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Response to Bråbäck et al.

We wish to thank Bråbäck et al. for their interest in our recent review on epigenetic inheritance in allergic disease (1) and for alerting us to errors in the table. We have requested these be corrected. As highlighted in our review, in the study of multigenerational effects it is important to distinguish between inter- 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. note out that 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 regards to smoking, most studies have focused on the effect of grandmaternal smoking on grandchild asthma. For grandchildren in the maternal line however this cannot distinguish between intergenerational and true transgenerational effects as 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 that is associated with effects on disease risk in offspring implies transgenerational effects as the gametes that will form the offspring are not yet formed. Whether there is then in addition further effects of grandparental exposure is separate question. In the study of the RHINE cohort by Svanes et al.,(2) there was a clear effect of early age (before the age of 15) smoke exposure in fathers on asthma risk in offspring. In this study, grandmaternal smoking status was associated with risk of non-allergic early-onset asthma in offspring (OR 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 was associated with more non-allergic early-onset asthma in his children, but this association was not present if

the paternal grandmother smoked ($P_{\text{interaction}} = 0.02$). Thus it appears that complex relationships exist between level of exposure, timing and gender in determining the effects of exposures between generations on asthma. Evidence of paternal line grandparental effects have also been demonstrated with regards to other exposures and/or outcomes. For example, compelling historical findings of paternal transgenerational effects of nutritional exposures in humans come from the Överkalix population in northern Sweden (summarised in Pembrey et al. (3)).

In summary, as highlighted by Pembrey et al., 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 the confirmation of multigenerational effects have.(4)

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