Hypertension Research (2023) 46:2056–2058
https://doi.org/10.1038/s41440-023-01328-5

COMMENT

Asthma as risk for incident cardiovascular disease and its subtypes

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Keywords Asthma · Cardiovascular disease · Epidemiology

Received: 23 April 2023 / Revised: 8 May 2023 / Accepted: 10 May 2023 / Published online: 25 May 2023

Various epidemiological studies have been reported that respiratory diseases increased the risk of incident cardiovascular disease (CVD). Previous reports including meta-analysis of prospective cohort studies have shown that moderate or severe obstructive sleep apnea increased the risk of the incidence and subsequent death from CVD, especially stroke [1, 2]. Similarly, chronic obstructive pulmonary disease (COPD) exacerbations also increased the risk of the incidence and subsequent death from CVD [3]. Until recently, the association between respiratory disease and the incidence of CVD has been considered to be strongly influenced by traditional risk factors for CVD such as smoking and obesity. However, the significant association between respiratory diseases and incident CVD was unchanged after adjustment for traditional risk factors for CVD, and respiratory disease may induce the incidence of CVD by a mechanism that is not mediated by traditional risk factors for CVD.

The association between asthma, as well as sleep apnea syndrome and COPD, and the incidence and subsequent death from CVD and its subtypes have been reported in previous studies. In a recent meta-analysis of cohort studies, asthma increased the risk of CVD death (Risk ratio (RR): 1.25, 95% confidence interval (CI): 1.14–1.38) [4]. Regarding subtypes of CVD, patients with active asthma had a higher risk of stroke, especially ischemic stroke, but inactive asthma was not associated with an increased risk of stroke in a recent meta-analysis of observational studies [5]. Another meta-analysis of cohort studies reported that asthma increased risk of subsequent coronary heart disease in women over 18 years of age, but statistical heterogeneity was high across studies [6]. Based on these previous findings, Lee et al. reported that asthma was associated with an increased risk of the incidence of myocardial infarction (MI) using competition risk analysis in hypertensive Korean patients (Sub-distribution hazard ratio (SHR): 1.23, 95% CI: 1.17–1.29) [7]. They also reported the risk of incident MI was particularly high in patients with asthma treated with long-acting β2-agonist (LABA) inhalers or systemic corticosteroids, and the finding was consistent with the results from Nord-Trøndelag health study (HUNT) [8]. These results indicate active asthma may be an important risk factor for incident atherosclerotic CVD.

There are three possible mechanisms by which asthma is associated with the development of CVD (Fig. 1). First, chronic airway inflammation due to asthma contributes to systemic inflammation, and chronic systemic inflammation is expected to lead to the increased vulnerability of blood vessels, activation of coagulability, and dysfunction of vascular endothelial cells, contributing to the progression of atherosclerosis. Second, chronic airway obstruction due to prolonged asthma leads to decreased pulmonary function and hypoxemia, and hypoxia may play an important role in the progression of atherosclerosis by promoting lipid accumulation in macrophages, increased secretion of inflammatory mediators, inducing ATP depletion and angiogenesis [9]. Third, medications for asthma may contribute to the incidence of CVD. For example, a previous cohort study in the United Kingdom reported long-term steroid treatment was associated with an increased risk of CVD in patients with immune-mediated inflammatory diseases [10]. Similarly, although it is controversial issue, the use of inhaled long-acting β2-agonists (LABAs) or long-acting antimuscarinic antagonists (LAMAs) for COPD patients might be associated with an increased risk of CVD [11]. The detailed mechanism by which asthma causes CVD remains unclear, and further basic research will be required to elucidate the mechanism.

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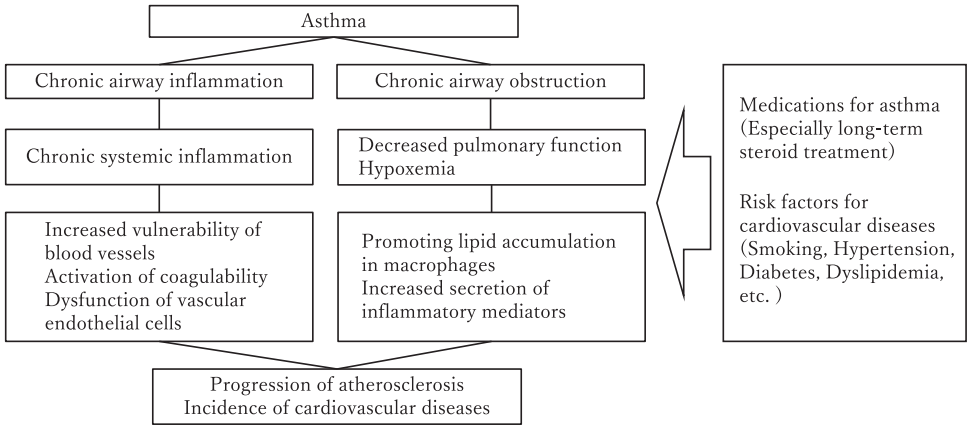

Fig. 1 Possible mechanisms between asthma and the incidence of cardiovascular diseases

There are several important points to consider when evaluating research articles that have examined the association between asthma and the incidence and subsequent death from CVD. First, the definition of asthma has not been standardized across studies. The definition of asthma includes the diagnosis of the physician, the ICD codes, and/or current medical history of asthma using self-reported questionnaire, and thus, it is necessary to check for misclassification when evaluating research articles. In particular, few studies have examined the association with the incidence and subsequent death from CVD limited to patients with asthma who do not complicate COPD, and future research examining the risk of cardiovascular disease in only patients with asthma who do not complicate COPD may be warranted. Next, several medications for asthma increase the risk of incidence and subsequent death from CVD. In particular, long-term steroid treatment is known to cause diabetes and dyslipidemia, which are both major risk factors for CVD, and may increase the risk of CVD. Therefore, the risk of CVD incidence and/or death from CVD in patients with severe asthma who are receiving medications for asthma may be overestimated. Lastly, most studies have not measured the presence of other diseases that cause systemic inflammation, and the impact of these systemic diseases on the association between asthma and the incidence of CVD is unknown. If systemic inflammation is the major mechanism by which asthma causes CVD, patients with other systemic inflammatory diseases should be excluded.

In summary, many observational studies have reported that asthma, regardless of the presence of hypertension, increased the risk of incidence and subsequent death from CVD. However, it is difficult to reach definitive conclusions about whether asthma should be treated to prevent the incidence of CVD because it is not practical to design interventional studies to examine whether treatment for asthma reduces the incidence and subsequent death from CVD. Nevertheless, these studies suggested that it is important to provide appropriate management of asthma for patients with asthma who have risk factors for CVD, as well as more intensive management of risk factors for CVD, including smoking, hypertension, diabetes, and dyslipidemia.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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