Commentary: A step towards understanding asthma in low- and middle-income countries

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Children growing up on a farm in Europe or North America have rather consistently been observed to less often suffer from asthma and allergic diseases.¹ The hypothesis of possible protective effects of early life contact with a farming environment has opened a way for new understanding of the asthma and allergy epidemic in the Western world in the past few decades. A recent publication showed that children living on farms were exposed to a wider range of microbes, and this explained a substantial fraction of the inverse relation between asthma and growing up on a farm.² This suggests that within a complex farming environment, microbial diversity may be of central importance for the observed protective effects. Microbial stimulation is essential for the development of immunological competence early in life.³ A rapidly expanding field of research relates the human microbiota to immunological maturation and systemic inflammation, with potential impact on chronic pulmonary disease as well as a number of other chronic inflammatory diseases.⁴,⁵

Farm environment and animals are, however, very complex exposures, including a variety of biological exposures and subject to selection. There is some evidence that consumption of raw farm milk is of importance for observed protective influence of farm
exposure on asthma.\textsuperscript{6} The role of allergens in allergic diseases has been the focus of research for decades, and a farming environment certainly provides exposure to a number of potent allergens. Airways irritants like ammonia and dusts are prevalent in a farming environment, as are a number of chemical substances like pesticides. In adult farmers, the farming environment may cause asthma, respiratory symptoms and mucosal symptoms like eye irritation. The ‘farming environment’ exposure is further complicated by the fact that a farming environment and contact with animals are not random exposures, but subject to selection based on a variety of mechanisms. Complex selection might have taken place over several generations. In a Western world population of today almost everybody descended from farmers, whereas a comparatively small number are farmers themselves.

Our knowledge on asthma and allergic diseases almost entirely relates to the Western world. With the exception of a few published papers from low- and middle-income countries (LMICs)\textsuperscript{7} the major scientific effort to elucidate these diseases is based on studies from Europe and Northern America. However, there is increasing concern about the rise of non-communicable diseases including chronic lung diseases in the non-affluent parts of the world. In fact, the largest burden of chronic diseases today is present in LMICs and not in the rich parts of world (www.who.int/nmh/en). The ‘10/90 dilemma in health science’ points to the problem that only 10\% of medical research concern the health problems of 90\% of the world’s people.\textsuperscript{8}

The article by Brunekreef et al.,\textsuperscript{9} in this issue of the \textit{IJJE}, investigating the farming allergy association in affluent and non-affluent societies, is a step towards a global research agenda for asthma and allergic diseases. The analyses show increased risk for childhood symptoms of wheeze, rhinoconjunctivitis and eczema in relation to contact with farm animals among children living in non-affluent countries, whereas no such association was found in affluent societies. The findings are based on the International Study of Asthma and Allergies in Childhood (ISAAC) study including study centres across the world, mostly in urban and sub-urban societies. The authors conclude that there is a great need for further understanding of asthma and allergic diseases in non-affluent parts of the world. The comparison of a well-known risk association between affluent and non-affluent societies is most important, addressing whether scientific results from the Western world may be applicable in the much less investigated non-affluent parts of the world. The current article shows significant differences, which render such generalization impossible with regard to this issue.

The differences in results from the present study compared with previous studies from Northern America and Europe may relate to differences in the measured exposure, related exposures, host factors and phenotypes of disease. The measured exposure ‘early life exposure to farm animals at least once/week’ differs from the exposure ‘growing up on a farm’ investigated in most previous North American and European studies. The current measure may imply occasional exposure, with limited exposure to agents of a farming environment that might confer protection at higher exposure. This might explain the null results in affluent societies in the present study, whereas previous analyses of affluent societies fairly consistently show protective effects.

Concerning the demonstrated difference between affluent and non-affluent societies, other explanations may be more important. The environmental factors related to farm animal exposure are likely to differ widely between societies. The authors observe that a large proportion of the ISAAC children live in large, poor cities; and that farm animal contact in a poor urban setting may imply a very different exposure from that experienced on farms in affluent societies. The background microbial environment must be widely different, and the article discusses a possible role of endotoxins and of helminth infection. Further, the chemical environment is likely to differ, including concomitant exposure to a variety of airborne pollutants in poor urban settings.

Immunological characteristics may vary substantially between populations of affluent and non-affluent parts of the world, related to e.g. differences in intrauterine environment, survival pressure and microbial pressure. Vaccines against infectious diseases may be less efficient in LMICs, and altered immunological response due to helminth infection is one suspected explanation.\textsuperscript{10} Growing up in less hygienic circumstances, children of non-affluent countries are exposed a large microbial pressure; and there might be a relatively low threshold from which increased biodiversity is no longer beneficial for immune stimulation but only carries the disadvantage of infectious diseases.

At last, it is not unlikely that phenotypes of asthma and allergic disease differ between the investigated societies. As mentioned by the authors, asthma in non-affluent societies is believed to be mostly non-atopic. However, there is very limited research concerning asthma phenotypes in LMICs.

\textbf{Conclusion}

Urban livestock farming is widespread in LMICs, and understanding which factors underlie the increase in risk for asthma and allergic diseases in exposed children may be of considerable public health importance.

Another important conclusion from this study is to alert researchers and policy makers from generalizing conclusions from Western societies to non-affluent parts of the world. Successful research on the causes
of asthma in low- and middle-income societies requires high-quality research that is performed on site. This can be obtained by ‘partnership’ between research institutions in rich and poor countries, which leaves an institutional memory of knowledge and competence in non-affluent countries when specific research projects are terminated. Whereas educating researchers from LMIC may benefit our universities, only high-quality research institutions on site can solve the global problem of children’s asthma and allergic disease.

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**References**