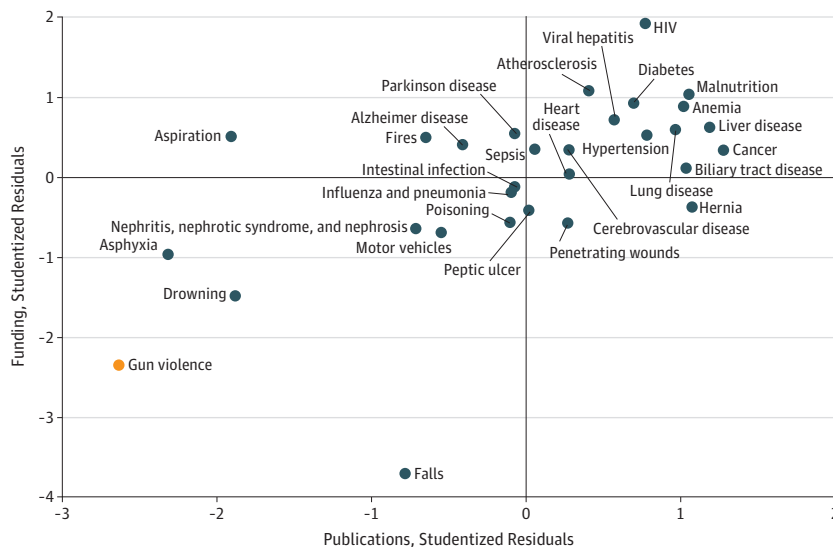


Figure 2. Studentized Residual Predicted vs Observed Funding and Publication Volumes for 30 Leading Causes of Death in the United States



HIV indicates human immunodeficiency virus. Mortality rate was used to predict funding and research volume. Studentized residuals (residual divided by estimated standard error) were calculated to give a standardized estimate of predicted vs observed funding and publication volume. The 4 quadrants represent observed funding greater than predicted, observed publication volume less than predicted (upper-left); observed funding and publication volume greater than predicted (upper-right); observed funding less than predicted, observed publication volume greater than predicted (lower-right); observed funding and publication volume less than predicted (lower-left).

COMMENT & RESPONSE

Allergenic Food Introduction and Childhood Risk of Allergic or Autoimmune Disease

To the Editor Dr Ierodiakonou and colleagues presented a comprehensive synthesis of the evidence on timing of complementary feeding and childhood atopic and autoimmune diseases.¹ We have a number of concerns.

First, we wonder what hypothesis relates allergenic foods to autoimmune conditions.

Second, we wonder what the basis was for the selection of the allergenic foods considered in the review. Selecting certain foods assumes an established immunological basis for them as opposed to other foods. However, other foods (eg, roots, fruits, and meat) also have been found to be important.² Evidence also indicates that food diversity is important, not just the timing of specific foods.³ Knowledge of the mechanisms of actions is far from certain, but we find the authors' statement that there are no data showing feeding one allergenic food influences allergy to a different allergenic food to be incorrect.²

Third, some of our previous studies were included in this systematic review (references 24, 26, 31, and 32 in the article) based on the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study and the Study of Eczema and Asthma to Observe the Influence of Nutrition (SEATON) cohort in Aberdeen. Unexpectedly, the findings in relation to asthma were neither described in the article nor included in any meta-analysis. This was also true for the Western Australian cohort⁴ and the Dutch Influence of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood (LISA) cohort.⁵

Fourth, even though the authors indicated "asthma/wheeze" as an outcome, there was no indication that asthma was investigated, even when the studies included asthma as

an outcome. Only wheeze was an outcome reported throughout the review. The asthma findings in our studies were some of the strongest results compared with other atopic outcomes. We believe that a meta-analysis of timing of infant feeding and asthma was possible. Asthma is a critical outcome, especially when diagnosis has been confirmed by a physician, as in these studies. Physician-diagnosed asthma should be differentiated from wheeze given its clinical implications in the spectrum of atopic disease and should therefore have been included in the review as a separate outcome.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply Our systematic review was 1 of 3 systematic reviews commissioned by the UK Food Standards Agency covering a range of early dietary exposures and risk of allergic or autoimmune disease.¹ Many of the answers to the queries raised by Drs Nwaru and Virtanen can be found in the full Food Standards Agency report (<https://www.food.gov.uk/science/research/allergy-research/fs305005b>).

For autoimmune conditions, others have reported on associations between cow's milk exposure in infancy and risk of type 1 diabetes mellitus as well as timing of wheat or gluten exposure in infancy and risk of celiac disease or type 1 diabetes mellitus.²⁻⁴ There is less evidence for associations between other allergenic foods and autoimmune disease, but the environmental determinants of these diseases are largely unknown, so to inform national infant feeding guidance, we thought it was important to take a comprehensive and open-minded approach.

The definition of allergenic foods in our review was that used in the US Congress food allergen labeling law.⁵ We evaluated timing of introduction of other foods (including roots, fruits, and vegetables) in our third systematic review, currently under peer review.

Nwaru and Virtanen highlight their DIPP cohort finding that early egg and fish introduction were associated with reduced risk of allergic sensitization to other allergens. We did include these data in our analyses, within the full Food Standards Agency report ("Allergic Sensitization Observational Data" section). The DIPP data for egg are not supported by some other observational studies such as the LISA cohort. The DIPP data for fish are supported by 2 other prospective cohort studies, and this very low-certainty evidence that early fish introduction is associated with reduced allergic sensitization was reported in the text and summary of findings (Table 4 in the article). In the intervention trials of allergenic food avoidance or early allergenic food introduction, we found no evidence that early introduction of one allergenic food can influence risk of either allergic sensitization or clinical allergy to a different allergenic food.

We included wheeze data from the DIPP, SEATON, and Western Australian cohort studies, in addition to 27 other observational studies (eTable 4 in the Supplement to the article). The findings are in the Food Standards Agency report ("Wheeze Observational Data" section) and are summarized in eTable 11 in the Supplement to the article. Opportunities for pooling data were limited, partly because estimates of association reported as hazard ratios were meta-analyzed separately from odds ratios. We did not find consistent associations between timing of allergenic food introduction and wheeze across all the studies, and we found no consistent association in intervention trials. The LISA study did not report analyses of timing of introduction of the allergenic foods specified in our protocol and risk of wheezing. The investigators did report associations with timing of solid food introduction, which we have analyzed as part of our third systematic review. Finally, we did evaluate asthma as part of this systematic review but reported most asthma definitions within the category of recurrent wheeze, unless the definition of asthma was limited to a single episode of wheezing.

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Generalizability in Pragmatic Trials

To the Editor In the *JAMA* Guide to Statistics and Methods article, Drs Sox and Lewis¹ stated that pragmatic trials are designed to address real-world effectiveness questions relevant to decision makers. To maximize the generalizability of study results, the authors underscored the need to include a diverse population of study participants recruited from heterogeneous practice settings.

Although the strategy of applying flexible inclusion criteria to increase the applicability of results to usual practice is widely recommended,^{2,3} an excessive focus on generalizability through the inclusion of heterogeneous patients may hinder physicians and regulators' ability to identify which option is more appropriate for each patient. The inclusion of heterogeneous patients may dilute potential differences between subgroups.

The emphasis on generalizability may be understandable under the population-oriented research approach that has pervaded the scientific community in the last decades, but it is not so reasonable under the patient-oriented research approach that supports the practice of patient-centered medicine. True pragmatic research requires understanding heterogeneity. The seminal article by Schwartz and Lellouch,⁴ which defined explanatory and pragmatic "attitudes" in therapeutic trials, was published nearly 50 years ago. The moment has come to revisit and broaden the concept of pragmatic trials to incorporate new research strategies oriented toward improving outcomes for individual patients.

New patient-oriented research strategies should be grounded not only in technological and methodological advances, such as genomics, randomized registry studies, and single-patient (n-of-1) trials, but also on the progressive