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Title: Lower respiratory tract infections appear to be the most important risk factor for current asthma in subarctic schoolchildren

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Short title: Risk factors for asthma in schoolchildren

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ABSTRACT

Aim: The aim of this study was to identify possible risk factors for current asthma revealed by two studies in Northern Norway in 1985 and 2008 and to evaluate these factors contribution to the increased prevalence of asthma over these 23 years,

Methods: As part of the 'Asthma and allergy study among schoolchildren in Nordland county' we performed a case-control study (70.0% attendance) comparing 153 children with current asthma (cases) to their non-asthmatic controls. The results from this 2008 study were compared to a similar case-control study (93.2% attendance) performed in 1985 based on 62 current asthmatics.

Results: In 1985 the most important risk factors for current asthma were repeated lower respiratory tract infections (LRTIs) with adjusted odds ratio (aOR) 52.11, together with urticaria ever and atopic disease in the family. In 2008 the most important risk factors were food allergy with aOR7.06, LRTIs during the first 3 years of life with aOR 5.80 and hospitalisation caused by LRTIs.

Conclusion: In both studies, LRTI was the most important risk factor for current asthma. Whether or not LRTIs have contributed to the increased asthma prevalence in this population over 23 years is unresolved.

Key words: asthma, case-control, risk factors, schoolchildren, subarctic

Key notes:

- Two case-control studies in 1985 and 2008 demonstrated that lower respiratory tract infections were the most important risk factor for current asthma in subarctic schoolchildren populations.
- Atopic diseases in the family had impact on current asthma, only in the 1985 study.
- Whether or not lower respiratory tract infections have contributed to increased asthma prevalence in this population is still unresolved.

INTRODUCTIONS

The substantial increase in the reported prevalence of asthma in the latter part of the 20th century has been termed the 'asthma epidemic' (1). Despite decades of research, there has not been a significant breakthrough in the understanding of mechanisms, genetics, and effective preventive strategies for asthma. Asthma is a complex disease. Changes in the prevalence may be due to multiple genetic, and environmental determinants, each contributing a relatively small effect (1,2). Rapid increase in asthma prevalence may indicate that environmental factors have a greater impact than genetic factors, even if parental asthma and, or, allergic rhinoconjunctivitis (AR) have often been identified as the strongest risk factors (3,4).

During the period 1985-2008, three cross-sectional surveys to estimate the prevalence of parental reported asthma, AR and eczema (5-7) were conducted among schoolchildren (7-14 years) in Nordland county, Norway. The results showed an increase in the prevalence of asthma ever from 7.3% to 17.6% and an increase in the prevalence of current asthma from 4.8% to 9.9% (7). As part of the study 'Asthma and allergy among schoolchildren in Nordland County' we used data from the questionnaire-based surveys in 1985 and 2008 to perform case-control studies designed to explore possible risk factors by comparing children with current asthma to non-asthmatic controls. The aim was to identify possible risk factors for current asthma in 1985 and 2008 respectively, and to evaluate their contribution to the increase in asthma prevalence in this population over 23 years.

PATIENTS AND METHODS

Study design

In 1985, a cross-sectional questionnaire-based survey concerning asthma, AR and eczema was distributed to randomly selected schoolchildren in Northern Norway aged 7-13 years (5,8). 'Asthma ever' was considered if the parent answered yes to the question: Has the pupil ever had asthma? And, or, to the question: Does the pupil experience wheeze, periods of coughing or acute shortness of breath (asthma) due to external factors? The same questionnaire was used in identical surveys in 1995 and in 2008, throughout Northern Norway and in Nordland county (6,7).

To validate the questionnaire and to verify diagnosis and risk factors for asthma, case-control studies based on the cross-sectional surveys were performed in 1985 and 2008, but not in 1995. Pupils who reported ever having asthma (cases) together with non-asthmatic controls matched for age, gender and school affiliation were invited to participate. Preferably, cases and controls went to the same school; however, when this premise was violated due to the small number of pupils at the school, the control was chosen from the same geographic area. Participating children together with their parents/guardians completed a questionnaire and a structured interview. The interview covered birth data, socio-economic conditions, health status, infections and asthma, second-hand smoke exposure and household animals. A clinical examination including height, and weight measurements and assessment of skin, upper airway, lung and heart was performed. In addition clinical testing was performed. In both 1985 and 2008 parents signed a written consent for their children's participation.

Based on the clinical assessment (interview and clinical examination) children were categorised as asthmatic or non-asthmatic and asthma severity was classified according to modified Kjell Aas scale, a system proposed by Norwegian paediatric allergologist (9) in 1985 and to the GINA guidelines (10) in 2008. The assessments fulfilling the definition criteria for current asthma (cases) and non-asthmatics age- and gender-matched controls were then compared.

The 1985 study

In 1985, 4870 schoolchildren (94.9% response rate) aged 7-13 years (51.4% male) from Nordland county participated in the cross-sectional questionnaire-based survey. Parents reported asthma ever in 353 children (7.3%) (Figure 1). Approximately one third of the children reporting asthma ever randomly selected, together with non-asthmatic controls were invited to participate in a case-control study during 1986-1987 (Figure 1). The children lived in different geographical areas in Nordland, representing both coast and inland. Of the 222 invited children, 207 (93.2% attendance) were enrolled in the case-control study. In addition to a structured interview, the participants underwent a clinical examination and clinical testing including spirometry and specific Immunoglobulin E (IgE). Skin prick tests (SPTs) were performed in cases only. One of the authors (JH), a paediatrician, conducted all interviews, examinations and tests. Data from this case-control study is previously unpublished.

The 2008 study

In 2008, 4150 (63.8% attendance) schoolchildren aged 7-14 years participated in the cross-sectional survey (7). Using identical definitions as in 1985, 729 (17.6%) children reported asthma ever (Figure 2). Pupils who reported ever having asthma (cases) and who lived within two hour by car to the study locations in four different geographical areas in Nordland county, along with two age and gender matched non-asthmatic controls were invited to participate. Of the invited, 801 children (70% attendance) were enrolled to the case control study. More controls (428) than cases (373) participated (Figure 2).

In addition to a second questionnaire, a structured interview and clinical examination, spirometry, exercise treadmill testing (EIB test), SPTs, measurements of exhaled nitrogen oxide (FE_{NO}), sIgE and total IgE were obtained, a process described in detail elsewhere (11,12). The participants were examined at least two weeks after any suspected respiratory tract infection during the school term from March 2009 to June 2010. Two of the authors (THE and BE) conducted all interviews and procedures. The same medical instruments were used to secure standardised measurements conditions.

Definitions

The children's final diagnoses were confirmed by the doctor performing the clinical assessment, based on the information from the structured interviews and the clinical examination in the case-control studies.

Asthma ever was defined as at least two of the three criteria being fulfilled; 1) recurrent dyspnoea, chest tightness and/or wheezing; 2) doctor's diagnosis of asthma; 3) use of asthma medication (ß-2 agonist, sodium cromoglycate,

corticosteroids, leukotriene antagonists and/or aminophylline) (13). Current asthma was defined as asthma above plus symptoms and, or, asthma medication within the last year.

Allergic rhinoconjunctivitis (AR) was defined as a history of watery rhinorrhea, blocked nose, sneezing, or nasal itching accompanied by itchy watery eyes in absence of airway infection.

Eczema was defined as an itchy rash lasting at least 4 weeks combined with lesions on the face, elbows or knee flexures, or a high degree of itching and lesions elsewhere.

Food allergy was defined as a history of IgE mediated food allergy symptoms as evaluated by a doctor.

Current AR, eczema and food allergy was defined as symptoms within the last year.

Allergic sensitisation was defined as: a positive SPT (wheal diameter ≥3 mm larger than the negative control) and/or a positive sIgE (>0.35 kU/L) to > 1/14 of the allergens tested for.

Atopic disease in the family was defined as a positive response to the question: Does anyone in the family (parents and siblings) suffer from asthma, AR, eczema or urticaria.

Statistical analyses

Continuous variables are presented as means with standard deviation (SD) or 95% confidence intervals (95% CI) and categorical data as counts and percentages (%). To assess possible differences between groups we used Pearson`s chi square-test for categorical data and Student's t-test for continuous data. When comparing the matched case-control groups, McNamara's chi square-test was used for categorical

variables and paired-sample t-test continuous variables. All tests were two-sided using a significance level of 0.05. Odds ratios were estimated by conditional logistic regression using Cox proportional hazards model with a constant dependent variable. Building the model we first assessed whether an independent variable was a potential confounder. Of potential risk factors, the most relevant relationships were assessed in unadjusted analysis and factors with an unadjusted p-value < 0.25 were included in the model. Variables considered as mediators or colliders were not included. Variables in the multivariable model were excluded in a stepwise fashion to increase the strength of the model regardless of significance. The final model included statistically significant covariates as well as confounders whether or not formally statistically significant at the 5% level. All analyses were made using the Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM Corporation, Armonk, New York, USA).

Ethical approval

The Regional Committee for Medical and Health Research Ethics, Northern Norway and the Norwegian Data Inspectorate approved both studies.

RESULTS

Demographic data from the study populations in 1985 (n = 207) and 2008 (n = 801) are displayed together with data from the subgroups of current asthmatic cases and non-asthmatic controls in each study (Table 1). In both case-control studies, we found a male dominance of 65.7% in 1985 and 61.2% in 2008, and the mean age was 11.4 years (SD 1.6) and 12.5 years (SD 1.9), respectively. Atopic disease in the family was significantly different between cases and controls (Table 1). Otherwise,

the subgroups were similar in terms of demographic data and clinical characteristics. Comparing demographic and clinical data between genders displayed a significant difference in the prevalence of AR in the 2008 study (boys 38.4% and girls 30.5%; p = 0.024), while there were no differences in 1985 (data not shown).

The 1985 study

In 1985, a total of 105 cases and 102 controls participated. Of the 105 cases, 62 fulfilled the criteria for current asthma (Figure 1). Following the severity definitions (9), 39 suffered from mild asthma, 20 suffered from moderate asthma and three suffered from severe asthma. Comparing these to their respective controls revealed associations between some variables and the outcome current asthma (Table 2). The variables not included were either confounding factors or colliders or did not strengthen the model. The final model revealed significant differences between cases and their matched controls in [aOR (95% CI)]; repeated LRTIs OR 52.11 (95% CI 4.62-587.97), urticaria ever in the child OR 11.27 (95% CI 1.01-125.33), atopy in the family OR 13.20 (95% CI 1.60-108.63) and duration of breastfeeding OR 1.35 (95% CI 1.02-1.80) (Table 2). Analysis of gender specific risk factors for the 1985 survey was not performed since the small number of female pairs (12/19 pairs with complete data) rendered the results uncertain due to lack of statistical power.

The 2008 study

Of the 323 cases, 153 fulfilled the criteria for current asthma (Figure 2). According to the GINA guidelines (10) 69 of the cases suffered from intermittent asthma and 84 suffered from mild persistent asthma. Comparing them to their controls revealed associations between a number of variables and the outcome current asthma (Table

3). After establishing the final model, the majority of associations failed to maintain their significance. The final model included a total of seven variables: duration of breastfeeding, mean number of hours watching television and/or data during weekdays, AR, food allergy, LRTI during the first three years of life, hospitalisation caused by LRTIs and allergic sensitisation (Table 3). The variables not included were either confounding factors or colliders or did not strengthen the model. The explained variance for current asthma by all seven variables was 61% with the most important risk factors; food allergy OR 7.06 (95% CI 1.61-31.07), LRTI during the first 3 years of life OR 5.80 (95% CI 1.96-17.21), and hospitalisation caused by LRTIs OR 4.60 (95% CI 1.01-20.96) (Table 3). The only factor associated with a reduced risk for current asthma was length of breastfeeding OR 0.93 (95% CI 0.87-0.99). Restricting the model to include only statistically significant variables did not affect the estimated ORs or the explained variance (R^2 =61%) to any relevant extent.

Analysing the present data by gender displayed some differences from the data for all children. For boys (80/97 matched case-control pairs) food allergy OR 18.32 (95% CI 1.54-217.74), LRTIs during the first 3 years of life OR 8.87 (95% CI 2.07-37.96) and AR OR 4.12 (95% CI 1.10-15.4) were significantly different between cases and controls, while allergic sensitisation, duration of breastfeeding and time spent in front of television or data was not. For girls (44/56 matched case-control pairs) LRTI during the first 3 years of life OR 7.70 (95% 1.18-50.36), duration of breastfeeding OR 0.89 (95% 0.79-0.99) and time spent in front of television or data OR 1.65 (95% CI 1.11-2.45) were significantly different between the cases and controls. Analyses of gender specific risk factors did not reveal a gender-dependent association of parental asthma and, or, allergic diseases (result not shown).

DISCUSSION

The main finding in the present study was that one or repeated LRTIs during the first three years of life, reported by the parents, was the strongest risk for current asthma in both 1985 and 2008, together with severe LRTIs in the 2008 study. These results were supported by others studies showing that early severe LRTIs are associated with up to a four-fold risk of subsequent wheezing during early school years (14). In addition the number and severity of early life bronchial obstructive episodes has been shown to have the greatest impact on risk of pubertal asthma (15). Recent research from Copenhagen Prospective Studies on Asthma in Childhood revealed that otherwise healthy children experienced a median of 10 episodes of respiratory tract infections (one episode per child for LRTIs) during the first 3 years of life (16). Findings in this Danish study suggest that host factors are the major determinants of infection susceptibility in early childhood (16). Whether the infection susceptibility in early childhood has changed during recent decades making an increase in the incidence of respiratory tract infections, is unknown. Whether LRTIs has contributed to the increased asthma prevalence in our study population needs further investigations.

Males (> 60%) dominated both case-control cohorts, in accordance with a significantly higher prevalence for asthma ever and current asthma in boys in the original study groups (7). Until teenage years, the prevalence of asthma is higher among boys than girls, and then a shift takes place probably due to a higher

incidence and lower remission prevalence in girls (17). Since the mean ages were 12.5 and 11.4 years respectively, male dominance was expected.

Although gender difference in asthma prevalence is well documented, gender-dependant risk factors for wheeze or asthma have not been fully elucidated (18). Stratification by gender in the 2008 study displayed gender-dependant risk factors: comorbidity of AR and food allergies was significantly different between cases and controls in boys. Although these associations were strong, this could be the result of a higher prevalence of AR in boys in the original study groups (7) and twice as many matched pair of boys than girls in the study.

Despite the known coexistence of asthma and food allergy, the mechanisms are still unresolved. Food allergy and atopic dermatitis commonly coexist at the beginning of the 'atopic march'. Questioned has been asked as to whether the observed association between asthma and food allergy is related to co-manifestation or if it is a consequence of food allergy itself (19). AR and asthma frequently coexist (20). Our findings are in line with results from the Environment and childhood asthma study from Oslo, Norway (21) and support the hypothesis that asthma and combinations of allergic comorbidities may represent a gender-related phenotype. Increased prevalence of AR between 1985-2008 (7) may indicate that it has contributed to the increased prevalence of asthma.

The greatest distinctions between the results in 1985 and 2008 were the lack of a protective effect of breastfeeding on current asthma and the significance of atopy in the family. As with other Scandinavia studies (22), results from the 2008 study

indicate that breastfeeding for a longer period was protective against the development of current asthma. However, the result from the 1985 study showed the opposite: longer duration of breastfeeding being a risk factor for current asthma. This may be an example of inverse causation where debut of asthma symptoms tends to prolong the duration of breast-feeding because of the general belief in its protective effect. Such inverse causation could be misinterpreted, drawing the conclusion that longer breast-feeding leads to asthma, when in fact it is reverse (22,23). Breast-feeding presumably has a protective effect against viral respiratory infections (24). In the present study where LRTI shows a strong association towards current asthma, the association to breastfeeding might be brought about by its protective effect against LRTIs (25).

In the 1985 study, current asthma was associated with family atopy, but not parental atopy alone. Unlike other studies (3,4), we were unable to find an association between current and parental asthma, AR and/or eczema in the 2008 survey. Between the case-control studies, a substantial increase (up to 70%) in the prevalence of atopic diseases among family members in Nordland has been demonstrated (7). This high prevalence regardless of asthma status in the child, may partly explain the difference. Some researchers have claimed there is a gender-dependent association of parental atopy with childhood asthma (26), but we did not find such an association. In addition, we were unable to find any association between current asthma and allergic sensitisation, second-hand smoke exposure, animal household and socio-economic factors.

In the 2008 case-control study no cases suffered from moderate or severe asthma in contrast to the 1985 study where 23 of 62 children did. Even if the severity definitions used in the two studies were not identical, we believe this may reflect a change in disease severity. Similarly, the ISAAC studies have revealed that the overall increase in asthma prevalence reflects milder disease (27) and a decreasing prevalence of severe asthma symptoms (28). The West Sweden Asthma Study (WSAS) using multi-symptom asthma as a marker for severe asthma (29), found a strong association with a familiar history of asthma and allergy, female gender and a high body mass index. These factors lacking significance in our study might suggest that risk spectrums may be linked to the severity of asthma or even represent a phenotype.

Strength and limitations

The study cohorts in 1985 and 2008 were large and consisted of unselected children in Nordland county randomly selected, making the study group a representative fraction of the general childhood population. In 1985, both the cross-sectional survey and the case-control study had high response rates, making results more reliable. A major advantage of the case-control studies was the substantial clinical characterisation of the participating children together with detailed questionnaires and structured interviews. In addition, we studied children with current asthma to ensure more reliable cases regarding recall biases and increased awareness in the population.

The study had some limitations. Asthma and allergic diseases have been given considerable public health and media attention, especially in western societies, in the

same period as the ‘asthma epidemic’ has arisen. The increased awareness may have contributed to selection bias in the study, since study subjects suffering from a disease may be more willing to participate than healthy subjects (23). The response rate of the original cohort in 2008 (63.8%) was lower than desirable (7). Although a high participation rate is preferable to avoid selection biases, most empirical work suggests that lower participation rates are not likely to have a substantial influence on the measures of interest (30). As always with retrospective studies, recall bias was a risk. Parents with children suffering from asthma, more likely could recount their children’s disease history to fit the diagnosis in question. The studies form 1985 and 2008 were not identical in respect of screening of variables and clinical testing, and this was a limitation. Caution was necessary in drawing conclusions, but nonetheless we believe that the data and analysis were useful to the overall discussion concerning asthma prevalence. Finally, the reviewers were not blinded to the previous parent reported asthma status of the child in the case-control studies. Ideally, the reviewers should have been blinded to avoid misclassification based on prejudice or beliefs. That this was not possible is one of the unfortunate disadvantages of conducting research in environments outside of the university. However, the reviewers had no knowledge about the specific answers to individual questions in the cross-sectional survey. Thus, we believe that this has only influenced the results to a minor degree.

CONCLUSION

Based on similar case-control studies in 1985 and 2008 in a subarctic childhood population, one or repeated lower respiratory tract

infections during the first three years of life was identified to be the most important risk factor for current asthma when adjusting for other variables. Whether or not lower respiratory tract infections have contributed to the increased asthma prevalence in this population over these 23 years is still unresolved. Atopic diseases in the family yielded importance in 1985, while food allergy, AR and duration of breastfeeding had an impact in the 2008 study. The increased prevalence of AR in the period 1985-2008 (7), may indicate that AR has contributed to the increased asthma prevalence in the study population. Thus, for more solid conclusions further investigations are needed.

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Declaration of interest

The authors have no conflicts of interest to declare.

ABBREVIATIONS

AR	allergic rhinoconjunctivitis
CI	confidence interval
IgE	immunoglobulin E
LRTIs	lower respiratory tract infections
OR	odds ratio
SPT	skin prick t

Table 1. Demographic data given for the study groups in the two case-control studies from 1985 and 2008. Data are displayed for each study in exact numbers and percentages (%) or standard deviation (SD) in brackets, for all children and for the subgroups current asthmatic cases and non-asthmatic controls.

	Case-control studies									
	1985					**2008**				
	n	**All children**	Current asthmatic cases	Non-asthmatic controls	p value	**n**	**All children**	Current asthmatic cases	Non-asthmatic controls	p value
Number of study subjects (n)		207	62	62			801	153	153	
Asthma ever as evaluated by a doctor (%)	207	105 (50.7)				801	323 (40.3)			
Gender (male) (%)	207	136 (65.7)	43 (69.4)	43 (69.4)	1.000	801	490 (61.2)	97 (63.4)	97 (63.4)	1.000
Age (years) (m ± SD)*	207	11.4 (1.6)	11.2 (1.4)	11.3 (1.5)	0.946	801	12.5 (1.9)	12.6 (1.9)	12.5 (1.9)	0.810
BMI** (kg/m2) (m ± SD)*	194	17.7 (2.5)	17.9 (2.2)	17.4 (1.8)	0.237	801	19.9 (3.9)	20.6 (4.4)	19.4 (3.6)	0.007
Birth weight (grams) (m ± SD)*	202	3464 (568.2)	3390 (569)	3232 (930)	0.263	777	3509 (656.7)	3449 (669)	3538 (631)	0.242
Number of siblings (m ± SD)*	204	1.7 (1.2)	1.7 (1.0)	1.6 (1.0)	0.646	790	1,9 (1.0)	2.0 (1.0)	2.1 (1.0)	0.773
Passive smoke exposition first year of life (%)	204	150 (73.5)	45 (72.6)	44 (72.1)	0.956	791	323 (40.8)	65 (42.8)	62 (40.8)	0.727
Familiar atopy (%)	205	120 (58.5)	47 (77.0)	30 (49.2)	0.001	794	587 (73.9)	127 (84.7)	104 (68.0)	0.001
Parental atopy (%)	205	94 (45.4)	38 (62.3)	23 (37.7)	0.007	799	478 (59.8)	93 (60.8)	78 (51.0)	0.084
Parental asthma (%)		24 (11.6)	11 (18.0)	3 (4.9)	0.023		200 (25.0)	51 (33.3)	29 (19.0)	0.004
Parental allergic rhinoconjunctivitis (%)		33 (15.9)	17 (27.9)	6 (9.8)	0.011		274 (34.3)	62 (40.5)	47 (30.7)	0.073

*Mean ± standard deviation

**BMI (body mass index) = weight/height^2

Table 2. The potential risk factors (univariable p < 0.25) between the case-control groups in the 1985 study. Adjusted odds ratios (OR) are displayed for the variables included in the final multivariable model.

Risk factor	Current asthmatics n = 62	Non - asthmatics n = 62	n pairs	OR	p value	n pairs	Adjusted OR (95% CI)
Demographic characteristics							
Duration of breastfeeding (months) (m ± SD)*	5.1 (6.2)	3.5 (2.8)	49	1.10	0.096	43	1.35 (1.02-1.80)
BMI** (kg/m2) (m ± SD)*	17.8 (2.2)	17.4 (1.8)	51	1.14	0.221		
Passive smoke exposition today (%)	28 (46.7)	34 (57.6)	59	0.61	0.198		
Household animals in the first year of life (%)	30 (49.2)	24 (40.7)	61	0.81	0.159		
Animals in the household today (%)	25 (41.7)	31 (54.4)	57	0.63	0.213		
Furry pets in household today (%)	18 (30.0)	28 (49.1)	58	0.42	0.040		
Comorbidity in the child							
Colic (> 3 weeks) during the first months of life (%)	18 (29.5)	7 (11.7)	61	3.00	0.033		
Allergic rhinoconjunctivitis (%)	50 (80.6)	7 (11.3)	62	65.29	0.001		
Eczema (%)	19 (31.1)	7 (11.3)	62	3.60	0.011		
Food allergy (%)	15 (24.6)	5 (8.2)	62	4.67	0.015		
Urticaria (%)	18 (30.5)	5 (8.8)	56	4.67	0.015	43	11.27 (1.01-125.33)
Airway infections during the child first 3 years of life							
Repeated RTIs during the first 3 years of life	34 (55.7)	5 (8.5)	59	10.33	0.000	43	52.11 (4.62-587.97)
Familiar history of atopic diseases							
Family atopy (%)	46 (76.7)	30 (50.0)	61	3.13	0.005	43	13.20 (1.60-108.63)
Parental atopy (%)	37 (61.7)	23 (38.3)	61	2.67	0.012		
Parental asthma (%)	11 (18.3)	3 (5.0)	61	5.00	0.038		

The difference prevalence (%) between the current asthmatic cases and non-asthmatic controls is quantified by odds ratios (OR).
P-values or corresponding 95 % confidence intervals (95% CI) are presented.
*Mean ± standard deviation
**BMI (body mass index) = weight/height^2

Table 3. The potential risk factors (univariable p < 0.25) between the case-control groups in the 2008 study. Adjusted odds ratios (OR) are displayed for the variables included in the final multivariable model.

Risk factor	Current asthmatics n = 153	Non - asthmatics n = 153	n pairs	OR	p value	n pairs	Adjusted OR (95% CI)
Demographic characteristics							
Mothers smoking in pregnancy or in the first year of life (%)	51 (33.3)	38 (24.8)	153	1.54	0.102		
Birth weight (grams) (m ± SD)*	3449 (669)	3538 (631)	148	1.00	0.193		
Exclusively breastfeeding (%)	115 (75.7)	125 (82.8)	150	0.65	0.112		
Duration of breastfeeding (months)(m ± SD)*	9.4 (6.0)	12.3 (8.6)	145	0.94	0.001	122	0.93 (0.87-0.99)
BMI** (kg/m2) (m ± SD)*	20.6 (4.4)	19.4 (3.6)	153	1.09	0.007		
Fathers education (years) (m ± SD)*	13.0 (2.9)	13.6 (2.7)	143	0.92	0.059		
Mean number of hours in front of television and/or data during weekdays (SD)*	3.7 (2.4)	3.0 (1.8)	142	1.18	0.007	122	1.34 (1.07-1.68)
Mean number of hours in front of television and/or data during weekends (SD)*	4.7 (2.4)	4.1 (1.8)	135	1.21	0.009		
Animals in the household today (%)	67 (43.8)	84 (54.9)	153	0.62	0.049		
Furry pets in household today (%)	56 (36.6)	78 (51.0)	153	0.53	0.011		
Comorbidity in the child							
Colic (> 3 weeks) during the first months of life (%)	36 (23.5)	26 (17.0)	153	1.50	0.160		
Allergic rhinoconjunctivitis (%)	94 (61.4)	35 (22.9)	153	5.21	0.000	122	2.51 (1.03-6.15)
Food allergy (%)	38 (24.8)	6 (3.9)	153	11.67	0.000	122	7.06 (1.61-31.07)
Eczema (%)	85 (55.6)	58 (37.9)	153	1.93	0.004		
Urticaria (%)	41 (26.8)	23 (15.0)	153	1.95	0.018		
Allergic sensitization (positive SPT and/or positive sIgE)	117 (78.0)	64 (45.7)	138	3.44	0.000	122	2.16 (0.92-5.06)
At least one positive specific IgE (%)	94 (74.6)	57 (43.2)	108	3.21	0.000		
At least one positive SPT (%)***	100 (84.7)	33 (76.7)	33	2.33	0.220		

Airway infections during the child first 3 years of life							
Hospitalization caused by LRTIs the first 3 years of life (%)****	41 (27.0)	9 (6.0)	150	7.40	0.000	122	4.60 (1.01-20.96)
Number of treatments with antibiotics (SD)*	4.0 (6.0)	1.5 (2.4)	136	1.28	0.000		
A common cold during the first 6 months of life (%)	60 (41.7)	29 (19.6)	139	3.29	0.000		
A LRTI during the first year of life (%)****	45 (29.6)	8 (5.3)	151	8.20	0.00		
A LRTI during the first 3 years of life (%)****	64 (41.8)	14 (9.2)	153	6.56	0.000	122	5.80 (1.96-17.21)
Tonisilitt during the first year of life (%)	4 (2.7)	13 (8.5)	150	0.18	0.027		
Otitis media during the first year of life (%)	15 (10.0)	24 (15.7)	150	0.61	0.143		
Laryngittis during the first year of life (%)	21 (14.0)	10 (6.5)	150	2.38	0.040		
Laryngittis during the first 3 year of life (%)	28 (18.5)	20 (13.1)	151	1.44	0.230		
Familiar history of atopic diseases							
Familiar atopy (asthma, AR and/or eczema) (%)	127 (83.0)	104 (68.0)	150	2.47	0.002		
Parental atopy (asthma, AR and/or eczema) (%)	93 (60.8)	78 (51.0)	150	2.04	0.005		
Familiar asthma (%)	77 (50.3)	44 (28.8)	150	2.55	0.000		
Parental asthma (%)	51 (33.3)	29 (19.0)	150	2.28	0.004		
Mother asthma (%)	29 (19.3)	17 (11.1)	150	2.00	0.041		
Father asthma (%)	26 (17.3)	13 (8.5)	150	2.18	0.032		
Familiar AR (%)	77 (51.3)	64 (41.8)	150	1.43	0.106		
Parental AR (%)	62 (41.3)	47(30.7)	150	1.55	0.058		
Mother AR (%)	44 (29.3)	32 (20.9)	150	1.54	0.087		
Familiar eczema (%)	71 (47.3)	57 (37.3)	150	1.59	0.058		

The difference prevalence (%) between the current asthmatic cases and non-asthmatic controls is quantified by odds ratios (OR).
P-values or corresponding 95 % confidence intervals (95% CI) are presented.
*Mean ± standard deviation
**BMI (body mass index) = weight/height^2
***skin prick test (SPT)
*** lower respiratory infectious disease (LRTI)

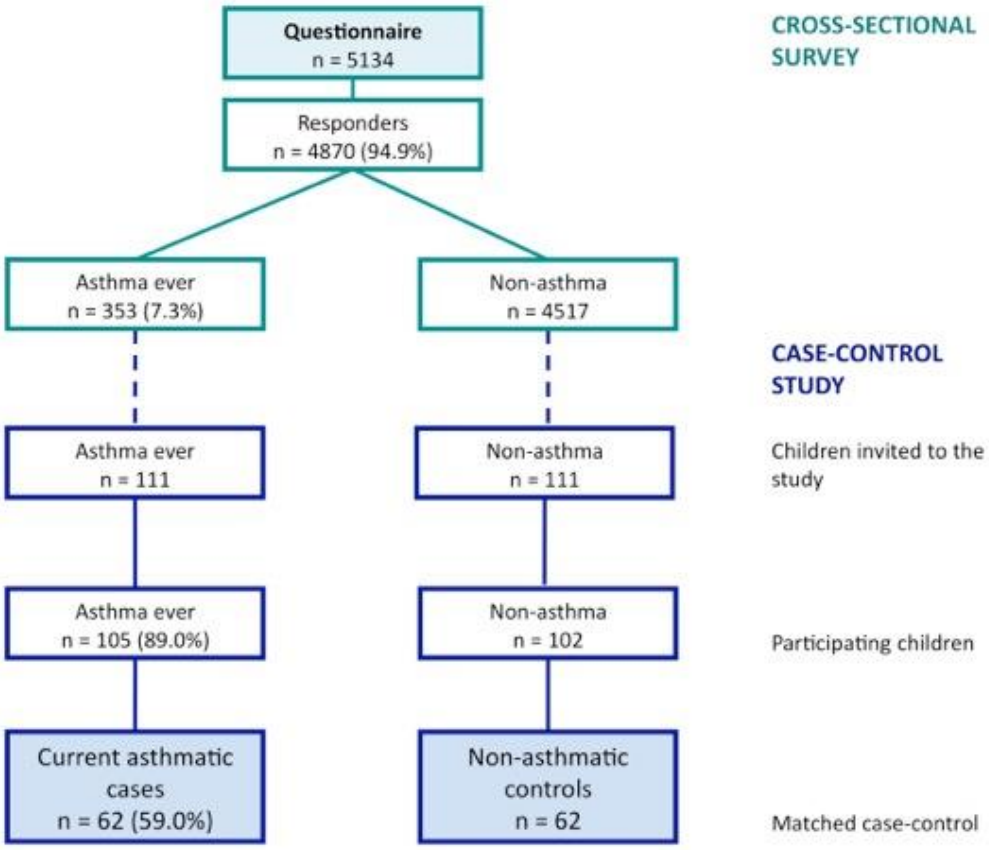

Figure 1. Subject flow chart in the study of asthma and allergic diseases among schoolchildren in Nordland county 1985.

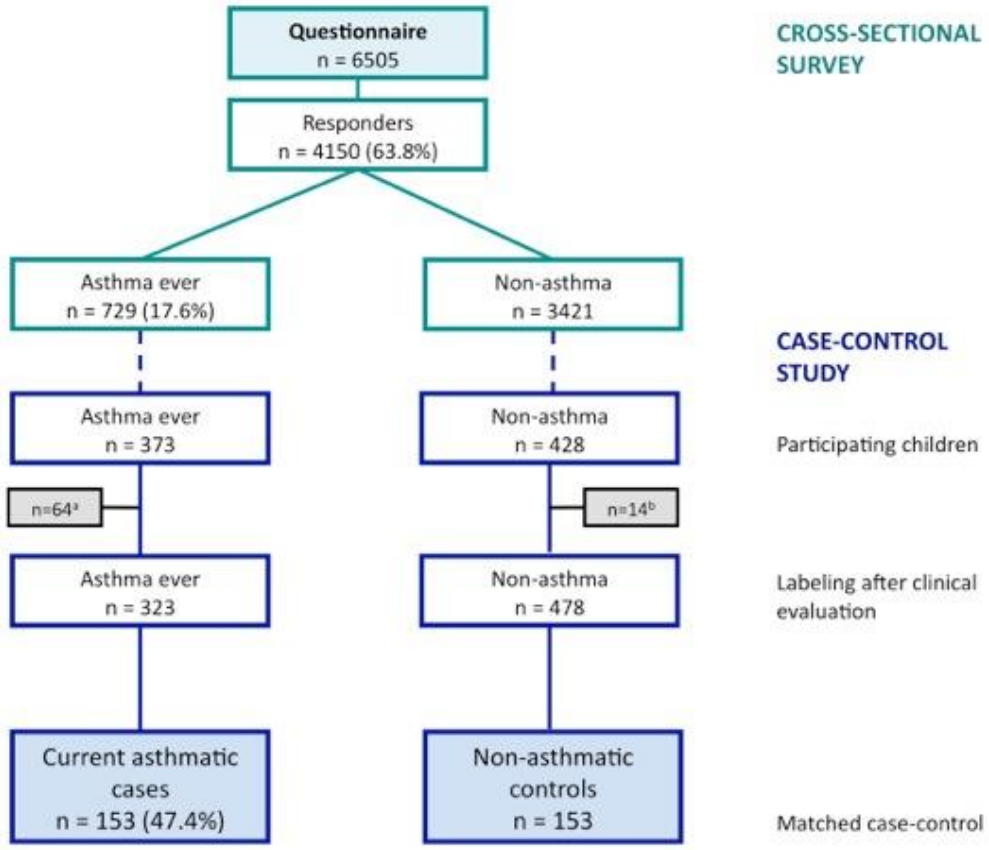

Figure 2. Subject flow chart in Asthma and allergy among schoolchildren in Nordland county 2008.

[a]*Subjects misclassified as non-asthmatics (n=14).*

[b]*Subjects categorized as non-asthmatic after clinical assessment (n=64).*

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