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Progress in the Application of Mendelian Randomization Analysis in Allergic Rhinitis

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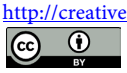

Abstract

Allergic rhinitis (AR) is a non-infectious chronic inflammatory disease of the nasal mucosa mediated mainly by immunoglobulin E (IgE) in atopic individuals after exposure to allergens, with the typical symptoms of paroxysmal sneezing, watery runny nose, itchy nose and nasal congestion. Mendelian randomization (MR), an innovative epidemiological approach that uses common genetic variants as instrumental variables for exposure, thus enabling prediction of their causal relationship with outcomes, has been widely used in recent years in studies related to AR. This paper provides a review of the method and its progress in the field of allergic rhinitis research.

Keywords

Allergic Rhinitis, Mendelian Randomisation Analysis, Risk Factors, Review

1. Introduction

Allergic rhinitis (AR) is a non-infectious chronic inflammatory disease of the nasal mucosa mediated mainly by immunoglobulin E (IgE) after exposure to allergens in atopic individuals. Typical symptoms are paroxysmal sneezing, watery runny nose, itchy nose, and nasal congestion; it may be accompanied by ocular symptoms including itchy, watery eyes, and burning sensation, eye redness and burning sensation, etc., mostly seen in pollen allergy patients [1]. AR is a common clinical chronic rhinitis that affects 10 - 20 percent of the world's population and has become a global health problem [2]. Currently, there is no complete cure for AR, and the principle of treatment is "combination of prevention and treatment, four-in-one", including environmental control, drug treatment, immunotherapy and health education [3] [4].

Mendelian randomization (MR) is an innovative epidemiological approach that uses common genetic variants as instrumental variables for exposure, thus enabling prediction of their causal relationship with outcomes [5]-[7]. MR simulates the process of random assignment to populations by exploiting the property of random splitting and combination of genetic variants during gamete formation: whether an individual is born with a genetic variant that affects a particular phenotype is random, and the genetic variant is determined during gamete formation, a process that is usually uncorrelated with acquired environmental confounders. Thus, differences in an outcome between those who carry the variant and those who do not can be attributed to variation in exposure factors, thus excluding confounding factors [8]. Compared to other research methods, MR is less affected by reverse causality and confounding factors. It thus provides new methods for exploring complex pathogenic mechanisms and is increasingly being used in a variety of fields. This paper provides an overview of the development, fundamentals, three major assumptions, strengths and limitations of MR analysis and its research progress in AR, aiming to provide new ideas for causal association research in AR.

2. Introduction to MR

2.1. Development of MR

The concept and methodology of MR was first proposed by Professor Fisher in 1936, who, based on the principles of Mendelian genetics, regarded randomly assigned genotypes as "natural randomisation experiments" for assessing the causality of the adjustment of a factor to a specific phenotype. However, due to various reasons at that time, such as: fewer genotypes, fewer phenotypes, and no corresponding computational tools, there has been no research progress. It was not until 2003 that George *et al.* [9] first published an MR article in IJE, suggesting that MR could help to understand the environmental determinants of disease, thus formalising the research framework and study design of MR. Afterwards, the method was widely applied for research.

2.2. The Basic Principles of MR

MR is an analytical methodology that applies statistical modelling of genetic variation as an instrumental variable for specific exposure risks and thus explores causal associations between exposure factors and outcomes [10]. The methodology uses random assignment of genetic variants to simulate a randomised controlled trial (RCT) using instrumental variables (IVs) associated with risk factors and disease to test for causal associations between the two. MR is more effective in overcoming the effects of confounders and bias caused by other factors.

2.3. The Three Main Assumptions of MR

MR is based on 3 hypotheses: 1) Correlation hypothesis: instrumental variables and exposure factors are strongly correlated, and instrumental variables with F-statistics greater than 10 are usually selected for MR analyses [11]; 2) Exclusion of

restrictive assumptions：instrumental variables and confounders are uncorrelated [12]; 3) Assumption of independence: instrumental variables are not directly related to the outcome and their effect on the outcome can only be seen through exposure [13].

2.4. Strengths and Limitations of MR

The reliability of MR studies is intermediate between that of RCTs and observational studies [14]. MR helps to distinguish causation from non-causation and helps to rule out reverse causation and confusion. MR is less time-consuming and less expensive than RCTs and observational studies, is not subject to traditional confounders, and the genetic variants remain unchanged after birth, and their associations with outcomes are chronologically plausible [15]. MR can also take advantage of the large sample sizes available in genetic datasets to provide accurate estimates of causal effects. However, MR has some limitations, firstly, limited ability to test for non-linear effects; secondly, limited ability to detect small effects; and thirdly, group-specific effects. In addition, the Beavis effect, phenotypic heterogeneity, etc. can affect the reliability of MR findings [16].

3. Applications of MR in AR Research

3.1. AR and Respiratory Diseases

With the growing popularity of the concepts of "combined airway disease" and "atopic processes", there is now a growing consensus that asthma is related to allergic diseases, especially AR [17]. Previous observational studies have concluded that allergic disease is a risk factor for asthma [18]-[20], but the prevalence of AR increases with increasing lower respiratory symptoms of asthma [21] [22]. Therefore, the causal relationship between AR and asthma cannot be clarified in traditional research methods. Thus, Zhang *et al.* [23] found that asthma increased the risk of AR by two-sample MR analysis. Another team also came to the same conclusion by analysing the MR of the two samples and concluded that AR also had a causal effect on the FEV1/FVC ratio [24]. The above findings provide strong evidence for a causal relationship between asthma and AR, so we can use asthma treatment as a preventive and therapeutic strategy for AR.

3.2. AR and Immune-Related Diseases

Previous studies have shown that both AR and immune-related diseases are caused by immune system dysregulation [25] and that there is a causal relationship between common immune-related diseases and AR [26]. Common immune-related diseases include Atopic Dermatitis (AD), Graves' disease (GD), Multiple sclerosis (MS), Crohn's disease (CD), Rheumatoid Arthritis (RA), Ulcerative colitis (UC), and Systemic lupus erythematosus (SLE). Previous studies have found an increased risk of AR in children with AD compared to children without AD. In addition, patients with AD who developed IgE sensitisation at 2 - 4 years of age had a higher risk of AR than patients with AD without IgE sensitization [27] [28].

Previous studies have also found that people with CD are more susceptible to allergic diseases than the normal population [29]. Epidemiology also confirms an increased risk of AR in children with CD [30]. Zhao *et al.* [26] conducted an MR analysis of common immune-related diseases and AR and confirmed that AD and CD increase the risk of AR in people of European origin, whereas GD and SLE may be protective factors for AR. Another team also found that CD increased the overall risk of allergic disease through MR analysis [31]. The above studies provide strong evidence for a causal relationship between AD, CD, GD, SLE and AR, so we can use the treatment of AD, CD, GD and SLE as a preventive and therapeutic strategy for AR.

3.3. AR and Intestinal Flora

Many studies in recent years have shown that the gut microbiota can influence many physiological systems such as immune response, biometabolism, and inflammatory processes. Observational studies have reported significant changes in the abundance of certain intestinal flora in patients with AR compared to healthy individuals, suggesting a potential correlation between intestinal flora and AR [32]-[34]. However, the classification of the gut flora in relation to AR remains ambiguous. Thus, Jin *et al.* [35] identified causal relationships between 11 bacterial taxa and AR through a two-way, two-sample MR analysis, but the results remained stable for only four bacterial taxa after cross-validation. Among them, the order Coriobacteriia and its sub-taxa: the order Coriobacteriales and the family Coriobacteriaceae, are protective against AR; whereas the family Victivallaceae increases the risk of AR onset. However, reverse bidirectional two-sample MR analyses did not show any evidence of reverse causality between AR and gut flora. These studies provide new directions for future prevention and treatment of AR by targeting dysregulation of specific bacterial taxa.

3.4. AR and Systemic Inflammatory Cytokines

A growing body of research suggests that various types of cells, cytokines, and chemokines play a crucial role in AR [36]; however, the exact role and contribution of inflammatory factors in the genetic mechanisms of AR pathogenesis is unclear. Therefore, Zhang *et al.* [37] performed a two-sample MR analysis to investigate the causal effect of 26 circulating inflammatory cytokines on AR. Higher levels of circulating IL-18 and macrophage inflammatory protein-1α (MIP-1α) were found to potentially increase the risk of AR; conversely, higher levels of circulating TRAIL were associated with a reduced risk of AR. After bonferroni correction, only the TRAIL results were statistically significant (p-value < 0.0019). Sensitivity analyses yielded directionally consistent results. Not coincidentally, Li *et al.* [38] similarly found that elevated circulating levels of MIP-1α and TNF-α may increase the risk of AR. Therefore, regulating the secretion of inflammatory factors will be an important direction for AR treatment, and the mechanisms associated with these inflammatory factors will provide more possibilities for AR drug development.

3.5. AR and Immune Cell Phenotypes

AR is an allergic inflammatory disease with a predominantly Th2 immune response, and immune cells play a key role in its development. Chen *et al.* [39] found Naive CD8br %CD8br, CD3 on CD39+ activated Treg, and HVEM on CD45RA-CD4+ to be protective factors for AR by MR analysis. Xu *et al.* [40] found by MR analysis that Im MDSC %CD33dim HLA DR- CD66b-, EM CD8br AC, Transitional %B cell, CD28+ CD45RA+ CD8dim AC, CD28+ CD45RA- CD8dim AC, CD38 on CD3- CD19-, CD28 on CD39+ secreting Treg, CD127 on CD4+, CCR2 on CD14+ CD16+ monocyle, CD39 on CD39+ CD8br, CD11b on CD66b++ myeloid cell, HLA DR on B cell, and 12 other immunophenotypes were risk factors for AR; 26 immunophenotypes such as CD20 on B cell, CD20 on lgD+ CD38- naive were protective factors for AR. The above MR studies on immune cell phenotypes and AR provide new ideas for future prevention and treatment.

3.6. AR and Metabolites

Metabolomics is a new research direction that explores the process of disease development through the detection of various metabolites produced by cellular metabolism. Metabolites can affect the development of AR through different pathways. MR analysis by Chen *et al.* [39] identified N-methylhydroxyproline, N-acetylneuraminic acid, and 1-stearoyl-2-arachidonic acid-gpc as risk factors for the development of AR, whereas Naive CD8+ T cells could exert a protective effect against AR by decreasing N-methylhydroxyproline levels. Two-sample MR analysis by Tu *et al.* [41] revealed that 1-arachidonoylglycerophosphoinositol was the most reliable causal cyclic metabolite of AR, and that alanine had the greatest protective effect against AR when present as a urinary metabolite. The MR studies of AR described above provide genetic evidence for finding drug targets for AR.

3.7. AR and Nutrients

Previous observational studies have shown a complex relationship between dietary micronutrients and the development of AR. MR analysis by Long *et al.* [42] found that elevated serum phosphorus and selenium concentrations were associated with a reduced risk of developing AR.

4. Summary and Prospects

This paper systematically reviews recent studies in the field of AR using MR analysis and reveals a causal relationship between AR and asthma, AD, CD, GD, SLE, intestinal flora, systemic inflammatory cytokines, some immune cell phenotypes, metabolites, and nutrients based on currently published MR studies. However, a causal relationship between AR and multiple sclerosis, rheumatoid arthritis, ulcerative colitis, and vitamin D is not supported. Among other things, we found that prior asthma and atopic dermatitis were strongly associated with the development of AR in the current study. Therefore, in order to stop the development of AR, we should pay attention to the treatment of AR-related diseases. It is worth

noting that some of the MR findings were not the same as those of previous epidemiological studies, and we should be cautious in interpreting these discrepancies, taking into account factors such as sample size, target population, and research methodology, and further increasing the number of study participants, sample size, and designing more randomised trials in the future to reveal the associations and biological mechanisms. Although MR has made many advances in exploring the risk factors for the development of AR, and providing reliable guidance for the prevention and treatment of AR; however, we believe that with the rapid development of genetic pathology and statistics, MR still has great potential to be applied in the field of AR in the future, to explore the relationship between more diseases and AR, and to provide more new ideas for the intervention and diagnosis and treatment of AR.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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