Gastroesophageal Reflux, Atopic Dermatitis, and Asthma: Finally Evidence for Causal Links?

Asthma and gastroesophageal reflux disease (GERD) are common conditions with high comorbidity rates that have long suggested a causal mechanism between these two diseases (1). Despite epidemiologic ties, however, causal mechanisms have not been previously established. Estimates on coprevalence of these conditions vary widely on the basis of study population and size, though the prevalence of GERD among those with asthma is consistently higher than the general population (2, 3). The presence of GERD and asthma has been linked to an increased risk of exacerbations (4) and worse asthma-related quality of life (5), making this an important, potentially modifiable risk factor in the management of asthma. Although there is a strong epidemiologic tie between GERD and asthma, randomized control trials evaluating the impact of GERD treatment with proton pump inhibitors among those with asthma are conflicting (6, 7). It is worth noting that none of the GERD treatment trials have found improvement in spirometry. In addition, it is possible that cough attributed to uncontrolled asthma is being driven by GERD itself and is a confounder rather than on the causal pathway.

The proposed causal mechanisms between these seemingly disparate diseases provide possible bidirectional mechanisms. GERD may be driving the development or worsening of asthma via microaspiration of gastric contents, which is hypothesized to lead to airway inflammation (8), or via increased vagal nerve stimulation from reflux of acidic gastric contents leading to bronchoconstriction (9). Conversely, asthma may drive the development of GERD via changes in chest to abdomen pressure gradients from hyperinflation, leading to lower esophageal sphincter tone (10). In all theories, there is not a shared genetic or environmental mechanism driving both diseases; instead, one condition drives the development of the other. There are clear knowledge gaps regarding whether the relationship between these diseases is causal or merely coincidental, given the underlying high prevalence of both diseases.

In this issue of the *Journal*, Ahn and colleagues (pp. 130–137) attempt to address this question using a two-sample bidirectional Mendelian randomization (MR) method (11). They used three distinct approaches to determine if a causal relationship exists, the direction and magnitude of such a relationship between asthma, GERD, and atopic dermatitis (AD) using data from three large genome-wide association studies (GWAS) of European ancestry. Using an inverse variance-weighted method, the authors found a bidirectional relationship between GERD and asthma, with a higher magnitude of association for GERD on the risk of asthma (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.09–1.35) than that of asthma on GERD risk (OR, 1.06; 95% CI, 1.03–1.09). The largest reported effect sizes were the bidirectional relationship between asthma and AD. A significant association was found between GERD on AD risk, but not for AD on GERD risk.

Epidemiologic data support the bidirectional relationships demonstrated by Ahn and colleagues. In a national sample, Kim and colleagues found an increased hazard ratio (HR) of asthma comparing those with GERD to control subjects (HR, 1.46; 95% CI, 1.42–1.49) and of GERD when comparing those with asthma to control subjects (HR, 1.36; 95% CI, 1.33–1.39) (12). It is worth noting that there is a paucity of epidemiologic data regarding the relationship between GERD and AD. The evidence of a causal link of GERD on AD reported in this study is novel and warrants replication in other studies.

The use of MR takes advantage of the natural, random assortment of genetic variants in a population and assumes that the genetic variants associated with a risk factor are not also associated with confounders, therefore if variants are associated with differences in the outcome of interest, that association is thought to be causal. The use of GWAS studies with large sample sizes, as was done in this study, mitigates the potential limitation of inadequate statistical power. Minimizing, and ideally eliminating, pleiotropy is necessary to meet the causal assumptions of MR. Ahn and colleagues used several techniques to minimize pleiotropy and evaluate the robustness of their effect estimates. To identify independent instrument variables for MR, stringent linkage disequilibrium thresholds were used to ensure the independence of single-nucleotide polymorphisms from each GWAS meta-analysis and F-statistics to assess the strength of the instrument variables that were used. Three statistical approaches to MR, random effect inverse variance-weighted method, MR-Egger regression, and MR-pleiotropy residual sum and outlier, were used to determine the causal effects, assess for robustness, and minimize the influence of pleiotropy on their results. Combined, these approaches strengthen the causal relationships reported in their study.

Although the methodologic approaches were rigorous, there are several limitations primarily stemming from the datasets used that should be considered. As these were publicly available, summary-level GWAS datasets, assessment for effect modification was not possible. The MR methods should, ideally, account for confounding; however, it is possible that effect modification exists in the relationship between GERD and asthma. Both obesity and obstructive sleep apnea have been linked to GERD and asthma in epidemiologic studies (1). The mechanisms driving these relationships have not been fully identified and may be influencing the causal relationship between GERD and asthma. Finally, only European ancestry cohorts were

Supported by the National Heart, Lung, and Blood Institute (R01 HL125734, T32HL007085-46, and R25GM143298).

Originally Published in Press as DOI: 10.1164/rccm.202210-1953ED on October 27, 2022

Am J Respir Crit Care Med Vol 207, Iss 2, pp 117–129, Jan 15, 2023
Internet address: www.atsjournals.org

studied, which limits generalizability and requires replication in other ancestry groups.

This study provides valuable evidence of a causal link between asthma, GERD, and AD and advances our understanding of the bidirectional relationship of these comorbidities; however, it does not provide insight into functional genetic effects that lead to these relationships. The largest effect sizes were between AD and asthma. On the one hand, this is not surprising given studies showing shared genetic risk between these diseases (13). The atopic march theory, however, supposes that some AD serves as a precursor to asthma (14, 15), and mechanistic studies are needed to determine whether this is the case or whether this relationship reflects simply shared genetic risk. Furthermore, additional studies are needed to better understand the genetic influences on the risk of asthma among those with GERD and vice versa. Assuming this relationship is truly bidirectional, as this MR study and epidemiologic data would suggest, there are likely distinct genetic variants associated with each pathway that may help better understand the mechanisms and genetic factors driving the development of each comorbid condition. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Galectin-3 Inhibition in COVID-19

Galectins have emerged as molecules that are involved in many immune processes, including neutrophil migration, cytokine release, and the control of T and B cell death (1). Galectin-3, in particular, is highly expressed in monocytes, macrophages, neutrophils, fibroblasts, epithelial cells, and endothelial cells and is secreted in response to inflammatory stimuli (2), potentially amplifying the host inflammatory response during infection (3). It is a marker of severity in acute respiratory distress syndrome (ARDS) not related to coronavirus disease (COVID-19) (4) and has also been recently proposed as a biomarker for COVID-19 severity (5). Galectin-3 stimulates the release of IL-1, IL-6, and tumor necrosis factor alpha (6), which are considered to be important in the pathogenesis of severe COVID-19. A specific galectin-3 inhibitor may have the

This work was not supported by any grants, but outside of this work the authors disclose potential conflicts of interest as stated.

Originally Published in Press as DOI: 10.1164/rccm.202209-1758ED on September 26, 2022