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CORRESPONDENCE

Early-life house dust mite allergens, childhood mite sensitization, and respiratory outcomes

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To the editor: With great interest, we read the article by Casas et al. (1) on the association between house dust mite allergens and sensitization, wheezing, and asthma in early life. We recognize the relevance of a large multinational cohort analysis to explore the increased morbidity in asthmatic and sensitized children in relation to house dust mite. Although the results were clear and nicely presented, we would like to discuss a few issues.

At first, the authors defined asthma by the presence of two of the following three conditions: physician-diagnosed asthma, current parental-reported wheezing (last 12 months), and current asthma medication intake (last 12 months). We were wondering whether this definition could cause underreporting of the number of patients with asthma. Was it not possible to classify children according to the ISAAC criteria? Did the authors consider the recall bias of the parents, the reliability of the documentation/registration of the diagnosis, and medical use in the different countries? If this is the case, it could unwillingly cause differences between the included cohorts.

Secondly, there were data missing during the follow-up. For instance, the blood samples were used for the analysis of the sIgE, and thus, the sensitization of the child was 59% at baseline and 41% after follow-up. It was not fully clear how the missing data were taken into account during the analysis. Could it be that the overall outcomes were distorted by the fact those data were missing.

Thirdly, we noticed there was an intervention study included in the cohort (PIAMA-NHS) (2). In the potential confounder section, we missed information about possible interventions, for example, house cleaning or treatment during the follow-up. This might have influenced the results. In what way were interventions dealt with, also considering the other cohorts?

Finally, to what extent are the conclusions drawn from the results supported by the study results? According to the authors, there is a geographical variation in allergen concentrations. These observed differences between the cohorts might at least partially be explained by the fact the cohorts used different locations for dust collection and the measurements were taken in different seasons. The authors did not find an association between house dust mite allergen concentration and respiratory outcomes. But, what was the statistical power of the combined cohorts to investigate this association? Could the identified lack of an association be due to a type II error?

In conclusion, the impact of house dust mite allergens is interesting. We comment the authors with this valuable study and are looking forward to their response.

Conflicts of interest

All authors declare no conflicts of interest.

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Reply

We would like to thank Eikenboom et al. (1) for their interest in our study and for giving us the opportunity to clarify some aspects of our study (2). The first comment by Eikenboom et al. concerns the definition of asthma that we used in our study and its potential for misclassification. With our strict definition (two out of three conditions) we cannot rule out that some individuals with asthma are classified as non-asthmatics. However, specificity is also important in studies of risk factors of asthma and the validity of the estimation depends on the positive predictive value (3). Since asthma is a complex condition there are no guidelines on how to define asthma in epidemiological research. To date, several definitions have been used (4, 5). In our study, we define asthma by reports of wheezing, doctor-diagnosed asthma and asthma medication as this is more specific and reliable than the use of symptoms only.

Differences between cohorts were considered in our statistical analyses. In sensitivity analyses, we included cohort as a fixed effect to control for differences between cohorts. Moreover, we explored to what extent the associations observed between allergens and health outcomes were driven by only one cohort by excluding one cohort at a time from the models. The effect estimates when using cohort as a fixed effect or when excluding one cohort at a time were not different from those including all cohorts and cohort as a random effect.

Eikenboom et al. express concerns regarding the impact of missing data on our results. This is of particular concern for HDM sensitization. Information on serum specific immunoglobuline E was available for <60% of the children. Significant differences in wheezing and asthma were found between children with and without information on sensitization in MAS, LISAplus and BAMSE. Regarding wheezing, asthma up to age 6 years and asthma after age 6, information was available for 78%, 96% and 78% of the population, respectively. Statistically significant differences in parental education were observed for wheezing in INMA-Menorca, LISAplus and MAS and for asthma after age 6 in PIAMA-NHS. Nevertheless, the sensitivity analyses excluding these cohorts did not lead to different results in any of the outcomes.

The design of the PIAMA birth cohort is somewhat complex. Briefly, the PIAMA birth cohort includes an Intervention Study and an observational Natural History Study. The characteristics of both arms of the PIAMA cohort and the aim of this specific design are explained elsewhere (6). In our study, we included individuals from the Natural History Study who received neither active nor placebo intervention.

Finally, Eikenboom et al. raise the question about the interpretation of negative results. In our study, we did not find statistically significant associations of allergen concentrations with wheezing or asthma. The general recommendation to avoid type II errors is to perform a statistical power calculation. Since the formula for statistical power calculation considers, among others, the magnitude of the differences, a post-hoc power calculation to investigate this type of errors is not the best option (7). Instead, it is preferable to base our judgements on the consistency with previous studies, the magnitude of the effect estimates and the size of the confidence intervals. In this field, our study is the largest performed to date and it is consistent with most previous studies. The Odds Ratios for wheezing and asthma in our study were overall close to 1 and their 95% confidence intervals were not large. Therefore, we may conclude that the lack of statistical significance in the effect estimates is most likely due to a lack of effect rather than to a type II error.

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