Do farm-grown lungs breathe better?

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In *Thorax*, Campbell *et al*[1] report an association of growing up on a farm with better adult lung function. On closer investigation, this effect was confined to the FEV_1 in female participants in the study. A novel finding and a paper worth reading—but what may be harder to glean is its relevance and implication for future research.

The 'farm-effect' on allergic disease has been well established in numerous studies. Recent systematic reviews with meta-analyses show a strong protective effect of growing up on a farm on childhood atopy[2] and a lesser effect on childhood asthma.[3] In these meta-analyses, the effect estimates for the 'farm-effect' on asthma were much more heterogeneous than those on any atopic sensitisation.[2 3] This may be driven by the mix of different farm exposures shown to be important.[4] It has also been suggested that the increased heterogeneity in estimates of the 'farm-effect' on asthma is partly driven by the mix of asthma phenotypes in the respective studies.[3]

Indeed, the present study by Campbell *et al* is one of the few studies presenting results completely stratified by atopy to investigate this further. Here, the authors conclude that protective effects on atopic asthma, atopic bronchial hyperresponsiveness (BHR) and atopic nasal symptoms in comparison to non-atopic subjects without asthma, BHR and nasal symptoms, respectively, exist. On closer investigation of the presented data, these associations are fully driven by the 'farm effect' on atopy. No separate 'farm-effect' on asthma, BHR or nasal symptoms shows up when comparing diseased with non-diseased separately within the two strata of atopic and non-atopic subjects. It has been previously shown that effect estimates for atopic asthma depend on the choice of the reference group in case of strong overall effects on atopy.[5] It is remarkable that early life exposure to farming environments has sustained effects on adult atopic sensitisation. However, added effects on asthma, BHR and nasal symptoms as suggested by previous studies in childhood[6] and adulthood[7] are not supported by the present study.[1]

The result of a 'farm-effect' on lung function has been investigated to a lesser extent, and direct comparison with previous studies is hindered by differing scaling of the lung function parameters. Higher FEV_1/FVC values among those growing up on a farm have been found in one previous study among atopic children only[6] but not in two other studies among all children.[8 9] The association in the present study was attenuated after further adjustment, including adjustment for parental smoking, but no stratification for atopy was presented. Personal smoking did not seem to confound the association but residual confounding due to crude measures of smoking history cannot be excluded. The stronger association with higher FEV_1 in the present study was more apparent in women and varied across participating centres. Such an isolated lung function parameter is hard to interpret in the absence of findings for FVC and the FEV_1/FVC ratio, as FEV_1 can represent lung volume and airway obstruction. Whether the on-average 110 mL higher FEV_1 in women who grew up on a farm can be replicated in other studies, whether this effect persists after accounting for atopy, and whether it is clinically meaningful remains, thus, to be elucidated.

What may be more interesting in this context is the sex-specificity of the 'farm-effect'. A stronger effect on women has been previously shown among adults[10–12] as well as children and adolescents,[8 13 14] although it has been reversed,[15] absent or only marginally statistically significant in the data of other studies.[16 17] The sex-specificity may point towards (1) unaccounted-for disease heterogeneity between women and men, (2) differing exposure to farming environments, including occupational exposure in adult life but also other exposure in early life, (3) differing confounding lifestyle factors, such as smoking and (4) differing physiological, hormonal or growth characteristics affecting lung physiology. Whereas personal smoking, body weight and body height have been adjusted for in the present study, other proposed factors remain as possible explanations. Age at onset of asthma may also play a role since one report on childhood and adolescence has shown that sex-specific associations of exposure to farming with asthma are age-dependent.[14]

Of note, the study population in the present study covers a wide age range. Although age is adjusted for, previous publications, including another one also using European Community Respiratory Health Survey (ECRHS) data, have indicated cohort effects.[18 19] Cohort effects may exist if the mode of farming changed over time, for example, farms were recently only run part-time which attenuates the effect.[20 21] Moreover, no information on age at onset of atopy or atopic asthma is shown. The 'farm-effect' documented in the present study may be a sustained effect from childhood onwards. Alternatively, it may be an effect on later-onset atopy or atopic asthma, as indicated by data from the RHINE study which includes part of the ECRHS study population.[12] Arguably, a substantial portion of adult-onset or late-onset disease may be misclassified due to lack of recall of childhood disease in mid-adult ages.

While critics may argue for alternative explanations of the 'farm-effect' (eg, genetics, access to or utilisation of healthcare), its environmental component seems established beyond reasonable doubt. One good example is the dramatic increase of atopy in a rural region of Poland accompanied by a decrease of exposure to farming during the same time.[22] Another prominent example is the exploitation of two populations, the Amish and the Hutterites.[23] In this comparison, the model of exposure to farming environments is distilled to its environmental core.

Not all protection from atopy relates to farming in this study. Campbell *et al*[1] also define a 'biodiversity score' based on childhood exposure to cats, dogs, day care, bedroom-sharing and older siblings. One might argue that the aforementioned factors are proxies for other than microbial exposures and that the simple dichotomisation and assumed additive effects are not the optimal operationalisation. Moreover, upbringing in a village also shows some protection, but it remains unclear whether this effect is to some extend attributable to the 'biodiversity score'. Possibly, the effect of such a score is only discernible in inner-city environments where other outdoor exposures (eg, greenness) are lacking. Nonetheless, the analyses show that the protective 'farm-effect' is stronger than

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what individuals brought up in inner cities can experience by exposure to pets, day care and siblings. Also, given that these exposures are probably as difficult to intervene on as is the place of upbringing, we should consider keeping on searching for the most important environmental exposures underlying the farm-effect for future preventive efforts.

So, do farm-grown lungs breathe better? The present study does not add much to answer this question. But in addition to all the previous evidence, it is another reminder from a large-scale study that effects of childhood exposure to farming environments on atopy and thereby atopic disease may well extend into adulthood. This makes the mechanisms underlying the 'farm-effect' particularly important for future preventive efforts. How shall we proceed? Exploring disease heterogeneity and sub-phenotypes including age at onset as well as investigating sex-specificity should be added to the investigative toolbox. In addition, making use of model populations may be promising in future efforts to unravel elements in the mix of exposures or pathophysiological mechanisms that are associated with growing up on a farm.

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Correction: *Do farm-grown lungs breathe better?*

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The authors include the additional Conflicts of Interest for their article:

Erika von Mutius is listed as inventor on the following patents:
- Publication number EP 1411977: Composition containing bacterial antigens used for the prophylaxis and the treatment of allergic diseases.
- Publication number EP1637147: Stable dust extract for allergy protection
- Publication number EP 1964570: Pharmaceutical compound to protect against allergies and inflammatory diseases

Erika von Mutius is listed as inventor and has received royalties on the following patent:
- Publication number EP2361632: Specific environmental bacteria for the protection from and/or the treatment of allergic, chronic inflammatory and/or autoimmune disorders.

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