

Long-term outcomes of early childhood wheezing

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Purpose of review

To summarize the currently available data on the long-term outcome until young adulthood after early childhood wheezing. Asthma and lung function abnormalities were evaluated, with special attention to early-life risk factors.

Recent findings

In postbronchiolitis studies, 30–40% of the patients hospitalized for wheezing at less than 24 months of age have had asthma at 17–20 years of age. In the Tucson birth cohort study, the respective figure after wheezing at less than 36 months of age was 30% at 22 years of age. Relapses after many nonsymptomatic years have been common. In postbronchiolitis studies, lung function has been reduced in 31–36%, concerning also postbronchodilator measurements. Thus, the changes in airways seem to be structural, being present from infancy until adulthood, as found in the Tucson study. Parental asthma, repeated early-life wheezing and early passive smoking have been the most important early-life predictors of both adulthood asthma and lung function abnormalities.

Summary

Early childhood wheezing increases the risk for asthma and lung function abnormalities in young adulthood. Not only chronic childhood asthma continuing until adulthood but also asthma beginning in early adulthood seems to have its origin in early childhood.

Keywords

adulthood, asthma, childhood, lung function, outcome, tobacco smoke, wheezing

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Introduction

One-third of all children suffer from wheezing during the first 3 years of life [1], and 1–3% of children less than 2 years of age are hospitalized for wheezing [2]. However, young wheezing children form a heterogeneous group with different genotypes and phenotypes, leading to different outcomes. Both genes and environmental factors, like viruses, tobacco smoke and inhaled allergens, modify the phenotypes of early childhood wheezing. In addition, there seems to be an interaction between genetic and environmental factors and both have an association with the age and the immunological maturity of the children [3,4].

Currently, early childhood wheezing is generally classified into three main phenotypes: transient early wheezing (60% of the cases), nonatopic persistent wheezing (20%) and atopic persistent wheezing (20%). The wheezing tendency and increased bronchial responsiveness recover by the age of 3 years in transient wheezers and by the age of 6 years in nonatopic persistent wheezers, but both seem to continue through childhood and adolescence in atopic persistent wheezers [1,5]. Abnormalities in lung function after early childhood wheezing seem to continue at least until teen age, as documented in both birth cohort

and postbronchiolitis studies [1,2]. Asthma or asthma-like symptoms are more common in young adults than in adolescents. There is increasing evidence that these cases may more likely be relapses after early childhood wheezing than novel asthma cases [2,6,7*]. Therefore, prospective follow-up studies continuing until adulthood, and even through the whole life span, and covering early-life risk factors for asthma, asthma prevention and asthma treatment are needed [8].

The aims of the present review were to summarize the currently available prospective data on the long-term outcome until adulthood after early childhood wheezing. Early wheezing was restricted to the age of less than 36 months, and only studies performed in children with no severe underlying illness were included. Both clinical outcome, which usually means the presence of asthma or asthma-like symptoms, and lung function status were evaluated. Special attention was paid to early-life risk factors for subsequent asthma and lung function abnormalities.

Early childhood wheezing: definitions

Bronchiolitis was originally a pathological description, which has become to be used as a clinical diagnosis.

Bronchiolitis starts as an acute respiratory infection with upper respiratory tract symptoms progressing to cough, tachypnea, hyperinflation, chest retractions and crackles, wheezes or both [9]. Most cases are caused by respiratory syncytial virus (RSV), but recent studies [10,11] have highlighted the role of rhinoviruses, metapneumovirus (MPV) and human bocavirus. The diagnosis of bronchiolitis has been used only for first-time wheezers, and the age limit has been 12 months in Europe and 24 months in America [9]. In Europe, subsequent wheezing and first wheezing in children more than 12 months of age have been called wheezy bronchitis. In America, subsequent wheezing and first wheezing in children more than 24 months of age have been simply called transient wheezing if stopped before 3 years of age and persistent wheezing if continued after 3 years of age. Repeated wheezing is often called asthma, but the criteria of asthma diagnosis vary between different countries. Thus, early childhood wheezing includes both bronchiolitis and wheezy bronchitis cases, as well as those asthma cases that start before the age of 3 years.

How to study outcome after early childhood wheezing

In clinical medicine, the design of the study is necessary to be taken into account when interpreting the results. Not only the cases but also the number and selection criteria of the controls have an important impact on the results of the study.

Postbronchiolitis studies

Prospective postbronchiolitis studies, or retrospective studies in children with early-life treatment for wheezing, elucidate postbronchiolitis events, usually subsequent wheezing or asthma, in a selected group of children. Thus, the whole spectrum of the early-life wheezing illness, as well as the later consequences of the mild presentations of early-life wheezing in the population, is not included in the analyses. However, there is an enrichment of the later expected events, which diminishes the demanded size of the study group. For example, two-thirds of the children hospitalized for wheezing at less than 2 years of age will suffer from subsequent wheezing and 30–40% of them will have asthma at teen or adult age [2]. Even during long-term follow-ups, repeated physical studies, lung function studies and challenge tests to reveal bronchial responsiveness can be done for all participants, with no need to later randomize to subgroups [10,12].

Birth cohort studies

Prospective birth cohort studies elucidate the incidence of an illness allowing evaluation of the risk factors of the

disease, as well as the confounding and the disease-modifying factors, and including the whole spectrum of the illness in the analyses. As there is no enrichment of the events, the required size of the cohort depends on the expected frequency of the events in the cohort – that is, in the nonselected child population. Concerning early childhood wheezing, mild symptoms are common occurrences in a third of all children, but severe symptoms requiring emergency room visits or even hospitalizations are present in only 1–3% of the children [1,2,5]. To include also severe cases, large cohorts are needed, and they are realistic to be followed up only by questionnaires sent to the parents. In questionnaire studies, the quality of the data is lower than in clinical studies. In addition, more objective studies, such as lung function measurements and tests for bronchial responsiveness, can be done only for a part of the study participants.

How to control

When assessing the outcome after bronchiolitis or after early childhood wheezing, the results are highly dependent on the number of controls, that is, the power of the study, and on how the controls have been selected. For example, during an RSV outbreak, all or nearly all young children in the area are exposed to the virus, but most of them are nonsymptomatic. This exposure is difficult to take into account in the analyses. Therefore, only symptomatic children, or even those hospitalized for an RSV infection, represent the RSV-exposed children in the analyses. An important question is whether we should use, when studying the outcome after early-life wheezing, healthy controls, healthy population-based controls, nonselected population-based controls, controls with the same clinical presentation (but different cause), controls with the same cause (but different presentation), or population data from the epidemiological surveys if available. Likewise, an exposure to seasonal pollens is universal during the season. However, sensitization to inhaled allergens seems to be nonbeneficial, although an exposure with no sensitization may be even beneficial. In addition, an exposure and sensitization to animal dander seem not to depend on the keeping of animals at home [13]. Prenatal and postnatal early-life tobacco smoke exposure are an example of an exposure that is harmful and can actively be avoided.

Adulthood outcome after early childhood wheezing

The main sequels after early childhood wheezing in young adults are asthma and abnormalities in lung function. Whether there is any connection with chronic obstructive lung disease remains to be seen when the follow-up studies have continued over the middle age.

Asthma

There are only two prospective follow-up studies after hospitalization for early childhood wheezing, one from Finland and one from Sweden, which have continued until adulthood [14–16,17[•],18,19^{••},20^{••}] (Table 1). In these studies, over half of the children hospitalized at less than 24 months of age have wheezed at 2–3 years, 25–54% at 4–6 years and 15–30% at 7–10 years of age [2]. The figure is higher than the 4–10% prevalence of asthma among school children in Scandinavian countries at that time [21,22]. The prevalence of asthma at the age of 17–20 years was surprisingly similar, 41–43% (27–31% with stringent criteria), in both the Finnish and Swedish studies [15,16] (Table 2). The prevalence of asthma was significantly lower, 11 and 15% (5% with stringent criteria), in controls in both the cohorts, respectively [15,16]. These figures mean that relapses are common, after many symptom-free years at school age, in young adults who have been hospitalized for wheezing in their early life. In adjusted analyses, recurrence of wheezing at less than 2 years of age was an independent predictor of asthma in adulthood [15,16]. These controlled studies from Finland and Sweden were the first prospective studies that demonstrated the long-term, from infancy until adulthood, outcome after hospitalization for wheezing. The results changed the earlier belief of the beneficial course of early childhood wheezing: the increased risk for asthma and lung function abnormalities was shown to continue and even increase in young adulthood [15,16].

The Tucson Respiratory Study, using data from a population-based unselected birth cohort, is the only birth cohort study having continued until adulthood, thus far [18,19^{••},20^{••}] (Table 1). The study group identified the phenotypes of early childhood wheezing and their different outcomes until 16 years of age [1,18]. From 16 to 22 years of age, the incidence of asthma was 12.6/1000 person-years [20^{••}]. At 22 years of age, 27% of asthma cases were new and 73% were chronic or relapsed asthma cases. The figures were 13% (new) and 59% (chronic or relapsed) after early persistent wheezing and only 9 and 13%, respectively, after early transient wheezing

(Table 2). The first wheezing episodes had taken place during the first 6 years of life in two-thirds of those who have asthma at 22 years of age [20^{••}].

Thus, asthma presenting in early adulthood, including most new asthma cases, has its origin in early childhood, and the presentation in early childhood is more often persistent than transient wheezing.

Lung function

Lung function was measured by flow-volume spirometry (FVS) at 17–20 years of age in both the Finnish and Swedish postbronchiolitis studies [15,17[•]]. On average, lung function was within normal limits. However, abnormal lung function parameters were present in 31% of the patients, compared with 16% in controls, in the Swedish study [17[•]] and in 36% of the patients, compared with 11% in controls, in the Finnish study [15]. In the Swedish study, the participants in the cohort had significantly lower FEV1/FVC ratios and MEF₅₀ values both before and after bronchodilator treatment, suggesting the changes are structural and thus permanent [17[•]] (Table 2).

In the Tucson birth cohort, transient and persistent wheezers had reduced lung function by spirometry, compared with never wheezers at 16 years of age, whereas late-onset wheezers had lung function halfway between never wheezers and transient or persistent wheezers [4,19^{••}]. The findings were consistently seen in FEV1, FEV1/FVC and MEF_{25–50} values. Reduced lung function was seen in patients with transient wheezing, although they had been symptom-free from 3 to 16 years of age. This finding confirms the persistence of impaired lung function developed during the first 3 months of life or even during pregnancy.

Maximal expiratory flow at functional residual capacity (Vmax_{FRC}) was studied in a subgroup of the Tucson birth cohort at a mean age of 2.3 months, before any wheezing or even infection had taken place [5]. Over 20 years later, lung function was studied by spirometry in the same patients, and low Vmax_{FRC} in infancy was associated with

Table 1 Baseline information on the three prospective studies after early childhood wheezing continued until adulthood

Characteristics	Kuopio study ^a	Gothenburg study ^b	Tucson study ^c
Design	Prospective postbronchiolitis	Prospective postbronchiolitis	Prospective birth cohort
Onset of follow-up	1981–1982	1984–1985	1980
Definition of early childhood	<24 months	<24 months	<36 months
Severity of wheezing	Hospital-treated	Hospital-treated	All cases
Controls	Infants from nonatopic families, hospitalized nonwheezing infants	Nonselected population-based, no prospective follow-up	Nonselected population-based, no prospective follow-up as part of the cohort

^aReferences [14,15].

^bReferences [16,17[•]].

^cReferences [1,18,19^{••},20^{••}].

Table 2 Outcome in young adults after early-childhood wheezing in three prospective studies continued until adulthood

Characteristics	Kuopio study ^a	Gothenburg study ^b	Tucson study ^c
Age	18–20 years	17–18 years	22 years
Patients with early-life wheezing	83	101	277
Participants in adulthood	54 (65%)	88 (80%)	221 (80%) ^d
Adults with symptom-based asthma ^e	22 (41%)	38 (43%)	67 (30%)
Relapsing wheezing	Not reported	22 ^f	14
Chronic wheezing	Not reported	11 ^f	53
Adults with doctor-diagnosed asthma ^g	16 (30%)	24 (27%)	Not reported
Relapse	9	Not reported	Not reported
Chronic asthma	7	Not reported	Not reported
Adults with lung function abnormalities	19 (36%)	27 (31%)	Not reported

^a References [15].^b References [16,17*].^c References [19**,20**].^d Includes 135 (61%) transient wheezers (wheezing at <3 years of age, but no longer at 6 years of age) and 86 (39%) persistent wheezers (wheezing at both <3 years of age and 6 years of age).^e Physician-diagnosed asthma ever and wheezing symptoms during the previous year in the Kuopio and the Tucson cohorts, mild asthma symptoms with no maintenance medication in the Gothenburg cohort.^f Complete data available in 33/38 asthma cases.^g Ongoing maintenance medication for asthma or a pathological peak expiratory flow (pef) follow-up measurement in a symptomatic patient in the Kuopio cohort and ongoing maintenance medication in the Gothenburg cohort.

reduced FEV₁, FEV₁/FVC ratio and FEF₅₀ in young adults [19**]. Poor airway function after birth was an independent risk factor for airflow obstruction in young adults. On the contrary, lung function in infancy explained only 10% (postbronchodilator values) to 14% (prebronchodilator values) of the variation in FEV₁, FEV₁/FVC ratio and FEF₅₀. In the studies from Australia, reduced lung function after birth was associated with wheezing at less than 3 years of age and remained reduced until at least 11 years of age. However, longer follow-up results are lacking, thus far [23,24].

Early-life risk factors

Asthma in parents, early-life atopy in children manifesting as atopic dermatitis or intestinal food allergy, early-life sensitization (but not exposure) to inhaled allergens and either eosinophilia or the lack of an infection-induced eosinopenic response have been the significant risk factors, present at the time of early childhood wheezing, for later asthma until adulthood [2,12, 25–30].

In the Finnish postbronchiolitis study [31*], subsequent wheezing and later asthma, including the relapsing asthma in young adults, were associated with viral cause of early-life wheezing infection. They were more common if the first wheezing episode was not caused by RSV (Table 3). The results in the later postbronchiolitis follow-up studies [10,12] until 12–13 years of age with PCR tests for rhinoviruses available have confirmed that non-RSV bronchiolitis, in most cases caused by rhinoviruses, has a poorer outcome than has RSV bronchiolitis.

In the Swedish postbronchiolitis study [32*], early-life exposure to tobacco smoke was a significant risk factor for

both asthma and lung function abnormalities in young adults (Table 3). In multivariate analyses, both prenatal and postnatal exposures to passive smoking were significant risk factors independently of each other. Prenatal tobacco exposure was associated with permanent worsening of lung function [17*,32*] (Table 4). Exposure to maternal smoking increased the asthma risk mainly through the development of bronchial reactivity, whereas postnatal smoking increased the asthma risk through the later active smoking of the child [16,32*] (Table 3).

According to the results of the Tucson birth cohort study, physician-diagnosed asthma in a parent and physician-diagnosed atopic dermatitis in an infant have been the major risk factors, and physician-diagnosed allergic rhinitis, wheezing apart from colds and blood eosinophilia (>4%) have been the minor risk factors for chronic childhood asthma, that is asthma continuing beyond 6 years of age [25,27]. The influence of breastfeeding was dependent on the asthma and allergy status of the family. Long, more than 4 months, duration of breastfeeding had a favorable effect on lung growth, but in the presence of maternal asthma, long breastfeeding was associated with decreased airflows [33]. When the cohort was followed-up until 16 years of age, no significant changes were seen in the patterns of wheezing prevalence or levels of lung function between 6 and 16 years of age. When the children grow older, they face multiple environmental and other confounding and disease-modifying factors and thus the effects of infantile and early-life risk factors are weakened. At the age of 22 years, persistent wheezing in early life and low airway function or bronchial hyper-responsiveness at 6 years of age predicted chronic asthma, whereas low airway function or bronchial hyper-responsiveness at 6 years of age and late onset and persistent wheezing predicted new asthma in young adults [19**]

Table 3 Early-life risk factors for asthma in young adults after early-childhood wheezing in three prospective studies continued until adulthood

Risk factor	Kuopio study ^a	Gothenburg study ^b	Tucson study ^c
Asthma in parents	Yes	Not reported	Yes ^d
Atopy in family	No	Yes	Not reported
Female sex	No	Yes	Yes
Atopy (IgE >60/atopic dermatitis) <2 years of age	Yes	Not reported	Not reported
Atopic dermatitis <2 years of age	No	Not reported	Yes ^e
Passive smoking in infancy	No	Yes	Not reported
Maternal smoking during pregnancy	Not registered	Yes	Not reported
Wheezing during RSV infection	No	No	Not reported
Wheezing during non-RSV infection	Yes	Not reported	Not reported
Persistent wheezing from < 3 until 6 years of age	Not reported	Not reported	Yes
Recurrent wheezing episodes (>2) at < 3 years of age	Yes	Not reported	
Poor lung function after birth ^f	Not measured	Not measured	Yes
Blood eosinophilia	No	Not reported	Not reported
Lack of eosinopenic response during acute infection	Yes	Not reported	Not reported
Furred pets at home in infancy	No	No	Not reported
Sensitization to inhalant allergens <3–6 years of age	No ^g	Not reported	Yes
Breastfeeding ≥4 months	No	Not reported	Not reported

In the Tucson study, the algorithm to present asthma risk until 13 years of age includes two main criteria (doctor-diagnosed asthma in parents and doctor-diagnosed atopic dermatitis in the child) and three minor criteria (doctor-diagnosed allergic rhinitis, wheezing apart from colds, blood eosinophilia ≥4%) [25]. RSV, respiratory syncytial virus.

^aReferences [14,28–30,31*].

^bReferences [16,17*,32*].

^cReferences [19*,20*].

^dRisk factor for newly diagnosed asthma.

^eRisk factor for chronic asthma.

^fThe lowest quartile in Vmax_{FRC} measurement at mean age of 2.3 months.

^gA significant predictor for asthma until 16 years of age, but not thereafter.

(Table 3). Active smoking and obesity, both seen in increasing amounts at teen age, are the most important disease-modifying factors [34,35]. Thus, infantile risk factors seem to predict chronic childhood asthma, which continues until adulthood – and even asthma with the onset or relapse in early adulthood.

No interventions are likely to influence the genetic risk factors of asthma, as well as most environmental risk or disease-modifying factors. For example, early pet contacts may be either beneficial or nonbeneficial, depending on the age and immunological maturity of the child

and the amount of exposure. Although early exposure to livestock and pets seems to protect from later asthma and allergy, early sensitization to animal dander, pollens and other inhaled allergens obviously increases the risk [13,28,36,37]. During virus and pollen seasons, nearly all children are exposed to the viruses and pollens. In population studies, an early RSV infection has increased the asthma risk until 13 years of age, but no longer [38]. In line, the influence of an early rhinovirus infection seems to diminish by age [10,12]. The only beneficial intervention with no doubt is avoiding tobacco smoke exposure in early life, particularly during pregnancy.

Table 4 Early-life risk factors for lung function abnormalities in young adults after early-childhood wheezing in two prospective postbronchiolitis studies continued until adulthood

Risk factor	Kuopio study ^a	Gothenburg study ^b
Asthma in parents	Yes	No
Atopy in parents	Yes	No
Passive smoking in infancy	Yes	Yes
Either	No	Yes
Father	No	Yes
Mother	Yes	Yes
Maternal smoking during pregnancy	Not registered	Yes
Onset and recurrence of wheezing at <1 year	Yes	Not reported
Viral cause (RSV vs. non-RSV) of bronchiolitis	No	No
Lack of eosinopenic response during acute infection	Yes	Not reported
Breastfeeding <4 months	No	Not reported

In the Tucson study, poor lung function after birth was a significant predictor for lung function abnormalities in adulthood; no other risk factors were presented [19**].

^aReferences [14,29,30,31*].

^bReferences [16,17*].

Conclusion

Most children with early childhood wheezing outgrow their symptoms during school years, but asthma relapses are common in young adults. In addition, early childhood wheezing is associated with permanent changes in the airways continuing until adulthood. The outcome after RSV bronchiolitis is more beneficial than after wheezing by other viruses. Recent studies highlight the effect of early-life exposure to tobacco smoke, especially if started during pregnancy, as one of the major risk factors for later wheezing, asthma and abnormal lung function. Opposite to many other risk factors, tobacco smoke exposure can be avoided if the parents are motivated.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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