

Response to Invited Commentary

Dogaru et al. Respond to “Does Breastfeeding Protect Against ‘Asthma’?”

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We thank Michael Kramer for his insightful comments (1) on our systematic review and meta-analysis on breastfeeding and childhood asthma (2). Following a concise summary of our findings, he points out the high heterogeneity of the results and addresses issues that might explain this, namely the phenotypic variability of asthma, lack of objective measurements, variable degrees of measurement bias, and residual confounding.

We entirely agree with Professor Kramer that “asthma” is a label applied to a heterogeneous syndrome, consisting of several distinct phenotypes, each with its own pathophysiological mechanisms and risk factors (3, 4). Transient wheeze induced by viral infections in an infant is likely a different entity than chronic, multitrigger asthma in an atopic schoolchild. Not accounting for this phenotypic variability might explain part of the heterogeneity we found, but not all. Arguably, breastfeeding can act as protective mechanism for either phenotype through different mechanisms influencing respiratory infections and/or priming the immune system. We think that a big part of the heterogeneity is due to poor or incomplete operational definitions of asthma by the studies analyzed. The definitions of the outcome varied greatly, from “wheezing in the past 12 months” through “Does your child have asthma?” and to more elaborated constructions such as “3 reported episodes of wheeze during first 2 years of life treated with inhaled steroids or signs of hyperactivity without upper respiratory infection.” These definitions describe different outcomes in terms of phenotype and severity and are sometimes incomplete or have insufficient validity. It is essential that asthma studies define and measure more clearly the particular phenotype(s) they are studying by including more standardized asthma-specific survey questions and, whenever possible, objective measurements such as different tests of lung function, bronchial responsiveness, and airway inflammation. Equally important, studies should

report more clearly the age at first diagnosis and the history of the condition; these things were rather fuzzy in the studies we analyzed.

For a true assessment of a dose-response relationship, breastfeeding should ideally be recorded as duration in months or—less preferred—by using several categories. Only 4 studies used a continuous variable, whereas a third compared breastfeeding “ever” with “never.” The rest used variables with 3–6 categories, which were incompatible across many studies. This made it difficult to investigate dose-response relationships in a consistent way, so we decided on a pragmatic approach and dichotomized breastfeeding duration into more versus less. It might be possible to attempt a follow-up study on a smaller sample of suitable studies and perform a dose-response meta-analysis. It is imperative that studies of breastfeeding record it as a continuous measure. It does not require additional measurement, and maternal recall is reliable (5, 6).

A measurement bias due to nonblinding of the observers is also possible, particularly for studies of parent-reported outcomes. However, in more than half of the studies (55 of 117) breastfeeding was not the main exposure; this makes this type of bias less likely.

Finally, residual confounding is likely a major source of heterogeneity. There was great variability in the number and type of confounders considered; 40 of 117 studies did not adjust for confounders. Daycare attendance may indeed be relevant, and only 16 of 117 studies adjusted for it. Infants who attend daycare are more exposed to infections; they are also less likely to be breastfed and thus to benefit from breastfeeding’s protective effect. We recognize that we should have introduced this information in our study quality’s list of “essential confounders.”

We concur with Professor Kramer’s conclusions and recommendations; we need studies with better diagnostic

criteria, better operational definitions of the constructs analyzed, better control for confounders, and, overall, better study design.

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