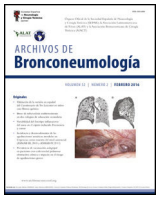
Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE
Bronconeumología

www.archbronconeumol.org



Editorial

Inflammation Without Borders: The Interconnected Pathways of Asthma and Heart Disease

Asthma and heart disease are among the most common global non-communicable diseases with significant health and cost impacts. An estimated 262 million people live with asthma which, in 2021, was linked to 455,000 death globally [1]. In the U.S., over 25 million children and adults live with asthma which caused 9.8 million asthma attacks in 2021 with an estimated annual cost of $80 billion [2]. Fortunately, the mortality rate due to asthma around the world has been decreasing. Contrary to this, cardiovascular disease (CVD) continues to be the leading cause of death worldwide with 20.5 million deaths in 2021 [3]. While it is mainly a disease of adults, about 1 in 5 individuals over age 20 has coronary artery disease in the U.S. Beyond its incredible toll on human life, the financial cost of CVD is also enormous. Between 2020 and 2021, $418 billion were spent in medical care, medicines and lost productivity due to CVD in the U.S. alone.

While respiratory diseases and CVD have distinct clinical presentation and management strategies, accumulating evidence suggests that they share common risk factors and pathophysiologic mechanisms and indeed can co-exist in the same patient. Longitudinal studies suggest an association between asthma and CVD. Indeed, asthma and CVD share common risk factors such as smoking, exposure to environmental pollution, underlying allergic inflammation, metabolic syndrome, obesity, and sleep apnea. Data from a prospective population-based cohort (the Framingham Offspring Study) demonstrated a clear association between asthma and CVD incidence (hazard ratio, 1.28; 95% CI 1.07–1.54) [4]. The study also noted a higher rate of CVD in women with asthma compared to men. Furthermore, longitudinal analysis of the Nord-Trondelag County cohort in Norway suggested that adults with active asthma had 29% higher risk of developing acute myocardial infarction (AMI) compared to adults without asthma [5]. Additionally, there appears to be a dose–response relationship between asthma control and AMI with patients with uncontrolled asthma having 73% higher risk of AMI compared to those with controlled asthma. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, patients with persistent asthma were noted to have higher carotid plaque scores and elevated inflammatory biomarkers produced by dysregulated immune cells [6]. A meta-analysis of seven cohort and nested case–control studies with 1,405,508 subjects with asthma showed that asthma was associated with higher risk of atrial fibrillation (odds ratio 1.15; 95% CI 1.01–1.29) [7]. Another meta-analysis of 18 studies examined the risk ratios of four different cardiovascular disease in subjects with and without asthma. Patients with asthma were at higher risk of heart failure (relative risk [RR], 2.10; 95% CI 1.98–2.22) and myocardial infarction (RR 1.39; 95% CI 1.16–1.66), whereas only those with active asthma had high risk of atrial fibrillation (RR 1.70; 95% CI 1.45–2.00) [8]. The presence of airway obstruction and asthma may often be under-recognized in patients with cardiac disease because symptoms may overlap and thus the diagnosis of asthma is often challenging. In a study of 475 subjects with known obstructive coronary artery disease who underwent spirometry, undiagnosed airflow limitation was seen in 10.7% [9]. However, it is unclear how many of these patients had COPD vs asthma.

The exact pathophysiological mechanisms linking cardiovascular disease and asthma are not well understood. Nonetheless, asthma and CVD share several common inflammatory pathways which suggest bidirectional interactions. Studies have linked excessive release of cysteinyl leukotrienes from eosinophils, which are prevalent cells in type-2 asthma, with CVD pathogenesis [10]. Several cytokines such as interleukin (IL)-1β, IL-6, IL-17, interferon (IFN)-γ, tumor necrosis factor (TNF)-α also play important roles as common inflammatory drivers, which may partly explain this bidirectional relationship of these two conditions [11]. Specifically, IL-6 and TNF-α, which are known to be associated with the neutrophilic asthma endotype, are thought to be key drivers of atherosclerosis [11]. Leukotrienes (LT) mediate mucus hypersecretion, airway edema and bronchospasm in asthma and have also been increasingly expressed in the cardiac conduction system [12]. Furthermore, LTB4 is among the powerful inducers of IL-6 [12]. Oxidative stress due to imbalance of reactive oxidative species and antioxidants is also common to both asthma and CVD. Bronchial epithelial cells, smooth muscle cells, mast cells, macrophages and eosinophils are a major source of vascular endothelial growth factor (VEGF), which plays a role in vascular remodeling. Increased blood pressure and hypoxemia during acute asthma attacks have also been proposed to influence the link with heart disease in patients with asthma. Allergic asthma has also been linked with accelerated atherosclerosis in mice deficient in apolipoprotein E. Leakage of clotting and tissue factor in the airways of subjects with asthma can impair anticoagulant activity and attenuate fibrinolysis [13]. Adipose tissue including those in epicardial and periaortic areas are rich in inflammatory cells, which release mediators that can cause Type 2 inflammation which may confer a protective role in CVD. Prolonged asthma can lead to airway remodeling and lung function decline. Studies have linked lung

https://doi.org/10.1016/j.arbres.2025.09.012

Please cite this article as: M. Adrish and N.A. Hanania, Inflammation Without Borders: The Interconnected Pathways of Asthma and Heart Disease, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2025.09.012

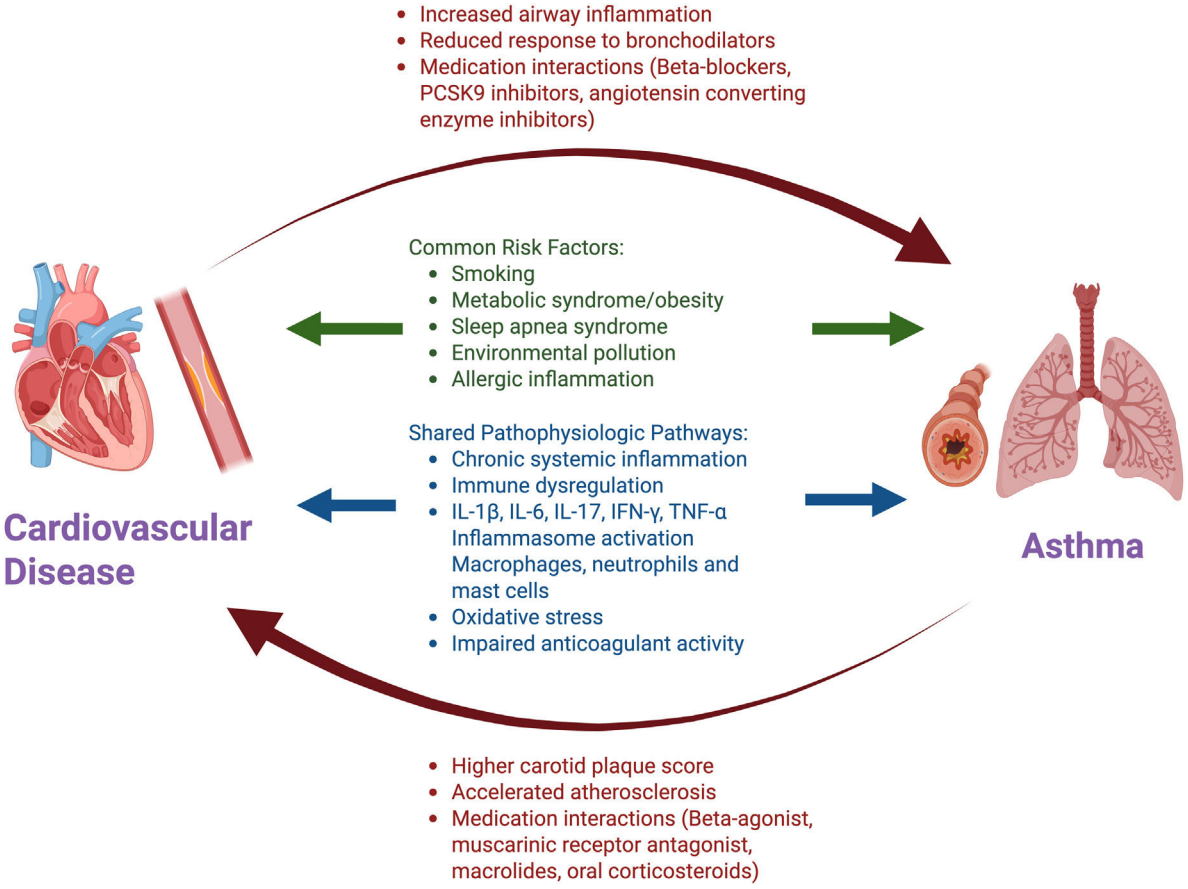


Fig. 1. The interconnected pathways of asthma and heart disease.

function decline with development of CVD [14]. Together these common pathways promote both airway remodeling in asthma and endothelial dysfunction seen in CVD.

Beyond common inflammatory pathways, pharmacologic treatments for one condition can be associated with adverse effects on the other. β_2 agonists commonly used in asthma increase heart rate, reduce serum potassium levels and may increase risk of CVD [15]. Anticholinergics in some studies showed increased CVD risk such as atrial fibrillation although these have not been consistently described in all studies. Systemic corticosteroids may also increase CVD risk, whereas inhaled corticosteroids may have a protective role. Similarly, leukotriene modifiers may also have beneficial role in CVD. The long-term safety data on omalizumab on cardiovascular risk has also been debated with one study showing higher cardiovascular event rate and others showing protective effect [16]. On the other hand, data on anti-IL5 and anti-IL-4 antibodies suggest a decreased risk of CVD. Among the medications used to treat CVD, β_1 adrenoreceptor antagonists may exacerbate asthma. Angiotensin converting enzyme inhibitors have been linked with dry cough and bronchospasm due to increased bradykinin levels. PCSK9 inhibitors have been linked with an increased risk of asthma in European population [15].

In summary, the cardiovascular and respiratory systems share many risk factors and inflammatory pathways which may explain the bidirectional relationship between asthma and heart disease (Fig. 1). T2-low asthma appear to be linked to higher CVD risk, whereas T2 cytokines appear to confer protection against cardiovascular insults, while being pathogenic at the same time for asthma. Addressing common risk factors such as obesity, metabolic syndrome, tobacco use and sleep apnea, as well as carefully selecting pharmacotherapy to minimize cross reactivity between asthma and CVD would likely be a part of any comprehensive treatment approach.

Several challenges and unanswered questions exist in evaluating the link between asthma and heart disease. The overlapping symptoms, such as dyspnea and chest discomfort, may lead to the underdiagnosis of asthma in patients with CVD and vice versa. The impact of race, ethnicity and social determinants of health on asthma-CVD risk is also not well established and need to be evaluated further, especially due to observed disparities in outcomes across populations. Moreover, role of hormonal influences of sex hormones such as estrogen and testosterone remain poorly understood, despite their well-known impact in airway and CVD. There is also a lack of validated biomarkers to differentiate between asthma related and CVD related inflammation which also adds additional barriers to early disease detection as well as co management. Longitudinal data on cardiovascular impact of asthma severity, exacerbation frequency and airway inflammation is also limited. Conversely, the mechanism by which CVD influences asthma outcomes, whether via altered pulmonary hemodynamics, systemic inflammation or medication cross reactivity, are also not well understood. There are also therapeutic uncertainties. While emerging data on the cardiovascular safety of biologics, which are cornerstone of severe asthma therapy, is encouraging, real-world and long-term follow up across diverse patient populations needs to be further established. Similarly, newer CVD therapeutics including angiotensin receptor-neprilysin Inhibitors, glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors and ivabradine appear to be safe in asthma, but their effect of immune modulation and chronic airway inflammation is not fully characterized. These observations challenge our incomplete understanding of these complex interactions. Future research

should also focus on understanding shared pathophysiological pathways that drive asthma and CVD, particularly the immune and inflammatory mediators. A multi-omics approach integrating genomics, metabolomics, and transcriptomics data may also provide deeper understanding of the overlapping molecular pathways. In addition, randomized clinical trials and prospective studies are needed to further understand cross reactivity and long-term safety of newer therapies. Finally, there is a need for developing multidisciplinary guidelines that address precision medicine tailored to asthma-CVD overlap.

Conflict of interests

NAH reports serving as an advisor/consultant and his institution receives research grant support from GSK, Astra Zeneca, Sanofi, Regeneron, Genentech, Amgen and Chiesi. MA declares no conflict of interest.

References

[1] World Health Organization. Asthma. WHO; 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/asthma. [Accessed 14 September 2024].
[2] Centers for Disease Control and Prevention. Most recent national asthma data. U.S. Department of Health & Human Services; 2023. Available from: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. [Accessed 14 September 2024].
[3] World Heart Federation. World Heart Report 2023: confronting the world's number one killer; 2023. Available from: https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf. [Accessed 14 September 2024].
[4] Pollevick ME, Xu KY, Mhango G, Federmann EG, Vedanthan R, Busse P, et al. The relationship between asthma and cardiovascular disease: an examination of the Framingham Offspring Study. Chest 2021;159(4):1338–45, http://dx.doi.org/10.1016/j.chest.2020.11.053.
[5] Cepelis A, Brumpton BM, Laugsand LE, Dalen H, Langhammer A, Janszky I, et al. Asthma, asthma control and risk of acute myocardial infarction: HUNT study. Eur J Epidemiol 2019;34(10):967–77, http://dx.doi.org/10.1007/s10654-019-00562-x.
[6] Tattersall MC, Dasiewicz AS, McClelland RL, Jarjour NN, Korcarz CE, Mitchell CC, et al. Persistent asthma is associated with carotid plaque in MESA. J Am Heart Assoc 2019;11(23), http://dx.doi.org/10.1161/JAHA.122.026644, e026644.
[7] Nogueira-Garcia B, Alves M, Pinto FJ, Caldeira D. The association between asthma and atrial fibrillation: systematic review and meta-analysis. Sci Rep 2024;14(1), http://dx.doi.org/10.1038/s41598-023-50466-w, 2241.
[8] Hua ML, Li L, Diao LL. Bronchial asthma and risk of 4 specific cardiovascular diseases and cardiovascular mortality: a meta-analysis of cohort studies. Eur Rev Med Pharmacol Sci 2022;26(14):5081–91, http://dx.doi.org/10.26355/eurrev_202207_29294.
[9] Ko FW, Yan BP, Lam YY, Chu JH, Chan KP, Hui DS. Undiagnosed airflow limitation is common in patients with coronary artery disease and associated with cardiac stress. Respirology 2016;21(1):137–42, http://dx.doi.org/10.1111/resp.12668.
[10] Hung MJ, Mao CT, Hung MY, Chen TH. Impact of asthma on the development of coronary vasospastic angina: a population-based cohort study. Medicine (Baltimore) 2015;94(42), http://dx.doi.org/10.1097/MD.0000000000001880, e1880.
[11] Iribarren C, Tolstykh IV, Eisner MD. Are patients with asthma at increased risk of coronary heart disease? Int J Epidemiol 2004;33(4):743–8, http://dx.doi.org/10.1093/ije/dyh081.
[12] Tattersall MC, Guo M, Korcarz CE, Gepner AD, Kaufman JD, Liu KJ, et al. Asthma predicts cardiovascular disease events: the multi-ethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol 2015;35(6):1520–5, http://dx.doi.org/10.1161/ATVBAHA.115.305452.
[13] de Boer JD, Majoor CJ, van 't Veer C, Bel EH, van der Poll T. Asthma and coagulation. Blood 2012;119(14):3236–44, http://dx.doi.org/10.1182/blood-2011-11-391532.
[14] Ramalho SHR, Shah AM. Lung function and cardiovascular disease: a link. Trends Cardiovasc Med 2021;31(2):93–8, http://dx.doi.org/10.1016/j.tcm.2019.12.009.
[15] Cazzola M, Page CP, Hanania NA, Calzetta L, Matera MG, Rogliani P. Asthma and cardiovascular diseases: navigating mutual pharmacological interferences. Drugs 2024;84(10):1251–73, http://dx.doi.org/10.1007/s40265-024-02086-5.
[16] Guo J, Zhang Y, Liu T, Levy BD, Libby P, Shi GP. Allergic asthma is a risk factor for human cardiovascular diseases. Nat Cardiovasc Res 2022;1(5):417–30, http://dx.doi.org/10.1038/s44161-022-00067-z.

Muhammad Adrish, Nicola A. Hanania*
Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX, USA

*Corresponding author.
E-mail address: hanania@bcm.edu (N.A. Hanania).