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REGULAR ARTICLE

An increased asthma risk continued until young adulthood after early-childhood hospitalisation for wheezing

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Abstract

Aim: The aim of this cohort study was to evaluate doctor-diagnosed and self-reported asthma in young adults after early-childhood hospitalisation for wheezing.

Methods: In this prospective-controlled follow-up, questionnaires were sent to 95 subjects aged 24–28 years, who had been hospitalised for their first episodes of wheezing under 24 months of age. Fifty-eight cases and 100 controls returned the questionnaires.

Results: The risk of doctor-diagnosed asthma was 2.14-fold (95% confidence interval 0.61–7.41), and the risk of self-reported asthma 2.39-fold (1.14–4.99) in cases compared to controls. The increased risk of self-reported asthma remained as statistically significant in analyses adjusted for current smoking, overweight and allergic rhinitis. Study subjects presented with wheezing symptoms, use of bronchodilators and inhaled corticosteroids, and with seasonal symptoms presumptive for allergic rhinitis during the last 12 months, more often than controls. The identification of a respiratory syncytial virus or rhinovirus during hospitalisation in early childhood was not anymore associated with asthma risk in adulthood. As expected, previous asthma during early childhood was a strong risk factor for asthma in young adulthood.

Conclusion: In this controlled questionnaire study, early-childhood hospitalisation for lower respiratory infection with wheezing was an independently significant risk factor of asthma in young adults.

KEYWORDS
adulthood asthma, bronchiolitis, early-life wheezing, prospective design, questionnaire study

1 | INTRODUCTION

The risk of asthma has been increased in children who have presented with wheezing during lower respiratory infection in early childhood in many follow-up studies, and this increased asthma risk seems to continue beyond puberty.[1] Four prospective cohort studies consisting of patients hospitalised for infection-associated wheezing in early childhood were started in Finland and Sweden in the 1980s and 1990s, and in these cohorts, outcomes have been published until 16–20 years of age.[2–5] At that age, doctor-diagnosed (or allergy-related) asthma was present in 30% of cases in three studies,[2,4,5] compared to 1%–5% of controls.[4,5]

Abbreviations: BMI, body mass index; CI, Confidence interval; OR, Odds ratio; RSV, respiratory syncytial virus.

Self-reported (or symptom-based) asthma was present in 39%–64% of cases,[2–5] compared to 9%–15% of controls.[3–5] Two of these research groups have published the results on clinical outcomes assessed at 27–30 years of ages.[6,7] Doctor-diagnosed asthma was present in 31% and 37% of cases, compared to 7% and 11% of controls, respectively.[6,7] Self-reported symptom-based asthma was present in 35.4% of cases, compared to 14.5% of controls.[7] Thus, about a third of the former patients hospitalised for infection-associated wheezing in early childhood presented with asthma in young adulthood.

Hospitalisation for wheezing in young childhood is usually associated with respiratory virus infection, mainly caused by respiratory syncytial virus (RSV) or rhinovirus,[1] and especially the role of rhinoviruses in the later development of asthma is highlighted.[8] This was also seen in the previous questionnaire and follow-up studies of this present cohort of originally 100 children hospitalised for their first episode of wheezing under 24 months of age. Within the cohort, self-reported asthma was more common after wheezing induced by rhinoviruses (83.3%) than after wheezing induced by RSV (47.6%) at the median age of 16.5 years.[5] Two years later 49 former wheezing patients and 60 controls attended a clinical visit, and self-reported doctor-diagnosed asthma was present in 64.3% after rhinovirus positive and in 42.9% after RSV positive episodes, and in 11.7% of controls.[9]

The aim of the present study was to investigate the occurrence of doctor-diagnosed and self-reported asthma in young adults after hospitalisation for their first episode of wheezing under 24 months of age, compared to population-based controls. In addition, we evaluated potential risk factors for asthma with a focus on current factors, such as weight, allergy and smoking, and RSV and rhinovirus identification during early-childhood hospitalisation.

Key Notes

- Asthma risk is increased after infection-induced wheezing in early childhood.
- The analyses of controlled questionnaire data, performed as part of the long-term prospective cohort study, showed that hospitalisation for infection-associated wheezing under age 24 months increased the risk of adulthood asthma over 2-fold at age 24–28 years independently from current confounders, such as overweight, smoking or allergic rhinitis.
- Studies after early-childhood wheezing need to be prospective and continue until adulthood.

2 | MATERIALS AND METHODS

2.1 | Design

One hundred children were hospitalised for the first infection-associated episode of wheezing at age younger than 24 months in 1992–1993 in Kuopio University Hospital, Finland,[10] and 92 of them participated in the prospectively scheduled follow-ups during 12 months after hospitalisation.[11] Later control visits were arranged in 1999 at the median age of 7.2 years,[12] and in 2004 at the median age of 12.3 years.[13] In 2008, 67 former bronchiolitis patients attended a post questionnaire study at the median age of 16.5 years,[5] and in 2010, 49 attended a clinical follow-up visit at the median age of 18.8 years.[9]

The present study was carried out in 2018, when the study subjects of the cohort were 24–28 years old. A structured questionnaire was sent to 95 of 100 former bronchiolitis patients with current address available, and 58 (61%), 35 males and 23 females, answered. Amongst the original patients, one had earlier declined future contacts and two had died.

For the present study, population-based controls, born like the cases in the primary area of Kuopio University Hospital and matched for gender and birth month, were obtained by a ratio of 4:1 for the 97 (70 males and 27 females) cases from the Population Register Center of Finland. The questionnaire was sent to 388 controls, and 100 (26%) of them answered. Since case-control analyses were not possible, all controls (60 males and 40 females) were included in the combined control group.

The data collected at the previously scheduled follow-ups of this cohort were not analysed in the present study, but instead, all analyses were based on the newly collected questionnaire data to ensure the comparability with the data of the controls. Data on virus aetiology associated with wheezing was an exception. RSV and five other respiratory viruses were studied by antigen detection during hospitalisation at younger than 24 months of age,[10,22] supplemented later by polymerase chain reaction for rhinoviruses in frozen samples.[12] None of the controls was hospitalised due to infection or wheezing under 24 months of age.

2.2 | Questionnaire data

The questionnaire was structured and modified from that used in the corresponding previous study phase.[5] The main modification was that active smoking was added. The questions concerned the presence of wheezing symptoms, prolonged (>4 weeks) cough apart from the infection, repeated night cough, nasal symptoms suggestive for allergic rhinitis and skin symptoms suggestive for atopic dermatitis. The presence of doctor-diagnosed asthma, the use of maintenance medication for asthma (inhaled corticosteroids or leukotriene antagonists), and the need of on-demand bronchodilator medication for wheezing or asthma were asked. Previous and current doctor-diagnosed asthma were recorded. The time when the asthma diagnosis was settled was asked and classified into two groups: during the preceding 24 months or more than 24 months ago. The presence of respiratory and skin symptoms and the use of asthma medication were recorded only for the

TABLE 1 Data on current weight status, smoking, asthma-presumptive symptoms and treatments for asthma collected at the median age of 26.5 years by posted questionnaires from 58 patients hospitalised for wheezing in early childhood and from 100 population controls

Current weight status, smoking, symptoms and treatments	Infection-induced wheezing group ($n = 58$)	Control group ($n = 100$)	OR (95% CI)
Body mass index >25 (kg/m^2)	32 (55.2%)	40 (40.0%)	1.79 (0.93–3.44)
Body mass index >30 (kg/m^2)	13 (22.4%)	18 (18.0%)	1.28 (0.58–2.86)
Current smoking	17 (29.3%)	22/99 (22.2%)	1.45 (0.69–3.04)
Wheezing symptoms	20 (34.5%)	14 (14.0%)	**3.23 (1.48–7.07)**
Prolonged cough	4 (7.7%)	9 (9.0%)	2.00 (0.75–5.33)
Night cough	2 (3.4%)	5 (5.0%)	0.68 (0.13–3.62)
Allergic rhinitis	28 (48.3%)	35 (35.0%)	**2.13 (1.10–4.12)**
Atopic dermatitis	15 (25.9%)	24 (24.0%)	1.17 (0.55–2.47)
Use of bronchodilators during last 12 months	15 (25.9%)	7 (7.0%)	**4.64 (1.76–12.19)**
Use of inhaled corticosteroids during last 12 months	7 (12.0%)	3 (3.0%)	**4.52 (1.12–18.26)**

Note: Logistic regression adjusted for age and sex.
Abbreviations:CI, confidence interval; OR, odds ratio.
Bold values are statistically significant.

preceding 12 months. The attendants were asked to estimate how many cigarettes they smoked daily, and the daily consumption of one or more cigarettes during the preceding 12 months was defined as current smoking. The attendants were requested to record their current weights and heights, which were used for the calculation of body mass indexes (BMI), and BMI >25 was considered as overweight and BMI >30 as obesity.

2.3 | Definition of asthma and allergy

Bronchial asthma was defined by two different ways reflecting the degree of certainty of the diagnosis.[14] (1) Current doctor-diagnosed asthma: either asthma diagnosed by a doctor during the preceding 24 months, or the use of maintenance medication for asthma during the preceding 12 months. (2) Current self-reported asthma: either a weekly use of on-demand bronchodilators, or asthma diagnosed by a doctor previously and the presence of asthma-presumptive symptoms during the preceding 12 months. Current doctor-diagnosed asthma was included. Previous asthma was defined as reporting of asthma diagnosed by a doctor earlier than 24 months ago, or as reporting maintenance medication for asthma earlier than 12 months ago.

The months when runny or stuffy nose occurred were recorded for the preceding 12 months. The calendar year was divided into four periods (spring from March to May, summer from June to August, autumn from September to November and winter from December to February). Rhinitis was regarded as allergic if nasal symptoms occurred apart from infection during the spring or summer times. Atopic dermatitis was considered if the subjects reported itching eczema in typical areas.

2.4 | Statistics

The data were analysed using the SPSS 25.0 statistical package (SPSS Inc.). Logistic regression adjusted for age and sex was used in the basic statistical analyses. In multivariate analyses comparing study versus control groups and asthma versus no-asthma groups, logistic regression was in addition adjusted for current smoking and overweight, and further for allergic rhinitis. The results are expressed as odds ratios (OR) and 95% confidence intervals (95% CI). When RSV positive and rhinovirus positive cases were analysed as risk factors for asthma, the assumption was that none of the controls had presented with wheezing induced by RSV or rhinovirus at age younger than two years.

2.5 | Ethics

This follow-up study was approved by Ethics Committee of Kuopio University and Kuopio University Hospital District. The participants accepted the use of the collected data by undersigning a specific permission form, posted with the study questionnaire.

3 | RESULTS

The median age of the 58 study subjects was 26.5 years and that of the controls was also 26.5 years. Thirty-six cases (62.0%) reported previous asthma in childhood, compared to 12.0% of 100 controls (OR 12.0, 95% CI 5.38–26.8). Early-childhood wheezing was associated with RSV infection in 14 (24.1%) and by rhinovirus infection in 10 (17.2%) cases. Five RSV positive cases but none of rhinovirus

positive cases were dual viral infections. By definition, none of the controls was hospitalised for virus-induced wheezing.

More than half of the subjects in the cohort (55.2%) were overweight (BMI >25) and 22.4% were obese (BMI > 30) (Table 1). The differences in overweight or obesity between cases and controls were not significant. Seventeen cases (29.3%) versus 22.2% of controls smoked (Table 1).

Twenty cases (34.5%) versus 14.0% of controls reported wheezing symptoms (OR 3.23), and 28 cases (48.3%) versus 35.0% of controls reported symptoms of allergic rhinitis (OR 2.13) (Table 1). Instead, there were no significant differences between cases and controls in reporting of prolonged cough, night cough or atopic dermatitis (Table 1).

Weekly use of bronchodilators was more common (25.9%) in cases than in controls (7.0%, OR 4.6), as was the use of inhaled corticosteroids during the last 12 months (12% vs. 3.0%, OR 4.5) (Table 1).

Six cases (10.3%) had doctor-diagnosed asthma compared to 5.0% of the controls ($p = 0.22$), and the difference changed to significant in analyses adjusted for current overweight, smoking and allergic rhinitis (Table 2). The respective figures for self-reported asthma were 21 (36.2%) versus 11.0% ($p = 0.001$), and the difference between cases and controls remained significant in adjusted analyses (Table 2). Thus, the risk of self-reported asthma in adulthood after hospitalisation for wheezing in early childhood was about threefold compared with population-based controls and early-childhood hospitalisation for infection-associated wheezing was a significant risk factor of asthma independently from overweight, smoking and allergic rhinitis. The risk of self-reported asthma was 1.25-fold (95% CI 0.33–4.55), when early-childhood wheezing was associated with RSV, 1.72-fold (0.36–8.14) when associated with RSV alone, and 1.15-fold (0.24–5.53) when associated with rhinovirus.

When the cases and controls were combined, altogether 31 subjects presented with self-reported asthma, and they differed from those 127 without self-reported asthma in the presence of previous asthma, current overweight (BMI >25) and symptomatic allergic rhinitis during the last 12 months (Table 3). Eleven cases had doctor-diagnosed asthma, which was a too-low figure for any risk factor analyses.

4 | DISCUSSION

There are four main results in this prospective long-term follow-up study on asthma at the median age of 26.5 years after hospitalisation for infection-associated wheezing under 2 years of age. First, self-reported asthma was three-fold more common in early-childhood wheezers than in matched population controls. Doctor-diagnosed asthma was also more common, but the figures were too small for reliable conclusions. Second, wheezing symptoms and symptoms of allergic rhinitis during the last 12 months were more common in cases than in controls. Thus, the former wheezing patients were prone to respiratory allergy still in adulthood. Third, the finding that infection-induced wheezing in early childhood was associated with asthma in young adults was robust to adjustments with current smoking, overweight and allergic rhinitis. This means that hospitalisation for infection-induced wheezing in early childhood was an independently significant risk factor for asthma in adulthood. However, RSV or rhinovirus identifications during hospitalisation in early childhood were not anymore associated with asthma risk in adulthood.

Two previous prospective studies have been published on follow-up after hospitalisation for wheezing continuing until 25–30 years of age.[6,7] In the Swedish study, current doctor-diagnosed asthma was found in 36.6% of 82 former early-childhood wheezers

TABLE 2 The risk of asthma in young adults after hospitalisation for wheezing in early childhood, compared by multivariate logistic regression to population controls without early-childhood wheezing history

Definition of asthma	Infection-induced wheezing group ($n = 58$)	p	Control group ($n = 100$)
Current doctor-diagnosed asthma	6 (10.3%)	0.220[d]	5 (5.0%)
OR (95% CI)[a]	1.66 (0.73–3.79)		1.00
OR (95% CI)[b]	2.00 (0.52–7.65)		1.00
OR (95% CI)[c]	**7.45 (1.49–37.24)**		1.00
Current self-reported asthma	21 (36.2%)	0.001[d]	11 (11.0%)
OR (95% CI)[a]	1.11 (0.64–1.94)		1.00
OR (95% CI)[b]	**3.09 (1.22–7.78)**		1.00
OR (95% CI)[c]	**3.15 (1.43–8.59)**		1.00

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Logistic regression adjusted for age and sex.

[b]Logistic regression adjusted for age, sex, overweight and smoking (yes, no).

[c]Logistic regression adjusted for sex, age, overweight, smoking and allergic rhinitis (yes, no).

[d]p with logistic regression adjusted for age and sex.

Bold values are statistically significant.

TABLE 3 Questionnaire data in 31 young adults with current self-reported asthma (doctor-diagnosed included), when the cases and controls were combined, compared with those 127 without asthma

Questionnaire data	Current self-reported asthma ($n = 31$) n (%)	No asthma ($n = 127$) n (%)	OR (95% CI)[a]
Previous asthma	28 (90.3)	21 (16.5)	**35.0 (11.0–111.5)**
Allergic rhinitis	27 (87.0)	43 (33.9)	**3.49 (1.52–7.98)**
Atopic dermatitis	14 (45.2)	27/126 (21.3)	2.28 (0.96–5.41)
Body mass index >25 (kg/m^2)	23 (74.2)	52/124 (40.9)	**3.30 (1.39–7.79)**
Body mass index >30 (kg/m^2)	8 (25.8)	24/124 (18.9)	1.33 (0.51–3.52)
Current smoking	12 (38.7)	31/126 (24.4)	1.07 (0.43–2.65)

Note: For definition, see the text.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Logistic regression adjusted for sex and age.

Bold values are statistically significant.

at the mean age of 27.0 years, compared with 6.8% of the controls.[6] In the Finnish study, current doctor-diagnosed asthma was found in 31.3% and self-reported asthma in 35.4% of 48 former early-childhood wheezers at the mean age of 29.5 years, compared with 10.9% and 14.5% of the controls, respectively.[7] The present figure of 10.3% for doctor-diagnosed asthma was lower, but that of 36.2% for self-reported asthma was rather similar to the figures of the two previous studies.[6,7] These differences may reflect the criteria of doctor-diagnosed asthma, which were strict in our study, mainly based on regular use of maintenance medication for asthma. In addition, our study was a pure questionnaire study, and so, we were not able to diagnose asthma in study subjects who, as seen in the answers in the questionnaires, often presented with asthma-presumptive symptoms. For example, 34.4% of the former early-childhood wheezers reported wheezing symptoms during the last 12 months. In a previous Finnish follow-up study after early-childhood wheezing, one-third of young adults with asthma were without asthma diagnosis, and even half of the asthma diagnoses were done at the control visit.[2] It is well known that young adults underestimate their symptoms, when compared, for example with lung function results.[15]

Exposure to tobacco smoke, overweight and allergic rhinitis are well-known risk factors of asthma in children and adults. Exposure to tobacco smoke is a risk factor of hospitalisation for childhood wheezing, and therefore, the confirmation of the role of early-life exposure in the development of later asthma may not be successful in within-the-group analyses, as was seen also in the present cohort.[5,9,12,13] In the Swedish cohort, maternal and paternal, or prenatal and post-natal smoking, increased later asthma risk via different pathways[16]: maternal smoking via increased bronchial reactivity and paternal smoking via an increased probability to start active smoking in adolescence. Obesity-associated asthma maybe even a distinct phenotype of asthma, presenting from puberty onwards.[17,18] Allergic rhinitis and asthma in children are so closely associated, that some researchers have formatted a hypothesis of united airways combining respiratory allergy, bronchial reactivity and asthma.[19,20]

Since the first observation on the link from rhinovirus-induced wheezing in infancy to emergence of childhood asthma in 2003,[13] the role of rhinoviruses in bronchiolitis, early-childhood wheezing and subsequent asthma has been well documented.[8,21,22] In a large American post-bronchiolitis cohort, rhinovirus increased later asthma risk only with presence of concomitant atopic sensitization.[23] In the present study, rhinovirus findings in early childhood were not anymore significant risk factors of adulthood asthma, although such association was seen in the earlier phases of the follow-up.[12,13]

A long-term follow-up until the median age of 26.5 years after hospitalisation for wheezing in early childhood and the current design including matched population-based controls were the main strengths of this cohort study. However, there are some limitations also. Firstly, the drop-out rate of 40% between study participants was high but understandable due to the long, over 25 years follow-up time. Persistence of asthma or asthma symptoms could be the reason to participate in this questionnaire study, meaning that the reported incidence of asthma was higher than the actual incidence is in similar high-risk populations. Secondly, only 26% of the invited controls attended. This raises a question, whether the control group was biased, including more symptomatic individuals than the background population in question. However, such bias more likely decreases than increases the differences between cases and controls. Against these worries, the detection rates of asthma were not higher than in other similar cohort studies in either cases or controls, and in addition, a participant of a questionnaire study does not receive any healthcare services. Since the main outcomes, doctor-diagnosed and self-reported adulthood asthma, were rather rare, the power of the study was not enough to reveal all available differences between the groups.

5 | CONCLUSION

This prospective controlled cohort study including participants hospitalised for infection-associated wheezing under the age of two years confirmed the earlier result observed in two respective cohort studies, that early-life infection-associated wheezing increases the asthma risk at least until 25–30 years of age.[6,8] In the present cohort, the risk was about three-fold compared to population-based controls, and the result could be confirmed in adjusted analyses. Thus,

the increased risk was independent from current confounding factors, such as allergic rhinitis, tobacco smoking and overweight.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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