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Age-specific influence of wheezing phenotypes on preadolescent and adolescent health-related quality of life.

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ABSTRACT

Introduction: Asthma is associated with diminished health-related quality of life (HRQoL). Particularly in adolescence, asthma may be underdiagnosed and undertreated or poorly managed. Therefore, we aimed to determine the association between childhood wheezing phenotypes rather than asthma and adolescent HRQoL in children aged 10 to 17 years.

Methods: We analysed data from two prospective population-based cohort studies (n=604 and n=1804) conducted in southern Germany with baseline assessments in 2000 and 2006 and follow-ups at frequent intervals. Parent-reported wheeze was categorized into never, early transient, persistent, and late-onset wheeze. We assessed child-reported HRQoL in seven scales using the validated KINDL-R. Multivariate linear regression models were computed.

Results: Participants with late-onset wheeze had significantly lower values in all HRQoL scales but physical well-being compared to never wheezers. Early transient wheeze was negatively associated with three HRQoL scales only (family, school, and total). These effects were confined to the oldest age group (≥ 13.5 years) in one study. Persistent wheeze was not associated with HRQoL.

Conclusions: In teenagers, late-onset wheezers seem to be particularly vulnerable for impairments in psychosocial aspects of health-related quality of life. They may therefore require particular attention with regard to education about asthma management and potentially family-based psychosocial intervention.

Keywords: wheezing phenotypes, quality of life, child, adolescent, cohort study

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Introduction

Health-related quality of life (HRQoL) is reduced in asthmatic and wheezy children and teens compared to the general population. This has been shown with regard to diminished emotional functioning,(1,2) mental health,(3–5) in part markedly lower scores on “physical well-being”, “bodily pain” or mean general health (1–3) as well as more negative social outcomes.(1,3,4,6) Following international guidelines on asthma, successful asthma management significantly improves HRQoL.(7) Moreover, measuring HRQoL can add valuable information to better assess the impact of poor asthma control and/or its severity on those children affected.(8,9)

Most of the previous studies on HRQoL have investigated asthma based on a reported diagnosis or a clinical assessment which may comprise heterogeneous subtypes of the disease. Furthermore, asthma is subject to underdiagnosis particularly among teenagers; therefore investigation of wheeze in this age group remains important.(10) For epidemiological research, a distinction between early transient, persistent, and late-onset wheeze has been recommended.(11)

In which way these wheezing phenotypes are associated with diminished HRQoL has to date been reported in one study only.(12) In four year-old children, persistent wheeze and “late-onset” wheeze were associated with lower quality of life regarding general health perceptions and physical health but not psychosocial health.(12)

Much like wheeze, HRQoL seems to show age- and sex-specific differences.(13,14) HRQoL declines around puberty in healthy populations and female teenagers report lower HRQoL than their
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male counterparts.(13,14) So far, no population-based study has explored the association between wheezing phenotypes and HRQoL in children older than four years of age. The objective of our analyses was to close this gap accounting for age- and sex-specific patterns using data from two prospective population-based cohort studies. These two studies are displayed side-by-side to provide sufficient evidence across all age ranges of pre-adolescence and early adolescence.

MATERIALS AND Methods

Data from two prospective population-based cohort studies, KIDS and GABRIELA, conducted in southern Germany were analysed.

KIDS

The baseline assessment of this birth cohort study was conducted between 11/2000 and 11/2001.(15) In brief, all women who came to the University Clinics of Ulm for the delivery of a baby were assessed for eligibility. Women who left the hospital immediately after birth or whose infant was transferred to paediatric care after delivery were excluded. Further exclusion criteria were: birth weight of child less than 2500g, or giving birth after less than 32 gestational weeks. At baseline, the sample consisted of 1090 healthy children born to 1066 mothers who were able to understand German, Turkish or Russian (67% of all 1593 eligible mothers). Follow-ups were conducted in years 1, 2, 3, 4, 6, 8 and 11 after baseline assessing sociodemographic variables, lifestyle, and health information using self-administered parental questionnaires. The study was approved by the ethics boards of Ulm University, of the University of Heidelberg, and of the Physicians' Boards of the states Baden-Wuerttemberg and Bavaria.

GABRIELA

In this prospective population-based cohort study, demographic characteristics, lifestyle, exposure to farming environments, and health information were assessed using self-administered parental questionnaires in a disproportionate random sample (n=2,495) drawn stratified by exposure to farming environments. The baseline assessment (n=2,248, 90.1%) was conducted in rural areas around Ulm, southern Germany, among elementary school children (most between 6 and 10 years of age) in 2006/07 as part of the larger multi-phase GABRIEL Advanced Surveys.(16) In 2011, a follow-up including assessment of child-reported child HRQoL was conducted (participation rate 81%). The study was approved by the ethics board of Ulm University.

HRQoL

The validated KidKINDL-R Child Version for 7-13 year-olds, an instrument to assess generic child-reported child HRQoL, consists of 24 five-point Likert-scaled questions referring to the previous two weeks.(17) Six HRQoL scales are covered: physical well-being, emotional well-being, self-esteem, family, friends, and school. These scales were also collapsed into a total score by summation. Scores were transformed to values ranging from 0 to 100 with higher scores representing better quality of life. Scales containing more than 30% missing values were excluded. In KIDS, child-reported HRQoL was assessed in the 11-year follow-up. In GABRIELA, child-reported HRQoL was assessed in the 2011 follow-up among 10.3- to 16.8-year-old children. The reliability of KINDL-R was high in KIDS and GABRIELA (Cronbach's alpha >0.72 for both).

Wheeze and wheezing phenotypes

Questions to assess wheeze were derived from the International Study of Asthma and Allergies in Childhood.(18) Parents were asked to report wheeze in the child (ever, since the last follow-up, in the past 12 months, or combined with the age of onset). Children with reported asthma medication

but no report of wheeze in one reporting period were assumed to have wheeze in that reporting period. Wheezing phenotypes were classified into four categories.⁽¹¹⁾ *Early transient* wheezers were children who had wheeze before 3 years of age and none later in life. *Persistent* wheezers were those who started to wheeze before three years of age and continued to wheeze later in life. *Late-onset* wheezers were children with symptoms starting after three years of age. The reference group consisted of *never* wheezers who did not report any wheeze ever in life.

In GABRIELA, wheeze phenotypes were classified based on the baseline assessment in which parents reported wheeze and its age of onset retrospectively. In KIDS, data on wheeze were assessed in each follow-up. Making use of this rich data to reduce misclassification, children were able to be transient wheezers with only one report of wheeze before 3 years of age. However, due to the expected longer duration of symptoms, children had to have at least two reports of wheeze after the age of 3 years to be classified as persistent and late-onset wheezers. Furthermore, in KIDS, children who had wheeze before the age of three years, remitted and then started again after age six years were not classified into any of the four categories described above (n=12). In GABRIELA, 263 of 1804 participating children were not classified because of missing values at baseline or wheezing patterns which were not easily interpretable. The same was true for 100 of 604 children in KIDS.

Putative confounding variables

Covariates were mainly selected based on previous literature.⁽¹²⁾ Putative confounders (yes/no unless stated otherwise) were sex (female/male), maternal education (≤ 12 years, > 12 years), maternal smoking during pregnancy, familial hay fever, familial asthma, familial eczema, doctor-diagnosed atopic eczema, doctor-diagnosed hay fever, number of siblings (none, ≥ 1), infant birth weight (< 2500 g, 2500-3999g, ≥ 4000 g for GABRIELA and < 3000 g, 3000-3999g, ≥ 4000 g for KIDS). Further putative confounders assessed at baseline for GABRIELA and at 11 years for KIDS

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were current parental smoking and body mass index, the latter classified into underweight (< 10th percentile), normal, and overweight (> 90th percentile), according to a German reference population (19) which may lead to an underestimation of overweight compared to international classifications.(20) In the rural GABRIELA cohort, exposure to farming environments was no putative confounder because it has been previously shown to have no influence on the association between HRQoL and asthma in this study.(21)

Statistical analyses

The baseline characteristics of the study population were summarized descriptively. Linear regression models were used for KIDS whereas stratified weighted regression models were computed for GABRIELA to account for the stratified random sampling. Particularly in GABRIELA, the outcome variables were approximately normally distributed. Estimates are reported together with 95% confidence intervals. Interaction between wheeze phenotype and sex was tested by fitting a multiplicative interaction term in the models.

Separate models were calculated for each outcome variable (7 scales of HRQoL) and every explanatory variable, i.e. early transient, persistent, and late-onset wheeze (each compared to never wheezers). Due to the different age structure between KIDS and GABRIELA and *a priori* expected differences across ages, all GABRIELA association analyses were age-stratified by age (10-<11.5 years, 11.5-<13.5 years, $\geq$ 13.5 years).

Covariates were evaluated one by one in the larger study, GABRIELA, and selected as confounders for both studies if they changed the crude bivariate association between each wheezing phenotype and HRQoL scale by more than 10% and were significantly associated to the outcome. Consequently, final models differed across wheezing phenotypes and scales of HRQoL. Substantial collinearity, particularly between infant atopic diseases and familial atopic diseases, was ruled out by correlation analyses (all $r < 0.3$). The main confounders in most of the models were familial hay

fever, familial asthma, and familial eczema, parental reports of doctor-diagnosed atopic eczema and hay fever in the child, and asthma medication.

All statistical analyses were performed with SAS® 9.3 (The SAS Institute, Cary, NC, USA).

RESULTS

Table 1 shows the characteristics of the study populations. The prevalence of wheezing phenotypes was similar in both studies with a higher proportion of early transient wheezers and a lower proportion of late-onset wheezers in KIDS compared to GABRIELA. Of note, the latter discrepancy was more pronounced among those younger than 11.5 years in GABRIELA in which the prevalence of late-onset wheeze reached 7.2%. The only major difference for children who were not assigned a wheezing phenotype compared to those classified was that in KIDS, a higher proportion of their mothers had high education whereas in GABRIELA a higher proportion of their mothers had lower education (data not shown). Subsequent results are therefore adjusted for maternal education.

Table 2 displays crude, table 3 adjusted associations between wheezing phenotypes and HRQoL scales. When contrasting wheezing phenotypes with never wheezers in children below 11.5 years of age, the only indication for association was between late-onset wheeze and the HRQoL scale “family”. Here, late-onset wheezers around 11 years of age in KIDS and GABRIELA tended to have higher HRQoL “family” scores whereas among the older children there were clearly lower HRQoL “family” scores in the adjusted models (table 3).

In the oldest age group, there were clear inverse associations of late-onset wheeze with most HRQoL scales: “mental well-being”, “self-esteem”, “family”, “social contact”, “school”, and as a result also in “total”. Furthermore, for early transient wheeze, there were also inverse associations

with the HRQoL scales “family”, “school”, and “total”. We did not detect an effect of any wheezing phenotype on physical well-being regardless of the child’s age.

Effect modification by sex was specifically investigated in the oldest age group in which puberty was assumed to have set on for most children. After stratification, male late-onset wheezers tended to have lower scores in all HRQoL scales but “school” and “physical well-being” compared to female late-onset wheezers. However, the interaction with sex did not reach statistical significance for any of the scales (data not shown). Among persistent wheezers, boys (n=17) reported markedly lower scores for “social contacts” than girls (n=12; β and 95%CI: -6.3 (-13.9; 1.2) vs. 4.3 (-1.2; 9.7), respectively, $p_{\text{int}}=0.0052$); other HRQoL scales did not differ across sexes (data not shown).

DISCUSSION

We present analyses of two large prospective cohort studies covering different age ranges. Outcome ascertainment in both studies is similar and the KIDS study was added to increase the evidence on the smaller subset of younger children in GABRIELA. The results in the older age group in GABRIELA show that late-onset wheeze and to a smaller extent also early transient wheeze, but not persistent wheeze were associated with diminished psychosocial well-being in teenagers. For younger children, there was only indication for an association between late-onset wheeze and the HRQoL with regard to family life.

Definitions of wheezing phenotypes are not fully comparable between both presented studies. In GABRIELA, wheezing phenotypes were based on information retrospectively collected at baseline which leaves the possibility of misclassification due to the recall period of several years. In KIDS, yearly data in infancy were available and we were thus able to apply more stringent criteria to define the wheezing phenotypes. While potentially decreasing heterogeneity within and misclassification of the wheezing phenotypes, the applied restrictions implicate smaller sample sizes, especially in the analyses stratified for sex.

Furthermore, we were not able to account for some factors associated with HRQoL, e.g. further psychiatric diseases (like anxiety or depression) in the children or their parents, severity of asthma or asthma control. The latter may be important because late-onset wheeze may reflect more currently established wheeze which is yet undertreated or not well controlled and therefore has larger impact on HRQoL. However, we did explore the effects of two major determinants of HRQoL: age and sex.

In both analysed cohorts, the participants score higher on all HRQoL scales than children between 11 and 17 years in the representative BELLA study, a part of the nationwide German health interview and examination survey for children and adolescents (KiGGS).(17) However, the pattern across the scales was very similar to the BELLA study with self-esteem yielding the lowest scores and emotional well-being and family yielding the highest scores. The general upward shift of the scores may be due to younger ages in our studies as well as to the fact that we employed self-administered questionnaires whereas the BELLA study used a standardised computer-assisted telephone interview.

A recently published study revealed strong physical and psychosocial implications of late-onset and persistent wheeze on HRQoL in early childhood at age four years.(12) Our study extends this field of research into adolescence. It could be argued that different disease perception in adolescence or a longer time of adaption to diseases can have advantageous effects on HRQoL.(22,23) Specifically for persistent wheeze, our older study population may have profited from an adaption which in turn may explain the lack of association with HRQoL. However, a previous study showed that illness duration did not influence HRQoL in children aged 7-14 years.(6) Besides, adaptive changes would not explain why also early transient wheezers seem to suffer from reduced HRQoL in later childhood regarding satisfaction with family and school.

Due to the time span between manifestation of early transient wheeze and assessment of HRQoL, a possible explanation for the detected associations could be residual confounding despite our efforts. This article is protected by copyright. All rights reserved.

to control for many potential confounding factors. Another explanation may be that parents of children who wheeze in infancy tend to be overprotective and rigid reducing children's everyday activity.(6) Permanent supervision of the child may lead to a lack of independence with negative consequences on the child's development. However, the associations in our results seem not fully consistent: self-esteem and - in contrast to family and school - social contacts were not affected by early transient wheeze.

Several studies have shown a strong impact of wheeze on physical functioning (1–3,12) or activity limitations.(6,24,25) These associations were found across childhood from 2 months to 17 years of age in Europe (2,3,6,12,24,25) and the US.(1) All but one study assessed child-reported HRQoL although not using the same instrument as we did. Indeed, in our instrument the scale on physical well-being is comprised of items on bodily pain whereas in the other instruments the scales on physical functioning are comprised of items on daily physical activities. This may explain the discrepant results.

Our analyses identify adolescence as a difficult period with regard to psychosocial well-being for late-onset wheezers. This is in line with studies indicating emotional problems or psychiatric comorbidity in asthmatic adolescents.(1,5) Chronically ill children and teens feel frustrated, distanced from others, or have the impression that they cannot keep up with peers. They often experience rejection, and higher levels of negative peer sociability.(4,24,26) It remains unclear whether developmental tasks during puberty, like individuation and fitting in with peers and the social environment,(26) worsen these feelings in teenagers compared to younger children. Furthermore, mental harm tended to be greater in teenage boys than girls albeit not reaching statistical significance. Surprisingly, other studies suggest a clear reverse distribution.(24,27–29) Clearly, our study may be underpowered to find sex-specific differences in teenagers.

Of note are the strong associations with HRQoL related to family life in our study. Another study comparing 11-15 year old asthmatics to a non-diseased population found no reduced family
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cohesion but lower values on family activities in asthmatics.(3) A bidirectional relationship between parental psychological functioning and severe, poorly managed asthma in the child may exist since having a child with asthma is challenging for families and thereby increases psychological stress.(30)

In conclusion, our data from two population-based cohort studies show that late-onset wheeze and to a lesser extent early transient wheeze were associated with diminished psychosocial well-being in teenagers. Further studies with larger sample sizes are warranted to reassess sex-specific effects. Late-onset wheeze seems to be highly demanding in teenagers with impairments in health-related quality of life. Therefore, a special focus should be put on this subgroup of patients with particular attention to education about asthma management and potentially family-based psychosocial intervention

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Table 1: Description of the study populations

	KIDS (n=604)	GABRIELA (n=1804 ¹)
	n (%)	n (%)
female sex	315 (52.2)	907 (51.0)
age at HRQoL assessment: μ /median (Q1;Q3)	11.0 / 11.0 (11.0;11.1)	12.9 / 12.9 (11.9; 13.8)
<11.5 yrs	604 (100.0)	246 (13.2)
11.5-<13.5 yrs	-	935 (53.4)
$\geq$ 13.5 yrs	-	623 (33.4)
number of siblings		
0	179 (35.5)	108 (7.5)
1	243 (48.2)	713 (45.8)
$\geq$ 2	82 (16.3)	976 (46.7)
maternal nationality non-German	51 (8.4)	0 (0.0)
maternal education > 12 years	284 (47.5)	343 (22.8)
maternal smoking during pregnancy (yes)	28 (6.0)	139 (9.1)
parental smoking after pregnancy (yes)	140 (23.3)	463 (28.6)
birth weight		
low	118 (19.6)	101 (5.8)
middle	419 (69.6)	1498 (84.3)
high	65 (10.8)	189 (9.9)
familial asthma history	64 (10.6)	232 (15.7)
familial hay fever history	234 (38.7)	568 (39.8)
familial eczema history	53 (8.8)	449 (26.7)
wheezing phenotypes of index children		
never	334 (55.3)	1153 (61.1)
early transient	115 (19.0)	214 (11.8)
persistent	34 (5.6)	86 (5.5)
late-onset	21 (3.5)	88 (5.7)
not classified	100 (16.6)	263 (15.9)
infant eczema	39 (6.5)	323 (19.3)
infant hay fever	69 (11.5)	271 (20.2)
BMI		
underweight	70 (13.0)	104 (7.3)

normal	429 (79.7)	1457 (82.7)
overweight	39 (7.2)	199 (10.0)
HRQoL dimensions in children ²		
physical well-being: μ /median (Q1;Q3)	78.8 / 81.3 (68.8; 87.5)	75.5 / 74.2 (66.9; 85.4)
mental well-being: μ /median (Q1;Q3)	84.8 / 87.5 (81.3; 93.8)	82.1 / 80.7 (72.5; 86.9)
self-esteem: μ /median (Q1;Q3)	63.6 / 62.5 (50.0; 75.0)	61.9 / 60.0 (47.7; 69.9)
family: μ /median (Q1;Q3)	87.3 / 87.5 (81.3; 93.8)	82.7 / 84.4 (71.6; 92.6)
social contacts: μ /median (Q1;Q3)	80.3 / 81.3 (75.0; 93.8)	79.5 / 78.4 (68.5; 87.5)
school: μ /median (Q1;Q3)	80.0 / 81.3 (75.0; 93.8)	72.0 / 71.1 (60.1; 80.7)
total: μ /median (Q1;Q3)	79.1 / 79.3 (74.0; 85.4)	75.6 / 76.1 (69.6; 82.2)

abbreviations: HRQoL=health related quality of life; yrs=years; g=gram; μ =arithmetic mean;

Q1=25th percentile; Q3=75th percentile

¹ unweighted n

² high scores indicate high HRQoL

Table 2: Crude associations of wheezing phenotypes with child-reported health related quality of life¹

HRQOL	wheezing phenotype	KIDS	GABRIELA		
		11.0 yrs n=480 ²	<11.5 yrs n=212 ²	11.5-<13.5 yrs n=798 ²	$\geq$ 13.5 yrs n=531 ²
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
physical well-being	never	ref	ref	ref	ref
	early transient	-1.2 (-4.6; 2.3)	-4.1 (-12.4; 4.1)	-2.4 (-7.2; 2.5)	-1.2 (-5.9; 3.6)
	persistent	3.8 (-1.8; 9.4)	3.7 (-9.9; 17.3)	-2.2 (-8.4; 3.9)	-3.2 (-13.0; 6.7)
	late-onset	-5.9 (-13.0; 1.2)	-4.1 (-15.0; 6.7)	-4.1 (-9.7; 1.5)	-6.3 (-14.0; 1.4)
mental well-being	never	ref	ref	ref	ref
	early transient	-0.8 (-3.3; 1.8)	-0.7 (-6.9; 5.4)	-0.6 (-3.8; 2.6)	-2.3 (-5.7; 1.1)
	persistent	-0.4 (-4.4; 3.6)	-2.2 (-13.0; 8.6)	-0.4 (-4.0; 3.3)	-0.6 (-5.1; 4.0)
	late-onset	1.8 (-3.4; 7.0)	0.4 (-7.9; 8.8)	-2.4 (-8.8; 4.1)	-6.7 (-10.7; -2.8)
self-esteem	never	ref	ref	ref	ref
	early transient	-1.4 (-5.2; 2.5)	-1.5 (-7.7; 4.8)	2.6 (-2.1; 7.2)	-2.4 (-7.1; 2.3)
	persistent	-3.3 (-9.4; 2.9)	-0.7 (-7.7; 6.2)	0.4 (-5.5; 6.4)	-2.4 (-10.8; 6.1)
	late-onset	2.6 (-5.3; 10.4)	4.0 (-9.3; 17.3)	1.6 (-5.8; 8.9)	-7.9 (-12.2; -3.7)
family	never	ref	ref	ref	ref
	early transient	0.3 (-2.2; 2.8)	-0.8 (-6.0; 4.3)	-2.0 (-6.0; 2.1)	-8.1 (-13.1; -3.1)

	persistent	-0.3 (-4.5; 3.9)	0.4 (-5.0; 5.9)	-1.3 (-7.0; 4.5)	-1.9 (-8.2; 4.4)
	late-onset	3.6 (-1.7; 8.9)	4.5 (-0.1; 9.2)	-6.4 (-13.7; 1.0)	-10.2 (-18.6; -1.7)
social contacts	never	ref	ref	ref	ref
	early transient	-0.1 (-3.3; 3.2)	-1.9 (-9.2; 5.5)	1.8 (-1.8; 5.4)	-2.3 (-6.6; 2.0)
	persistent	1.9 (-3.3; 7.2)	4.6 (-3.5; 12.7)	-1.1 (-7.3; 5.1)	0.1 (-5.3; 5.5)
	late-onset	0.8 (-6.1; 7.7)	-0.2 (-17.7; 17.2)	-1.5 (-8.6; 5.5)	-7.5 (-14.5; -0.4)
school	never	ref	ref	ref	ref
	early transient	-1.1 (-4.2; 1.9)	0.1 (-5.5; 5.6)	3.1 (-1.3; 7.4)	-5.7 (-11.0; -0.4)
	persistent	0.0 (-5.1; 5.0)	0.1 (-8.8; 9.1)	-1.3 (-7.1; 4.5)	1.3 (-6.4; 8.9)
	late-onset	-4.4 (-10.9; 2.2)	-10.0 (-21.5; 1.6)	-1.7 (-10.6; 7.1)	-9.9 (-16.8; -2.9)
total	never	ref	ref	ref	ref
	early transient	-0.7 (-2.9; 1.4)	-1.2 (-5.8; 3.3)	0.3 (-2.5; 3.1)	-3.5 (-6.7; -0.3)
	persistent	0.2 (-3.1; 3.6)	1.2 (-4.5; 6.8)	-1.8 (-6.1; 2.6)	-1.1 (-6.2; 4.0)
	late-onset	-0.3 (-4.7; 4.1)	-0.6 (-7.0; 5.8)	-2.3 (-8.4; 3.8)	-7.8 (-11.5; -4.1)

Abbreviations: HRQoL=health related quality of life; yrs=years; β =beta estimate; CI=confidence interval; ref=reference

bold face indicates statistically significant results

¹ high scores indicate high HRQoL

² n with information on wheezing phenotype and HRQoL (unweighted)

Table 3: Adjusted¹ associations of wheezing phenotypes with child-reported health related quality of life²

HRQOL	wheezing phenotype	KIDS	GABRIELA		
		11.0 yrs n=480 ²	<11.5 yrs n=212 ²	11.5-<13.5 yrs n=798 ²	≥13.5 yrs n=531 ²
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
physical well-being	never	ref	ref	ref	ref
	early transient	-1.3 (-4.7; 2.2)	-4.7 (-12.8; 3.3)	-2.4 (-7.2; 2.4)	-0.5 (-5.5; 4.5)
	early persistent	4.5 (-1.7; 10.7)	6.1 (-5.8; 18.0)	-0.3 (-6.3; 5.8)	-2.1 (-13.5; 9.3)
	late-onset	-4.1 (-11.2; 2.9)	3.0 (-9.9; 15.8)	-3.0 (-8.9; 2.8)	-5.1 (-12.5; 2.3)
mental well-being	never	ref	ref	ref	ref
	early transient	-0.7 (-3.2; 1.9)	-1.0 (-6.7; 4.7)	-0.6 (-3.8; 2.6)	-2.3 (-5.8; 1.2)
	early persistent	-1.3 (-5.7; 3.0)	-2.2 (-12.8; 8.5)	-0.1 (-4.2; 3.9)	-0.6 (-5.5; 4.4)
	late-onset	2.0 (-3.2; 7.2)	0.5 (-8.0; 8.9)	-1.2 (-7.4; 5.1)	-6.2 (-10.0; -2.4)
self-esteem	never	ref	ref	ref	ref

	early transient	-1.2 (-5.2; 2.7)	-1.5 (-7.7; 4.7)	2.8 (-1.9; 7.5)	-1.9 (-6.6; 2.8)
	early persistent	-3.1 (-9.3; 3.1)	-0.3 (-8.2; 7.6)	1.4 (-4.8; 7.6)	-1.4 (-9.9; 7.1)
	late-onset	2.6 (-5.3; 10.5)	3.6 (-10.1; 17.3)	4.1 (-3.5; 11.8)	-7.8 (-12.5; -3.2)
family	never	ref	ref	ref	ref
	early transient	0.3 (-2.2; 2.8)	-0.8 (-6.0; 4.3)	-2.0 (-6.0; 2.1)	-8.1 (-13.1; -3.1)
	early persistent	-0.9 (-5.2; 3.3)	0.8 (-3.6; 5.2)	-2.2 (-8.1; 3.8)	-2.1 (-8.4; 4.3)
	late-onset	3.4 (-1.9; 8.6)	7.3 (0.2; 14.3)	-7.1 (-14.6; 0.4)	-12.7 (-21.2; -4.1)
social contacts	never	ref	ref	ref	ref
	early transient	0.0 (-3.2; 3.3)	-2.3 (-10.2; 5.6)	1.8 (-1.8; 5.4)	-2.3 (-6.5; 2.0)
	early persistent	2.5 (-3.3; 8.3)	3.8 (-3.5; 11.1)	0.6 (-6.8; 8.0)	-0.7 (-5.6; 4.1)
	late-onset	0.6 (-6.4; 7.5)	2.1 (-13.7; 17.8)	-0.4 (-8.0; 7.2)	-7.1 (-13.9; -0.4)
school	never	ref	ref	ref	ref
	early transient	-1.2 (-4.2; 1.9)	-0.1 (-5.8; 5.6)	3.0 (-1.4; 7.4)	-5.8 (-11.0; -0.5)
	early persistent	-1.3 (-6.9; 4.2)	-1.0 (-9.7; 7.6)	-1.0 (-6.9; 5.0)	2.1 (-5.9; 10.1)
	late-onset	-4.7 (-11.3; 1.9)	-4.9 (-14.9; 5.2)	-1.6 (-10.8; 7.7)	-10.0 (-17.2; -2.9)
total	never	ref	ref	ref	ref
	early transient	-0.7 (-2.9; 1.4)	-1.2 (-5.8; 3.3)	0.3 (-2.5; 3.1)	-3.5 (-6.7; -0.3)
	early persistent	0.0 (-3.7; 3.7)	1.0 (-4.0; 6.1)	-1.1 (-5.8; 3.6)	-1.0 (-6.6; 4.6)
	late-onset	-0.3 (-4.7; 4.2)	0.8 (-5.1; 6.6)	-1.8 (-8.1; 4.5)	-7.8 (-11.4; -4.1)

Abbreviations: HRQoL=health related quality of life; yrs=years; β =beta estimate; CI=confidence interval; ref=reference

bold face indicates statistically significant results

¹ adjustment differed for every HRQoL scale and wheezing phenotype resulting from analyses for confounding (see method section); confounders included in at least one model were: siblings, maternal education, infant birth weight, familial hay fever, familial asthma, familial eczema, infant eczema, infant hay fever, asthma medication, body mass index.

² high scores indicate high HRQoL

³ n with information on wheezing phenotype and HRQoL (unweighted)