

CORRESPONDENCE

Potential confounders in the asthma–diet association: how causal approach could help?

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In a recent issue of the journal, Nurmatov et al. (1) highlighted an inadequate handling of confounding and effect modification in most epidemiological studies investigating the role of diet on the development of childhood asthma and allergies. Besides the etiologic role of nutrients on asthma through biological mechanisms, diet is also an essential aspect of lifestyle, with specificities between countries and social groups because of cultural, social, and environmental factors. In this context, Nurmatov et al. proposed a comprehensive set of confounders and effect modifiers that should systematically be considered. It included maternal characteristics, birth measurements, socioeconomic characteristics, environmental exposures, and nutritional factors. We agree with Nurmatov et al. on how important it is to properly consider confounders and effect modifiers when investigating the role of diet as determinants in asthma and allergies. However, how to properly account for confounders is conceptually challenging and warrants further discussion.

First, potential confounders and effect modifiers are numerous and most of them are strongly correlated. Up to now, the method used to control for confounding was to investigate the possible effect of each risk factor adjusted for all the other risks factors, leading to the issue of overadjustment. Also, each nutritional factor (diet, obesity, and physical activity), intrinsically linked altogether (i.e. body composition being the result of dietary behavior and physical activity), has been suggested to play a role on asthma. Addressing the diet–asthma association therefore implies to account for these interrelations. Up to now, very few studies have investigated the joint roles of nutritional factors as determinants of asthma (2). Recent approaches to causal inference offer a framework that may help addressing these issues. Direct acyclic graphs (DAGs) are causal graphs in which all the arcs are arrows (directed) and no directed path forms a closed loop (acyclic; ref. 3). DAGs may help to decide how to enter variables in a model, to identify potential biases arising from other adjustments, as well as to distinguish confounders from intermediate variables (ref. 3; Fig. 1).

In addition, from a longitudinal perspective, these interrelations are time-dependent. Besides the potential role of each nutritional factors on asthma at a given time t , asthma may modify nutritional factors at time $t + 1$ (for instance, decrease the practice of physical activity), and each nutritional factor may modify another nutritional factor at time $t + 1$. Thus, there is time-dependent confounding, and standard methods of analysis may be biased. In longitudinal epidemiological studies, the complex situations of time-dependent confounding can be addressed using a novel

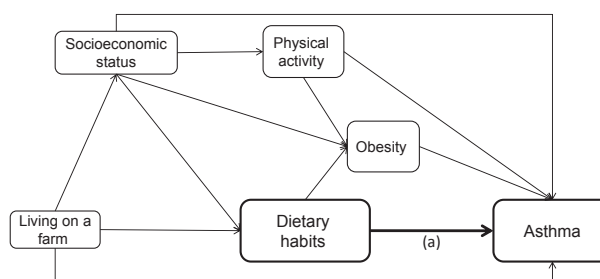


Figure 1 Example of the causal association between diet and asthma, taking into account ‘potential confounders’ using Direct Acyclic Graph (DAG). Assessing the causal association between dietary habits and asthma (arrow a) needs to take into account strongly correlated ‘potential confounders’ (1). For example, while a farming environment in childhood may have a protective effect on asthma till adulthood, it might also influence dietary habits till adulthood (6), as well as socioeconomic status later in life. Further, according to this DAG, obesity is a mediator in the effect of diet on asthma, and physical activity is a confounder in the assessment of the effect of obesity on asthma. If we adjust for obesity and physical activity when studying the effect of diet on asthma, we will get biased results.

approach from the field of causal inference, marginal structural models (MSM). These models, applicable only with repeated data, enable to create a pseudopopulation in which there exists no time-dependent confounding. For that purpose, each subject is assigned a weight which represents the inverse of the calculated probability of receiving the observed history of exposure, given a chosen set of covariates. MSM have been developed in the frame of the counterfactual approach to causality. Counterfactuals are defined as the outcome that would have been observed under a different exposure. MSM have been used in various settings, to study the effect of early-life socioeconomic status on heart disease, diabetes, and stroke (4) or in the context of dietary factors, to study the joint effect of physical activity and body composition on functional limitation (5). MSM are easily implemented with standard software, and designing the model is the most challenging.

In conclusion, beyond the choice of appropriate confounder and effect modifiers, the analytic strategy should be carefully chosen, and MSM might be an appropriate approach to address confounding and effect modification in the context of complex and time-dependent interrelations, such as the diet–asthma association, when repeated data are available.

Authors' contribution

Annabelle Bédard & Raphaële Varraso – primary manuscript preparation. All authors contributed to the drafting of the report and approved the final version.

Conflict of interest

All authors have no conflict of interest to report.

A. Bédard^{1,2}, O. Dumas^{1,2}, F. Kauffmann^{1,2},
J. Garcia-Aymerich^{3,4,5,6}, V. Siroux^{7,8}, R. Varraso^{1,2}
¹Inserm, CESP Centre for Research in Epidemiology and
Population Health, U1018, Respiratory and Environmental

Epidemiology Team,

²Université Paris Sud 11, UMRS 1018, Villejuif, France

³Centre for Research in Environmental Epidemiology (CREAL),

⁴Municipal Institute of Medical Research
(IMIM-Hospital del Mar),

⁵CIBER Epidemiologia y Salud Pública (CIBERESP),

⁶Department of Experimental and Health Sciences, Universitat
Pompeu Fabra, Barcelona, Spain

⁷Inserm U823, Centre de Recherche Albert Bonniot, La Tronche,

⁸Université Joseph Fourier, Grenoble, France

E-mail: annabelle.bedard@inserm.fr

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REPLY

Bédard et al. (1) have, in response to our recent article on the need to improve the handling of confounding and effect modification in epidemiologic studies of diet and allergy in childhood, helpfully proposed two important methodological techniques to enhance the choice of confounders and ensure their appropriate adjustment. Direct acyclic graphs (DAGs) are graphical tools to conceptualize and guide appropriate selection of variables into explanatory models, whereas marginal structural models (MSM) have applications in a longitudinal framework where the exposure of interest is time-dependent in the midst of other time-dependent covariates. These approaches are a welcome development in advancing causal inference from observational epidemiologic studies as the range of dietary and social variables that need to be considered is potentially very large, but also because traditional adjustment techniques may be inadequate, thus more advanced methods may offer new insights through which to strengthen this evidence base. Researchers should therefore consider and utilize these approaches where appropriate and if their data structures permit.

The use of DAGs requires an adequate understanding of the conceptual framework of all the evidence at hand, consequently requires the collaboration of methodologists, clinicians, and other relevant expertise. Usually, these needs may not readily be available to most researchers, thus most

researchers may still opt for the traditional confounding selection methods. However, efficient confounder selection at the analysis stage is only feasible when adequate steps have been undertaken at the planning stage of the study to collect the potential confounding factors of interest. Furthermore, since the MSM technique has specific application in the context of repeated longitudinal data, its application in studying the diet-allergy relationship has limited relevance at the present. This is because, at present very limited data exist in which dietary data and information on other covariates have been collected longitudinally. In our recent review of this evidence base, only a few studies employed longitudinal collection of dietary data (2); consequently, the use of the traditional statistical estimation techniques has persisted. With proper improvements in data collection by incorporating repeated data structures, we believe that the MSM technique will have more relevance in future.

While further developments in these epidemiologic techniques and their application are expected, we note that the issue of multicollinearity, which arises as a result of a range of non-independent covariates in a model, can also be addressed by the advancement of other techniques that could be used within the framework of available traditional analytical techniques (3). Of particular interest is the use of propensity score matching, in which the confounding effect of

covariates is reduced and the estimates of effects can be confidently attributed to the exposure of interest. Propensity score matching has gained strong popularity within medical research as an important technique to enhance causal reasoning in observational epidemiologic studies, and has been applied in the context of diet-allergy relationship in childhood (4).

Above all, regardless of the sophistication of the confounding handling technique, concerns about the risk of residual and unmeasured confounding and other biases continue to potentially undermine the strength of evidence from observational epidemiologic studies. Consequently, Mendelian randomization has been proposed as an alternative to overcome these inherent limitations (5). This approach has been gaining popularity in the context of the causal role of dietary factors in the onset of several human diseases. Through the identifi-

cation of potential dietary genes of interest, these genes can be confidently linked to the allergic disease phenotypes of interest. The wide application of Mendelian randomization to study the role of diet in the development of allergies and asthma, in our view, will greatly enhance this evidence base.

B. I. Nwaru¹, U. Nurmatov², G. Devereux³, A. Sheikh²

¹*School of Health Sciences, University of Tampere, Tampere, Finland*

²*Allergy & Respiratory Research Group, Medical School, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK*

³*Department of Child Health, Royal Aberdeen Children's Hospital, University of Aberdeen, Aberdeen, UK*
E-mail: aziz.sheikh@ed.ac.uk

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