Animal fur and asthma: an indoor farmyard phenomenon?

Julian Crane

Affiliation: Dept of Medicine, University of Otago, Wellington, New Zealand.

Correspondence: Julian Crane, University of Otago, PO Box 7343, Wellington, 6001, New Zealand.
E-mail: Julian.Crane@otago.ac.nz

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How do animal furs protect children from asthma and allergy? Is it time to trial furs and other farm type exposures? http://ow.ly/Nce0O

The relationships between allergen exposure, sensitisation and the development of allergic disease have, since their first description, been complicated, often counterintuitive, and rarely straightforward. Ever since Charles Blackley put himself through a private medical education in order to study his own severe "summer catarrh", allergens and their human targets have been behaving oddly. Blackley [1] suggested a hypothesis (circa 1870s) that his summer catarrh or hay fever might be associated with exposure to seasonal grass pollens (the current belief at the time was that it was caused by increased temperatures in summer). He confirmed his hypothesis in a series of elegant and painstaking experiments, often on himself. At a time when hay fever was distinctly uncommon, he headed to local farming communities around the rapidly developing city of Manchester, to study probable sufferers. To his surprise, the very people exposed relentlessly to grass pollens in their daily working lives rarely reported hay fever symptoms. It might be argued that with this observation he also suggested the earliest stirrings of what would become part of the hygiene hypothesis, namely that people who live on farms get less allergic disease.

In this issue of the *European Respiratory Journal*, Tischer *et al.* [2] add a further interesting strand to these complex and still poorly understood relationships by suggesting protective effects from indoor farmyard exposures, namely infants who are put to sleep on animal furs in Germany (>50% of infants) have less reported wheezing and asthma in later childhood. In a subgroup of these children, their peripheral T-cells make more interferon-γ (T-helper cell (Th)1 response) than children who do not sleep on animal furs. This protection appears to wear off with age, not surprisingly, and may be stronger for infants whose parents self-report allergic disease. Sleeping on animal fur was also associated with reduced atopy at 10 years of age in this subgroup. Of course, as the authors point out, these associations may not be causal. Reverse causation is always a potential issue in studies of self-selected interventions. This seems unlikely here given that the use of animal furs was equally distributed between families with and without asthma. Animal furs may be a marker of other protective behaviours associated with their use, and by 10 years of age only just over half of the children were included in the analyses. Exposure was only measured by self-report at 3 months and ongoing exposure throughout childhood may be important for the protective effect. Other bedding materials might increase asthma risk rather than furs giving protection, for example volatile organic compounds in synthetic bedding materials [3].

Notwithstanding these cautions, we must now consider adding early exposure to animal furs to an ever growing list of potentially slightly unhygienic practices that seem to be associated with a reduced asthma and/or allergy risk. These include parental mouth cleaning of pacifiers [4], hand washing dishes [5], using feather bedding materials [6], having a pet in the house [7], drinking unpasteurised milk [8] and regular visits to animal stables [9]. At first glance, putting an infant on an animal fur (presumably largely sheepskins) to sleep might be expected to have similar effects to coming into close contact with farm animals. But these furs will probably have been highly treated and sterilised and have few traces of the farmyard by the time they are used by infants. Furthermore, sheepskins have been previously found to

Received: May 18 2015 | Accepted: May 20 2015

Conflict of interest: None declared.

harbour large quantities of house dust mite allergen [10], and in some studies sleeping on them in infancy has been shown to be a significant independent risk factor for the development of asthma and wheezing [11]. However, this discrepancy can probably be easily put to bed. Positive associations between sheepskins and asthma have been shown in Australia and New Zealand, where both sheep and house dust mites are plentiful, and where the predominant sensitising aeroallergens are from mites. While TISCHER *et al.* [2] showed more house dust mite allergen on mattresses that had a sheepskin on them, they do not report the actual levels. These are, however, likely to be orders of magnitude less than in Australasia. For example, we have shown geometric mean house dust mite allergen (Der p 1) levels of 83 $\mu g \cdot m^{-2}$ in the sheepskin bedding of 15 month-old infants and 35 $\mu g \cdot m^{-2}$ in non-sheepskin bedding in New Zealand [10]. This compares with a median level of 0.223 $\mu g \cdot m^{-2}$ at 18 months in infant bedding from five German cities in the MAS (Multicentre Allergy Study) study [12]. This 370-fold difference is likely to play a causal role in sensitising and then maintaining IgE mediated airway inflammation and perhaps overwhelming the possible Th1 stimulating properties of sheepskins themselves. Interestingly, cat allergen (Fel d 1) was also 172-fold higher in New Zealand beds than in German ones. Higher levels of endotoxin (Th1 promoting) might be expected in animal furs given the heavy biological load to which they are likely to be subjected by infants and the difficulty in washing them. To date, endotoxin levels do not seem to have been measured in animal furs. TISCHER *et al.* [2] found higher levels of endotoxin in the mattresses of infants with animal furs, but the protective effect was independent of mattress endotoxin level. Before we leave mites three other observations are worth recalling. GREEN *et al.* [13] suggested that the sudden appearance of asthma and mite sensitisation in parts of the highlands of Papua New Guinea might be related to the introduction of Australian blankets infested with house dust mites. The relationships between aeroallergen exposures and asthma do not appear to be straightforward with evidence of a non-linear relationship between exposure and disease for both cat [14] and mite allergens [15]. Lastly and somewhat counterintuitively, at least one prospective cohort study that used cleaning and barrier methods to effectively reduce house dust mite allergen exposure from birth, found more allergen sensitisation in the reduced allergen group with no effect on early asthma symptoms [16]. Thus, allergen–disease relationships are not straightforward and are likely to depend on many factors including dose and timing of exposure.

Assuming that the inverse relationship between animal fur exposure and asthma is causal, why should treated animal furs confer an asthma and allergy protective effect? The authors suggest that a more complex microbial milieu on the fur might be important and this clearly needs to be examined. Given the soft comforting properties of animal fur, infants are likely to be in close contact and thus able to inhale locally generated aerosols that could provide appropriate immune stimulation and protection from future asthma and allergy.

Similar protective effects have been observed for early exposure to feather bedding materials [6, 17, 18]. Again, this raises the obvious issue of whether feather bedding is protective or the alternative, usually synthetic materials are a risk. One consequence of using feather bedding materials may be reduced mite allergen exposure, simply as a consequence of the finer weave of the envelope material required to contain feathers which restricts the movement of mites into the bedding material [19]. But, as we have seen, this relationship is not straightforward and does not appear likely to explain the animal fur effect.

An intriguing alternative has been suggested by TOVEY *et al.* [20]. These authors suggest that many of the protective effects associated with the hygiene hypothesis involve intensive exposure to animal or human dander (kids, cats and cows), and that house dust contains large quantities of human skin flakes capable of being inhaled. These contain potentially immunoactive constituents including a variety of antigens, glycolipids and small peptides. Feather bedding is a potent source of airborne feather fragments [20] and may provide exposure to a complex array of keratin xenoantigens. Thus, it is conceivable that the intriguing protective effect of animal furs (perhaps in a low house dust mite environment) may arise in the same way and is certainly worthy of further investigation.

TISCHER *et al.* [2] conclude by suggesting that animal fur could be an effective means of creating environments associated with higher microbial exposure. This is a familiar conclusion to those studies that have shown a protective effect from a wide variety of early infant practices and exposures. These studies raise the question of whether we should be trying to bring the farmyard into our overly hygienic indoor environments by exposing infants to multiple human, animal and microbial products in a manner that is both safe and immunostimulatory. The alternative is to wait until all of the relevant immunobiology is understood and characterised, but this may be a very long wait indeed. Furthermore, the hypothesis may be wrong and in the end only randomised trials will provide sufficient evidence to change practice. Is it time to bite the bullet and trial bringing multiple elements of the farmyard indoors?

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 DOI: 10.1183/13993003.00782-2015

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