

The impact of preschool wheezing patterns on health-related quality of life at age 4 years

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CHQ-PF28 (Child Health Questionnaire-Parent Form 28 items)

HRQOL (Health-Related Quality of Life)

ABSTRACT

We assessed whether dynamic preschool wheezing patterns affect health-related quality of life (HRQOL) at age 4 years.

The study included 3878 children participating a prospective cohort study. Information on preschool wheezing was obtained by questionnaires and children were categorised into: never, early, late and persistent wheezing. At age 4 years HRQOL was measured, using the Child Health Questionnaire (CHQ).

Persistent wheezing was associated with reduced scores for 9 out of 13 CHQ scales. No differences in psychosocial CHQ scores ($p>0.05$), but lower physical CHQ scores were found in children with late and persistent wheezing, compared to children who never wheezed ($p<0.001$). Mean scores on general health perceptions were respectively 8 and 12 points lower (on a 0-100 scale) in children with late and persistent wheezing ($p<0.001$), and children with 1-3 episodes and ≥ 4 episodes of wheezing in the 4th year respectively scored 7 and 24 points lower ($p<0.001$), compared to children who never wheezed.

Persistent wheezing during preschool age independently affects child's HRQOL, particularly general health perceptions and physical domains at age 4 years. HRQOL was more affected by frequent wheezing episodes in the 4th year of life, rather than by duration of wheezing at age 0-4 years.

KEYWORDS: Asthma symptoms, Child Health Questionnaire-Parent Form 28 items, Preschool children, Well-being, Wheezing

INTRODUCTION

Wheezing is highly prevalent in children, especially in the first years of life. Wheezing is the most important symptom of asthma and is one of the leading causes of morbidity in early childhood (1). During the past decade, the use of health-related quality of life (HRQOL) as an essential outcome measure of asthma treatment and management has increased (2-3). HRQOL assesses the functional impact of asthma symptoms across multiple clinical relevant domains. Ultimately, the goal of asthma management is to achieve both optimal disease control and HRQOL improvements (4-5). Recent findings suggest that clinical efforts to improve health outcomes in pediatric asthma should target those at-risk for poor HRQOL (6).

Several studies have investigated the impact of asthma on children's HRQOL, focussing on severity of asthma symptoms (7-10). The majority of these studies have been cross sectional (7-9). The available evidence suggests an association between wheezing and HRQOL (8-9), but the dynamics of how wheezing over time affects children's HRQOL remains unclear. Wheezing symptoms are often non-specific, and might partly be due to respiratory tract infections. Cross sectional studies on the association between preschool wheezing and HRQOL have been inconclusive.

It is important to understand the impact of wheezing patterns on HRQOL in preschoolers, because inadequate management of asthma in children between age 2 and 8 years seems common (11). We hypothesised that HRQOL is more likely to be impaired in preschool children with persistent wheezing, compared to children with transient or without wheezing.

The aim of our study was to assess whether dynamic preschool wheezing patterns affect child's HRQOL at age 4 years, using the parent form of the Child Health Questionnaire (CHQ-PF28). In particular, we explored whether children with early, late and persistent preschool wheezing had lower HRQOL scores at age 4 years, compared to children without preschool wheezing. This study will help to identify the HRQOL domains needing attention in 4 year olds with different wheezing patterns. If our hypothesis will be confirmed, this study will highlight the importance of early attention to preschool child's wheezing symptoms and domains of HRQOL.

METHODS

Design and cohort

This study is embedded within Generation R, a population-based prospective cohort study (12-13). The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki.

The Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study. Informed consent was obtained from participating parents. Consent for postnatal follow-up was available for 7295 children (figure 1). Information on wheezing patterns and at least one CHQ-PF28 scale was available for 3878 children (53% of the postnatal cohort).

Wheezing

Symptoms of wheezing were assessed by core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) at the ages of 1, 2, 3 and 4 years (14). Response rates for these questionnaires, completed by parents, were 71%, 76%, 72%, 73% respectively. Based on a parentally reported history of wheezing taken from the four questionnaires, preschool children were assigned to the following categories (15-16): Never wheezing: no wheezing in the first 4 years of life (n=1996); early wheezing: at least 1 episode of wheezing in the first 3 years and no wheezing in the 4th year (n=1334); late wheezing: no wheezing in the first 3 years and wheezing in the 4th year (n=95) and persistent wheezing: at least 1 episode of wheezing in the first 3 years and wheezing in the 4th year (n=453). Additionally, at age 4 years, parental reports on frequency of wheezing (1-3 episodes, ≥ 4 episodes) were collected (14).

Health-related quality of life (HRQOL)

The CHQ-PF28 was used to measure HRQOL of the child at age 4 years (17). Based on 28 items, the CHQ-PF28 measures the HRQOL of children and their families across 13 scales (see table 1) (18-19). The following eight multi-item scales measure the child's HRQOL: *Physical functioning*, *Role functioning: emotional*, *Role functioning: physical*, *Bodily pain*, *General behaviour*, *Mental health*, *Self esteem*, *General health perceptions*. These multi-item scales are summarised into a *Physical summary measure* and a *Psychosocial summary measure*. Furthermore there is the *Change in health* item and the *Family cohesion* item. The impact of the child's health on the caregiver's and family's HRQOL is measured across the remaining three multi-item scales: *Parental impact: emotional*, *Parental impact: time*, *Family activities*. All scale measures are transformed to scores ranging from 0 to 100. Lower scores correspond to lower HRQOL. Summary measures are standardised with a mean of 50 and standard deviation of 10 to reflect general US population norms for children (18-19).

Covariates

The effect of wheezing patterns on children's HRQOL is likely to be influenced by the following covariates. These were selected based on current literature on determinants of HRQOL in children (20-21).

Maternal characteristics were age, educational level, household income, ethnicity, single motherhood, smoking during pregnancy, atopy and psychopathology. Information about maternal age, the highest attained maternal educational level (low, moderate, high), maternal ethnicity (Dutch, other western, non-western) and single motherhood (yes, no), maternal smoking during pregnancy (yes, no) and maternal atopy (yes, no) were obtained at enrolment in the study by questionnaires. Maternal educational level and maternal ethnicity were defined according to the classification of Statistics Netherlands (22-23). Data on household income ($<€1600/\text{month}$, $\geq €1600/\text{month}$) was obtained at the child's age of 3 years, using the 2005 monthly general labour income as the cut-off point (24). Maternal psychopathology (score in tertiles) was assessed at the child's age of 2 months using the Global Severity Index (GSI) of the Brief Symptom Inventory (a validated self-report measure, which consists of 53 positive and negative self-appraisal statements) (25). Respective item scores were summed to derive a total score of the GSI (range: 0-200). Total scores were divided into tertiles (cut-off points: 3 and 10).

Child's characteristics were gender, gestational age at birth, birth weight, exposure to tobacco smoke exposure. Information on gender (boy, girl), gestational age at birth (weeks) and birth weight (grams), were obtained from medical records. Tobacco smoke exposure (yes, no) was measured at age 2 years, using parental reported questionnaires.

Data analyses

Characteristics of the study population were calculated and stratified by wheezing pattern. P values for differences between wheezing patterns were calculated by means of the Chi-square test for categorical variables and UNIANOVA for continuous variables. To investigate the association between wheezing patterns and HRQOL, differences in mean HRQOL scores of early, late and persistent wheezing were compared separately with the mean HRQOL scores of those without preschool wheezing. In order to indicate the relevance of statistically significant differences, effect sizes (d) were calculated by dividing the difference in mean scores between wheezing patterns by the largest standard deviation. Cohen suggests that d values of 0.2, 0.5, and 0.8 respectively represent small, medium, and large effect sizes (27).

Linear regression models were computed with wheezing patterns as the determinant and each of the CHQ-PF28 scales as outcomes. In multivariate linear regression analyses maternal and child's characteristics were added to these models. Additionally, the association between frequency of wheezing in the 4th year of life and HRQOL was studied, using linear regression models. A Bonferroni correction was implemented to account for the number of analyses conducted.

Missing values in the covariates ranged from 0% (gender) to 19% (maternal psychopathology). Missingness of the outcome was independent of the exposure and vice versa. Because the missing covariates were not completely at random, complete-case analysis was likely to introduce biased results. A multiple imputation method was used to impute missing covariates (28). Ten imputed datasets were generated using a fully conditional specified model to handle missing values. Imputations were based on the relations between all variables in the study. No differences in results were observed between analyses with imputed missing data or complete cases.

Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Complete data on wheezing patterns were available in 3878 children. Table 2 shows the characteristics of the study population, stratified by wheezing pattern. In total 51.5% (n=1996) of the children never wheezed (the reference group), 34.4% (n=1334) wheezed early, 2.4% (n=95) wheezed late and 11.7% (n=453) wheezed persistently during the preschool age. All characteristics in table 2,

except maternal age at enrolment, were associated with wheezing patterns ($p < 0.05$). Compared with the reference group, maternal psychopathology ($p < 0.05$) was different for all wheezing patterns. Compared with the reference group, the proportions of single motherhood ($p < 0.01$), smoking during pregnancy ($p < 0.05$), maternal atopy ($p < 0.001$), gestational age ($p < 0.01$) and birth-weight ($p < 0.01$) were different for early and persistent wheezing. Children with late and persistent wheezing more often had low maternal educational level (compared to the reference group, $p < 0.01$). Children with persistent wheezing were more often non-Dutch and from low-income families ($< €1600/\text{month}$) compared with the reference group ($p < 0.001$).

Table 3 shows mean CHQ-PF28 scores at age 4 years for children with early wheezing, late wheezing and persistent wheezing compared to children who never wheezed. Based on parent reports, children with early, late and persistent wheezing had lower scores than the reference group (except for the scale *Change in health*). On average, parents of children with early and persistent wheezing reported more often an improvement in health, compared to the reference group ($p < 0.001$). Relevant differences in CHQ-PF28 scores were found in children with persistent wheezing for the scales: *Bodily pain*, *General health perceptions*, *Parental impact (emotional and time)*. Most effect sizes were small, except for scale *General health perceptions* in children with persistent wheezing ($d = 0.78$).

After adjustment for maternal and child's characteristics, children with persistent wheezing had lower scores on all CHQ-PF28 scales, except for *General behaviour*, *Mental health*, *Self esteem*, *Family Cohesion* and *Change in health*. Scores on *Change in health* are higher rated in children with early and persistent wheezing compared to children who never wheezed (adjusted regression coefficient [$a\beta$]=4.4, 95% Confidence Interval [CI]: 3.1 to 5.6 and $a\beta$ =8.5, 95% CI: 6.7 to 10.4, respectively) (table 4). On the scales *Bodily pain* and the *Physical summary measure*, not only parents of children with persistent wheezing, but also parents of children with late wheezing reported significantly poorer HRQOL compared to parents of children who never wheezed. The strongest associations were found for scores on *General health perceptions* in children with early, late and persistent wheezing compared to children who never wheezed ($a\beta$ =-3.0, 95% CI: -4.0 to -2.0; $a\beta$ =-7.8, 95% CI: -10.9 to -4.7 and $a\beta$ =-12.3, 95% CI: -13.8 to -10.7, respectively). These associations remained statistically significant after applying a Bonferroni correction for multiple testing ($p < 0.003$; i.e. 0.05/15).

The majority of wheezing children had relative infrequent symptoms (1-3 episodes a year) in the 4th year of life and experienced only a limited reduction in HRQOL (online supplementary table S2). Only in the small group with frequent wheezing (>4 episodes a year) we observed a substantial impact on the child's well-being, particularly on the scores of *General health perceptions* ($a\beta=-23.7$, 95% CI: -26.7 to -20.7, compared to children without wheezing in the 4th year) as well as on physical domains of HRQOL and parental concerns (effect estimates of *Bodily pain*: $a\beta=-10.8$, 95% CI: -14.5 to 7.1 and effect estimates of *Parental impact: emotional*: $a\beta=-11.6$, 95% CI: -14.7 to -8.6).

Non response analyses

Excluded children, with missing data on wheezing patterns and HRQOL (n=3417), were compared with included children, who had information on wheezing patterns and HRQOL (n=3878) (online supplementary table S1). Differences were present in all covariates, except for gender, respiratory tract infections and maternal atopy ($p>0.05$).

DISCUSSION

This longitudinal cohort study shows low scores on *General health perceptions* and also on the *Physical summary scale* of HRQOL in children with late and persistent wheezing, independent of several maternal and child's characteristics. HRQOL was more affected by frequent wheezing episodes in the 4th year, than by duration of wheezing at age 0-4 years. No differences in scores on the *Psychosocial summary scale* were found between children with different wheezing patterns. Persistent wheezing in preschool children has an impact on the family, affecting the scales *Family activities* and *Parental impact (emotional and time)*. Although most observed effects of early and late wheezing on child's HRQOL are small, an almost large effect ($d=0.78$) of persistent wheezing was found on *General health perceptions*, already at preschool age. The low scores on *General health perceptions* should be interpreted as a subjective evaluation of child's general health: parents of children with persistent wheezing believe that their child's health is poor and likely to get worse.

Several studies previously assessed the association between wheezing and HRQOL in childhood (2, 7-8, 10) and observed that wheezing was associated with poor HRQOL. However, these studies used a cross-sectional design that made it impossible to explore the relative impact of wheezing patterns during preschool age. By using a longitudinal design, our study shows that exposure to wheezing during preschool age affects general health perceptions and more specifically

affects physical domains of HRQOL at age 4 years. Additionally we found that HRQOL was more affected by frequent wheezing episodes in the 4th year, than by duration of wheezing at age 0-4 years.

Impairment at age 4 years is most pronounced for 9 out of 13 CHQ-PF28 scales in children with persistent wheezing, compared to children who never wheezed. Comparing the associations between preschool wheezing patterns and *Physical* and *Psychosocial summary measures* (table 3 and 4), our findings support a previous finding in school-aged children: that a child's asthma particularly impairs the physical domains of HRQOL (2). Similar to studies in adolescents (29), we also observed that wheezing has an impact on parental perceptions with regard to children's *General health* and *Bodily pain* at preschool age. However, we did not observe any impact on *Self esteem* or *Mental health* (29), suggesting that perhaps the impact emerges after preschool age. The observation that a positive change in health was reported by parents for children with early and persistent wheezing compared to children who never wheezed is not unexpected. These children had previous wheezing symptoms and it is likely that these children were already free of symptoms at the time of completing the questionnaire.

This study benefits from a large sample size and a longitudinal design, which enabled us to classify wheezing symptoms into longitudinal patterns. A prospective design with repeated measurements may be especially important in pediatric asthma research. Recent longitudinal studies have made clear that childhood asthma can be highly variable with respect to symptoms as well as time course (15-16).

The results of this study should be viewed in light of several limitations. Mothers of children who were included were higher educated, more healthy and more frequently of Dutch origin than those of children who were excluded. Therefore, selection bias may have occurred; for example if non-participating parents (due to non-response or lost to follow-up) whose children had wheezing symptoms systematically provided higher (or lower) scores on child's HRQOL compared to participating parents whose children had wheezing symptoms. Furthermore, the children in this study may not fully represent the general population as all of them resided in Rotterdam.

Wheezing and HRQOL were measured by parental reports. Parental reports of wheezing are widely accepted in epidemiological studies and reliably reflects the incidence of wheezing in preschool children (30). When children don't have the cognitive ability to report their own HRQOL, proxy reports by parent are appropriate sources of information about HRQOL (31). Both overestimation and

underestimation of HRQOL scores may have occurred. Petsios et al. have shown that parents may tend to overestimate HRQOL of their asthmatic school- aged child. Also it cannot be totally ruled out that current wheezing was associated with increased parental awareness, leading to an underestimation of child's HRQOL. Information about HRQOL was prospectively collected without direct reference to wheezing and we did adjust for relevant parent-related characteristics in our analyses (single parenthood, low educational level, family income and maternal psychopathology) and found that some differences in child's HRQOL between children with different wheezing patterns remained present. Regardless, it is possible that the differences that we found may have been affected by parent-related characteristics other than the ones that we studied (32). Additional research incorporating child self-report is needed during follow-up at school age to substantiate our findings (33).

We used Cohen's *d* for the interpretation of relevant differences in HRQOL. Although this is an accepted method, there are still insufficient data to understand the relative impact of the observed score differences. Empirically defined cut-off points for *minimal important differences* for HRQOL measures such as the CHQ-PF28 are important in future research.

The CHQ-PF28 is a generic HRQOL questionnaire and has the advantage of measuring multiple dimensions of HRQOL across a diversity of conditions to understand the relative impact of diseases and conditions for children and their families. As such, it is possible to compare the HRQOL of children with and without certain symptoms. However, the use of both a general HRQOL questionnaire in concert with a condition-specific measure may further enrich our understanding of the relative and specific impact on children's health and well-being. For example, an asthma specific measure may provide insight into the specific impact of sleeping problems due to wheezing while the generic questionnaire may help to position this impact relative to children who may also experience this issue but have not been diagnosed with asthma (e.g., children with ADHD or cancer).

Although we were able to adjust for important maternal and child characteristics, it should be acknowledged that, in the present study, unmeasured variables, such as detailed information on health care use, genetic factors (6) or treatment responsiveness, could (in part) explain the association between wheezing patterns and HRQOL (32).

In conclusion, dynamic patterns of preschool wheezing showed differential effects on HRQOL at age 4 years, independent of several maternal and child's characteristics. Particularly, persistent wheezing during preschool age affects general health perceptions and physical domains at age 4 years. HRQOL

was more affected by frequent wheezing episodes in the 4th year, than by duration of wheezing at age 0-4 years. These findings suggest the need to study how improvement of HRQOL among children with persistent wheezing symptoms might be promoted, with specific attention to the physical domain in children with frequent preschool wheezing.

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STATEMENT OF INTEREST

None declared.

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Table 1. CHQ-PF28 scales, number of items per scale and score interpretation (Total N=3878)*

CHQ-PF28 scales	Number of items	Available data N (%)	Description low score	Description high score
Physical functioning	3	3845 (99.1)	Child is limited a lot in performing all physical activities, including self care, because of health	Child performs all types of physical activities, including the most vigorous, without limitations attributable to health
Role functioning: emotional	1	3855 (99.4)	Child is limited a lot in school work or activities with friends as a result of emotional or behaviour problems	Child has no limitations in schoolwork or activities with friends as a result of emotional or behaviour problems
Role functioning: physical	1	3857 (99.5)	Child is limited a lot in school work or activities with friends as a result of physical health	Child has no limitations in schoolwork or activities with friends as a result of physical health
Bodily pain	1	3855 (99.4)	Child has extremely severe, frequent, and limiting bodily pain	Child has no pain or limitations because of pain
General behaviour	4	3863 (99.6)	Child very often exhibits aggressive, immature, delinquent behaviour	Child never exhibits aggressive, immature, delinquent behaviour
Mental health	3	3852 (99.3)	Child has feelings of anxiety and depression all of the time	Child feels peaceful, happy, and calm all of the time
Self esteem	3	3814 (98.3)	Child is very dissatisfied with abilities, looks, family/peer relationships, and life overall	Child is very satisfied with abilities, looks, family/peer relationships' and life overall
General health perceptions	4	3840 (99.0)	Parent believes child's health is poor and likely to get worse	Parent believes child's health is excellent and will continue to be so
Parental impact: emotional	2	3826 (98.7)	Parent experiences a great deal of emotional worry/concern as a result of child's physical and/or psychosocial health	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health
Parental impact: time	2	3825 (98.6)	Parent experiences a lot of limitations in time available for personal needs because of child's physical and/or psychosocial health	Parent doesn't experience limitations in time available for personal needs because of child's physical and/or psychosocial health
Family activities	2	3707 (95.6)	The child's health very often limits and interrupts family activities or is a source of family tension	The child's health never limits or interrupts family activities or is a source of family tension
Family cohesion	1	3707 (95.6)	Family's ability to get along is rated "poor"	Family's ability to get along is rated "excellent"
Change in health	1	3845 (99.1)	Child's health is much worse now than one year ago	Child's health is much better now than one year ago

*Reproduced with permission from the principal author JM Landgraf (18-19). CHQ-PF28=Child Health Questionnaire Parental Form, including 28 items.

Table 2. Characteristics of the study population by preschool wheezing pattern (n=3878)

		Preschool wheezing pattern				
Characteristics		Never n=1996 (51.7)	Early n=1334 (34.1)	Late n=95 (2.5)	Persistent n=453 (11.7)	p Value [*]
<i>Maternal characteristics</i>						
Age at enrolment (years)		31.8 (4.3)	31.7 (4.3)	31.4 (5.1)	31.5 (4.9)	0.184
Educational level	Low	228 (11.5)	159 (12.1)	20 (21.1)	73 (16.5)	< 0.001
	Middle	495 (24.9)	354 (26.9)	28 (29.5)	151 (34.1)	
	High	1264 (63.6)	802 (61.0)	47 (49.5)	219 (49.4)	
Household income (€/month)	< 1600	209 (11.1)	138 (11.8)	15 (17.4)	85 (21.6)	< 0.001
	≥ 1600	1680 (88.9)	1029 (88.2)	71 (82.6)	309 (78.4)	
Ethnicity	Dutch	1407 (71.2)	908 (69.1)	59 (62.8)	253 (58.4)	< 0.001
	Other western	237 (12.0)	188 (14.3)	13 (13.8)	85 (19.6)	
	Non-western	333 (16.8)	218 (16.6)	22 (23.4)	95 (21.9)	
Single motherhood	Yes	110 (5.7)	102 (7.9)	5 (5.4)	43 (10.0)	0.001
Smoking during pregnancy	Yes	331 (19.6)	254 (23.0)	14 (16.7)	101 (27.7)	0.001
Atopy	Yes	640 (36.6)	502 (43.9)	30 (35.7)	172 (46.0)	<0.001
Psychopathology	Highest tertile	443 (26.0)	359 (34.9)	33 (38.8)	148 (43.8)	<0.001
	Middle tertile	561 (33.0)	334 (32.4)	28 (32.9)	107 (31.7)	
	Lowest tertile	689 (41.0)	337 (32.7)	24 (28.2)	83 (24.6)	
<i>Child's characteristics</i>						
Gender	Boy	903 (45.2)	733 (54.9)	54 (56.8)	254 (56.1)	< 0.001
Gestational age (weeks)		40.0 (1.6)	39.7 (1.9)	40.1 (1.5)	39.7 (1.9)	< 0.001
Birth weight (grams)		3480 (537)	3414 (589)	3517 (542)	3395 (616)	0.002
Respiratory tract infections	Yes	660 (34.8)	620 (54.2)	34 (37.4)	228 (60.2)	< 0.001
Postnatal tobacco smoke exposure	Yes	271 (13.7)	191 (15.1)	17 (17.9)	88 (21.0)	< 0.001
Doctor-diagnosed asthma	Yes	12 (0.6)	63 (5.1)	1 (1.1)	78 (19.2)	< 0.001
Frequency of wheezing (4 th year)	Never	1996 (100)	1334 (100)	0 (0)	0 (0)	< 0.001
	1-3 times	0 (0)	(0)	78 (87.6)	339 (79.6)	
	≥ 4 times	0 (0)	(0)	11 (12.4)	87 (20.4)	

Values are absolute numbers (percentages) for categorical variables or means (standard deviation) for continuous variables. *UNIANOVA for continuous variables and Chi-squared tests for categorical variables. All maternal characteristics, except psychopathology, were obtained at enrolment in the study by questionnaires. Maternal educational level and ethnicity were defined according to the classification of Statistics Netherlands (22-23). Household income was obtained at age 3 years (24). Maternal psychopathology was assessed at child's age 2 months using the Global Severity Index (25). Child's gender, gestational age at birth and birth weight were obtained from medical records. Using questionnaires, child's respiratory tract infections, tobacco smoke exposure and doctor-diagnosed asthma were measured at the ages of 1, 2 and 3 years, respectively.

Table 3. CHQ-PF28 scale scores (mean \pm standard deviation) for children with early, late and persistent wheezing compared to children who never wheezed (n=3878)

CHQ-PF28 scales	CHQ PF-28 scale scores (mean \pm standard deviation)						Effect size ³
	Never wheezing (n=1996)	Early wheezing (n=1334)	Effect size ¹	Late wheezing (n=95)	Effect size ²	Persistent wheezing (n=453)	
Physical functioning	98.4 \pm 8.8	98.2 \pm 9.6	0.02	96.9 \pm 11.9*	0.13	94.8 \pm 15.5***	0.24
Role functioning: emotional	98.7 \pm 8.1	98.2 \pm 9.5*	0.06	97.5 \pm 10.2	0.12	96.3 \pm 15.7***	0.16
Role functioning: physical	98.1 \pm 10.2	97.8 \pm 10.6	0.03	96.8 \pm 11.0*	0.12	94.4 \pm 18.2***	0.20
Bodily pain	88.5 \pm 16.7	88.1 \pm 16.7	0.02	85.3 \pm 18.4	0.17	82.6 \pm 18.9***	0.31
General behaviour	73.7 \pm 14.0	71.9 \pm 14.3***	0.13	70.7 \pm 14.9*	0.21	71.6 \pm 15.7**	0.14
Mental health	83.9 \pm 13.7	82.8 \pm 13.4**	0.08	81.5 \pm 13.7	0.18	81.9 \pm 14.4**	0.14
Self esteem	83.8 \pm 14.7	83.0 \pm 14.4	0.06	82.1 \pm 13.9	0.12	83.5 \pm 14.8	0.02
General health perceptions	91.1 \pm 12.1	87.2 \pm 15.2***	0.26	82.0 \pm 18.9***	0.49	76.4 \pm 18.9***	0.78
Parental impact: emotional	90.1 \pm 13.0	88.6 \pm 13.8**	0.11	85.3 \pm 19.0*	0.25	84.5 \pm 16.6***	0.33
Parental impact: time	94.6 \pm 12.6	93.7 \pm 13.6*	0.07	92.1 \pm 16.4	0.15	89.6 \pm 18.2***	0.28
Family activities	89.2 \pm 16.3	87.4 \pm 17.2***	0.10	85.8 \pm 18.7	0.18	84.9 \pm 19.2***	0.22
Family cohesion	78.0 \pm 17.6	76.9 \pm 17.7	0.06	74.5 \pm 18.4	0.19	73.8 \pm 19.4***	0.22
Change in health	56.1 \pm 15.1	60.9 \pm 18.7***	-0.26	56.4 \pm 18.3	-0.02	65.6 \pm 21.6***	-0.44
Physical summary score	58.1 \pm 5.6	57.5 \pm 6.0**	0.10	55.7 \pm 7.3***	0.33	54.0 \pm 8.7***	0.47
Psychosocial summary score	53.8 \pm 6.2	53.0 \pm 6.4***	0.11	52.3 \pm 7.1	0.20	52.7 \pm 7.2**	0.15

Cohen's effect sizes (d) for differences in HRQOL between preschool wheezing patterns: ¹Early wheezing versus never wheezing ²Late wheezing versus never wheezing ³Persistent wheezing versus never wheezing. *p \leq 0.05, **p \leq 0.01, ***p \leq 0.001, p-values are based on Mann-Whitney U test (26) for differences between wheezing patterns (never wheezing is the reference group). CHQ-PF28=Child Health Questionnaire Parental Form 28 items.

Table 4. Crude and adjusted associations between preschool wheezing patterns and the CHQ-PF28 scores at age 4 years (n=3878)

<i>CHQ-PF28 Scale</i>	<i>Model</i>	<i>Never wheezing N=1996</i>	<i>Early wheezing* N=1334</i>	<i>Late wheezing* N=95</i>	<i>Persistent wheezing* N=453</i>
Physical functioning	Crude		-0.1 (-0.8; 0.7)	-1.9 (-4.2; 0.3)	-3.2 (-4.3; -2.1)
	Adjusted	Reference	0.2 (-0.6; 0.9)	-1.5 (-3.7; 0.8)	-2.6 (-3.7; -1.5)
Role functioning: emotional	Crude		-0.3 (-1.0; 0.3)	-1.2 (-3.3; 0.8)	-1.9 (-2.9; -0.9)
	Adjusted	Reference	-0.1 (-0.8; 0.6)	-0.8 (-2.9; 1.2)	-1.4 (-2.5; -0.4)
Role functioning: physical	Crude		-0.2 (-1.1; 0.6)	-1.3 (-3.9; 1.2)	-2.9 (-4.2; -1.7)
	Adjusted	Reference	-0.1 (-0.9; 0.8)	-1.0 (-3.5; 1.5)	-2.6 (-3.8; -1.3)
Bodily pain	Crude		-0.4 (-1.6; 0.9)	-4.6 (-8.3; -0.8)	-5.1 (-7.0; -3.3)
	Adjusted	Reference	-0.2 (-1.4; 1.1)	-4.4 (-8.2; -0.6)	-4.9 (-6.8; -3.0)
General behaviour	Crude		-1.6 (-2.7; -0.6)	-3.4 (-6.7; -0.2)	-2.4 (-4.0; -0.8)
	Adjusted	Reference	-0.7 (-1.8; 0.3)	-2.6 (-5.8; 0.5)	-0.9 (-2.5; 0.7)
Mental health	Crude		-1.1 (-2.1; -0.1)	-2.3 (-5.4; 0.7)	-2.0 (-3.5; -0.5)
	Adjusted	Reference	-0.4 (-1.4; 0.6)	-1.9 (-4.9; 1.1)	-1.1 (-2.6; 0.4)
Self esteem	Crude		-0.6 (-1.7; 0.5)	-1.2 (-4.5; 2.0)	-0.4 (-2.0; 1.2)
	Adjusted	Reference	-0.1 (-1.2; 1.0)	-0.8 (-4.0; 2.5)	-0.4 (-1.3; 2.0)
General health perceptions	Crude		-3.9 (-4.9; -2.8)	-8.9 (-12.1; -5.8)	-14.0 (-15.5; -12.4)
	Adjusted	Reference	-3.0 (-4.0; -2.0)	-7.8 (-10.9; -4.7)	-12.3 (-13.8; -10.7)
Parental impact: emotional	Crude		-1.1 (-2.1; -0.1)	-5.0 (-8.1; -1.9)	-5.0 (-6.5; -3.5)
	Adjusted	Reference	-0.4 (-1.4; 0.7)	-4.5 (-7.6; 1.4)	-3.8 (-5.4; -2.3)
Parental impact: time	Crude		-0.9 (-1.9; 0.0)	-2.2 (-5.1; 0.8)	-4.4 (-5.9; -2.9)
	Adjusted	Reference	-0.5 (-1.4; 0.5)	-1.7 (-4.7; 1.2)	-3.4 (-4.9; -2.0)
Family activities	Crude		-1.5 (-2.8; -0.3)	-2.2 (-5.9; 1.5)	-3.6 (-5.4; -1.7)
	Adjusted	Reference	-0.9 (-2.1; 0.4)	-1.6 (-5.3; 2.1)	-2.2 (-4.1; -0.4)
Family cohesion	Crude		-1.5 (-2.8; -0.2)	-3.1 (-7.0; 0.9)	-3.8 (-5.7; -1.8)
	Adjusted	Reference	-0.6 (-1.9; 0.7)	-1.6 (-5.5; 2.3)	-1.7 (-3.7; 0.2)
Physical summary score	Crude		-0.5 (-1.0; -0.1)	-2.4 (-3.8; -1.0)	-4.1 (-4.8; -3.4)
	Adjusted	Reference	-0.4 (-0.9; 0.1)	-2.1 (-3.5; -0.8)	-3.7 (-4.4; -3.0)
Psychosocial summary score	Crude		-0.6 (-1.1; -0.2)	-1.4 (-2.8; 0.0)	-1.0 (-1.7; -0.3)
	Adjusted	Reference	-0.2 (-0.7; 0.2)	-1.1 (-2.5; 0.3)	-0.4 (-1.1; 0.3)
Change in health	Crude		5.0 (3.7; 6.2)	-0.4 (-4.2; 3.5)	10.0 (8.1; 11.9)
	Adjusted	Reference	4.4 (3.1; 5.6)	-1.3 (-5.1; 2.4)	8.5 (6.7; 10.4)

Values are regression coefficients and 95% confidence intervals estimated by linear regression models. *Based on a parentally reported history of wheezing at age 0-4 years, children were assigned to the following categories (15-16): never, early, late and preschool persistent wheezing. Each wheezing subgroup is compared to children who never wheezed. The crude model shows the association between wheezing patterns and the CHQ-PF28 scales, unadjusted for covariates. The adjusted model is adjusted for covariates (including potential confounders): maternal age, maternal educational level and maternal ethnicity, household income, single motherhood, smoking during pregnancy, maternal atopy, maternal psychopathology, child's gender, gestational age and birth weight, child's exact age at measurement of HRQOL and child's exposure to tobacco smoking. Scales are analysed combined using the Physical Summary Score and Psychosocial Summary Score. Bold numbers indicate a significant difference in HRQOL score relative to the reference group. CHQ-PF28=Child Health Questionnaire Parental Form 28 items. See table 2 for the definition of the scales.

FIGURES

Figure 1. Flowchart of participants included for analysis

