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Making causal inferences in allergy epidemiology studies

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The epidemiology of allergic disease is intriguing and should in theory allow us to find a pathway to disease prevention. In this month, we focus on the use of different analytical approaches to understand causality in epidemiological studies of allergic disease. Our first free-to-read Editor's Choice article used a classic cohort study design to evaluate the relationship between diet during pregnancy and development of allergic conditions in offspring.¹ Venter et al. used the Colorado Healthy Start pre-birth cohort study to evaluate the possibility that dietary intake of advanced glycation end products (AGEs) might promote allergic disease in the developing child. AGEs are created when foods are heated, as reducing sugars react with free amino groups on proteins. Also called the Maillard or browning reaction, the production of AGEs is common when foods are heated or processed to improve flavour, shelf-life or hygiene and the processing or cooking method is the main determinant of AGE content. Modern diets are high in AGEs, and these are thought to promote oxidative stress and inflammation, being associated with various chronic health conditions including diabetes and cardiovascular disease. For infants, dried powder formula milk can carry a significant AGE exposure, and AGE levels are especially high in hydrolysed formula products. The question posed by Dr Venter's team was whether high AGE consumption by pregnant women—for example in the form of fried meat—could influence in-utero development and thereby impact on risk of allergic disease. Reassuringly, the team found no evidence for an association between their diary-based assessment of maternal AGE consumption during the second and third trimesters of pregnancy and asthma, eczema or allergic rhinitis development in the first 8 years of life. So mothers who wish to eat a well-cooked steak during pregnancy can breathe a sigh of relief that there is one less thing to feel guilty about. Similar work is needed to understand the implications of processed food exposure in the postnatal period—direct AGE exposure can be very high for infants fed hydrolysed formula, and murine studies suggest that processing of food allergens can increase sensitizing potential and early diet may influence allergic disease outcomes (Figure 1).^{2, 3}

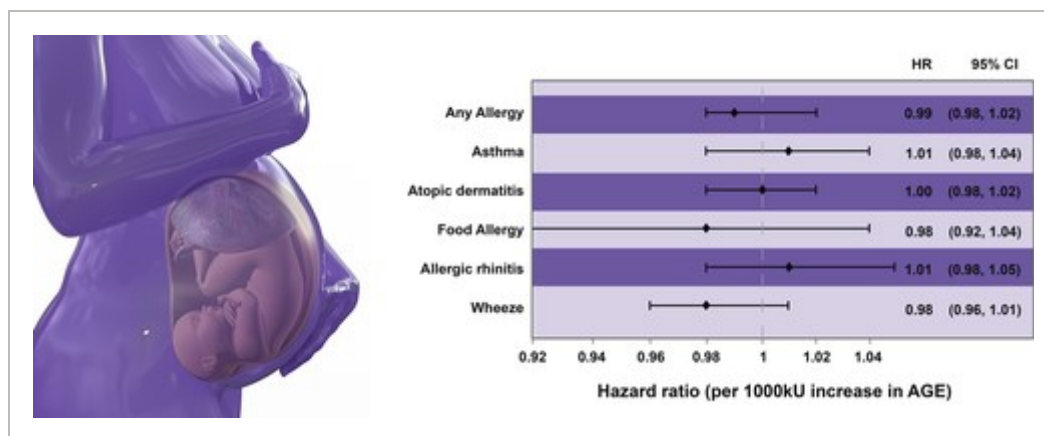


FIGURE 1

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Graphical representation of findings from the Colorado Healthy Start study, where estimates of maternal dietary intake of advanced glycation end products (AGEs) during pregnancy were not associated with the development of allergic conditions in their child during their first 8 years¹

The early origins of asthma is a subject that has attracted much attention from epidemiologists and in the ISAAC survey early antibiotic use was found to be associated with childhood asthma at age 6–7 years.^{4,5} In a similar experimental set-up, Cunha et al. used classical epidemiological methods to evaluate relationships between antibiotic exposure during pregnancy or infancy and the development of asthma.⁶ This team used the Born in Bradford birth cohort in England to explore the association between prenatal or early-life antibiotic exposure, derived from electronic health records, and asthma diagnosis between the age of 5 and 8 years, also derived from electronic health records. In this study, the team found a positive association between antibiotic use, both prenatally to the mother and postnatally to the child, and increased risk of asthma. In a classical epidemiological approach, they adjusted for plausible confounding variables and evaluated siblings and pre-pregnancy antibiotic exposure in order to try to account for hidden confounding. The findings look quite convincing, that there may be a causal association between antibiotic exposure during pregnancy or early postnatal life and increased risk of developing asthma. However, the authors are unable to exclude the possibility that unmeasured variables, such as aspects of healthcare-seeking behaviour, might mean that the same people who seek and achieve antibiotic treatment for themselves during pregnancy or their child in the first 2 years, also seek and achieve an asthma diagnosis or prescription during the first 5–8 years of their child's life.

One approach to dealing with the problem of confounding in observational studies, and one which can potentially help us to make causal inferences, is the use of Instrumental Variable (IV) analysis. This is a statistical approach that uses a variable which is known to be associated with the explanatory variable but is known not to be independently associated with the outcome. One specific form of IV analysis is Mendelian randomization—here a

genetic risk factor for the explanatory variable (the “exposure”) is used as the IV. In this issue Budu-Aggrey et al. present a Mendelian randomization analysis of the relationship between allergic disease and mental health. They used the UK Biobank of over 400,000 adults with self-reported health status and genetic information as a resource to investigate whether asthma, eczema, hayfever or “any allergic disease” is associated with mental health—specifically major depressive disorder, anxiety, bipolar disorder, schizophrenia or neuroticism.⁷ They used Single Nucleotide Polymorphisms (SNPs) known from previous genome-wide association studies to be associated with allergic diseases, but with no direct connection with mental health issues as the IV; they then reversed the analysis by using SNPs known to be associated with mental health issues but with no direct association with allergic diseases as the IV, as shown in Figure 2. The power of the Mendelian randomization approach is shown in the study findings—in simple observational analyses, the group found strong associations between allergic disease and mental health issues. So it is clear in this sample of UK adults that there is co-occurrence of depression and each of the three allergic diseases studied, and to a lesser extent between anxiety or neuroticism and allergic disease. Mendelian randomization analyses, however, suggest that these associations are not causal in either direction. Once the IVs were incorporated into the analysis, there was no convincing evidence for a causal relationship between allergic diseases and mental health issues in either direction. This suggests that the co-association between allergy and mental health is likely to be due to confounding variables, such as healthcare-seeking behaviour, rather than a causal relationship. Previous work has found relationships between infantile eczema and later childhood hyperactivity/attention deficit, and highlighted the wellbeing impact of food allergy and anaphylaxis—so more work like that of Budu-Aggrey et al. is needed for other age groups, other allergic conditions and other mental health outcomes.^{8,9} However, the striking differences in odds ratios and effect estimates between standard and IV analysis in this study are a nice demonstration of the power of Mendelian randomization to investigate hidden confounding in observational studies (Figure 2).

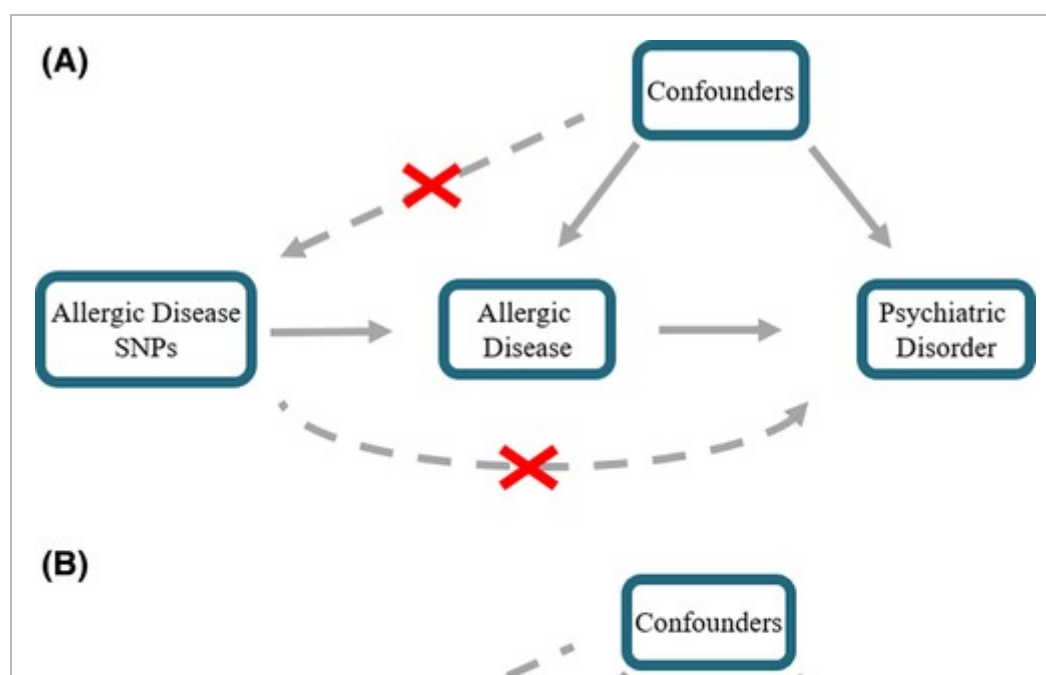




FIGURE 2

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Approach taken in the Mendelian Randomization analysis of Budu-Aggrey et al. using data from around 450,000 adults in the UK Biobank.⁷ The group used Single Nucleotide Polymorphisms (SNPs) known to be associated with allergic disease or psychiatric disorders but not both, in order to understand whether or not the observed associations between allergic disease and psychiatric disorders are likely to be causal

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