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REVIEW

Birthweight and PCOS: systematic review and meta-analysis

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STUDY QUESTION: Are intrauterine conditions, reflected in birthweight, associated with the development of polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Our study indicates that a low birthweight as a summary measure of intrauterine environment may be associated with PCOS when diagnosed according to the Rotterdam criteria.

WHAT IS ALREADY KNOWN: The etiology of PCOS is still largely unknown. Besides subfertility, women diagnosed with PCOS have an increased risk of chronic health issues. PCOS has been linked to adverse prenatal conditions, including a low birthweight.

STUDY DESIGN, SIZE, DURATION: A systematic search of the literature and meta-analysis of pooled data was undertaken, according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines.

PARTICIPANTS/MATERIALS, SETTING, METHOD: The following online databases were systematically searched: PubMed, EMBASE, CINAHL (via EBSCO) and Cochrane library up to 10 June 2017, with no language or date restrictions.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 1484 studies were identified of which 16 met the inclusion criteria and 14 provided data for meta-analysis. The exposure variable birthweight was either analyzed as a categorical variable using the birthweight categories <2.5, 2.5–4 and >4 kg, or as a continuous variable. We composed a birthweight category consisting of birthweights <2.5 kg plus birthweights >4 kg, reflecting extreme birthweights. In a subset analysis, we investigated the association between a low birthweight and PCOS while differentiating between Rotterdam and NIH criteria. When diagnosed according to the Rotterdam criteria, women born with birthweights lower than 2.5 kg had an odds ratio [95% CI] of 1.76 [1.14,2.70] for PCOS compared to women born with birthweights higher than 2.5 kg. For the latter analysis, we were able include 1252 women (I^2 = 16%). There was no significant effect of birthweight on PCOS when diagnosed according to NIH criteria.

LIMITATIONS REASONS FOR CAUTION: The funnel plot of the studies providing data for the meta-analysis and the subset analysis indicates a publication bias.

WIDER IMPLICATIONS OF THE FINDINGS: A low birthweight could be a risk factor for PCOS when diagnosed according to the Rotterdam criteria.

STUDY FUNDING/COMPETING INTERESTS: None.

TRIAL REGISTRATION NUMBER: The protocol of this study was registered at PROSPERO under registration number CRD42016048972.

Key words: polycystic ovary syndrome / birthweight / systematic review / meta-analysis / developmental origins of health and disease / Rotterdam criteria / National Institutes for Health criteria / low birthweight

WHAT DOES THIS MEAN FOR PATIENTS?

Polycystic ovary syndrome (PCOS) is one of the most common causes of female fertility problems. Symptoms often first arise fairly early in life, and it is thought that PCOS could be related to the environment in the womb before birth.

Being born with a low birthweight is seen as an indication of the conditions in the womb, and so this study analyses existing research on PCOS and birthweight to see whether there are any links between the two. More than a thousand PCOS studies were assessed and 14 were found to be suitable to be included in the analysis.

It was found that the way PCOS was diagnosed made a difference to the outcome. When the most common way of deciding who has PCOS was used as the definition, there was a link between having PCOS and having been born with a low birthweight. When a more stringent definition was used, the studies did not show a link.

Introduction

With a documented prevalence of up to 20% depending on diagnostic criteria, polycystic ovary syndrome (PCOS) is one of the most common causes for reduced fertility in women (Sirmans and Pate, 2013). The diagnostic criteria for PCOS have been subject to change over the last decades. The US National Institutes for health (NIH) criteria, published in 1990, require the presence of hyperandrogenism and menstrual dysfunction to diagnose PCOS (Zawadski and Dunaif, 1992). The Rotterdam criteria, first published in 2003, require two out of three of the following features; oligo-anovulation, hyperandrogenism and polycystic ovary morphology (PCOM) by ultrasound (Rotterdam, 2004). In 2006, the Androgen Excess Society published new diagnostic criteria which required the presence of clinical or biochemical hyperandrogenism in the presence of either PCOM or menstrual dysfunction to diagnose PCOS (Azziz *et al.*, 2006). The majority of women diagnosed with PCOS present with fertility issues. However, an increased risk of obesity, insulin resistance, cardiovascular disease and overall mortality are also highly associated with PCOS (Wild, 2002; Orio *et al.*, 2016; RCOG Ledger, 2014).

While the etiology of PCOS remains largely unclear, the clinical manifestations of PCOS often present themselves during childhood or puberty suggesting early life or prenatal influences. A 'two-hit' hypothesis has been suggested where two insults during specific developmental windows are required for the development of PCOS. The first hit being prenatal or early childhood influences such as hyperandrogenism due to genetic or environmental factors (Bremer, 2010; Diamanti-Kandarakis *et al.*, 2008). Animal studies in non-human primates indicate that elevated prenatal testosterone levels during critical periods of gestation can cause a PCOS-like phenotype, as well as intrauterine growth restriction (Dumesic *et al.*, 2007) (Abbott *et al.*, 2013).

In the last decades, epidemiological and animal studies have also provided compelling evidence for the association between adverse perinatal conditions, often using birthweight as a marker, and an increased risk of cardiovascular disease and insulin resistance (Gluckman and Hanson, 2006).

As PCOS and adverse perinatal conditions both are established risk factors for insulin resistance and cardiovascular disease, the question remains if these two risk factors are related. Adverse perinatal conditions could be the starting point of the pathogenesis of PCOS followed by metabolic syndrome or an additional risk factor in the chain of factors leading to PCOS as well as an independent risk factor for metabolic syndrome.

This review seeks to establish, through a systematic examination of the available literature and meta-analysis of pooled data, the association of intrauterine conditions, as reflected in birthweight, with the development of PCOS.

Materials and Methods

Search strategies

This review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines. The protocol of this study is registered at PROSPERO under registration number CRD42016048972. A comprehensive search was performed in the bibliographic databases PubMed, EMBASE.com, CINAHL (via EBSCO) and Cochrane library (via Wiley) with no language or date restrictions from inception to 10 June 2017. Additionally, the reference lists of relevant studies, review articles and opinion papers were checked by snowball search to identify any secondary references. Search terms included controlled terms (MeSH in Pubmed, EMtree in EMBASE.com), as well as free-text terms (Cochrane Library). The following terms were used (including synonyms and closely related words) as index terms or free-text words for 'birthweight' or 'gestational age' and the outcome variable 'Polycystic ovary syndrome' with aid of a clinical librarian (L.J.S.). Detailed information on the search strategy is listed in the Supplementary Data.

Study selection and eligibility

After identifying and excluding duplicate studies, two independent reviewers (S.S. and E.V.H.H.) evaluated titles and abstracts for suitability using a customized inclusion–exclusion chart. Any disagreement between reviewers was resolved through consensus and if consensus could not be reached the article was added to the full-text selection. Studies were included if they

- were cross-sectional, case–control, cohort or intervention studies;
- were conducted in adult humans;
- reported cases with PCOS diagnosis and diagnostic criteria for PCOS;
- described a control group of women not diagnosed with PCOS, self-reported or after medical examination;
- reported birthweight and/or gestational age, self-reported or extracted from medical files; and
- reported birth parameters that were related to women who were diagnosed with PCOS.

Full texts were retrieved for studies that satisfied all selection criteria and independently reviewed by two authors (S.S. and E.V.H.H.) for eligibility using the same inclusion–exclusion chart.

Quality assessment and data extraction

Selected studies were assessed independently for methodological validity by two reviewers using the Newcastle–Ottawa scale with a maximum of nine stars (see website: Wells GA). Included studies were classified as low-quality (0–4 stars), moderate-quality (5–6) and high-quality (7–9). Any disagreement between reviewers was resolved through consensus and if consensus could not be reached a third reviewer (C.B.L.) was consulted.

A piloted data extraction form was used to extract relevant information. The form included questions on publication year, study design, baseline population, number of participants, definition of outcome variable, type of exposure and reported risk estimates. In case of multiple publications on identical populations, only the most recent publication was included.

Data synthesis and analysis

After data extraction and methodological quality assessment, data were transferred to Review Manager (2014) for analysis. Odds ratios and 95% CI were calculated for each study. The Mantel–Haenszel method was used for combining results across studies. We performed meta-analysis of pooled data when data were sufficiently homogeneous. We assessed heterogeneity by eyeball test and the I^2 statistic: the latter was distinguished as high heterogeneity, i.e. not fit to be pooled, when $I^2 \geq 75$–100% (Higgins *et al*., 2003). We reported the results of our meta-analysis using the random effect model as we still expected some heterogeneity in our data owing to the differences in diagnostic criteria for PCOS between studies.

The exposure variable birthweights reported in pounds were converted into kilograms and was either analyzed as a categorical or a continuous variable. Four comparisons were examined in meta-analyses. First, birthweight was dichotomized at 2.5 kg to compare the risk of developing PCOS above and below this value. Second, similarly, birthweights were dichotomized to compare those above and below 4 kg. Third, to investigate a possible non-linear U-shaped relation between birthweight and PCOS, we composed a birthweight category (birthweight extremes) consisting of birthweights <2.5 kg plus birthweights above 4 kg, comparing it to birthweights between 2.5 and 4 kg (normal birthweight). Finally, birthweight was also analyzed as a continuous variable, comparing mean birthweights of women diagnosed with PCOS and controls.

Subset analysis

We performed a subset analysis differentiating between studies where PCOS was diagnosed according to the Rotterdam criteria versus studies using NIH criteria. This analysis was performed to see if the effect of birthweight on PCOS differs depending on diagnostic criteria.

To investigate bias through study design, a subset analysis was performed differentiating between cohort studies and case–control studies as case–control studies are more prone to selection bias. We also performed a subset analysis distinguishing between studies of low/moderate quality and high quality. Additionally, studies using birthweight from medical files were compared to studies using self-reported birthweights and we performed a sensitivity analysis distinguishing between larger studies (more than 300 participants) and smaller studies (<300 participants). Publication bias was evaluated through a funnel plot, plotting log odds ratio against odds ratio.

Statistical analysis

Analyses were performed using Review Manager Version 5.3 (Cochrane Community, Copenhagen, Denmark).

Results

Identification of relevant studies

The search strategy identified 1479 unique citations (from 2622 in total) and five additional studies were included through the snowball search. Screening on title and abstract resulted in 32 eligible studies. Full text articles of these studies were retrieved for further evaluation. In total, 16 studies were included in the final selection, 14 of which provided data for statistical analysis of pooled data. The selection process is visualized in Fig. 1 and characteristics of the final 16 articles are listed in Table I.

Characteristics of included studies

Nine of the final 16 studies were case–control studies, six cohort studies and one cross-sectional study. De Melo *et al*. (2010) described their study design as a prospective cohort, and while the original design was indeed a prospective birth cohort, the data selection for this article met the criteria of a nested case–control study. Characteristics of the primary study populations are listed in Table I. Table II shows the results of quality assessment using the Newcastle–Ottawa scale.

We could not extract data from Michelmore *et al*. (2001) and Davies *et al*. (2012). Michelmore *et al*. (2001) reported on women with PCOM subsequently and categorized them according to severity of additional PCOS symptoms in a previous publication (Michelmore *et al*., 1999). We were not able to directly link the reported birthweights to any given PCOS category. Davies *et al*. (2012) categorized women according to NIH as well as Rotterdam criteria and reported relative risks. We could not, however, extract data for pooled analysis.

Exposure variable birthweight

The primary exposure variable was birthweight. In 8 out of 16 studies, birthweights were extracted from birth registers or medical records, six studies listed self-reported birthweights and two studies did not provide information on how birthweights were obtained.

Outcome variable PCOS

Studies used various criteria for the outcome variable PCOS. Eight studies defined PCOS according to the Rotterdam criteria, three according to NIH criteria, one study described cases according to both criteria, two studies had PCOM as outcome and two studies used hospital discharge diagnosis, which is a combination of different criteria. Even though Cresswell (Cresswell *et al*., 1997) selected PCOM as their outcome variable, the article provided sufficient information on clinical features such as hyperandrogenism and oligomenorrhea to reallocate the PCOM population as PCOS according to Rotterdam criteria. The study of Michelmore *et al*. (2001) also reported on women with PCOM was not added to the meta-analysis. In all other cases, we used the author's definition for PCOS. To prevent an overestimation of PCOS in the Danish population, Mumm *et al*. (2013) used the discharges diagnostic code PCOS while excluding other related diagnoses with similar symptoms. This resulted in a remarkably low prevalence of PCOS; 0.6% in the total population.

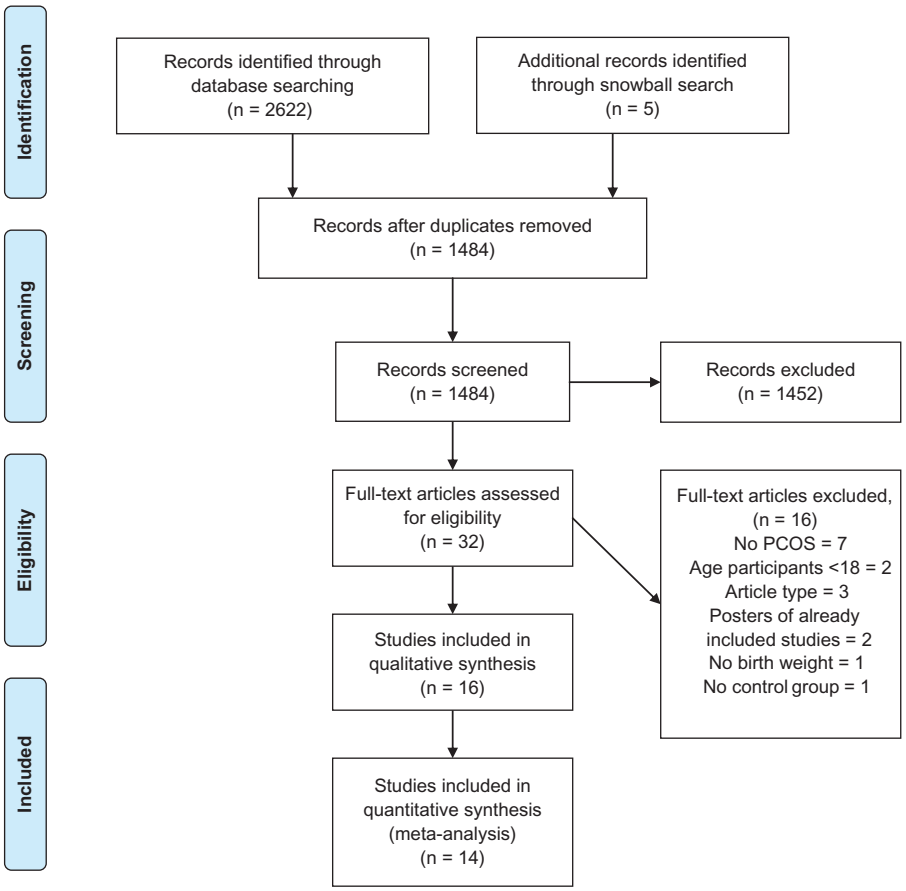

Figure 1 Flow chart of study selection process. PCOS, polycystic ovary syndrome.

Characteristics of the control populations

Seven case–control studies compared birthweights between PCOS patients (cases) and controls while two case–control studies investigated the prevalence of PCOS in women born small for gestational age or with a low birthweight (cases), and women born appropriate for gestational age or with an average birthweight (controls).

Minooee *et al.* (2015, 2016), Paschou *et al.* (2015), Legro *et al.* (2010) and Sverrisdottir *et al.* (2008) defined cases as PCOS patients and included controls using following criteria: no polycystic ovaries on ultrasonography, performed by the investigators; no signs of hirsutism, examined by a physician; and no ovulatory dysfunction, using information from standardized questionnaires. In addition, Sverrisdottir *et al.* (2008) matched women for age and weight, while Legro *et al.* (2010) also evaluated hyperandrogenism through blood tests. Sadrzadeh *et al.* (2016) ruled out ovulatory dysfunction by using information from standardized questionnaires on gynecological history. The control group of Stracquadanio and Ciotta (2017) consisted of healthy women with no evidence of clinical or biochemical hyperandrogenism and normal insulinemia and regular menstrual cycles.

The following two case–control studies defined cases based on a low birthweight. De Melo *et al.* (2010) selected every third women born AGA from their original cohort as controls. Pandolfi *et al.* (2008) selected the next full term singleton born after the selected low birthweight women (case) from medical records as controls.

Birth cohorts were used by following authors: Mumm *et al.* (2013), Davies *et al.* (2012), Laitinen *et al.* (2003) and Cresswell *et al.* (1997). The cohort of Ibáñez *et al.* (2008) consisted of women clinically diagnosed with hyperandrogenism between 2005 and 2006 in a single hospital and Sadrzadeh *et al.* (2003) described all women receiving IVF between 1980 and 1995 in The Netherlands.

Statistical relation between a low birthweight and PCOS

Thirteen studies reported on birthweights lower than 2.5 kg in relation to the diagnosis PCOS. Heterogeneity of the data was assessed as moderate, $I^2 = 53\%$, and a total of 528 894 women were included in the pooled analysis. The pooled odds ratio [95% CI] for PCOS was 1.24 [0.93, 1.65] among women who had a birthweight lower than 2.5 kg compared to women with a birthweight above 2.5 kg (Fig. 2).

Statistical relation between a high birthweight and PCOS

To investigate the association between a higher than average birthweight and developing PCOS, the data from eight studies were

Table I Characteristics of the 16 included studies of birthweight and the development of PCOS, listed by study design and year of publication.

Lead author, publication date, country	Study type	PCOS definition	Birthweight and gestational age source	Gestational age	Primary study population	*N*	Remark
Stracquadanio, 2017, Italy	Case–control	Rotterdam criteria	Self-reported	All participants born after 37 wk of gestation	PCOS outpatients and hospital controls	373	
Minooee, 2016, Iran	Case–control	Rotterdam criteria	Unknown	Not reported	PCOS outpatients and hospital controls	140	
Sadrzadeh, 2016, Netherlands	Case–control	Rotterdam criteria	Self-reported	Term categories, below 37, between 37 and 41, above 41 wk	PCOS outpatients and hospital controls or advertisement	161	
Paschou, 2015, Greece	Case–control	NIH criteria	Self-reported	All participants born after 38 wk of gestation	PCOS outpatients, students or hospital staff as controls	344	
Minooee, 2015, Iran	Case–control	Rotterdam criteria	Unknown	Not reported	PCOS outpatients and hospital controls	140	Study in original language
Legro, 2010, USA	Case–control	NIH criteria	Self-reported	Mean gestational age for each birthweight category reported	PCOS patients, not described how controls were selected	553	Part of a larger study
De Melo, 2010, Brazil	Nested case–control	Rotterdam criteria	Medical files	All participants born after 37 wk of gestation. SGA defined as 10th, AGA defined as between 10th and 90th percentiles for gestational age	All women born SGA between 1-6-1978 and 31-5-1979 in Ribeirao Preto and random selected controls (1 out of 3) out of the same cohort	165	Authors describe study as a cohort study but design for this particular manuscript meets the criteria of a nested case–control study
Pandolfi, 2008, Italy	Case–control	NIH criteria	Medical files	LBW group consist of preterm and term with birthweight below 2.5 kg. Control group consists of term deliveries with birthweight equal or above 3 kg	Randomly recruited women born with LBW from regional records and next full term singleton as control	70	
Sverrisdottir, 2008, Sweden	Case–control	Rotterdam criteria	Medical files	Mean gestational age for PCOS and non-PCOS group	Women diagnosed with PCOS and controls from hospital records or advertisement	38	
Mumm, 2013, Denmark	Cohort	Discharges diagnostic code PCOS, excluding other related diagnosis	Medical files	Not reported when born in 1973–78. When born in 1978–91, SGA defined as 10th, LGA as 90th percentile for gestational age	Linkage individual data from national register with national patient register. Women born between 1973 and 1991	523 755	The prevalence of PCOS in this study is 0.6%
Davies, 2012, Australia	Cohort	Rotterdam and NIH criteria both listed	Medical files	Term categories, below 37, between 37–42, above 42 wk	Female births between 1973 and 1975 at one hospital	948	Unable to extract data for meta-analysis
Ibanez, 2008, Spain	Cohort	Rotterdam criteria	Medical files	Not reported	Cohort of women seen between 2005 and 2006 all clinically diagnosed with hyperandrogenism	86	Data only includes in the meta-analysis with birthweight as a continuous variable
Laitinen, 2003, Finland	Cohort	Rotterdam criteria	Medical files	Preterm defined as below 37 wk gestation, SGA was defined as 10th percentile for gestational age	1966 birth cohort	2007	Self-reported signs of hyperandrogenism and oligomenorrhea
Sadrzadeh, 2003, Netherlands	Cohort	Clinical PCOS diagnosis	Self- reported	Not reported	Women receiving IVF between 1980 and 1995 in one of the 12 IVF centers in the Netherlands	911	Diagnostic criteria differ between centers

Continued

Table I *Continued*

Lead author, publication date, country	Study type	PCOS definition	Birthweight and gestational age source	Gestational age	Primary study population	*N*	Remark
Cresswell, 1997, UK	Cohort	Polycystic ovary	Medical files	Weeks of gestation	Birth cohort of women born between 1952 and 1953 at Jessop Hospital, Sheffield	235	Authors selection criteria was PCO but all women with PCO had clinically elevated testosterone levels, meeting Rotterdam criteria
Michelmore, 2001, UK	Cross-sectional	Polycystic ovary	Self- reported	Not reported	Volunteers	224	Unable to extract data for meta-analysis

PCOS, polycystic ovary syndrome; SGA, small for gestational age; AGA, appropriate for gestational age; LBW, low birthweight; wk, week; *N* , number of women in study.

pooled. Women born with birthweights above 4 kg had an odds ratio [95% CI] of 1.15 [0.78, 1.68] for PCOS compared to women born with birthweights <4 kg after pooling data on 525 601 women for meta-analysis ($I^2 = 39\%$) (Fig. 3).

U-shaped relation of birthweight and PCOS

To investigate a U-shaped association between birthweight and PCOS, we created a birthweight category of extreme birthweights, combining women born with a low birthweight of <2.5 kg with women with high birthweights, above 4 kg. When comparing this birthweight category with women born with an average birthweight, between 2.5 and 4 kg, we were able to include 528,892 women from 13 studies ($I^2 = 66\%$) for meta-analysis. Women born with extreme birthweights had an odds ratio [95% CI] of 1.13 [0.99, 1.30] for PCOS compared to women born with an average birthweight. The forest plot is visualized in Fig. 4.

Birthweight analyzed as a continuous variable

When comparing women diagnosed with PCOS versus controls, the mean difference [95% CI] in birthweight was calculated. Seven studies, reporting mean birthweights for 2628 women, could be included for meta-analysis [$I^2 = 40\%$] resulting in a 38.51 g higher birthweight [−44, 121] among women diagnosed with PCOS (not shown).

PCOS, as defined by Rotterdam or NIH criteria

When pooling data from seven studies using the Rotterdam criteria, we find a significant association between women born with a birthweight <2.5 kg and women with birthweights above 2.5 kg, with an odds ratio [95% CI] of 1.76 [1.14, 2.70] including 1252 women [$I^2 = 16\%$] (Fig. 5). A low birthweight does not seem to have a relation to PCOS when diagnosed according to NIH criteria. The odds ratio [95% CI] for a birthweight lower than 2.5 kg versus above 2.5 kg of 2972 women from four studies diagnosed according to NIH criteria was 1.16 [0.53, 2.55], $I^2 = 72\%$ (Fig. 6). When selecting studies using Rotterdam criteria the heterogeneity decreases significantly, however, this is not the case with the NIH studies. In case of the NIH studies, the case–control study of Pandolfi *et al.* (2008) causes the high heterogeneity. When we exclude Pandolfi *et al.* (2008) from the analysis the heterogeneity drops to 0% in the NIH group. In contrast to the other three studies using the NIH criteria, Pandolfi *et al.* (2008) defined the cases as women born with a low birthweight versus women born with an average birthweight. Women already diagnosed with PCOS formed the case group in the other studies.

Owing to the limited number of studies reporting on a birthweight higher than 4 kg and also using the NIH criteria (two studies), we did not perform a subset analysis investigating the effect of a birthweight higher than 4 kg according to different diagnostic criteria.

Subset analysis

To investigate bias through study design, we conducted a subset analysis distinguishing between case–control and cohort studies testing the U-shaped association between birthweight and consequential PCOS diagnosis. When data of the nine case–control studies were pooled, we calculated an odds ratio [95% CI] of 1.26 [1.01, 1.57] including 1984 women. The pooled odds ratio [95% CI] of the four cohort studies was 1.00 [0.91, 1.09] including 526 908 women. We also conducted a subset analysis differentiating between high-quality studies and low or moderate-quality studies. Five studies scored seven or higher on quality, the calculated odds ratio [95% CI] of these studies was 1.34 [0.92, 1.94] including 525 136 women. The eight studies with quality scores lower than seven had similar odds [95% CI] of 1.11 [0.93, 1.32] including 3756 women. When comparing studies using birthweight from medical files to studies using self-reported birthweights we found no significant difference (data not shown).

Publication bias and sensitively analysis

The funnel plot presented (Fig. 7) is from the analysis where most of the studies could be included, investigating a U-shaped association between birthweight and PCOS (Fig. 4). The skewed funnel plot indicates a publication bias. Studies reporting a positive association between birthweight and consequential PCOS diagnosis and large studies seem to be over-represented, while smaller studies reporting negative or no association seem to be missing in the published literature.

Table II Quality assessment of studies included in the meta-analysis, using the Newcastle–Ottawa Scale.

NOS for case–control studies

Lead author, publication date	Case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of assortment for cases and controls	Nonresponse rate	Total score (max. 9)
Stracquadanio, 2017	*			*	**		*		5
Minooee, 2016	*			*	*		*		4
Sadrzadeh, 2016	*			*	*		*		4
Paschou, 2015	*			*	*	*			4
Minooee, 2015	*	*		*	*		*		5
Legro, 2010	*			*	*				3
De Melo, 2010	*	*	*	*	*	*	*	*	8
Pandolfi, 2008		*	*	*	*	*	*	*	7
Sverrisdottir, 2008	*		*	*		*	*		5

NOS for cohort studies

Lead author, publication date	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability of cohorts	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score (max. 9)
Mumm, 2013	*	*	*	*		*	*	*	7
Davies, 2012	*	*	*	*		*	*		6
Ibanez, 2008		*	*	*		*	*		5
Laitinen, 2003	*	*	*	*	*		*		6
Sadrzadeh, 2003	*	*		*	**	*	*		7
Cresswell, 1997	*	*	*	*	*	*	*	*	8

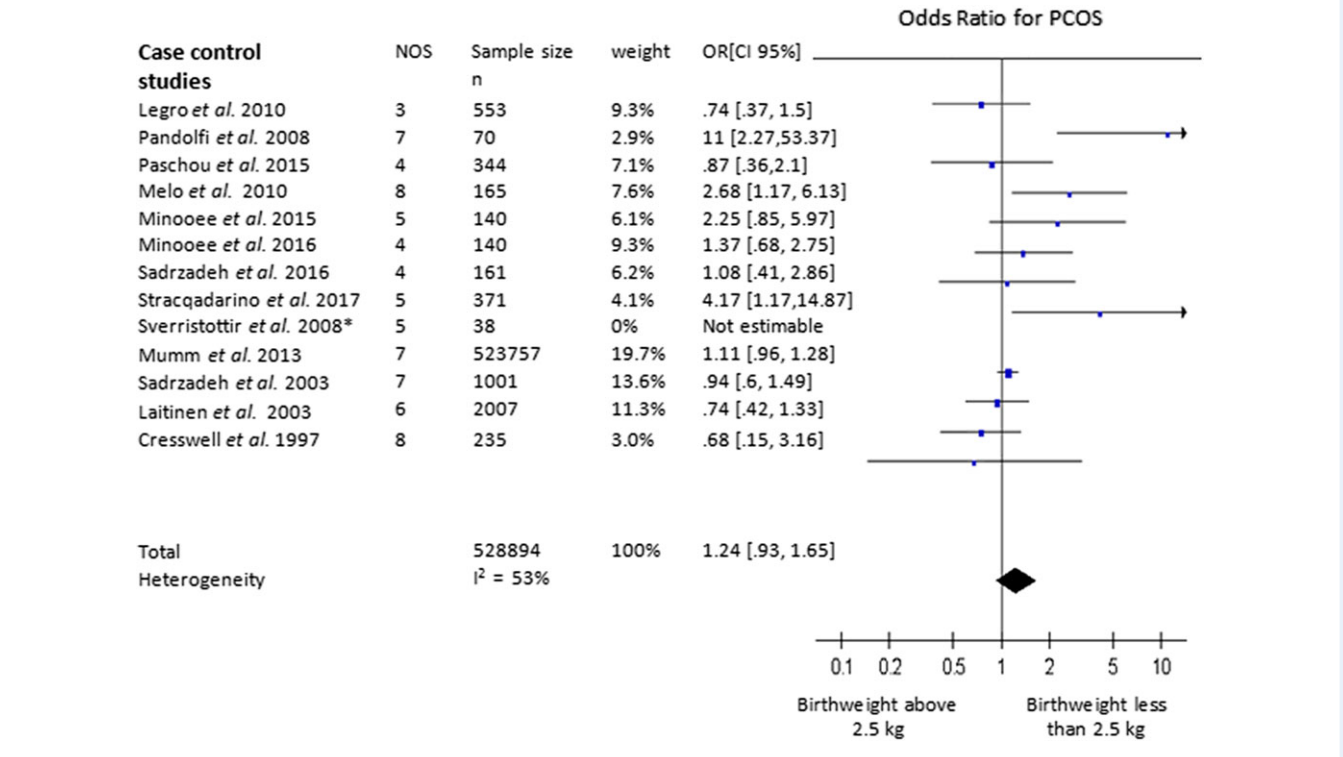

Figure 2 Odds ratio for PCOS; comparison between women born with low birthweights, <2.5 kg and women born with birthweights above 2.5 kg. OR, odds ratio; NOS, Newcastle–Ottawa Scale for quality, maximum of 9. *None of the participants had a birthweight <2.5 kg.

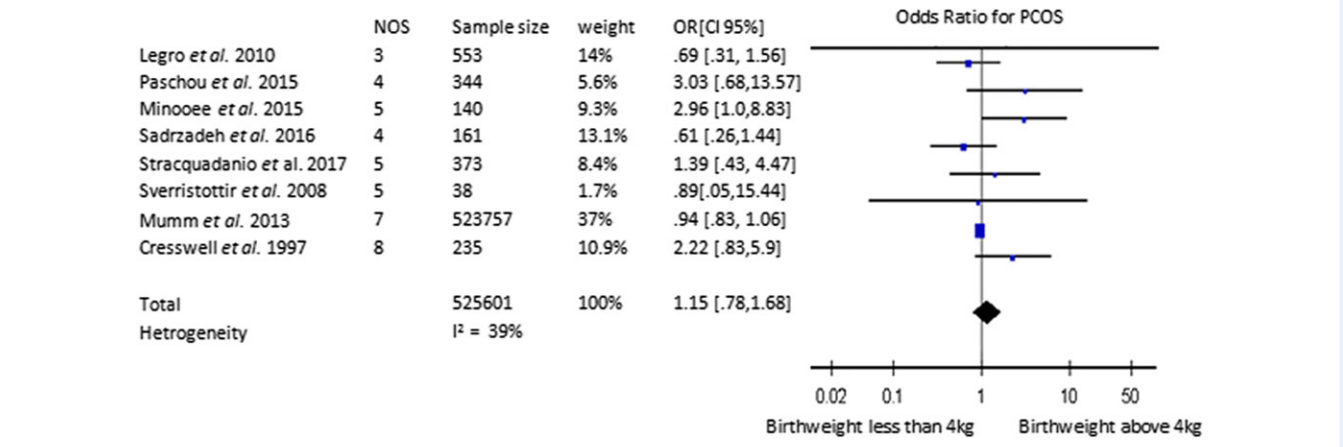

Figure 3 Odds ratio for PCOS; comparison between women born with birthweights above 4 kg and women born with birthweights <4 kg.

Six studies had a sample size larger than 300 participants, and the calculated odds ratio [95% CI] of these studies was 1.03 [0.92, 1.16] including 527 943 women. The seven studies with a sample size smaller than 300 had similar odds [95% CI] of 1.41 [1.02, 1.95], including 949 women.

Discussion

To our knowledge, this is the first systematic review on the relation between PCOS and birthweight. A relation between birthweight and PCOS seems to depend on which criteria were used to diagnose

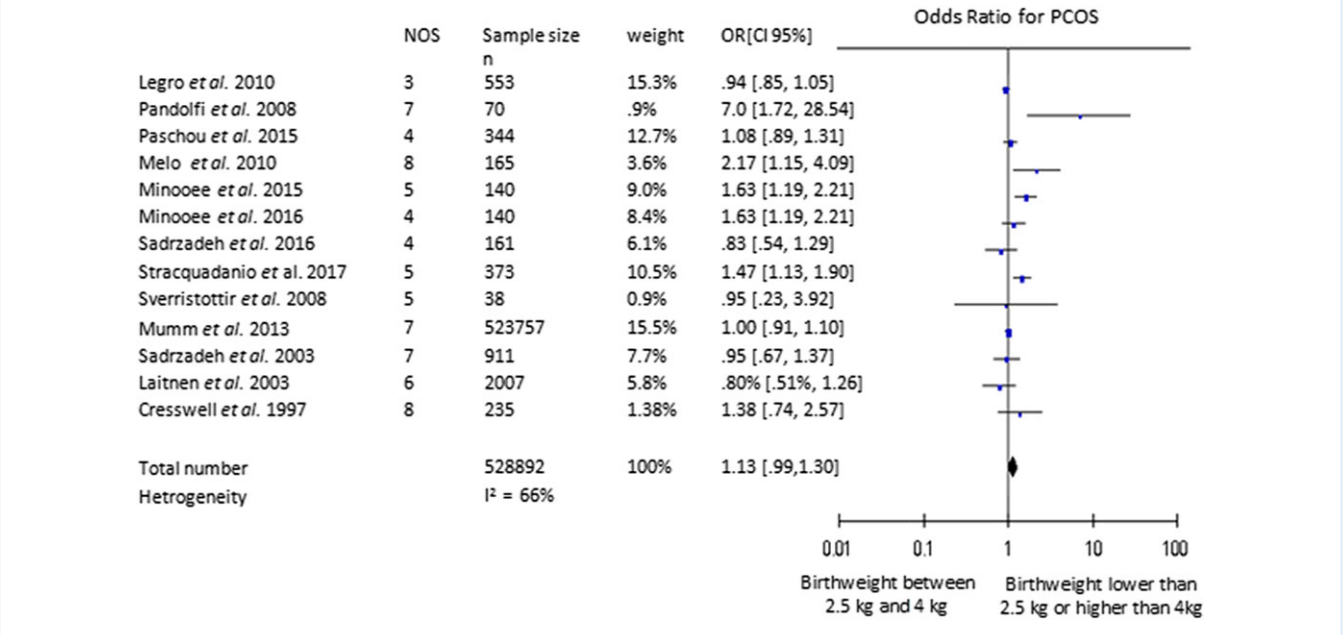

Figure 4 Odds ratio for PCOS among women with extreme birthweights. Data comprising birthweights <2.5 kg plus birthweights above 4 kg, were compared to birthweights between 2.5 and 4 kg.

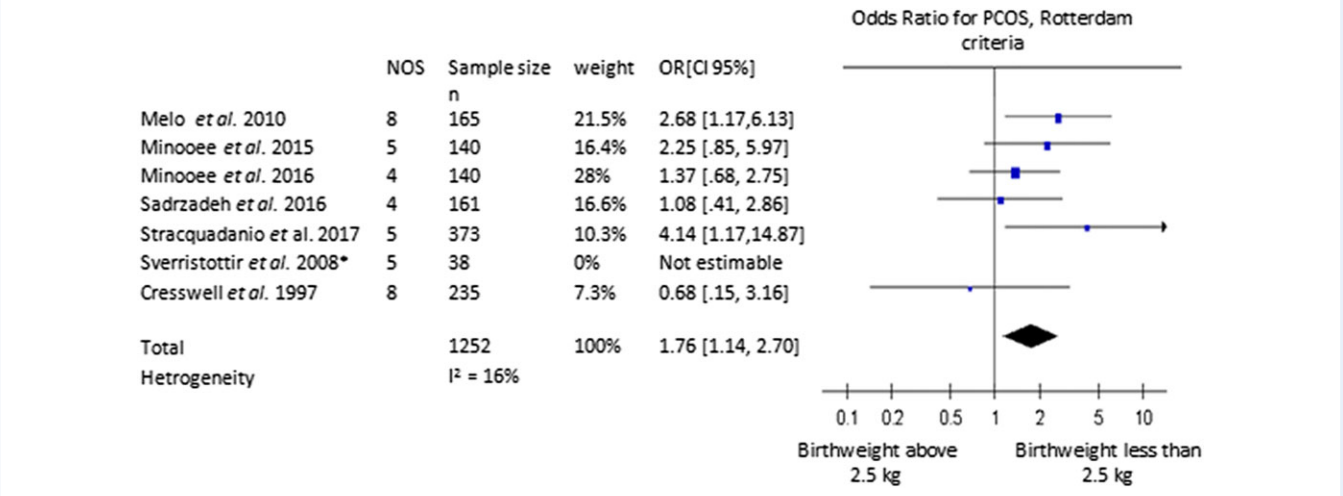

Figure 5 Subset analysis: odds ratio for PCOS according to Rotterdam criteria; comparison of women born with low birthweights, <2.5 kg, and women born with birthweights above 2.5 kg. *None of the participants had a birthweight <2.5 kg.

PCOS. When systematically reviewing and meta-analyzing published data, we find that women with birthweights lower than 2.5 kg are 1.76 times more likely to be diagnosed with PCOS, when using the Rotterdam criteria. Our data suggest that birthweight does not affect the prevalence of PCOS when diagnosed according to NIH criteria.

In 2003, during the Rotterdam consensus, workshop PCOM was added to the NIH criteria (Azizz, 2005). Women diagnosed with PCOS according to the Rotterdam criteria are, therefore, more likely to have PCOM than women diagnosed according to NIH criteria. We speculate that the association between a low birthweight and PCOS could be mediated by the higher prevalence of PCOM among women diagnosed according to the Rotterdam criteria.

Two specific intrauterine exposures may affect birthweight, which is a crude summary measure of intrauterine conditions and possible subsequent PCOS: namely exposure to high androgen levels, and maternal hyperinsulinism, possibly in combination with genetic predisposition.

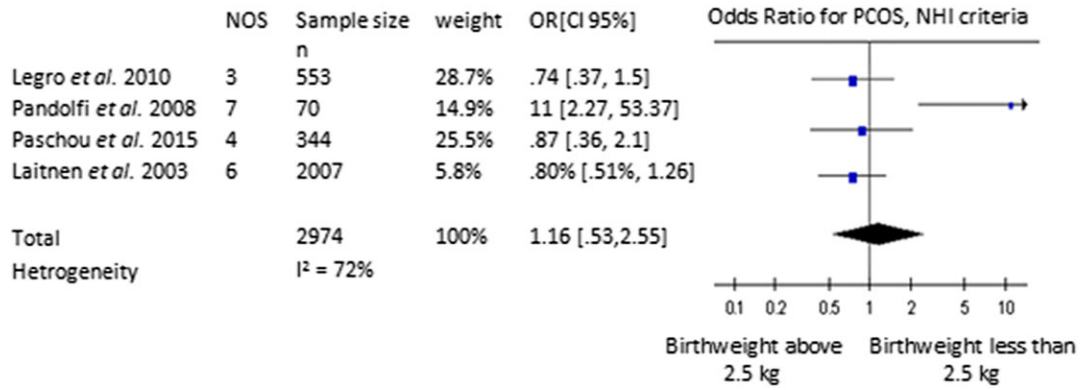

Figure 6 Subset analysis: odds ratio for PCOS according to National Institutes for Health criteria; comparison of women born with low birthweights, <2.5 kg, and women born with birthweights above 2.5 kg.

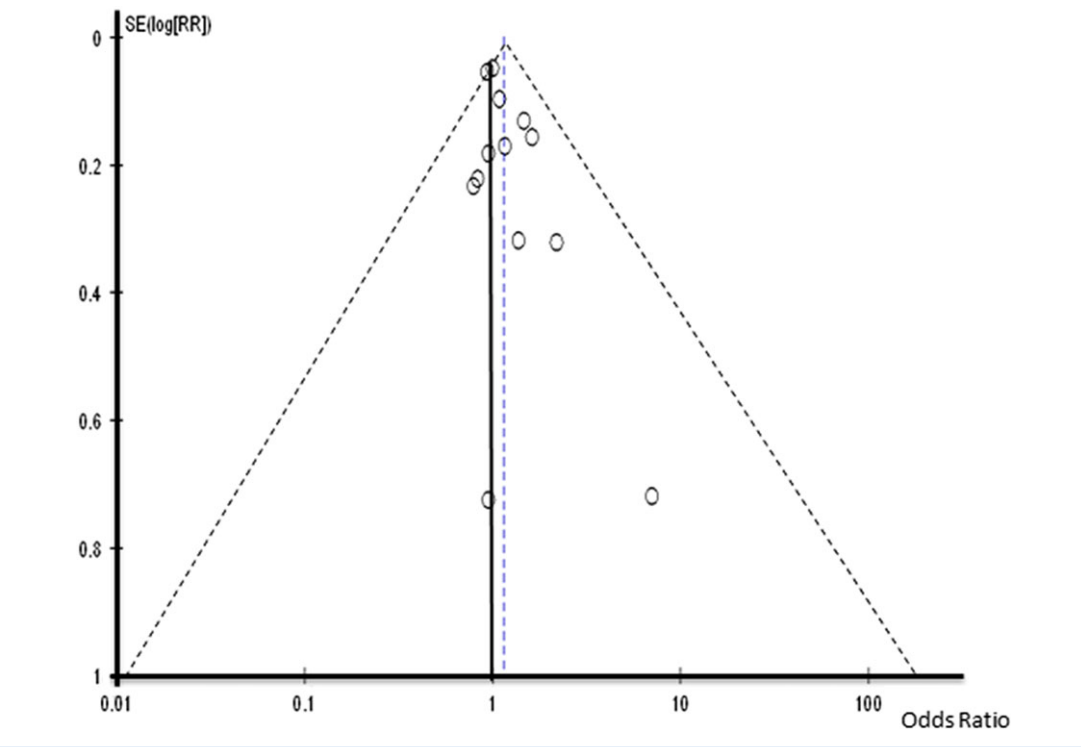

Figure 7 Funnel plot of the 13 studies investigating the association between extreme birthweights (birthweights <2.5 kg plus birthweights above 4 kg) and PCOS.

Animal studies in non-human primates suggest that fetal exposure to androgens primes the hypothalamic–pituitary–ovary axis in such a way that it sets off a reaction leading to intrauterine growth retardation, metabolic dysfunction and PCOM (Abbott *et al.*, 1998; Eisner *et al.*, 2002). However, the human fetus is protected from excess maternal androgens by sex hormone-binding globulin and placental aromatase, which converts androgens into estrogens. Therefore, in this condition, a fetal origin of androgen, either of ovarian or adrenal, is presumed (Abbott *et al.*, 2002).

Pregnant women previously diagnosed with PCOS have an increased risk of developing (gestational) diabetes resulting in large for gestational age offspring (Ehrenberg *et al.*, 2004). Owing to the high heritability of PCOS (Vink *et al.*, 2006), large for gestational age daughters born to mothers with PCOS have an increased risk of developing

PCOS, explaining the association between a relatively high birthweight and an increased risk for PCOS. The hyperinsulinemic state of pregnant women with diabetes and the consequential placental aromatase inhibition resulting in elevated fetal androgen levels could induce PCOS (Desoye and Hauguel-de Mouzon, 2007). Mumm *et al.* (2013) show that large for gestational age women born to diabetic mothers have an increased risk to develop PCOS, with the relatively leanest women amongst them having the highest risk. There was a limited number of studies reporting on a higher than average birthweight and using the NIH criteria; therefore, we could not test an effect of high birthweight on PCOS later in life.

Our study has some weaknesses. While cohort studies can ultimately detect rare exposures, because of the long follow-up period between exposure and outcome there are currently only a few studies reporting on this subject and none of them was designed to prospectively investigate the relation between perinatal conditions and PCOS. By including case–control as well as cohort studies we increased to the power of our analysis. However, observational case–control studies are generally less comparable because of differences and challenges in choosing an appropriate control group. The definition of the case group also differed significantly between studies. While some studies selected cases on birthweight and investigated the association with PCOS, others selected on PCOS and compared birthweights between groups. Additionally, case–control studies by design cannot address the causality of any associations they find.

Remarkably Mumm *et al.* (2013), with the largest included cohort study, reported a PCOS prevalence of 0.6%. As this is much lower than international reports on the prevalence of PCOS, we assume an underestimation but cannot predict how this might affect the association between birthweight and PCOS. We were also unable to include Mumm *et al.* (2013) and Sadrzadeh *et al.* (2003) in the subset analysis differentiating between diagnostic criteria as these two studies selected the PCOS patients using various clinical criteria over a longer period of time.

Although the effect measure of our sensitivity analysis between larger and smaller studies is comparable, in contrast to the pooled effect measure of the smaller studies the effect measure of the larger studies did not reach statistical significance. This result, as well as the skewed funnel plot, indicates publication bias where smaller studies yielding negative results are excluded from publication. On the other hand, larger and smaller studies differ in more aspects than only sample size. Six out of seven studies including <300 participants applied the Rotterdam criteria. The larger studies consist of three studies using the NIH criteria, one using Rotterdam criteria and two using hospital discharge diagnosis, and as stated above the prevalence of PCOS in the Mumm *et al.* (2013) study, by far the largest study, was much lower than expected. The skewed funnel plot suggests publication bias but as in all systematic reviews it is debatable if the skewed funnel plot can be explained by an under-representation of small studies yielding negative results or other sources of heterogeneity (Sterne *et al.*, 2011).

Finally, a point of concern is that most studies did not provide enough information on gestational age to distinguish between women born with a low birthweight but appropriate for gestational age and women born small for gestational age.

Future prospective studies collecting perinatal information, maternal endocrine status, as well as fetal androgen levels while distinguishing between low birthweight, high birthweight, and small and large for gestational age should clarify the relation between birth conditions, PCOM and PCOS.

In conclusion, the analysis suggests that low birthweight might be associated with an increased risk of PCOS diagnosed according to Rotterdam criteria. Birthweight does not affect the risk of PCOS when diagnosed according to NIH criteria.

Supplementary Data

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

Authors' roles

S.S. was involved in writing the study protocol, identifying unique studies, abstract and full text selection, quality assessment, data extraction and writing the article. E.V.H.H. was involved abstract and full text selection, quality assessment, data extraction and writing the article. L. J.S. was involved in designing the search strategy. R.C.P. was involved in writing the study protocol and article. C.B.L. was involved in writing the study protocol and article. All authors critically reviewed the article and approved the final version.

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Conflict of interest

None declared.

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