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REVIEW ARTICLE

Asthma and Lung Function in Adulthood After Early-Childhood Wheezing

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ABSTRACT

The risk of asthma and lung function reduction is increased in children who have presented with wheezing associated with respiratory tract infection in early childhood. Three prospective cohort studies consisting of patients hospitalized for infection-associated wheezing at <24 months of age, which started in Finland and Sweden in the 1980`s and 1990`s, have reported outcomes at >25 years of age. These three cohorts are even globally the only cohorts consisting of early-childhood wheezers followed prospectively until adulthood. Initially, the studies were not controlled, and the risk of asthma and reduced lung function and the risk factors in question were assessed by analyses within the cohorts. Matched population-based controls without wheezing history in early childhood were recruited for the studies in adulthood. One follow-up included only questionnaire data without lung function results. Two studies included control visits, and one of them presented clinical and lung function data, and the other clinical and bronchial reactivity data. Respiratory syncytial virus was identified on admission in all three post-wheezing cohorts, and rhinoviruses in the newest cohort from the 1990`s.

The present narrative review summarizes data on asthma and lung function reduction in adults aged >25 years after hospitalization for wheezing at age <24 months compared to population-based controls in the three until now published prospective post-wheezing cohorts. The frequency of doctor-diagnosed asthma varied from 10.3% to 36.6%, and that of self-reported symptom-based asthma from 35.4% to 40.7%. The differences between cases and controls were significant and robust to adjustments with current smoking and allergic rhinitis, which were associated with asthma in all cohorts. One cohort study reported lung function results, and both baseline and post-bronchodilator forced expiratory volumes were lower in cases than in controls. About 10-15% of former early-childhood wheezers presented with irreversible lung function reduction characteristic to chronic obstructive lung disease. Family asthma was associated with current asthma, but other early risk factors, with exception of blood eosinophilia in one cohort, were not anymore predictive.

In conclusion, hospitalization for infection-associated wheezing at <24 months of age was an independently significant risk factor of asthma in adults at >25 years of age.

Introduction

The risk of asthma has been increased in children who have presented with wheezing during lower respiratory tract infection in early childhood, and this increased asthma risk has continued beyond puberty [1,2]. Three prospective cohort studies consisting of patients hospitalized for infection-associated wheezing at <24 months of age, which started in Finland and Sweden in the 1980`s and 1990`s, have reported clinical and lung function outcomes until >25 years of age [3-7]. These are the only thus far published cohorts consisting of early-childhood wheezers followed prospectively from the wheezing episode until adulthood. The outcomes of these cohorts in adolescence at 10-18 years of age were summarized in two previous reviews [1,2].

Initially, these studies were not controlled, and the risks of asthma and reduced lung function, as well as the predictive factors, were assessed by analyses within the cohorts. Matched population-based controls without wheezing or hospitalization histories at <24 months of age were recruited for the adulthood follow-ups of the studies [3-7]. One of the cohorts comprised only questionnaire data [7], which means that lung function measurements were not available and new asthma diagnoses could not be done by the researchers. Two cohorts included control visits, and one of them presented both clinical and lung function data [4,5], and the other clinical and bronchial reactivity data [6].

Respiratory syncytial virus (RSV) and rhinoviruses predominate in the triggers of early-childhood wheezing. RSV was identified on admission at <24 months of age by antigen or antibody assays in all three cohorts [3-6] and rhinoviruses by genome detection in one cohort [7].

The present narrative review aims to summarize the available data on asthma and lung function reduction in adults aged >25 years, who were hospitalized for wheezing at <24 months of age, in three until now published prospective post-wheezing cohorts. Birth cohorts and retrospective reports were not included in this review. In addition, potential early-life, previous childhood and current adulthood risk factors for asthma are evaluated, including RSV and rhinovirus identifications on admission for early-childhood wheezing.

Wheezing in childhood – definitions

Early-childhood infection-associated wheezing, which is in the focus of the present review, consists of a heterogeneous group of clinical conditions, such as bronchiolitis, wheezy (wheezing) bronchitis, transient wheezing, and even first episodes of early-onset asthma. Bronchiolitis starts as acute upper respiratory tract infection which spreads to lower airways, and symptoms progress to cough, rapid breathing, chest retractions, and crackles or wheezes on auscultation [8,9]. The diagnosis of bronchiolitis has usually been limited to the first-time wheezing episode, and the upper age limit has been 12 months in Europe and 24 months in America [8,9]. Infants diagnosed with bronchiolitis during the first year of life differ from those diagnosed at a later age for clinical characteristics, viral findings, and immediate and later outcomes, although there is a grey area before and after 12 months of age [10]. In Europe, repeated wheezing at age <12 months and first wheezing at age >12 months have been called as wheezy (wheezing) bronchitis. In America, repeated wheezing at age <24 months and first wheezing at age >24 months have been called as transient wheezing if stopped before 36 and persistent wheezing if continued after 36 months of age, based mainly on birth cohort data [2,11,12]. The criteria of asthma in early childhood vary between different countries, mainly because of different health care and health insurance systems.

Outcome after early-childhood wheezing at 17-20 years of age

Asthma

Two reviews on outcomes after early-childhood wheezing, published in 2008-2009, contained the results of the Kuopio 1981-1982 and Gothenburg 1983-1984 cohorts until 17-20 years of age [1,2,13-15]. At that time, these two cohorts were the only prospectively until late adolescence / young adulthood followed cohorts after early-childhood wheezing. Data from the Kuopio 1992-1993 cohort, which allowed separate evaluation of RSV and rhinovirus positive cases [16], and the Swedish post-bronchiolitis cohort, which consisted of children hospitalized for RSV bronchiolitis at <12 months of age, were published later [17]. In the cohorts consisting of early-childhood wheezers, in line with birth cohorts and studies on natural history of childhood asthma [12,18,19], the prevalence of symptomatic childhood asthma gradually decreased until early school age reaching at that age a plateau which continued until puberty [1,2,16,17].

As summarized in the previous reviews [1,2], the prevalence of doctor-diagnosed asthma at 17-20 years of age was 30% in the Kuopio 1981-1982 cohort from Finland [1,13] and 43% in the Gothenburg 1984-1985 cohort from Sweden [1,14]. The numbers of early-childhood wheezers attending the study at 17-20 years of age were 67-81%, respectively,

which means that a third or less dropped out during the long follow-up of nearly 20 years. In the Finnish Kuopio 1981-1982 cohort, the prevalence of self-reported asthma was 41% [13], which was close to the corresponding Swedish figure for doctor-diagnosed asthma, confirming that the results on asthma prevalence are highly dependent on study designs and definitions. The figures mean, when compared with earlier phases of the studies [1], that asthma relapses were common during or following puberty even after many symptom-free years. Interestingly, a third of asthma diagnoses in the Kuopio 1981-1982 cohort were done at the 17-20 years control visit consisting of doctoral interview and examination, and home peak flow monitoring and methacholine inhalation challenge test [1,13].

The results of the Finnish 1992-1993 cohort at the median age of 16.5 years [16], were published after the above-mentioned reviews [1,2]. In the questionnaire study, 30% of 67 former early-childhood wheezers reported doctor-diagnosed asthma, compared to 5% in 155 population-based controls with no wheezing or hospitalization history at <24 months of age [16]. The respective figures for self-reported asthma were 64% and 11%. The risk of self-reported asthma was 13 times higher after RSV-induced and 44 times higher after rhinovirus-induced wheezing compared to controls [16]. Two years later, 49 cases and 60 population-based controls attended a clinical follow-up study [20]. Doctor-diagnosed asthma was present in 64% of those with rhinovirus-induced wheezing and in 43% of those with RSV-induced wheezing at <24 months of age, compared to 12% in controls.

In addition to the three cohorts after wheezing at <24 months of age, two cohorts have reported clinical and lung function outcomes at on average 18 years of age after bronchiolitis at <12 months of age [17,21]. These cohorts, although wheezing is not essential for the diagnosis of bronchiolitis, are shortly reviewed and discussed when appropriate.

The Swedish post-bronchiolitis cohort consisting originally of 47 subjects hospitalized for RSV bronchiolitis at <12 months of age and 93 controls recruited in infancy were re-examined at 18 years of age, and nearly all, 46 and 92 respectively, attended [17]. The prevalence of asthma and/or repeated wheezing in young adulthood (39%) was higher in former bronchiolitis patients than in controls (9%). The respective figures for sensitization to seasonal allergens were 40% and 14%, which suggests that the risk of allergic asthma was increased after RSV bronchiolitis.

The Norwegian cohort enrolled 225 young adults aged 17-20 years, who had been hospitalized for bronchiolitis in infancy at <12 months of age, and in addition 167 matched population-based controls [21]. In the cohort, 131 had attended a control study at 11 years of age, but no follow-ups were performed between that visit and the current study. The follow-up in young adulthood consisted of questionnaires for asthma and examinations of lung function, but no doctoral examinations allowing new asthma diagnoses were done [21]. Thus, asthma diagnoses were doctor-diagnosed but self-reported by the questionnaires. Current asthma was more frequent (25%) in the post-bronchiolitis group than in the control group (13%). RSV had been routinely identified by antigen detection on admission in infancy, and asthma prevalence did not differ between RSV-positive and RSV-negative groups.

Lung function

The reviews summarizing outcomes after early-childhood wheezing at 17-20 years of age after wheezing at age <24 months included lung function results of the Kuopio 1981-1982 cohort from Finland [1,2,12], and the results of the respective Gothenburg 1984-1985 cohort from Sweden were published later [15].

The Finnish cohort study reported baseline spirometry, but post-bronchodilator spirometry and bronchodilation tests were not studied [13]. All parameters for forced expiratory flows, such as forced expiratory flow in one second (FEV1), FEV1/forced vital capacity (FVC), mid-expiratory flows at 50% (MEF50) and at 25% (MEF25) of FVC were, when analyzed as continuous variables, lower in 53 cases than in 45 controls [13]. On average, however, lung function parameters were within normal limits in both cases and controls. Baseline spirometry was abnormal in 36% in the post-wheezing group, when the criterion was an abnormal value in any parameter, and also MEF50 and MEF25 were included [13]. Hyper-responsiveness to methacholine was present in 41%, when also mild findings were included [13]. The respective figures were 21% and 11% in controls followed from birth as part of another study. These controls were highly selected since they were, at the time of enrollment during the first week of life, recruited from families without any asthma or allergy history, which may have increased the differences between cases and controls. Bronchodilation tests and post-bronchodilator measurements were not done, which means that we do not know, how common were permanent lung function deficiencies.

The Swedish cohort study included spirometry and bronchodilation test, and so, also post-bronchodilator results were available [15]. FEV1/FVC and MEF50 were lower in 55 early-childhood wheezers than in 82 population-based controls both before and after bronchodilator administration. FVC and FEV1 did not differ between cases and controls, and MEF25 was not measured. Lung function reduction was most evident in females who presented with current asthma but reduced pre-bronchodilator FEV1/FVC was also seen in symptom-free cohort subjects more often than in controls [15].

The control visit of the Kuopio 1992-1993 cohort at 17-20 years of age included spirometry and bronchodilation test, and so, also post-bronchodilator results were available [20]. FVC, FEV1 and FEV1/FVC did not differ between 49 former early-childhood wheezers and 60 population-based controls either before or after bronchodilator administration. Baseline MEF50 was, on average, significantly lower in cases than in controls as an only significant difference between the groups. Categorized data on how many cases or controls had irreversible bronchial obstruction, were not published.

In the Kuopio 1992-1993 cohort, lung function at 17-20 years of age could be evaluated in relation to the causative agent of early-childhood wheezing. Fourteen rhinovirus-positive cases presented with significantly higher FEV1, FEV1/FVC and MEF50 responses to bronchodilators than 60 controls, and 14 RSV-positive cases presented with significantly lower pre-bronchodilator FVC [20]. The results suggest that RSV and rhinoviruses may modify the airways through different mechanisms during early-childhood infections.

The Swedish post-bronchiolitis cohort study, which consisted of RSV-positive cases hospitalized at <12 months of age, reported lung function results at 18 years of age [17]. The results of spirometry were given only as continuous variables. Both baseline and post-bronchodilator FEV1, FEV1/FVC and forced expiratory flow (FEF) at 25-75% of FVC were lower in the former RSV bronchiolitis patients than in controls. Likewise, the FEV1 responses to bronchodilator administrations were greater in cases [17]. Overall, lung function was reduced in study subjects with or without current asthma, but not in asthmatic controls [17].

The Norwegian post-bronchiolitis cohort, which consisted of RSV-positive and RSV- negative cases hospitalized at <12 months of age, reported lung function results at 18 years of age [21]. Lung function results were reported as continuous parameters, and baseline and post-bronchodilator FEV1, FEV1/FVC and FEF25-50 were lower in the 114 former bronchiolitis patients than in 139 controls, without any significant differences between the original RSV and non-RSV cases [21]. Categorized data were not presented, which means that the occurrence of permanent or irreversible lung function reduction after infant bronchiolitis could not be estimated.

Outcome after early-childhood wheezing at 27-30 years of age

Cohorts

Basic data of the three prospective follow-up studies from hospitalization for wheezing at <24 months of age to adulthood at >25 years of age, which are summarized in this review, are presented in Table 1. The oldest cohort, Kuopio 1981-1982 cohort from Finland, was investigated at 27.3 (median) years of age first in a questionnaire study [3] and at 29.5 (median) years of age in a clinical study [4,5], and 73% and 58% of the subjects recruited at <24 months of age attended, respectively (Table 1). Originally, 53% of the 81 children were younger than 12 months, 73% were first-time wheezers, and RSV was identified by antigen or antibody assays in 40% of wheezing episodes [22]. Population-based controls without any early-life wheezing or hospitalization history were recruited for the study in adulthood.

Table 1. Basic data of the three prospective follow-up studies from hospitalization for wheezing at <24 months of age until adulthood at >25 years of age.

Study characteristics	Kuopio 1981-1982 cohort	Kuopio 1981-1982 cohort	Gothenburg 1984-1985 cohort	Kuopio 1992-1993 cohort
Design	Posted questionnaires in 2008	Clinical control visits in 2010	Clinical control visits in 2009-2011	Posted questionnaires in 2018
Study group on admission	81 children*	81 children*	101 children	100 children
Age <12 months	43(53%)*	43(53%)*	Not reported&	67(67%)
First-time wheezers	60(72%)*	60(72%)*	57(56%%)	87(87%)
Respiratory syncytial virus	32(40%)*	32(40)*	28(28%)	25(25%)
Study group at follow-up	59(73%) adults	48(58%) adults	82(82%) adults	58(63%) adults
Age at follow-up	Median 27.3 years	Median 29.5 years	Median 27.0 years	Median 26.5 years
Controls#	104 adults	138 adults	1,210 adults$	100 adults

* The same cohort; # Unselected population-based controls matched for age, sex and living area, no follow-up; &Median age 7 months; $ Questionnaire data alone available

The Gothenburg 1984-1985 post-wheezing cohort from Sweden was investigated at 27.0 (median) years of age by questionnaires, interviews, and bronchial responsivity tests [6], and 82% of the cohort recruited at <24 months of age attended the study (Table 1). Originally, 56% were first-time wheezers, and RSV was identified by antibody tests in 28% of wheezing episodes [22]. The number of infants younger than 12 months of age was not reported, but the median age of the cohort on admission was 7 months [23]. Interestingly, as many as 1210 unselected population-based adults recruited for another study were exploited also in this post-wheezing study.

The newest Kuopio 1992-1993 post-wheezing cohort from Finland was investigated at 26.5 (median) years of age by using postal questionnaires only [3], and 63% of the cohort recruited at <24 months of age attended the study (Table 1). Originally, 67% of children were younger than 12 months, 87% were first-time wheezers, and RSV was identified by antigen or antibody assays in 25% of wheezing episodes [24]. Intentionally, the cohort was collected between two major epidemics of RSV infections. Rhinoviruses were later studied by polymerase chain reaction in frozen samples and were identified in 33% of cases [25]. Population-based controls without any early-life wheezing or hospitalization history were recruited for the study in adulthood.

Asthma

The occurrence of asthma after early-childhood wheezing in adulthood at >25 years of age in the Kuopio 1981-1982 post-wheezing cohort from Finland was investigated by postal questionnaires and clinical follow-up visits two years apart [3,4]. In the questionnaire study, 20% of 59 early-childhood wheezers reported doctor-diagnosed asthma and 41% self-reported asthma, the figures being 5 to 12 times higher than in population-based controls without early-childhood wheezing or hospitalization histories (Table 2). In multivariate analyses, odds ratios (OR) were 5.2 and 12.2, respectively [3]. In the clinical study two years later, 31% of 48 early-childhood wheezers had doctor-diagnosed asthma and 35% self-reported asthma, the figures being 1.5-3 times higher than in controls (Table 2). The higher prevalence of doctor-diagnosed asthma in the clinical study, compared with the prevalence in the questionnaire study, comes from those asthma diagnoses, which were done at the control visit [4]. In the questionnaire study, multivariate analyses were adjusted for allergic rhinitis, and in the clinical study, for smoking and allergic rhinitis.

Table 2. Asthma in adults at >25 years of age after hospitalization for wheezing at <24 months of age.

Outcome	Kuopio 1981-1982 cohort, questionnaire study (N=59)	Kuopio 1981-1982 cohort, clinical study (N=48)	Gothenburg 1984-1985 cohort, clinical study (N=82)	Kuopio 1992-1993 cohort, questionnaire study (N=58)
Doctor-diagnosed asthma	12(20.3%) vs. 5(4.8%) OR 5.2(1.7-15.8)*	15(31.3%) vs. 15(10.9%) in controls *P* 0.002#	30(36.6%) vs. 76(6.8%) in controls OR 7.9(4.8-13.1)$	6(10.3%) vs. 5(5.0%) in controls OR 7.5(1.5-37.2)&
Self-reported asthma	24(40.7%) vs. 7(6.7%) OR 12.2(4.4-33.7)*	17(35.4%) vs. 5(22.7%) in controls *P* 0.003 #	Not reported	21(36.2%) vs. 11(11.0%) in controls OR 3.15(1.4-8.6)&

OR, Odds ratio; CI, Confidence interval; * OR (95% CI) adjusted for age, sex, and allergic rhinitis; # *P* value adjusted for age, sex, smoking and allergic rhinitis; $ OR (95% CI) adjusted for age, sex, family asthma, smoking, and allergic rhinitis; & OR (95%CI) adjusted for age, sex, and allergic rhinitis

When 40 subjects hospitalized for RSV-induced wheezing were compared with 80 controls in subgroup analyses, the risk of self-reported asthma was 11.4 times higher in the RSV group comparted to controls [26]. When 48 subjects hospitalized originally for wheezing infection and those 22 hospitalized for non-wheezing viral pneumonia were analyzed jointly, self-reported asthma at age >25 years was associated with history of early-childhood wheezing, whereas lower quality of life at age >25 years was associated with history of non-wheezing pneumonia [27]. The powers of these supplementary analyses were not sufficient to evaluate respective associations with doctor-diagnosed asthma.

In the Gothenburg 1984-1985 post-wheezing cohort from Sweden, 37% of 82 early-childhood wheezers had doctor-diagnosed asthma in adulthood at >25 years of age, the figure being 5.3 times higher than in controls (Table 2). Multivariate analyses were adjusted for smoking and allergic rhinitis and adjusted OR for doctor-diagnosed asthma was 7.9. Self-reported asthma was not studied (Table 2).

In the Kuopio 1992-1993 cohort from Finland, 10% of the 58 early-childhood wheezers attending the study at >25 years of age presented with doctor-diagnosed asthma and 36% with self-reported asthma, the figures being 2-3.5 times higher than in controls (Table 2). The data were collected by postal questionnaires. Multivariate analyses were adjusted for allergic rhinitis and adjusted OR was 7.5 for doctor-diagnosed asthma and 3.2 for self-reported asthma, respectively [3].

In all three reviewed cohorts, hospitalization for infection-associated wheezing at <24 months of age was a significant risk factor of asthma at >25 years of age in analyses adjusted for allergic rhinitis, which confirmed that early-childhood wheezing was a significant predictor for asthma >25 years later independently from allergy, which often co-existed with asthma.

Lung function

Lung function results in former early-childhood wheezers at 27-30 years of age have been published from the Finnish 1981-1982 post-wheezing cohort (Table 3). Baseline and post-bronchodilator spirometry was performed by 47 study subjects and 138 population-based controls matched by sex, age and birth area. When analyses were done using continuous variables, FVC, FEV1 and FEV1/FVC were all lower in cases than in controls in both baseline and postbronchodilator measurements [5]. The analyses were adjusted for current asthma and daily smoking. Interestingly, evidence was found that there are young adults who have irreversible bronchial obstruction at 27-30 years of age after hospitalization for wheezing in early childhood (Table 3). Post-bronchodilator FEV1 was pathological, <88% of predicted, in 21% of cases and 4% of controls (OR 5.6, 95%CI 1.7-18.2) [5]. Likewise, using the currently available international criteria based on reductions defined by standard deviations in the population, 15% of cases and 1% of controls had FEV1/FVC <5th percentile (OR 7.1, 95%CI 1.3-37.2) [5]. Thus, 15% of former early-life wheezers presented lung function reduction which fulfilled the lung function criteria of chronic obstructive pulmonary disease (COPD) before the age of 30 years, although symptoms presumptive for COPD disease were not present.

Table 3. Lung function in adults at >25 years of age after hospitalization for wheezing or respiratory syncytial virus infection at <24 months of age.

Lung function parameter	Kuopio 1981-1982 cohort, wheezing infections (N=47)	Kuopio 1981-1982 cohort, RSV infections (N=42)
Pre-bronchodilator		
FVC	98(94-101), p=0.025	98(95-101), p=0.078
FEV1	86(83-90), p<0.001	87(83-91), p<0.001
FEV1/FVC%	89(86-92), p<0.001	89(86-91), p<0.01
Post-bronchodilator		
FVC	98(94-101), p=0.026	98(95-101), p=0.089
FEV1	90(87-93), p<0.001	91(87-95), p<0.001
FEV1/FVC%	93(90-95), p<0.001	93(91-95), p<0.001
FEV1 response	4.1(35-52), p=0.603	3.7(3.1-62), p=0.358

Statistics: Means (95% confidence intervals), p-values vs. controls by Analysis of Co-variance, adjusted for age, sex, current smoking and current asthma (Wheezing cohort) or current allergic rhinitis (RSV cohort).

When 43 subjects hospitalized for either RSV-induced wheezing or RSV pneumonia were studied jointly in subgroup analyses, both pre-bronchodilator and post-bronchodilator FEV1 and FEV1/FVC were, on average, lower in cases than in controls [28]. However, the figures on how many had reduced values in spirometry were not presented. Likewise, the results were not given separately for subjects in the RSV-induced wheezing and RSV pneumonia groups. The results show that hospitalization for RSV infection of lower respiratory tract in early childhood was associated with an increased risk of permanent reversible and irreversible obstructive lung function reduction in adulthood.

Risk factors

As summarized previously [1,2], asthma and atopy in the family, parental smoking, female gender, blood eosinophilia, wheezing induced by other viruses than RSV and repeated wheezing at <24 months of age were significant predictors of asthma at 17-20 years of age in the Finnish and Swedish prospective post-wheezing cohorts. Interestingly, atopy in wheezing <24 months old children, such as atopic dermatitis, increased immunoglobulin E (IgE) or presence of specific IgE, which predicted asthma risk at 6-13 years of age [29,30], were not anymore significant predictors of asthma at 17-20 years of age [1,2]. In the Swedish post-bronchiolitis cohort, which consisted of RSV-positive cases, high blood eosinophils on admission were the only early-life risk factor for asthma at 18 years of age [19]. In the recently published Norwegian post-bronchiolitis cohort, previous asthma ever was the only childhood factor that predicted asthma at 18 years of age [21].

There is wide consensus that passive smoking and respiratory virus infections in early childhood are associated with the risks of wheezing, subsequent and repeated wheezing, and later emergence of asthma [31,32]. However, controlling of passive smoking and that of exposures to different viruses in early childhood are difficult in long-term follow-ups. In line, the number of respiratory episodes in the first years of life, but not any particular viral trigger, was associated with later asthma in a Danish high-risk cohort [33].

Studies after early-childhood wheezing have often failed to show an association between early-life exposure to tobacco smoke and subsequent wheezing or later asthma, evidently because parental smoking predisposes young children to both infections, wheezing during infection and hospitalization for wheezing [1,2]. In the Swedish Gothenburg 1984-1985 post-wheezing cohort, prenatal and postnatal early-life maternal smoking led to bronchial hyper-responsiveness and further to asthma at the age of 17-20 years [15,34]. Instead, paternal smoking increased the risk of active smoking in adolescence, which further increased the risk of asthma. In the Finnish Kuopio 1981-1982 post-wheezing cohort, passive smoking in early life was associated with an increased risk of reduced lung function at 17-20 years of age [13].

The long-term influence of wheezing-associated viruses could be evaluated in the Finnish Kuopio 1992-1993 cohort, since both RSV and rhinoviruses were studied, and their frequencies were rather equal [25]. In the analyses within the cohort, asthma was more common at 5-7 years of age after early-childhood wheezing induced by rhinoviruses compared to those induced by RSV [25], but not anymore at 11-13 years of age [30]. The obvious reason for the lost significance by time was lower power in the analyses due to drop-outs, and in addition, other risk factors the study subjects faced during long-term follow-ups diluted the effects of early-childhood factors.

Table 4 summarizes early-life, previous childhood, and current adulthood risk factors for asthma at >25 years of age in the three Finnish and Swedish cohorts prospectively followed from hospitalization for wheezing at <24 months of age. The results are dependent on the strategies of the analyses, that is whether potential risk factors were compared between asthmatics and non-asthmatics within the cohort, or between asthmatics in the cohort and controls.

Table 4. Early, childhood and current risk factors of asthma and lung function reduction in adults at >25 years of age after hospitalization for wheezing at <24 months of age in three prospective studies. Only statistically significant risk factors are presented.

Cohort **Outcome**	**Risk factor**	**Risk level** **OR (95%CI)**
Kuopio 1981-1982 cohort, clinical study Self-reported asthma N=17/48		
	Repeated wheezing at age 1-2 years	3.2 (1.1-16.8)¤
	Blood eosinophils low on admission$	0.2 (0.05-0,70)¤
	Blood eosinophils high on convalescence£	6.1 (1.2-31.8)¤
Kuopio 1981-1982 cohort, questionnaire study Self-reported asthma, N=24/59		
	Asthma in parents	2.6 (1.0-6.9)^
	Asthma in siblings	7.5 (2.8-20.2)^
	Current smoking	4.0 (1.5-10.5)^
	Current allergic rhinitis	2.7 (1.0-6.8)^
	Previous asthma	In all 24 cases
Gothenburg 1984-1985 cohort, clinical study Doctor-diagnosed asthma, N=30/82		
	Female gender	2.7 (1.1-6.8)*
	Family asthma	3.9 (1.5-10.4)*
	Previous asthma	6.5 (2.4-17.7)*
	Current allergy#	9.6 (2.9-31.5)*
	Allergic rhinitis&	2.6 (1.0-6.6)*
Kuopio 1992-1993 cohort, questionnaire study Self-reported asthma, N=31/158		
	Previous asthma	35.0(11.0-111.5)**
	Current allergic rhinitis	3.5 (1.5-8.0)**
	Overweight	2.3 (1.4-7.8)**

¤Adjusted for current daily smoking, versus non-asthmatic within the cohort; ^Adjusted for age and sex, versus population-based controls; *Non-adjusted analyses, compared to non-asthmatics within the cohort; only allergy was significant in adjusted analyses; **Current asthmatics vs. non-asthmatics, cases and controls combined; $<0.25x10^9 cells/L on admission; the protective effect was robust to adjustments with age, gender, current smoking, and atopy in infancy; £<0.25x10^9 cells/L on convalescence (4-6 weeks); the risk-increasing effect was robust to adjustments with age, gender, current smoking, and atopy in infancy; #Atopic sensitization plus rhinitis, conjunctivitis or eczema; &Doctor-diagnosed cases only included.

In the questionnaire study of the Finnish Kuopio 1981-1982 post-wheezing cohort at the median age of 27.3 years, asthma in parents or in siblings, current smoking, current allergic rhinitis, and previous asthma were significant risk factors for self-reported asthma (doctor-diagnosed asthma included) when compared with population controls [3]. However, the power of the study was not enough to show similar associations for doctor-diagnosed asthma, and not to analyze the differences between asthmatics and non-asthmatics within the cohort [3]. In the clinical study two years later, repeated wheezing at <24 months of age was the only significant risk factor for asthma at the median age of 29.5 years [4]. The cohort and controls did nod differ for current allergy, but the relation between allergy and current asthma was not presented.

In the Swedish Gothenburg 1984-1985 post-wheezing cohort, family history of asthma was the

only significant early-life risk factors for asthma at the median age of 27.0 years, and allergy, consisting of allergic rhinitis, atopic sensitization, food allergy and atopic dermatitis, was the only current risk factor for asthma in adulthood [6]. In these analyses, asthmatics and non-asthmatics were compared within the cohort. When both early and current potential confounders were incorporated in the same multivariate model, only current allergy, in addition to early-childhood wheezing, remained as statistically significant [6]. Early exposure to tobacco smoke, which increased asthma risk at 17-20 years of age through different pathways for maternal and paternal smoking [34], was not any more significant ten years later.

In the questionnaire study of the Finnish Kuopio 1992-1993 post-wheezing cohort at the median age of 26.5 years, none of the previous or current risk factors were significantly associated with doctor-diagnosed asthma [7]. However, when self-reported asthma in cases and controls were combined and compared with the corresponding non-asthma group, previous asthma, current allergic rhinitis, and overweight were significant risk factors [7]. When analyses were adjusted for allergic rhinitis, early-childhood wheezing turned out to be an independently significant risk factor for self-reported asthma but not, due to under-powered analyses, for doctor-diagnosed asthma.

Blood eosinophils seem to be the most constant early-childhood risk factor for later asthma in post-wheezing follow-ups, and this association has continued until adolescence in three different post-wheezing cohorts [17,35,37]. In the Finnish Kuopio 1981-1982 post-wheezing cohort, low eosinophils of $<0.25 \times 19^9$/L on admission at <24 months of age decreased and high eosinophils of $>0.45 \times 19^9$/L on convalescence 4-6 weeks later increased the risk of adulthood asthma at the median age of 29.5 years [36]. Interestingly, similar association were not seen for high eosinophils on admission or low eosinophils on convalescence, and the association between eosinophilia and asthma seems to be independent from allergy [38].

Methodological discussion

The post-wheezing cohort studies included in this review were initially non-controlled [1,2]. but controls were recruited for the follow-up in adulthood [3-7]. When assessing the outcome after early-childhood wheezing, or after bronchiolitis as well, the results are dependent not only on the numbers and characteristics of the cases, but as well on the numbers, characteristics, and selection criteria of controls. Use of controls is a strong research tool, which can be utilized to increase the statistical power of the study, especially if the studied outcomes are rare [39]. The other side of the coin is that poor choice of controls can lead to wrong results. Optimally, controls are collected from the same population where the cases come from, which came true in all three post-wheezing follow-ups reviewed in this article. Two studies used population-based but selected controls, since subjects with early-life wheezing or hospitalization histories were excluded [3,4,7]. One of the studies, the Gothenburg 1984-1985 post-wheezing cohort study, exploited unselected controls from another study, and their large number (1210 subjects) substantially increased the power of the analyses [6]. In all three post-wheezing cohorts, the numbers of cases were rather low, 81-101 on admission at <24 months of age, and the drop-out numbers were noticeable, and further, the most important outcomes such as doctor-diagnosed asthma were rare [3,4,7]. In addition, the participation among controls was low, meaning a risk of bias since symptomatic subjects are more willing to attend medical studies than non-symptomatic ones [40].

Concerning the validity of an observational study, selection bias, information bias, and confounding are present to some degree in all surveys [41,42]. These biases are umbrella terms for biases named and grouped by different ways. Undoubtedly, varying biases were present in the reviewed cohort studies [3-7]. Confounding was controlled by including confounders, such as smoking, and disease-modifying factors, such as allergic rhinitis, as co-variates in multivariate analyses. These analyses confirmed that early-childhood wheezing was an independently significant risk factor for asthma at >25 years of age [3,4,6,7]. More comprehensive presentation of different biases and their potential effects on the internal and external validities of the included studies and on the conclusions drawn from them are out of scope of the present review.

Respiratory viruses in early childhood are important background factors in asthma and lung function studies after early-childhood wheezing. During an RSV epidemic, for example, all or nearly all young children in the area in question are exposed to the virus, but majority of them present with mild or no symptoms. This exposure is impossible to be taken account in the selection of controls and in the planning of analyses. In addition, the viral results in symptomatic cases depend on the sensitivities and specificities of the used tests. Symptomatic children, or those hospitalized because they have severe symptoms, are included as cases in the cohorts, and

cannot belong to the control groups. This raises a question, whether we should use in comparisons when studying the outcome after early-childhood wheezing, healthy hospital-based controls (such as those coming to elective surgery, when e.g. blood sampling is easy and ethically justified), initially healthy population-based controls (those with early-childhood wheezing excluded), controls with the same clinical presentation but different cause (such as wheezing RSV versus wheezing rhinovirus infection), controls with the same cause but different clinical presentation (such as wheezing versus non-wheezing RSV or rhinovirus infection), or unselected population data from official registers or from epidemiological population-based surveys if available, as summarized previously [2]. All these strategies, except use of healthy hospital-based controls, were used in the reviewed cohort studies, when appropriate [3-7].

Risk factors for adulthood asthma after early-childhood wheezing can be grouped by different ways, often classified into early-life, previous childhood, and current factors, as was done also in the reviewed cohorts [3-7]. In the case of asthma in adults, early-life and other childhood factors are usually considered as risk factors and current factors as confounders (e.g. smoking and obesity) or disease-modifying factors (e.g. allergic rhinitis). Technically, risk factors, confounders and disease-modifying factors are managed similarly by including them as co-variates in multivariate analyses. In principle, there are three possible ways to evaluate the association of earlier or current factors with asthma, which are comparisons of risk factors between asthmatics and non-asthmatics within the cohort, or between asthmatics in the cohort and non-asthmatics controls, or between asthmatics in the cohort and all controls. All these strategies were used in the reviewed cohort studies when appropriate [3,4,6,7]. Power can be increased by combining asthmatics in the case and control groups and belonging to the case or control group can be added as one of the co-variates in the analyses, as was done in the *ad hoc* analyses of the Kuopio 1992-1993 post-wheezing cohort in adulthood [7]. In prospective long-term follow-ups, analyses within cohorts are practically always under-powered due to drop-outs and low frequencies of the outcome [41,42], such as asthma or lung function deficiency in adults, which was seen also in the reviewed cohorts [3-7]. This explains partly the differences in asthma-predictive factors and in the role of doctor-diagnosed asthma between the >25 years results and the earlier phases of the same cohorts [1,2, 13-16].

When asthmatics are compared with population-based controls, only simple data on early-life factors, such as gender, asthma or allergy in family, or doctor-diagnosed atopic dermatitis in the children, can be reliably collected afterwards, which was taken account also in the reviewed studies [3-7]. The challenges are similar as in retrospective cohort studies [42]. In addition, some diseases in family members may emerge or improve during long-term follow-ups, asthma or allergy as examples. Importantly, the collection of risk factor data should be carried out by the same way from cases and controls, although cases have been followed for years and more detailed early data would be available from them. When controls are recruited later, the quality of early-childhood information is poorer, and the risk of information bias is higher than in prospective follow-ups of both cases and controls. In the reviewed post-wheezing cohort studies, population controls were recruited for the adulthood phases of the studies, although early-childhood wheezers were prospectively followed from the index wheezing episodes [3-7]. Therefore, certain previous data, such as those based on laboratory or other tests could be used only in analyses within the post-wheezing group, and in the analyses, only blood eosinophils retained their statistical significance at >25 years of age [3,4,6].

Prospective birth cohort studies elucidate the incidence of the whole spectrum of the disease in question and allow reliable evaluation of the outcomes and their risk factors as well as the confounding and disease-modifying factors. However, there are no enrichment of the disease or clinical events, and therefore, the required size of the cohort highly depends on the frequency of the studied outcomes in the population [41,42]. In the case of early-childhood wheezing, mild symptoms are common in the child population occurring even in a third of young children [11,12], but severe symptoms needing emergency room visits or even hospitalizations are rather rare, occurring in 1-3% of young children [1,2]. Less than half of severe early-childhood wheezers present later with asthma and/or lung function deficiency, and the figures are substantially dependent on the age when the follow-up is carried out [40]. Wheezing children tend to outgrow from their symptoms, and the prevalence of asthma and/or wheezing is lowest at 7-13 years of age, but after puberty, the figures increase again [1,2,17,18]. For these reasons, large birth cohorts are needed to show statistical significances, and the follow-ups of such large cohorts are realistic only by postal questionnaires. The quality of the data is poorer in questionnaire studies than in clinical

studies, and objective data, such as results of lung function or bronchial reactivity tests, cannot be obtained. Birth cohort studies were not included in the present review with a focus on prospective follow-ups until adulthood after infection-induced wheezing at age <24 months.

Conclusion

The risks of adulthood asthma and lung function reduction were increased at >25 years of age after hospitalization for infection-associated wheezing at <24 months of age in three prospective post-wheezing cohorts. The asthma risk was increased independently from allergic rhinitis, which is known to be an important disease-modifying factor in asthma. Interestingly, lung function reduction was permanent and irreversible fulfilling the lung function criteria of COPD in 10-15% of previous early-childhood wheezers in one cohort followed for nearly 30 years [5].

The influence of early-childhood risk factors for asthma diluted gradually during the long-term follow-up, and finally at the age of >25 years, blood eosinophils in early childhood and asthma in later childhood were the only significant predictors of asthma. Interestingly, low eosinophils were associated with a decreased risk and high eosinophils with an increased risk of asthma [37]. The association of RSV-induced early-childhood wheezing with lung function reduction and that of rhinovirus-induced early-childhood wheezing with asthma, which were evident in the previous phases of the reviewed studies, was not anymore seen at >25 years of age.

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