Asthma and cardiovascular disease: embracing disease heterogeneity is required

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To the Editor:

We read with interest the recent original research investigation by Valencia-Hernández *et al*. [1]. This observational study used two approaches to investigate the association of asthma and coronary heart disease (CHD): medical records and Mendelian randomisation (MR). Their results differ compared to many other prior studies investigating the association of asthma and CHD [2]. We applaud the authors for the thoroughness of the investigation; however, we have identified key methodological considerations in this study which may account for differences in the conclusions, compared to prior studies.

In the first approach, the investigators employed analysis of UK medical records [1]. The outcome of CHD was assessed using International Classification of Diseases, 10th Revision (ICD-10) codes and models adjusted for various biological confounders. There are several important methodological limitations of this approach. First, ICD-10 codes do not distinguish between type 1 (plaque rupture) and type 2 (myocardial injury: troponin release in primary non-cardiac condition) events [3]. This is an important distinction, as a type 1 event is a traditional (primary) coronary plaque rupture event, but a type 2 event represents an elevated troponin biomarker in a secondary non-cardiac process (*e.g.* sepsis, shock, kidney disease and anaemia) [3]. Treatment methods differ considerably, with type 1 events necessitating anti-platelet and anti-thrombotic treatments, and revascularisation, while in type 2 events the primary organ system dysfunction is the focus of therapy [3]. With advancements in troponin biomarker assays and enhanced detection methods, the prevalence of type 2 myocardial events has significantly increased over the past decade, now mirroring that of type 1 myocardial events [4]. The rising prevalence of non-type 1 CHD events and the lack of specificity in ICD-10 coded datasets bias these results to the null. Large cohort studies use several methods to increase specificity and ascertain the type of CHD event, including review of death certificates, medical records and adjudication events committees including independent physician adjudicators blinded to participant study data review [2]. Second, the investigators describe an association with asthma and CHD which is attenuated after adjustment for general practitioner (GP) consultations. This adjustment was intended to prevent detection bias. Adjustment for healthcare interactions can especially be helpful if this leads to increased diagnosis of medical conditions. Acute coronary syndrome (type 1 myocardial infarction) on the other hand, is due to sudden coronary atherothrombotic plaque disruption and is not a diagnosis commonly made in an outpatient clinic, rather it is made based on data and the clinical presentation typically in the emergency room setting. It is known that individuals living with asthma commonly have other multiple medical comorbidities which require more frequent outpatient follow-up. Adjusting for outpatient GP visits in this model may not have had the intended consequence. Finally, the exposure “asthma” was used as a homogenous exposure, without accounting for the heterogeneity of asthma phenotypes. Prior cohort observational studies have highlighted that the association of asthma and CHD varies based on the clinical phenotype of asthma [5]. Combining all asthma patients together does not account for the range of immune and inflammatory biological mechanisms that underly each asthma subtype.

In the second analysis, the authors performed an MR study using the UK Biobank, Coronary Artery Disease Genome-wide Replication and Meta-analysis consortium, and the Trans-National Asthma Genetic Consortium. The authors took meticulous statistical approaches to address genetic pleiotropy, but despite this, given asthma heterogeneity and the pleiotropy between asthma and other metabolic traits, the instrument variable assumptions may not have been met. Importantly, investigators using the UK Biobank

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have previously described shared genetic correlations of late-onset and non-atopic asthma phenotypes and metabolic dysfunction traits such as glycaemic control and body mass index (BMI) [6]. There is strong evidence from MR studies that BMI causally increased the risk of certain asthma phenotypes [6]. The current MR study of asthma and CHD included several single nucleotide polymorphisms which share the metabolic dysfunction/asthma genetic correlations. Accounting for the genetic correlation of specific asthma phenotypes and metabolic dysfunction is difficult in MR studies, as metabolic dysfunction is a risk factor for cardiovascular disease.

More than 20 years ago, landmark studies described a clear and consistent increase in CHD events in individuals with higher levels of systemic inflammation [7]. Subsequent large clinical trials demonstrated that treating systemic inflammation alone reduces cardiovascular events [8]. Numerous studies have demonstrated that individuals living with more significant clinical phenotypes of asthma have higher levels of systemic inflammation and these levels are dynamic [9]. Adult and paediatric cohort studies have demonstrated consistent signals of increased arterial injury, arterial wall remodelling and plaque, the precedent of cardiovascular events in teenagers and adults living with asthma [10]. We appreciate the investigation by Valencia-Hernández *et al*. [1], as it underscores the importance of accounting for the heterogenous nature of asthma. It highlights a critical knowledge gap in defining individuals living with asthma who have elevated cardiovascular risk, and we respectfully disagree with the accompanying editorial [11]; therapies that address systemic inflammation may indeed improve asthma symptoms while reducing CHD risk.

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