REVIEW ARTICLE

Asthma in Relation to Coronary Heart Disease: A Systematic Review and Meta-analysis

Pallavi Mishra[1], Prashant Hisalkar[2], Neerja Mallick[3]

Abstract

Aim and background: Asthma is a clinical condition in which constriction of the airway occurs. It is a heterogeneous syndrome that manifesting different phenotypes. Coronary artery disease makes the arteries hardened and inflamed. Similarly, airway swelling occurs in asthma. Lipid accumulation and inflammation are the two common characteristics of coronary artery diseases. Therefore, many authors have described higher cardiovascular disease (CVD) risk in asthmatics.

Materials and methods: The search strategy selected 10 published articles that were related to asthma and coronary artery disease and published from May 2004 to April 2018.

Results: In this study, the pooled analysis indicated that asthma overall was significantly associated with CHD [OR 2.26 (1.45, 3.52), $p = 0.0003$]. The values for heterogeneity test were higher ($I^2 = 99\%$, $p < 0.00001$).

Discussion: In this pooled analysis, we found that asthmatic patients have associated with a higher risk for coronary heart disease. Similarly, several previous studies also supported a positive association between asthma and the incidence of coronary heart disease.

Keywords: Asthma, Coronary heart disease, Inflammation, Meta-analysis, Systematic review.

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Introduction

Asthma is a chronic inflammatory pulmonary disorder. It is a clinical condition in which constriction of the airway occurs. It affects 300 million people worldwide and global prevalence is approximately 4.5%.[1,2] Many studies considered that asthma is a group of diseases called heterogeneous syndrome that manifesting different phenotypes.[3–5] Recently found that the mechanisms of adult-onset asthma may include several metabolic and inflammatory components that are common to other diseases such as obesity, metabolic syndrome, diabetes mellitus type 2 (DM2), cardiovascular diseases (CVD), and psychiatric diseases.[5]

Coronary heart disease is also a major cause of death among adults in the United States.[6] It is a part of CVD.[7] Coronary artery disease makes the arteries hardened and inflamed. Similarly, airway swelling occurs in asthma. Lipid accumulation and inflammation are the two common characteristics of coronary artery diseases.[8–12] Therefore, many authors have described higher CVD risk in asthmatics.[13–20]

Materials and Methods

Article Search

This meta-analysis was performed based on prospective follow-up studies. Our sources of evidence were electronic databases, Cochrane CENTRAL database, medical journals, grey literature (e.g., meeting abstracts), trail registers, the world wide web, and other drug companies. The title for searching was asthma, coronary artery disease, and heart disease. Moreover, the highly cited references were also selected manually.

Inclusion Criteria

The selection was done in the following manner: (1) Studies published from May 2004 to April 2018. (2) Articles related to asthma and coronary artery disease or heart disease. (3) Full-text articles were considered. (4) Articles that were published in the English language only.

Exclusion Criteria

Review articles, pooled data, studies published before 2004, articles are written in other languages, and articles that were not given detailed information were excluded.

Quality Assessment

The assessment of quality was done by the Newcastle-Ottawa scale. In this, we measured the quality of included studies, comparability among groups, and probability of risk factors.

Data Analysis

Statistical analysis was done by using the software RevMan 5.3 from Cochrane.

[1,3]People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh, India

[2]Department of Biochemistry, Government Medical College, Dungarpur, Rajasthan, India

Corresponding Author: Prashant Hisalkar, Department of Biochemistry, Government Medical College, Dungarpur, Rajasthan, India, Phone: +91 9422610220, e-mail: pjhisalkar@yahoo.co.in

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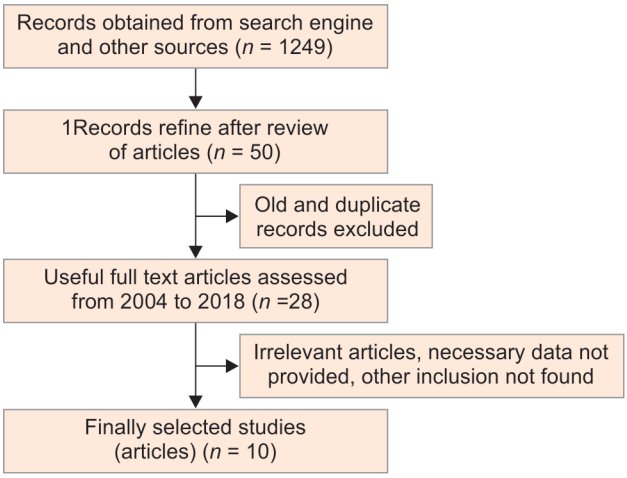
Results

Flowchart 1 shows the search process of the study to get suitable articles for meta-analysis. The initial baseline search obtained 1,249 records from various search engines. After the first screening of the abstract, 1,199 articles were removed and only 50 articles were selected. Among 50 articles, only 28 full-text articles were selected which were published between 2004 and 2018. After keen observation of these 28 articles, 18 articles were not provided relevant data. Therefore, only 10 articles that fulfill the inclusion criteria were finally taken for meta-analysis.

Figure 1 forest plot represents a graphical display of results from individual studies on a common scale. Each study is indicated by a square and horizontal line. The area of the square shows the weightage of the study, i.e., sample size. Larger the sample size, narrow the confidence interval which gives higher precision. The horizontal line indicates 95% CI. The aggregate effect size is displayed as diamond. It also indicates a summary risk estimate with its corresponding 95% CI. If squares and diamonds touch the null line shows non-significant results, unlike this study. Pooled analysis indicated that asthma overall was significantly associated with CHD [OR 2.26 (1.45, 3.52), $p = 0.0003$]. The values for heterogeneity test were higher ($I^2 = 99\%$, $p < 0.00001$). The relative risk of study groups was 1.12. The relative risk and odds ratio provides important information regarding the effect of the risk factor on the outcome. The relative risk and odds ratio of 1 suggests that there is no difference between the two groups. A value >1 suggests increasing risk while a value <1 suggests the reduction of risk.

Flowchart 1: PRISMA flow diagram



Discussion

In this pooled analysis, we found that asthmatic patients have associated with a higher risk for coronary heart disease. Similarly, several previous studies also support a positive association between asthma and the incidence of coronary heart disease. In a condition of asthma, there are several pro-inflammatory agents such as C-reactive protein, interleukin-6, interleukin-1, tumor necrosis factor-α, and platelet-activating factor secreted which enhanced vascular inflammation and atherosclerosis.[13,21–23] Along with this, a recent study discovered that the degree of arterial inflammation was higher in asthmatics compared to non-asthmatics.[24] In some studies, long-term use of asthma medication like inhaled or oral corticosteroids or β-agonists were also associated with the risk of CHD.[25–28] The acute exacerbation of asthma results in hypoxia and tachycardia which may lead to symptoms of CHD. The hormone estrogen also regulates the allergic inflammation, migration of immune cells, releases of pro-inflammatory cytokines and leukotrienes which cause the severity of asthma more in women vs men.[29,30] One possible explanation for the relationship between CHD and child-onset asthma is that child-onset asthma may trigger due to some allergic conditions or environmental irritants but the causes of adult-onset asthma is intrinsic such as hormones, hardening of chest walls, and cigarette smoking. These intrinsic factors could increase CHD risk.[31–33]

Etiopathogenesis of asthma and CAD is complex and multifactorial. Mostly, CAD is acquired, dependent on lifestyle, and usually rises after the age of 40. The main cause of CAD is atherosclerosis. Several other traditional risk factors involve high blood pressure, dyslipidemia, diabetes mellitus, smoking, pro-inflammatory activity, obesity, and family history.[34] β2 agonists delivered to the airways by inhalation or by oral route, provide rapid and effective reversal of acute airway obstruction caused by bronchoconstriction. Apart from beneficial effects, there are some significant adverse drug reactions with β2 agonists. Tremor and tachycardia are common adverse effects; however, tolerance generally develops to tremors. Arterial O_2 may fall when treatment of acute exacerbation of asthma begun; this may be due to drug-

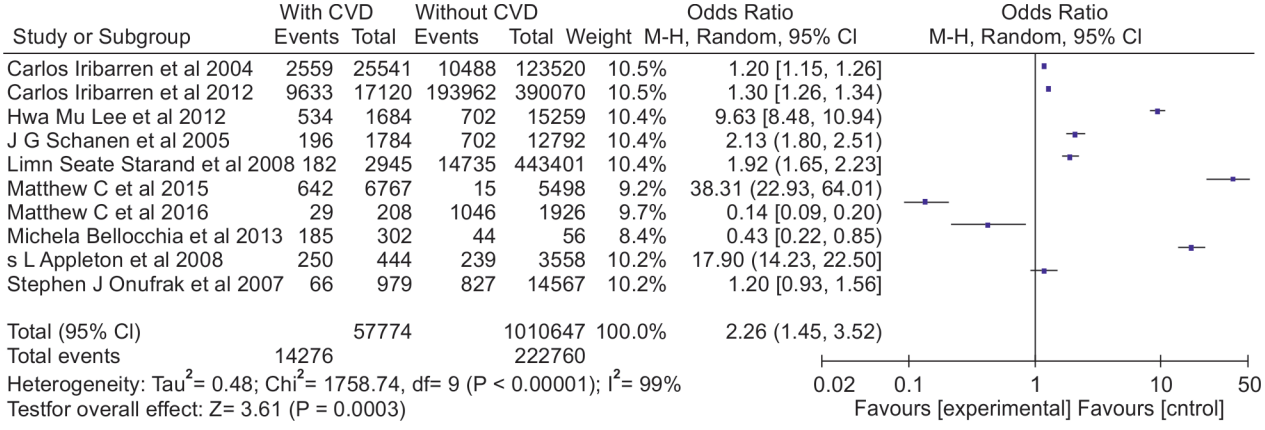


Fig. 1: Forest plot

induced pulmonary vascular dilation.[35] Atherosclerosis is triggered by endothelial destruction due to mechanical, chemical, and biological factors.[36] As the result of this inflammatory response occur and the adhesion molecules will be produced due to the stimulation of endothelial cells, macrophages, and vascular smooth muscle cells which stimulate the entering of monocytes into sub-endothelial space.[37]

The mechanism of CAD is explained in several ways. Free radicals damage the lipoprotein structure which is trapped by a scavenger, receptors present in macrophages, and transformed to foam cells.[38,39] Second, the rennin-angiotensin system also plays an important role in the pathogenesis of atherosclerosis, particularly angiotensin II. It is an enzyme that causes endothelial dysfunction by synthesizes the adhesion molecules, inflammatory cytokines, and free radicals.[40] Some researchers demonstrate an auto-immune nature for atherosclerosis.[41,42]

The role of inflammation is important in process of atherogenesis. Macrophages, mast cells, and *T*-lymphocytes are the cells of the immune system which are a major component of atheromatous plaque. These cells participate in the mischievous immune cycle and activate each other via bidirectional stimuli. For example, mast cells can activate macrophages and may enhance *T*-cell activation.[40] IgE interacts with allergen on the surface of mast cells and basophils cause degranulation and secretion of mediators such as histamine, tryptase, chymase, carboxypeptidase, leukotrienes, prostaglandins, and cytokines. The activity of mast cells, basophils, and eosinophils is regulated by Th2 lymphocytes and produces cytokines (IL-6). Biogenic amines are responsible for the manifestation of the symptoms which increase the permeability of blood vessels and cause edema. Histamine causes the contraction of smooth muscles of internal organs (like bronchi).[43]

Strand et al. conducted a study between 1998 and 2011 on 446,346 participants in which 2,945 deaths were caused by CVD, 780 death due to CHD, and 1,146 death from a stroke during the follow-up. They have divided asthma into two categories: (1) active asthma and (2) no-asthma. They found that active asthmatics were significantly associated with increased risk of CVD patients and men were more susceptible than women.[44] Tattersall et al. observed a total of 223 CVD events (179 in the non-asthma cohort, 22 in the late-onset asthma cohort, and 7 in the early-onset asthma cohort) during follow-up. Late-onset asthmatics have more CVD events.[45,46] Similarly, Tattersall et al. were analyzed inflammatory markers such as CRP and IL-6 and found that higher level in persistent asthmatics compared with intermittent asthmatics and non-asthmatics. They assumed that elevated systemic inflammatory markers in persistent asthmatics may contribute to increased CVD risk. However, further studies are needed to elaborate on this mechanism.[13] Iribarren studied the asthma cohort and non-asthma cohort. In all coronary heart disease analyzes, 113,025 subjects were experienced 6,396 events in asthma cases and found that statistically highly significant relation. In this study, women have a stronger association than men.[14]

The inflammatory pathogenesis of asthma and CAD may have significant overlap. 5-Lipoxygenase enzymatic pathway is partially responsible for inflammation in asthma. In this pathway, arachidonic acid is converted into leukotriene A4 in presence of enzyme 5-lipoxygenase and this leukotriene then formed four different leukotrienes. These leukotrienes are paracrine inflammatory substances generated in immune cells which can be responsible for acute and chronic inflammation.[9] Contraction in smooth muscles, tissue, and migration of eosinophils are functions of leukotrienes in bronchioles.

Enhance the level of leukotrienes and 5-lipoxygenase enzyme present in atherosclerotic plaque. The 5-lipoxygenase pathway is also responsible for CVD events because a higher level of this enzyme and leukotrienes causes plaque instability.[9,10]

Resting heart rate was lower in asthmatic individuals than in controls although not significant. It suggests an increase in the parasympathetic drive in asthmatic individuals. The resting BP, especially the diastolic BP, was on a higher side in asthmatic patients. This may be because of the increased α-adrenergic drive in asthmatic patients as quoted by other workers who got similar findings. Some authors got resting tachycardia in asthmatic patients.[47]

This meta-analysis provides evidence for a prospective relationship between asthma and the incidence of coronary heart disease. With the help of this study, we may add more awareness for heart disease to society. In this patient population, health professionals should closely scrutinize known CVD risk factors and asthma.

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