

Correspondence

Reply

To the Editor:

We wish to thank Bråbäck et al.¹ for their interest in our recent review on epigenetic inheritance in allergic disease² and for alerting us to errors in the table. We have requested that these be corrected.

As highlighted in our review, in the study of multigenerational effects, it is important to distinguish between intergenerational and transgenerational effects, those that are occurring without any possibility of direct effects of the exposure in question on the generation in which disease risk is being assessed. In addition, it is important to assess disease outcomes stratified by sex; as Bråbäck et al.¹ note, many such studies have observed sex-specific patterns in the effects of exposures, such as grandmaternal smoking through the paternal and maternal line. Specifically with regard to smoking, most studies have focused on the effect of grandmaternal smoking on asthma in grandchildren. However, for grandchildren in the maternal line, this cannot distinguish between intergenerational and true transgenerational effects because the oocytes that will form the grandchild will be exposed when the mother is *in utero*.

In contrast, in the paternal line exposure before the onset of puberty, which is associated with effects on disease risk in offspring, implies transgenerational effects because the gametes that will form the offspring are not yet formed. Whether there are then also further effects of grandparental exposure is a separate question. In the study of the RHINE cohort by Svanes et al.,³ there was a clear effect of early-age (before the age of 15 years) smoke exposure in fathers on asthma risk in offspring. In this study grandmaternal smoking status was associated with risk of nonallergic early-onset asthma in offspring (odds ratio, 1.3; 95% CI, 1.0-1.6) and was also observed to modify the association between the father's own smoking status and asthma in his offspring. If the paternal grandmother did not smoke, the father's own smoking before age 15 years was associated with more nonallergic early-onset asthma in his children, but this association was not present if the paternal grandmother smoked ($P_{\text{interaction}} = .02$). Thus it appears that complex relationships exist between level of exposure, timing, and sex in determining the effects of exposures between generations on asthma.

Evidence of paternal-line grandparental effects have also been demonstrated with regard to other exposures, outcomes, or both. For example, compelling historical findings of paternal

transgenerational effects of nutritional exposures in human subjects come from the Överkalix population in northern Sweden (summarized by Pembrey et al.⁴).

In summary, as highlighted by Pembrey et al.,⁴ in future studies it will be important to pay particular attention to parental/ancestral exposures, both in terms of dose and timing of the exposure in relation to the person's stage of development and in both maternal and paternal lines. We await with interest the results of future studies of such studies given the important practical consequences for public health policies based on the confirmation of multigenerational effects.⁵

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