SHORT REPORT

Living at high altitude and risk of hospitalisation for atopic asthma in children: results from a large prospective birth-cohort study

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Background: Asthma is among the most common chronic diseases in childhood and is steadily increasing in prevalence. Better characterisation of factors that determine the risk of hospitalisation for atopic asthma in childhood may help design prevention programmes and improve our understanding of disease pathobiology. This study will focus on the altitude of residence.

Methods: This is an ongoing prospective birth-cohort study that enrolled all live-born infants in the Tyrol. Between 1994 and 1999, baseline data were collected for 33 808 infants. From 2000 to 2005, all children hospitalised for atopic asthma at the age of ⩾6 years (n = 305) were identified by a careful search of hospital databases. Disease status was ascertained from the typical medical history, a thorough examination and proof of atopy.

Results: Living at higher altitude was associated with an enhanced risk of hospitalisation for atopic asthma (multivariate RRs (95% confidence interval 2.08 (1.45 to 2.98) and 1.49 (1.05 to 2.11) for a comparison between altitude categories ⩾1200 m and 900–1199 m versus <900 m; p<0.001). This finding applied equally to hospital admissions in spring, summer, autumn and winter. When altitude of residence was analysed as a continuous variable, the risk for asthma hospitalisation increased by 7% for each 100-m increase in altitude (p = 0.013).

Conclusions: This large prospective study shows a significant association between the risk of hospitalisation for atopic asthma and altitude of residence between 450 and 1800 m. The underlying mechanisms remain to be elucidated, but it is tempting to speculate about a role for altitude characteristics such as the decline in outdoor temperature and air humidity and increase in ozone levels, which may trigger airway hyperresponsiveness and attenuate lung function.

Asthma is among the most common chronic diseases in childhood and imposes an increasing economic and health burden.[1] Previous studies have suggested that factors acting early in life, birth characteristics and sociodemographic variables may predispose to or render individuals resistant to childhood asthma.[2–6] The potential effects of altitude, however, are not well established despite the fact that altitude has been shown to affect the onset and course of various diseases of the respiratory system.

This study investigated the association between altitude of residence and hospitalisation for atopic childhood asthma in a large prospective birth-cohort study (n = 33 808) while controlling for a variety of other established or putative risk predictors.

METHODS

Study area

The survey area of this study was the Tyrol, a federal state in the western part of Austria with 650 000 inhabitants and an area of 12 650 km^2. It is a mountainous region located in the Alps with a wide range of altitudes of permanent residence (450–1800 m above sea level). The Alpine climate, which predominates in the survey area, is characterised by a cold period during the late autumn and winter months (average monthly temperature, 2.4 to −2.7°C), and moderate temperatures in spring and hot humid summers. Temperatures decrease at a rate of 0.5–1.0°C/100 m of altitude. Annual migration rates are low in the study area, with only 1.1% of families with young children moving out of the Tyrol and another 2.1% changing residence within the Tyrol. Among the latter group, 40% of moves occurred between the city of Innsbruck and closely surrounding area located at the same level of altitude.

Participants and clinical characteristics

Data on pregnancy, birth and neonatal characteristics were prospectively collected 4–6 weeks after birth for all live-born infants between April 1994 and December 1999 (n = 45 642). The participation rate was high at 74.1% (n = 33 808). The standardised questionnaire used in the current study is part of the public health programme in the Tyrol and was approved by the appropriate committee of the local Board of Health. Altitude of the place of residence was divided into three groups: <900, 900–1199 and ⩾1200 m. Living environment was coded ''urban'' (>100 000 inhabitants), ''suburban'' (10 000–100 000 inhabitants) or ''rural'' (<10 000 inhabitants).

Ascertainment of asthma cases

Data on hospitalisation for atopic asthma of children aged 6–10 years (born April 1994 to December 1999) were extracted from computer databases of all children's hospitals in Tyrol. Children aged ⩽5 years were not included in the current investigation, because there are many different causes of wheezing in this age range. Firstly, a search was made for diagnoses 493.0 of the *International Classification of Disease*, ninth Revision and J45.0 of the *International Classification of Disease,* 10th Revision. Secondly, the diagnosis was confirmed by two paediatric pulmonologists (EH and DM) on the basis of a critical review of the hospital medical records, applying the uniform criteria; a diagnosis of asthma required a medical history of three episodes of wheezing confirmed by clinical examination on hospital admission and a proof of atopy (positive skin-prick test reaction to at least one common aeroallergen and/or elevation of specific IgE in serum). The skin-prick test reaction to common aeroallergens (grass pollen mix, hazel, birch pollen, cat dander, house dust mite (*Dermatophagoides pteronyssinus)*, *Alternaria alternata and Cladosporium herbarum*) was considered positive if the weal diameter was 3 mm greater than a negative control with saline solution 15 min after testing. The level of specific IgE was

Abbreviations: ICD-9, International Classification of Disease-Ninth Revision; ICD-10, International Classification of Disease, Tenth Revision.

Table 1 Association of neonatal, sociodemographic and environmental characteristics with hospitalisation for atopic childhood asthma (n = 33 808)

Variable	Children at risk n	Children hospitalised for asthma n	Children hospitalised for asthma per 1000 children at risk*	p Value†
Sex				
Male	17 219	210	12.2	<0.001
Female	16 589	95	5.7	
Season of birth				
Cold months	10 126	92	9.1	0.935
Other months	23 682	213	9	
Birth weight (g)				
<2500	1666	26	15.6	0.004
⩾2500	32 142	279	8.7	
Mother's age at delivery (years)				
<23	3886	33	8.5	0.711
⩾23	29 922	272	9.1	
Number of siblings				
⩽1 sibling	25 655	248	9.7	0.028
2 or 3 siblings	7171	46	6.4	
⩾4 siblings	982	11	11.2	
Single parenthood				
No	30 381	278	9.2	0.455
Yes	3427	27	7.9	
Educational level‡				
<12 years	22 032	163	7.4	0.042
12 years	4012	45	11.2	
⩾12 years	4441	38	8.6	
Farming environment				
No	32 658	303	9.3	0.004
Yes	1150	2	1.7	
Living environment				
Urban	4186	70	16.7	<0.001
Suburban	4010	24	6	
Rural	25 612	211	8.2	
Altitude of residence				
<900 m	13 627	120	8.8	0.057
900–1199 m	11 537	90	7.8	
⩾1200 m	8644	95	11	
Neonatal admission to hospital				
No	31 269	263	8.4	<0.001
Yes	2539	42	16.5	
Initial breastfeeding				
No	4580	54	11.8	0.033
Yes	29 228	251	8.6	
Prone sleeping position				
No	32 071	289	9	0.932
Yes	1737	16	9.2	
Postnatal smoking				
No	27 718	233	8.4	0.011
Yes	6090	72	11.8	
Prenatal smoking				
No	28 904	250	8.6	0.079
Yes	4904	55	11.2	

*Hospitalisations for atopic asthma were considered only in children aged ⩾6 years.
†p Value for comparison of frequencies of hospitalisation between variable categories.
‡Information on social status was available in 30 485 children only.

Table 2 Association between altitude of residence and risk of hospitalisation for atopic childhood asthma (n = 33 808)

Model	RR (95% CI)	p Value
Univariate analysis		
Altitude of residence (m)		0.151
<900	1.00	
900–1199	0.89 (0.67 to 1.16)	0.383
⩾1200	1.25 (0.95 to 1.64)	0.105
Multivariate analysis		
Altitude of residence (m)		<0.001
<900	1.00	
900–1199	1.49 (1.05 to 2.11)	0.026
⩾1200	2.08 (1.45 to 2.98)	<0.001
per 100-m increase	1.07 (1.01 to 1.12)	0.013
Multivariate analysis (winter hospitalisations for atopic asthma n = 68)		
Altitude of residence (m)		0.041
<900	1	
900–1199	1.71 (0.77 to 3.80)	0.188
⩾1200	2.33 (1.03 to 5.27)	0.042
Multivariate analysis (spring hospitalisations for atopic asthma n = 78)		
Altitude of residence (m)		0.047
<900	1	
900–1199	1.61 (0.82 to 3.16)	0.169
⩾1200	2.05 (1.01 to 4.16)	0.047
Multivariate analysis (summer hospitalisations for atopic asthma n = 68)		
Altitude of residence (m)		0.034
<900	1	
900–1199	1.36 (0.62 to 2.99)	0.441
⩾1200	2.22 (1.03 to 4.81)	0.043
Multivariate analysis (autumn hospitalisations for atopic asthma n = 91)		
Altitude of residence (m)		0.047
<900	1	
900–1199	1.36 (0.75 to 2.46)	0.026
⩾1200	1.87 (1.00 to 3.48)	0.049

RRs and 95% CIs were estimated from logistic regression analyses. The multivariate analyses were fitted with a forward-stepwise selection procedure, allowing for all variables in table 1, and included the following variables: sex, living environment, neonatal admission to hospital, farming environment, lack of breast feeding, postnatal smoking and low birth weight.

measured by radioallergosorbent assay and considered raised if the level was 3.5 kU/l for the specific allergen.

Statistical analysis

Data analysis was performed using SPSS V.12.0 for Windows. Associations between categorised baseline variables and hospitalisation for atopic childhood asthma were analysed with the χ^2 test. RRs were estimated from logistic regression analysis, applying hospitalisation for asthma as the dependent variable. Altitude was treated as either a three-category or a continuous variable. Multivariate models were fitted with a forward-stepwise selection procedure (probability values for entry and removal of variables were 0.10 and 0.15, respectively) and variables selected for inclusion from all those listed in table 1. The test procedure was based on maximum-likelihood estimators. Differential associations in subgroups were tested by including interaction terms. In subsidiary analysis, separate equations were fitted for spring, summer, autumn and winter hospitalisations.

RESULTS

A critical review of hospital admission records identified 367 children aged 6–10 years with atopic asthma who had required at least one hospitalisation in the period between 2000 and 2005. Neonatal questionnaires had been returned in 305 of these cases. The asthma attacks leading to hospitalisation were definitely food-related or induced by strenuous exercise in 1% of cases each, whereas 29.2% of cases had respiratory infection on hospital admission. A total of 78, 68, 91 and 68 hospitalisations for asthma occurred in spring, summer, autumn and winter, respectively.

The mean altitude of residence was 740 m. Altitude did not show significant correlations with most of the variables listed in table 1, especially not with parental educational level or neonatal admission to hospital, which may be viewed as surrogates for social status and access to healthcare. However, altitude was strongly and inversely associated with an urban living environment ($p<0.001$), with this finding emerging from the fact that the only large city in the survey area is located in a low-altitude geographical region.

In univariate analyses, the risk for asthma hospitalisation was modestly increased at higher altitude (table 2). The association gained significance after adjusting for urban living environment, which in itself predicted a high asthma risk (RRs (95% CI) 2.05 (1.43 to 2.93) and 1.47 (1.03 to 2.08) for comparison of altitude categories (⩾1200 and 900–1199 m vs <900 m; $p<0.001$). Significance was maintained in the multivariate model fitted with a forward-stepwise selection procedure (table 2). The risk profile further comprised male sex, urban living environment, neonatal admission to hospital, lack of breastfeeding, postnatal smoking, living on a farm (inverse risk) and number of siblings (inverse risk). Findings were robust in boys and girls and subgroups relating to different levels of parental education (interaction terms $p>0.05$ each), and were equally applicable to spring, summer, autumn and winter hospitalisations for asthma (table 2). Finally, when altitude was treated as a continuous variable, the main findings were replicated.

DISCUSSION

Previous comparatively small and cross-sectional studies have revealed a positive association between the prevalence of asthma and altitude of residence in Norway, Japan, Mexico, New Mexico and Costa Rica,[7–11] but this was not a uniform finding.[12 13] Our study is the first large prospective birth-cohort study to show that living at higher altitude is associated with an increased risk of hospitalisation for atopic asthma. This finding may be caused by mechanisms promoting asthma manifestation and triggering severe asthma attacks. Characteristics of high altitude potentially relevant in this context include the decline in outdoor temperature and air humidity, both of which have been linked to bronchial hyper-responsiveness and may act as mediators for severe asthma episodes in sensitised individuals.[14] Further possible pathophysiological clues are higher ozone levels and concentrations of particulate matter, which increase up to an altitude of 1200–1500 m in the study area.[15] In a study from Austria and southwest Germany, reproducibly decreased lung function and compromised airway development were found in children exposed to high levels of ambient ozone.[16] Exposure to particulate matter impairs lung function parameters.[17] Reduced lung function early in life, in turn, has recently been shown to be associated with the risk for asthma at 10 years of age.[18]

The fact that the main association applied equally to spring, summer, autumn and winter hospitalisations (table 2) clearly indicates that neither of the typical seasonal triggers for asthma attacks such as infections in autumn, cold in autumn and winter, and pollen in spring and summer is of considerable or exclusive relevance in this scenario. Finally, our results are not in conflict with the well-known fact that *Dermatophagoides* species, a major trigger for asthma in sensitised atopic subjects, is scarcely found

What is already known on this topic

- Risk factors such as male sex, urban living environment, neonatal admission to hospital, lack of breastfeeding, postnatal smoking and low birth weight are associated with the manifestation and course of atopic asthma.
- In addition, a low disease risk was found among children living on a farm and children with more siblings.

What this study adds

- Risk predictors for hospitalisation for atopic asthma were assessed in the largest prospective birth-cohort study currently available (n = 33 808).
- Children living at higher altitude faced an increased risk of hospitalisation for atopic asthma.

above 1750 m, because in the Tyrol permanent residence ends at this threshold.

The main merits of our study are its prospective design and size (n = 33 808). Size clearly exceeds that of comparable birth-cohort studies focusing on neonatal characteristics, most of which included a few thousand infants.[2–6] Furthermore, ascertainment of asthma did not rely on the parents' responses to the questionnaire or on the patient's self-report, but on a thorough in-hospital examination by a specialist in paediatric pulmonology. In each case the diagnosis was confirmed by proof of atopy. Finally, the study area is particularly appropriate for studying altitude effects given the broad range of altitude inhabited and homogeneous climatic conditions and diet throughout the Tyrol. In this context, it should be mentioned that in the Tyrol, healthcare is free of charge and access to healthcare does not differ between sociodemographic groups nor between families living at distinct altitudes, making confounding by selective hospital admission unlikely.

There are limitations to the study. Firstly, this study was designed primarily to assess risk factors for sudden infant death syndrome[19 20] and was later extended to childhood asthma. Accordingly, some variables meaningful for the current analysis, such as family history of asthma and pet contact, were not systematically assessed. However, these variables are unlikely to confound the association obtained. Secondly, a minor proportion of families moved out of the survey area during the study period (1.1% per year). Because these families no longer contribute to the population of hospitalised people with asthma, frequencies in table 1 and RRs in table 2 may be modestly underestimated. Moreover, our computations did not consider migration within the survey area. However, the proportion of subjects who moved to an area with a distinct altitude was again low at an estimated annual 0.5–1.0% (maximum 1.3%) and may have had modest weakening effects on the key association, if any.

In conclusion, our study provides solid evidence that children living at higher altitudes face an enhanced risk of hospitalisation for asthma. A thorough characterisation of the underlying mechanisms may give new insights into the disease pathophysiology and assist in further improving prevention programmes.

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Contributors: K-K obtained the funding, designed and supervised the study, and prepared the manuscript draft. EH contributed to study design, participated in data collection and ascertainment of asthma cases, and contributed to manuscript writing. WM, RS, CH, FMF, MS, KHG and HR participated in the birth-cohort study and contributed to the identification of patients having asthma in outlying hospitals. DM also participated in data collection and ascertainment of asthma cases. SK contributed to statistical analyses, interpretation of results and manuscript writing. All authors have reviewed the final draft of the complete manuscript and approved its submission for publication.

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