Prevalence of Asthma in Polycystic Ovary Syndrome Women: A Meta-analysis

Honghao Sun

Center for Reproductive Medicine, Shengjing hospital, China Medical University <https://orcid.org/0000-0003-2121-6719>

Da Li

Center for Reproductive Medicine, Shengjing hospital, China Medical University

Jiao Jiao

Center for Reproductive Medicine, Shengjing hospital, China Medical University

Qing Liu

Key Laboratory of Health ministry for congenital Malformation, Shengjing hospital, China Medical University

Jiansu Bian

Center for Reproductive Medicine, Shengjing hospital, China Medical University

Xiuxia Wang (✉ wangxxsj@126.com)

Shengjing Hospital, China Medical University

Research

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Abstract

Background: A few publications have reported the prevalence of asthma in polycystic ovary syndrome (PCOS) patients. But it remains debatable whether PCOS is an independent risk factor of asthma. Thus we carried out this systematic review and meta-analysis to assess the association between PCOS and asthma.

Methods: PubMed, Embase, web of science, Scopus, Cochrane trial register, China National Knowledge Infrastructure (CNKI) and Wanfang Databases were searched for studies published from inception to October 2020. We extracted the data and performed the meta-analysis under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We used a random-effects model and calculated the odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results: A total of 6 articles concerning 26876 PCOS women and 156143 healthy controls were included. According to the result of the study, PCOS patients have increased risk of asthma (OR=1.75, 95%CI=1.40–2.19, $I^2=91.2\%$, $P=0.000$, random-effects model). When stratified by region, diagnostic criteria for asthma and study design, the results did not show significant difference.

Conclusions: PCOS leads to higher asthma risk, and this association is independent to region, diagnostic criteria for asthma and study design.

Background

Polycystic ovary syndrome (PCOS) is characterized by chronic anovulation, insulin resistance and hyperandrogenism. Its prevalence differs with ethnicity and country, from 5.6%(China)^[1] to 16.0%(Middle Eastern)^[2]. Its prevalence increased rapidly from age 12 to 14, peaked between 15 and 24 years old, and then gradually decreased, reaching the lowest point before menopause^[3]. Its pathogenic mechanism is not yet clear. The possible pathogenic factors including genetic factor, environmental factor, endocrine factor and other factors.

PCOS patients have a higher risk of metabolic disorders^[4] and are more easily to be diagnosed as hypertension^[5], cardiovascular disease^[6], diabetes^[7] and non-alcoholic fatty liver^[8]. Asthma is a chronic inflammatory airway disorder symbolized by coughing, wheezing, breath shortness, sharing a lot of characteristics with PCOS. PCOS is always associated to irregular menstruation cycle and hormone disorder. Females have a higher asthma prevalence compared with males. Fluctuations of hormones in menstruation cycle will lead to the alternation of asthma relieve allergen-mediated airway inflammation^[9]. Patients have more severe asthma symptoms, and decreased peak flow rates during premenstrual phase than in menstrual phase^[10]. Asthma symptoms also worsen in menopausal women^[11]. PCOS patients have prolonged premenstrual phase and are more likely to be anovulation, thus may result in increased asthma risk. Nearly half of PCOS patients suffer from metabolic syndrome. at the

same time, metabolic syndrome, together with low serum HDL, larger waist circumference, insulin resistance are all risk factors of asthma^[12].

Despite the fact that PCOS has been recognized as a risk factor of various diseases such as hypertension and diabetes. There are still few articles concerning the prevalence of asthma in PCOS patients, and the underlying mechanisms of PCOS affecting asthma is still doubtful.

In order to get better understanding on the co-existence of PCOS and asthma, we performed this meta-analysis on the prevalence of asthma in PCOS patients. Studies based on different population and different study type were analysed respectively. In this study, we aim to figure out whether asthma prevention and early treatment are beneficial to improve life quality of PCOS patients.

Materials And Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^[13]. Ethics approval is not required when human subjects were not involved.

Search strategy

In this meta-analysis, a comprehensive search was performed on PubMed, Embase, web of science, Scopus, Cochrane trial register, China National Knowledge Infrastructure (CNKI) and Wanfang Databases from inception to October, 2020. Article was restricted to human studies. language limitation was not applied. We used a combined search strategy for PCOS and asthma. For PCOS, the following terms were used "PCOS", "polycystic ovary syndrome", "polycystic ovary", "Stein Leventhal Syndrome". For asthma, the following terms were used: "asthma", "wheezing". All Potential studies were browsed by two independent reviewers, and elementary selection was conducted. If there was a controversy on inclusion of one article, two additional authors (J.J. and L.D.) will view the article and made the decision. All studies concerning the difference of the prevalence of asthma between PCOS patients and controls were included. We also browsed the references of included articles for more potential articles.

Inclusion criteria

Observational studies, such as cross-sectional studies, case-control studies and cohort studies comparing the prevalence of asthma in PCOS patients with controls were included in the meta-analysis. Necessary information must be available in studies to calculate the odds ratio [OR], otherwise a risk ratio (OR, relative risk [RR], or hazard ratio[RR]) should be directly provided.

Exclusion criteria

All abstracts, review articles, meta-analyses, letters, case reports and expert opinions were excluded. Studies without complete data or lack control group were also removed. For articles that based on same population source, only the latest and most detailed report was included.

Data extraction and quality assessment

Two independent reviewers(S.H.H. and W.X.X.) extracted following data from article texts and tables: Title, author names, year of publication, study design, geographic region, characteristics of PCOS and matched control population, diagnostic criteria for PCOS and asthma and the event number of PCOS and matched control population. Adjusted risk ratio such as adjusted odds ratio [aOR], adjusted relative risk[aRR] was also collected if given.

The quality of the Included studies were assessed by two investigators (S.H.H. and W.X.X.), using the Newcastle-Ottawa Scale (NOS) separately. If they have different opinions, two other reviewers (L.D.and J.J) will resolve the disagreement. Only high quality (obtaining $\geq 70\%$ of the highest score) or moderate quality (obtaining 40-70% of the highest score) articles will be included.

Statistical analysis

The odds ratio (OR) and 95% confidence intervals (CIs) were used to measure the difference of asthma prevalence between PCOS patients and matched control group. I^2 test, Galbraith plot and funnel plot analyses were used to detect heterogeneity. Random-effects model was applied due to significantly heterogeneity was found. We also performed subgroup analyses on geographic region, study design and diagnostic criteria for PCOS. Begg's test and Egger's test were applied to detect potential publication bias. Statistical analyses were conducted using Stata software version 11.0.

Results

Summary of the literature search

A total of 465 records was identified using our search Strategy as figure.1 demonstrates. Among these publications, 144 were excluded due to duplication. Titles and abstracts of 321 articles were reviewed, 307 articles were excluded according to the given inclusion and exclusion criteria. The rest 12 potentially related articles were assessed by full-text reading. 4 studies based on same population source or did not have appropriate control group were further excluded^[14-17]. 2 articles were removed from the meta-analysis due to no useful estimate was reported or not enough data was used to calculate it^[18, 19]. 6 articles were finally included in the meta-analysis^[20-25].

Study characteristics

Characteristics of the studies included were summarized in Table 1. Six studies were included capturing 26876 women with PCOS and 156143 controls. Of the 6 studies, 4 were prospective cohort study and 2 were retrospective cohort study. Half of those studies used the Rotterdam criteria for PCOS diagnosis and another half used the ICD criteria. Subjects included in the meta-analysis were from three different countries including Australia, Norway and Denmark. The diagnostic criteria for asthma varied from articles, in three studies the diagnosis is made based on medical record, and in another one based on doctor's diagnosis. Three rest studies were based on questionnaire. There was no substantial publication bias found in funnel plot and in Begg's test and Egger's test.

Asthma in PCOS patients

6 studies that comparing PCOS patients with matched controls regarding to asthma risk were included. The random-effects model was applied due to a significant heterogeneity was found ($I^2=91.2\%$, P -heterogeneity=0.000). Comparing to the control group, the PCOS group had a significantly higher risk of asthma (OR=1.75, 95%CI=1.40–2.19) (Fig.2). Subgroup analyses were also performed grouped by geographic region, diagnostic criteria for asthma and study design. When classified by geographic region. We found approximately increased PCOS-associated asthma risk in PCOS patients from all involved countries such as Australia (OR=1.89, 95% CI=1.10–3.25), Denmark (OR=1.43, 95% CI=1.29–1.58) and Norway (OR=2.50, 95% CI=1.47–4.25) (Fig.4). Suggesting that PCOS-associated asthma risk is independent to geographic region. According to the conclusion of subgroup analysis grouped by diagnostic criteria for asthma, different diagnostic criteria did not affect the impact of PCOS on asthma significantly, whether the diagnosis is based on medical records (OR =1.82, 95% CI=1.30–2.54) or on questionnaire (OR=1.59, 95% CI=1.15–2.22) (Fig.5). When sorted by study design, both prospective cohort studies (OR=1.44, 95% CI=1.32–1.57) and retrospect studies (OR =2.46, 95% CI=2.16–2.82) (Fig.6) believed PCOS is a risk factor of asthma independent to study design.

Discussion

Currently, the incidence of asthma among PCOS patients still remains controversial. In recent years, more than a dozen articles from different countries have reported the prevalence of asthma in PCOS patients^[26-28]. However, due to the differences in race, population, patient age, BMI and other factors, the results were not consistent. Therefore, we performed this meta-analysis. To our knowledge, it is the first systematic evaluation of asthma incidence in polycystic ovary syndrome. Six articles were included including 26876 cases of PCOS women and 156143 cases of control. The incidence of asthma was found to be 1.75 fold higher in PCOS women, suggesting that PCOS is a risk factor for asthma.

The underlying mechanism of the co-existence of PCOS with asthma may be explained from the following aspects: 1. Both PCOS and asthma are associated with hormonal abnormalities and menstrual

cycle disorders. 2. PCOS leads to a series of metabolic disorders, such as hyperandrogen, insulin resistance, obesity and hypertension, which are susceptible factors for asthma; 3. Asthma usually co-exists with systemic inflammation, which may result in cytokine disorders. Hormone disorder and menstrual cycle disorder are important symptoms of PCOS. Various studies found that asthma is associated with menstrual disorders and hormone disturbance. Asthma symptoms varies with menstruation cycle^[10]. The cyclic deterioration of asthma symptoms during the luteal phase or during the first days of menstruation were termed premenstrual asthma (PMA)^[29]. Asthma attacks happen more frequently in premenstrual phase. Asthmatic girls have earlier menstruation than healthy girls, and the severity of asthma changes with the age of menarche. Asthmatic girls(50.0%) were more likely to have menstrual disorders than healthy girls(27.8%). while few of asthmatic girls(68.0%) show the symptom of algomenorrhea than healthy girls(80.6%)^[30]. In addition, the forced vital capacity (FVC) of women with menstrual irregularity or oligo menorrhea was significantly lower than that of women with regular menstruations^[31]. Another population-based study also showed that oligomenorrhea is risk factor of asthma symptoms (OR:1.76; 95% CI:1.29-2.40), oligomenorrhea and BMI positively correlate with asthma symptoms and negatively correlate with FVC and forced Expiratory Volume in the first second (FEV1)^[32].

Metabolic syndrome is a syndrome characterized by dyslipidemia, hypertension, insulin resistance, and abdominal obesity. It is estimated that around half of PCOS patients suffer from the metabolic syndrome^[33]. Metabolic syndrome^[34] and obesity^[35] are both risk factors for asthma, asthma symptoms worsen with the degree of metabolic syndrome. Obese individuals have a higher risk of developing asthma over time, and have a poorer response to asthma treatment. At the same time weight loss improves the symptoms of asthma in those patients. Supposing that metabolic syndrome may act as a linking center between PCOS and asthma, metabolic syndrome co-exists with PCOS aggravate asthma syndrome.

PCOS usually co-exists with systematic inflammation. Excessive activation of inflammatory cytokines will lead to airway hyper responsiveness and may finally result in asthma. High levels of CRP are found in both lean and obese PCOS patients^[36]. IL-18 is another important cytokine in PCOS which can stimulate TNF, IL-6 and CRP. IL-18 and CRP levels are raised in PCOS patients^[37]. Moreover, IL-17 and TNF are well known markers of low grade systemic inflammation among patients with PCOS. As for asthma, serum levels of IL-17, IL-18, TNF and CRP are associated with asthma symptoms and impaired lung function^[38]. Systematic inflammation may be another center of the crosstalk between PCOS and asthma .

Due to various reasons, this study still has some shortages and limitations. Up to now, the reports on the incidence of asthma in PCOS patients were limited. And this meta analysis only contains studies from three countries, prevalence data from other countries were absent. In addition, most of the asthma diagnosis in included studies were made based on "case record" or "self-report", without clear and unified diagnostic criteria. Further more, there is no subgroup analysis of different asthma types, whether they are drug-induced or allergic, and whether the age of onset is in childhood or in adulthood. In addition, only 2 articles adjusted the odds ratio by age, BMI and other factors, while the others only provided rough odds

ratio. Thus, high-quality studies on the association between PCOS and asthma were still needed to resolve the dispute.

Conclusions

The results of the current study show that PCOS is an independent risk factor of asthma, regardless to region, diagnostic criteria for asthma and study design.

Abbreviations

PCOS: polycystic ovary syndrome; CI: confidence interval; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; OR: odds ratio; RR: relative risk.

Declarations

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None

Authors' contributions

Xiuxia Wang and Da Li designed the study, Honghao Sun and Jiao jiao contributed to literature search, data extraction and statistics, Qing Liu and Jiansu Bian prepared the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analysed in the current study are available from the corresponding author if required.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

References searched and selection of studies in the meta-analysis.

Figure 1

References searched and selection of studies in the meta-analysis.

Figure 1

References searched and selection of studies in the meta-analysis.

Asthma risk of PCOS patients comparing to control

Figure 2

Forest plot comparing the odds of asthma in PCOS patients and in controls

Asthma risk of PCOS patients comparing to control

Figure 2

Forest plot comparing the odds of asthma in PCOS patients and in controls

Asthma risk of PCOS patients comparing to control

Figure 2

Forest plot comparing the odds of asthma in PCOS patients and in controls

Figure 3

Funnel plot of the included studies in the meta-analysis

Figure 3

Funnel plot of the included studies in the meta-analysis

Figure 3

Funnel plot of the included studies in the meta-analysis

Subgroup analysis on geographic region

Figure 4

Forest plot of subgroup analysis grouped by geographic region: 1. Australia 2.Denmark 3. Norway

Subgroup analysis on geographic region

Figure 4

Forest plot of subgroup analysis grouped by geographic region: 1. Australia 2.Denmark 3. Norway

Subgroup analysis on geographic region

Figure 4

Forest plot of subgroup analysis grouped by geographic region: 1. Australia 2.Denmark 3. Norway

Subgroup analysis on diagnosis criteria of asthma

Figure 5

Forest plot of subgroup analysis grouped by diagnostic criteria for asthma: 1. Questionnaire 2. Medical record

Subgroup analysis on diagnosis criteria of asthma

Figure 5

Forest plot of subgroup analysis grouped by diagnostic criteria for asthma: 1. Questionnaire 2. Medical record

Subgroup analysis on diagnosis criteria of asthma

Figure 5

Forest plot of subgroup analysis grouped by diagnostic criteria for asthma: 1. Questionnaire 2. Medical record

Subgroup analysis on study design

Figure 6

Forest plot of subgroup analysis grouped by study design: 1. Prospective cohort study 2. Retrospective cohort study

Subgroup analysis on study design

Figure 6

Forest plot of subgroup analysis grouped by study design: 1. Prospective cohort study 2. Retrospective cohort study

Subgroup analysis on study design

Figure 6

Forest plot of subgroup analysis grouped by study design: 1. Prospective cohort study 2. Retrospective cohort study

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