

Elucidating the causes of asthma: how can we do better?

An editorial¹ in *The Lancet Respiratory Medicine* highlights the challenge of trying to achieve more accurate, balanced, and responsible reporting of epidemiological studies of asthma risk factors in the media. Reducing hype in press releases, and trying to prevent uncritical reporting by the media, is important. A high proportion of associations between exposures and asthma in observational studies are likely to have arisen through chance, bias, or confounding, and randomised evidence confirming they are causal is scarce. If we are to determine which modifiable factors are causal, and reduce publication of misleading findings, then there is a need to improve research methods in asthma epidemiology. Recommendations, guiding authors of causal inference studies on how best to control for confounders and to interpret and report their results, have been positively welcomed.²

How else can more robust evidence be obtained to inform and justify randomised controlled trials, and increase the chance of confirming causality? Meta-analysis of observational studies has become rather an industry, and although replication of findings is important, the notion that meta-analysis provides stronger evidence for causality should be dispelled. If associations from the component studies are biased or confounded, then the pooled effect estimate will be too. An exception is if similar associations are seen across populations with very different confounder structures. There are numerous ways in which greater rigour could be achieved with respect to study design, data analysis, and interpretation and reporting of results. First, use genetic epidemiology in adequately powered samples to

minimise confounding and strengthen causal inference. One powerful approach is Mendelian randomisation, a form of instrumental variable analysis, in which a genetic variant is used as an unconfounded proxy for a specific exposure of interest. This method can only be used if a suitable polymorphism is available, requires core assumptions to be satisfied for a genetic variant to be a valid instrument for causal inference, and usually needs a study sample of at least 10 000 individuals for adequate statistical power. Nevertheless, Mendelian randomisation has the potential to confirm or refute whether previous observational associations are causal or not.³ Another approach is to show a-priori, biologically plausible, gene-environment interactions, which could shed light on mechanisms and inform personalised prevention strategies by identifying susceptible individuals who would benefit most from an intervention. It is crucial that such interactions are replicated in different populations; however, few have been. Second, use family-based designs, such as sibling control, negative parental control, and twin studies, to confirm or rule out unmeasured confounding, especially with respect to prenatal risk factors.³ Third, seek to replicate observational findings across different populations in the same paper; some journals are starting to request this, in line with genetic studies. Fourth, report absolute and attributable risks, not just odds ratios and relative risks, to put research findings into perspective, clarify the public health importance, and reduce hype by enabling fuller interpretation and better communication of risk. For example, in the case of prenatal paracetamol exposure and childhood asthma, by estimating the aetiological fraction we showed that, even if the link were causal, this exposure could only explain a very small proportion of asthma in the population.⁴ In the quest to discover the causes of asthma, epidemiology is a vital

tool, and the approaches outlined in this Correspondence could make it more effective. Other approaches, which could hasten progress towards the goal of primary prevention, by generating randomised evidence faster than can be achieved through time-consuming and expensive de-novo trials in humans, include increasing collaboration between epidemiologists and laboratory scientists, and using epidemiology to inform animal experiments;⁵ and identifying trials, originally done with other outcomes in mind, in which randomised modification of early life exposures of interest (eg, nutrient supplementation) has already occurred. Children can then be followed up opportunistically to measure respiratory and allergic outcomes, thus enabling more definitive confirmation or refutation of causality than can be achieved in observational studies.⁶

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