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The Importance of Family History in Asthma during the First 27 Years of Life

To the Editor:



Asthma in parents has been previously reported to influence the risk of asthma in children (1). However, hereditary patterns are complex, and several important questions remain unsolved, such as influence of heredity in different age periods (2–5) and potential additional effect of having siblings with asthma. Because the previous studies on these topics have provided controversial results and have been mostly cross-sectional in design, we conducted a prospective population-based 20-year cohort study to investigate whether asthma in parents and/or siblings is associated with the time-of-onset of asthma. No previous study has investigated this from early childhood into adulthood or by taking into account the time of onset of asthma.

This was a prospective population-based 20-year cohort study of a random sample of children of the city of Espoo, Finland, born between January 1984 and March 1990 (6–8). In 2010–2011 we conducted the 20-year follow-up directed at all 2,568 participants of the baseline population and 1,623 responded (63.2%). Our cohort analysis included 2,562 subjects who contributed information for the effect estimates until the end of the study period or as long as they were known to be at risk for asthma. The study protocol was approved by the Ethics Committee of the Oulu University Hospital.

Our outcome of interest was new doctor-diagnosed asthma of the study subject including the age of onset inquired by the questionnaire in all three data collections. Data on asthma was completed from the National Social Insurance Institution's reimbursement records, by a telephone interview or by imputation using the cohort onset age distribution. The information on parental asthma was asked in the baseline, 6-year and 20-year questionnaire surveys and the siblings' asthma status in the 6- and 20-year follow-ups.

The analysis used the time to onset of asthma (incidence time) which enabled assessing hazard rate ratio as the measure of effect (9). We adjusted in the analyses for the following potential confounders: age, sex, family socioeconomic status at baseline, duration of breastfeeding, second-hand smoke exposure at the age of 0–3 years and maternal smoking in pregnancy. The hazard rate ratios were

calculated using the proc phreg procedure in SAS statistical software package (SAS, version 9.3; SAS Institute, Cary, NC).

If either of the parents had asthma, the risk of the child developing asthma was significantly increased throughout the study period with a slightly declining trend of effect estimate with increasing age period (Table 1). Figure 1 illustrates that subjects with maternal asthma developed asthma at an earlier age compared with those with paternal asthma, but the differences in occurrence disappeared by the end of the follow-up. An exception to the trend of decreasing risk over age was when both parents had asthma: in that group the risk of developing asthma actually increased over time (adjusted hazard rate ratio [HR^a]_{0–6} 2.39 vs. HR^a _{0–27} 3.83). Siblings conveyed a strong independent risk for the study subject to develop asthma. This risk was even higher when more than half of the subject's siblings had asthma, indicating a dose-response pattern. The person's risk of developing asthma was the highest when both siblings and parents had asthma (from HR^a _{0–6} 3.39 to HR^a _{0–27} 3.54) and this difference was greater among males than females (females, HR^a _{0–6} 2.67 to HR^a _{0–27} 3.31; males, HR^a _{0–6} 4.32 to HR^a _{0–27} 3.87).

Some additional sex-specific differences were observed in the results. Among females, the hazard rate ratios related to maternal asthma were from HR^a _{0–6} 2.40 to HR^a _{0–27} 1.74. In contrast among males, the adjusted hazard rate ratios related to maternal asthma were greater in magnitude: from HR^a _{0–6} 3.24 to HR^a _{0–27} 2.18. The sex differences were the opposite in relation to paternal asthma, as the females were at higher risk of developing asthma if the father had asthma (females, from HR^a _{0–6} 3.18 to HR^a _{0–27} 2.63 vs. males, from HR^a _{0–6} 2.10 to HR^a _{0–27} 1.61). For females, no clear dose-response pattern with increasing number of siblings having asthma was detectable, whereas among males the risk of personal asthma increased clearly with more than half of the siblings having asthma (Table 1).

In summary, the influence of heredity on the risk of developing asthma declined over age, but remained significant even in the older age periods. As an exception, the influence of heredity increased over time when both parents had asthma. This could indicate strong gene-environment interactions: it is possible that when both parents have asthma they are careful in their home environment and lifestyle to take into consideration the known allergens and other suggested causes of asthma. When the child grows older, he/she presumably is exposed to these allergens and other exposures, and due to his/her high hereditary risk has an increased risk of developing asthma in the older age.

According to our systematic literature search, our study is unique among studies looking at the risk of asthma in relation hereditary patterns in that the analyses apply the age of onset and assess the independent impact of having siblings with asthma. The subjects at the 20-year follow-up had a similar demographic profile than those at baseline, suggesting that selection bias is not a problem in this study.

The results of our prospective population-based cohort study provide evidence that the incidence of asthma during the first 27 years of life is strongly related to family history of asthma. The results suggest that children with maternal asthma develop asthma on average earlier than those with paternal asthma (Figure 1), which is reflected in the effect estimates (Table 1). This is consistent with another recent study in Finnish subjects with adult-onset asthma (10). The risk of personal asthma increased in relation to both parents' asthma and siblings' asthma, and showed a dose-response pattern with increasing number of siblings having asthma. The incidence rates of asthma were the highest among those who had more than one first-degree relative with asthma, including parents and siblings. Some sex-specific differences in the risk of asthma in relation to heredity were detected. Our results underline the usefulness of asking about asthma in siblings in addition to parental asthma in clinical practice.

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TABLE 1. SEX-SPECIFIC RISK OF ASTHMA IN CHILDREN AND YOUNG ADULTS IN RELATION TO FAMILY HISTORY OF ASTHMA

Heredity of asthma	0–6 yr HR* (95% CI) [†]	0–12 yr HR* (95% CI) [‡]	0–18 yr HR* (95% CI) [§]	0–27 yr HR* (95% CI)
No parental asthma	1.00	1.00	1.00	1.00
Maternal asthma				
All	2.74 (1.73–4.35)	2.29 (1.59–3.31)	1.97 (1.39–2.79)	1.91 (1.36–2.69)
Females	2.40 (1.26–4.57)	1.99 (1.17–3.38)	1.75 (1.08–2.85)	1.74 (1.10–2.77)
Males	3.24 (1.67–6.26)	2.67 (1.61–4.44)	2.29 (1.39–3.79)	2.18 (1.32–3.60)
Paternal asthma				
All	2.57 (1.50–4.38)	2.04 (1.32–3.16)	2.01 (1.35–3.00)	2.01 (1.37–2.96)
Females	3.18 (1.54–6.56)	2.94 (1.62–5.32)	2.66 (1.54–4.61)	2.63 (1.55–4.47)
Males	2.10 (0.95–4.65)	1.47 (0.77–2.83)	1.60 (0.90–2.85)	1.61 (0.92–2.81)
Both parents with asthma				
All	2.39 (0.75–7.56)	3.82 (1.87–7.78)	3.60 (1.84–7.04)	3.83 (2.03–7.24)
Females	1.69 (0.23–12.36)	2.11 (0.52–8.62)	2.50 (0.79–7.91)	2.35 (0.74–7.43)
Males	2.86 (0.69–11.92)	5.06 (2.19–11.68)	4.55 (1.98–10.46)	5.11 (2.36–11.07)
No siblings with asthma	1.00	1.00	1.00	1.00
Sibling/several siblings with asthma				
All**	2.60 (1.66–4.06)	2.51 (1.80–3.51)	2.35 (1.73–3.20)	2.33 (1.73–3.14)
Females**	2.48 (1.31–4.68)	2.83 (1.75–4.56)	2.60 (1.69–4.00)	2.59 (1.72–3.90)
Males**	2.78 (1.49–5.22)	2.33 (1.45–3.72)	2.19 (1.40–3.43)	2.14 (1.38–3.33)
≤1/2 of siblings with asthma				
All**	2.09 (1.16–3.78)	2.10 (1.36–3.23)	2.03 (1.37–3.02)	1.99 (1.36–2.92)
Females**	2.29 (1.06–4.95)	2.83 (1.62–4.93)	2.67 (1.63–4.38)	2.63 (1.64–4.21)
Males**	1.83 (0.72–4.65)	1.43 (0.69–2.96)	1.38 (0.70–2.74)	1.29 (0.65–2.55)
>1/2 of siblings with asthma				
All**	3.41 (1.90–6.15)	3.20 (2.04–5.02)	2.89 (1.89–4.44)	2.92 (1.94–4.41)
Females**	2.83 (1.11–7.26)	2.83 (1.34–5.94)	2.46 (1.23–4.93)	2.51 (1.30–4.86)
Males**	4.12 (1.92–8.82)	3.60 (2.04–6.36)	3.36 (1.95–5.81)	3.40 (2.01–5.78)
No risk factor	1.00	1.00	1.00	1.00
Parental asthma only				
All	2.88 (1.88–4.42)	2.17 (1.54–3.04)	1.98 (1.45–2.71)	1.94 (1.43–2.63)
Females	3.02 (1.68–5.45)	2.30 (1.40–3.78)	2.03 (1.30–3.18)	2.00 (1.30–3.08)
Males	2.85 (1.53–5.33)	2.09 (1.30–3.33)	1.99 (1.28–3.09)	1.93 (1.26–2.97)
Only siblings with asthma				
All	2.82 (1.65–4.81)	2.27 (1.50–3.44)	2.13 (1.46–3.12)	2.10 (1.45–3.03)
Females	2.76 (1.32–5.79)	2.61 (1.47–4.62)	2.30 (1.37–3.86)	2.36 (1.44–3.86)
Males	2.94 (1.36–6.37)	2.01 (1.09–3.70)	2.00 (1.13–3.52)	1.86 (1.06–3.26)
Both risk factors				
All	3.39 (1.69–6.81)	3.95 (2.44–6.41)	3.46 (2.19–5.46)	3.54 (2.29–5.47)
Females	2.67 (0.94–7.56)	3.59 (1.77–7.29)	3.29 (1.74–6.21)	3.31 (1.80–6.09)
Males	4.32 (1.68–11.16)	4.40 (2.26–8.57)	3.75 (1.93–7.26)	3.87 (2.06–7.29)

Definition of abbreviations: CI = confidence interval; HR = adjusted hazard rate ratio.

* Adjusted for sex, maternal smoking in pregnancy, SHS in early childhood, duration of breastfeeding, family socioeconomic status at baseline, and age.

[†] 132 new cases of asthma from 0 to 6 yr.

[‡] 99 new cases of asthma from 7 to 12 yr.

[§] 45 new cases of asthma from 13 to 18 yr.

^{||} 19 new cases of asthma from 18 to 27 yr.

** Adjusted for no siblings.

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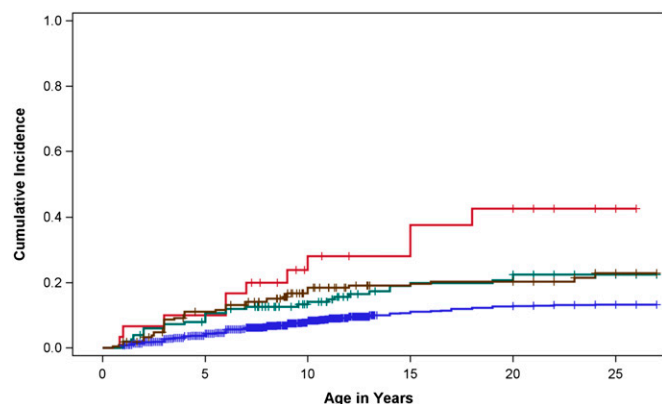


Figure 1. The development of asthma according to parental asthma status. The curves indicate the cumulative incidence of asthma (y axis) from birth to the age of 27 (x axis): No parental asthma (blue line), maternal asthma (brown line), paternal asthma (green line) and both parents with asthma (red line).

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Pediatric Chest Computed Tomography at a Radiation Dose Approaching a Chest Radiograph

To the Editor:



Chest computed tomography (CT) is a valuable diagnostic tool for several pediatric diseases, but concerns in the lay press and among doctors have been strong (1). Although there is no debate about its powerful morphological visualization of the lungs and its added value to patient history, physical examination, and pulmonary function tests, CT is not incorporated in major guidelines for monitoring diseases such as cystic fibrosis (CF) and primary immunodeficiencies (2, 3). This is mainly due to radiation dose concerns and these could, until now, not be taken away.

The first CTs in the early 1970s were reconstructed with an advanced and computationally demanding technique called iterative reconstruction (4). Given the long reconstruction-times, solutions were sought and a simple reconstruction technique called filtered back-projection was introduced clinically. The downside of filtered back-projection is image noise, which increases with lower radiation

doses. Hence, the growing concerns about cumulative radiation dose in pediatric-CT could not be solved. With the exponential increase of computational power it has now become a reality to introduce iterative reconstruction into clinical routine (4).

We used a 256-slice CT-scanner (iCT; Philips-Healthcare, Best, The Netherlands) to image a 12-year-old boy with CF with unexplained worsening of lung function. The three-dimensional whole chest exam was acquired within 2 seconds at a radiation dose of 0.38 mSv (80 kVp, 28 mAs), which approaches the radiation dose of a chest radiograph (in this case only three or four chest radiographs).

The ultra low-dose CT reconstructed with prototype iterative model-based reconstruction clearly visualized bronchiectasis with hyperdense mucus, tiny tree-in-bud opacities, parenchyma density differences due to airway obstruction and vasoconstriction, a fatty pancreas, and a normal liver density. Some of these findings were not visualized on the filtered back-projection images due to the large amount of noise (Figure 1 [see next page]). The hyperdense mucus is radiologically suspect for allergic bronchopulmonary aspergillosis, which is the presumed cause of worsening lung function. The fatty pancreas is associated with exocrine pancreas insufficiency that is present in 85% of patients with CF. CT is able to quantify the fat-content of the liver, and steatosis may progress to cirrhosis in CF.

Possible advantages of this novel chest imaging technique are the three-dimensional aspect, when compared with plain radiography, its dose saving potential when compared with routine CT and its superior morphological detail when compared with magnetic resonance imaging. We demonstrated technical feasibility of CT-imaging at a radiation dose that now approaches chest radiography in a child with CF radiologically suspected of having allergic bronchopulmonary aspergillosis. Now we know that iterative model-based reconstruction is technically feasible, the next steps will be to evaluate its reproducibility, diagnostic accuracy and cost-effective improvements in patient outcome in comparison with clinically indicated routine dose CT scans and plain radiographs (5).

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