

Long-term health-related quality-of-life data in subjects with a history of wheezing in early childhood

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ABSTRACT

Background: Wheezing in early childhood has implications for respiratory morbidity in later life.

Objectives: We evaluated respiratory health-related quality of life (HRQoL) in young adults ages 17–20 years with a history of early childhood wheezing.

Methods: Between 1992 and 1993, 100 children ages < 24 months were treated in the hospital for a lower respiratory tract infection with wheezing, and we followed up this cohort. In 2010, 49 of the patients (cases) and 60 population-based controls attended a clinical follow-up. St. George's Respiratory Questionnaire (SGRQ) was used to evaluate respiratory HRQoL, expressed as symptom, activity, impact, and total scores.

Results: The median (interquartile range) SGRQ symptom scores were higher (13.7 [3.8–29.1]) in the 49 subjects (cases) with early childhood wheezing compared with the 60 population controls (7.8 [0.0–18.3]; $p = 0.019$). However, there were no between-group differences in total scores or in other SGRQ domains. Current asthma was a major risk factor for reduced HRQoL. In univariate analyses, the median symptom scores were 20.2 in those with asthma and 7.8 in those without asthma ($p < 0.001$), and, in multivariate analyses, the odds ratio (OR) was 8.7 for high total scores (95% confidence intervals, 2.1–36.6). Other factors associated with reduced HRQoL were current allergy (OR 4.4 for symptom scores), overweight (OR 3.3 for activity scores), tobacco smoking (OR 4.3 for symptom scores), and female sex (OR 3.2 for impact score). Furthermore, we performed post hoc analyses by excluding those with asthma and those who smoked, and found no significant differences on SGRQ scores between the subjects (cases) and the controls.

Conclusion: Hospitalization for wheezing in early childhood mainly had indirect effects on HRQoL by increasing the risk of asthma.

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Wheezing, a major reason for hospitalization in early childhood, may affect respiratory health up to adult age.¹ Prospective cohort studies conducted in Finland and Sweden with long observation times reported a marked increase in the risk of asthma and reduced lung function among individuals ages 25–31 years who had been hospitalized with wheezing during early childhood.^{2–5} Health-related quality of life (HRQoL) measures self-perceived health, and various HRQoL questionnaires are available for children and adults.⁶ In previous studies, hospitalization for bronchiolitis was associated with reduced HRQoL in infants and toddlers.^{7–10}

In Dutch and Norwegian studies, HRQoL was lower in the subjects (cases) than in the controls 2–9 months after infant bronchiolitis when measured by the Infant Toddler Quality of Life questionnaire.^{8,10} In the Norwegian study, the severity of bronchiolitis, measured by the length of hospital stay and the need of ventilatory support, was associated with reduced HRQoL 9 months later.⁹ In the Dutch study, HRQoL, measured by the TNO-AZL Preschool Children Quality of Life Questionnaire at the age of 3 years, was lower in those with a history of bronchiolitis in infancy than in the controls.⁷

There are only a few published studies available with long-term HRQoL data of patients after having wheezing in early childhood. One previous cohort study evaluated the association between wheezing in early childhood and HRQoL in adulthood.² Finnish subjects who were hospitalized for wheezing when they were ages < 24 months had lower HRQoL measured by St. George's Respiratory Questionnaire (SGRQ) at the mean age of 29.5 years compared with population controls.²

We prospectively followed up a cohort of 100 infants who were hospitalized for lower respiratory tract infection (LRTI) with wheezing at Kuopio University

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Hospital, Finland, in 1992–1993. Forty-nine of them attended a follow-up visit in 2010, at 17–20 years of age.¹¹ Our aim was to evaluate HRQoL by using the SGRQ in young adults who had had early childhood wheezing and to compare the results with the controls. In addition, we studied early life and current risk factors potentially associated with reduced HRQoL.

METHODS

For this study, we combined the data from the original hospital admission of the cohort (“original cohort”) and from the fifth follow-up visit performed at the ages 17–20 years in 2010.

Original Cohort

The original cohort consisted of 100 children who were hospitalized for LRTI with wheezing at the median age of 10 months (range, 1–23 months) at Kuopio University Hospital, Finland, in 1992–1993.¹² Most (87%) presented with wheezing for the first time, and none had previously been hospitalized for LRTI or wheezing.¹² Nasopharyngeal aspirates were taken from all the children on admission. Viral infections were diagnosed by antigen detection for respiratory syncytial virus (RSV) and influenza, parainfluenza, and adenoviruses,¹² and by polymerase chain reaction for rhinovirus (RV) and enterovirus and coronaviruses.¹³

Follow-up Visit in 2010

As described previously, 49 (49%) of the original study subjects attended for the latest follow-up visit in 2010 at 17–20 years of age.¹¹ Among them, RSV was found in 14, RV in 14, other viruses in 12, and no virus in 9 subjects (cases) during the early childhood hospitalization for wheezing. Population-based controls matched for sex and age, who were born in the same area (Kuopio University Hospital district), as were the subjects (cases), were recruited, and 60 (15%) attended the 2010 follow-up.¹¹

All the participants completed a questionnaire, which included questions about asthma and allergy symptoms, and current smoking as well as asthma and allergy diagnoses and treatments before the follow-up visit. To assess HRQoL, the participants completed a respiratory disease-specific questionnaire (the SGRQ). The questionnaire has been validated in adults with asthma and chronic obstructive pulmonary disease in different countries.¹⁴ The follow-up visit consisted of an interview and examination by a physician, skin-prick tests to eight airborne allergens, home peak expiratory flow monitoring for 2 weeks before the visit,¹¹ measurement of weight and height, and calculation of the body mass index.¹¹

Current asthma was defined as a previous diagnosis of asthma, combined with symptoms presumptive

for asthma, such as recurrent wheezing, prolonged cough, chronic night cough, or maintenance medication with inhaled corticosteroids (ICS) during the past 12 months.¹¹ In addition, the subjects (cases) who had abnormal results on home peak expiratory flow monitoring and reported asthma-presumptive symptoms and/or repeated use of bronchodilators were defined as having current asthma. Current allergy was defined as the presence of allergic rhinitis, allergic conjunctivitis, or atopic eczema, in addition to atopic sensitization (one or more positive skin-prick test results) at the follow-up visit.¹¹

The mean ages of the subjects (cases) and the controls were 18.8 and 18.7 years, respectively, and 39% (subjects [cases]) and 55% (controls) were girls. As described earlier, 26 subjects (cases) (53%) and 7 controls (12%) presented with current asthma, and 10 subjects (cases) (20%) and 5 controls (8%) used ICS for asthma.¹¹ Twenty-eight subjects (cases) (57%) and 27 controls (45%) reported current allergy, and 16 (33%) and 18 (30%), respectively, reported daily smoking.¹¹

HRQoL

SGRQ is a respiratory disease-specific instrument developed to measure the health of adults with obstructive lung diseases.¹⁵ SGRQ contains 50 items, and the scores are calculated for three domains: symptom scores, activity scores (activities that cause breathlessness or activities that are limited due to breathlessness), and impact scores (social or mental disturbances that result from airway disease). The total score is based on the scores from the three domains, with 100 denoting the worst possible and zero denoting the best possible respiratory HRQoL. A between-group difference of four or more points in the SGRQ scores was previously established as clinically relevant.¹⁵

Statistics

SPSS 25.0 software (IBM Corp., Armonk, NY) was used for the statistical analyses. SGRQ scores were non-normally distributed; therefore, the results were expressed as medians and interquartile ranges (IQR). The Mann–Whitney U test was used in univariate paired comparisons between the groups. In multivariate analyses, we used logistic regression after conversion of the SGRQ scores to categorized variables. The median scores of the controls without asthma were used as cutoff points. Such a cutoff limit was 5.94 for symptom scores, 0.0 for activity scores, 0.0 for impact scores, and 1.62 for the total scores. The included covariates were wheezing in early childhood or virus-specific wheezing group, or current asthma, allergy, tobacco smoking, overweight (body mass index >25 kg/m²), and sex. The results of the logistic regression

analyses are presented as odd ratios (OR), with their 95% confidence intervals (CI).

Ethics

The study was approved by the ethics committee of the Pohjois-Savo Health Care District, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all the participants.

RESULTS

The subjects (cases) who were hospitalized for wheezing in early childhood had significantly higher median (IQR) SGRQ symptom scores at ages of 17–20 years (13.7 [3.8–29.1]) than had the population-based controls (7.8 [0.0–18.3]; $p = 0.019$). However, there were no significant differences in the activity or impact scores or total SGRQ scores between the subjects (cases) and controls (Table 1). The subjects (cases) with RV-associated early childhood wheezing and subjects (cases) with wheezing associated with viruses other than RV or RSV had higher SGRQ symptom scores than did the controls, although there were no significant differences in their activity, impact, or total SGRQ scores (Table 2). There also were no significant differences in any SGRQ scores when the virus-specific groups were compared with each other (data not shown). The SGRQ scores were higher in 33 participants with current asthma than in those 76 participants without current asthma when the combined data of the subjects (cases) and the controls were analyzed (Table 3). The difference in the medians was 4.6 for the total SGRQ scores, 12.5 for symptom scores, 5.3 for activity scores, 4.0 for impact scores. (Table 3).

In supplemental analyses, the SGRQ scores of those 15 participants who used ICS were higher than of those 94 participants who did not use ICS. The median (IQR) values were 37.1 (7.8–52.2) versus 10.2 (0.0–19.2) ($p = 0.002$) for symptom scores, 12.2 (0.0–29.5) versus 0.0 (0.0–5.3) ($p = 0.001$) for activity scores, 4.0 (0.0–18.8) versus 0.0 (0.0–4.1) ($p = 0.011$) for impact scores, and 13.1 (4.8–23.4) versus 2.3 (0.0–6.3) ($p = 0.001$) for total scores, respectively. Thus,

the difference in the median values was 10.8 for the total SGRQ scores, 26.9 for symptom scores, 12.2 for activity scores, and 4.0 for impact scores.

In the univariate analyses of continuous SGRQ scores, the symptom scores were higher in those participants with current allergy or who smoked tobacco than in those participants without current allergy or smoking (Table 3). The differences in the median symptom scores were 7.6 (allergy) and 6.8 (smoking). There were statistically significant, although low, differences in the activity scores between the participants who were overweight and normal weight, and in the impact and total scores between females and males participants (Table 3).

In the multivariate analyses of categorized SGRQ scores, wheezing in early childhood was associated with high total scores (OR 3.1 [95% CI, 1.2–8.0]) (Table 4). Current allergy was associated with high symptom scores (OR 4.4 [95% CI, 1.7–11.4]) and high activity scores (3.5; 1.3–9.6). Current tobacco smoking was associated with high symptom scores (OR 4.3 [95% CI, 1.5–12.7]), and overweight with high activity scores (3.3; 1.2–9.0). In addition, female sex was associated with high impact scores (OR 3.2 [95% CI, 1.3–7.4]) (Table 4).

When current asthma was included in the multivariate model, early childhood wheezing lost its significance, but current asthma retained a significant association with scores in all SGRQ domains (Table 5). The ORs and 95% CIs for high symptom scores, high activity scores, high impact scores, and high total scores were OR 3.8 (95% CI, 1.1–12.7), OR 3.8 (95% CI, 1.1–12.8), OR 8.7 (95% CI, 2.4–31.4), and OR 8.7 (95% CI, 2.1–36.6), respectively (Table 5).

In *post hoc* analyses, the participants with current asthma and smoking were excluded. Fourteen subjects (cases) and 36 controls were included, and there were no statistically significant differences anymore in any SGRQ scores between the subjects (cases) and the controls. In univariate analyses, the median (IQR) symptom scores were 2.5 (0–11.4) in subjects (cases) and 2.5 (0–13.7) in controls ($p = 0.862$); activity scores were 0 (0–0) and 0 (0–0) ($p = 0.551$); impact scores were 0 (0–0) and 0 (0–0) ($p = 0.054$); and total scores were 0.9 (0–3.7) and 1.5 (0–5.0) ($p = 0.498$), respectively.

Table 1 Health-related quality of life of the subject (cases) hospitalized with wheezing in early childhood and population-based controls as assessed by SGRQ scores

SGRQ Domain Score	Subjects (cases), median (IQR) (n = 49)	Controls, median (IQR) (n = 60)	p
Symptom	13.7 (3.8–29.1)*	7.8 (0.0–18.3)	0.019
Activity	0.0 (0.0–11.3)	0.0 (0.0–5.8)	0.477
Impact	0.0 (0.0–4.9)	0.0 (0.0–4.3)	0.825
Total	3.9 (1.7–11.9)	1.9 (0.0–7.4)	0.080

SGRQ = St. George’s Respiratory Questionnaire; IQR = interquartile range.

*Clinically relevant difference (>4 points) between the median scores between the subjects (cases) and the controls.

Table 2 The scores calculated from the St. George's Respiratory Questionnaire in relation to the viral etiology of wheezing in early childhood

Subjects (cases)	Symptom Score		Activity Score		Impact Score		Total Score	
	Median (IQR)	p*	Median (IQR)	p*	Median (IQR)	p*	Median (IQR)	p*
RV (n = 14)	16.3 (8.9–28.2)	0.035	0.0 (0.0–12.7)	0.658	0.0 (0.0–3.7)	0.555	3.4 (1.8–13.6)	0.191
RSV (n = 14)	6.4 (0.0–14.0)	0.825	0.0 (0.0–7.3)	0.748	0.0 (0.0–2.7)	0.683	2.2 (0.0–5.4)	0.905
Other viruses (n = 12)	20.8 (3.3–36.2)#	0.049	2.6 (0.0–11.9)	0.141	1.7 (0.0–7.1)	0.402	4.2 (2.0–13.05)	0.083
Controls (n = 60)	7.8 (0.0–18.3)	—	0.0 (0.0–5.8)	—	0.0 (0.0–4.3)	—	1.9 (0.0–7.4)	—

IQR = Interquartile range; RV = positive for rhinovirus; RSV = positive for respiratory syncytial virus.

*Nonadjusted p values (subjects [cases] vs controls); no statistically significant differences between the virus-induced wheezing groups.

#Clinically relevant difference (>4 points) between the median scores of the virus-induced wheezing groups (cases) and the controls.

DISCUSSION

This cohort study included 49 young adults who were hospitalized for LRTI with wheezing in early childhood and followed up prospectively thereafter, and 60 population-based controls. At the median age of 18.8 years, the subjects (cases) had lower HRQoLs

assessed by SGRQ symptom and total scores than did the controls. Wheezing in early childhood was associated with higher total scores in multivariate analyses adjusted for sex and current allergy, tobacco smoking, and overweight, but this association was lost when current asthma was included in the model. Current

Table 3 Factors associated with HRQoL of the 109 young adults in univariate analyses, with HRQoL measured by using the St. George's Respiratory Questionnaire

	Symptom Score		Activity Score		Impact Score		Total Score	
	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p	Median (IQR)	p
Current asthma (n = 33)	20.2 (9.4–39.4)*		5.3 (0.0–20.4)*		4.0 (0.0–10.0)*		6.3 (3.1–16.9)*	
No asthma (n = 76)	7.8 (0.0–18.3)	<0.001	0.0 (0.0–0.0)	0.003	0.0 (0.0–4.0)	<0.001	1.7 (1.7–5.7)	<0.001
Current allergy (n = 55)	13.1 (5.1–29.1)*		0.0 (0.0–11.2)		1.6 (0.0–8.1)		3.9 (1.6–13.0)	
No current allergy (n = 54)	5.5 (0.0–18.2)	0.011	0.0 (0.0–0.0)	0.043	0.0 (0.0–4.1)	0.119	2.3 (0.0–6.0)	0.021
Tobacco smoker (n = 34)	14.6 (7.1–31.6)*		0.0 (0.0–19.0)		0.8 (0.0–10.0)		4.0 (1.6–14.1)	
Nonsmoker (n = 75)	7.8 (0.0–20.0)	0.033	0.0 (0.0–6.0)	0.667	0.0 (0.0–4.1)	0.286	2.0 (0.0–6.5)	0.077
BMI, ≥ 25 kg/m ² (n = 36)	13.7 (0.0–26.7)		0.0 (0.0–31.6)		0.0 (0.0–10.9)		4.2 (0.3–16.3)	
BMI < 25 kg/m ² (n = 73)	10.2 (0.0–20.1)	0.345	0.0 (0.0–2.6)	0.011	0.0 (0.0–4.1)	0.752	2.4 (0.8–6.1)	0.126
Females (n = 52)	11.7 (0.0–28.7)		0.0 (0.0–21.9)		1.7 (0.0–9.9)		4.6 (1.2–15.2)	
Males (n = 57)	10.2 (0.0–19.0)	0.186	0.0 (0.0–2.6)	0.054	0.0 (0.0–1.7)	0.009	2.2 (0.4–5.6)	0.034

HRQoL = Health-related quality of life; IQR = interquartile range; BMI = body mass index.

*Clinically relevant differences (> 4 points) in median scores between the groups in paired comparisons.

Table 4 Factors possibly associated with HRQoL of the 109 young adults in multivariate analyses, with HRQoL measured by using the St. George's Respiratory Questionnaire: First regression model

	Symptom Score, OR (95% CI) (r2 = 21.9%)	Activity Score, OR (95% CI) (r2 = 21.5%)	Impact Score, OR (95% CI) (r2 = 11.7%)	Total Score, OR (95% CI) (r2 = 18.4%)
Wheezing in infancy	1.7 (0.7–4.3)	2.1 (0.8–5.4)	1.3 (0.5–3.0)	3.1 (1.2–8.0)
Current allergy	4.4 (1.7–11.4)	3.5 (1.3–9.6)	1.5 (0.6–3.5)	2.0 (0.8–5.0)
Tobacco smoking	4.3 (1.5–12.7)	1.2 (0.4–3.5)	1.6 (0.6–4.1)	2.2 (0.8–6.0)
BMI > 25 kg/m2	1.2 (0.5–3.2)	3.3 (1.2–9.0)	0.8 (0.3–1.9)	1.3 (0.5–3.3)
Sex	1.6 (0.7–3.9)	2.2 (0.9–5.7)	3.2 (1.3–7.4)	2.6 (1.0–6.2)

HRQoL = Health-related quality of life; OR = odds ratio; CI = confidence interval; r2= regression coefficient; BMI = body mass index.

asthma was associated with higher scores in all SGRQ domains. Furthermore, current allergy was associated with higher symptom and activity scores, and current tobacco smoking was associated with higher symptom scores.

Three previous studies demonstrated that HRQoL was impaired from 2 months to 3 years after bronchiolitis in infancy, when age-specific HRQoL methods were used.^{7,8,10} Furthermore, there are few studies on long-term HRQoL data available among subjects with a history of bronchiolitis or wheezing in early childhood. Only one previous cohort study evaluated HRQoL measured by the SGRQ instrument as long as nearly 30 years after early childhood wheezing.² In the study, all the SGRQ domains (i.e., symptom, activity, and impact scores) were significantly higher in the cases than in the controls.²

In the present study, almost 20 years after early childhood wheezing, there was a clinically relevant difference in SGRQ symptom scores between the subjects (cases) and the controls. The results of these two cohorts suggested that respiratory health may persistently reduce

earlier in those with a history of early childhood wheezing compared with those without such wheezing history. This reduction could be seen on HRQoL at the age of 30 years but only in symptom scores at the age of 20 years.

In the present study, the HRQoL of the subjects (cases) with asthma was lower than the HRQoL of the subjects without asthma. Even larger differences in the median scores were observed between those who used ICS and those who did not. This strengthened our results because ICS treatment is a proxy of chronic or severe asthma. In addition, all the observed associations retained their significance in multivariate analyses adjusted for the most relevant risk factors, which highlights asthma as an independent risk factor for reduced HRQoL in young adults.

In line with our findings, many other studies have shown that asthma has reduced the HRQoL in adolescents and young adults. For example, a large study in the United States demonstrated worse self-reported health and impaired physical and mental health in adolescents with symptomatic asthma compared with those without asthma.¹⁶ In young adults with asthma,

Table 5 Factors possibly associated with HRQoL of 109 young adults in multivariate analyses, with HRQoL measured by using the St. George's Respiratory Questionnaire: Second regression model, including factors in the first model and current asthma

	Symptom Score, OR (95% CI) (r2 = 27.3%)	Activity Score, OR (95% CI) (r2 = 27.2%)	Impact Score, OR (95% CI) (r2 = 26.7%)	Total Score, OR (95% CI) (r2 = 30.8%)
Wheezing in infancy	1.0 (0.4–2.9)	1.2 (0.4–3.6)	0.5 (0.2–1.5)	1.5 (0.5–4.4)
Current allergy	3.7 (1.4–10.0)	3.0 (1.1–8.4)	1.1 (0.4–2.8)	1.6 (0.6–4.2)
Tobacco smoking	4.9 (1.7–14.7)	1.4 (0.5–4.3)	2.0 (0.7–5.5)	2.7 (0.9–7.5)
BMI > 25 kg/m2	1.4 (0.5–3.7)	4.3 (1.5–12.2)	1.0 (0.4–2.6)	1.6 (0.6–4.2)
Sex	1.5 (0.6–3.7)	2.1 (0.8–5.4)	3.1 (1.3–7.8)	2.4 (0.9–6.1)
Current asthma	3.8 (1.1–12.7)	3.8 (1.1–12.8)	8.7 (2.4–31.4)	(2.1–36.6)

HRQoL = Health-related quality of life; OR = odds ratio; CI = confidence interval; r2= regression coefficient; BMI = body mass index.

generic quality of life, as measured by the 36-Item Short Form questionnaire, was similar to that of population-based controls, but asthma was associated with lower HRQoL according to the asthma-specific Living with Asthma questionnaire in a Swedish study.¹⁷ In addition, female sex and reduced lung function predicted lower HRQoL during a 5-year follow-up study of individuals with asthma at the median age of 26 years.¹⁷ Moreover, in a Swedish cohort study, adolescents with uncontrolled asthma had the lowest generic HRQoL, as measured by the KIDSCREEN-10 questionnaire.¹⁸

Many previous studies have documented an increased prevalence of childhood asthma after RSV-induced wheezing in infancy,^{19–21} but the results on long-term outcomes have been controversial.^{5,19,22} Instead, RV-induced wheezing in infancy has been consistently associated with asthma and atopic diseases in later life.²³ In an earlier follow-up visit of this present cohort, the mean risk of asthma at the age of 7 years was 10-fold higher when wheezing in early childhood was associated with RV infection compared with RSV infection.¹³ In the present study, wheezing in early childhood was associated with reduced HRQoL in the young adults assessed by using the SGRQ instrument; however, current asthma showed a stronger association with reduced HRQoL.

Our findings suggested that wheezing in early childhood can have, in addition to direct influences due to airway damage, indirect influences on later HRQoL by increasing the risk of asthma. In the present study, tobacco smoking exhibited an expected association with higher symptom scores, although none of the subjects (cases) were ages > 20 years. In line with this result, a review that included 54 studies confirmed an association between smoking and lower quality of life, and an increase in the numbers of cigarettes smoked strengthened the association.²⁴

The main limitation of the present study was the small number of participants because only 49 of the original patients with wheezing and 60 controls participated. These low figures meant that the analyses were underpowered. The attention rate was half in the subjects (cases) and only 15% in the controls, which meant a risk of selection bias because the subjects (cases) who were symptomatic usually attended the studies more often than the nonsymptomatic ones. Thus, the observed differences between the subjects (cases) and the controls were more probably under- than overestimations of real differences. The patients with wheezing were enrolled in this cohort at the time of hospitalization in early childhood 17–20 years earlier, and, although prospectively followed up thereafter, drop-outs were understandable. The SGRQ instrument provides a high-quality measurement of HRQoL, with good validity and reliability. It can be used for different respiratory diseases, and its

domains have shown a high correlation with measures of disease activity.¹⁴

CONCLUSION

Infection-associated wheezing in early childhood did not affect HRQoL directly at the mean age of 19 years. However, early childhood wheezing was an independent risk factor for asthma,¹¹ which reduced HRQoL, especially in those who presented with the higher symptom scores.

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