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PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis

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BACKGROUND: Patients with polycystic ovary syndrome (PCOS) are at risk of arterial disease. We examined the risk of (non)fatal coronary heart disease (CHD) or stroke in patients with PCOS and ovulatory women without PCOS, and assessed whether obesity might explain a higher risk of CHD or stroke.

METHODS: We performed a systematic review and meta-analysis of controlled observational studies. Four definitions of PCOS were considered: World Health Organization type II anovulation, National Institutes of Health criteria, Rotterdam consensus and Androgen-excess criteria. Obesity was defined as BMI $> 30\ kg/m^2$ and/or waist circumference >88 cm. Study quality was assessed using the Newcastle–Ottawa Scale. Primary outcome was fatal/non-fatal CHD or stroke. Definitions of CHD and stroke were based on criteria used by the various authors. The effect measure was the pooled relative risk in a random effects model. Risk ratios and rate ratios were combined here.

RESULTS: After identifying 1340 articles, 5 follow-up studies published between 2000 and 2008 were included. The studies showed heterogeneity in design, definitions and quality. In a random effects model the relative risk for CHD or stroke were 2.02 comparing women with PCOS to women without PCOS (95% confidence interval 1.47, 2.76). Pooling the two studies with risk estimates adjusted for BMI showed a relative risk of 1.55 (1.27, 1.89).

CONCLUSIONS: This meta-analysis showed a 2-fold risk of arterial disease for patients with PCOS relative to women without PCOS. BMI adjustment did not affect this finding, suggesting the increased risk for cardiovascular events in PCOS is not completely related to a higher BMI in patients with PCOS.

Key words: polycystic ovary syndrome / systematic review / arterial disease / obesity / BMI

Introduction

Since the publication by Stein and Leventhal (1935) on polycystic ovary syndrome (PCOS), one biological definition [World Health Organization (WHO) II anovulation; WHO II; WHO (1973)] and three consensus definitions have been published on PCOS: National Institutes of Health (NIH) in 1990 (Zawadski, 1992), Rotterdam in 2003 (R'dam; Rotterdam, 2004) and Androgen-excess PCOS in 2006 (AE; Azziz *et al.*, 2009). In the NIH definition the symptoms hyperandrogenism and anovulation were considered as important features of PCOS. The Rotterdam consensus work group added polycystic ovary morphology to these two criteria, whereas the Androgen-excess PCOS criteria were the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) and the exclusion of related disorders.

Apart from anovulation, increased BMI is a common feature in women with PCOS, with a prevalence of 30–70% (Zawadski, 1992; Azziz *et al.*, 2004; Ehrmann, 2005; Broekmans *et al.*, 2006; Vrbikova and Hainer, 2009). Since the 90s of the last century an association between PCOS and cardiovascular disease, predominantly arterial disease, has been recognized. The American Society for Reproductive Medicine (ASRM) Practice Committee associated PCOS with an increased risk for cardiovascular diseases (ASRM, 2008). In a search in PubMed (14 September 2010), 481 hits were retrieved by inserting 'PCOS' and the MeSH term 'cardiovascular disease', and 197 of these hits were reviews. As PCOS is associated with obesity, it is still under debate whether in PCOS the possible increased risk for cardiovascular events (such as myocardial infarction or stroke), is merely related to obesity. Or does PCOS per se contribute to this increased risk, independent of obesity?

Therefore, we examined in this systematic review whether patients with PCOS, defined according to the currently used WHO (WHO, 1973), NIH (Zawadski, 1992), Rotterdam (Rotterdam, 2004) and AE PCOS (Azziz *et al.*, 2009) criteria, have a higher risk of fatal or non-fatal coronary heart disease (CHD) or stroke relative to ovulatory women without PCOS. Further, we assessed whether obesity among patients with PCOS might explain a possible higher risk of CHD or stroke.

Methods

Identification of trials and eligibility criteria

Controlled studies comparing women with PCOS to women without PCOS were considered for eligibility. We selected reports with categorical data on any of the following outcomes: incident CHD and/or stroke (non-fatal or fatal). Studies without a control group or that did not distinguish women with or without PCOS were not included. Comparison of PCOS to non-PCOS can only be assessed in observational studies, thereby restricting this meta-analysis to non-randomized studies.

For study inclusion, PCOS should have been defined according to the WHO (WHO, 1973), NIH (Zawadski, 1992), Rotterdam (Rotterdam, 2004) or AE (Azziz *et al.*, 2009) criteria and the control group should be PCOS-free. For the definition of obesity and waist circumference associated with health risk, we used the criteria of the American Medical Association (2010) and WHO (2006) for women: obesity (>30 kg/m^2) and waist circumference >88 cm (Whitlock *et al.*, 2009). The definition of CHD and stroke was based on the criteria used by the various authors.

Relevant studies were identified from the Cochrane Central Register of Controlled Trials (CENTRAL) using the keyword PCOS and cardiovascular disease. The National Center for Biotechnology Information Pubmed database was searched for articles published before January 2010 using any combination of the terms 'PCOS, polycystic ovarian syndrome, adipositas, obesity, myocardial infarction, stroke, cerebrovascular accident, cardiac disease, arterial occlusive disease, heart disease, cardiac disease'. The EMBASE, CINAHL, POPLINE and LILACS databases were searched in a similar fashion for additional articles. The detailed search strategy is displayed in Appendix 1. Review articles were cross-referenced with the results of the expanded search. Manual searches were performed of the reference lists of selected articles. The search was not limited by language or publication status. Data extraction was independently performed by three investigators (P.G., S.W.M.D., F.M.H.). Disagreement was resolved by consensus.

Quality assessment

The quality of the included studies was assessed according to the Newcastle–Ottawa Scale (Higgins and Green, 2009), a validated scale for meta-analysis of observational studies. We scored (max. nine points) the following items important for risk of bias assessment in non-randomized cohort studies: representativeness of the exposed cohort; adequate selection of controls; adequate definition of the outcome (CHD/stroke); adequacy of follow-up; comparability of exposed and non-exposed women (two points). Low methodological quality was not an exclusion criterion.

Data analysis

The primary outcome of the meta-analysis was the pooled risk ratio for CHD or stroke or mortality related to CHD or stroke for women with PCOS compared with women without PCOS. In a second analysis we calculated the BMI-adjusted pooled risk ratio. Studies reporting risk ratios as well as studies reporting rate ratios were eligible. For all studies the risk ratio and its accompanying Standard error were extracted. On the basis of the expected heterogeneity of the included studies we performed a random effects model by default. Heterogeneity was calculated with the I^2 statistics. All analyses were performed with STATA 10.0, StataCorp LP, TX, USA.

Results

Literature search and study characteristics

The initial search (Fig. 1) yielded 1340 hits, 332 of which were duplicates. A total of 996 articles were not relevant for the research question, leaving 12 articles for detailed evaluation. In the reference list of those 12 publications, two additional articles were identified, providing 14 articles for the current review. Nine studies were excluded for the following reasons:

(i) surrogate endpoints for CHD (Dahlgren *et al.*, 1992a, b; Birdsall and Farquhar, 1997; Elting *et al.*, 2001; Moini and Eslami, 2009),
(ii) controls were mothers of daughters with PCOS (Cheang *et al.*, 2008),
(iii) PCOS definition not compatible with one of the four PCOS definitions of our study (WHO II, NIH, R'dam, AE) (Krentz *et al.*, 2007) and
(iv) double publication (Pierpoint *et al.*, 1998; Wild *et al.*, 2000a).

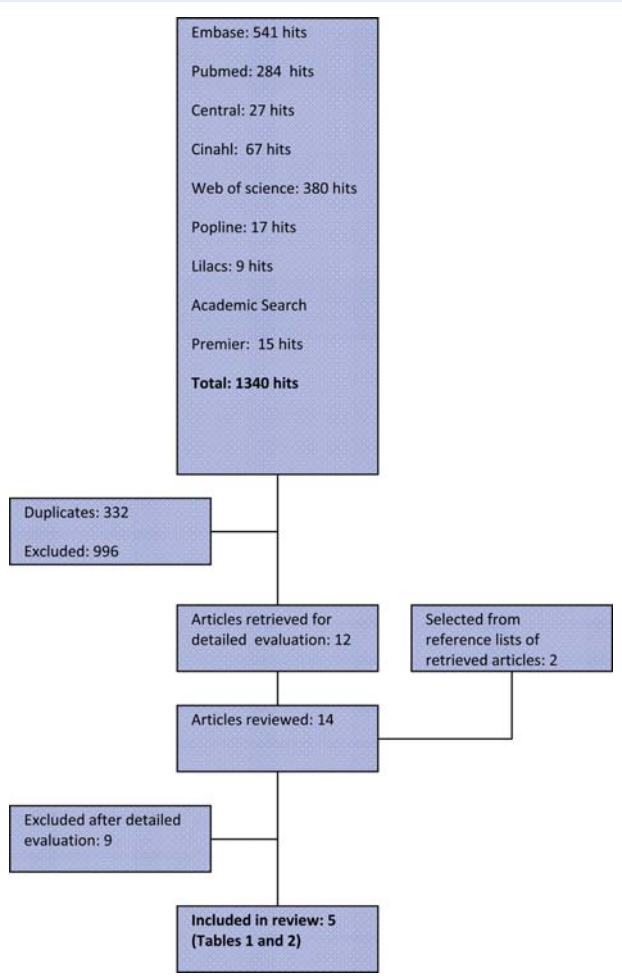

Figure 1 Search selection for studies on PCOS, CHD, stroke and the influence of obesity.

Finally, a total of five studies were included (Cibula *et al.*, 2000; Wild *et al.*, 2000b; Solomon *et al.*, 2002; Lunde and Tanbo, 2007; Shaw *et al.*, 2008; Table I for detailed information).

All five studies examined a cohort. All five studies used the WHO II anovulation criterion, three the NIH (Cibula *et al.*, 2000; Lunde and Tanbo, 2007; Shaw *et al.*, 2008), four the R'dam (Shaw *et al.*, 2008; Wild *et al.*, 2000b; Cibula *et al.*, 2000; Lunde and Tanbo, 2007) and four the AE definition (Cibula *et al.*, 2000; Wild *et al.*, 2000b; Lunde and Tanbo, 2007; Shaw *et al.*, 2008). Race was mentioned by Cibula *et al.* (2000) 'all Caucasians', by Solomon *et al.* (2002) '98% Caucasians' and Wild *et al.*, (2000b) '99% white etnic origin'. Shaw *et al.* (2008), Solomon *et al.* (2002) and Wild *et al.* (2000b) presented data of fatal cases due to acute myocardial infarction (AMI) and stroke. Lunde and Tanbo (2007) used hard clinical outcome of AMI, whereas Solomon *et al.* (2002) included 17% probable cases of non-fatal acute myocardial infarction/stroke in their analyses and Cibula *et al.* (2000) used no hard clinical outcome of non-fatal CHD ('chest pain evaluated as definite or possible angina, a history of definite or possible myocardial infarction, a history of transluminal percutaneous coronary angioplasty or coronary artery bypass grafting'). None of the five studies presented separate data for obesity (BMI and/or waist circumference) in the cases and controls. Four studies provided risk ratios, one study a rate ratio.

Table II shows the assessment of methodological quality according the Newcastle–Ottawa Scale (Higgins and Green, 2009). One study scored seven out of nine points (Shaw *et al.*, 2008) and one study scored six points (Solomon *et al.*, 2002), indicating high-quality. Three studies scored four points or less (Cibula *et al.*, 2000; Wild *et al.*, 2000b; Lunde and Tanbo, 2007), indicating low quality.

Meta-analysis

The relative risk for cardiovascular events ranged from 0.92 to 4.24. Four of five studies showed individually a significant increased risk for women with PCOS. The pooled relative risk from a random effects model was 2.02 (95% confidence interval 1.47, 2.76), showing a 2-fold increased risk for CHD/stroke in women with PCOS. The I^2 showed moderate heterogeneity (42%) (Fig. 2). Two studies provided BMI-adjusted risk estimates (Wild *et al.*, 2000b; Solomon *et al.*, 2002; Fig. 3). The pooled relative risk adjusted for BMI was 1.55 (95% confidence interval 1.27, 1.89). In both analyses most weight came from the Solomon study (Solomon *et al.*, 2002) that scored six out of nine points with the Newcastle–Ottawa Scale.

Discussion

The present meta-analysis was performed to assess the risk for cardiovascular events in PCOS. The five included studies showed heterogeneity in design, definitions and quality. A significant 2-fold risk of CHD and stroke for patients with PCOS relative to women without PCOS was found. Moreover, the risk was still increased by 55% in the studies that adjusted for BMI. This shows that increased BMI is not the sole cause of the increased cardiovascular risk in women with PCOS. The largest weight in the meta-analysis was provided by a high-quality study. In a systematic review on impaired glucose tolerance, type 2 diabetes and metabolic syndrome in PCOS, Moran *et al.* (2010) recently

Table I Characteristics of included studies.

Author	Year of publication	Study design	PCOS definition	Participants (*n*)	End-point	Effect measure	Relative risk (95% CI)
Cibula *et al.* (2000)	2000	Retrospective follow-up study	WHO II, NIH, R'dam, AE	PCOS 28, Controls 752	Non-fatal CHD and stroke	Risk ratio	4.24 (1.96, 9.17)
Lunde and Tanbo (2007)	2007	Retrospective follow-up study	WHO II, NIH, R'dam, AE	PCOS 131, Controls 723	Non-fatal CHD	Risk ratio	0.92
Shaw *et al.* (2008)	2008	Prospective follow-up study	WHO II, NIH, R'dam, AE	PCOS 104, Controls 286	Fatal + non-fatal CHD and stroke	Hazard ratio	2.3 (1.4, 3.8)
Solomon *et al.* (2002)	2002	Prospective follow-up study	WHO II	PCOS 49 292[a], Control 715 293	Fatal + non-fatal CHD and stroke	Rate ratio	1.67 (1.35, 2.06)
Wild *et al.* (2000b)	2000	Retrospective follow-up study	WHO II, AE, R'dam	PCOS 319, Control 1060	Non-fatal CHD and stroke	Odds ratio	1.9 (1.1, 3.3)

PCOS, polycystic ovary syndrome; CHD, coronary heart disease; CI, confidence interval; WHO, World Health Organization; NIH, National Institutes of Health; R'dam, Rotterdam; AE, Androgen-excess PCOS.
[a]Person years.

Table II Assessment of methodological quality (based on Newcastle–Ottawa Scale).

	Exposed cohort representative	Adequate control selection	Adequate end-point definition	Outcome unknown from start	Matched or adj. analysis (Comp.)[a]	Hard clinical outcome	Follow-up in patients >60 years	Adequate follow-up	Total
Cibula *et al.* (2000)	0	0	1	0	0	0	0	0	1
Lunde and Tanbo (2007)	0	0	1	0	1	1	0	1	4
Shaw *et al.* (2008)	0	1	1	1	1	1	1	1	7
Solomon *et al.* (2002)	1	1	1	1	1	1	0	0	6
Wild *et al.* (2000b)	1	0	1	1	1	0	0	0	4

[a]Comparability: two points.

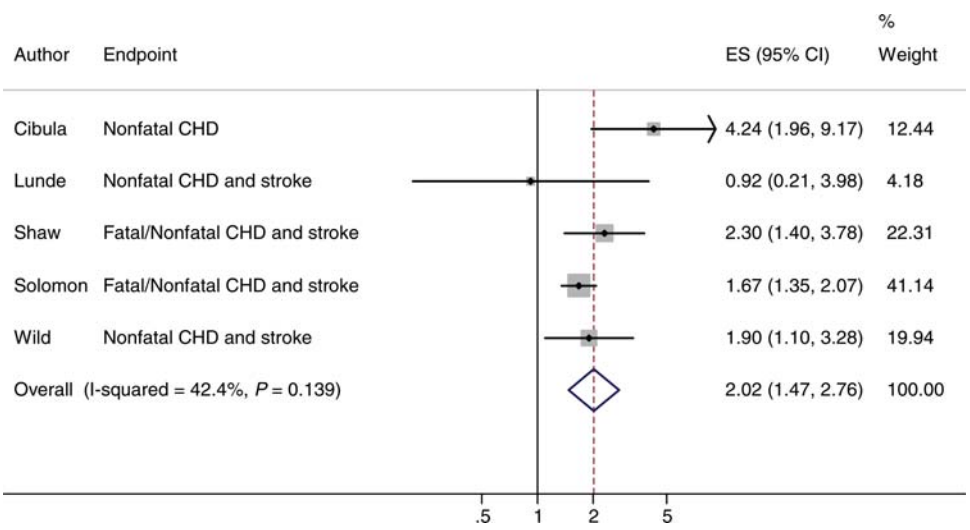

Figure 2 Meta-analysis of five cohort studies on the risk of CHD and stroke in PCOS. ES, effect size.

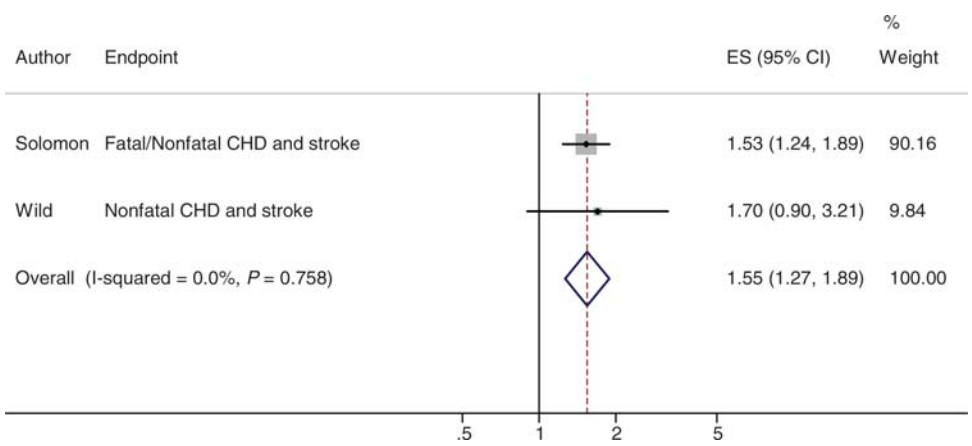

Figure 3 Meta-analysis of two cohort studies on the risk of CHD and stroke in PCOS adjusted for BMI. (Solomon *et al.* $\geq$25 kg/m^{2}and Wild *et al.* $\geq$30 kg/m^2). ES, effect size.

found that women with PCOS had increased prevalence of impaired glucose tolerance, type 2 diabetes in both BMI and non-BMI-matched studies.

This meta-analysis has several limitations. First, the definitions of PCOS used were not identical for all studies. Whereas anovulation is a characteristic of all definitions, it could not be estimated from the data whether the specific features of the other PCOS definitions (NIH, Rotterdam and AE) compared with the WHO anovulation have an effect on this risk. Second, hard clinical outcome data were not always used and separate data for coronary disease and stroke were not available in all five studies.

What are the implications of the results? We have shown that PCOS is associated with an increased cardiovascular risk. However, we are far from causality as formulated by Hill (1965) and various important questions remain to be investigated. Although increased BMI was not the sole cause of the increased risk for cardiovascular events, the role of BMI should be investigated in more detail in prospective studies. It is an open question whether the other distinguishing features of PCOS, such as hyperandrogenism, are causing the risk excess (Jovanovic *et al.*, 2010). A possible interference of infertility and of fertility treatments for patients with anovulation—the most explicit feature of ovarian dysfunction—on their arterial health might be involved.

Implications for practice

Our study showed that PCOS should be considered as a risk factor for cardiovascular disease; importantly, this risk is partially independent of BMI. Nevertheless, weight reduction remains an important aim of treatment in overweight patients with PCOS.

Implications for research

(i) Conduct observational studies according to STROBE guidelines (von Elm *et al.*, 2007),
(ii) use internationally accepted and clinically relevant definitions,
(iii) use hard clinical endpoints.

Authors' roles

P.C.M.G., F.M.H.: Study concept and design. P.C.M.G., S.W.M.D., F.M.H.: Acquisition of data. P.C.M.G., O.M.D., J.A.R., S.W.M.D., F.M.H.: Analysis and interpretation of data. P.C.M.G., O.M.D., J.A.R., S.W.M.D., F.M.H.: Drafting of the manuscript. O.M.D.: Statistical analysis.

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Appendix 1: Search methods for identification of studies

Search strategies

EMBASE database search strategy

(Exp polycystic ovary syndrome/OR (((pco or pcos or pcod) AND (ovary or ovarian or ovaria)) OR polycystic ovary syndrome* OR polycystic ovarian syndrome* OR cystic ovary OR micropolycystic ovary OR micropolycystic ovaries OR multiple follicle cyst OR ovary polycystic syndrome OR polycystic ovarian disease OR polycystic ovary OR polycystic ovaries OR polycystic ovary disease OR polycystic ovary syndrome).mp) AND (Stroke/OR Exp heart diseases/OR (Myocardial infarct* or stroke or cerebrovascular accident* or heart infarct* or heart disease* or cardiac disease*).mp OR exp peripheral occlusive artery disease/OR Cerebrovascular accident/OR (arterial disease* OR artery diseas*).mp OR (heart OR myocardial OR cardiac OR cerebrovascular OR arterial OR coronary).ti).

NCBI-pubmed database search strategy

(((pco[tw] OR pcos[tw] OR pcod[tw]) AND (ovary[tw] OR ovarian[tw] OR ovarial[tw] OR ovaries[tw])) OR polycystic ovary syndrome OR polycystic ovary syndrome*[tw] OR polycystic ovarian syndrome OR cystic ovary OR micropolycystic ovary OR micropolycystic ovaries OR multiple follicle cyst OR ovary polycystic syndrome OR polycystic ovarian disease OR polycystic ovary OR polycystic ovaries OR polycystic ovary disease OR polycystic ovary syndrome) AND (myocardial infarction OR "stroke"[Text word] OR "stroke"[MeSH Terms] OR cerebrovascular accident*[Text Word] OR "heart diseases"[MeSH Terms] OR heart disease*[Text Word] OR cardiac disease*[tw] OR "Arterial Occlusive Diseases"[Mesh] OR heart[ti] OR myocardial[ti] OR cardiac[ti] OR cerebrovascular[ti] OR arterial[ti] OR coronary[ti] OR "arterial disease" OR "arterial diseases" OR "artery disease" OR "artery diseases").