

EDITORIAL

Clinical and Experimental Allergy

Early life influences on the development of allergy and asthma – how early is early?

S. W. Turner* and G. Devereux†

Departments of *Child Health and †Environmental and Occupational Medicine, University of Aberdeen, Aberdeen, UK

There is an accumulating body of evidence to support the concept that early life exposures are critical in determining susceptibility to asthma and allergic disease in childhood and possibly adulthood. In this issue, Wong and colleagues report the results of an epidemiological survey of 2–6-year-old children living in Hong Kong [1], extending similar work in older children by this group [2, 3]. Perhaps the most striking result from this study is the observation that the children born in mainland China who migrated to Hong Kong at a median age of 2.7 years were less likely to wheeze and have atopic disease than children born and raised in Hong Kong. This is consistent with this group's study of older children (9–11 years) who migrated to Hong Kong at median age 3.4 years [2]. Similarly, the reunification of East and West Germany in October 1990 was subsequently associated with an increase in the burden of atopic disease among the children born in East Germany and this was attributed to a 'Westernised' lifestyle from the age of 3 years [4]. The absence of an increase in asthma in the German study led the authors to conclude that 'factors operating very early in life may be particularly important for the acquisition of childhood asthma, whereas the development of atopic sensitization and hayfever may also be affected by factors occurring beyond infancy [4].' The findings and conclusions from the German study were supported by a similar study comparing children in Sweden and Estonia, again before and after the collapse of the Soviet Union [5]. Interestingly a 4-year follow-up did not find a demonstrable increase in any atopic disease among the Estonian children as might have been expected, despite significant lifestyle changes. The authors postulated that lifestyle changes in the first few years of life are important to the development of atopy in later childhood and suggested that because the

studied children were aged 3–4 years at the time of national transfer to a market economy, this change had occurred too late to influence the development of asthma and atopic disease [5]. The consistency of results from these international epidemiological studies suggests that the critical time period for the establishment of childhood asthma occurs between conception and about age 3 years.

The hygiene hypothesis postulates that the increase in atopic disease is a consequence of altered exposure to microbial constituents and there is evidence to suggest that early life exposures to microbial constituents before the age of 1 year are important [6]. A number of studies have consistently demonstrated that children raised on farms, with presumed high exposure to microbial constituents, have a lower prevalence of atopic disease in childhood as well as adulthood, however, any protective effect on susceptibility for asthma appears to be limited to atopic asthma [7–10]. It appears that exposure to animal sheds and unpasteurized farm milk during the first year of life confers protection against atopic disease [7]. In addition, maternal exposure to animal sheds during pregnancy is also associated with reduced prevalence of atopic disease in children [7]. In a similar study, the greatest reduction in risk for atopic disease was seen among adults who started regular visits to animal stables during the first year of life or between ages 3 and 5 [10]. While it is generally accepted that early life microbial exposure is important in the development of atopic disease, there is increasing evidence that dietary exposures during early life are also related to the development of asthma.

Recent reports from longitudinal birth cohort studies have related maternal dietary exposures during pregnancy to asthma and atopic disease in early childhood. Umbilical-cord selenium concentrations from neonates participating in the UK population-based Avon Longitudinal Study of Parents and Children have been shown to be negatively associated with persistent childhood wheeze at 0–6 and 30–42 months [11]. The Project Viva birth cohort in the United States has reported beneficial associations between increased maternal intake of vitamin

Correspondence:

Dr G. Devereux, Department of Environmental and Occupational Medicine, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZB, UK.

E-mail: g.devereux@abdn.ac.uk

E, vitamin D and zinc intakes during pregnancy and reduced likelihood of recurrent wheeze during the first 2 years of life [12, 13]. In a Scottish population-based birth cohort, similar beneficial associations have been reported between increased maternal vitamin E intake during pregnancy and reduced likelihood of wheeze, asthma, atopic sensitization, and increased ventilatory function in 5-year-old children [14]. In addition, beneficial associations were reported between increased maternal zinc and vitamin D intakes during pregnancy and reduced wheeze and eczema outcomes in 5-year-old children [14, 15]. Importantly these associations were independent of the children's current diet at age 5 years.

There are some important inconsistencies between atopy and asthma that are worth consideration: (1) not all atopic children have asthma, (2) atopic sensitization in rural Africa is dissociated from asthma [16], (3) some children apparently grow out of their asthma. One mechanistic hypothesis proposes that the development of childhood atopic asthma is a consequence of exposures between conception and about 3 years of age that influence both the developing airways and immune system.

Airway development predominantly occurs antenatally [17] and early life factors that impair airway development during this critical period of organogenesis and rapid growth have the potential to exert disproportionately potent long-term effects. Longitudinal studies of lung function from infancy into childhood indicate that children with reduced ventilatory function in early life are more likely to develop childhood wheeze, and asthma, particularly if they develop atopic sensitization [18]. It is thus pertinent that some of the positionally cloned genes associated with asthma are expressed in mesenchymal airway cells, e.g. ADAM33 [19], GPRA [20]. ADAM33 protein isoforms are expressed in human embryonic bronchi and the surrounding mesenchyme at 8–10 weeks gestation [19], leading to the suggestion that ADAM33 plays a role in co-ordinating the branching morphogenesis of the human lung that influences subsequent susceptibility to asthma [21].

The initial early life interactions between allergens and T-helper (Th) cells are likely to be critical in determining whether a Th2 biased response emerges, there is some debate as to whether these interactions occur antenatally. Early life exposures that bias the initial encounters between allergen and Th cells towards the Th2 phenotype are likely to be disproportionately exaggerated by the natural regulatory mechanisms that promote further Th cell differentiation towards the Th2 phenotype and powerfully inhibit development of the reciprocal Th1 phenotype [22].

A widely advocated mechanism to explain the hygiene hypothesis is that early life exposure to microbial components, such as endotoxin, initiate innate immune responses that reduce the likelihood of Th2 polarization [23]. The hygiene hypothesis does not include an effect on early life

airway development and this would account for the principal association with atopic sensitization, rather than asthma. In contrast, dietary nutrients such as vitamin E have been shown in animal models to influence both fetal lung growth [24] and Th1/Th2 immune differentiation [25] and recent work in humans has reported associations between maternal vitamin E intake during pregnancy and cord blood mononuclear cell responses in neonates [26] and post-bronchodilator forced expiratory volume in 1 s in 5-year-old children [14]. These considerations may explain the closer associations between early life dietary exposures and asthma rather than with atopic sensitization.

The development of asthma and atopic disease in children is complex and incompletely understood, however, while it is apparent that early life exposures are clearly relevant, exposures later in life are likely to augment or ameliorate earlier influences. Postulated 'dietary' and 'hygiene' mechanisms are not exclusive, the development of asthma probably requires multiple exposures and, in genetically predisposed individuals, dietary and microbial exposures may interact resulting in the more severe asthma phenotypes. Further work is required to identify those specific early life exposures that influence the development of asthma and atopic outcomes in children, and possibly adults.

References

- 1 Wong GWK, Leung TF, Ma Y, Liu EKH, Yung E, Lai CKW. Symptoms of asthma and atopic disorders in preschool children: prevalence and risk factors. *Clin Exp Allergy* 2007; **37**:174–9.
- 2 Wong GWK, Hui DSC, Chan HH *et al.* Prevalence of respiratory and atopic disorders in Chinese schoolchildren. *Clin Exp Allergy* 2001; **31**:1225–31.
- 3 Wong GWK, Ko FWS, Hui DSC *et al.* Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey. *Br Med J* 2004; **329**:486–9.
- 4 von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998; **351**:862–6.
- 5 Riikjarv MA, Annus T, Braback L, Rahu K, Bjorksten B. Similar prevalence of respiratory symptoms and atopy in Estonian schoolchildren with changing lifestyle over 4 yrs. *Eur Respir J* 2000; **16**:86–90.
- 6 Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000; **55** (Suppl. 1):S2–10.
- 7 Riedler JB-FC, Eder W, Schreuer M *et al.* Early life exposure to farming provides protection against the development of asthma and allergy. *Lancet* 2001; **358**:1129–33.
- 8 Klintberg B, Berglund N, Lilja G, Wickman M, van Hage-Hamsten M. Fewer allergic respiratory disorders among farmers' children in a closed birth cohort from Sweden. *Eur Respir J* 2001; **17**:1151–7.
- 9 Ernst P, Cormier Y. Relative scarcity of asthma and atopy among adolescents raised on a farm. *Am J Respir Crit Care Med* 2000; **161**:1563–6.

- 10 Radon K, Ehrenstein V, Praml G, Nowak D. Childhood visits to animal buildings and atopic diseases in adulthood: an age-dependent relationship. *Am J Ind Med* 2004; **46**:349–56.
- 11 Shaheen SO, Newson RB, Henderson AJ, Emmett PM, Sherriff A, Cooke M. Umbilical cord trace elements and minerals and risk of early childhood wheezing and eczema. *Eur Respir J* 2004; **24**: 292–7.
- 12 Litonjua AA, Rifas-Shiman S, Ly NP *et al.* Maternal antioxidant intake in pregnancy and wheezing illnesses at 2 years of age. *Am J Clin Nutrition* 2006; **84**:903–11.
- 13 Camargo CA, Rifas-Shiman SL, Litonjua AA *et al.* Prospective study of maternal intake of vitamin D during pregnancy and risk of wheezing illnesses in children at age 2 years [abstract]. *J Allergy Clin Immunol* 2006; **117**:721–2.
- 14 Devereux G, Turner SW, Craig LCA *et al.* Reduced maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med* 2006; **174**: 499–507.
- 15 Devereux G, Litonjua AA, Turner SW *et al.* Maternal vitamin D intake during pregnancy and early childhood wheeze. *Am J Clin Nutrition* (in press).
- 16 Dagoye D, Bekele Z, Woldemichael K *et al.* Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. *Am J Respir Crit Care Med* 2003; **167**:1369–73.
- 17 Stick S. Pediatric origins of adult lung disease. The contribution of airway development to paediatric and adult lung disease. *Thorax* 2000; **55**:587–94.
- 18 Turner SW, Palmer LJ, Rye PJ *et al.* The relationship between infant airway function childhood airway responsiveness, and asthma. *Am J Respir Crit Care Med* 2004; **169**:921–7.
- 19 Haitchi HM, Powell RM, Shaw TJ *et al.* ADAM33 expression in asthmatic airways and human embryonic lungs. *Am J Respir Crit Care Med* 2005; **171**:958–65.
- 20 Vendelin J, Pulkkinen V, Rehn M *et al.* Characterization of GPRA, a novel G protein-coupled receptor related to asthma. *Am J Respir Cell Mol Biol* 2005; **33**:262–70.
- 21 Holgate ST, Yang Y, Haitchi HM *et al.* The genetics of asthma: ADAM33 as an example of a susceptibility gene. *Proc Am Thoracic Soc* 2006; **3**:440–3.
- 22 Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996; **383**:787–93.
- 23 Schaub B, Lauener R, von Mutius E. The many faces of the hygiene hypothesis. *J Allergy Clinical Immunol* 2006; **117**: 969–77.
- 24 Islam S, Narra V, Manganaro T, Cote G, Donahoe PK, Schnitzer JJ. Prenatal vitamin E treatment improves lung growth in fetal rats with congenital diaphragmatic hernia. *J Pediatr Surg* 1999; **34**:172–7.
- 25 Li-Weber M, Giasisi M, Trieber MK, Krammer PH. Vitamin E inhibits IL-4 gene expression in peripheral blood T-cells. *Eur J Immunol* 2002; **32**:2401–8.
- 26 Devereux G, Barker RN, Seaton A. Ante-natal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002; **32**:43–50.