

Bronchial asthma and risk of 4 specific cardiovascular diseases and cardiovascular mortality: a meta-analysis of cohort studies

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Abstract. – **OBJECTIVE:** It has been shown that asthma is significantly associated with the risk of cardiovascular disease (CVD). Under this background, this study aimed to systematically classify and summarize the epidemiological evidence of asthma and the risk of 4 specific cardiovascular diseases (CVDs) and cardiovascular mortality (CVM).

MATERIALS AND METHODS: PubMed and Embase databases were searched from inception to December 1st, 2021 in order to identify relevant studies. The random-model was used to assess the pooled results. All pooled results were expressed as risk ratios (RRs) and corresponding 95% confidence intervals (CIs).

RESULTS: Finally, a total of 18 studies were included in the present meta-analysis. Compared with non-asthmatic group, patients with asthma had significantly increased risks of subsequent cardiovascular heart disease (CHD, RR 1.33; 1.19-1.50, $I^2=80.3\%$; $p<0.001$), and CVM (RR 1.35; 1.15-1.59, $I^2=0\%$; $p<0.001$). Similarly, the risks of heart failure (HF, RR 2.10; 1.98-2.22, $I^2=17.4\%$; $p<0.001$) and myocardial infarction (MI, RR 1.39; 1.16-1.66, $I^2=59.3\%$; $p<0.001$) were higher in the asthmatic population. However, the higher risk of atrial fibrillation (RR 1.70; 1.45-2.00, $I^2=0\%$; $p<0.001$) was observed only in the active asthmatic population.

CONCLUSIONS: In general, asthma is associated with subsequent increased risks of CHD, MI, AF, HF, and CVM. In addition, among patients with asthma, females have a higher risk of CHD than males, while active asthmatic patients have a higher risk of CVM than non-active asthmatic patients.

Key Words:

Asthma, Cardiovascular mortality, Cardiovascular heart disease, Cardiovascular diseases.

It often starts in childhood and is a major cause of morbidity in adulthood². Currently, asthma remains a major global medical and economic burden, which leads to approximately 495,000 deaths per year³. Its prevalence continues to increase in many parts of the world⁴.

Bronchial asthma that causes low-grade systemic inflammation and lung function decline is strongly associated with an increased risk of subsequent cardiovascular disease (CVD), which has been well described in previous studies⁵⁻⁷. Moreover, cardiovascular disease is an important kind of co-morbidity in asthmatics, with asthmatics three times more likely to develop CVD than non-asthmatic patients⁸. Certainly, asthma and CVD share many risk factors and diseases that are involved in similar pathophysiological pathways⁹⁻¹¹, which may provide some potential theoretical basis for the investigation. In addition, asthma can induce the expression of prothrombotic factors and endothelial dysfunction, further promoting atherosclerotic thrombosis^{12,13}.

Previous studies^{5-7,14,15} on the relationship between asthma and CVD, CVD have mostly been analyzed as a whole or with coronary artery disease (CAD) as the primary study endpoint, while the relationship with other specific CVDs [e.g., atrial fibrillation (AF), heart failure (HF) and myocardial infarction (MI)] remains unclear. Although several recent epidemiological studies¹⁶⁻¹⁸ have revealed a strong association between asthma and the risk of atrial fibrillation, heart failure, and myocardial infarction, they should be further summarized and updated. Therefore, this study aims to systematically summarize the epidemiological evidence on the association of asthma with 4 specific CVDs (namely CAD, AF, HF, and MI). Meanwhile, the relations of asthma and the risk of cardiovascular mortality are further investigated with the aim of providing some directions for public prevention.

Introduction

Bronchial asthma is a common chronic airway inflammatory disease, which is characterized by reversible airway obstruction and bronchospasm¹.

Materials and Methods

Search Strategy

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P)¹⁹. PubMed and Embase databases were searched from inception to December 1st, 2021 in order to identify relevant studies. Two groups of medical subject headings (MeSH), including “asthma” and “cardiovascular diseases”, were adopted for ensuring a comprehensive search. In addition, previous meta-analyses and systematic reviews were also reviewed, if applicable. A detailed search strategy is provided in [Appendix 1](#). Under the registration number of INPLASY202220083, this meta-analysis was registered with INSLASY (inplasy.com).

Study Selection

In line with the PICOS criteria, the study inclusion criteria were as follows. 1) The study population was the asthmatic population aged >18 years. 2) The control or reference group of the study included non-asthmatic patients. 3) The endpoint of the study was the occurrence of 4 specific CVDs, including CAD, AF, HF, or MI. 4) The study type was limited to cohort studies. 5) Studies provided maximum covariate-adjusted risk ratios (RRs), odds ratios (ORs), hazard ratios (HRs), and corresponding 95% confidence intervals (CIs). The study exclusion criteria were shown below. 1) The study population was the non-asthmatic population. 2) The study types were case-control or cross-sectional studies. 3) The study endpoint did not include the occurrence of CVD. 4) Maximum covariate-adjusted RRs, ORs, or HRs were unavailable or could not be calculated. 5) Letters, case reports, or conference abstracts were excluded.

Data Extraction and Quality Assessment

Two investigators (Hua and Li) independently carried out data collection, publication quality assurance, bias assessment, and participant characteristics extraction. The following data were extracted using the Unified Data List, including first author, publication year, study design, country, follow-up, age of the population, percentage of female, sample size, case group, control group, ascertainment of outcome, and outcome. In addition, the maximum covariate-adjusted ORs, RRs, and HRs were extracted. Besides, the study quality was assessed by the Newcastle-Ottawa Scale

(NOS) score²⁰, with an overall score of 9 stars. To be specific, the NOS consists of 3 sections, namely, selection (n=4 stars), comparability (n=2 stars), and outcomes (n=3 stars). The study follow-up period of over 10 years was considered as adequate. Studies with a NOS score over 6 stars were considered as high-quality studies, whereas those with a NOS score less than 6 stars as low-quality studies. Any disagreement or dispute during these processes was resolved by mutual negotiation.

Statistical Analysis

Due to different classification strategies for asthma (including gender, degree of control, and smoking history), the CVD risk for overall asthma patients was not provided. Only results for subgroups were reported. On this basis, before such studies were pooled with other studies, initially, their subgroups were incorporated, and the pooled results were the CVD risk for the overall population. In this study, our outcomes included 4 specific CVDs (CHD, AF, HF, and MI) and CVM. In addition, if the study outcome was acute coronary syndrome, it was classified as MI for analysis. Broadly, there existed minor differences between different effect values (including ORs, RRs, and HRs) if the incidence of the outcome was low (<10%)²¹. Therefore, all the pooled results were expressed as RRs and their corresponding 95% CIs. Inter-study heterogeneity was evaluated using the I^2 statistic, where I^2 values of 25%, 50%, and 75% indicate low, moderate, and high inconsistency, respectively. Subgroup analysis was performed to explore the potential sources of heterogeneity and to compare different groups. Meta-regression would be conducted if the included studies were larger than 10²². Sensitivity analyses were conducted by eliminating one study at a time to examine its impact on the combined results. To estimate the combined RRs more conservatively, the random-effects model was adopted since it better explained the heterogeneity between studies. Apart from that, publication bias was assessed by the Begg's and Egger's tests^{23,24}, when the number of included studies was more than five. Here, it should be mentioned that all data analyses were performed through Stata 12.0. The commands have been uploaded as [Appendix 2](#). The two-tailed p -value less than 0.05 indicated statistical significance.

Results

A total of 10,262 studies were obtained from the PubMed and Embase databases, as shown

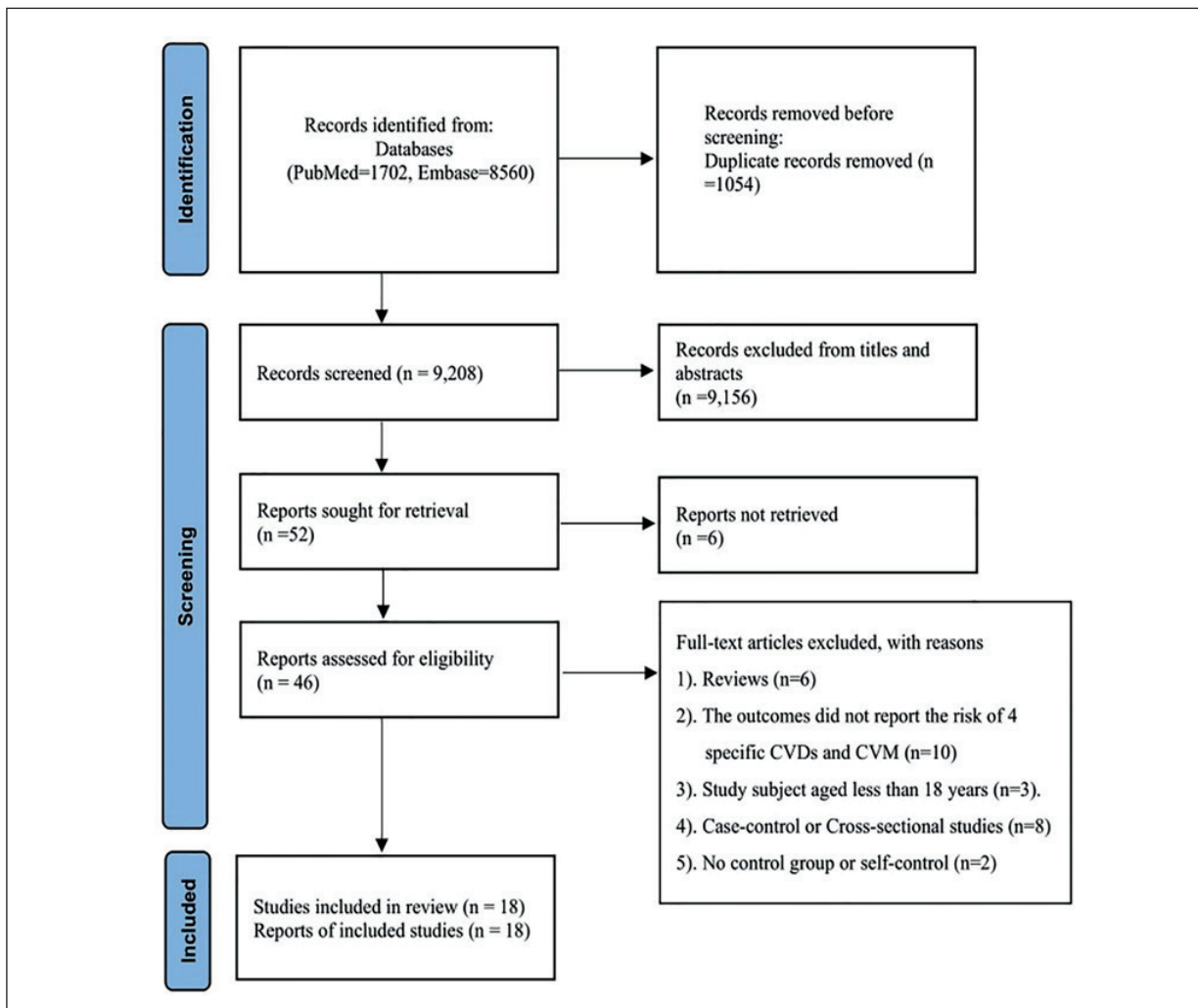


Figure 1. The flow chart of search.

in Figure 1. Manual search was also conducted whereas no additional study was identified. Of these 10,262 studies, 1,054 were excluded after screening the titles and abstracts due to duplication, whereas 9,156 were deleted due to irrelevance. The full-texts of the remaining 46 studies were carefully read, of which, 28 were excluded for the following reasons: 1) reviews (n=6); 2) the outcomes did not report the risk of 4 specific CVDs and CVM (n=10); 3) the study subjects aged less than 18 years (n=3); 4) case-control and cross-sectional studies (n=8); 5) conference abstracts (n=4); and 6) no control group or self-control (n=2). Finally, 18 cohort studies were included in the present meta-analysis^{6,25-41}.

Table I presents baseline characteristics of all the included studies. Among these 18 cohort studies, 13 studies mentioned the connection between

asthma and 4 specific CVDs, and 5 reported the association of asthma with CVM. The quality of the included studies is assessed in **Supplementary Table I**. Of these 18 studies, 10 were rated as 8 stars, 7 as 7 stars and 1 as 6 stars. All the studies had the scores of 6 stars or higher and were considered as high-quality studies.

Meta-analysis

Asthma and CHD, AF, HF, and MI

It was observed from Figure 2 that 7 studies recruiting 792,379 participants revealed the association of asthma with subsequent CHD risk. Compared with the non-asthmatic group, the risk of subsequent CHD significantly increased in the asthmatic population, regardless of the population gender (RR 1.33; 1.19-1.50, I²=80.3%; p<0.001).

Table I. Baseline characteristics of the 18 included studies.

Author, year	Study Design	Country	Follow-up (year)	Age (year)	Female (%)	Sample Size	Case Group	Control Group	Ascertainment of Outcome	Outcomes
Cepelis et al ²⁶ , 2019	PC	Norway	Mean 17.2	46.3	53	57,104	Active Asthma Non-active Asthma	No Asthma	ICD-9 ICD-10	MI
Carter et al ²⁷ , 2019	PC	UK	5.2	48.5	63.3	60,424	Asthma	No Asthma	ICD-10	AF
Tattersall et al ²⁸ , 2020	PC	USA	Median 12.9	62	53	6,814	Active Asthma Non-active Asthma	No Asthma	ICD-9	AF
Lemmetyinen et al ²⁹ , 2018	PC	Finland	15.6	52.2	64.9	2,941	Active Asthma Non-active Asthma	No Asthma	ICD-10	CVM
Yeh et al ³⁰ , 2017	RC	China	1996-2011	63.8	35.8	17,439	Asthma	No Asthma	ICD-9	CHD HF
Strand et al ³¹ , 2018	PC	Norway	1994-2011	40	50.9	446,346	Active Asthma Non-active Asthma	No Asthma	ICD-9 ICD-10	CVM
He et al ³² , 2021	PC	China	7.5	>20	51.9	37,015	Active Asthma Non-active Asthma	No Asthma	ICD-10	CVM
Çolak et al ³³ , 2015	PC	Denmark	4.5	20-100	60	94,079	Asthma	No Asthma	ICD-8 ICD-10	CHD MI
Chung et al ³⁴ , 2014	RC	China	1996-2011	50.6	55.4	38,840	Asthma	No Asthma	ICD-9	MI
Iribarren et al ³⁵ , 2004	RC	USA	Median 27	41	53.8	151,620	Asthma	No Asthma	Medical Records	CHD
Marco et al ³⁶ , 2005	PC	Italy	7.05	32.7	49.6	6,301	Asthma	No Asthma	Medical Records	CVM
Onufrak et al ³⁷ , 2008	PC	USA	1987-2001	45-64	56.9	14,567	Asthma	No Asthma	Medical Records	CHD
Bellia et al ³⁸ , 2007	PC	Italy	4.8	73.5	52.4	1,237	Asthma	No Asthma	Medical Records	CVM
Iribarren et al ³⁹ , 2012	RC	USA	5.2	45	66	407,190	Asthma	No Asthma	ICD-9	CHD HF; MI
Soriano et al ⁴⁰ , 2005	RC	UK	>1	29.8	53.6	7,931	Asthma	No Asthma	Medical Records	MI
Ingebrigtsen et al ²⁵ , 2020	PC	Denmark	5.7	57.9	39	91,692	Asthma	No Asthma	ICD-8 ICD-10	CHD HF
Cepelis et al ⁴¹ , 2018	PC	Norway	15.4	46.5	52.8	54,567	Asthma	No Asthma	ICD-10	AF
Schanen et al ⁶ , 2005	PC	USA	14	45-64	48.8	15,792	Asthma	No Asthma	Medical Records	CHD

PC, prospective cohort. RC, retrospective cohort. ICS, inhaled corticosteroid. ICD, International Statistical Classification of Diseases. MI, myocardial infarction. HF, heart failure. AF, Atrial fibrillation. CHD, coronary heart diseases. CVM, cardiovascular mortality.

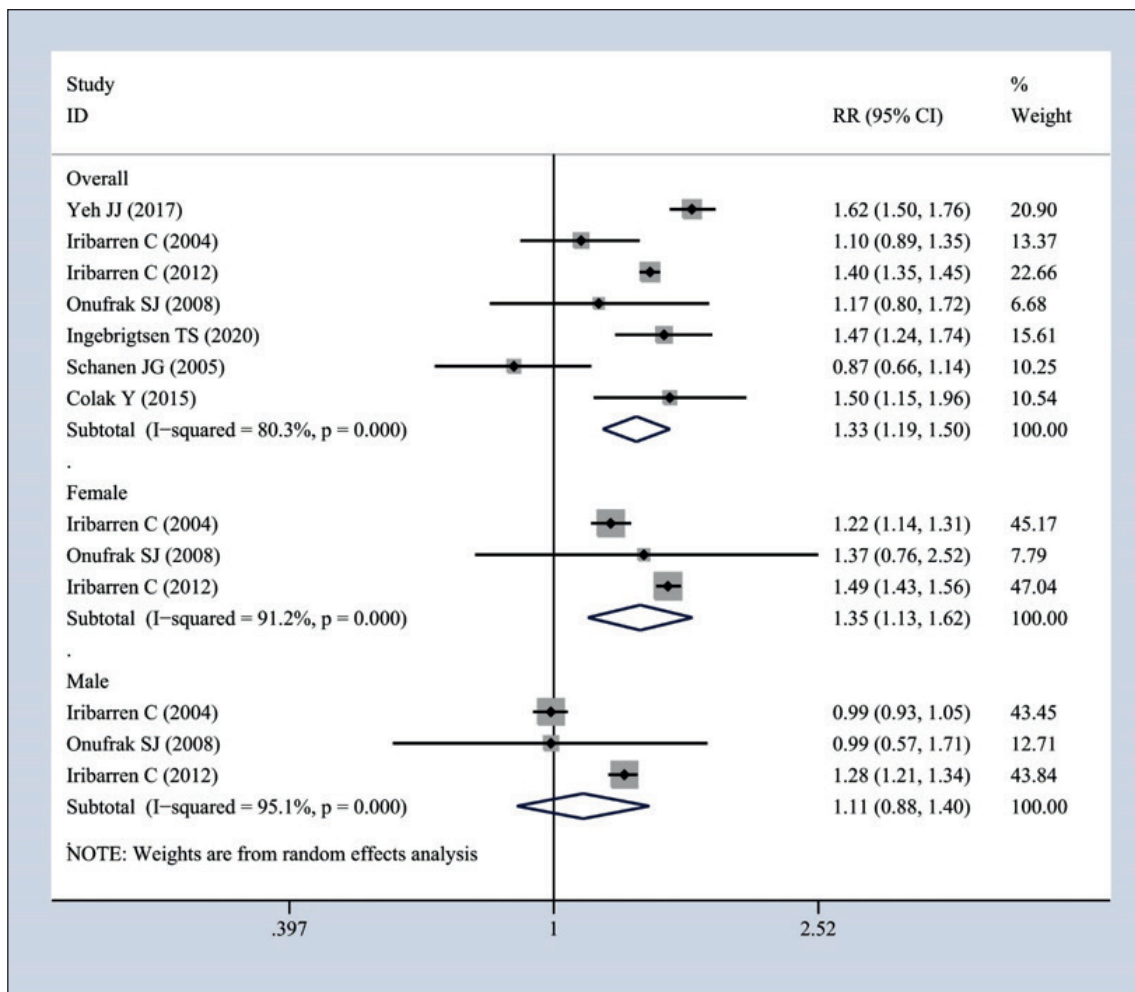


Figure 2. Forest plot of asthma and CAD risk in overall, male, and female asthmatics.

Meanwhile, when stratified by population gender, an increased risk of subsequent CHD was detected in female asthmatics (RR 1.35; 1.13-1.62, $I^2=91.2\%$; $p=0.001$), while this association was not found in males (RR 1.1; 0.88-1.40, $I^2=95.1\%$; $p=0.385$). Begg's ($p=0.368$) and Egger's ($p=0.470$) tests demonstrated that there was no significant publication bias. Besides, sensitivity analyses in asthma (overall) and CHD suggested that the pooled results remained stable after eliminating each individual study.

It was shown in Figure 3 that 3 studies enrolling 121,805 participants reported the association between asthma and AF, 2 including 61,381 participants mentioned the relation of active asthma with atrial fibrillation (AF), 3 involving 516,321 participants stated the connection between asthma and HF, and 4 enrolling 598,299 participants reported the correlation of asthma with MI. Com-

pared with the non-asthmatic group, the risk of subsequent AF was not significantly enhanced in the overall asthmatic population (RR 1.15; 0.96-1.37, $I^2=79.3\%$; $p=0.126$), whereas the risk of subsequent AF was significantly elevated in the active asthmatic population (RR 1.70; 1.45-2.00, $I^2=0\%$; $p<0.001$). Similarly, the risks of HF (RR 2.10; 1.98-2.22, $I^2=17.4\%$; $p<0.001$) and MI (RR 1.39; 1.16-1.66, $I^2=59.3\%$; $p<0.001$) were higher in the asthmatic population. Sensitivity analyses in asthma and MI indicated that the pooled results were stable after eliminating each study individually.

Asthma and CVM

According to Figure 4, 5 studies involving 493,840 participants mentioned the association of asthma with subsequent CVM risk. Compared with the non-asthmatic group, the risk of subse-

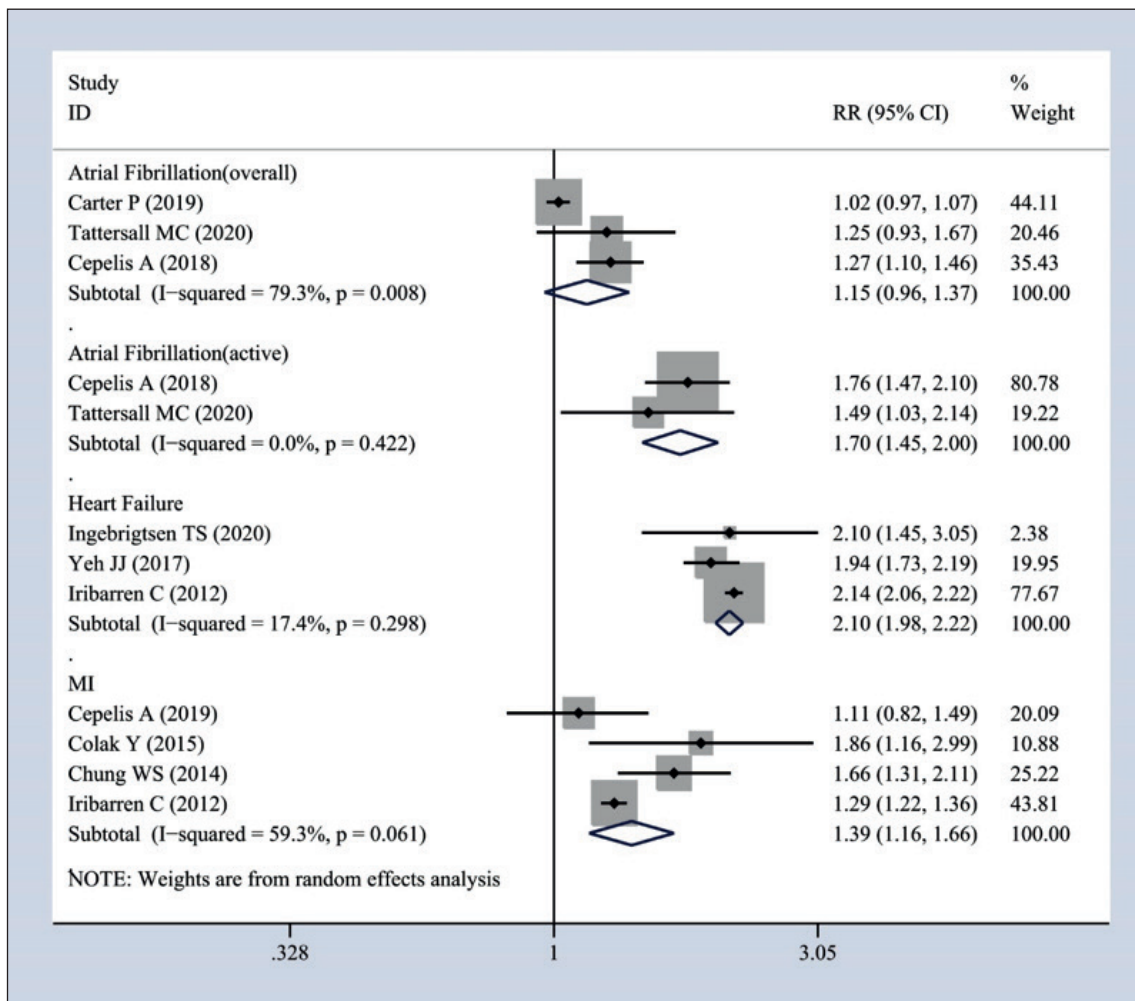


Figure 3. Forest plot of asthma and the risk of AF (in overall and active asthmatics), HF, and MI.

quent CVM significantly increased in the asthmatic population, regardless of the asthma stage (RR 1.18; 1.05-1.33, $I^2=0\%$; $p=0.005$). When stratified by asthma stage, an increased risk of subsequent CVM was observed in the active asthmatics (RR 1.35; 1.15-1.59, $I^2=0\%$; $p<0.001$), but not in the non-active asthmatics (RR 0.96; 0.79-1.18, $I^2=0\%$; $p=0.703$). Begg's ($p=1.0$) and Egger's ($p=0.312$) tests revealed that there existed no significant publication bias. Besides, sensitivity analyses in asthma (overall) and CVM demonstrated that the pooled results were stable after eliminating each study individually.

Subgroup analyses

Due to the current limitations in the number of studies, the number of studies included for some outcomes was too low. Therefore, we analyzed the outcomes that were mentioned in more than

4 studies. Subgroup analyses of the pooled outcomes were conducted by the following clinical characteristics, including study design, country, publication year, sample size of study, study quality and duration of follow-up. Subgroup analyses of asthma and CHD suggested that study quality, the country and duration of follow-up might be the sources of heterogeneity between studies. Nevertheless, the heterogeneity between asthma and MI still could not be well explained by subgroup analysis (**Supplementary Table II**).

Discussion

This meta-analysis showed that the risks of overall CVD and CVM significantly increased in the asthmatic population compared with the normal population. Meanwhile, the risk of specific

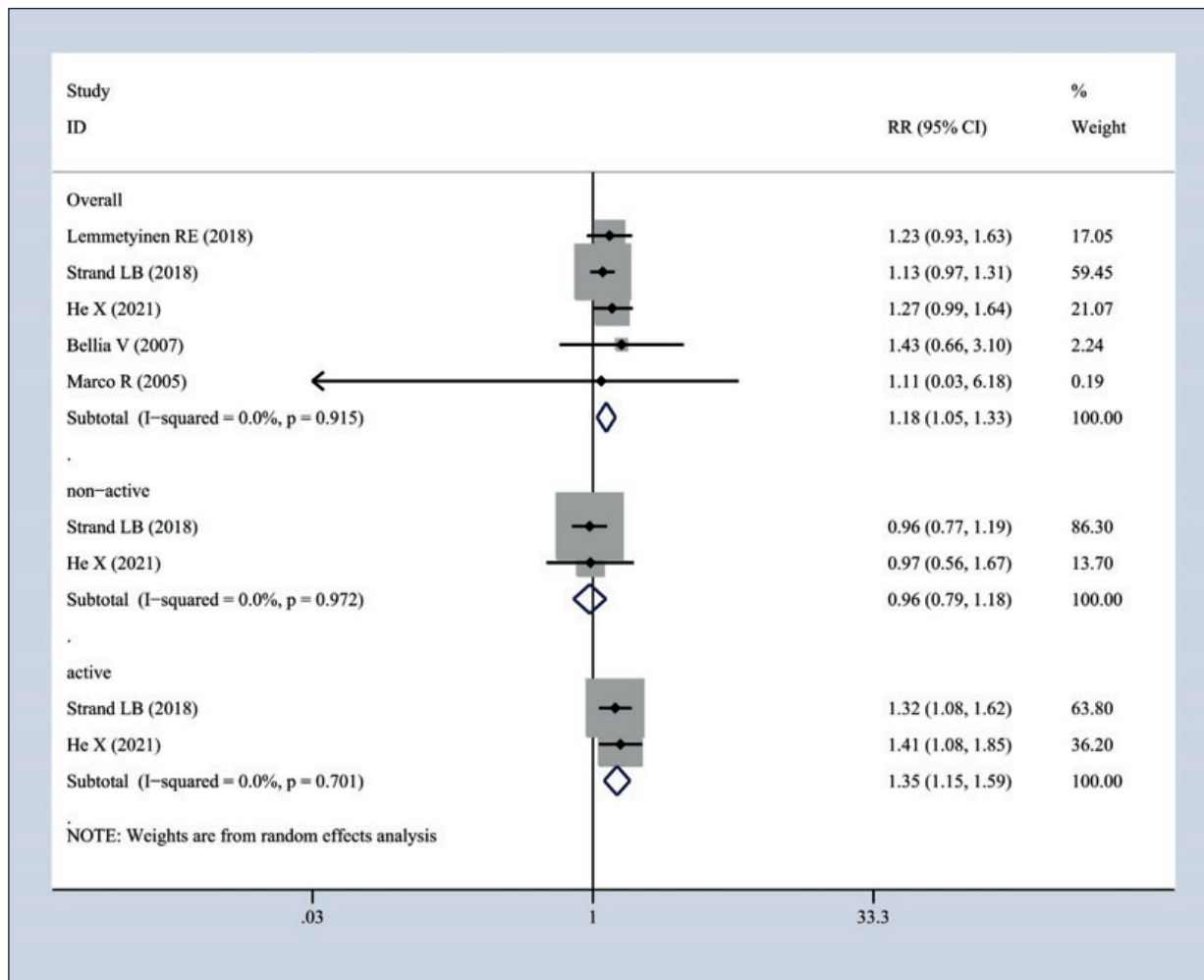


Figure 4. Forest plot of asthma and CVM risk in total, active, and non-active asthmatics.

CVD, including CHD, MI, AF, and HF significantly elevated in the asthmatic population. To our knowledge, 3 previous meta-analyses^{1,42,43} have reported the association between asthma and related CVD. Liu et al¹ pointed out that asthma was significantly associated with a higher risk of CHD based on seven cohort studies. Similarly, Wang et al⁴² revealed an evident association between asthma and the risk of CHD based on 11 trials. Xu et al⁴³ showed that asthma was associated with an increased risk of CVD and all-cause mortality to a great extent. Furthermore, our findings suggest that asthma is significantly associated with a higher risk of CHD, as well as with the risk of AF, HF, MI and CVM. Therefore, from the perspective of study scope, our findings can validate and complement the previous results.

Currently, the pathogenesis by which asthma affects CVDs remains unclear while several possible

mechanisms have been proposed to explain the observed association with the risk of asthma-related CVDs. Chronic inflammation, a hallmark of asthma, may play an important role in the association between asthma and CVD. At first, when an asthma attack occurs, the airway inflammatory response is driven by T-cell helper type 2 (Th2), usually followed closely by systemic inflammation⁴⁴, cardiac arrhythmias, and MI. Previous studies^{45,46} have reported that the levels of inflammatory biomarkers including c-reactive protein (CRP), interleukin (IL)-1 β , tumor necrosis factor- α (TNF- α), IL-6, IL-8, and fibrinogen significantly increase in asthmatic patients, which may thus promote the progression of atherosclerosis and consequently lead to CVD events. Second, lung function decline also exerts an important role in the association between asthma and the risk of CVDs⁴⁷. Prolonged asthma may cause irreversible airway remodeling, thereby inducing airway obstruction

and lung function decline. Meanwhile, it has been demonstrated that forced expiratory volume in one second (FEV1) is strongly associated with the risk of CVD⁴⁷. Third, the use of some anti-asthma medications including oral or inhaled glucocorticoids and beta-adrenergic agonists, may have potentially cardiotoxic effects, thereby increasing the risk of subsequent CVD⁴⁸. Finally, asthma and CVD often share numerous risk factors, such as air pollution, obesity, psychological stress, smoking or physical inactivity, which can partially explain the association between asthma and the CVD risk⁴⁹. Furthermore, asthma is significantly associated with the development of other CVDs. During an asthma attack, the airway inflammatory response drives the release of Th2⁵⁰, which further induces systemic inflammation, and this may partially explain the increased risk of CVD in activated asthmatics. Asthma-induced elevation of inflammatory platelet-activating factor (PAF) not only leads to airway hyperresponsiveness in asthmatics, but also generates an increased risk of MI in these patients⁵¹. In addition, chronic systemic inflammation will induce atrial electrical and structural remodeling, thus setting the stage for the development of AF⁵². Moreover, in asthmatic patients, leukotriene levels are increased and leukotriene receptors are highly expressed in the heart, which are closely associated with the conduction system⁵³. Increased leisure activity has been reported to be significantly associated with the risks of CVD and HF²⁵, and asthmatic patients tend to have reduced activity tolerance, while this further increases the risks of CHD and HF. The present study suggested a sex difference in the risk of CHD among asthmatic patients while its precise mechanism remained unknown. In fact, there is a significant gender disparity in asthma. During childhood, boys have an increased prevalence of asthma, while in adulthood, women have an increased prevalence and severity of asthma, which is closely related to sex hormone differences⁵⁴. Besides, it has been shown that estrogen levels increase dramatically in females after puberty, which can regulate mast cells to induce a significant increase in leukotriene levels *in vivo*^{55,56}. Nevertheless, this is strongly associated with the development and progression of atherosclerosis⁵⁷. At the same time, the severity of asthma is enhanced noticeably in adult females compared to adult males, and long-term or excessive use of corticosteroids adds the risk of various metabolic disorders, thus further increasing the risk of CHD^{54,58}. In addition, a positive association between plasma cortisol and the severity of coronary heart disease has been found^{59,60}. These aspects may partially explain the higher risk of CHD in female asthmatics.

Notably, our meta-analysis has the following advantages. First, based on previous studies, this is the first study to systematically summarize the association between asthma and overall CVD, CVM, and some specific CVDs. This has updated and complemented previous studies. Second, the high quality of the studies included in this study ensures the reliability of the findings.

Inevitably, certain limitations should also be noted in this work. First, high heterogeneity was detected in some of the outcomes, and the potential sources of heterogeneity were partially explained by subgroup analyses. Although the effect values included in the analysis were adjusted for maximum covariates, the effect of the residual variables on the results was not excluded. Second, most of the included studies were distributed in the Americas, Europe, and Asia, while few of them were from other regions. In addition, ethnic heterogeneity should be further clarified in future studies. Third, due to the limited number of existing studies, the pooled results that included a small number of studies were not conducted for further subgroup analysis or meta-regression analysis. Fourth, different studies adopted different strategies for asthma classification, including gender, smoking history, stage of onset, and degree of control. Further stratified analyses should be performed to explain more future studies.

Conclusions

To conclude, asthma is associated with the subsequent risks of CHD, MI, AF, HF, and CVM. Among asthmatics, females have a higher risk of CHD than males, while active asthmatic patients have an increased risk of CVM than non-active asthmatic patients. These data have suggested the necessity of early detection and intervention in asthma patients who may be associated with potential CVD events or CVM.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

None.

Authors' Contributions

Hua and Diao designed the study. Hua and Li did the literature searches, and designed the data extraction form. Hua and Li collected the data. Hua did the statistical analyses.

Hua, Li and Diao supervised the entire project. All authors critically revised subsequent drafts. All authors read and approved the submitted manuscript.

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