirteen studies (Cibula *et al.*, 2000; Wild *et al.*, 2000; Lo *et al.*, 2006; Talbott *et al.*, 2007; Schmidt *et al.*, 2011; Wang *et al.*, 2011; Hudecova *et al.*, 2011a,b; Iftikhar *et al.*, 2012; Morgan *et al.*, 2012; Hart and Doherty, 2015; Ollila *et al.*, 2016; Kazemi Jaliseh *et al.*, 2017; Rubin *et al.*, 2017) were included in the meta-analysis for T2D. Ten studies reported a higher rate of T2D among women with PCOS

Table II Characteristics of the included retrospective cohort studies.

First author, year of publication	Title	Journal, country of publication	Population Number Age (years) BMI (kg/m^2)	PCOS criteria	Selection of controls	Follow-up duration	Outcomes	Matching criteria/ adjusted
Cibula *et al.* (2000)	Increased risk of NIDDM, arterial hypertension and coronary artery disease in perimenopausal women with a history of the PCOS	*Human Reproduction*, UK Czech Republic, 1960–1981	n PCOS: 28 n Control: 752 Age PCOS: 51.9 ± 4.6 Age Control: 51.0 ± 4.21 BMI PCOS: 28.0 ± 4.21 BMI Control: 28.2 ± 5.42	Oligo or amenorrhoea, hirsutism, anovulatory infertility, typical appearance ovaries at surgery	Women selected from 3209 women representing a random population sample of nine districts of the Czech Republic	20–40 years	Coronary heart disease, T2D, HT (self-reported) LDL-C, HDL-C, TC, TG	Matched: Age
Glintborg *et al.* (2018)	Cardiovascular disease in a nationwide population of Danish women with PCOS	*Cardiovascular Diabetology*, UK Denmark, 1995–2015	n PCOS: 17995 n Control: 52329 Age: 29 (IQR 23–35) BMI: unknown	ICD 10 diagnosis; E28.2 (PCOS) and/or L68.0 (hirsutism)	Women selected from the Danish civil population register	Median 11.1 years (IQR 6.9–16.0)	Non-fatal vascular event, non-fatal cerebrovascular event, HT (ICD codes: G45–46, I63–66, I10–13)	Matched: Age
Hart and Doherty (2015)	The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage	*The Journal of Clinical Endocrinology & Metabolism*, USA Australia, 1980–2011	n PCOS: 2566 n Control: 25660 Age: Median 35.8 (IQR 31–39.9) BMI: not reported	ICD 10: E28.2 for PCOS or ICD-9: 256.4 for PCO	Women selected from the population-based administrative health datasets Within Western Australia without PCOS	Precise follow-up duration unclear	Non-fatal coronary heart disease, non-fatal cerebrovascular disease, T2D, HT (ICD codes)	Matched: Age Adjusted: Obesity
Hudecova *et al.* (2010)[a]	Endothelial function in patients with PCOS a long-term follow-up study	*Fertility and Sterility*, USA Sweden, 1987–1995	n PCOS: 67 n Control: 66 Age PCOS: 43.3 ± 6.1 Age Control: 43.6 ± 6.3 BMI PCOS: 27.6 ± 5.5 BMI Control: 25.4 ± 3.6	Rotterdam 2003 (one criteria had to be PCO)	Healthy women also residing from Uppsala county were randomly selected from population registers	Not reported	TC; LDL	Matched: Age
Hudecova *et al.* (2011a)	Diabetes and impaired glucose tolerance in patients with PCOS a long-term follow-up study	*Human Reproduction*, UK Sweden, 1987–1995	n PCOS: 84 n Control: 87 Age PCOS: 43.0 ± 5.8 Age Control: 43.7 ± 6.2 BMI PCOS[b]: 27.6 ± 5.6 BMI Control: 25.6 ± 4.2	Rotterdam 2003 (one criteria had to be PCO)	Healthy women also residing from Uppsala county were randomly selected from population registers	Mean 13.9 years Range (11–20)	T2D (intravenous glucose tolerance test or oral glucose tolerance test, if patients were not already known to have diabetes)	Matched: Age
Hudecova *et al.* (2011b)[a]	Prevalence of metabolic syndrome in women with a previous diagnosis of PCOS long-term follow-up	*Fertility and Sterility*, USA Sweden, 1987–1995	n PCOS: 84 n Control: 87 Age PCOS: 43.0 ± 5.8 Age Control: 43.7 ± 6.2 BMI PCOS[b]: 28.3 ± 6.0 BMI Control: 25.7 ± 4.4	Rotterdam 2003 (one criteria had to be PCO)	Healthy women also residing from Uppsala county were randomly selected from population registers	Mean 13.9 years Range (11–20)	HDL-C, TG	Matched: Age Adjusted: BMI, postmenopausal status, hormone use

(continued)

Table II Continued

First author, year of publication	Title	Journal, country of publication	Population Number Age (years) BMI (kg/m^2)	PCOS criteria	Selection of controls	Follow-up duration	Outcomes	Matching criteria/ adjusted
Iftikhar *et al.* (2012)	Risk of cardiovascular events in patients with PCOS	*The Netherlands Journal of Medicine*, The Netherlands USA, 1966–1988	n PCOS: 309 n Control: 343 Age PCOS: 44.4 ± 12.9 Age Control: 48.8 ± 10.2 BMI PCOS: 29.4 ± 7.77 BMI Control: 28.3 ± 7.47	Rotterdam 2003	Women who also received medical care in Olmsted County during the same time period as the PCOS cases	23.7 (13.7) years	Fatal cardiovascular events (dead certificates), non-fatal cardiovascular events (myocardial infarction, unstable angina, CABG) (medical records), non-fatal cerebrovascular events, T2D, HT (self-reported or medical record)	Matched: Age, year of birth Adjusted: Age at last follow-up, BMI, Infertility treatment, postmenopausal hormone therapy, family history HT
Lo *et al.* (2006)	Epidemiology and adverse cardiovascular risk profile of diagnosed PCOS	*The Journal of Clinical Endocrinology & Metabolism*, USA USA, 1994–2004	n PCOS: 11035 n Control: 55175 Age PCOS: 30.7 ± 7.2 Age Control: 30.8 ± 7.5 BMI: BMI ≤ 24, PCOS: 13.6% BMI ≤ 24, Control: 39.6% BMI 25–29, PCOS: 19.4% vs. 29.0% BMI 25–29, Control: 29.0% BMI ≥ 30, PCOS: 67.0% BMI ≥ 30, Control: 31.4%	ICD-9 code 256.4 (PCOS)	Women without PCOS who received ambulatory care within Kaiser Permanente of Northern California, a large, integrated healthcare delivery system	Unclear 1–10 years	Non-fatal coronary heart disease, non-fatal cerebrovascular disease, peripheral vascular disease T2D, HT (ICD-9 and current procedure terminology codes for diagnoses and relevant procedure terminology codes for diagnoses and relevant procedures found in ambulatory visit, hospital discharge and billing databases)	Matched: Age Adjusted: BMI; T2D; dyslipidaemia (for T2D, HT)
Lunde and Tanbo (2007)	PCOS a follow-up study on diabetes mellitus, cardiovascular disease and malignancy 15-25 years after ovarian wedge resection	*Gynecological Endocrinology*, UK Norway, 1970–1980	n PCOS: 136 n Control: 723 Age: not reported BMI PCOS: 24.7 (17-36.9) BMI Control: not reported	Polycystic ovaries and two or more of menstrual irregularity, hirsutism, infertility or obesity	Subset of women from the Norwegian county health survey	15–25 years	Non-fatal cardiovascular events (Medical records), HT (self-reported)	Matched: Age
Morgan *et al.* (2012)	Evaluation of adverse outcome in young women with PCOS versus matched reference controls: a retrospective observational study	*Journal of Clinical Endocrinology and Metabolism*, USA UK, 1990–2011	n PCOS: 21 740 n Control: 86 936 Age PCOS: 27.1 ± 7.1 Age Control: 27.1 ± 7.1 (at baseline) BMI PCOS: 28.7 ± 8.2 BMI Control: 25.5 ± 5.8	Read code classification (PCOS)	Women without PCOS selected from the same primary care practice	PCOS: 4.7 years (IQR 2–8.6) Control: 5.8 years (IQR 2.7–9.6)	Non-fatal vascular events (myocardial infarction, stroke, angina, central of peripheral revascularization), T2D (Read code classification)	Matched: (1) Primary care visits, age (2) BMI Adjusted: BMI, primary care visits, age

(continued)

Table II Continued

First author, year of publication	Title	Journal, country of publication	Population Number Age (years) BMI (kg/m^2)	PCOS criteria	Selection of controls	Follow-up duration	Outcomes	Matching criteria/ adjusted
Rubin *et al.* (2017)	Development and risk factors of type 2 diabetes in a nationwide population of women with PCOS	*Journal of Clinical Endocrinology & Metabolism*, USA Denmark, 1995–2015	n PCOS: 18477 n Control: 54680 Age PCOS: 29 (IQR 24–36) Age Control: 29 (IQR 24–36) BMI: unknown	ICD 10 diagnosis; E28.2 (PCOS) and/or L68.0 (hirsutism)	Women selected from the Danish civil population register	Median 11.1 years (IQR 6.9–16.0)	T2D (ICD 10 E11, E14 or prescription of drugs A10)	Matched: Age Adjusted: Combined oral contraceptive pill
Talbott *et al.* (1995)[c]	Coronary heart disease risk factors in women with PCOS	*Arteriosclerosis, Thrombosis and Vascular Biology*, USA USA, 1970–1990	n PCOS: 206 n Control: 206 Age PCOS: 35.9 ± 7.4 Age Control: 37.2 ± 7.8 BMI PCOS: 30.5 ± 8.3 BMI Control: 26.3 ±6.5	Chronic anovulation, hirsutism and/or LH/FSH ratio > 2 nmol/l	Women from the neighbourhood were selected using a combination of voters' registration tapes for the greater Pittsburgh area and Cole's Cross Reference Directory of households	14 years	HT (self-reported), TC	Matched: Age, Race, neighbourhood
Talbott *et al.* (2007)[c]	PCOS: a significant contributor to the overall burden of type 2 diabetes in women	*Journal of Women's Health*, USA USA, 1970–2002	n PCOS: 149 n Control: 166 Age PCOS: 47.3 ± 5.6 Age Control: 49.4 ± 5.8 BMI PCOS: 32.6 ± 8.8 BMI Control: 28.3 ± 6.1	Chronic anovulation and clinical or biochemical hyperandrogenism or LH/FSH ratio >2nmol/l	Women from the neighbourhood were selected using a combination of voters' registration tapes for the greater Pittsburgh area and Cole's Cross Reference Directory of households	9–32 years	T2D (self-reported and assessed by MD) LDL-C, HDL-C, TG	Matched: Age, Race, neighbourhood
Wild *et al.* (2000)	Cardiovascular disease in women with PCOS at long-term follow-up: a retrospective cohort study	*Clinical Endocrinology*, UK UK, 1979–1999	n PCOS: 319 n Control: 1060 Age PCOS: 56.7 (range 38–98) Age Control: 56.7 (range 38–98) BMI PCOS: 27.1 BMI Control: 26.2	(1) Histological evidence with clinical evidence of ovarian dysfunction (2) Histological evidence with clinical information not available, macroscopic evidence with clinical evidence of ovarian dysfunction, or clinical diagnosis by an experienced consultant	Women were selected from the same GP practice	31 years (range 15–47)	Non-fatal coronary heart disease, non-fatal cerebrovascular disease, T2D, HT (self-reported, recorded by GP) TC, LDL-C, HDL-C, TG	Matched: Age, GP practice

[a]Overlapping population; overlapping outcomes are reported based on Hudecova *et al.* (2011b).
[b]Non-diabetic women.
[c]Overlapping population; overlapping outcomes are reported based on Talbott *et al.* (2007).
GP, general practitioner; CABG, coronary artery bypass grafting; NIDDM, non-insulin-dependent diabetes mellitus.

Table III Quality assessment of included studies using The Newcastle-Ottawa Scale.

	Study design[1]	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Summary quality score
Carmina *et al.* (2013)	P	–	–	*	*	**	*	*	*/–	Moderate
Cibula *et al.* (2000)	R	*	–	*	–	*	*	*	–	Moderate
Glintborg *et al.* (2018)	R	*	*	*	*	*	*	*	*	High
Hart and Doherty (2015)	R	*	*	*	–	**	*	*	*	High
Hudecova *et al.* (2010)	R	*	*	*	–	**	*	*	–	High
Hudecova *et al.* (2011a)	R	*	*	*	*	*	*	*	–	High
Hudecova *et al.* (2011b)	R	*	*	*	–	**	*	*	–	High
Iftikhar *et al.* (2012)	R	*	*	*	–	**	*	*	*	High
Kazemi Jaliseh *et al.* (2017)	P	*	*	*	*	**	*	*	*	High
Lo *et al.* (2006)	R	*	*	*	–	**	*	–	*	High
Lunde and Tanbo (2007)	R	–	–	*	–	*	*	*	*	Moderate
Merz *et al.* (2016)	P	–	*	–	*	*	*	*	*	Moderate
Meun *et al.* (2018)	P	*	*	*	*	**	–	*	*	High
Morgan *et al.* (2012)	R	*	*	*	*	**	*	*	*	Moderate
Ollila *et al.* (2016)	P	*	*	–	*	**	*	*	–	Moderate
Rubin *et al.* (2017)	R	*	*	*	*	**	*	*	*	High
Schmidt *et al.* (2011)	P	–	–	–	–	**	*/–	*	*	Moderate
Talbott *et al.* (1995)	R	*	*	*	–	**	*/–	*	–	Moderate
Talbott *et al.* (2007)	R	–	*	*	–	**	*/–	*	–	Moderate
Ramezani Tehrani *et al.* (2015)	P	*	*	*	*	**	*	*	–	High
Udesen *et al.* (2019)	P	*	*	*	*	*	*	*	–	High
Wang *et al.* (2011)	P	*	*	*	–	**	*	*	*	High
Wild *et al.* (2000)	R	*	*	–	–	**	*/–	*	–	Moderate

[1]P, Prospective cohort study; R, Retrospective cohort study; – indicates high risk of bias; *indicates low risk of bias.

compared to those without PCOS. Wild *et al.* (2000) and Talbott *et al.* (2007) reported no higher rate in T2D after adjusting for age and BMI (Supplementary Table SII). The meta-analysis showed a higher rate of T2D among women with PCOS compared to women without PCOS (5.9% vs 2.0%; RR: 3.00, 95% CI 2.56 to 3.51; I^2 = 83%) (Fig. 2c). Subgroup analyses by study design showed a higher rate of T2D among women with PCOS based on four prospective studies (RR: 2.26, 95% CI 1.74 to 2.94; I^2 = 0%) and nine retrospective studies (RR: 3.29, 95% CI 2.77 to 3.91; I^2 = 86%). Exclusion of two outliers in the meta-analyses for T2D (Lo *et al.*, 2006; Iftikhar *et al.*, 2012), led to a decrease in the I^2 statistic from 83% to 36%, and a smaller point estimate for T2D among women with PCOS compared to women without PCOS (RR: 3.04, 95% CI 2.77 to 3.35). Visual inspection of the funnel plot for the meta-analysis of T2D among women with PCOS compared to women without PCOS did not indicate publication bias (Fig. 2d). Sensitivity meta-analysis including seven high-quality studies also showed a higher rate of T2D among women with PCOS compared to women without PCOS (7.6% vs 2.4%; RR: 3.07, 95% CI 2.48 to 3.80; I^2 = 88%) (Supplementary Table SXIII).

Lipid concentrations

The study of Carmina et al. (2013) compared the lipid concentrations of 67 women with PCOS who remained anovulatory over time and 30 who became ovulatory separately to a control group without PCOS (Supplementary Tables SIII–SVI). The pooled mean lipid concentrations and SD of the women with PCOS were included in the meta-analyses.

Total cholesterol. Seven studies (Talbott et al., 1995; Cibula et al., 2000; Hudecova et al., 2010; Schmidt et al., 2011; Carmina et al., 2013; Ramezani Tehrani et al., 2015; Udesen et al., 2019) were included in the meta-analysis for TC concentration (mg/dl). Two studies (Talbott et al., 1995; Carmina et al., 2013) reported a statistically significantly higher TC concentration among women with PCOS compared to those without PCOS (Supplementary Table SIII). The meta-analysis for TC concentration showed a higher TC concentration among women with PCOS compared to women without PCOS (MD: 7.14 95% CI 1.58 to 12.70 mg/dl; $I^2 = 32\%$) (Fig. 3a). Subgroup analyses by study design showed no difference in TC concentration based on four prospective studies (MD: 7.27 95% CI −3.43 to 17.97 mg/dl; $I^2 = 56\%$), but a higher TC concentration among women with PCOS based on three retrospective studies (MD: 7.30 95% CI 1.60 to 13.00 mg/dl; $I^2 = 0\%$). Subgroup analyses for four studies that diagnosed PCOS using the Rotterdam 2003 criteria showed no difference in TC concentration among women with PCOS compared to women without PCOS (MD: 5.91 95% CI −6.66 to 18.48 mg/dl; $I^2 = 60\%$) (Hudecova et al., 2010; Schmidt et al., 2011; Carmina et al., 2013; Udesen et al., 2019). Sensitivity meta-analysis including three high-quality studies did not show a higher TC concentration among women with PCOS (MD: 3.33 95% CI −3.99 to 10.66 mg/dl; $I^2 = 0\%$) (Supplementary Table SXIV).

Low-density lipoprotein cholesterol. Seven studies (Talbott et al., 1995; Cibula et al., 2000; Hudecova et al., 2010; Schmidt et al., 2011; Carmina et al., 2013; Ramezani Tehrani et al., 2015; Udesen et al., 2019) were included in the meta-analysis for LDL-C concentration (mg/dl). Carmina et al. (2013) reported a statistically significant higher LDL-C concentration among anovulatory women with PCOS compared to those without PCOS (Supplementary Table SIV). The meta-analysis for LDL-C concentration showed no difference in LDL-C concentration among women with PCOS compared to women without PCOS (MD: 3.32 95% CI −4.11 to 10.75 mg/dl; $I^2 = 69\%$) (Fig. 3b). Subgroup analyses by study design showed no difference in LDL-C concentration based on four prospective studies (MD: 4.41 95% CI −7.89 to 16.71 mg/dl; $I^2 = 79\%$) and three retrospective studies (MD: −0.17 95% CI −6.20 to 5.86 mg/dl; $I^2 = 0\%$). Subgroup analyses for three studies, which diagnosed PCOS using the Rotterdam 2003 criteria, showed no difference in LDL-C concentration among women with PCOS compared to women without PCOS (MD: 5.18 95% CI −7.33 to 17.69 mg/dl; $I^2 = 74\%$) (Hudecova et al., 2010; Schmidt et al., 2011; Carmina et al., 2013; Udesen et al., 2019). Sensitivity meta-analysis including three high-quality studies also showed no difference in LDL-C concentration (MD: 1.30 95% CI −4.82 to 7.42 mg/dl; $I^2 = 0\%$) (Supplementary Table SXIV).

High-density lipoprotein cholesterol. Seven studies (Talbott et al., 1995; Cibula et al., 2000; Schmidt et al., 2011; Hudecova et al., 2011a,b; Carmina et al., 2013; Ramezani Tehrani et al., 2015; Udesen et al., 2019) were included in the meta-analysis for HDL-C concentration (mg/dl). Two studies (Talbott et al., 2007; Carmina et al., 2013) reported a statistically significant lower HDL-C concentrations among women with PCOS compared to those without PCOS (Supplementary Table SV). The meta-analysis for HDL-C concentration showed a lower HDL-C concentration among women with PCOS compared to women without PCOS (MD: −2.45 95% CI −4.51 to −0.38 mg/dl; $I^2 = 38\%$) (Fig. 3c). Subgroup analyses by study design showed no difference in HDL-C concentration based on four prospective studies (MD: −0.83 95% CI −3.04 to 1.39 mg/dl; $I^2 = 15\%$), but a lower HDL-C concentration based on three retrospective studies (MD: −4.58 95% CI −6.96 to −2.20 mg/dl; $I^2 = 0\%$). Subgroup analyses for four studies which diagnosed PCOS using the Rotterdam 2003 criteria also showed a lower HDL-C concentration among women with PCOS compared to women without PCOS (MD: −2.33 95% CI −4.53 to −0.12 mg/dl; $I^2 = 0\%$) (Hudecova et al., 2010; Schmidt et al., 2011; Carmina et al., 2013; Udesen et al., 2019). Sensitivity meta-analysis including three high-quality studies did not show a lower HDL-C concentration among women with PCOS (MD: −0.47 95% CI −4.41 to 3.48 mg/dl; $I^2 = 30\%$) (Supplementary Table SXIV).

Triglycerides. Five studies (Talbott et al., 1995; Cibula et al., 2000; Schmidt et al., 2011; Hudecova et al., 2011a,b; Carmina et al., 2013) were included in the meta-analysis for TG concentration (mg/dl). Three studies (Talbott et al., 2007; Schmidt et al., 2011; Hudecova et al., 2011a,b) reported statistically significant higher TG concentrations among women with PCOS (Supplementary Table SVI). The meta-analysis for TG concentration showed no difference in TG concentration among women with PCOS compared to women without PCOS (MD: 18.53 95% CI −0.58 to 37.64 mg/dl; $I^2 = 79\%$) (Fig. 3d). Subgroup analyses by study design showed no difference in TG concentration based on two prospective studies (MD: 15.02 95% CI −15.91 to 45.95 mg/dl; $I^2 = 72\%$) and three retrospective studies (MD: 21.45 95% CI −9.70 to 52.60 mg/dl; $I^2 = 82\%$). Subgroup analyses for three studies, which diagnosed PCOS using the Rotterdam 2003 criteria, showed no difference in TG concentration among women with PCOS compared to women without PCOS (MD: 22.15 95% CI −4.00 to 48.30 mg/dl; $I^2 = 83\%$) (Hudecova et al., 2010; Schmidt et al., 2011; Carmina et al., 2013). Sensitivity meta-analysis based on study quality could not be performed because only one study for this outcome was rated to be of high quality (Supplementary Table SXIV).

Non-fatal cardiovascular disease events

Coronary events. Seven studies (Cibula et al., 2000; Wild et al., 2000; Lo et al., 2006; Lunde and Tanbo, 2007; Schmidt et al., 2011; Iftikhar et al., 2012; Hart and Doherty, 2015) were included in the meta-analysis for non-fatal coronary events. Hart and Doherty (2015) reported a statistically significant higher rate of coronary events among women with PCOS compared to those without PCOS, while adjusting for obesity. Cibula et al. (2000) reported a higher unadjusted risk (Supplementary Table SVII). The meta-analysis showed no difference in non-fatal coronary events among women with PCOS compared to women without PCOS (0.6% vs 0.35%; RR: 1.78, 95% CI 0.99 to 3.23; $I^2 = 80\%$) (Fig. 4a). Subgroup analyses by study design showed no difference in coronary events based on six retrospective studies (RR: 1.86, 95% CI 0.97 to 3.55; $I^2 = 83\%$). Sensitivity meta-analysis including four high-quality studies also showed no difference in non-fatal coronary events among women with PCOS compared to women

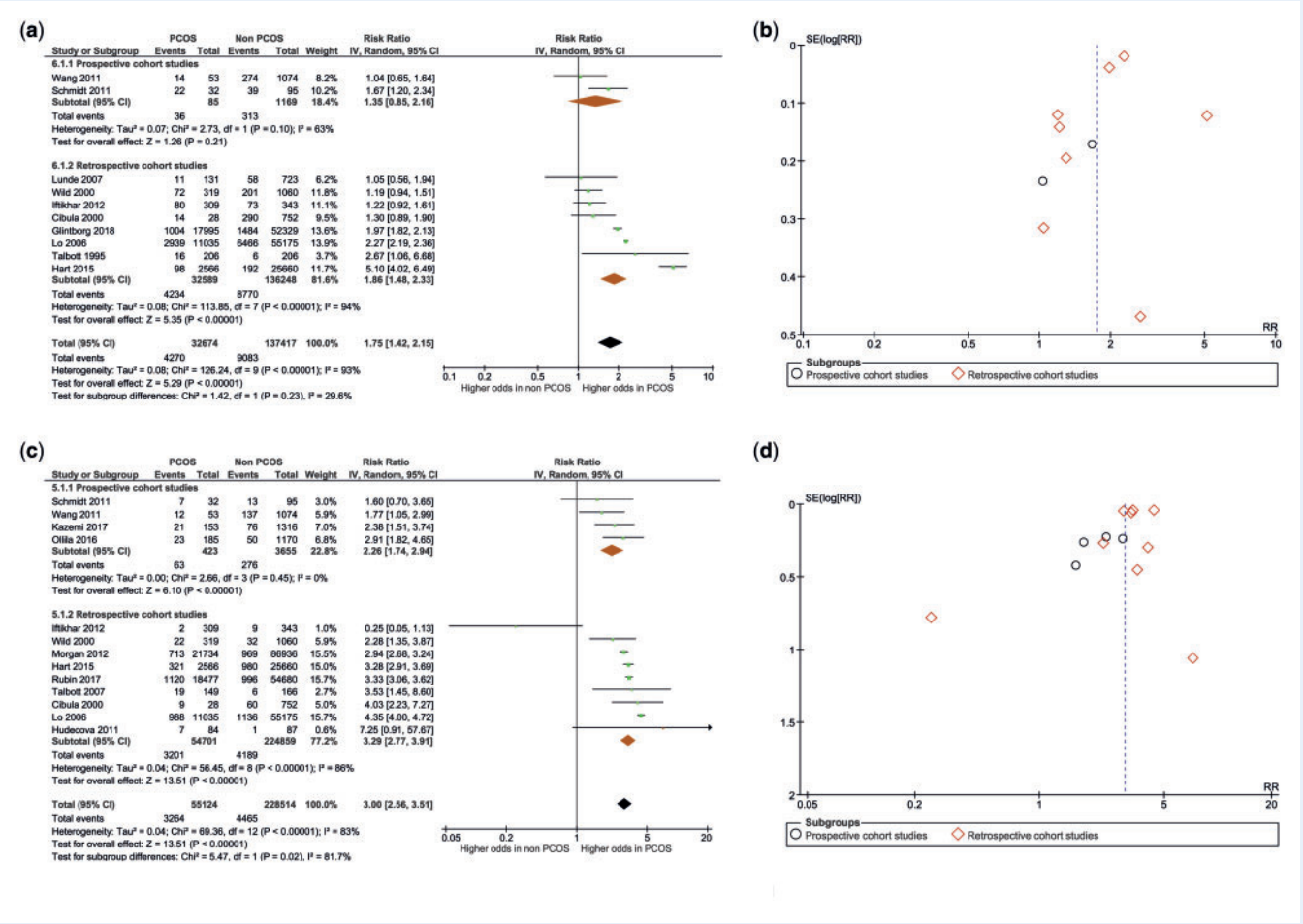

Figure 2. Forest plots and funnel plot for meta-analysis of hypertension and type 2 diabetes among women with PCOS compared to women without PCOS. (**a**) Forest plot for hypertension (HT); (**b**) Funnel plot for meta-analysis of HT; (**c**) Forest plot for and type 2 diabetes (T2D); (**d**) Funnel plot for meta-analysis of T2D. The dashed lines in the funnel plots indicate the aggregated point estimate for the corresponding meta-analysis.

without PCOS (0.47% vs 0.29%; RR: 1.99, 95% CI 0.83 to 4.80; I^2 = 89%) (Supplementary Table SXIII).

Cerebrovascular events. Eight studies were included in the meta-analysis for non-fatal cerebrovascular events (Wild *et al.*, 2000; Lo *et al.*, 2006; Lunde and Tanbo, 2007; Schmidt *et al.*, 2011; Iftikhar *et al.*, 2012; Hart and Doherty, 2015; Glintborg *et al.*, 2018; Meun *et al.*, 2018). Hart and Doherty (2015) and Wild *et al.* (2000) reported a statistically significant higher rate of cerebrovascular events in women with PCOS compared to those without PCOS, while adjusting for measures of obesity (Supplementary Table SVIII). The meta-analysis showed a higher rate for cerebrovascular events among women with PCOS compared to women without PCOS (0.6% vs 0.4%; RR: 1.41, 95% CI 1.02 to 1.94; I^2 = 57%) (Fig. 4b). Subgroup analyses by study design showed no difference in cerebrovascular events based on two prospective studies (RR: 1.11, 95% CI 0.52 to 2.37; I^2 = 48%); but a higher rate in the PCOS group including six retrospective studies (RR: 1.52, 95% CI 1.02 to 2.25; I^2 = 64%). Sensitivity meta-analysis including six high-quality studies no longer showed a difference in non-fatal cerebrovascular events among women with PCOS compared to women without PCOS (0.83% vs 0.54%; RR: 1.27, 95% CI 0.89 to 1.81; I^2 = 60%) (Supplementary Table SXIII).

Composite outcomes for non-fatal cardiovascular disease events. Two retrospective studies (Morgan *et al.*, 2012; Glintborg *et al.*, 2018) did not report separately for coronary or cerebrovascular events (Supplementary Table SIX) and could therefore not be included in the meta-analyses for non-fatal coronary and cerebrovascular events. Glintborg *et al.* (2018), which was one of these two studies, reported a higher unadjusted rate of CVD events after excluding women with HT or dyslipidaemia when they compared women with PCOS to those without PCOS. Morgan *et al.* (2012) reported no difference in large-vessel-disease (myocardial infarction, stroke, angina, central or peripheral revascularization) based on READ code classifications. The meta-analysis showed no difference in composite outcome rate for non-fatal cardiovascular events among women with PCOS compared to women without PCOS (3.3% vs 2.0%; RR: 1.25, 95% CI 0.92 to 1.69; I^2 = 70%) (Fig. 4c). Sensitivity meta-analysis based on study quality could not be performed because only one study for this outcome was rated to be of high quality (Supplementary Table SXIII).

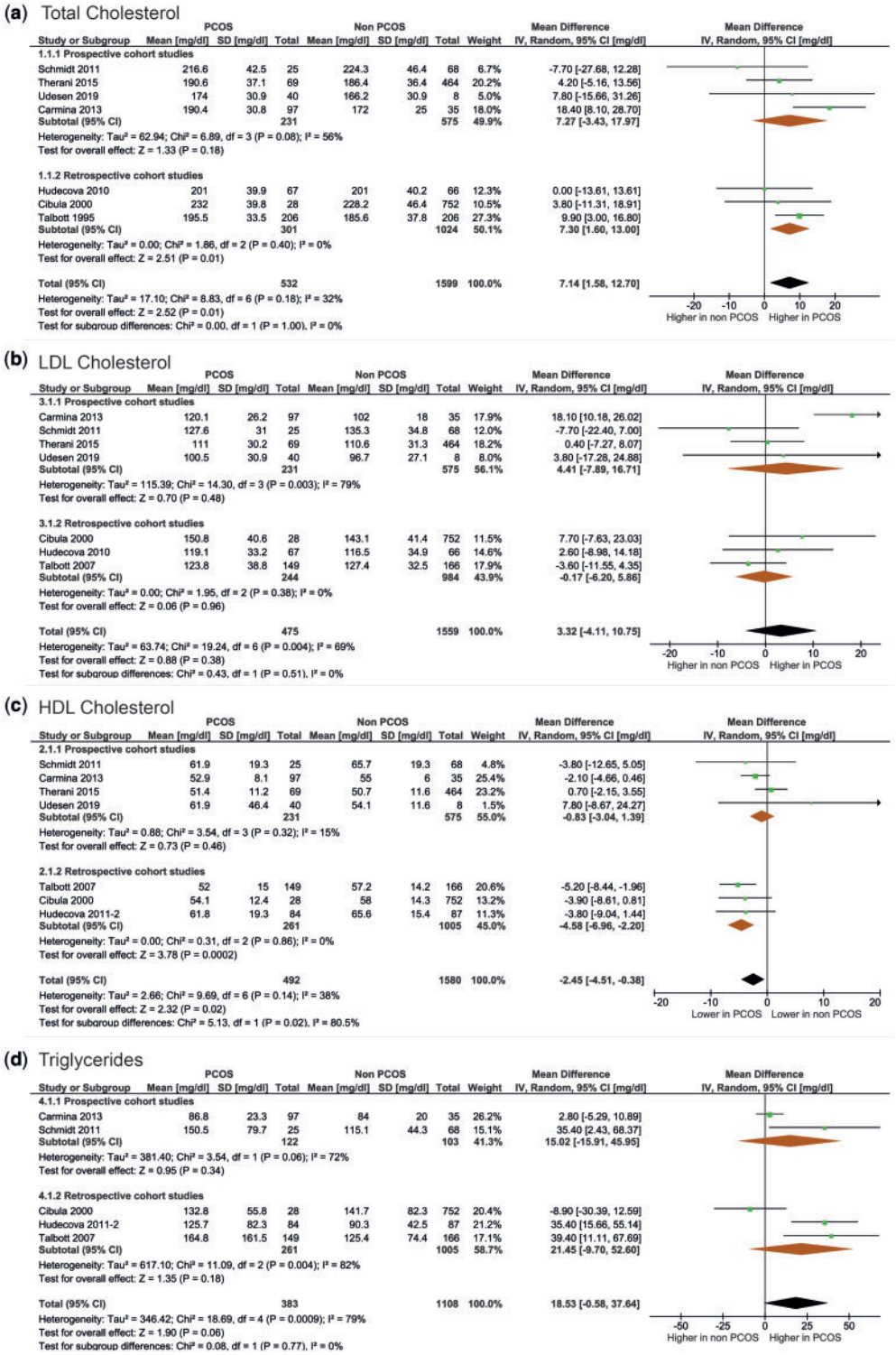

Figure 3. Forest plot for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides (mg/dl) concentration among women with PCOS compared to women without PCOS. Forest plots for (**a**) total cholesterol (TC); (**b**) low-density lipoprotein cholesterol (LDL-C); (**c**) high-density lipoprotein cholesterol (HDL-C); (**d**) triglycerides (TG).

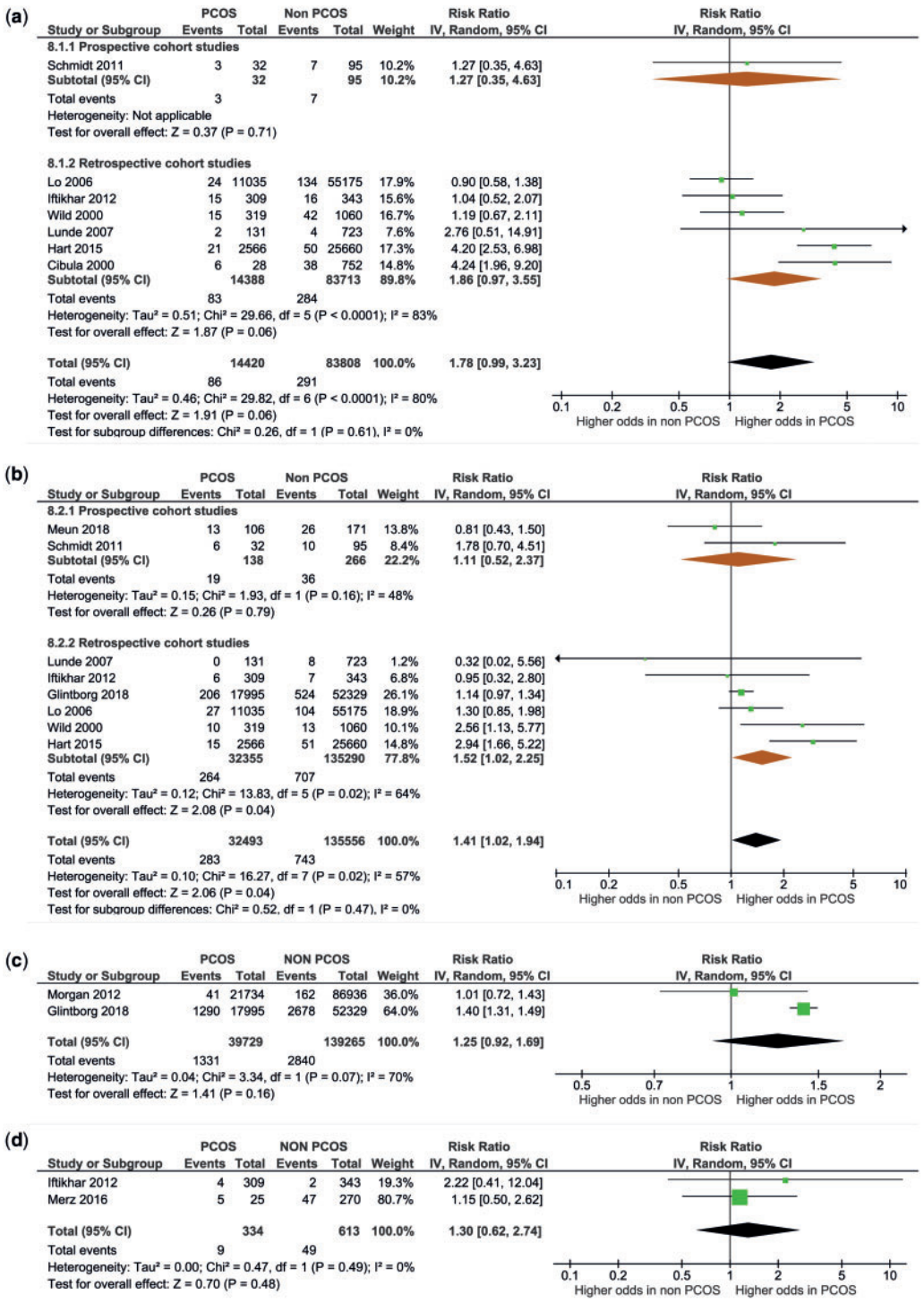

Figure 4. Forest plot for non-fatal coronary events, non-fatal cerebrovascular events, composite outcome for non-fatal cardiovascular disease events and composite outcomes for fatal and non-fatal cardiovascular disease events among women with PCOS compared to women without PCOS. Forest plots for (**a**) non-fatal coronary events; (**b**) non-fatal cerebrovascular events; (**c**) composite outcome for non-fatal cardiovascular disease events; (**d**) composite outcome for fatal cardiovascular disease events.

Fatal cardiovascular disease events

Fatal coronary events. Schmidt *et al.* (2011) reported on the number of deaths caused by myocardial infarction in women with PCOS compared to those without PCOS, based on ICD codes. There was no statistically significant difference in mortality rate between women with and without PCOS (RR: 14.48, 95% CI 0.14 to 15.83) (Supplementary Table SX).

Fatal cerebrovascular events. Schmidt *et al.* (2011) reported on the number of deaths caused by cerebral haemorrhage in women with PCOS compared to those without PCOS, based on ICD codes. There was no statistically significant difference in mortality rate between women with and without PCOS (RR: 0.58, 95% CI 0.03 to 11.81) (Supplementary Table SXI).

Composite outcomes for fatal cardiovascular disease events. Two studies (Iftikhar *et al.*, 2012; Merz *et al.*, 2016) were included in a meta-analysis on composite outcomes for fatal CVD events. Merz *et al.* (2016) included sudden cardiac death, end-stage congestive heart failure, acute myocardial infarction, peripheral heart disease, and cerebrovascular accident in their composite outcome for fatal CVD event. Iftikhar *et al.* (2012) included all CVD-related deaths in their composite outcome for fatal CVD event. Neither study reported a difference in composite outcome rate for fatal CVD event among women with PCOS compared to women without PCOS, while adjusting for confounders (Supplementary Table SXII). Meta-analysis showed no difference in composite outcome rate for fatal CVD between women with PCOS and women without PCOS (2.7% vs 8.0%; RR: 1.30, 95% CI 0.62 to 2.74) (Fig. 4d). Sensitivity meta-analysis based on study quality could not be performed because only one study for this outcome was rated to be of high quality (Supplementary Table SXIII).

Discussion

In this systematic review of the literature, based on 23 studies, we found that women with PCOS were more likely to be diagnosed with cardiometabolic risk factors, such as T2D and HT, and had a more adverse lipid profile in comparison to women without PCOS. Women with PCOS also had a higher risk for non-fatal cerebrovascular disease events but not of coronary disease events. Sensitivity meta-analyses including high-quality studies only provided evidence of increased T2D and HT risks in women with PCOS in comparison to women without PCOS. The paucity of mortality data did not allow us to draw conclusions concerning fatal outcomes. We were unable to assess the extent to which increased cardiometabolic risk among women with PCOS was independent of obesity.

The underlying pathways linking PCOS to T2D, HT, dyslipidaemia and overt cardiovascular events are complex and involve many interacting cardiovascular and metabolic factors (Meschia *et al.*, 2014). Intrinsic insulin resistance, often present and linked to hyperandrogenism in women with PCOS, is also associated with cardiometabolic disease (Ginsberg, 2000; Baptiste *et al.*, 2010; Stepto *et al.*, 2013; Cassar *et al.*, 2016). Insulin resistance leads to increased lipolysis from adipose tissue and facilitates dyslipidaemia, which has a toxic effect on the pancreatic islet cells (Cerf, 2013). As a result, apoptosis of pancreatic islet cells is induced, increasing the risk for glucose intolerance and eventually chronic hyperglycaemia and T2D (Sharma and Alonso, 2014; Oh *et al.*, 2018). Insulin resistance is also linked to HT through the impairment of the insulin specific endothelial pathway, resulting in vasoconstriction through a diminished nitrogen oxide production (Muniyappa *et al.*, 2007). Finally, hyperinsulinaemia leads to vascular inflammation and water retention in the kidney which contributes to an elevated blood pressure (Zhou *et al.*, 2014). Dyslipidaemia and elevated blood pressure are important factors in aggravating the process of atherosclerosis eventually leading to cardiovascular events (Tuñón *et al.*, 2007).

This systematic review and meta-analysis reports on all important cardiometabolic outcomes based on longitudinal studies. The search strategy and systematic methods, including quality assessment, publication bias assessment, subgroup analyses for study design, sensitivity analyses and follow-up duration, are among the strengths of this study. Our study has some limitations, mostly concerning clinical and statistical heterogeneity. The criteria for PCOS diagnosis were not identical between studies (Tables I and II), and only for lipids were a sufficient number of studies using the same diagnostic criteria available to perform a subgroup analysis. Therefore, we could not differentiate cardiometabolic risk factors and CVD event risks by diagnostic criteria for PCOS (El Hayek *et al.*, 2016). Furthermore, the diagnostic criteria for clinical outcomes were heterogeneous between studies. The clinical heterogeneity between the studies we included might affect the generalizability of our findings to specific clinical settings in which one of the various diagnostic criteria are used. This is a major limitation of our study and other studies investigating the relationship between PCOS and CVD. Considerable heterogeneity ($I^2 > 70\%$) was present in the meta-analyses for non-fatal coronary events, HT, T2D, and TG (Moher *et al.*, 2009; Higgins, 2011), but exclusion of outliers reduced the heterogeneity without altering the conclusions (Fletcher, 2007). For non-fatal coronary events and TG no outliers could be detected, however step-wise *post hoc* exclusion of studies of which the CI was most deviating from the summary CI also reduced the heterogeneity in the meta-analysis of non-fatal coronary events without consequences for the conclusion.

Kakoly *et al.* (2018) showed that risk of T2D in PCOS is increased by obesity and different in women with PCOS from Europe compared to Asia, based on meta-regression analyses. However, due to the low number of included studies per meta-analysis and lack of uniform data on possible confounding factors such as BMI in the included studies, we refrained from performing meta-regression analyses (Thompson and Higgins, 2002). In addition, included studies were performed in countries with predominantly Caucasian women, therefore we did not perform subgroup analyses based on ethnicity as described in our protocol. Consequently, our results are particularly generalizable to the Caucasian population.

Most of the included studies were of retrospective design and these studies included the largest number of women. In general, the retrospective studies had larger point estimates than the prospective studies. Although the direction of the overall effect was similar, the meta-analysis for T2D and HDL-C showed considerate heterogeneity ($I^2 > 70\%$) between the point estimates of the prospective and retrospective studies. The heterogeneity is likely to be based on an overestimation of the effect in the retrospective studies (Vandenbroucke, 2008). For all other outcomes, the heterogeneity between the subgroup analyses based on study design was low, indicating that the overall results of these meta-analyses were independent of study

design (Higgins, 2011). The higher risk estimates for HT and T2D based on retrospective studies in comparison to the prospective studies could be explained by ascertainment bias, because women with a PCOS diagnosis might have had more intensive screening for these outcomes than women without PCOS.

The follow-up studies included in this meta-analysis corrected for various confounders including obesity (Tables I and II). This makes it impossible to study whether the effects are independent of obesity, an important confounder in the relationship between PCOS and cardiometabolic risk (Lim *et al.*, 2012). This question might be better answered by an individual patient data meta-analysis. The eligible studies were, however, performed many years back, which may present a barrier to retrieving the data (Tierney *et al.*, 2015). The publication of anonymized datasets and standardized registration of the PCOS phenotype (presence of clinical or biochemical hyperandrogenism; menstrual irregularities or polycystic ovaries on ultrasonography) and obesity among studies would allow us to investigate which women diagnosed with PCOS have an increased cardiometabolic risk independent of obesity (Jovanovic *et al.*, 2010; Bil *et al.*, 2016). The development of a core outcome set for PCOS, which is currently underway, may help achieve this goal (http://www.comet-initiative.org/studies/details/1115).

Based on the current unadjusted meta-analyses, the magnitude of the risk increase in PCOS is comparable to having a first degree family history of T2D (hazard ratio: 2.72, 95% CI 2.48 to 2.99) (Scott *et al.*, 2013). PCOS is a stronger risk factor for stroke than a family history of CVD (odds ratio: 1.38, 95% CI 1.01 to 1.88) (Valerio *et al.*, 2016). Given the increase in cardiometabolic risk, it is understandable that cardiometabolic screening of women with PCOS is regularly suggested in international guidelines (Huang and Coviello, 2012; Andersen and Glintborg, 2018). However, it is important to consider that increased risk alone does not justify screening (Andermann *et al.*, 2008). Screening should only be performed if it leads to earlier recognition of modifiable cardiometabolic risk factors and if treatment leads to better health outcomes (Andermann *et al.*, 2008). PCOS is often diagnosed in young women who have a low absolute risk of overt cardiometabolic disease. Screening for CVD in a relatively low-risk population may be associated with low yield of preventable cases, considerable costs and possible harms incurred by overdiagnosis (Lipitz-Snyderman and Bach, 2013). A randomized trial comparing screening of established cardiometabolic risk factors, such as HT, T2D and dyslipidaemia, in women with PCOS to no screening, in combination with long-term follow-up to evaluate the effect of treatment on cardiometabolic outcomes (blood pressure, glucose metabolism and lipids) and event rates (fatal and non-fatal coronary or cerebrovascular events) to usual care, would provide the best answer as to whether screening is effective (Bell *et al.*, 2015). However, these screening studies are non-existent and are unlikely to be performed in the near future, since they take decades to perform, due to the time between the diagnosis of PCOS and CVD events. Despite the absence of compelling evidence in support of the effectiveness of CVD risk screening in PCOS, the newest international guideline on PCOS management advises such screening in all women with PCOS irrespective of BMI (Wild *et al.*, 2010; Teede *et al.*, 2018). The guideline advises annual blood pressure evaluation and glycaemic status evaluation every 1–3 years in all women with PCOS (Teede *et al.*, 2018). However, if the added cardiometabolic risk of PCOS on top of traditional risk factors is small or if patients with PCOS who are at risk for cardiometabolic disease already qualify for screening because of their obesity status, it is unlikely to be cost-effective to screen all women with PCOS. We suggest a high-quality longitudinal study in PCOS women stratified for obesity status, prior to universal screening of all women with PCOS, including those who are lean (Andermann *et al.*, 2008). Furthermore, early consequences of PCOS, such as menstrual cycle disturbances and infertility, could be used as a window of opportunity to prevent long-term cardiometabolic consequences by increasing awareness about the importance of a healthy lifestyle, and providing support to optimize modifiable lifestyle factors such as smoking and obesity (Piepoli *et al.*, 2016; van Dammen *et al.*, 2018).

In conclusion, we found that women with PCOS have a substantially increased crude risk for future HT and T2D. Also, PCOS might lead to adverse lipid serum concentrations and increase in non-fatal cerebrovascular events, although sensitivity meta-analyses including only high-quality studies did not indicate these associations. We were unable to establish point estimates that accounts for excess obesity rates among women with PCOS. Whether screening strategies can amend this cardiometabolic risk should be investigated.

Supplementary data

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

Authors' roles

All authors were involved in the design of the study. J.L. performed the electronic searches. V.W., L.v.D. and A.K. executed the study (performed the study selection, data extraction and quality assessment). V.W. performed the data analyses. All authors were involved in the drafting of the manuscript and critical discussion. All authors approved the final manuscript.

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Conflict of interest

J.S.E.L. has received grants and consultancy fees from the following companies (in alphabetical order): Ansh Labs, Danone, The Dutch heart Association, Euroscreen, Ferring, Merck Serono, Titus Healthcare and ZonMW. The Department of Reproductive Medicine of the UMCG received an unrestricted educational grant from Ferring Pharmaceuticals BV, The Netherlands. All other authors have nothing to declare.

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