Asthma-Related Symptoms and Health-Related Quality of Life in Children

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Asthma-Related Symptoms and
Health-Related Quality of Life in Children

Astma-gerelateerde symptomen en
gezondheidsgerelateerde kwaliteit van leven bij kinderen

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General Introduction

1.1 Background

Asthma during childhood represents an important public health problem (1-4). In developed (industrialized) countries asthma is a highly prevalent chronic condition that accounts for considerable morbidity, reduced health-related quality of life, and substantial healthcare costs (1-4). Healthcare costs include both direct costs (due to hospitalizations, visits to the general practitioner or specialist, emergency visits, anti-asthma medication, diagnostic tests and procedures) and indirect costs (loss of working days and school absence).

The World Health Organization defines asthma as a chronic inflammatory disorder of the airways associated with increased bronchial hyperresponsiveness (5). Genetic factors predispose certain individuals to develop asthma, and certain environmental factors can trigger symptomatic episodes of asthma. In susceptible individuals the inflammation causes recurrent episodes of wheezing, shortness of breath, chest tightness, and dry cough, particularly at night or in the early morning (4). These symptoms are usually associated with variable airflow limitation that is at least partially reversible either spontaneously or with treatment (4). The underlying inflammation also causes increased airway hyperresponsiveness to a variety of triggers, such as exercise, cold air, and exposure to allergens and smoke.

Asthma is heterogeneous of nature with reversible and variable signs and symptoms over time. Wheezing is the most characteristic symptom. A diagnosis of asthma in school-aged children is usually based on the child's symptoms, medical history, physical examination, and lung function tests (6, 7). Physicians generally look for signs of airflow obstruction and whether the obstruction is at least partially reversible. Factors that trigger symptoms may be evident and conventional lung function tests can support the diagnosis.

Asthma cannot be clearly diagnosed in preschool children, due to the non-specificity of the symptoms and the fact that a qualitatively good lung function test cannot be carried out at such a young age (8). The current Dutch general practitioners evidence-based childhood asthma guidelines for children under the age of six are therefore based on the presence of asthma-related symptoms defined as recurrent attacks of wheezing (6, 7). Shortness of breath is often not apparent. The diagnosis of

asthma in preschool children is therefore limited to reported symptoms by parents or caregivers.

In absence of a systematic detection procedure, it is likely that asthma-related symptoms could be underreported by parents or caregivers and could be underdiagnosed and undertreated as a result (9). Validated early detection procedures for children are available in the literature (10-12). Detected children can be managed effectively by a package of measures including monitoring by the general practitioner, health education, non-pharmacological interventions (avoidance of exposure to smoke and allergic triggers), and if indicated pharmacological treatment with bronchodilators or inhalation corticosteroids (6, 7). Early detection and adequate management of asthma in young children could therefore have a direct health effect by facilitating lung development with reduced symptoms, also later in life and improved health-related quality of life.

In this thesis we will primarily focus on the measurements of asthma-related symptoms and health-related quality of life among preschool children. Subsequently, we will evaluate the association between asthma-related symptoms and health-related quality of life in childhood. In that way, we could ultimately assess whether asthma-related symptoms and health-related quality of life can be used as outcome measures in a randomized controlled trial for early detection of asthma in preschool children.

1.2 Measurements of Asthma-Related Symptoms and Health-Related Quality of Life in Preschool Children

Given the fact that there is no gold standard for the diagnosis of asthma in preschool children, we cannot directly assess the validity of measurements of asthma-related symptoms among preschool children. In epidemiological studies, asthma has often been defined as self-reported asthma (with or without a physician diagnosis) or as self-reported asthma-related symptoms (wheezing, shortness of breath, chest tightness and dry cough at night or in the early morning). In school-aged children the diagnosis of asthma can be supported by conventional lung function tests. Unfortunately, no conventional lung function tests are available to support the diagnosis in preschool children. In the absence of an objective measure, it is difficult to assess the accuracy and validity of asthma-related symptoms as reported by a

proxy, who is usually one of the parents. Therefore it is unknown whether parents can indicate the presence of asthma-related symptoms among preschool children.

At the same time, measuring health-related quality of life in preschool children is difficult, because preschool children do not have the cognitive ability to complete quality of life questionnaires by themselves. Health-related quality of life can be seen as a method of translating an individual's experience of illness into a quantifiable outcome. It can be defined as the individual's perception of problems in health status, combined with the affective responses to such problems (13). From the 1990's onwards, health-related quality of life is an essential outcome measure in pediatric research. There are several feasible, reliable and validated pediatric health-related quality of life questionnaires, both generic and disease-specific questionnaires (14). Generally, generic questionnaires are less sensitive to the impact of specific diseases on health-related quality of life than disease-specific questionnaires (14).

Both generic and asthma-specific questionnaires are available to measure health-related quality of life in children above the age of five years. Measurement of both generic and asthma-specific health-related quality of life would be the most appropriate approach to assess an individual's perception of quality of life. Unfortunately, no asthma-specific questionnaires are available to measure health-related quality of life among preschool children.

Two generic questionnaires, the TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL) and the Infant Toddler Quality of Life Questionnaire (ITQOL) are available to measure health-related quality of life in preschool children.
The ITQOL consists of 103-items divided over ten multi-item scales and two single-item scales to be completed by parents. It covers a broad range of dimensions focusing on physical and psychosocial functioning of the child as well as on components of parental and family impact. The ITQOL has been translated into Dutch following international standards (15) and validated in a general population sample and a respiratory disease sample in the Netherlands (16). For the majority of scales the ITQOL discriminated between preschool children with a few and with many parent-reported chronic conditions, between preschool children with and without doctor-diagnosed respiratory disease, and between preschool children with a low and with a high parent-reported medical consumption (16).

The TAPQOL, which is in Dutch originally, consists of 43-items divided over 12 multi-item scales to be completed by parents. It consists of five scales for physical functioning, two scales for social functioning, one scale for cognitive functioning and three scales for emotional functioning (17). The TAPQOL discriminated between preschool children with and without parent-reported chronic conditions for the physical scales only (18).

Although the ITQOL and TAPQOL are generic instruments for the measurement of health-related quality of life in preschool children, both questionnaires were able to detect decrements in health-related quality of life among preschool children with parent-reported chronic conditions and with physician-diagnosed respiratory symptoms. Since very young children lack the cognitive abilities to complete questionnaires by themselves, it is inevitable to use reports from a proxy, who is usually one of the parents. It is unknown whether parents are able to indicate the health-related quality of life of their preschool children with asthma-related symptoms in an accurate and valid way using a generic health-related quality of life instrument.

1.3 Main Research Questions

In this thesis the following research questions will be addressed:

(i) Can the prevalence of asthma-related symptoms among preschool children be measured using proxy-reported data?

(ii) Can health-related quality of life be assessed among preschool children with asthma-related symptoms using proxy-reported data?

(iii) What is the association between asthma-related symptoms and health-related quality of life in children?

1.4 Early Detection of Asthma in Preschool Children

In the Netherlands, the preventive youth healthcare system is a well-organized and legally enforced segment of the public health system. About 85% of all children are periodically monitored at a Child Health Center throughout the first four years of life (19). In a study funded by the Netherlands Organization for Health Research and Development (ZonMw) in which experts as well as organizations and professionals were asked to prioritize future outcome research in the area of preventive youth healthcare interventions (20). The systematic early detection of asthma in preventive

youth healthcare was prioritized and was considered feasible and essential in the routine Dutch youth healthcare system. To evaluate the effectiveness of early detection of asthma in preschool children a cluster randomized controlled trial has been designed and implemented within the framework of the Generation R Study.

The Generation R Study is a prospective population based cohort study from fetal life until young adulthood (21, 22). The Generation R cohort includes 9778 mothers and 9897 children living in Rotterdam, a city with 600,000 inhabitants in the Netherlands. In total, 8880 (91%) mothers were enrolled during pregnancy and 898 (9%) after birth of their child (22, 23). The Generation R children were born between April 2002 and January 2006. Of all eligible children in the study area, defined by postal codes, 61% participated (23, 24). The Generation R cohort includes 7893 children who are participating in the postnatal phase and who will be followed until young adulthood. The Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study. Written informed consent was obtained from all participants.

Cluster randomization

The principal cohort for the early detection of asthma consisted of all children participating in the postnatal phase of the Generation R Study and living in the intervention area, defined by postal codes 3010-3070. Physicians and nurses from the 16 participating preventive Child Health Centers in Rotterdam North periodically monitor these children. Randomization was done at the level of the Child Health Centers. Prior to randomization, the participating Child Health Centers were stratified for the socio-economic status of their neighborhood, and then randomly classified into the intervention group (eight Child Health Centers) or the control group (eight Child Health Centers). For details see Figure 1.

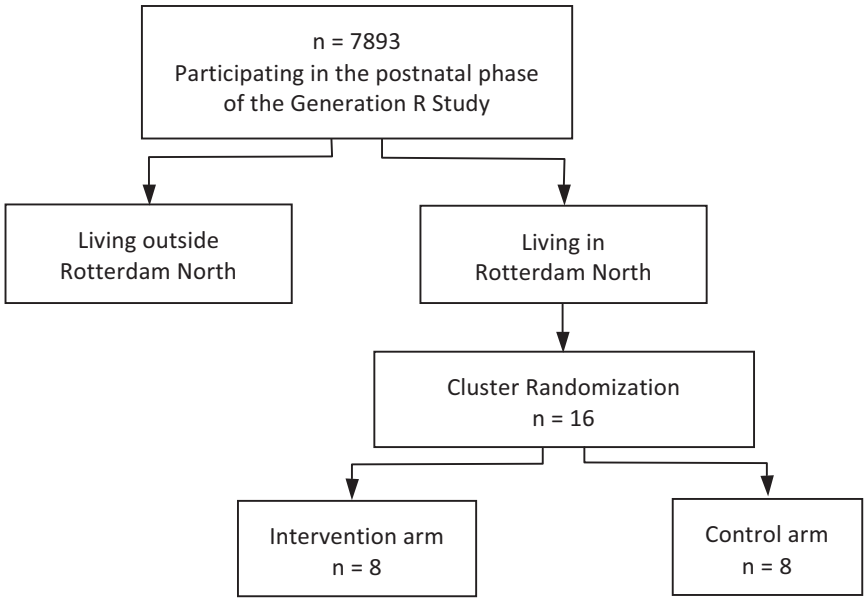

Figure 1. Flow chart of participants of the randomized controlled trial for early detection of asthma in preschool children.

The intervention Child Health Centers

At the intervention Child Health Centers the physician performs the screening procedure. The instrument for the early detection of asthma is a short questionnaire including items on the presence of asthma-related symptoms during the past year and past month, the use of anti-asthma medication and exposure to smoke. The physician interviews the parents during the regular free-of-charge visits to the Child Health Centers. On average, the interview takes about one minute and is carried out when the child is 14, 24, 36 and 45 months of age. For details see Table 1.

Criteria for intervention

Referral to the general practitioner is indicated when the child had three or more episodes of asthma-related symptoms during the past year, had symptoms during the past month or still experiences symptoms, and had not been monitored by the general practitioner or specialist (including medical treatment). When a child had three or more episodes of asthma-related symptoms during the past year, irrespective of having symptoms during the past month, the parents will receive a brochure with information on non-pharmacological interventions, including avoidance of a smoky environment, avoidance of allergic triggers, and better ventilation of the family house.

Table 1. Questionnaire for early detection of asthma in preschool children.

1. Has your child had wheezing or a whistling noise in the chest during the past year?

□ Unknown

□ No

□ Yes, 1 or 2 times

□ Yes, 3 times or more

2. Has your child had shortness of breath during the past year?

□ Unknown

□ No

□ Yes, 1 or 2 times

□ Yes, 3 times or more

3. Has your child had wheezing or a whistling noise in the chest during the past four weeks?

□ Unknown

□ No

□ Yes

4. Has your child had shortness of breath during the past four weeks?

□ Unknown

□ No

□ Yes

5. Has your child had anti-asthma medication (prescription from the general practitioner or child specialist)?

□ Unknown

□ No

□ Yes, the name of the medication is ☐

6. Has your child been exposed to smoke?

□ Unknown

□ No

□ Yes, sometimes

□ Yes, on regular basis

□ Yes, often or daily

The control Child Health Centers

At the control Child Health Centers no screening procedure is performed, but the current routine practice is continued. Of course, parents may spontaneously mention asthma-related symptoms or the physician may notice asthma-related symptoms. In the absence of a systematic early detection procedure, it is expected that fewer cases will be detected, on average later than at the intervention Child Health Centers.

Outcome measures

Two outcome measures are studied. The first is the prevalence of asthma-related symptoms (at age 12/14, 24, 36, and 45/48 months) and the second is health-related quality of life (at age 12, 24, 36, and 48 months). In both the intervention and control group health-related quality of life will be measured by means of proxy-reports through self-administered written questionnaires. At baseline (age 12 months) no significant differences in both outcomes were observed between the intervention and control group children (data not shown).

Hypotheses

Evaluation of the early detection of asthma among preschool children is actually based on two important hypotheses. First, we hypothesized that early detection and adequate management of asthma among preschool children will reduce the prevalence of asthma-related symptoms among preschool children, and will reduce the prevalence of physician-diagnosed asthma at older age. Second, we hypothesized that early detection and adequate management of asthma among preschool children will improve their health-related quality of life.

1.5 Structure of the Thesis

Part I, **chapters 2 and 3**, describe different studies comparing measurements of asthma-related symptoms and asthma, with special focus on the measured prevalence of asthma among preschool children. **Chapter 2** evaluates the agreement in the prevalence of asthma or COPD derived from self-reports or proxy-reports through a health interview survey versus general practitioners registration in their medical records. This study made use of data collected within the framework of the second Dutch National Survey of General Practice. **Chapter 3** evaluates the agreement in the prevalence of wheezing or shortness of breath in the first year of life by comparing parent-reported wheezing or shortness of breath as assessed by

self-administered written questionnaire and by physician interview. This study made use of data from the Generation R Study.

Part II, gives an overview of health-related quality of life measures in children, both generic and disease-specific instruments. In **Chapter 4** recent studies on feasibility, reliability, and validity of pediatric health-related quality of life questionnaires are summarized. In addition, this chapter gives an overview of recent applications of health-related quality of life measures in children.

Part III, **Chapters 5 to 7**, the association between asthma-related symptoms and health-related quality of life in children is investigated among specific age groups using different health-related quality of life instruments. **Chapter 5** examines the association between wheezing attacks and health-related quality of life among adolescents using self-reported data. The Child Health Questionnaire-Child Form was used to assess health-related quality of life and the frequency of wheezing attacks was based on selected questions from the International Studies of Asthma and Allergies in Childhood. **Chapter 6** examines the association between wheezing and shortness of breath and health-related quality of life in preschool children aged 2-48 months using parent-reported data from a random general population sample in the Netherlands. The TNO-AZL Preschool Children Quality of Life Questionnaire was used to assess health-related quality of life and the prevalence of wheezing and shortness of breath was based on selected and adapted questions from the International Studies of Asthma and Allergies in Childhood. **Chapter 7** examines the association between asthma-like symptoms in the first year of life and health-related quality of life at age 12 months, and the association of these symptoms with family activities and family cohesion, and with parents' emotional health and parents' time to meet their own needs. The Infant Toddler Quality of Life Questionnaire was used to measure health-related quality of life and the prevalence of asthma-like symptoms was based on selected and adapted questions from the International Studies of Asthma and Allergies in Childhood. This study made use of data collected within the framework of the Generation R Study.

Finally, the last part of this thesis, the General Discussion, is a discussion in which the main results of the studies are integrated and interpreted. **Chapter 8** summarizes the main results of the studies, presents explanations for the findings, discusses measurements of asthma-related symptoms and health-related quality of life among preschool children, discusses the association between asthma-related symptoms and

health-related quality of life among children, and presents overall recommendations and conclusions.

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Part I

Measurements of Asthma-Related Symptoms

2

Prevalence Estimates of Asthma or COPD from a Health Interview Survey and from General Practitioner Registration: What's the Difference?

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European Journal of Public Health. February 2006; 16(1): 101-105.

2.1 Abstract

Background: The aim of this study was to compare prevalence estimates of asthma or chronic obstructive pulmonary disease (COPD) derived from self-report in a health interview survey and from general practitioners' (GPs') medical records, and to explain any differences.

Methods: The presence of asthma or COPD was measured by self-report in a random sample of 104 general practices in the Netherlands (n = 19,685) participating in the second Dutch National Survey of General Practice (DNSGP-2). This was compared with the presence of GP-diagnosed asthma or COPD in the same population as recorded using the International Classification of Primary Care (ICPC) by their GPs during a 12-month period. Gender, age, health insurance, ethnic background, educational level, tobacco exposure, other symptoms and conditions were evaluated as explanatory variables using logistic models.

Results: The prevalence of self-reported asthma or COPD (9.7%) was almost twice as high as the prevalence based on GP information (5.2%). The medical records of patients who reported having asthma or COPD, without having a diagnosis in their medical records, usually included other respiratory conditions. Patients reporting no asthma or COPD, but whose medical records carried a diagnosis of asthma or COPD, were relatively older ($p < 0.01$) and tended to be exposed to smoking in their home ($p < 0.05$).

Conclusions: Two methods for estimating prevalence of asthma or COPD yielded different results: compared with GP medical records, self-reported prevalence shows an overestimation in people who suffer from other respiratory conditions and an underestimation in elderly persons living in a smoky environment.

2.2 Introduction

The most commonly used method to obtain data in epidemiologic studies is through personal interviews or self-administered questionnaires (1-8). Whether or not the data obtained by these methods are more accurate than physician-reported data is questionable (9-15). Several studies have reported that conditions such as asthma, sinusitis and chronic bronchitis are all more likely to be reported by the patient, but not diagnosed by their general practitioner (GP) (16). A comparison of self-reports of chronic conditions with medical history data in patients aged 55-85 years revealed that the accuracy of self-reporting was associated with the chronic condition; chronic non-specific lung disease, for example, was reported with moderate accuracy (17). However, various studies on asthma or chronic obstructive pulmonary disease (COPD) in the Netherlands reported that prevalence estimates in the general population were approximately four times higher than that observed in studies in general practices (18-20). The prevalence depended largely on whether asthma or COPD was defined as a GP diagnosis or whether it was defined as the presence of respiratory symptoms.

It is difficult to compare results of these studies, since there are considerable differences in the methods used and the study populations included. The aim of the present study was therefore to assess the similarities and differences between prevalence estimates from a structured health interview and estimates from a computerized longitudinal contact-based GP registration on the individual level, in order to develop a better understanding of the differences between these prevalence estimation methods. We also sought to gain insight into which groups of patients demonstrated agreement between the self-reported data and their medical records, which groups did not and the underlying characteristics of both. Groups without agreement are especially relevant target groups for prevention and health education (21-23). For example, patients who have asthma or COPD, but who do not consult a GP, should do so to prevent chronic and troublesome symptoms; those who do not report asthma or COPD, are apparently not aware of it and should be involved in primary care.

The research questions were: (i) To what extent do patients' self-reports on asthma or COPD differ from the data reported by the GPs; and (ii) To what extent can the observed differences be explained by general patient characteristics (gender, age,

health insurance, ethnic origin and educational level) and by health characteristics (self-reported smoking status and self-reported health status)?

2.3 Methods

Design

The present study made use of data collected within the framework of the second Dutch National Survey of General Practice (DNSGP-2), which was carried out in 104 general practices in the Netherlands in 2001, and comprised 195 GPs (in total 165 GP full time equivalents), representative of all Dutch GPs (24). The DNSGP-2 provides nationally representative data on both patients' self-reported and GP-diagnosed asthma or COPD (24). DNSGP-2 encompasses a population of 400,912 registered patients, who are a good representation of the Dutch population on the characteristics age, gender and type of health insurance (24). Over a 12-month period all consultations with participating patients were recorded in the practice computer by the participating GPs. GP diagnoses were made according to the current evidence-based guidelines of Dutch general practitioners (25,26). Diagnoses of all consultations were coded according to the International Classification of Primary Care (ICPC) and were clustered into episodes for the same disease (27-30). From a random sample of the practice population (n = 19,685), on average 80 Dutch-speaking patients per full-time participating GP, supplementary information was collected by means of a health interview survey (n = 12,699; response rate 64.5%). Questionnaires were administered by trained interviewers during a face-to-face interview. To avoid seasonal patterns in morbidity, all interviews were carried out within the space of one year (2001) and distributed equally across all four seasons. Children aged 0-11 years were interviewed by means of a proxy interview with a parent, and from 12-17 years old, with one parent present.

Patient self-reports and GP information on asthma or COPD

The health interview included questions on the presence of 19 chronic conditions. The prevalence of self-reported asthma or COPD was based on the answers to the following question from the interview: 'Have you experienced frequent spells of asthma, chronic bronchitis, lung emphysema or chronic non-specific lung disease during the past 12 months?' Answers were coded 'yes' or 'no'. Prevalence of GP-diagnosed asthma or COPD was estimated from GP registration. Asthma or COPD was defined as being present if the patient had experienced one or more episodes

coded as ICPC R96 (asthma) or R91 (chronic bronchitis) or R95 (pulmonary emphysema/COPD) in the course of a single year.

Patient characteristics

Information on patient characteristics was obtained from the health interview. It included information on gender, age, health insurance (private or public health insurance), ethnicity (native or non-native; on the basis of country of birth of the patient and both parents) and educational level [low (none, elementary), middle (high school) or high (college or university)]. Smoking status was defined by current smoking (yes or no) and by whether smoking occurred in the patient's home (yes or no). The health interview also included questions on the presence of acute symptoms during the past 14 days. Health characteristics were defined in three ways: (i) as the presence of self-reported acute respiratory symptoms (coughing or dyspnea; yes or no); (ii) as the presence of self-reported non-respiratory acute symptoms (none or one versus more than one); and (iii) as the presence of self-reported chronic diseases other than asthma or COPD (none or one versus more than one).

Definitions

The presence of asthma or COPD according to both GP and patient was referred to as *concordance*. The presence of asthma or COPD according to the GP only was referred to as *underreporting*. If asthma or COPD was present according to the patient, but not according to the GP, this was referred to as *overreporting*.

Statistical analysis

Patients with missing values on the question about asthma or COPD were excluded from the present analysis (n = 28). Because of incomplete GP registration on morbidity items, we also excluded all patients from nine general practices (n = 708). Consequently, the analyses were performed in the remaining study population of 11,963 patients. We stratified the study population according to whether or not the GP had been consulted, regardless of the reason for consultation. Baseline characteristics for the study population were calculated and expressed as a proportion. Differences in proportions of a particular characteristic were tested with the χ^2-test. Agreement between GP and patient on the prevalence of asthma or COPD was investigated by cross-tabulation and was expressed as Cohen's kappa (31).

The independent contribution of general patient characteristics and health characteristics to the presence or absence of *concordance* was subsequently investigated by multivariate logistic regression analyses. We computed two models. In the first, the outcome variable *overreporting* was defined as the proportion of self-reported asthma or COPD that was not diagnosed by the GP. In the second, the outcome variable *underreporting* was defined as the proportion of GP-diagnosed asthma or COPD that was not reported by the patient. The reference category in both models was the proportion of all patients in which both patient and GP reported asthma or COPD to be present (*concordanc*e). If both patient and GP reported asthma or COPD to be absent, they were not included in the logistic model.

All patient characteristics described above were included in the logistic models. Each characteristic was first studied in bivariate models. Subsequently, multivariate models were constructed using a manual enter selection method, deleting those variables with the highest *p*-values, until all remaining variables had a *p*-value of 0.05 or less. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 10.0.

2.4 Results

The study population (mean age of 39 ± 23 years, 46% were men and 64% had a public health insurance) differed only slightly from the practice population (mean age 38 ± 22 years, 50% were men and 67% had a public health insurance). Patients who consulted their GP during the registration year (as compared with those who did not) were more likely to be women, to be older, to have more self-reported acute symptoms (respiratory and non-respiratory) and to have chronic diseases other than asthma and COPD (Table 1). All other characteristics did not differ significantly between patients with and without GP consults.

Of the patients with self-reported asthma or COPD (n = 1008), 914 had consulted their GP (91%) while 94 patients had not (9%). Patients with self-reported asthma or COPD who had not consulted their GP, as compared with those who had, were more likely to be men (58% versus 45%, $p < 0.05$), to be younger than 20 years of age (58% versus 27%, $p < 0.001$), and to have less acute respiratory symptoms (46% versus 61%, $p < 0.05$) and other chronic diseases (43% versus 61%, $p < 0.05$), data not shown.

Table 1. General characteristics of the study population, stratified for having consulted their GP.

	Study population	With GP consultation	Without GP consultation
	n = 11,963	n = 9411	n = 2552
General characteristics			
Gender, % men	46.1	43.1 [a]	57.1
Age			
% ≤ 20 years	25.6	22.7	36.2
% 20-39 years	22.9	22.6	24.0
% 40-59 years	30.4	31.1	27.9
% ≥ 60 years	21.1	23.6 [a]	11.9
Health insurance, % public	64.1	66.1	56.5
Ethnicity, % non-native	10.1	10.5	8.7
Educational level			
% low	21.1	21.3	20.3
% middle	59.8	60.2	58.1
% high	19.1	18.5	21.6
Health characteristics			
Current smoking, % yes	29.4	29.0	30.8
Environmental smoking, % yes	41.1	40.6	42.8
Acute respiratory symptoms, % yes	22.5	24.2 [a]	16.4
Other acute symptoms, % >1	72.2	75.7 [a]	59.6
Other chronic diseases, % >1	30.5	35.4 [b]	12.5

For differences between patients with and without having consulted their GP: [a] $p < 0.05$ and [b] $p < 0.01$

Of the patients who had consulted their GP (n = 9411), 914 reported having asthma or COPD (9.7%), while 486 had asthma or COPD according to their GP (5.2%). *Concordance* was observed in 35% (321/914) of patients with self-reported asthma or COPD and in 66% (321/486) of those with GP-diagnosed asthma or COPD (Table 2). From all patients with self-reported asthma or COPD, 65% had no such diagnosis in their medical records (n = 593; *overreporting*). Of the patients carrying a diagnosis of asthma or COPD according to their GP, 34% failed to report having asthma or COPD (n = 165; *underreporting*).

Table 2. Patients with self-reported asthma or COPD compared with patients with GP-diagnosed asthma or COPD.

	GP-diagnosed asthma or COPD		
	Present	Not present	
Self-reported asthma or COPD			
Present	321	593	914
Not present	165	8332	8479
	486	8925	9411

Self-reported asthma or COPD 914/9411 (9.7%)	*Overreporting* 593/914 (64.8%)
GP-diagnosed asthma or COPD 486/9411 (5.2%)	*Underreporting* 165/486 (34.0%)
Observed agreement (321+8332)/9411 (91.9%)	Cohen's kappa 0.42

Table 3 shows the distribution of patient characteristics among groups of patients who demonstrated *concordance* and those who did not. Older patients aged 60 and above, were more often in the *underreporting* group (39% versus 31%, $p < 0.05$) and less often in the *overreporting* group (23% versus 31%, $p < 0.05$). Patients, who were exposed to smoke in their house, were more often in the *underreporting* group (47% versus 38%, $p < 0.05$). Those who had a lower educational level were more often in the *overreporting* group (23% versus 31%, $p < 0.05$). A higher prevalence of acute respiratory symptoms (72%), which often accompany asthma or COPD, was observed in the *concording* group when compared to the *overreporting* (54%) and *underreporting* (33%) groups. Finally, the *underreporting* group generally had a better self-reported health status, reporting fewer acute symptoms and chronic diseases ($p < 0.001$).

Table 3. Characteristics of subgroups of patients with and without agreement with their GP

	Overreporting	*Concordance*	*Underreporting*
	n = 593	n = 321	n = 165
General characteristics			
Gender, % Men	42.7	47.7	55.8
Age			
% < 5 years	8.1	5.6	8.5
% 5-19 years	19.1	23.1	18.2
% 20-39 years	20.4	15.3	12.1
% 40-59 years	29.3	25.2	21.8
% ≥ 60 years	23.1 [a]	30.8	39.4 [a]
Health insurance, % public	69.4	66.7	72.6
Ethnicity, % non-native	10.0	8.7	11.0
Educational level			
% lower	22.7 [a]	31.1	35.6
% middle	61.6	54.6	51.5
% higher	15.8	14.3	12.9
Health characteristics			
Current smoking, % yes	28.8	28.7	32.3
Environmental smoking, % yes	39.6	38.3	47.3
Acute respiratory symptoms, % yes	53.8 [b]	72.3	32.7 [b]
Other acute symptoms, % > 1	86.7	86.6	72.1 [b]
Other chronic diseases, % > 1	68.8	63.6	39.4 [b]

For difference between *overreporting*/*underreporting* and *concordance*: [a] $p < 0.05$ and [b] $p < 0.001$

The results of multivariate analyses (Table 4) show that the observed agreement between patients and GP was more profound if accompanying respiratory symptoms were taken into account: for *overreporting* (adjusted odds ratio 0.45; 95% confidence interval 0.34-0.61) and for *underreporting* (adjusted odds ratio 0.17; 95% confidence interval 0.11-0.27). *Underreporting* was also associated with higher age (adjusted odds ratio 3.10; 95% confidence interval 1.70-5.63), smoking in the patients' house (adjusted odds ratio 1.75; 95% confidence interval 1.12-2.74) and with less chronic conditions (adjusted odds ratio 0.31; 95% confidence interval 0.19-0.49).

Table 4. Odds ratios (OR) and 95% confidence intervals (95% CI) for overreporting and underreporting.

	Overreporting (n = 593)		***Underreporting*** (n = 165)	
	Bivariate	Multivariate	Bivariate	Multivariate
	OR [95% CI]		OR [95% CI]	
General characteristics				
Gender: men vs. women	0.82 [0.62-1.07]		1.38 [0.95-2.02]	
Age: 20-39 vs. <20	1.41 [0.93-2.15]		0.85 [0.45-1.61]	
Age: 40-59 vs. <20	1.23 [0.85-1.77]		0.93 [0.55-1.58]	
Age: ≥60 vs. <20	0.79 [0.55-1.14]		1.37 [0.85-2.21]	3.10 [1.70-5.63]
Health insurance: public vs. private	1.14 [0.85-1.52]		1.32 [0.87-2.00]	
Ethnicity: non-native vs. native	1.17 [0.71-1.93]		1.31 [0.67-2.53]	
Educational level: middle vs. lower	1.55 [1.08-2.20]		0.82 [0.52-1.31]	
Educational level: higher vs. lower	1.51 [0.92-2.46]		0.78 [0.40-1.55]	
Health characteristics				
Current smoking: yes vs. no	1.01 [0.72-1.41]		1.19 [0.75-1.87]	
Environmental smoking: yes vs. no	1.06 [0.80-1.40]		1.44 [0.99-2.11]	1.75 [1.12-2.74]
Acute respiratory symptoms: yes vs. no	0.45 [0.33-0.60]	0.45 [0.34-0.61]	0.19 [0.12-0.28]	0.17 [0.11-0.27]
Other acute symptoms: 0-1 vs. >1	1.01 [0.68-1.50]		0.40 [0.25-0.64]	
Other chronic diseases: 0-1 vs. >1	1.27 [0.95-1.68]		0.37 [0.25-0.55]	0.31 [0.19-0.49]

2.5 Discussion

This is one of the first studies to evaluate the difference between the prevalence of self-reported and GP-diagnosed asthma or COPD on the level of the individual patient in a large population study. The prevalence of self-reported asthma or COPD (9.7%) was almost twice as high compared with the prevalence estimated from the GP computer records (5.2%). The observed difference in prevalence was higher in previous studies in the Netherlands (18-20). In those studies the prevalence was not compared at the individual level and different populations were included. The observed agreement was high (92%), while the kappa statistic was low (0.4). The kappa has the disadvantage that it is affected by the prevalence (Table 2) and emerges into low values. This phenomenon of *high agreement but low kappa* has been described in previous studies (32, 33).

A limitation of our study is that we could not distinguish between asthma and COPD. Several studies have reported that asthma is often underdiagnosed and undertreated due to underpresentation (34-36). Since asthma is episodic in nature, some patients might have been free of symptoms during the registration year, which explains why they had not visited their GP. Children who had asthma during first years of life often

have periods free of symptoms and therefore do not need to consult their GP. On the other hand, *underreporting* is associated with older age, implying that this group most probably consists of patients with COPD.
Another limitation of our study is that the health interview was restricted to the Dutch-speaking practice population. The results of our study should therefore be applied with great care to the non-Dutch-speaking practice population. Our analyses were restricted to those patients who consulted their GP during the registration year. Therefore, the conclusions of our study are probably not valid for the healthiest people: those who did not consult their GP at all. Another possibility is that some misclassification may have occurred when the diagnosis were made by the GPs and in the coding of the diseases. For example, some GP may diagnose and code a patient with recurrent wheezing with coughing as asthma, while others register the same event as chronic wheezing.

According to their GP medical records patients in the *overreporting* group (65% of patients with self-reported asthma or COPD) were more likely to be diagnosed with other respiratory conditions, including shortness of breath, wheezing and coughing. Asthma and COPD are clinically characterized by respiratory symptoms such as shortness of breath, wheezing and coughing. Patients may attribute their respiratory symptoms or even conditions like acute bronchitis or sinusitis to asthma or COPD (17). A patient who has dyspnea may well receive a prescription and subsequently report this as asthma or COPD.

Patients in the *underreporting* group (34% of the GP-diagnosed patients) were more likely to be older and to live in an environment where they were exposed to smoking. With the exception of the elderly, this group had fewer acute respiratory symptoms and chronic diseases. Older patients may be unaware of their condition, and therefore fail to report this. Patients who smoke generally have respiratory symptoms, but do not always report them, because they are aware that smoking is associated with their symptoms. Some patients have symptom-free periods; others have made adjustments to their lives and did not report their condition during the health interview.

In conclusion, both methods were found to have their own advantages and disadvantages. The self-reported prevalence of asthma or COPD, when compared with GP registration, is associated with an overestimation in people who suffer from other

respiratory conditions and with an underestimation in elderly persons living in a smoky environment who have fewer chronic diseases. These findings should certainly be taken into account when deciding on a method to measure prevalence rates. Overall, we strongly recommend that the underestimation found in the elderly be further studied. These patients are in all likelihood COPD patients. We also recommend future studies to include a capacity to distinguish between asthma and COPD.

2.6 Key Points

- Explain differences between the prevalence of self-reported and GP-diagnosed asthma or COPD on the level of the individual patient.
- The prevalence of self-reported asthma or COPD (9.7%) was almost twice as high as the prevalence based on GP-information (5.2%).
- The self-reported prevalence of asthma or COPD is associated with an underestimation in elderly persons living in a smoky environment.
- The self-reported prevalence of asthma or COPD is associated with an overestimation in people who suffer from other respiratory conditions.
- The underestimation of asthma or COPD in the elderly should be further studied.

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3

A Comparison of Parent-Reported Wheezing or Shortness of Breath among Infants as Assessed by Questionnaire and Physician Interview: the Generation R Study

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Submitted

3.1 Abstract

Purpose: The prevalence of asthma among preschool children is difficult to determine with accuracy because no gold standard is available for the diagnosis. The aim of this study was to compare parent-reported wheezing or shortness of breath among infants as assessed by questionnaire and physician interview.

Methods: We studied 1202 children participating in the Generation R Study. Their parents completed a written questionnaire at home when their infant was 12 months old, including items on wheezing or shortness of breath. During the regular free-of-charge Child Health Center visit at age 14 months, the physician interviewed the parents to assess the presence of wheezing or shortness of breath.

Results: The prevalence of wheezing or shortness of breath estimated from questionnaires was significantly higher than the prevalence estimated from physician interview (36% vs. 20%; $p < 0.001$): observed agreement 73%, kappa 0.36. Only 41% of questionnaire-reported symptoms were assessed through the physician interview, while 73% of physician-interviewed symptoms were reported in the questionnaire. Compared with infants in the subgroup with agreement on the presence of wheezing or shortness of breath, the infants in the subgroups without agreement significantly less often received anti-asthma medication and significantly less often had abnormal respiratory sounds or bronchiolitis or croup. The mothers in the subgroups without agreement were significantly less often working. The proportion of infants receiving anti-asthma medication was significantly higher in physician interview data than in questionnaire data (23% vs. 4%; $p < 0.001$).

Conclusions: The physician interview yielded lower prevalence rates for wheezing or shortness of breath than questionnaires. Agreement between questionnaire data and physician interview data was more profound when the infant received anti-asthma medication, had abnormal respiratory sounds, had bronchiolitis, had croup and when the mother was working. These findings should be taken into account when deciding upon a method to measure the prevalence of asthma among infants.

3.2 Introduction

The prevalence of asthma in young children is difficult to determine with accuracy given the fact that no conventional lung test or gold standard is available for the diagnosis. Asthma assessment among young children is therefore based on asthma-like symptoms reported by parents through self-administered written questionnaires or through personal interviews (1).

Many epidemiological studies on asthma in preschool children are based upon parent-reported symptoms in written questionnaires. Parent-reported data are often more readily available and cheaper than alternatives. The validity of parent-reported asthma is questionable, since the accuracy and potential bias usually cannot be assessed. A study that compared asthma prevalence among preschool children aged 1-6 year reported that 40% of the children claimed by their parents to have asthma had no medical record of asthma (2). Another study reported that conditions such as asthma have a two times higher self-reported prevalence compared with the prevalence based on general practitioner medical records (3). Other studies have reported that respiratory symptoms and asthma-like symptoms are reported with moderate accuracy (4-6).

The aim of the present study was to compare parent reports of wheezing or shortness of breath among infants from self-administered written questionnaires and parent reports elicited during a structured interview by the physician, and to examine which factors might influence the agreement. In addition, we also examined the characteristics of subgroups with or without agreement on wheezing or shortness of breath. We were particularly interested in characterizing subgroups without agreement, in order to evaluate which estimation method best predicted the prevalence of wheezing or shortness of breath among infants for research purposes: questionnaire or physician interview.

3.3 Methods

Study population

The present study was embedded in the Generation R Study, a prospective population based cohort study from fetal life until young adulthood (7, 8). The Generation R Study was designed to identify early environmental and genetic determinants of growth, development and health in fetal life, childhood, and young adulthood. Detailed information on the design and method of the Generation R Study has been

described in previous studies (9). The Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study. Written informed consent was obtained from all participants.

The Generation R cohort includes 7893 children who are participating in the postnatal phase and who were born between April 2002 and January 2006. Within the framework of the Generation R Study, a cluster randomized controlled trial was designed to evaluate the effectiveness of early detection of asthma among preschool children. The principal cohort consisted of Generation R children participating in the postnatal phase and living in Rotterdam, defined by postal codes 3010-3070. Randomization was done at the level of the Child Health Centers; in total 16 Child Health Centers are participating. Prior to randomization, the participating Child Health Centers were stratified for the socio-economic status of their neighborhood, and then randomly assigned to the study group (eight Child Health Centers) or the control group (eight Child Health Centers).

Study population for analysis

Data collection of the Generation R cohort and the asthma early detection trial is still ongoing. The current analyses were based on available data of 1832 parents who visited an intervention Child Health Center for a regular free-of-charge preventive consultation between June 2005 and April 2007. The physician interviewed 1731 parents during the consultation at age 14 months. Reported data from the 12-month questionnaire was available for 1202 out of these 1731 children. All analyses were based on these 1202 children who were born between January 2004 and January 2006.

Questionnaire data

Information on wheezing or shortness of breath was obtained from a written questionnaire and was completed by one or both parents when the infant was 12 months old. The prevalence of parent-reported wheezing or shortness of breath was based on the answers to the following questions: ‘Has your child ever suffered from wheezing or a whistling noise in the chest?’ and ‘Has your child ever suffered from shortness or breath?’ Answers were coded as ‘yes’ or ‘no’. Information on infants’ and maternal characteristics was also obtained from questionnaires. Infants’ characteristics included gender (boy or girl), the presence of flu (yes or no), sore throat (yes or no), and other respiratory conditions (yes or no) including bronchiolitis,

croup and whooping cough. Information on maternal characteristics included age (in years), ethnicity (Dutch or non-Dutch), educational level (higher or else), working status (working ≤ 24 hours weekly or working more than 24 hours weekly), and respondent (mother only or else). Information on ethnicity and education was obtained from the first questionnaire at enrolment in the study. Ethnicity and educational level of the mother were classified according to the classification of Statistics Netherlands and were defined based on country of birth and highest finished education, respectively.

Interview data

The physician interviewed the parents during the 14-month visit to the Child Health Centers using a short questionnaire. The prevalence of parent-reported wheezing or shortness of breath from the interview was based on the answers to the following questions: 'Has your child ever suffered from wheezing or a whistling noise in the chest?' and 'Has your child ever suffered from shortness or breath?' Answers were coded as 'yes' or 'no'. In addition, parents were asked whether their child had wheezing or shortness of breath, whether their child received anti-asthma medication (yes or no), and whether their child was exposed to smoke in his or her direct environment (yes or no). The physician also reported whether the infant had abnormal respiratory sounds as measured by lung auscultation (yes or no) during the visit.

Statistical analysis

Descriptive variables of the study population are presented as mean with standard deviation for continuous variables and as proportion for dichotomous or categorical variables. The prevalence of wheezing, shortness of breath, combined wheezing and shortness of breath, and wheezing or shortness of breath was calculated for both assessments, and were compared at the individual level. The observed agreement on wheezing or shortness of breath between questionnaire and physician interview was investigated by cross-tabulation and was expressed as the percentage of the number of positive and negative answers from both data sources divided by the total study population. The agreement was also investigated by the kappa coefficient (κ), which is a measure of agreement adjusted for chance (10). The κ takes into account that agreement can be inflated due to skewed distributions (11, 12). The κ was interpreted using Landis and Koch criteria: $\kappa \leq 0.2$ indicates poor agreement; $0.2 < \kappa \leq 0.4$

indicates fair agreement; $0.4 < \kappa \leq 0.6$ indicates moderate agreement; $0.6 < \kappa \leq 0.8$ indicates good agreement; $0.8 < \kappa \leq 1.0$ indicates excellent agreement (13).

The independent contribution of infants' and maternal characteristics to the presence or absence of agreement on wheezing or shortness of breath was subsequently investigated using multivariate logistic regression analyses. We computed two models. In the first model, the outcome category *more reported symptoms in the questionnair*e was defined as the proportion of questionnaire-reported symptoms that was not available from physician interview. In the second model, the outcome category *less reported symptoms in the questionnair*e was defined as the proportion of physician-interviewed symptoms that was not reported in the questionnaire. The reference category in both models was the proportion of parents with agreement on the presence of wheezing or shortness of breath. The proportion of parents with agreement on the absence of wheezing or shortness of breath was not included in the logistic models. We used a manual backward selection method, removing variables with the highest *p*-value stepwise, until all remaining variables in the final multivariate models had a *p*-value less than 0.05. For all analyses *p*-values less than 0.05 were considered significant. All analyses were performed using the Statistical Package for the Social Sciences, version 15.0 for windows (SPSS Inc, Chicago, IL).

3.4 Results

The general characteristics of the study population are summarized in Table 1. Within our study population, the mean difference in age of the infant, between the moment that the questionnaire was completed and the physician interview was carried out, was 2.3 months. Fifty percent of the infants were boys, 17.0% were exposed to smoke in their direct environment, 8.6% received anti-asthma medication, 3.2% had abnormal respiratory sounds, and 1.6% - 46.2% had other respiratory conditions, including flu, sore throat, bronchiolitis, croup and whooping cough.

Table 1. General characteristics of the study population (n = 1202).

Infants' characteristics	
Age in months, mean ± SD	
When the questionnaire was completed	12.1 ± 0.6
When the interview was carried out	14.4 ± 0.6
Difference in age in months	2.3 ± 0.8
Gender, % boys	48.8
Exposure to smoke (interview data), % yes	17.0
Received anti-asthma medication (interview data), % yes	8.6
Abnormal respiratory sounds (interview data), % yes	3.2
Presence of flu (questionnaire data), % yes	46.2
Presence of sore throat (questionnaire data), % yes	13.1
Presence of bronchiolitis (questionnaire data), % yes	7.2
Presence of croup (questionnaire data), % yes	3.5
Presence of whooping cough (questionnaire data), % yes	1.6
Maternal characteristics (questionnaire data)	
Age in years, mean ± SD	31.5 ± 4.5
Ethnicity, % non-Dutch	36.4
Education, % with higher educational level	58.3
Working status, % not working	22.5
Respondent, % mother only	86.1

The prevalence of wheezing or shortness of breath from questionnaire (36%) was significantly higher than from physician interview (20%), $p < 0.001$ (Table 2). The observed agreement was 73%, while the κ indicated fair agreement (κ = 0.36; 95% confidence interval 0.33 - 0.37). Agreement (n = 178) on the presence of wheezing or shortness of breath was observed in 41% of parents who reported these symptoms in the questionnaire (n = 434) and in 73% of parents who reported these symptoms through the interview (n = 244).

Table 2. Agreement on wheezing or shortness of breath: self-administered questionnaire data compared with physician interview data (n = 1202).

	Physician interview data [2]		
	Present	Not present	
Questionnaire data [1]			
Present	**178**	**256**	**434**
Not present	**66**	702	768
	244	958	**1202**

[1] Wheezing or shortness of breath from self-administered questionnaires by parents 434/1202 (36%)

[2] Wheezing or shortness of breath from physician interview with parents 244/1202 (20%)

Observed agreement (178+702)/1202 (73%); Cohen's kappa 0.36 [0.33-0.39].

More reported symptoms in the questionnaire (yes in the questionnaire, no in the interview) 256/434 (59%).

Less reported symptoms in the questionnaire (no in the questionnaire, yes in the interview) 66/244 (27%).

From all questionnaire-reported wheezing or shortness of breath (n = 434), 59% were not elicited through the physician interview (256 parents reported more symptoms in the questionnaire), indicating that only 41% of questionnaire-reported symptoms were assessed through the physician interview. From all physician-interviewed wheezing or shortness of breath (n = 244), 27% were not reported in the questionnaire (66 parents reported less symptoms in the questionnaire), indicating that 73% of physician-interviewed symptoms were reported in the questionnaire.

The prevalence of wheezing (29% vs. 15%), shortness of breath (23% vs. 15%) and combined wheezing and shortness of breath (16% vs. 10%) estimated from the questionnaires was also significantly higher than the prevalence estimated from the physician-interview ($p < 0.001$). The observed agreement (κ) for wheezing, shortness of breath, and combined wheezing and shortness of breath were respectively 75% (0.30), 81% (0.39), and 85% (0.34).

Table 3 shows the distribution of characteristics of subgroups with and without agreement on the presence of wheezing or shortness of breath. Compared with infants in the subgroup with agreement, the infants in the subgroup with *more reported symptoms in the questionnaire* less often received anti-asthma medication (3.9% vs. 38.8%, $p < 0.001$), less often had abnormal respiratory sounds (2.0% vs. 11.8%, $p < 0.001$), less often had bronchiolitis (10.2% vs. 22.5%, $p < 0.001$), less often had croup (3.9% vs. 11.2%, $p = 0.003$), and their mothers were more often not working (19.9% vs. 11.8%, $p = 0.025$). Other infants' and maternal characteristics did not differ significantly between the subgroup with agreement and the subgroup with *more reported symptoms in the questionnaire*.

Compared with infants in the subgroup with agreement, the infants in the subgroup with *less reported symptoms in the questionnaire* less often received anti-asthma medication (22.7% vs. 38.8%, $p = 0.019$), less often had abnormal respiratory sounds (3.0% vs. 11.8%, $p = 0.037$), less often had bronchiolitis (9.1% vs. 22.5%, $p = 0.018$), less often had croup (3.0% vs. 11.2%, $p = 0.047$), and the mothers were more often not working (24.2% vs. 11.8%, $p = 0.016$). Other infants' and maternal characteristics did not differ significantly between the subgroup with agreement and the subgroup with *less reported symptoms in the questionnaire*.

Compared with the subgroup with *less reported symptoms in the questionnaire*, infants in the subgroup with *more reported symptoms in the questionnaire* more often had flu (53.5% vs. 43.9%; $p = 0.165$), and significantly less often received anti-asthma medication (3.9% vs. 22.7%; $p < 0.001$).

Table 3. Characteristics of the subgroup with agreement separately compared with the subgroups without agreement.

	More reported symptoms in the Q *Q yes, I no* (n = 256)	Agreement *Q yes, I yes* (n = 178)	*p*-value [1]
Infants' characteristics			
Difference in age in months, mean ± SD	2.2 ± 0.7	2.4 ± 0.8	**0.043**
Gender, % boys	55.1	56.2	0.820
Smoking exposure, % yes	17.2	15.7	0.688
Received anti-asthma medication, % yes	3.9	38.8	**<0.001**
Abnormal respiratory sounds, % yes	2.0	11.8	**<0.001**
Presence of flu, % yes	53.5	52.5	0.795
Presence of sore throat, % yes	16.4	22.5	0.112
Presence of bronchiolitis, % yes	10.2	22.5	**<0.001**
Presence of croup, % yes	3.9	11.2	**0.003**
Presence of whooping cough, % yes	2.3	1.1	0.353
Maternal characteristics			
Age in years, mean ± SD	31.6 ± 4.7	31.7 ± 4.4	0.834
Ethnicity, % non-Dutch	35.2	33.1	0.664
Educational level, % higher	64.0	60.6	0.490
Working status, % not working	19.9	11.8	**0.025**
Respondent, % mother only	87.5	86.0	0.639
	Less reported symptoms in the Q *Q no, I yes* (n = 66)	Agreement *Q yes, I yes* (n = 178)	*p*-value [2]
Infants' characteristics			
Difference in age in months, mean ± SD	2.3 ± 0.8	2.4 ± 0.8	0.592
Gender, % boys	45.5	56.2	0.136
Smoking exposure, % yes	15.2	15.7	0.912
Received anti-asthma medication, % yes	22.7	38.8	**0.019**
Abnormal respiratory sounds, % yes	3.0	11.8	**0.037**
Presence of flu, % yes	43.9	52.5	0.249
Presence of sore throat, % yes	15.2	22.5	0.208
Presence of bronchiolitis, % yes	9.1	22.5	**0.018**
Presence of croup, % yes	3.0	11.2	**0.047**
Presence of whooping cough, % yes	0.0	1.1	0.387
Maternal characteristics			
Age in years, mean ± SD	31.3 ± 4.5	31.7 ± 4.4	0.607
Ethnicity, % non-Dutch	33.3	33.1	0.978
Educational level, % higher	64.6	60.6	0.573
Working status, % not working	24.2	11.8	**0.016**
Respondent, % mother only	87.9	86.0	0.696

[1] *p*-value for differences in characteristics between the subgroup with *more reported symptoms in the questionnaire* and the subgroup with agreement. [2] *p*-value for differences in characteristics between the subgroup with *less reported symptoms in the questionnaire* and the subgroup with agreement. *p*-values less than 0.05 are presented in **bold**. Abbreviations: Q (Questionnaire data); I (Physician interview data).

Multivariate logistic regression models indicated that the agreement between questionnaire and physician interview was more profound when the infant received anti-asthma medication, had abnormal respiratory sounds, had bronchiolitis, had croup and when their mother was working (Table 4).

Independent determinants for *more reported symptoms in the questionnaire* were not receiving anti-asthma medication, the absence of abnormal respiratory sounds, not having bronchiolitis and not having croup. Not receiving anti-asthma medication and the absence of abnormal respiratory sounds were respectively associated with a 13.7 and 4.0 times increased risk for *more reported symptoms in the questionnaire*. Not having bronchiolitis or not having croup was respectively associated with a 2.4 and 4.0 times increased risk for *more reported symptoms in the questionnaire*.

Independent determinants for *less reported symptoms in the questionnaire* were not receiving anti-asthma medication, not having bronchiolitis and a non-working mother. Not receiving anti-asthma medication and not having bronchiolitis were respectively associated with a 2.1 and 2.7 times increased risk for *less reported symptoms in the questionnaire*. Not working mothers were associated with a 2.5 times increased risk for *less reported symptoms in the questionnaire*.

Table 4. Multivariate logistics regression analysis for more reported symptoms in the questionnaire and less reported symptoms in the questionnaire.

	More reported symptoms in the questionnaire [1] (n = 434) OR [95% CI]	
	Bivariate	Multivariate
Received anti-asthma medication: no vs. yes	15.6 [7.7 - 31.4]***	13.7 [6.7 - 28.0]***
Abnormal respiratory sounds: no vs. yes	6.7 [2.5 - 18.2]***	4.0 [1.3 - 12.3]*
Presence of bronchiolitis: no vs. yes	2.6 [1.5 - 4.4]**	2.4 [1.3 - 4.4]**
Presence of croup: no vs. yes	3.1 [1.4 - 6.8]**	4.0 [1.7 - 9.3]**
Working status: not working versus working	1.9 [1.1 - 3.2]*	---
	Less reported symptoms in the questionnaire [2] (n = 244) OR [95% CI]	
	Bivariate	Multivariate
Received anti-asthma medication: no vs. yes	2.2 [1.1 - 4.1]*	2.1 [1.1 - 4.1]*
Abnormal respiratory sounds: no vs. yes	4.3 [1.0 - 18.8]	---
Presence of bronchiolitis: no vs. yes	2.9 [1.7 - 7.2]*	2.7 [1.1 - 6.7]*
Presence of croup: no vs. yes	4.1 [0.9 - 17.8]	---
Working status: not working versus working	2.4 [1.2 - 4.9]*	2.5 [1.2 - 5.3]*

[1] Outcome variable is the subgroup with *more reported symptoms in the questionnaire* vs. the subgroup with *agreement*. [2] Outcome variable is the subgroup with *less reported symptoms in the questionnaire* vs. the subgroup with *agreement*. Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3.5 Discussion

We evaluated the agreement on the prevalence of wheezing or shortness of breath among infants, comparing parent-reported symptoms from self-administered written questionnaires with symptoms from physician interview with parents. The prevalence of wheezing or shortness of breath from questionnaires was significantly higher compared with the prevalence estimated from physician interview. The observed agreement was reasonable, but agreement estimated by κ was fair. Compared with physician interview data, the proportion of infants receiving anti-asthma medication was significantly higher in questionnaire data.

Although asthma is the most common cause of wheezing and shortness of breath in children and adults, wheezing and shortness of breath are relative non-specific for asthma at such young age (14). Other respiratory conditions among infants can present similar symptoms. For example, bronchiolitis, a respiratory infectious disease caused by the respiratory syncytial virus, can also produce wheezing or shortness of breath. In the present study, the presence of bronchiolitis or croup was associated

with agreement on wheezing or shortness of breath: the subgroups with more or less reported symptoms in the questionnaire significantly less often had bronchiolitis or croup. Compared with physician interview data, the prevalence of other respiratory conditions, including bronchiolitis and croup, but especially flu, was higher in the questionnaire data. Although the observed differences were not statistically significant, this could indicate that parents have a tendency to label other respiratory symptoms as asthma (15, 16).

Strength of our study is that our data were compared on the individual level. In this way, we were able to characterize the subgroup with agreement on the presence of wheezing or shortness of breath, the subgroup with *more reported symptoms in the questionnair*e and the subgroup *with less reported symptoms in the questionnaire*. The subgroup of parents who reported symptoms without agreement could be relevant target groups for secondary prevention and health education.
Results of a randomized prospective intervention study among 60 preschool children with newly diagnosed asthma, indicated that with extra support and health education in the form of group discussions, mothers and their preschool children showed health improvement (17). After six months of health education, mothers in the intervention group were less often disturbed at night, felt less helpless and frightened and the child's asthma less interfered with their work. After 18 months the exacerbation rate declined with 50% among children in the intervention group.

Parents who reported *more symptoms in the questionnaire* are most probably parents whose infants had wheezing or shortness of breath during cold or flu or due to other respiratory conditions. In our study population almost one out of two infants had flu or cold in the first year of life according to their parents. Another explanation for more reported symptoms is that perhaps someone else was present during the physician interview. The mothers predominated as respondents for the questionnaire. We are not aware who was present during the physician interview.
In the present study, *less reported symptoms in the questionnaire*, were strongly associated with received anti-asthma medication. This indicates that the physician most probably has the information on medical therapy of the infants. The physician has the tendency to report wheezing or shortness of breath when anti-asthma medication was received.

There are certain limitations to this study. Our analyses were based on 1202 infants who were born between January 2004 and January 2006. We were not able to assess the agreement on wheezing or shortness of breath among infants participating in the Generation R Study that were born before January 2004. Wheezing and shortness of breath were defined based on selected core questions from the International Study of Asthma and Allergies in Childhood (ISAAC) (18, 19). The ISAAC core questions were originally designed for children aged six years and up. To our knowledge there are no validated respiratory questionnaires for use in infants aged 12 months. We have used selected questions from the ISAAC core questionnaires as they were originally adapted for the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort (20). These questions were indeed made suitable for younger children and, although not formally validated, have been used in many papers from this cohort.

There is a controversy whether parent reports are accurate or not. Prior studies have shown that parents do not adequately perceive asthma-like symptoms in childhood (15, 16, 21). Another study reported that compared with pediatricians' records, parents were able to report asthma with accuracy, especially for younger children (22). We do not know whether parent-reported wheezing or shortness of breath assessed from physician interview is more accurate than parent-reported wheezing or shortness of breath from self-administered written questionnaires. The self-administered written questionnaire by parents was able to assess 73% of physician-interviewed wheezing or shortness of breath, and the physician interview was able to assess 41% of questionnaire reported wheezing or shortness of breath. We propose, in future studies, to evaluate whether parent reports through questionnaires or parental views elicited through a structured physician interview predict best the occurrence of asthma at later age, for example at age seven years. Further investigation is needed to assess whether parent-reported wheezing or shortness of breath through self-administered written questionnaires or physician-interviewed wheezing or shortness of breath are reliable sources of information for different epidemiological purposes.

3.6 Conclusions

Physician interview yielded lower prevalence rates for wheezing or shortness of breath during infancy than questionnaires. Compared with physician interview data, the proportion of infants receiving anti-asthma medication was significantly higher in

questionnaire data. Agreement between questionnaire data and physician interview data was more profound when the infant received anti-asthma medication, had abnormal respiratory sounds, had bronchiolitis, had croup and when the mother was working. These findings should be taken into account when deciding upon a method to measure the prevalence of asthma among infants.

3.7 Acknowledgements

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Part II

Measurements of Health-Related Quality of Life

4

Pediatric Health-Related Quality of Life Questionnaires in Clinical Trials

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4.1 Abstract

Purpose: This review summarizes recent studies on the feasibility, reliability and validity of pediatric health-related quality of life questionnaires and gives an overview of recent applications of these measures in pediatrics.

Recent findings: The often-applied short form of the Child Health Questionnaire (CHQ-PF28) provides reliable physical and psychosocial summary measures, but reliable estimates for each scale require the longer version (CHQ-PF50). In addition to this questionnaire, the Pediatric Quality of Life Inventory is another reliable and valid measure. The TNO-AZL Preschool Children Quality of Life questionnaire is a feasible and reliable measure for preschool children.

Generally, generic questionnaires are less sensitive to the impact of specific diseases than are disease-specific questionnaires. Parents' and self-reports provide different outlooks on quality of life, which complement each other.

Conclusions: There are several feasible, reliable and validated pediatric quality of life questionnaires that can be used in clinical trials. These include generic and disease-specific questionnaires and health profile measures, as well as preference-based measures in pediatric settings. Generally, a combination of these types of questionnaires would be the most appropriate approach. Moreover, a combination of parents' and self-reports should be applied. Appropriate selection of outcome measures will enhance the quality of pediatric studies and the ability to assess treatment effects in clinical trials.

4.2 Introduction

Based on the World Health Organization's definition of health as 'a state of complete physical and mental and social well-being, and not merely the absence of disease or infirmity', quality of life may be defined as 'physical, social and emotional aspects of a patient's well-being that are relevant and important to the individual' (1). Quality of life is a multidimensional concept. The restriction to health-related quality of life refers to the inclusion of dimensions that are relevant to health, and that are affected by ill health (e.g. the dimensions mobility, pain, psychological well-being).

Health-related quality of life questionnaires have been applied in adult populations for a long time. From the 1990s onwards, pediatric questionnaires have also been generally accepted. The relevant dimensions and the item content of pediatric quality of life questionnaires differ from those of adult questionnaires, and vary with

developmental age. In young children it is essential to use a proxy rater to complete the questionnaire; the proxy rater is generally one of the parents (2).

Health-related quality of life is an essential outcome measure in pediatric studies, complementary to clinical measures and mortality (2). This review summarizes recent studies about the feasibility, reliability and validity of pediatric health-related quality of life questionnaires and gives an overview of recent applications of these measures in pediatrics.

4.3 Generic Quality of Life Questionnaires

Several classifications of health-related quality of life questionnaires can be made. The most important distinction is between generic and disease-specific instruments (see below). First, we discuss generic questionnaires, which intend to measure all dimensions of health-related quality of life, and can therefore be applied in healthy populations as well as in any clinical population regardless of the type of medical condition (1). The advantage of generic questionnaires is that they provide a comprehensive overview of quality of life at the individual or group level. This has to be weighed up against the disadvantage that a generic questionnaire will not be able to provide a detailed or reliable measurement of dimensions that are specific for a certain condition (1,2).

Recent findings regarding four frequently applied generic questionnaires will be discussed: the Child Health Questionnaire (CHQ), the Pediatric Quality of Life Inventory (PedsQL), the TNO-AZL (Preschool) Children's Quality of Life questionnaire (TAPQoL/TACQoL) and the KIDSCREEN/DISABKIDS questionnaires.

The CHQ covers physical and psychosocial aspects. A PubMed search showed that since the first CHQ publication in 1998, some 150 pediatric papers in which the CHQ was used have been published. The CHQ is available in a large number of different languages and countries since a cross-cultural validation project was carried out in 32 countries (3). Recently, a Chinese cross-cultural validation was published (4). The CHQ has been applied to numerous clinical conditions including asthma and cystic fibrosis (5,6).

The most frequently applied version is the 50-item parent-form (CHQ-PF50) for children aged five years and older and consists of 11 multi-item and two single-item scales, of which four scales pertain to the impact of child's ill health on parents and the family (5-7). The CHQ permits the calculation of a physical summary measure and a psychosocial summary measure. A 28-item version with the same scales but fewer

items is available (CHQ-PF28) (5-7). Recently, a validation study of the 28-item CHQ-PF version showed that the summary measures of the CHQ-PF28 are highly reliable, as in the CHQ-PF50, but that not all separate CHQ-PF28 scales provide reliable estimates (8). It can be concluded that in clinical studies with little discretionary space for quality of life measurement, the CHQ-PF28 is a realistic option providing highly reliable summary measures, while studies that require reliable scale estimates (i.e. a full health profile; see below), the CHQ-PF50 is mandatory.

The CHQ also comprises an 87-item self-report questionnaire for adolescents and children at least ten years old - the CHQ-CF87 (4,9,10). Three years ago a preliminary version of an analogous quality of life measure for preschool children has been reported - the Infant Toddler Quality of Life Questionnaire (ITQOL) - with eight scales appropriate for the developmental stage of infants (82 items) and five parent-scales (impact of the infant's ill health; 21 items) (11).

The PedsQL generic questionnaire was first published in 1999, and a PubMed search showed that since the introduction, around 50 pediatric papers were published that made use of this instrument (12). The PedsQL scales have already been translated into various languages. Most of the existing translations, however, have not been validated or have not undergone a full linguistic validation and additional work is necessary. The PedsQL generic quality of life questionnaire consists of four scales (physical functioning, eight items; emotional functioning, five items; social functioning, five items; school functioning, five items) and is available for children aged five years and older and for adolescents. A parent and self-report questionnaire is available (12). The reliability and validity of the PedsQL has been firmly established and applications in several clinical subgroups have been reported, including, for example, recurrent respiratory papillomatosis (13); also data from school samples are available [14]. A translation of the PedsQL into German has been reported (15).

The TACQoL, a frequently used generic questionnaire, was introduced in 1998 (16). It has the unique feature that the child's or the parent's evaluation of the child's health status is considered. It contains seven scales of eight items: pain and symptoms, motor function, autonomy, cognitive and social function, positive and negative emotions.

Parent-forms as well as child and adolescent self-report forms are available. The TAPQoL questionnaire with 12 scales and items appropriate for (parents of) infants

was introduced in 2000 (17). A PubMed search showed that since the introduction, both instruments together have been applied in some 25 pediatric studies concerning various conditions including asthma (9,17). Health-related quality of life measures that have been designed and validated for preschool children, such as the TAPQOL, are relatively rare. A recent study underscored the feasibility and reliability of the TAPQOL for children aged 2-48 months old (18).

The KIDSCREEN and DISABKIDS generic health-related quality of life questionnaires were both carefully developed in several European countries, thereby ensuring cross-cultural validity from the start, which is a unique feature (19,20). The KIDSCREEN-52 includes 10 multi-item scales with a total of 52 items, and targets children and adolescents between eight and 18 years of age (19). Furthermore, the KIDSCREEN-27 and KIDSCREEN-10 index were developed simultaneously in the participating countries.

The DISABKIDS (56-items) is also a generic questionnaire but aims at children and adolescents with a chronic condition (20). It is only generic in the sense that it is applicable to children with various chronic conditions, but it consists of scales that are specifically relevant for children with disabilities: emotion, independence, physical, social inclusion, social exclusion, and medication (20). A long version and a short version are available. This measure can also be used for children over seven years who have not reached the level of reading ability necessary for the completion of the generic DISABKIDS questionnaire. Since 2001, PubMed showed about 14 papers with the KIDSCREEN or DISABKIDS measure.

4.4 Disease-Specific Quality of Life Questionnaires

As opposed to generic questionnaires, disease-specific questionnaires focus on those dimensions that are likely to be affected by a specific condition or treatment. Such questionnaires describe disease-specific quality of life domains in more detail and are generally considered to be more sensitive to change in clinical applications for which they were developed compared with generic questionnaires (2). Such questionnaires, however, do not cover all dimensions of quality of life, and are therefore appropriate for patients with one specific chronic condition. They do not allow comparisons between specific types of conditions when examining the impact on quality of life (2).

The above-mentioned generic quality of life questionnaires have been applied successfully in numerous specific condition groups, including allergic and respiratory

disease, with the advantage of providing a full health profile that can be compared with profiles of other condition groups or of a general population sample. Recent studies, however, have confirmed that generic measures are not always sensitive to the impact on quality of life of a specific condition and are not always sensitive to change due to treatment.

A study on the quality of life of children with cystic fibrosis showed that the CHQ was not adequately sensitive to the consequences of this condition; the disease-specific Cystic Fibrosis Questionnaire was more informative when evaluating the effects of cystic fibrosis (5). Similarly, a study on quality of life in adolescents born small for gestational age evaluating the effects of growth hormone therapy concluded that the generic CHQ did not reveal quality of life differences between treatment groups whereas a disease-specific measure (TACQoL-S) did reveal significant differences (9). It can be concluded that, whenever possible, a generic health-related quality of life measure should be accompanied by an appropriate disease-specific quality of life measure.

Some of the generic health-related quality of life measures discussed above have additional disease-specific modules. The DISABKIDS questionnaires, for example, include seven disease-specific modules for asthma, atopic dermatitis, juvenile idiopathic arthritis, cerebral palsy, cystic fibrosis, diabetes mellitus, and epilepsy (21). The DISABKIDS asthma module consists of the scale ‘impact’ (eight items) and ‘worry’ (five items); the atopic dermatitis module consists of the scale ‘impact’ (seven items) and ‘skin’ (five items); all of these scales have proven to be adequately reliable (21).

The PedsQL also includes disease-specific modules such as the PedsQL asthma module (22). The long version contains the following: asthma symptoms (11-items), treatment problems (11-items), worry (three items), and communication (three items); the short version only consists of the first two scales. A recent study confirmed the reliability and validity of the 22-item PedsQL asthma module (22).

Disease-specific health-related quality of life measures have also been developed independently of generic measures. For the field of asthma several specific measures have been developed with different contents. An often-applied measure is the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), developed by Raat and colleagues (23) for children and adolescents aged 7-17 years. It has three domains: symptoms (10 items), activity limitations (five items), and emotional function (eight items). Recently, the responsiveness, the longitudinal and the cross-sectional

construct validity of the PAQLQ were confirmed in a Dutch population of 238 children with asthma (23).

Other asthma specific questionnaires are the Child Asthma Questionnaire (CAQ) and the six items Functional Severity of Asthma Scale (24,25). The eight items Asthma Routines Questionnaire measures role assignment, burden, house cleaning, taking medications, timing of medications, medical visits, filling prescriptions, and personal family growth as a result of the disease (25).

4.5 Preference-Based Measures next to Health Profile Measures

The generic as well as the disease-specific health-related quality of life questionnaires discussed above all belong to the family of instruments labeled 'health profile measures' (1). Typically, such health profile measures consist of multiple-items, ordered in multi-item scales. The overview of all scale scores of a single patient, and the mean scores of a group of patients, constitutes a 'health profile'. Health profile measures should be distinguished from so-called 'preference-based measures'.

Preference-based measures, as a first step, also provide an overview of the health status of a patient (or group of patients) by indicating the 'level' (or mean level of a group) from no impairments at all to most severe impairment for each of the quality of life dimensions of that instrument. An expert such as a physician or nurse might classify a patient according to the levels of each dimension, but also a questionnaire consisting of several items may be applied to gather the information necessary for classification. As a second step, a single overall score may be assigned to reflect the level of quality of life of the patient as described by the preference-based instrument. This single overall score is generally obtained from a multi-attribute utility formula or comparable scoring system, based on the measured preferences of a representative panel, such as a random sample of the general population (26). Preference scores have the advantage that they can be applied as an adjustment factor in the calculation of quality-adjusted life years for cost-effectiveness analyses (1).

The Health Utilities Index (HUI) is an example of a preference-based generic health-related quality of life measure that is frequently applied in pediatric studies (26-29). The HUI system has a 15-item parent questionnaire and an analogous self-report form, which is used to classify the patient to one of the two current HUI health state classification systems: the HUI mark 2 system that contains six dimensions, each with four or five levels, or the HUI mark 3 system that contains eight dimensions, with five or six levels each (26). By applying the HUI2 or the HUI3 multi-attribute utility formula,

the utility of any health state can be estimated (26). Three other generic preference-based measures that might be applied in pediatric studies are the Quality of Well-Being Scale (QWB), the EQ-5D, and the SF-6D (28).

Recently, a multi-dimensional health status classification system (HSCS) to describe preschool (PS) children 2.5–5 years of age has been developed and validated; the HSCS-PS has 12 dimensions and three to five levels per dimension (30). A parent questionnaire is available to classify children according to the HSCS-PS, but a multi-attribute utility formula to estimate a single quality of life score for each health state still has to be developed (30).

4.6 Proxy-Report by Parents or Self-Report

Clearly, very young children lack the cognitive abilities to complete health-related quality of life measures by themselves. Self-reports have been applied successfully among children aged eight years or older. Simple-worded questionnaires may be applied by oral interviews with children that are as young as seven years (23). The DISABKIDS-smiley measure is simple and fast to complete and is aimed at cognitive levels of children between four and seven developmental years. Debates have arisen as to whether a proxy reporter such as a parent is capable of reporting on a subjective construct such as quality of life; others discussed who would rate specific dimensions higher - a child or the parent (2). Panepinto and colleagues (10) reported a study on child and parents' perception of quality of life in children with sickle cell anemia and found that compared with child reports, parents reported lower CHQ scores for some scales; the level of correlation between parents' and self-reports varied by CHQ scale. Varni and colleagues (12) reported in a PedsQL study regarding children and adolescents with cerebral palsy that the level of correlation between parent and child reports varied by scale. Houtzager and colleagues (31) reported that concordance between parent and self-reports of siblings of seriously ill children was low to moderate for most TACQoL scales. It can be concluded from these findings that parent reports and self-reports provide different outlooks on childhood quality of life. Both views are useful in providing a complete picture of the impact of disease on childhood health-related quality of life.

4.7 Consequences of Ill Health for Family Members

The CHQ is an instrument that incorporates scales on the impact of ill health on family wellbeing (see above). The Pediatric Asthma Caregiver's Quality of Life Questionnaire

(PACQoL), for example, is a specific questionnaire focusing on how a child's asthma affects the caregiver's quality of life: emotion (nine items), and activity limitations (four items) (25). In addition to the above-mentioned approaches that focus on the consequences for parents, in a recent study the quality of life impact on siblings of children diagnosed with cancer was evaluated. The study showed that in the first months after the diagnosis of cancer in a brother or sister, siblings have relatively lower quality of life than their peers (31,32).

4.8 Conclusions

Although adult health-related quality of life measures have a stronger track record, it can be concluded from this review that there are several feasible, reliable and validated pediatric quality of life questionnaires to be applied in clinical trials. This includes both generic and disease-specific questionnaires, and health profile measures, as well as preference-based measures in the pediatric setting. Furlong and colleagues (28) have proposed a useful framework for identifying appropriate sets of health-related quality of life measures in pediatric studies. Generally, a combination of the measurement types mentioned above will be the most appropriate approach. Moreover, whenever possible, a combination of parents' and self-reports should be applied. Appropriate selection of outcome measures will enhance the quality of pediatric studies and the ability to assess treatment effects in clinical trials.

4.9 References and Recommended Reading

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Part III

The Association between Asthma-Related Symptoms and Health-Related Quality of Life

5

Health-Related Quality of Life in Adolescents with Wheezing Attacks

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5.1 Abstract

Purpose: The purpose of this study was to evaluate health-related quality of life in adolescents with wheezing attacks using self-reported data and to determine independent associations between wheezing attacks and quality of life using multivariate linear regression models.

Methods: Our study sample included 933 of 1071 eligible adolescents who participated in a study in two Municipal Health Services in the Netherlands. Wheezing was defined based on selected questions from the International Study of Asthma and Allergies in Childhood. Quality of life was measured using the Child Health Questionnaire-Child Form (CHQ-CF). Higher scores indicated better quality of life.

Results: According to the adolescents, 72 (7.7%) and 24 (2.6%) had less than four and, at least four wheezing attacks during the past year, respectively. Compared with adolescents who never wheezed, adolescents with wheezing attacks had significantly lower quality of life scores for nine out of 10 CHQ-CF scales. Except for the *Role Physical* and *Family Activities* scales, relevant differences in quality of life were observed for all scales among adolescents who reported at least four wheezing attacks during the past year; most affected were the *Bodily Pain*, *General Health*, *Self Esteem* and *Mental Health* scales. In multivariate linear regression models, wheezing attacks remained significantly associated with quality of life for nine out of 10 CHQ-CF scales.

Conclusions: Wheezing attacks are independently associated with several dimensions of health-related quality of life in adolescents. Specifically, the presence of at least four wheezing attacks during the past year was associated with relevant deficits in quality of life.

5.2 Introduction

Wheezing or a whistling noise in the chest, the major clinical expression of asthma, has a high prevalence in children and adolescents (1). The measurement of health-related quality of life is becoming increasingly important in pediatric healthcare research (2). The World Health Organization has defined the term *health-related quality of life* as the individuals' perception of their position of life in the context of the culture and value systems in which they live and in relation to their goals, expectations and concerns (3). Various questionnaires, both disease-specific and generic instruments, have been developed to measure quality of life in children and adolescents with asthma and asthma-related symptoms (4). A generic quality of life questionnaire enables to compare quality of life between subgroups with and without a specific condition or disease (5). The Child Health Questionnaire-Child Form (CHQ-CF) is a generic questionnaire designed for children and adolescents aged 10 years and older (6). The association between asthma or asthma-related symptoms and quality of life using parent-reported data has been reported (4). Although adolescents' and parents' perceptions about the adolescents quality of life often differ (7), relatively few studies have assessed health-related quality of life among adolescents using self-reported data (8). Self-reports from children are preferred to parent reports, especially in adolescents over 11 years of age (9). No studies until now have reported the independent association between the degree of wheezing attacks (never had wheezing attacks, formerly had wheezing attacks, had mild wheezing attacks, had severe wheezing attacks) and generic health-related quality of life from the perspective of the adolescent themselves, controlling for demographic variables, life style factors and co-morbidity.

The aim of this study was to determine the independent association between wheezing attacks and generic health-related quality of life in adolescents using self-reported data. We assessed whether the frequency of wheezing attacks was negatively associated with quality of life. Our main hypotheses were that quality of life would be lower among adolescents with wheezing attacks and co-morbid conditions, especially among those who reported at least four wheezing attacks during the past year.

The following research questions were addressed: (i) Is health-related quality of life among adolescents with wheezing attacks lower compared with those without? (ii) Is the association between wheezing attacks and quality of life among adolescents

independent from other adolescent characteristics, such as age, gender, smoking behavior, and co-morbidity?

5.3 Methods

Study population

In 2003, 1071 adolescents from seven secondary schools belonging to 55 third-year classes with various educational levels in two Municipal Health Services in the Netherlands (Vlaardingen and Harderwijk), were invited to complete a questionnaire on health and health-related quality of life (10). Adolescents and their parents separately received written information about the study several weeks before data collection; parents were allowed to refuse their child's participation (passive consent), and participation by the students was voluntary. Adolescents completed the questionnaire either by paper and pencil or by internet at their school under supervision of a trained assistant (10); it has been shown that any differences in the measurement of quality of life by means of these two administration methods are negligible or small (11). Furthermore, both administration methods yielded equal results on the frequency of respiratory items (12). The Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study.

Wheezing

The presence of wheezing was based on the answers to the following questions that were selected from the International Study of Asthma and Allergies in Childhood (ISAAC) (13, 14): (i) 'Did you ever have wheezing'? Answers were coded 'yes' or 'no'; (ii) 'Did you have wheezing during the past year'? Answers were coded 'yes' or 'no'; (iii) 'How many wheezing attacks did you have during the past year'? Answers were coded '0' or '1-3' or '4-12' or '12 or more'. The adolescents were categorized into different subgroups according to their responses to these three questions.

Our main determinant was a four-category variable coded as *never*, *former*, *mild* and *severe* wheezing. *Never* wheezing (reference group) was defined as those who responded negatively to the question 'Did you ever have wheezing?'. *Former* wheezing was defined as those who responded positively to 'Did you ever have wheezing?' and negatively to 'Did you have wheezing during the past year?'. *Mild* wheezing was defined as those who responded positively to the question 'Did you have wheezing during the past year?' and reported less than four wheezing attacks.

Severe wheezing was defined as those who responded positively to the question 'Did you have wheezing during the past year?' and reported at least four wheezing attacks.

Health-related quality of life

The CHQ-CF was chosen to measure quality of life because it is the most widely used pediatric health-status measure that has been cross-culturally validated and standardized into several languages (15). The CHQ-CF has been translated into Dutch following the international standards (16). The CHQ-CF consists of 87-items with four, five or six response options, divided over 10 multi-item and two single-item scales. It covers a broad range of dimensions focusing on physical, and psychosocial functioning, as well as on components of family impact (see Addendum 1 for details). Physical dimensions include: *Physical Functioning*, *Role Functioning-Physical* (limitations as a result of physical health), *Bodily Pain*, and *General Health*. Psychosocial dimensions include: *Role Functioning-Emotional* (limitations as a result of emotional problems), *Role Functioning-Behavioral* (limitations as a result of behavioral problems), *Self Esteem*, *Mental Health*, *General Behavior*, and the single item scale *Change in Health*. The CHQ-CF assesses the association between health of the child and quality of life of the child and the association between health of the child and family. Limitations in the family were measured using the multi-item *Family Activities* and the single-item *Family Cohesion* scales. To reduce adolescents' burden, the item *Change in Health* was not evaluated in this study, and the CHQ-CF scales *Role Functioning-Emotional* and *Role Functioning-Behavioral* were combined into a single scale. The combination of two role functioning scales is a departure from the CHQ-CF instructions and in this regard makes the test analogous to the parent form of the CHQ (6). For each scale, items were summed (some recoded/recalibrated) and transformed into a 0-100 scale according to the CHQ manual, with higher scores indicating better quality of life (6).

Covariates

The covariates that were taken into account were age and gender of the adolescents, as well as ethnicity (mixed or non-Dutch and Dutch) and education (lower, intermediate and higher secondary), smoking behavior (never, ever and current smokers), co-morbidity (none, one or more than one conditions or diseases during the past year), and administration mode (paper and pencil versus internet). Ethnicity was defined based on the country of birth of the adolescent and both parents. If the

adolescent and both parents were born in the Netherlands, the adolescent was designated as Dutch. If the adolescent was born in the Netherlands but at least one of the parents was born in another country, the adolescent was designated as mixed-Dutch. If the adolescent was not born in the Netherlands, the adolescent was designated as non-Dutch. Preparatory secondary vocational education was designated as 'lower secondary education', secondary schools that prepare students for higher professional training as 'intermediate secondary education' and university preparatory secondary education as 'higher secondary education'. Smoking status was defined based on self-reports. Co-morbidity was defined as the presence of self-reported conditions or diseases during the past year, including migraine or regular headache, allergies, problems with hearing and seeing, severe or regular low back pain, and depression and/or anxiety.

Statistical analysis

General characteristics for the study population were calculated stratified for the main determinant, and expressed as mean with standard deviation (SD) for continuous variables and as a proportion for dichotomous or categorical variables. Differences in proportions of a particular characteristic between subgroups were tested with the χ^2-test; one-way analysis of variance was used to assess differences in age between subgroups (17).

To investigate the association between wheezing attacks and quality of life, the distribution of quality of life scores of the subgroups with wheezing attacks were separately compared with the distribution of quality of life scores of the reference group. Since the distributions of the CHQ-CF scores were skewed to the left, we performed all comparisons by using the non-parametric Mann-Whitney U test (17). We estimated effect sizes by dividing the difference in mean scores between subgroups by the largest SD. Cohen's effect sizes (d) were used for interpretation of relevant differences: $0.2 \leq d < 0.5$ is considered a small difference, $0.5 \leq d < 0.8$ is considered a moderate difference, and $d \geq 0.8$ is considered a large difference (18).

Multivariate linear regression models were fitted to investigate the independent contribution of wheezing attacks on each of the 10 CHQ-CF scales. In each model, the CHQ-CF scale was studied as dependent variable, wheezing as determinant, and the characteristics of the adolescent, co-morbidity and administration mode as covariates. We used a manual enter selection method, deleting variables with the highest *p*-value stepwise, until all remaining variables had a *p*-value less than 0.05. The association

between wheezing attacks and each of the 10 quality of life scales was first studied unadjusted.

For all analyses a value of $p < 0.05$ was considered significant. All analyses were performed using the Statistical Package for the Social Sciences, version 11.0 for windows (SPSS Inc, Chicago, IL).

5.4 Results

The response rate was 87% (n = 933). General characteristics of the study population (mean age of 15 years, 54% were girls), stratified for wheezing, are summarized in Table 1. According to the adolescents, 61 wheezed more than one year ago (6.5%), and 96 wheezed during the past year (10.3%); 72 (7.7%) and 24 (2.6%) reported less than four and at least four wheezing attacks, respectively. The number of adolescents who never wheezed (reference group) was 776 (83%).

Compared with the reference group, the proportion of adolescents with less than four wheezing attacks was different for gender, educational level, smoking behavior and co-morbidity (Table 1). Compared with the reference group, adolescents with at least four wheezing attacks, were more often girls ($p = 0.001$), more often had a lower educational level ($p = 0.005$) and less often had a higher educational level ($p = 0.002$), were less often never smokers ($p < 0.001$) and were more often current smokers ($p = 0.001$), and more often had co-morbid conditions (p for linear trend < 0.001). Compared with the reference group, adolescents with at least four wheezing attacks, more often had co-morbid conditions (p for linear trend = 0.006). No significant differences in proportions of a particular characteristic were observed between the subgroup *former* wheezing and the reference group.

Table 1. General characteristics of the study population, stratified for wheezing attacks (n = 933).

	Never wheezing[1] (n = 776)	Former wheezing[2] (n = 61)	Mild wheezing[3] (n = 72)	Severe wheezing[4] (n = 24)
Age (in years)				
mean ± SD	15 ± 0.7	15 ± 0.7	15 ± 0.7	15 ± 0.8
(range)	(13-17)	(14-17)	(14-17)	(14-17)
Gender				
% girls	**52.2**	47.5	**72.2**	65.2
% boys	**47.8**	52.5	**27.8**	34.8
Educational level				
% lower secondary	**56.6**	62.3	**73.6**	62.5
% intermediate secondary	19.1	21.3	18.1	20.8
% higher secondary	**24.4**	16.4	**8.3**	16.7
Ethnic background				
% Dutch	77.1	75.0	73.6	70.8
% mixed or non Dutch	22.9	25.0	26.4	29.2
Smoking behavior				
% never smokers	**49.2**	50.8	**27.8**	37.5
% former smokers	31.4	29.5	36.1	29.2
% current smokers	**19.3**	19.7	**36.1**	33.3
Additional symptoms related to wheezing				
sleeping problems due to wheezing, % yes	0	0	15.3	50.0
limited speech due to wheezing, % yes	0	0	8.3	37.5
dry cough at night (without a cold), % yes	13.1	18.0	34.7	29.2
Co-morbidity				
% 0 conditions or diseases over past year	**70.4**	59.0	**47.2**	**50.0**
% 1 condition or disease over past year	**22.4**	31.1	**33.3**	**33.3**
% >1 conditions or diseases over past year	**7.2**	9.8	**19.4**	**16.7**
Administration mode				
% paper	51.0	47.5	52.8	50.0
% internet	49.0	52.5	47.2	50.0

[1] 'Never wheezing': Subgroup of adolescents who never wheezed (reference group).

[2] 'Former wheezing': Subgroup of adolescents who wheezed more than one year ago.

[3] 'Mild wheezing': Subgroup of adolescents with less than four wheezing attacks during the past year.

[4] 'Severe wheezing': Subgroup of adolescents with at least four wheezing attacks during the past year.

Statistically significant differences between subgroups with wheezing and the reference group are presented in **bold**.

Health-related quality of life was expressed as mean CHQ-CF scale score and their respective SD (Table 2). Compared with the reference group, the subgroup *former* wheezing, had significantly lower scores for the *General Health* and *Self Esteem* scales; the differences in quality of life were small. Except for the *Role Physical* scale, adolescents with wheezing attacks during the past year had significantly reduced quality of life for all scales. Among the subgroup of adolescents with at least four wheezing attacks moderate differences in quality of life were observed for the *Family Activities*, *Bodily Pain*, *Mental Health*, *General Behavior,* and *General Health* scales ($0.46 \leq d \leq 0.70$). Moderate to large differences in quality of life were observed among the subgroup of adolescents with at least four wheezing attacks; in order of magnitude the *Family Activities*, *Role Functioning-Emotional-Behavioral*, Physical Functioning, *Family Cohesion*, *General Behavior*, *Self Esteem*, *Mental Health, General Health*, and *Bodily Pain* scales ($0.46 \leq d \leq 1.25$).

In multivariate linear regression models, wheezing attacks remained significantly associated with nine out of 10 CHQ-CF scales; the exception was the *Role Physical* scale (see Table 3); quality of life was consistently lower in the subgroups with wheezing attacks compared with the reference group. The association between wheezing attacks and quality of life was partly explained by the presence of other characteristics; especially by smoking and co-morbidity among adolescents with less than four wheezing attacks. In the multivariate model, for example, adolescents who never wheezed had a mean *Bodily Pain* score of 85.6, while adolescents who wheezed more than one year ago had a mean *Bodily Pain* score of 84.6 (85.6 minus 1.0). Adolescents with less than four and at least four wheezing attacks had a mean *Bodily Pain* score of 81.5 (85.6 minus 4.1) and 59.6 (85.6 minus 27.5), respectively. The amount of variance explained by the unadjusted models was small (range 0-6%), but was substantially larger in the multivariate models (range 5-33%).

Table 2. CHQ-CF scale scores (mean ± SD), stratified for subgroups of adolescents with and without wheezing attacks (n = 933).

CHQ-CF scores	Never wheezing[1] (n = 776)	Former wheezing [2] (n = 61)	Mild wheezing [3] (n = 72)	Severe wheezing [4] (n = 24)	Former versus never	Mild versus never	Severe versus never
	mean ± SD				d [5]		
PF	96 ± 6	96 ± 6	92 ± 10***	90 ± 14***	0.10	0.44	**0.48**
REB	90 ± 15	88 ± 19	83 ± 19***	80 ± 23**	0.13	0.43	**0.46**
RP	95 ± 12	96 ± 8	92 ± 17	94 ± 13	0.15	0.21	0.11
BP	76 ± 22	74 ± 19	66 ± 21***	46 ± 24***	0.08	**0.46**	**1.25**
GB	81 ± 10	79 ± 12	73 ± 13***	71 ± 13***	0.19	**0.55**	**0.75**
MH	77 ± 14	74 ± 16	67 ± 18***	61 ± 20***	0.15	**0.52**	**0.80**
SE	75 ± 11	72 ± 12**	71 ± 14**	64 ± 15***	0.34	0.34	**0.79**
GH	75 ± 16	69 ± 15**	63 ± 16***	57 ± 20***	0.35	**0.70**	**0.87**
FA	80 ± 17	77 ± 18	72 ± 19***	70 ± 24*	0.17	0.45	0.45
FC	73 ± 23	70 ± 18	62 ± 28**	59 ± 22**	0.13	0.35	**0.60**

[1] *Never wheezing*: Subgroup of adolescents who never wheezed (reference group)

[2] *Former wheezing*: Subgroup of adolescents who wheezed more than one year ago

[3] *Mild wheezing*: Subgroup of adolescents with less than four wheezing attacks during the past year

[4] *Severe wheezing*: Subgroup of adolescents with at least four wheezing attacks during the past year

[5] Effect sizes (d) for differences between subgroups of adolescents with wheezing and the reference group: $0.20 \leq d < 0.50$ is considered a small difference; $0.50 \leq d < 0.80$ is considered a moderate difference; $d \geq 0.80$ is considered a large difference. Effect sizes of $d \geq 0.5$ are presented in **bold** and are considered relevant differences.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$: *p*-values based on two-sided Mann-Whitney U tests between subgroups of adolescents with wheezing and the reference group.

Abbreviations: PF (Physical Functioning); REB (Role Functioning: Emotional/Behavioral); RP (Role Functioning: Physical); BP (Bodily Pain); GB (General Behavior); MH (Mental Health); SE (Self Esteem); GH (General Health); FA (Family Activity); FC (Family Cohesion).

All CHQ-CF scales were sensitive for co-morbidity and smoking; both variables were negatively associated with quality of life. Except for the *Role Physical* scale, girls compared with boys had lower quality of life scores, especially for the *Mental Health, Bodily Pain*, and *General Health* scales. The *General Health* and *General Behavior* scales were sensitive for ethnicity; Dutch adolescents scored higher on the *General Health* scale*,* but lower on the *General Behavior* scale. Adolescents with higher secondary educational level, compared with lower secondary level, had lower CHQ-CF scores for five scales; especially for the *Family Activity* scale. The *General Behavior* scale was sensitive for the administration mode. No scales were sensitive for age.

Table 3. Multivariate linear regression models for CHQ-CF score differences for subgroups of adolescents with and without wheezing attacks (n=933).

	PF		REB		RP		BP		GB		MH		SE		GH		FA		FC	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
Adjusted R square, %	4.4	10.9	2.3	9.4	0.3	5.2	5.4	17.1	4.5	18.8	5.0	33.1	3.6	19.1	6.0	24.8	2.4	16.6	1.7	8.4
Intercept	96.4	99.2	90.5	95.2	95.0	97.9	75.7	85.6	80.7	84.0	76.8	86.9	75.5	81.5	74.7	86.3	80.2	90.2	71.9	79.9
Wheezing					NS	NS														
Former versus never	-0.6	-0.4	-2.5	-2.1	+1.2	--	-1.4	-1.0	-2.2	-1.7	-2.4	-1.9	-3.9	-3.6	-5.3	-4.2	-3.1	-2.3	-2.3	-2.0
Mild versus never	-4.2	-2.7	-7.9	-4.9	-3.4	--	-9.7	-4.1	-7.3	-4.5	-9.5	-3.6	-4.8	-1.3	-11.5	-5.6	-8.7	-3.8	-9.9	-5.4
Severe versus never	-6.9	-6.4	-10.3	-9.2	-1.4	--	-29.9	-27.5	-9.6	-8.4	-15.8	-12.2	-11.8	-9.8	-17.6	-14.5	-10.6	-7.5	-13.1	-10.3
Age		NS		NS		NS		NS		NS		NS		NS		NS		NS		NS
Gender																				
Girls versus boys		-1.6		-2.2		NS		-8.0		-1.7		-9.3		-4.9		-6.2		-2.4		-3.8
Education								NS		NS		NS		NS						NS
Intermediate versus lower		+0.2		+1.2		+1.7		--		--		--		--		-1.2		-0.1		--
Higher versus lower		-1.3		-2.8		-1.5		--		--		--		--		-4.6		-8.4		--
Ethnicity																				
Mixed or non-Dutch versus Dutch		NS		NS		NS		NS		2.1		NS		NS		-3.4		NS		NS
Smoking																				
Former versus never		-0.9		-3.2		-2.1		-4.9		-3.9		-3.3		-3.0		-3.5		-3.2		-6.8
Current versus never		-2.2		-6.5		-5.1		-9.7		-6.4		-8.2		-5.5		-9.0		-9.2		-11.0
Co-morbidity																				
1 condition or disease versus 0		-1.6		-3.8		-2.4		-6.6		-4.2		-6.7		-3.8		-4.3		-2.8		-5.0
>1 conditions or diseases versus 0		-2.9		-9.0		-3.7		-12.0		-7.0		-14.4		-8.8		-12.9		-7.6		-8.7
Administration mode																				
PP versus internet		NS		NS		NS		NS		2.2		NS		NS		NS		NS		NS

Model I is the unadjusted model with wheezing as determinant and the CHQ-CF scale as outcome.

Model II is the adjusted model with wheezing as determinant, the CHQ-CF scale as outcome, and other characteristics as covariates.

Abbreviations: PF (Physical Functioning); REB (Role Functioning: Emotional/Behavioral); RP (Role Functioning: Physical); BP (Bodily Pain); GB (General Behavior); MH (Mental Health); SE (Self Esteem); GH (General Health); FA (Family Activity); FC (Family Cohesion); NS (not significant, and thus not included in the final multivariate model); PP (Paper and Pencil).

5.5 Discussion

This study evaluated generic health-related quality of life in adolescents with wheezing attacks using self-reported data in a general school population setting. Our study shows that wheezing was associated with reduced quality of life in adolescents for multiple domains of quality of life as measured by the CHQ. Quality of life was poorer in adolescents with wheezing attacks during the past year than in adolescents who wheezed more than one year ago. Specifically, we observed that compared with adolescents with less than four wheezing attacks during the past year, quality of life was lower among adolescents with at least four wheezing attacks during the past year.

We used Cohen's guidelines to interpret the extent of quality of life impairment because it gives an impression as to how much a specific scale is affected by the presence of wheezing attacks. Compared with adolescents who never wheezed, the *Bodily Pain* and *General Health* scales were most affected in adolescents with at least four wheezing attacks during the past year; indicating that on average these adolescents more often experienced severe and limiting pain and discomfort and more often believed that their health is poor and likely to get worse. In a study among adolescents in Finland, Merikallio and colleagues also reported that the physical domains of quality of life, compared with the psychosocial domains, were more affected in adolescents with wheezing over the past year (8).

What does the observed differences mean in terms of clinical relevance? In response to the question what constitutes a meaningful difference, we refer to Cohen who considered $d \geq 0.80$ a 'large difference' (18). Norman and colleagues later suggested to take $d \geq 0.50$ as 'minimal important difference' between subgroups in the absence of empirically defined cut-off points (19). Thus the presence of wheezing attacks among adolescents in the present study was not only associated with bodily pain and poor health, but also with dissatisfaction, anxiety and depression, and aggressive behavior. Wheezing attacks were not associated with limitations in performing schoolwork or activities with friends, and interruption in family activities were hardly observed. In adjusted multivariate regression models the differences in quality of life between the subgroups of adolescents with and without wheezing attacks were

smaller indicating that the association between wheezing attacks and quality of life among adolescents was independent from other adolescent's characteristics.

The strength of the present study is that the participation rate was high and therefore the chance of selection bias is small. Furthermore, because the prevalence of wheezing obtained in our study is comparable to the prevalence in the Netherlands (1), our findings may be representative for the general Dutch school population sample. Another strength of this study is that we used self-reported data from adolescents on health-related quality of life instead of reports by their parents (7). The discrepancy between perceptions of adolescents and their parents has been documented before, especially in the case of asthma and asthma-related symptoms (20). The association between wheezing attacks and quality of life was adjusted for several covariates including co-morbidity. We took into account that quality of life can be affected by the presence of other health conditions, socio-economic background, and behavior of the adolescents. Current smoking was a major confounder in the association between wheezing attacks and quality of life. We propose to further study the association between smoking and quality of life among adolescents.

A limitation of this study is that we evaluated one cross-sectional assessment and therefore could not assess whether changes in wheezing attacks relate to changes in quality of life over time. Furthermore, both health-related quality of life and wheezing attacks were reported by the adolescent and therefore represent only one subjective perspective. Using adolescent's perspective on both determinant and outcome in our study may account for the strong associations that were observed between wheezing attacks and quality of life. In our study a subgroup of 24 adolescents had at least four wheezing attacks during the past year. The relatively small size of this subgroup could explain why no relevant differences were observed for limitation in schoolwork or activities with friends due to physical problems. The association between wheezing and quality of life was studied adjusted for variables that were available within this study; we may have missed associations of variables that were not available. We used effect sizes for the interpretation of relevant differences in quality of life. Although this is an acceptable method for interpretation of the results (18), there are still insufficient data to understand the relative impact of the observed score differences (21).

We used a generic health-profile measure to compare subgroups with and without wheezing attacks, because we compared quality of life among subgroups of adolescents with no, a few, and many wheezing attacks in a general population setting. Although the CHQ-CF is a thoroughly validated and standardized questionnaire that covers a broad range of dimensions, we may have missed minor changes in quality of life of adolescents with wheezing attacks. The use of a disease-specific questionnaire in the same setting may reveal different results.

In conclusion, our study showed that wheezing attacks are related to many areas of health-related quality of life of adolescents, using the multidimensional CHQ-CF questionnaire. The quality of life profile is consistently lower in adolescents with wheezing attacks during the past year. Especially, the presence of at least four wheezing attacks demonstrated relevant deficits in quality of life.

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5.7 Addendum

Addendum 1. CHQ-CF scales, items per scale, and interpretation of low and high scores [1]

Scales (number of items)	Description of low score	Description of high score
Physical Functioning (9)	Child is limited a lot in performing all types of physical activities, including self-care, due to health.	Child performs all types of physical activities, including the most vigorous, without limitations due to health.
Role Functioning: Emotional [2] (3)	Child is limited a lot in schoolwork or activities with friends as a result of emotional problems.	Child has no limitations in schoolwork or activities with friends as a result of emotional problems.
Role Functioning: Behavioral [2] (3)	Child is limited a lot in schoolwork or activities with friends as a result of behavior problems.	Child has no limitations in schoolwork or activities with friends as a result of behavior problems.
Role Functioning: Physical (3)	Child is limited a lot in schoolwork 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 (2)	Child has extremely severe, frequent and limiting bodily pain.	Child has no pain or limitations due to pain.
General Behavior (17)	Child very often exhibits aggressive, immature, and delinquent behavior.	Child never exhibits aggressive, immature, and delinquent behavior.
Mental Health (16)	Child has feelings of anxiety and depression all of the time.	Child feels peaceful, happy and calm all of the time.
Self Esteem (14)	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 (12)	Child believes its health is poor and likely to get worse.	Child believes its health is excellent and will continue to be so.
Change in Health[3] (1)	Child's health is much worse now than one year ago.	Child's health is much better now than one year ago.
Family Activities (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 nor is a source of family tension.
Family Cohesion (1)	Family's ability to get along is rated 'poor'.	Family's ability to get along is rated 'excellent'.

[1] Reproduced with permission from the principal author Jeanne M. Landgraf. [2] The CHQ-CF scales *Role functioning-emotional* and *Role functioning-behavioral* were merged into a single scale *Role functioning-emotional/behavioral* in this study. [3] This single-item scale was not evaluated in this study.

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6

Health-Related Quality of Life in Preschool Children with Wheezing and Dyspnea: Preliminary Results from a Random General Population Sample

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6.1 Abstract

Background: Respiratory symptoms have a high prevalence among preschool children (5-20%). This study evaluated the impact of parent-reported respiratory symptoms on health-related quality of life (HRQOL) using the TNO-AZL Preschool Children Quality of Life (TAPQOL) questionnaire.

Methods: A random general population sample of 500 parents of 3-46-month old children was mailed a questionnaire containing the TAPQOL and questions on the prevalence of respiratory symptoms. The impact of respiratory symptoms on HRQOL was analyzed using the Mann-Whitney test and linear regression analysis.

Results: Response rate was 83%. The prevalence of combined wheezing and dyspnea during the past four weeks was 10%. For the *sleeping*, *appetite*, *lung problems*, *skin problems*, *communication*, and *positive mood* TAPQOL scales, HRQOL was significantly lower in the subgroup with wheezing and dyspnea (n = 41) than in the subgroup without symptoms (n = 321); large effect sizes were observed for *lung problems* (d = 2.06) and *sleeping* (d = 0.80). In multivariate analysis, adjusted for age and gender of the child, wheezing and dyspnea were associated with the scales *sleeping, appetite, lung problems, communication*, and *positive mood* ($p < 0.05$).

Conclusions: Decreases in HRQOL among preschoolers with parent-reported respiratory symptoms are measurable with the TAPQOL. We recommend studying the impact of doctor-diagnosed respiratory symptoms on HRQOL in future studies.

6.2 Introduction

Respiratory symptoms are a major cause of morbidity in preschool children (0-4 years) (1-3). The prevalence of these symptoms ranges from five to 20%, depending on the definition and methods of identifying cases (1-3). Respiratory symptoms may be associated with a negative impact on health-related quality of life (HRQOL) and family functioning (4, 5). The use of HRQOL as an additional outcome measure in medical research has increased during the past decades. Several studies have assessed the impact of respiratory symptoms on HRQOL in school-aged children (6-10). No studies are available concerning preschoolers. The aim of this study is to evaluate the impact of parent-reported respiratory symptoms during the past four weeks on HRQOL in preschool children using the TNO-AZL Preschool Children Quality of Life (TAPQOL) questionnaire (11, 12). In addition, independent associations between wheezing and dyspnea and TAPQOL scale scores were evaluated in multivariate regression models adjusted for age and gender of the child; previous studies have reported effects of these characteristics on TAPQOL scale scores (11, 12).

6.3 Methods

In 2002, parents of a random sample of 500 out of 9022 children aged 3-46 months in the general population of six communities, allocated to the service area of the Dutch 'Community Care Salland', were mailed the TAPQOL questionnaire, and respiratory symptoms items from the International Study of Asthma and Allergies in Childhood (ISAAC) (11, 13). The measurement properties of the respiratory symptoms have been evaluated for application in preschool children in the PIAMA study (14-16). The respiratory symptoms were defined as present if the parent reported at least one episode of the symptom during the past four weeks. The Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study.

The TAPQOL is a validated generic HRQOL instrument that has been specifically designed for preschool children (11, 12). It consists of 43-items divided over 12 multi-item scales that cover a broad range of domains relevant for preschool children: (i) physical functioning (*sleeping*, *appetite*, *lung problems*, *stomach problems*, *skin problems*, *motor functioning*), (ii) social functioning (*social functioning*, *problem behavior*), (iii) cognitive functioning (*communication*) and (iv) emotional functioning (*anxiety*, *positive mood*, *liveliness*). The *motor functioning*, *social functioning*, and *communication* scales are only appropriate for children aged 18 months and older.

The TAPQOL measures parent's perception of their child's HRQOL. The number of items per scale ranges from three to seven. Scale scores were obtained by adding item scores within scales, and transforming crude scale scores linearly to a 0-100 scale, with higher scores indicating better HRQOL. The psychometric properties of the TAPQOL were evaluated in previous studies (11, 12). These studies established that the TAPQOL, for it's majority of scales, is a feasible and reliable instrument to study HRQOL among preschool children in general population samples as well as in clinical samples.

Statistical analysis

We divided the sample of preschool children into three subgroups: (i) a subgroup of children without respiratory symptoms, neither wheezing nor dyspnea, (ii) a subgroup of children with one respiratory symptom, either wheezing or dyspnea (iii) a subgroup of children with two respiratory symptoms, both wheezing and dyspnea. Differences in prevalence of respiratory symptoms with regard to age and gender of the child were evaluated using the χ^2-test (17). To investigate the impact of respiratory symptoms on HRQOL, the mean TAPQOL scale scores of subgroups of children with wheezing and dyspnea were compared with the mean TAPQOL scale scores of the subgroup of children without these symptoms. One-sided Mann-Whitney U tests were applied as it was hypothesized that mean scores would be lower in subgroups of children with parent-reported respiratory symptoms (17). For all analyses *p*-values were considered significant if less than 0.05. Cohen's effect sizes (d) were expressed as the differences in mean TAPQOL scale scores between subgroups of children divided by the largest standard deviation (18). We investigated the independent contribution of wheezing and dyspnea on HRQOL in multivariate linear regression models adjusted for age and gender of the child; the TAPQOL scales were studied as dependent variables. All analyses were performed using the Statistical Package for the Social Sciences, version 11.0.

6.4 Results

The response rate was 83.0% (n = 415). Nine questionnaires (1.8%) were not eligible for analysis (non-Dutch families n = 5; missing data on respiratory symptoms n = 4). Mean respondent age was 33 years (standard deviation 7); 97% were mothers. The children ranged from 3-46 months of age (mean 25; standard deviation 14); 49% were girls.

The prevalence of parent-reported wheezing and dyspnea during the past four weeks was 10% (n = 41); the prevalence of wheezing or dyspnea was 11% (n = 44). Parents reported no respiratory symptoms in 79% of the preschool children (n = 321). Table 1 presents data on the distribution of age and gender of the child among different subgroups of children in the study population. Preschool children with parent-reported respiratory symptoms were relatively more often young (3-24 months) than old (25-48 months); $p < 0.05$. There were no statistical significant differences with regard to the prevalence of respiratory symptoms between boys and girls.

Table 1. Distribution of age and gender of the child among subgroups of children with and without respiratory symptoms in a random general population sample of preschool children (n = 406).

	Total population n = 406	No wheezing or dyspnea (no symptoms) n = 321	Wheezing or dyspnea [e] (one symptom) n = 44	Wheezing and dyspnea [f] (two symptoms) n = 41
Age [a]				
3-12	86 (21%)	60 (19%)	13 (30%) [c]	13 (32%) [d]
13-24	113 (28%)	83 (26%)	18 (41%) [c]	12 (29%) [d]
25-36	112 (28%)	94 (29%)	8 (18%) [c]	10 (24%) [d]
37-46	95 (23%)	84 (26%)	5 (11%) [c]	6 (15%) [d]
Gender [b]				
Girls	200 (49%)	159 (50%)	21 (49%) [b]	20 (49%)
Boys	205 (51%)	162 (50%)	22 (51%) [b]	21 (51%)

[a] Age in months, mean age 25 ± 14 months, range 3-46 months. [b] Data on gender of one child is missing. [c] *p*-value for linear trend: 0.003. [d] *p*-value for linear trend: 0.02. [e] *p*-value χ^2 test: 0.01; 71% (3-24 months) vs. 29% (25-46 months). [f] *p*-value χ^2 test: 0.047; 61% (3-24 months) vs. 39% (25-46 months).

Table 2 summarizes the impact of respiratory symptoms on HRQOL. The subgroup of children with wheezing and dyspnea had statistically significant lower mean scores for six TAPQOL scales (*sleeping*, *appetite*, *lung problems*, *skin problems*, *communication*, and *positive mood*) in comparison with the subgroup of children without respiratory symptoms; large effect sizes were observed for the TAPQOL scales *sleeping* (d = 0.80) and *lung problems* (d = 2.06). The TAPQOL scales *appetite*, *skin problems*, *communication*, and *positive mood*, showed significant differences, but small effect sizes. The subgroup of children with one respiratory symptom (either wheezing or dyspnea) had statistically significant lower mean scores for four TAPQOL scales (*appetite*, *lung problems*, *skin problems* and *stomach problems*) in comparison with the subgroup of children without respiratory symptoms; a large effect size was observed for the TAPQOL scale *lung problems* (d = 0.93).

Table 2. TAPQOL scale scores (mean ± standard deviation) for subgroups of children with respiratory symptoms compared with a subgroup of children without respiratory (n = 406).

	No wheezing or dyspnea [1] (n = 321) (no symptoms)	Wheezing or dyspnea (n = 44) (one symptom)			Wheezing and dyspnea (n = 41) (two symptoms)		
TAPQOL scores	mean ± SD	mean ± SD	*p*-value [2]	d [3]	mean ± SD	*p*-value [2]	d [3]
Sleeping	81 ± 18	77 ± 20	NS	0.20	65 ± 20	<0.001	0.80
Appetite	85 ± 13	81 ± 16	0.03	0.25	79 ± 17	0.013	0.46
Lung problems	97 ± 11	84 ± 14	<0.001	0.93	60 ± 17	<0.001	2.06
Skin problems	92 ± 12	89 ± 11	0.003	0.25	89 ± 14	0.034	0.21
Stomach problems	92 ± 12	86 ± 15	0.002	0.40	91 ± 16	NS	0.06
Motor functioning	98 ± 9	97 ± 7	NS	0.11	98 ± 6	NS	0
Social functioning	92 ± 15	91 ± 18	NS	0.06	91 ± 19	NS	0.05
Problem behavior	73 ± 17	70 ± 16	NS	0.18	72 ± 18	NS	0.06
Communication	90 ± 12	85 ± 15	NS	0.33	84 ± 17	0.021	0.35
Anxiety	77 ± 19	77 ± 17	NS	0	77 ± 22	NS	0
Positive mood	98 ± 10	98 ± 9	NS	0	94 ± 15	0.005	0.27
Liveliness	96 ± 12	96 ± 16	NS	0	94 ± 14	NS	0.14

[1] Reference group. [2] *p*-value based on one-sided Mann-Whitney U test for differences between subgroups of children with and the subgroup of children without respiratory symptoms. [3] Effect sizes (d) between 0.2 and 0.5 are considered a small effect, between 0.5 and 0.8 are considered a moderate effect, and effect sizes of 0.8 and larger are considered a large effect [18]. Abbreviations: NS (not significant); SD (standard deviation).

In multivariate linear regression analysis (Table 3), adjusted for age and gender of the child, wheezing and dyspnea were associated with five TAPQOL scales: *sleeping* (ß = -16.25, $p < 0.001$), *appetite* (ß = -8.40, $p < 0.01$), *lung problems* (ß = -36.54, $p < 0.001$), *communication* (ß = -5.62, $p < 0.05$), and *positive mood* (ß = 3.89, $p < 0.05$). The amount of variance explained by the models was high for the TAPQOL scale *lung problems* (41%); the amount of variance explained in the models for the other scales ranged from 0 to 19%.

Table 3. Multivariate linear regression analysis for different TAPQOL scales (dependent variables) and age[1], gender[2], wheezing and dyspnea[3] as independent variables.

TAPQOL scales	β	*p*-value	F	*p*-value	Adjusted R^2
Sleeping			10.33	<0.001	0.072
Age	0.69	NS			
Gender	-0.94	NS			
Wheezing and dyspnea	-16.25	<0.001			
Appetite			17.68	<0.001	0.123
Age	-4.20	<0.001			
Gender	-0.75	NS			
Wheezing and dyspnea	-8.40	0.001			
Lung problems			114.47	<0.001	0.492
Age	0.09	NS			
Gender	-2.22	NS			
Wheezing and dyspnea	-36.54	<0.001			
Skin problems			1.30	NS	0.003
Age	-0.72	NS			
Gender	-0.31	NS			
Wheezing and dyspnea	-3.48	NS			
Stomach problems			1.21	NS	0.002
Age	-0.99	NS			
Gender	-1.11	NS			
Wheezing and dyspnea	-2.09	NS			
Motor functioning			0.78	NS	0
Age	1.07	NS			
Gender	-0.57	NS			
Wheezing and dyspnea	-0.02	NS			
Social functioning			0.60	NS	0
Age	1.08	NS			
Gender	-1.96	NS			
Wheezing and dyspnea	-0.14	NS			
Problem behavior			36.14	<0.001	0.227
Age	-7.70	<0.001			
Gender	-1.36	NS			
Wheezing and dyspnea	-4.91	NS			
Communication			6.20	0.001	0.062
Age	2.25	0.037			
Gender	-4.24	0.007			
Wheezing and dyspnea	-5.62	0.036			
Anxiety			5.84	0.001	0.039
Age	-3.86	<0.001			
Gender	0.22	NS			
Wheezing and dyspnea	-1.82	NS			
Positive mood			1.83	NS	0.007
Age	-0.33	NS			
Gender	-0.79	NS			
Wheezing and dyspnea	-3.90	0.028			
Liveliness			0.46	NS	0
Age	0.34	NS			
Gender	-0.25	NS			
Wheezing and dyspnea	-1.81	NS			

[1] Age in months: 3-12 (reference category), 13-24, 25-36, 37-46. [2] Girls (reference category). [3] Children without *wheezing or dyspnea* (reference category), n = 321. Abbreviation: NS (not significant).

6.5 Discussion

This is the first study to assess HRQOL in preschool children with parent-reported respiratory symptoms in a random general population sample. HRQOL of subgroups of children with parent-reported respiratory symptoms was compared with HRQOL of the subgroup of children without these symptoms. With regard to specific TAPQOL scales, decrements in HRQOL were observed for both subgroups of children with respiratory symptoms; especially in the subgroup with combined wheezing and dyspnea.

This study showed that the TAPQOL is able to detect burdens associated with wheezing and dyspnea, but provided no evidence on the differential ability of the TAPQOL relative to other pediatric quality of life measures; we suggest to evaluate this in future studies. A limitation of this study is that we evaluated one cross-sectional assessment and therefore could not assess whether changes in respiratory symptoms relate to changes in HRQOL over time. Our data are based on proxy-reports by parents, which is indispensable for this age group. It is difficult to assess the adequacy of proxy ratings that may be confounded by many factors (19-22). In very young children the diagnosis of respiratory conditions generally is based on reports from parents; these items were included in this study; however our study was limited by the absence of a physician's evaluation of the reported respiratory symptoms. Furthermore, our data were restricted to reports from parents who read and speak Dutch. We are unaware of reports on HRQOL from non-Dutch speaking parents in the Netherlands.

Some TAPQOL scales were not able to detect HRQOL burdens associated with respiratory symptoms. The TAPQOL scales *sleeping* and *lung problems* were specifically affected by the presence of combined wheezing and dyspnea; the observed impact was independent of age and gender of the child. We may have missed associations with other characteristics, because we only adjusted for age and gender of the child. The amount of explained variance was relatively small, except in the model for the TAPQOL scale *lung problems*. We recommend studying other characteristics, both child's and parents' in future studies.

In conclusion, although the TAPQOL is a generic instrument for the measurement of HRQOL, this study showed that it is sensitive to measure decreases in HRQOL for

several relevant TAPQOL scales among preschool children with parent-reported respiratory symptoms. We also propose to evaluate the impact of doctor-diagnosed respiratory conditions in preschool children on HRQOL in future studies.

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7

Asthma-Like Symptoms in the First Year of Life and Health-Related Quality of Life at Age Twelve Months: the Generation R Study

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Submitted

7.1 Abstract

Purpose: This study compares health-related quality of life (HRQOL) among subgroups of infants with asthma-like symptoms to a subgroup of infants without such symptoms, and examines independent associations between asthma-like symptoms during the first year of life and HRQOL at age 12 months.

Methods: Our study sample included 5000 infants participating in the Generation R Study. Their parents completed structured questionnaires to obtain information on asthma-like symptoms, HRQOL, infants' and maternal characteristics. Asthma-like symptoms were defined according to the number of positive answers to 12-items on lower respiratory symptoms. HRQOL was measured using the Infant Toddler Quality of Life (ITQOL) questionnaire. Higher scores indicated better HRQOL.

Results: Infants with asthma-like symptoms had significantly lower HRQOL scores for all ITQOL scales. Among the subgroup with *severe* symptoms (4% of the infants) relevant deficits in HRQOL were observed for most ITQOL scales, particularly for the *General Health*, *Bodily Pain*, and *Family Activities* (effect sizes ≥ 0.8) scales. In multivariate linear models, asthma-like symptoms were independently associated with six ITQOL scales. The population attributable risks were especially high for the *Family Activities*, *General Health*, *Parental Emotional* and *Parental Time* scales.

Conclusions: Asthma-like symptoms during the first year of life are associated with impaired quality of life at age 12 months. At a population level, asthma-like symptoms were associated with lower HRQOL, regardless of symptom severity.

7.2 Introduction

Asthma-like symptoms, such as attacks of wheezing and shortness of breath, often accompanied by chest tightness and dry cough at night or in the early morning, represent an important public health problem (1). These symptoms are common during childhood and account for considerable morbidity, visits to the general practitioner or specialist, hospital admission, and substantial healthcare costs during the first years of life (1). Diagnosing asthma is difficult in preschool children, due to the non-specificity of the symptoms and the fact that conventional lung function tests cannot be carried out because of the lack of cooperation at this young age. The diagnosis asthma in young children is therefore labeled as a symptom diagnosis (1, 2).

The use of health-related quality of life (HRQOL) as an outcome measure in clinical studies among children with asthma-like symptoms has increased during the past decade. However, the association between asthma-like symptoms and HRQOL among infants has not been studied yet (3). Previous studies have reported the association between asthma-like symptoms and HRQOL among school-aged children (4-6). Only two studies have reported the association between asthma-like symptoms and HRQOL among toddlers (7, 8). Both studies observed relevant deficits in HRQOL among preschool children with wheezing and shortness of breath.

The primary aim of our study was to assess the association between asthma-like symptoms in the first year of life and HRQOL at age 12 months using the Infant Toddler Quality of Life (ITQOL) questionnaire. The ITQOL is a generic quality of life instrument to be completed by parents of infants and toddlers aged two months up to five years of age (9-12). It allows one to compare HRQOL between subgroups with and without asthma-like symptoms. It adopts the World Health Organization's definition of health, that is 'a state of complete physical, mental, and social well-being and not merely the absence of disease' (13). A secondary aim was to calculate population attributable risks (PAR) to express the impact of asthma-like symptoms on HRQOL at a population level. Our main hypothesis was that HRQOL would be lower among subgroups of infants with asthma-like symptoms compared with a subgroup without such symptoms. In particular we expect subgroups of infants with more severe symptoms to have more impaired quality of life.

7.3 Methods

Study population

The present study was embedded in the Generation R Study, a prospective population based cohort study from fetal life until young adulthood. The Generation R Study was designed to identify early environmental and genetic determinants of growth, development and health in fetal life, childhood, and young adulthood (14). Detailed information on the design and methods of the Generation R Study has been described previously (15, 16). Briefly, the Generation R cohort includes 9778 mothers and 9897 children living in Rotterdam, a city with 600,000 inhabitants in the Netherlands. Enrolment of mothers was aimed during pregnancy, but was also possible in the first month after birth of their infant. In total, 8880 (91%) and 898 (9%) mothers were enrolled during pregnancy and after birth of their infant, respectively (15). The children were born between April 2002 and January 2006. The cohort will be followed until young adulthood. Of all eligible children in the study area, defined by postal codes, 61% participated (15).

The Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam, approved this study. Written informed consent was obtained from all participants.

Study population for analysis

For the present analysis we used available data on infants whose mothers participated in the postnatal phase of the Generation R Study (n = 7893). Parents were asked to complete a written questionnaire when their infant was 12 months old in order to obtain information on asthma-like symptoms, HRQOL, infants' and maternal characteristics. A total of 5000 parents completed the questionnaire on their infant (response rate 63%). Of these 5000 infants, 2.2% were twins (n = 112). Since there were no differences in the association between asthma-like symptoms and HRQOL after exclusion of twins, they were included in the analysis.

Asthma-like symptoms

The presence of asthma-like symptoms was based on 12 questions concerning lower respiratory symptoms (see Addendum 2). All answers were coded 'yes' or 'no'. The severity of asthma-like symptoms was defined according to the number of questions with a positive answer. Infants were categorized into different subgroups according to the severity of asthma-like symptoms.

Our main determinant was a four-category variable coded as 0, 1-4, 5-8, and 9-12 positive answers. The subgroup without positive answers (reference group) was defined as those infants whose parents responded negatively to all 12 questions. The subgroups that scored 1-4, 5-8, and 9-12 positive answers were considered to have *mild*, *moderate* and *severe* asthma-like symptoms, respectively.

Health-related quality of life

HRQOL was assessed using the ITQOL which has been translated into Dutch following international standards and validated in a general population sample and a respiratory disease sample in the Netherlands (10, 17). At the time the present study was fielded, the pre-release developmental version of the ITQOL consisted of 103-items with four, five or six Likert-type response options, divided over 10 multi-item scales and two single-item scales (see Addendum 1). It covers a broad range of dimensions focusing on physical and psychosocial functioning of the infant, as well as on components of parental and family impact. Scales concerning the infants' quality of life include *Physical Functioning*, *Growth and Development*, *Temperament and Moods*, *Bodily Pain*, *General Health*, *General Behavior*, *Getting Along*, and *Change in Health*. Limitations in the family were measured using the *Family Activity* scale and *Family Cohesion* global item, while the *Parental Emotional* and *Parental Time* scales assess the impact of infants' health on parents.

For each scale, items were summed up (some recoded/recalibrated) and transformed into a scale from 0 (worst possible score) to 100 (best possible score) according to the standard procedure (9, 18). The *General Behavior*, *Getting Along*, and *Change in Health* scales were not assessed at age 12 months, because they only refer to infants older than one year.

Infants' and maternal characteristics

Information on date of birth, birth weight, and gender was obtained from birth records. Gestational age was established by fetal ultrasounds (19). Information on ethnicity and education was obtained by the first questionnaire at enrolment in the study. Ethnicity and educational level of the mother were classified according to the classification of Statistics Netherlands and were defined based on country of birth and highest finished education, respectively. Information on breastfeeding, the presence of other conditions or diseases, visits to the general practitioner and medical

specialist, and hospital admission, was obtained from written questionnaires and assessed when the infant was 12 months old.

The presence of other conditions or diseases during the past six months, was expressed as: (i) the number of respiratory diseases including flu, sore throat, bronchiolitis, pseudo croup, and whooping cough; and (ii) the number of non-respiratory diseases, including measles, impetigo, molluscum contagiosum, eczema, itchy rash, sepsis, meningitis, constipation and infections of the ear, eye, intestines, urine tract, and skin.

Statistical analysis

General characteristics for the study population were calculated, stratified for the main determinant, and expressed as mean with standard deviation for continuous variables and as a proportion for dichotomous or categorical variables. Differences in proportions of a particular characteristic between subgroups were tested with the χ^2-test; one-way analysis of variance was used to assess differences in continuous variables between subgroups of infants with asthma-like symptoms and the reference group (20).

To investigate the association between asthma-like symptoms and HRQOL, the distribution of quality of life scores of the subgroups with asthma-like symptoms were separately compared with the distribution of quality of life scores of the reference group. Since the distributions of the ITQOL scores were often skewed to the left, we performed all comparisons by using the non-parametric Mann-Whitney U test (20). In order to indicate the relevance of statistically significant differences, effect sizes (d) were calculated by dividing the difference in mean scores between subgroups by the largest standard deviation. Cohen's criteria were used for interpretation of relevant differences: $0.2 \leq d < 0.5$ is considered a small difference, $0.5 \leq d < 0.8$ is considered a moderate difference, and $d \geq 0.8$ is considered a large difference (21).

Multivariate linear regression models were fitted to investigate the independent association between the subgroups with versus without asthma-like symptoms and each of the nine ITQOL scales. In each multivariate model, the ITQOL scale was studied as dependent variable, asthma-like symptoms and the characteristics of the infant and mother as determinants. We used a manual backward selection method, deleting variables with the highest *p*-value stepwise, until all remaining determinants in the final multivariate model had a *p*-value less than 0.05. The associations between

the subgroups with versus without asthma-like symptoms and each of the nine ITQOL scales were first studied bivariately.

For the subgroups with versus without asthma-like symptoms we calculated crude and adjusted relative risks and PAR for low quality of life, using logistic regression models for each of the nine ITQOL scales. Low HRQOL was calculated by subtracting one standard deviation from the mean quality of life score. Crude logistic regression models were fitted with HRQOL (low versus high) as dependent variable and asthma-like symptoms as independent variable. The odds ratios from these models were used to calculate crude relative risks. The PAR was used to estimate the proportion of infants with low HRQOL that can be attributed to the presence of asthma-like symptoms in the first year of life. This was calculated based on the formula PAR = ((p(RR-1))/(p(RR-1)+1)) x 100; where p is the proportion of infants with asthma-like symptoms within the study population and RR is the relative risk of low quality of life in the study population. The nine crude logistic models were adjusted for infants' and maternal characteristics (Table 1) and were used to calculate adjusted risk estimates as described above. The logistic models were only adjusted for potential confounders; infants' and maternal characteristics that changed the odds ratios more than 10%.

All analyses were performed using SPSS, version 14.0 for windows (SPSS Inc, Chicago, IL).

7.4 Results

Asthma-like symptoms, defined as at least one positive answer to the 12 selected questions on lower respiratory symptoms, were reported for 50% of all infants during the first year of life. Thirty-five percent had *mild,* 11% had *moderate*, and 4% had *severe* symptoms. The characteristics of the study population, stratified for the main determinant, are presented in Table 1. Compared with the reference group, subgroups with asthma-like symptoms were more often boys ($p < 0.001$), were less often breastfed for six months ($p < 0.01$), more often had other (respiratory) conditions or diseases ($p < 0.001$), more often visited the general practitioner or medical specialist ($p < 0.001$), and were more often admitted to the hospital ($p < 0.001$).

Table 1. General characteristics of the study population, stratified for subgroups of infants with versus without asthma-like symptoms (n = 5000).

	Subgroup 1[1] (n = 2485)	Subgroup 2[2] (n = 1727)	Subgroup 3[3] (n = 599)	Subgroup 4[4] (n = 189)	Total (n = 5000)
Infants' characteristics					
Age in months*, mean ± SD	12.6 ± 1.7	12.6 ± 1.6	12.7 ± 2.0	13.0 ± 2.3	12.6 ± 1.7
*Gender****					
% girls	53	50	44	39	50
% boys	47	51	56	61	50
*Gestational age in weeks***					
mean ± SD[5]	39.9 ± 1.7	39.9 ± 1.8	39.7 ± 1.9	39.5 ± 1.9	39.9 ± 1.7
Birth weight in grams					
mean ± SD[5]	3439 ± 561	3443 ± 582	3423 ± 553	3384 ± 565	3436 ± 568
*Breastfeeding over 6 months***					
% no	69	72	76	77	71
% yes	31	28	24	23	29
*Other respiratory diseases (n)****					
% 0	54	39	27	16	44
% 1	40	47	46	39	43
% >1	6	14	27	46	13
*Non-respiratory diseases (n)****					
% 0	34	25	20	15	28
% 1	32	29	27	23	30
% >1	35	46	53	62	42
*Visits to the general practitioner (n)****					
% 0-1	61	42	27	10	49
% 2	29	41	42	38	35
% >2	10	17	31	52	16
*Visits to a medical specialist (n)****					
% 0	81	74	61	43	74
% 1	11	15	19	15	13
% >1	9	12	21	41	12
*Hospital admission****					
% no	95	94	90	79	94
% yes	5	6	10	21	6
Maternal characteristics					
Age in years, mean ± SD	31.2 ± 4.7	31.2 ± 4.6	31.1 ± 4.6	31.8 ± 4.8	31.2 ± 4.7
Ethnicity					
% Dutch	63	65	67	65	64
% non-Dutch	37	35	33	35	36
*Educational level***					
% primary and secondary	46	40	43	46	43
% higher	54	60	57	55	57
Civil status					
% married or living together	55	53	51	58	54
% single or unmarried or divorced	45	47	49	42	46
Respondent					
% no	16	15	16	13	15
% yes	85	84	85	87	85

[1] Subgroup of infants without asthma-like symptoms (no positive answers); the reference group.

[2] Subgroup of infants with *mild* asthma-like symptoms (1-4 positive answers).

[3] Subgroup of infants with *moderate* asthma-like symptoms (5-8 positive answers).

[4] Subgroup of infants with *severe* asthma-like symptoms (9-12 positive answers).

Abbreviation: SD (standard deviation).

Note 1: Proportions may not add up 100% exactly because of rounding up errors.

Note 2: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2. ITQOL scale scores for subgroups of infants with versus without asthma-like symptoms (n = 5000).

	ITQOL scores (mean ± standard deviation)				Effect sizes [5]		
	Subgroup 1 [1] (n = 2485)	Subgroup 2 [2] (n = 1727)	Subgroup 3 [3] (n = 599)	Subgroup 4 [4] (n = 189)	Subgroup 2 vs. 1	Subgroup 3 vs. 1	Subgroup 4 vs. 1
PF	94 ± 17	94 ± 16	92 ± 17	85 ± 22	*0.0*	*0.2*	*0.4*
GD	90 ± 11	88 ± 11	87 ± 10	84 ± 12	*0.1*	*0.2*	***0.5***
TM	80 ± 11	77 ± 11	76 ± 11	70 ± 13	*0.2*	*0.3*	***0.7***
BP	81 ± 15	78 ± 16	75 ± 15	66 ± 17	*0.2*	*0.4*	***0.9***
GH	78 ± 10	74 ± 11	70 ± 12	61 ± 15	*0.3*	***0.7***	***1.2***
PE	95 ± 08	93 ± 10	91 ± 10	86 ± 14	*0.2*	*0.3*	***0.6***
PT	92 ± 15	89 ± 16	88 ± 16	82 ± 21	*0.2*	*0.2*	***0.5***
FA	89 ± 14	85 ± 16	83 ± 17	73 ± 21	*0.3*	*0.4*	***0.8***
FC	87 ± 16	85 ± 17	84 ± 18	85 ± 17	0.1	*0.1*	0.1

[1] Subgroup of infants without asthma-like symptoms (no positive answers); the reference group.

[2] Subgroup of infants with *mild* asthma-like symptoms (1-4 positive answers).

[3] Subgroup of infants with *moderate* asthma-like symptoms (5-8 positive answers).

[4] Subgroup of infants with *severe* asthma-like symptoms (9-12 positive answers).

[5] Cohen's effect sizes (d) for differences in HRQOL between subgroups of infants with and without asthma-like symptoms: $0.2 \leq d < 0.5$ is considered a small difference, $0.5 \leq d < 0.8$ is considered a moderate difference, and $d \geq 0.8$ is considered a large difference. Effect sizes of $d \geq 0.5$ are presented in **bold**.

Note: *p*-values are based on Mann-Whitney U test for differences between subgroups of infants with asthma-like symptoms and the reference group. *p*-values < 0.05 are presented as *italic* effect sizes.

Abbreviations: PF (Physical Functioning); GD (Growth and Development); TM (Temperament and Moods); BP (Bodily Pain); GH (General Health); PE (Parental Emotional); PT (Parental Time); FA (Family Activities); FC (Family Cohesion).

In Table 2 HRQOL is expressed as mean ITQOL scale scores and standard deviations. Compared with the reference group, the subgroups with asthma-like symptoms had lower quality of life scores for all ITQOL scales. Except for the *Family Cohesion* and *Physical Functioning* scales, relevant differences in HRQOL ($d \geq 0.5$) were observed for all ITQOL scales in the subgroup with *severe* symptoms; particularly for the *General Health*, *Bodily Pain*, and *Family Activities* scales ($d \geq 0.8$). The subgroup with *moderate* symptoms had relevant differences in HRQOL for the *General Health* scale only ($d = 0.7$), while the subgroup with *mild* symptoms showed no relevant differences in HRQOL.

In bivariate linear regression models, asthma-like symptoms were significantly associated with HRQOL for all ITQOL scales (Table 3). In multivariate linear regression models, adjusted for infants' and maternal characteristics, asthma-like symptoms were independently associated with HRQOL for six out of nine ITQOL scales; the exceptions were the *Physical Functioning*, *Growth and Development* and *Family Cohesion* scales.

The adjusted relative risks for low HRQOL were especially high for the subgroup with *severe* symptoms (Table 4). This subgroup had a significantly increased risk for low HRQOL for the *General Health*, *Family Activity*, *Parental Emotional*, *Parental Time*, *Bodily Pain*, and *Temperament and Moods* scales (relative risk respectively 3.2, 2.9, 2.5, 2.5, 2.4 and 2.0). The subgroup with *moderate* symptoms had a significantly increased risk for low HRQOL for the *General Health*, *Family Activity* and *Parental Emotional* scales (relative risk respectively 1.8, 1.7 and 1.4), while the subgroup with *mild* symptoms had a significantly increased risk for low HRQOL for the *Family Activity* and *Parental Emotional* scales (relative risk respectively 1.5 and 1.3).

Adjusted PAR was especially high for the *Parental Time*, *Parental Emotional*, *General Health*, and *Family Activity* scales (PAR respectively 16.1, 19.3, 23.8 and 28.0). The PAR of 24% for the *General Health* scale indicates that within our study population approximately one out of four infants had an impaired general health due to the presence of asthma-like symptoms in the first year of life. The PAR of 28% for the *Family Activity* scale indicates that due to the presence of asthma-like symptoms among infants in the first year of life, 28% of the family activities were interrupted.

Table 3. Linear regression models for ITQOL score differences for subgroups of infants with versus without asthma-like symptoms (n = 5000).

	Subgroup 1[1] (n = 2485)	Subgroup 2[2] (n = 1727)	Subgroup 3[3] (n = 599)	Subgroup 4[4] (n = 189)
Physical Functioning				
Univariate***	94.2	-0.6	-2.6	-9.1
Multivariate	NS	NS	NS	NS
Growth and Development				
Univariate***	89.5	-1.4	-2.3	-5.8
Multivariate	NS	NS	NS	NS
Temperament and Moods				
Univariate***	79.6	-2.1	-3.9	-9.3
Multivariate***	85.6	-1.4	-2.1	-6.5
Bodily Pain				
Univariate***	81.3	-3.1	-6.2	-14.9
Multivariate***	78.4	-1.1	-2.2	-8.2
General Health				
Univariate***	77.9	-3.5	-8.0	-16.8
Multivariate***	69.7	-1.9	-3.9	-9.4
Parental Emotional				
Univariate***	94.8	-2.0	-3.5	-8.9
Multivariate***	98.3	-1.0	-1.1	-5.3
Parental Time				
Univariate***	91.9	-2.5	-3.8	-9.9
Multivariate***	96.9	-1.9	-2.1	-7.0
Family Activities				
Univariate***	89.2	-3.9	-6.4	-15.7
Multivariate***	95.3	-2.3	-2.8	-9.1
Family Cohesion				
Univariate***	86.6	-1.5	-2.4	-2.5
Multivariate	NS	NS	NS	NS

[1] Subgroup of infants without asthma-like symptoms (no positive answers); the reference group.

[2] Subgroup of infants with *mild* asthma-like symptoms (1-4 positive answers).

[3] Subgroup of infants with *moderate* asthma-like symptoms (5-8 positive answers).

[4] Subgroup of infants with *severe* asthma-like symptoms (9-12 positive answers).

Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, NS (not significant), and thus not included in the final multivariate model.

Note: The multivariate model was adjusted for infants' and maternal characteristics.

For example, the subgroup of infants without asthma-like symptoms had a mean quality of life score of 77.9 for General Health. Infants who had mild, moderate and severe symptoms had a mean quality of life of 74.4 (77.9 - 3.5), 69.9 (77.9-8.0) and 61.1 (77.9-16.8) for General Health, respectively. After adjustments for infants' and maternal characteristics the subgroup of infants without asthma-like symptoms had a mean quality of life score of 69.7 for General Health. Infants who had mild, moderate and severe symptoms had a mean quality of life score of 67.8 (69.7-1.9), 65.8 (69.7-3.9) and 60.3 (69.7-9.4) for General Health, respectively.

Table 4. Relative risk (RR) and population attributable risk (PAR) for low HRQOL[5] (n = 5000).

	Subgroup 2[2] vs. 1[1]		Subgroup 3[3] vs. 1[1]		Subgroup 4[4] vs. 1[1]		PAR
	RR [95% CI]	PAR[6]	RR [95% CI]	PAR[6]	RR [95% CI]	PAR[6]	total
Physical Functioning							
Crude	1.0 [0.8-1.3]	1.4	1.4 [1.0-1.7]	4.2	3.0 [2.6-3.8]	6.9	12.5
Adjusted	0.8 [0.8-1.3]	--	0.8 [1.0-1.5]	--	1.3 [0.8-2.3]	1.2	1.2
Growth and Development							
Crude	1.1 [0.9-1.2]	2.4	1.2 [1.0-1.4]	2.7	1.7 [1.4-2.0]	2.6	7.7
Adjusted	1.0 [0.8-1.1]	--	1.0 [0.8-1.2]	0.2	1.2 [0.9-1.5]	0.8	1.0
Temperament and Moods							
Crude	1.3 [1.1-1.4]	8.8	1.5 [1.3-1.8]	6.0	3.0 [2.7-3.3]	7.1	21.9
Adjusted	1.1 [0.9-1.3]	3.7	1.1 [0.9-1.4]	1.5	2.0 [1.7-2.3]	3.6	8.8
Bodily Pain							
Crude	1.4 [1.3-1.6]	12.4	1.8 [1.5-2.0]	8.5	5.3 [5.0-5.6]	13.9	34.8
Adjusted	1.1 [0.9-1.3]	3.3	1.0 [0.8-1.3]	0.1	2.4 [2.1-2.7]	5.1	8.5
General Health							
Crude	1.5 [1.4-1.7]	15.7	3.1 [2.9-3.3]	20.3	8.3 [8.0-8.6]	21.6	57.6
Adjusted	1.2 [1.0-1.4]	7.1	1.8 [1.6-2.0]	8.9	3.2 [2.9-3.6]	7.8	23.8
Parental Emotional							
Crude	1.6 [1.4-1.8]	17.2	2.2 [1.9-2.5]	12.7	5.2 [4.9-5.5]	13.7	43.6
Adjusted	1.3 [1.1-1.5]	9.4	1.4 [1.1-1.7]	4.5	2.5 [2.2-2.9]	5.4	19.3
Parental Time							
Crude	1.4 [1.5-1.6]	11.3	1.7 [1.4-1.9]	7.2	4.0 [3.6-4.3]	10.0	28.5
Adjusted	1.3 [1.0-1.5]	8.2	1.2 [0.9-1.5]	2.6	2.5 [2.1-2.8]	5.3	16.1
Family Activities							
Crude	1.7 [1.5-1.9]	19.7	2.3 [2.1-2.5]	13.7	5.1 [4.8-5.5]	13.5	46.9
Adjusted	1.5 [1.3-1.7]	14.2	1.7 [1.4-1.9]	7.2	2.9 [2.5-3.2]	6.6	28.0
Family Cohesion							
Crude	1.2 [1.0-1.4]	6.2	1.3 [1.1-1.5]	3.2	1.4 [1.0-1.7]	1.4	10.8
Adjusted	1.2 [0.9-1.4]	5.2	1.2 [1.0-1.4]	2.2	1.1 [0.8-1.5]	0.5	7.9

[1] Subgroup of infants without asthma-like symptoms (no positive answers); the reference group.

[2] Subgroup of infants with *mild* asthma-like symptoms (1-4 positive answers).

[3] Subgroup of infants with *moderate* asthma-like symptoms (5-8 positive answers).

[4] Subgroup of infants with *severe* asthma-like symptoms (9-12 positive answers).

[5] Low HRQOL is defined as an ITQOL score lower than the mean ITQOL score minus 1 standard deviation.

[6] Population attributable risk (PAR) = (p(RR-1))/(p(RR-1)+1) x 100; where p is the prevalence of asthma-like symptoms within the study population and RR is the relative risk of low HRQOL.

Note: The multivariate model was adjusted for infants' and maternal characteristics.

7.5 Discussion

This study evaluated generic HRQOL in infants with asthma-like symptoms using parent-reported data. We found that asthma-like symptoms in the first year of life are associated with impaired HRQOL in infants aged 12 months for multiple dimensions of HRQOL as measured by the ITQOL. In support of our hypothesis we observed that the severity of asthma-like symptoms (more positive answers) was negatively associated with HRQOL (lower HRQOL). Asthma-like symptoms during the first year of life were also associated with parents' emotional health and parents' time to meet their own needs; furthermore, these symptoms often interfered with family activities.

Our study is the first to assess HRQOL in infants at the age of 12 months. We used effect sizes to compare the relative magnitude of HRQOL impairment because it gives an impression as to how much a specific scale is affected by the presence of asthma-like symptoms. Compared with infants without asthma-like symptoms, the *General Health*, *Bodily Pain*, and *Family Activities* scales were most affected in infants with *severe* symptoms, indicating that these infants more often experienced severe and limiting pain and discomfort, their parents more often believed that their infants' health was poor and likely to get worse, and that their infants' health interrupted family activities.

What is the clinical relevance of our findings? If we consider an effect size of ≥ 0.8 a *large difference* (21) or an effect size of ≥ 0.5 a *minimal important difference* (22), there is are relevant associations between asthma-like symptoms in the first year of life and several dimensions of HRQOL, except for limitations in physical functioning of the infant and family cohesion.

Our study adds new information regarding the risk for low HRQOL in infants with asthma-like symptoms. At a population level, asthma-like symptoms were associated with an increased risk of having low quality of life for several dimensions of HRQOL, regardless of the symptom severity. Prevention of asthma-like symptoms in infants, for example by systematic monitoring and adequate management, could subsequently improve their health and HRQOL.

We used a generic questionnaire to compare HRQOL among subgroups of infants with versus without asthma-like symptoms, with the advantage that they provide a comprehensive overview of HRQOL at the subgroup level. However, generic questionnaires cannot assess the impact of certain conditions on specific aspects of HRQOL, for example problems with breathing and sleeping in the case of asthma-like symptoms. A valid asthma-specific HRQOL questionnaire for infants has yet to be developed.

There are some limitations to this study. Compared with the postnatal cohort of Generation R Study, our study population more often consisted of mothers who had a Dutch ethnicity (62.6 vs. 45.4%, $p < 0.001$) and mothers who were higher educated (54.3% vs. 37.4%; $p < 0.001$). Our results should therefore be applied with care to the total postnatal cohort of Generation R. Maternal age and infants' characteristics (gender, birth weight and gestational age) did not differ significantly. We were not able to compare infants participating in the Generation R Study and non-participating infants. We therefore do not know the possible direction of bias, if any.

The severity of asthma-like symptoms was defined based on selected questions on lower respiratory items from the International Study of Asthma and Allergies in Childhood (ISAAC). These questions were designed for children aged six years and up. To our knowledge there are no validated respiratory questionnaires for use in infants aged 12 months. We have used selected questions from the ISAAC core questionnaires as they were originally adapted for the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort. These questions were indeed made suitable for younger children and, although not formally validated, have been used in many papers from this cohort (23). Another limitation is that we were not able to grade the severity of asthma-like symptoms on hospital admissions, visits to the general practitioner or medical specialist. Although our dataset included information on hospital admissions and the number of visits to the general practitioner and medical specialist, the reason for admission or visit was not recorded. Therefore the severity of asthma-like symptoms was only graded on the presence of parent-reported lower respiratory symptoms.

Both asthma-like symptoms and HRQOL were reported by parents and therefore represent a subjective perspective. Using parents' perspective on both determinant and outcome in our study may account for the strong associations that were observed between the increased severity of asthma-like symptoms and decreased HRQOL. Therefore, it cannot be ruled out that the subgroup severity is associated with an increased parents' awareness of their infants' health.
We used effect sizes for the interpretation of relevant differences in HRQOL. Although this is an acceptable 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 measures such as the ITQOL and other HRQOL instruments are an important next step for the field.

In conclusion, we found that asthma-like symptoms during the first year of life are associated with impaired HRQOL in infants aged 12 months. The subgroup of infants with *severe* symptoms had relevant deficits in HRQOL and had an increased risk for low HRQOL. At a population level, asthma-like symptoms were associated with an increased risk for low quality of life, regardless of symptom severity. General practitioners and pediatricians should be aware of the negative impact of asthma-like symptoms on HRQOL in infants, and the impact of these symptoms on parents and family.

7.6 Acknowledgements

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7.7 Addenda

Addendum 1. ITQOL scales, number of items per scale and score interpretation [1].

Scale (number of items)	*Description of low scale scores*	*Description of high scale scores*
Physical Functioning (10)	Child is limited a lot in performing physical activities such as eating, sleeping, grasping, and playing due to health problems.	Child performs all types of physical activities such as eating, sleeping, grasping, and playing without limitations due to health problems.
Growth and Development (10)	Parent is very dissatisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament.	Parent is very satisfied with development (physical growth, motor, language, cognitive), habits (eating, feeding, sleeping) and overall temperament.
Bodily Pain (3)	Child has extremely severe, frequent and limiting bodily pain and discomfort.	Child has no pain or limitations due to pain and discomfort.
Temperament and Moods (18)	Child has very often certain moods and temperaments, such as sleeping and eating difficulties, crankiness, fussiness, unresponsiveness and lack of playfulness and alertness.	Child never has certain moods and temperaments, such as sleeping and eating difficulties, crankiness, fussiness, unresponsiveness and lack of playfulness and alertness.
General Behavior (13)	Parent believes child's behavior is poor and likely to get worse.	Parent believes child's behavior is excellent and will continue to be so.
Getting Along (15)	Child very often exhibits behavior problems, such as not following directions, hitting, and biting others, throwing tantrums, and being easily distracted, while positive behaviors, such as ability to cooperate, appear sorry, and adjustment to new situations are seldom shown.	Child never exhibits behavior problems, such as not following directions, hitting and biting others, throwing tantrums, and being easily distracted, while positive behaviors, such as ability to cooperate, appear sorry, and adjustment to new situations are frequently shown.
General Health (12)	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 Emotional (7)	Parent experiences a great deal of feelings of emotional worry and concern as a result of child's physical and/or psychosocial health and/or growth and development.	Parent doesn't experience feelings of emotional worry/concern as a result of child's physical and/or psychosocial health and/or growth and development.
Parental Time (7)	Parent experiences a lot of limitations in time available for personal needs due to child's physical and/or psychosocial health and/or growth and development.	Parent doesn't experience limitations in time available for personal needs due to child's physical and/or psychosocial health and/or growth and development.
Family Activities (6)	The child's health and/or growth and development very often limits and interrupts family activities or is a source of family tension.	The child's health and/or growth and development never limits and interrupts family activities or is not a source of family tension.
Family Cohesion (1)	Family's ability to get along is rated 'poor'.	Family's ability to get along is rated 'excellent'.
Change in Health (1)	Child's health is much worse now than 1 year ago.	Child's health is much better now than 1 year ago.

[1] Reproduced with permission from the principal author Jeanne M. Landgraf.

Addendum 2. Selected questions from the International Studies on Asthma and Allergies.

1. Has your child ever had wheezing or a whistling noise in the chest?
2. Has your child had wheezing or a whistling noise in the chest during the past four weeks?
3. Has your child ever had poor sleeping due to wheezing or a whistling noise in the chest?
4. Has your child had wheezing or a whistling noise in the chest during or after exertion (e.g. drinking)?
5. Has your child had wheezing or a whistling noise in the chest when it had a cold or flu?
6. Has your child had shortness or breath?
7. Has your child had shortness or breath during the past four weeks?
8. Has your child had poor sleeping due to shortness or breath?
9. Has your child had shortness or breath during or after exertion (e.g. drinking)?
10. Has your child had shortness or breath when it had a cold or flu?
11. Has your child had a dry cough at night, even though it did not have a cold or flu?
12. Has your child had chest (mucous) congestion at night, or has your child coughed up mucous on at least four days a week and during at least three months?

All answers were coded 'yes' or 'no'.

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8

General Discussion

8.1 Introduction

The objectives of this thesis were to evaluate the association between asthma-related symptoms and health-related quality of life in children and to evaluate whether asthma-related symptoms and health-related quality of life can be measured in an accurate and valid way among preschool children using proxy-reported data. The relevance of both objectives is based upon the following hypotheses. We hypothesized that early detection and adequate management of asthma among preschool children will reduce the prevalence of asthma among children, and subsequently will improve their health-related quality of life. Both asthma-related symptoms and health-related quality of life are being used as outcome measures in a randomized controlled trial for early detection of asthma in preschool children.

In this General Discussion, we discuss whether our objectives have been reached, and whether the research questions have been answered. In addition, we discuss methodological issues in measuring asthma-related symptoms and health-related quality of life among preschool children. First, we summarize the main findings.

8.2 Measurements of Asthma-Related Symptoms in Preschool Children

The diagnosis of asthma in school-aged children is based on the presence of symptoms, medical history, physical examination and lung function measurements. The diagnosis of asthma among preschool children is difficult to determine accurately. Only a small proportion of children in this age group can cooperate reliably with objective lung function measurements used to document one of the important features of asthma - variable airflow obstruction (1). The presently available objective measures are unlikely to be helpful in the majority of preschool children in a primary care setting. Consequently the diagnosis has to be based upon symptoms and physical examination (2). However, in the majority of preschool children there are no physical findings specific with the diagnosis of asthma. The diagnosis of asthma in preschool children is therefore dependent on medical history taking and parent-reported symptoms, and in absence of a gold standard it is difficult to assess the accuracy and validity of parent-reported symptoms. In addition, asthma-related symptoms, such as wheezing and shortness of breath, are not specific for asthma at such young age and there are periods when children are free of symptoms. The first part of this thesis presents different studies comparing the prevalence of asthma or asthma-related

symptoms from different administration methods, with special focus on the measured prevalence of asthma-related symptoms among preschool children.

Chapter 2 compares patients' self-reports or proxy-reports from a structured health interview survey with general practitioners medical records, within the framework of the second Dutch National Survey of General Practice. The prevalence of self-reported asthma or COPD (9.7%) was almost twice the prevalence based on general practitioner medical records (5.2%) for all ages. Although the observed agreement was high (92%), agreement measured by the kappa statistic was moderate (0.42). Among preschool children, the prevalence of parent-reported asthma (12.1%) was twice the prevalence based on general practitioner medical records (5.9%); high observed agreement (89%), but low kappa (0.31). Higher reporting of asthma by parents was more often seen when preschool children had accompanying respiratory symptoms, such as wheezing or cough. Parental over-interpretation of respiratory symptoms in young children is not uncommon and could at least partly explain the higher prevalence during the interview.

Chapter 3 compares parent-reported wheezing or shortness of breath among infants as assessed by self-administered written questionnaire and by physician interview during the regular free-of-charge consultation at preventive Child Health Centers, using data from the Generation R Study. The prevalence of wheezing or shortness of breath from the questionnaire (36%) was significantly higher than the prevalence based on a physician interview (20%). There was limited agreement between questionnaire data and physician interview data: observed agreement 70%, kappa 0.36. Agreement was higher when the infant received anti-asthma medication, had abnormal respiratory sounds or bronchiolitis or croup, and when the mother was working. When wheezing or shortness of breath was present according to questionnaire only, the subgroup included a high proportion of infants suffering from other respiratory conditions. When wheezing or shortness of breath was present according to physician interview only, the subgroup included a high proportion of infants receiving anti-asthma medication.

Can the prevalence of asthma-related symptoms be measured in preschool children using parent-reported data?

Although asthma is the most common cause of wheezing and shortness of breath, asthma is often attributed inappropriately to symptoms from other causes, also among preschool children (3). Wheezing due to airway narrowing is the most characteristic symptom that sounds like a musical whistle. Many parents use the same word to describe many other different noises (1,4). Studies using a video questionnaire or objective recording of respiratory sounds have demonstrated the unreliability of parents' recognition of wheeze (5, 6). The distinguishing characteristic of asthma is the response to bronchodilators or inhalation corticosteroids when the patient is symptomatic. This information was not available in our studies. In our studies, parents more frequently reported asthma-related symptoms in the questionnaire than during the physician interview, and asthma was more frequently reported during the health-interview than recorded in general practitioners' medical records. There is a controversy as to whether parent reports are accurate or not.

Pless compared parents' responses from a self-administered questionnaire with pediatricians' records (7). Parents of 288 children aged 11-13 years were studied. Parents were able to report asthma with accuracy. The observed agreement was 91%. Mothers responded more accurately than fathers and parents of younger children showed better recall. Education and occupation were not significantly associated with recall.

Another study examined the accuracy of symptom perception of 28 children and adolescents aged 6-18 years with asthma and their parents, as well as their interpretation and evaluation of the symptoms. Results revealed that accuracy can be affected by several factors, such as age of the child and ethnicity of the parent (8). Adolescents were more accurate than school-aged children, more accurate children had better morbidity outcomes, and African-American parents were more accurate than Caucasian parents. Socioeconomic status did not affect accuracy. Both children and parents missed early symptoms and waited too long prior to intervening in an exacerbation.

Another study revealed that among 90 school-aged children with the diagnosis of asthma no significant association was found between questionnaire reported symptoms by the child or the parent and forced expiratory volume in one second (9). Due to the absence of objective lung function measurement in preschool children, such a study cannot be performed for this age group.

In conclusion, the prevalence of asthma among preschool children remains difficult to determine in absence of a gold standard for diagnosis. The accuracy and validity of parent-reported symptoms are difficult to establish among preschool children. Parent-reported asthma as assessed by health interview survey, when compared with general practitioner medical records, includes a higher proportion of infants suffering from other respiratory conditions, including wheezing and cough. Parent-reported wheezing or shortness of breath as assessed by self-administered written questionnaires, when compared with assessment by physician interview, includes a lower proportion of infants receiving anti-asthma medication and having abnormal respiratory sounds when examined by the physician, but a higher proportion of infants suffering from other respiratory conditions, including flu, sore throat, bronchiolitis or croup.

Based on the results of these studies, we can not conclude whether parent reports on wheezing or shortness of breath through self-administered written questionnaires are more accurate and valid than physician-interviewed reports among infants or vice versa. We conclude that both methods have their own advantages and disadvantages. Parent reports through self-administered written questionnaires are often more readily available and cheaper than alternatives. Both methods have opportunities for error in symptom perception and evaluation. Parents may for example label other lower respiratory symptoms as wheezing or physicians may wrongly interpret the information on lower respiratory symptoms given by parents.

The results of our study indicated that among infants, wheezing or shortness of breath were more often reported by parents in the questionnaires. Agreement on the presence of wheezing or shortness of breath was observed when infants received anti-asthma medication, when infants had abnormal respiratory sounds when examined by the physician, when infants had bronchiolitis or croup, and when the mothers were working. These findings should be taken into account when deciding on a method to measure prevalence rates of asthma among preschool children.

For the early detection of asthma through preventive Child Health Centers we would recommend using a combination of parent reports as assessed by self-administered written questionnaire and by physician interview. Using only parent reports from self-administered written questionnaires, will probably result in a high proportion of false

positives (low specificity), indicating that a large proportion of preschool children will be referred to the general practitioner who do not have an increased risk to develop asthma in later life. In our study for example these would be infants suffering from other respiratory conditions. Using only physician-reports from a medical interview with parents will probably result in a high proportion of false negatives (low sensitivity), indicating that only a small proportion of preschool children who have an increased risk to develop asthma in later life will be referred to the general practitioner. In our study for example these would be infants who had frequent episodes of wheezing and shortness of breath during the past year without currently having symptoms and without being monitored by a general practitioner.

8.3 Measurements of Health-Related Quality of Life in Preschool Children

The most important distinction in health-related quality of life questionnaires is between generic and disease-specific instruments. Generic instruments intend to measure all dimensions of quality of life, and can therefore be applied in healthy populations as well as in subpopulations with asthma or asthma-related symptoms. Generally, generic questionnaires are less sensitive to the impact of specific diseases on health-related quality of life than disease-specific questionnaires.

Two validated generic questionnaires, the *TNO-AZL Preschool Children Quality of Life Questionnaire* (TAPQOL) and the *Infant Toddler Quality of Life Questionnaire* (ITQOL) are available to measure health-related quality of life in preschool children. The ITQOL has been validated in a general population sample and a respiratory disease sample in the Netherlands (10). For the majority of scales the ITQOL discriminated between preschool children with a few and with many parent-reported chronic conditions, between preschool children with and without doctor-diagnosed respiratory disease and with a low and high parent-reported medical consumption. The TAPQOL discriminated between preschool children with and without parent-reported chronic conditions for the physical functioning scales only: *sleeping*, *appetite*, *lung problems*, *skin problems*, and *motor functioning* (11). Infants aged 2-12 months with two or more parent-reported chronic conditions, compared with infants without parent-reported chronic conditions, had relevant differences in quality of life for *sleeping* (d = 1.5), *lung problems* (d = 2.2) and *skin problems* (d = 0.8). Toddlers aged 13-48 months with two or more parent-reported chronic conditions, compared with those without, had relevant differences in health-related quality of life for *lung problems*

(d = 0.9) and *skin problems* (d = 0.8). The study also revealed that the TAPQOL, originally developed for children aged one year and older, is feasible and reliable for infants aged 2-12 months.

Can health-related quality of life be measured in preschool children with asthma-related symptoms using parent-reported data?

The review indicated that both instruments could be used to measure health-related quality of life in preschool children with asthma-related symptoms. The ITQOL has the advantage that it includes a wide range of dimensions aimed at evaluating the impact of asthma-related symptoms on the physical and psychosocial health and development of infants and toddlers. Further, it evaluates the effects of asthma-related symptoms on parents' emotional health and time to meet their own needs, and on family activities and cohesion. The TAPQOL has the advantage that despite the fact that it is a generic questionnaire, it includes two scales that describe specific aspects of quality of life in asthmatics: *lung problems* and *sleeping*. Generally, a combination of generic and asthma-specific measurements best evaluate health-related quality of life in asthmatic children, and if possible, a combination of parents' and child's self-reports should be evaluated (12). Preschool children do not have the cognitive ability to complete questionnaires.

In absence of an asthma-specific questionnaire for the preschool group, a combination of the ITQOL and TAPQOL likely best describes health-related quality of life in preschool children with asthma-related symptoms. We would recommend using both instruments if possible. If only one questionnaire could be applied, depending on the setting of the study and the research question we would recommend either one. The TAPQOL is a shorter questionnaire and assesses some specific aspects of health-related quality of life in preschool children with asthma-related symptoms. We would recommend this instrument to evaluate health-related quality of life in preschool children with diagnosed asthma. The ITQOL is a longer questionnaire that has the advantage that it can assess the impact of asthma-related symptoms on several dimensions of health in preschool children as well as the impact of asthma-related symptoms on family and parents. In population studies, we would recommend this instrument. We would also recommend developing a shorter version of the ITQOL and an asthma-specific quality of life instrument for use in preschool children.

8.4 The Association between Asthma-Related Symptoms and Health-Related Quality of Life in Children

The third part of this thesis presents different studies evaluating the association between asthma-related symptoms and health-related quality in life in children, with special focus on generic health-related quality of life in preschool children with asthma-like symptoms. As mentioned in the previous paragraph, two generic questionnaires are available to evaluate health-related quality of life in preschool children. Both instruments were used to evaluate the association between asthma-related symptoms and health-related quality of life in preschool children.

Chapter 5 evaluates health-related quality of life among adolescents aged 13-17 years with wheezing attacks using the Child Health Questionnaire-Child Form (CHQ-CF). Compared with adolescents without wheezing, subgroups of adolescents with wheezing attacks had significantly lower quality of life scores for nine out of 10 CHQ-CF scales. Except for the *Role Physical* and *Family Activities* scales, relevant deficits in quality of life were observed for all scales among adolescents who reported at least four wheezing attacks in the past year; most affected were the *Bodily Pain* (d = 1.2), *General Health* (d = 0.9), *Self Esteem* (d = 0.8) and *Mental Health* (d = 0.8) scales.

In multivariate linear regression models, adjusted for adolescents' characteristics and co-morbidity, wheezing attacks remained significantly associated with quality of life for nine out of 10 CHQ-CF scales; the exception was the *Role Physical* scale. This study showed that wheezing attacks are related to many areas of health-related quality of life of adolescents, especially among those with more frequent attacks.

Chapter 6 evaluates health-related quality of life in preschool children aged 2-48 months with wheezing or shortness of breath using the TAPQOL in a random general population sample in the Netherlands. Compared with preschool children without wheezing or shortness of breath, subgroups of preschool children with wheezing or shortness of breath had significantly lower quality of life scores for several TAPQOL scales. Relevant differences in quality of life between the subgroup with versus without wheezing and shortness of breath were observed for *lung problem*s (d = 2.1) and *sleeping* (d = 0.8), while for the subgroup with either wheezing or shortness of breath, relevant difference in quality of life was observed for *lung problem*s (d = 0.9).

In multivariate linear regression models, adjusted for age and gender of the child, wheezing and shortness of breath remained significantly associated with quality of life for the *lung problem*s, *sleeping*, *appetite*, *communication*, and *positive mood* scales. This study showed that health-related quality of life is impaired in preschool children with wheezing or shortness of breath, especially among those who had both symptoms. Regardless of symptom severity, TAPQOL scales that measure physical health demonstrated significantly lower scores.

Chapter 7 evaluates health-related quality of life at age 12 months in infants with asthma-like symptoms using data from the Generation R Study. Subgroups of infants with asthma-like symptoms during the first year of life (such as wheezing, shortness of breath, chest tightness and dry cough at night without having a cold or chest infection) had significantly lower quality of life scores for all ITQOL scales.
Except for the *Family Cohesion* and *Physical Functioning* scales, relevant differences in health-related quality of life were observed for all ITQOL scales among the subgroup with *severe* asthma-like symptoms, especially for the *General Health* (d = 1.2), *Bodily Pain* (d = 0.9), and *Family Activities* (d = 0.8) scales. The subgroup of infants with *moderate* symptoms had relevant differences in health-related quality of life for the *General Health* scale, while the subgroup with *mild* symptoms showed no relevant differences.

In multivariate linear regression models, adjusted for infants' and maternal characteristics, asthma-like symptoms remained significantly associated with quality of life for the *General Health, Family Activities, Bodily Pain, Parental Time, Temperament and Moods,* and *Parental Emotional* scales. After adjustment no significant association between asthma-like symptoms and quality of life was observed for the *Physical Functioning*, *Growth and Development* and *Family Cohesion* scales. This study showed that health-related quality of life is impaired in infants with asthma-like symptoms, especially among those with more *severe* symptoms.
On a population level, the risk of having low quality of life was especially high for the *General Health* and *Family Activities* scales, regardless of symptom severity.

Results of the third part of this thesis revealed that asthma-related symptoms are strongly associated with several dimensions of health-related quality of life in children. But there are some methodological issues that need to be discussed.

First, both asthma-related symptoms and health-related quality of life are based on subjective measurements: self-reports or proxy-reports. Using reports from parents or adolescents on both determinant and outcome may partially explain the strong associations that were found between asthma-related symptoms and health-related quality.

Second, the observations in our studies among preschool children are based on parent reports, which are indispensable for this age group, because preschool children do not have the cognitive ability to complete questionnaires themselves. Several studies have reported that parents and adolescents' perspective on quality of life differ (13); this issue cannot be evaluated for preschool children. Although ratings by parents and adolescents do not agree exactly, there seems to be sufficient agreement between their assessments of quality of life to make the information that parents provide useful (14). It is difficult to assess the adequacy of parents ratings that may be influenced by many factors, such as parents perception of asthma and the interviewer technique (14, 15). Parents have to interpret the symptoms and well-being of their child, which may not be easy, especially in the case of very young children.

Third, we used a difference of half standard deviation or more ($d \geq 0.5$) as *minimal important difference* (relevant difference) between subgroups in the absence of empirically defined cut-off points (16). Although this is an acceptable approach for interpretation of differences in health-related quality of life between subgroups, there are still insufficient data to understand the relative impact of the observed score differences in clinical terms.

8.5 Implications for the Screening for Asthma in Preschool Children

Can asthma-related symptoms and health-related quality of life be used as outcome measures in a randomized controlled trial for early detection of asthma in preschool children using parent-reported data?

Several studies have indicated that preschool children who had repeated episodes of asthma-related symptoms in early years of life have an increased risk of developing asthma later in life (17). One study indicated poor airway function shortly after birth as a risk factor for airflow obstruction in young adults (18). Another study revealed that persistent wheeze during the first years of life is independently associated with

chronic asthma at age 22 years (19). Preschool children with asthma during the first five years of life have a three times increased risk to develop asthma during adolescence and early adulthood (20, 21). Recent research in the United States has revealed that children aged 5-11 years suffering from asthma are underdiagnosed. Their asthma is being controlled poorly, despite the fact that asthma can be managed effectively e.g. by daily inhaled corticosteroid treatment (22).
With application of a systematic early detection procedure for asthma among preschool children at preventive Child Health Centers, preschool children with asthma-related symptoms can be managed effectively based on the current guidelines from the Dutch College of General Practitioners (23). This intervention procedure could result in improved health-related quality of life for children, as well as for parents and family, and decreased health risks for children (less asthma in later life) with less absence from school for children and less absence from work for parents.

Systematic early detection of asthma-related symptoms could help to increase the awareness of asthma among youth healthcare workers and among parents of young children. Increasing awareness among physicians and nurses at the preventive Child Health Centers could help to detect children with asthma early, for example children with repeated episodes of wheezing and shortness of breath and with dry cough at night or during the early morning. Early detection may lead to early referral to the general practitioner and towards early treatment and management of symptoms. Treatment and management may include both pharmacological interventions, such as use of bronchodilators or inhaled corticosteroids, and non-pharmacological interventions, such as avoidance of exposure to smoke and other triggers. Increasing awareness among parents could lead to direct actions when early symptoms appear and to avoidance of exposure of their child to smoke or other triggers.

Early detection of asthma in the youth healthcare may be important regardless of symptom severity. Children with mild symptoms can be managed effectively by avoidance of triggers. Children with moderate symptoms can be managed effectively by both pharmacological and non-pharmacological interventions including avoidance of triggers. Early referral to the general practitioner and adequate treatment with bronchodilators and inhaled corticosteroids is expected to reduce the risk to develop asthma later in life. Children with severe symptoms can be managed effectively by medical treatment with daily inhaled corticosteroids and together with avoidance of

triggers these children can be prevented for having exacerbations. Better management of asthma is expected to lead to less asthma-related symptoms, and thus to overall improvement of health-related quality of life and less asthma in later life.

As described in detail in paragraph 8.3 two generic health-related quality of life questionnaires are available to measure health-related quality of life in preschool children. Both instruments are available in Dutch, and can be completed by parents. Furthermore, selected questions from the ISAAC and PIAMA study can be used to estimate the prevalence of asthma-related symptoms, such as wheezing, shortness of breath and (night) cough in preschool children. In absence of an objective measurement of asthma among preschool children, we still recommend use of selected questions on lower respiratory items for early detection of asthma in preschool children, because studies have shown that children with asthma relatively often had symptoms of asthma in their early years of life, such as wheezing, shortness of breath, and dry cough during the night or in the early morning (20, 21, 24).

Strategies for improvement of health-related quality of life in young children with asthma should include primary, secondary and tertiary prevention. At a population level, systematic early detection and monitoring of asthma among preschool children through preventive Child Health Centers may be effective. As tertiary preventive procedures, avoidance of exacerbations is important. For primary prevention a high-risk approach of existing parental morbidity of asthma and parental smoking are important factors. Avoidance of smoking in the direct environment of the child is an important preventive procedure.

8.6 Recommendations and Conclusions

Asthma is an important public health problem (25-27). Asthma and asthma-related symptoms are common during childhood and account for considerable morbidity, visits to the general practitioner or specialist, hospital admission, and substantial healthcare costs during the first years of life (1). Diagnosing asthma is difficult in preschool children, due to the non-specificity of the symptoms and the fact that conventional lung function tests cannot be carried out. Although the prevalence of asthma-related symptoms in epidemiological studies in preschool children is solely based on parent-reported symptoms, the accuracy and validity cannot be assessed in

absence of a gold standard. We recommend to compare parent reports through self-administered written questionnaires with parent reports elicited through an interview by the physician, at age two, three and four years, and study determinants of concordance and discordance. In that way we could evaluate whether parent reports as assessed by self-administered written questionnaires or by physician interview best predict the prevalence of asthma at the age of five years for example. Furthermore, we recommend to evaluate in longitudinal studies the predictive value of both parent reports through self-administered written questionnaires and parent reports elicited through physician interview regarding asthma-related symptoms for the emergence of asthma in later years of life, for example at the age of seven years or older or among adolescents.

The studies presented in this thesis showed relevant differences in health-related quality of life between children with versus without asthma-related symptoms. The association between asthma-related symptoms and health-related quality of life in school-aged children has been evaluated in several studies. Both general and disease-specific health-related quality of life was evaluated in school-aged children. We recommend that the association between asthma-related symptoms and health-related quality of life be further studied in preschool children. So far, only three studies evaluated generic heath-related quality of life in preschool children with asthma-related symptoms. Although the TAPQOL was able to evaluate specific aspects of health-related quality of life in preschool children with asthma-related symptoms, we recommend development of an asthma-specific health-related quality of life instrument for preschool children and a shorter version of the ITQOL. We also recommend that determinants of health-related quality of life in preschool children be studied.

Furthermore, we recommend that the feasibility and advantages of routine use of an asthma symptom questionnaire and health-related quality of life questionnaire be evaluated in the care for children with asthma. For example, children that are managed for asthma or asthma-related symptoms or their parents can complete an asthma symptom questionnaire and a health-related quality of life questionnaire on paper or on line, prior to each visit at the preventive Child Health Centers. Results from the questionnaires can be discussed with physicians or nurses as part of the face-to-face consultation.

Children diagnosed with asthma have retrospectively presented with asthma-related symptoms in early years of life, especially persistent wheezing (17-20). Early detection of asthma in preschool children by physicians and nurses at preventive Child Health Centers and adequate management of asthma-related symptoms by general practitioners could possibly improve health and health-related quality of life in children. Early detection of asthma through preventive Child Health Centers and adequate management of asthma are important factors to possibly reduce the burden of asthma in childhood.

Prior to implementation of systematic early detection procedures at preventive Child Health Centers, it is important to know whether it is effective to detect asthma early and consequently reducing asthma-related symptoms and improving health-related quality of life. A randomized controlled trial for early detection of asthma in preschool children has been designed and implemented within the framework of the Generation R Study, as described in paragraph 1.4. We have shown that asthma-related symptoms and health-related quality of life can be used as outcome measures in the asthma early detection trial among preschool children.

8.7 References

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Summary

Summary

Asthma during childhood represents an important public health problem. In developed (industrialized) countries asthma is a highly prevalent chronic condition that accounts for considerable morbidity, reduced health-related quality of life, and substantial healthcare costs. The World Health Organization defines asthma as a chronic inflammatory disorder of the airways associated with increased bronchial hyperresponsiveness to a variety of triggers. In susceptible individuals the inflammation causes recurrent episodes of wheezing, shortness of breath, chest tightness, and dry cough, particularly at night or in the early morning. These symptoms are usually associated with variable airflow limitation that is at least partially reversible either spontaneously or with treatment.

Asthma is heterogeneous of nature with reversible and variable signs and symptoms over time. Wheezing is the most characteristic symptom. A diagnosis of asthma in school-aged children is usually based on the child's symptoms, medical history, physical examination, and lung function tests. Physicians generally look for signs of airflow obstruction and whether the obstruction is at least partially reversible. Factors that trigger symptoms may be evident and conventional lung function tests can support the diagnosis. Asthma cannot be clearly diagnosed in preschool children, due to the non-specificity of the symptoms and the fact that a qualitatively good lung function test cannot be carried out at such a young age. The current Dutch General Practitioners evidence-based childhood asthma guidelines for children under the age of six are therefore based on the presence of asthma-related symptoms defined as recurrent attacks of wheezing. Shortness of breath is often not apparent. The diagnosis of asthma among young children is therefore limited to reported symptoms by parents or caregivers.

In absence of systematic detection of asthma, it is likely that asthma-related symptoms could be underdiagnosed and undertreated as a result of underpresentation by parents or caregivers. Early detection and adequate management of asthma in young children could therefore have a direct health effect by facilitating lung development with reduced symptoms, also later in life and increased health-related quality of life. Detected children can be managed effectively by a package of measures including monitoring by the general practitioner, health education, non-pharmacological interventions (avoidance of exposure to smoke and

allergic triggers), and if indicated pharmacological treatment with bronchodilators or inhalation corticosteroids.

In **chapter 1** we hypothesized that early detection and adequate management of asthma will reduce the frequency of asthma-related symptoms among preschool children, and subsequently will improve their health-related quality of life. The objective of this thesis was to evaluate the association between asthma-related symptoms and health-related quality of life in children. Additionally, we evaluated whether asthma-related symptoms and health-related quality of life can be measured in an accurate and valid way among preschool children using proxy-reported data. In that way, we could ultimately assess whether asthma-related symptoms and health-related quality of life can be used as outcome measures in a randomized controlled trial for early detection of asthma in preschool children.

Part I: Measurements of Asthma-Related Symptoms

The first part of this thesis describes different studies comparing measurements of asthma-related symptoms and asthma, with special focus on the measured prevalence of asthma during infancy.

Chapter 2 compares the prevalence of asthma or COPD as assessed by patients' self-reports or proxy-reports from a structured health interview survey and by general practitioners medical records, within the framework of the second Dutch National Survey of General Practice. The prevalence of self-reported asthma or COPD (9.7%) was almost twice the prevalence based on general practitioners medical records (5.2%) for all ages. The observed agreement was high (92%), but the kappa indicated moderate agreement ($\kappa = 0.42$). Among preschool children, the prevalence of parent-reported asthma (12.1%) was twice the prevalence based on medical records (5.9%); the observed agreement was high (89%), but the kappa was low ($\kappa = 0.31$). Higher reporting of asthma by parents was more often seen when preschool children had accompanying respiratory symptoms, such as wheezing or cough. Parental over-interpretation of respiratory symptoms in young children is not uncommon and could at least partly explain the higher prevalence in the self-reported data. Two methods for estimating the prevalence of asthma or COPD yielded different results: compared with general practitioner medical records, self-reported prevalence shows a higher

estimation in patients suffering from other respiratory conditions and a lower estimation in elderly persons living in a smoky environment.

Chapter 3 compares the prevalence of parent-reported wheezing or shortness of breath among infants as assessed by self-administered written questionnaires and by physician interview during a regular free-of-charge consultation using data from the Generation R Study. The physician interview yielded lower prevalence rates for wheezing or shortness of breath than questionnaires. The prevalence of wheezing or shortness of breath from questionnaires (36%) was significantly higher than the prevalence based on a physician interview (20%). There was limited agreement between questionnaire data and physician interview data: observed agreement 70%, kappa 0.36. Agreement was higher when the infant received anti-asthma medication, had abnormal respiratory sounds, had bronchiolitis or croup, and when the mother was working. When wheezing or shortness of breath was present according to questionnaire only, the subgroup included a high proportion of infants suffering from other respiratory conditions. When wheezing or shortness of breath was present according to the physician interview only, the subgroup included a high proportion of infants receiving anti-asthma medication.

Part II: Measurements of Health-Related Quality of Life

The second part of this thesis gives an overview of quality of life measures in children, both general and disease-specific instruments. In **Chapter 4** recent studies on feasibility, reliability, and validity of pediatric health-related quality of life questionnaires are summarized. In addition, this chapter gives an overview of recent applications of health-related quality of life measures in children.

The most important distinction in quality of life questionnaires is between generic and disease-specific health-related quality of life instruments. Generic instruments intend to measure all dimensions of quality of life, and can therefore be applied in healthy populations as well as in subpopulations with asthma or asthma-related symptoms. Two validated generic questionnaires, the TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL) and the Infant Toddler Quality of Life Questionnaire (ITQOL) are available to measure health-related quality of life in preschool children. The ITQOL has been validated in a general population sample and a respiratory disease sample in the Netherlands. For the majority of scales the ITQOL discriminated between

preschool children with a few and with many parent-reported chronic conditions, between preschool children with and without doctor-diagnosed respiratory disease and with a low and high parent-reported medical consumption. The TAPQOL discriminated between preschool children with and without parent-reported chronic conditions for the physical functioning scales only: *sleeping*, *appetite*, *lung problems*, *skin problems*, and *motor functioning*. Infants aged 2-12 months with two or more parent-reported chronic conditions, compared with infants without parent-reported chronic conditions, had relevant differences in quality of life for the *sleeping* (d = 1.5), *lung problems* (d = 2.2) and *skin problems* (d = 0.8) scales. Toddlers aged 13-48 months with two or more parent-reported chronic conditions, compared with those without, had relevant differences in quality of life for the *lung problems* (d = 0.9) and *skin problems* (d = 0.8) scales. The study also revealed that the TAPQOL, originally developed for children aged one year and older, is feasible and reliable for infants aged 2-12 months.

Part III: The Association between Asthma-Related Symptoms and Health-Related Quality of Life

The third part of this thesis presents three studies assessing the association between asthma-related symptoms and health-related quality in life in childhood, with special focus on health-related quality of life in preschool children with asthma-related symptoms.

Chapter 5 examines health-related quality of life among adolescents with wheezing attacks using self-reported data. The Child Health Questionnaire-Child Form (CHQ-CF) was used to assess health-related quality of life and the frequency of wheezing attacks was based on selected questions from the International Studies of Asthma and Allergies in Childhood. Compared with adolescents without wheezing, subgroups of adolescents with wheezing attacks had significantly lower quality of life scores for nine out of 10 CHQ-CF scales. Except for the *Role Physical* and *Family Activities* scales, relevant deficits in quality of life were observed for all scales among adolescents who reported at least four wheezing attacks in the past year; most affected were the *Bodily Pain* (d = 1.2), *General Health* (d = 0.9), *Self Esteem* (d = 0.8) and *Mental Health* (d = 0.8) scales. In multivariate linear regression models, wheezing attacks remained significantly associated with quality of life for nine out of 10 CHQ-CF scales. This study

showed that wheezing attacks are related to many areas of health-related quality of life of adolescents, especially among those with more frequent attacks.

Chapter 6 examines health-related quality of life in preschool children aged 2-48 months with wheezing or shortness of breath using the TAPQOL in a random general population sample in the Netherlands. Compared with preschool children without wheezing or shortness of breath, subgroups of preschool children with wheezing or shortness of breath had significantly lower quality of life scores for several TAPQOL scales. Relevant differences in quality of life between the subgroup with versus without wheezing and shortness of breath were observed for the *lung problem*s (d = 2.1) and *sleeping* (d = 0.8) scales, while for the subgroup with either wheezing or shortness of breath, relevant difference in quality of life was observed for the *lung problem*s (d = 0.9) scale. In multivariate linear regression models, adjusted for age and gender of the child, wheezing and shortness of breath remained significantly associated with quality of life for the *lung problem*s, *sleeping*, *appetite*, *communication*, and *positive mood* scales. This study showed that health-related quality of life is impaired in preschool children with wheezing and shortness of breath, especially among those who had both symptoms. Regardless of symptom severity, TAPQOL scales that measure physical health demonstrated significantly lower scores.

Chapter 7 examines health-related quality of life at age 12 months in infants with asthma-like symptoms using data from the Generation R Study. Subgroups of infants with asthma-like symptoms, such as wheezing, shortness of breath, night cough without cold and chest congestion, had significantly lower quality of life scores for all ITQOL scales. Except for the *Family Cohesion* and *Physical Functioning* scales, relevant differences in quality of life were observed for all ITQOL scales among the subgroup with *severe* asthma-like symptoms, especially for the *General Health* (d = 1.2), *Bodily Pain* (d = 0.9), and *Family Activities* (d = 0.8) scales. The subgroup of infants with *moderate* symptoms had relevant deficits in quality of life for the *General Health* (d = 0.7) scale, while the subgroup with *mild* symptoms showed no relevant differences in quality of life. In multivariate linear regression models, asthma-like symptoms remained significantly associated with quality of life for the *General Health, Family Activities, Bodily Pain, Parental Time, Temperament and Moods,* and *Parental Emotional* scales.

For the *General Health* and *Family Activities* scales, the risk for low health-related quality of life was three times higher for the subgroup with severe asthma-like symptoms. On the population level, the risks of having low quality of life, was especially high for *Family Activities* and *General Health* (adjusted population attributable risk of 28% and 24%, respectively) indicating for example that 24% of low quality of life for *General Health* can be attributed to the presence of asthma-like symptoms in the first year of life.

All three studies carried out as the third part of this thesis revealed that asthma-related symptoms are associated with multiple dimensions of health-related quality of life in childhood.

In **Chapter 8**, the general discussion, the main findings of this thesis are integrated and interpreted. Although there are important challenges facing researchers who wish to measure both asthma prevalence and health-related quality of life in children, this thesis found that asthma-related symptoms in children have a strong association with their quality of life.

Firstly, the prevalence of asthma among preschool children remains difficult to determine in absence of a gold standard for diagnosis. Both the accuracy and validity of parent-reported symptoms are difficult to establish. When wheezing or shortness of breath among infants was present according to parent reports in self-administered written questionnaires only, the subgroup included a high proportion of infants suffering from other respiratory conditions. When wheezing or shortness of breath among infants was present according to parent reports from the physician interview during a regular free-of-charge consultation only, the subgroup included a high proportion of infants receiving anti-asthma medication. When asthma was present among preschool children according to parent reports during a face-to-face health interview survey, but not in the general practitioner medical records, the subgroup of preschool children more often suffered from other respiratory symptoms.

Secondly, the most important distinction in health-related quality of life questionnaires is between generic and disease-specific instruments. Generic instruments intend to measure all dimensions of quality of life, and can therefore be applied in healthy populations as well as in subpopulations with asthma or asthma

symptoms. Generally, a combination of generic and asthma-specific measurements best evaluate health-related quality of life in asthmatic children, and if possible, a combination of parents and child's self-reports should be evaluated. Preschool children do not have the cognitive ability to complete questionnaires themselves. In absence of an asthma-specific questionnaire for the preschool group, a combination of the ITQOL and TAPQOL likely best describes health-related quality of life in preschool children with asthma-related symptoms. Although the TAPQOL is a generic questionnaire, it has the advantage of including two scales that describe specific aspects of health-related quality of life in asthmatics: *lung problems* and *sleeping*.

Thirdly, asthma-related symptoms are strongly associated with multiple dimensions of health-related quality of life in childhood. Wheezing attacks among adolescents are significantly associated with impaired health-related quality of life for all but one CHQ-CF scales. Wheezing or shortness of breath among preschool children aged 2-48 months are significantly associated with impaired health-related quality of life for the *lung problem*s, *sleeping*, *appetite*, *communication*, and *positive mood* TAPQOL scales. Asthma-like symptoms during the first year of life are significantly associated with impaired health-related quality of life for the *General Health, Family Activities, Bodily Pain, Parental Time, Temperament and Moods,* and *Parental Emotional* ITQOL scales.

We conclude that primary, secondary and tertiary prevention of asthma in early life years of life could improve health-related quality of life in children with asthma. Early detection of asthma in preschool children by physicians and nurses at preventive Child Health Centers and adequate management of asthma-related symptoms by general practitioners could improve health and health-related quality of life in children. Prior to implementation of systematic early detection procedures at preventive Child Health Centers, it is important to know whether it is effective to detect asthma early and consequently reducing asthma-related symptoms and improving health-related quality of life. We have shown that asthma-related symptoms and health-related quality of life can be used as outcome measures for an asthma early detection trial among preschool children. A cluster randomized controlled trial to evaluate the effectiveness of early detection of asthma in preschool children has been designed and implemented within the framework of the Generation R Study.

Samenvatting

Samenvatting

Astma bij kinderen vormt een belangrijk probleem voor de volksgezondheid. In ontwikkelde (geïndustrialiseerde) landen is astma een veel voorkomende chronische aandoening bij kinderen met aanzienlijke morbiditeit, verminderde gezondheidsgerelateerde kwaliteit van leven en substantiële kosten voor de gezondheidszorg. De Wereldgezondheidsorganisatie definieert astma als een chronische ontsteking van de luchtwegen geassocieerd met een verhoogde bronchiale hyperreactiviteit voor een veelheid aan prikkels. Bij gevoelige personen veroorzaakt de luchtwegontsteking terugkerende episodes van piepende ademhaling, kortademigheid, druk op de borst en droge hoest, vooral 's nachts of in de vroege ochtend. Deze symptomen zijn meestal geassocieerd met variabele luchtstroom beperking die ten minste gedeeltelijk omkeerbaar zijn, ofwel spontaan ofwel met behulp van medicatie.

Astma is heterogeen van aard met omkeerbare en variërende kenmerken en symptomen in de tijd. Piepende ademhaling is het meest kenmerkende symptoom. Een diagnose van astma bij schoolgaande kinderen is meestal gebaseerd op de aanwezigheid van symptomen, anamnese, lichamelijk onderzoek en longfunctietesten. Artsen zoeken in het algemeen naar kenmerken van luchtstroom beperking en tevens in hoeverre deze gedeeltelijk omkeerbaar is. Factoren die leiden tot symptomen kunnen aanwezig zijn en gangbare longfunctietesten kunnen de diagnose ondersteunen. Astma kan niet met zekerheid worden vastgesteld bij voorschoolse kinderen. Dit omdat astma zich presenteert met aspecifieke symptomen en het feit dat een kwalitatief goede longfunctietest niet kan worden uitgevoerd op een zo jonge leeftijd. De huidige *evidence-based* richtlijnen van het Nederlandse Huisartsen Genootschap betreffende astma bij kinderen onder de leeftijd van zes jaar zijn derhalve gebaseerd op de aanwezigheid van astma-gerelateerde symptomen gedefinieerd als terugkerende aanvallen van piepende ademhaling. Kortademigheid is veelal afwezig. De diagnose van astma bij voorschoolse kinderen is daardoor beperkt tot astma-achtige symptomen die door ouders of verzorgers worden gemeld.

Bij afwezigheid van systematische opsporing van astma, is het waarschijnlijk dat astma-gerelateerde symptomen ondergediagnosticeerd en onderbehandeld zijn als gevolg van onderrapportage door ouders of verzorgers. Vroegtijdige opsporing en adequate behandeling van astma bij jonge kinderen zou daardoor een direct

gezondheidseffect kunnen hebben. Vroegtijdige opsporing kan de ontwikkeling van longen bevorderen waardoor de frequentie van astma-gerelateerde symptomen kan afnemen en de gezondheidsgerelateerde kwaliteit van leven kan toenemen. Bovendien kan dit effect ook op latere leeftijd zichtbaar zijn. De opgespoorde kinderen kunnen effectief worden behandeld door een pakket van maatregelen waaronder controle door de huisarts, gezondheidsvoorlichting, niet-medicamenteuze interventies (zoals het vermijden van blootstelling aan rook en allergenen) en indien nodig medicamenteuze behandeling met luchtwegverwijdende middelen en/of ontstekingsremmende middelen.

In **hoofdstuk 1,** de inleiding van dit proefschrift, hebben we de volgende hypothesen gesteld: (i) vroegtijdige opsporing en adequate behandeling van astma bij voorschoolse kinderen zal de frequentie van astma-gerelateerde symptomen verminderen onder kinderen, en (ii) afname van de frequentie van astma-gerelateerde symptomen zal de gezondheidsgerelateerde kwaliteit van leven bij kinderen verbeteren. Dit proefschrift heeft als doel de associatie tussen astma-gerelateerde symptomen en gezondheidsgerelateerde kwaliteit van leven bij kinderen te evalueren. Daarnaast evalueren we of astma-gerelateerde symptomen en gezondheidsgerelateerde kwaliteit van leven op een accurate en valide wijze kunnen worden vastgesteld bij voorschoolse kinderen met behulp van *proxy* gegevens. Op die wijze kunnen we uiteindelijk nagaan in hoeverre astma-gerelateerde symptomen en gezondheidsgerelateerde kwaliteit van leven als uitkomstmaten gebruikt kunnen worden in een gerandomiseerde gecontroleerde interventiestudie naar de vroegtijdige opsporing van astma bij voorschoolse kinderen.

Deel I: Metingen van astma-gerelateerde symptomen

Het eerste deel van dit proefschrift beschrijft resultaten van twee studies waarbij de prevalentie van piepende ademhaling of kortademigheid en de prevalentie van astma uit twee verschillende gegevensbronnen worden vergeleken, met speciale aandacht voor de gemeten prevalentie bij voorschoolse kinderen.

In **hoofdstuk 2** wordt prevalentie van astma of COPD uit een gestructureerde mondelinge gezondheidsenquête met patiënten vergeleken met de prevalentie van astma of COPD uit medische dossiers van hun huisartsen. Deze studie maakt deel uit van de tweede Nationale Studie naar ziekten en verrichtingen in de huisartsenpraktijk.

De prevalentie van zelfgerapporteerd astma of COPD (9,7%) was bijna twee keer hoger dan de prevalentie geschat op basis van medische dossiers van huisartsen (5,2%) voor alle leeftijden. De waargenomen overeenstemming was hoog (92%), maar de kappa duidde op een matige overeenstemming (κ = 0,42). Onder voorschoolse kinderen was de prevalentie van ouder-gerapporteerd astma (12,1%) tweemaal de prevalentie geschat op basis van medische dossiers (5,9%). De waargenomen overeenstemming was hoog (89%), maar de kappa was laag (κ = 0,31). Ouders rapporteerden relatief vaker astma bij voorschoolse kinderen met andere luchtwegsymptomen, zoals piepende ademhaling of hoesten. Over-interpretatie van luchtwegsymptomen door ouders bij jonge kinderen is niet ongewoon en kan tenminste deels de hogere prevalentie in de gezondheidsenquête verklaren.
Twee methoden voor het schatten van de prevalentie van astma of COPD leverden verschillende resultaten op: in vergelijking met medische dossiers van hun huisarts toont de zelfgerapporteerde prevalentie een hogere schatting bij patiënten met andere luchtwegaandoeningen en een lagere schatting bij oudere personen die in een rokerige omgeving leven.

In **hoofdstuk 3** werd de prevalentie van ouder-gerapporteerde piepende ademhaling of kortademigheid bij zuigelingen uit schriftelijke vragenlijsten vergeleken met de prevalentie van piepende ademhaling of kortademigheid uit een interview met ouders door de arts tijdens een regulier consult op het consultatiebureau. Deze studie maakt deel uit van de Generation R studie. Het interview door de arts leverde een lagere prevalentie op voor piepende ademhaling of kortademigheid dan de vragenlijsten. De prevalentie van piepende ademhaling of kortademigheid uit vragenlijsten (36%) was significant hoger dan de prevalentie geschat op basis van het interview (20%). Er was beperkte overeenstemming tussen de vragenlijstgegevens en interviewgegevens: waargenomen overeenstemming 70% en kappa 0,36. De overeenstemming was hoger wanneer de zuigeling anti-astma medicatie kreeg, wanneer de zuigeling afwijkende longauscultatie of bronchiolitis of pseudo kroep had, èn wanneer de moeder werkzaam was. Wanneer piepende ademhaling of kortademigheid alleen in de vragenlijst gerapporteerd was, omvatte de subgroep relatief veel zuigelingen met andere luchtwegaandoeningen. Wanneer piepende ademhaling of kortademigheid niet in de vragenlijst gerapporteerd was, maar wel aanwezig was volgens het interview door de arts, omvatte de subgroep relatief veel zuigelingen die anti-astma medicatie kregen of een afwijkende longauscultatie hadden.

Deel II: Metingen van gezondheidsgerelateerde kwaliteit van leven

Het tweede deel van dit proefschrift geeft een overzicht van generieke en ziektespecifieke metingen van kwaliteit van leven bij kinderen. In **hoofdstuk 4** zijn recente studies over de haalbaarheid, betrouwbaarheid en validiteit van gezondheidsgerelateerde kwaliteit van leven vragenlijsten bij kinderen samengevat. Bovendien geeft dit hoofdstuk een overzicht van recente toepassingen van gezondheidsgerelateerde kwaliteit van leven metingen bij kinderen.

Vragenlijsten die kwaliteit van leven meten worden onderverdeeld in generieke vragenlijsten en ziektespecifieke vragenlijsten. Generieke vragenlijsten kunnen alle dimensies van kwaliteit van leven meten en kunnen daardoor zowel worden toegepast bij gezonde populaties als in subpopulaties met astma of astma-gerelateerde symptomen. Over het algemeen zijn generieke vragenlijsten minder gevoelig voor de gevolgen van astma of astma-gerelateerde symptomen op kwaliteit van leven dan ziektespecifieke vragenlijsten.

Twee gevalideerde generieke vragenlijsten, de *TNO-AZL Preschool Children Quality of Life Questionnaire* (TAPQOL) en de *Infant Toddler Quality of Life Questionnaire* (ITQOL) zijn beschikbaar om de gezondheidsgerelateerde kwaliteit van leven bij voorschoolse kinderen te meten. De ITQOL is gevalideerd in een steekproef van de algemene populatie en in een subpopulatie met luchtwegaandoeningen in Nederland. Voor het merendeel van de ITQOL schalen werd onderscheid gemaakt tussen voorschoolse kinderen met weinig en veel ouder-gerapporteerde chronische aandoeningen, tussen voorschoolse kinderen met en zonder artsgediagnosticeerde luchtwegaandoeningen en tussen voorschoolse kinderen met lage en hoge ouder-gerapporteerde medische consumptie. De TAPQOL maakt onderscheid tussen voorschoolse kinderen met en zonder ouder-gerapporteerde chronische aandoeningen voor de volgende schalen: *slapen*, *eetlust*, *longproblemen*, *huidproblemen* en *motorisch functioneren*. Vergeleken met zuigelingen van 2-12 maanden zonder ouder-gerapporteerde chronische aandoeningen, hadden zuigelingen van 2-12 maanden met minimaal twee ouder-gerapporteerde chronische aandoeningen, relevante verschillen in kwaliteit van leven voor *slapen* (d = 1,5), *longproblemen* (d = 2,2) en *huidproblemen* (d = 0,8). Peuters van 13-48 maanden oud met minimaal twee ouder-gerapporteerde chronische aandoeningen hadden in vergelijking met peuters van 13-48 maanden zonder ouder-gerapporteerde

chronische aandoeningen, relevante verschillen in kwaliteit van leven voor *longproblemen* (d = 0,9) en *huidproblemen* (d = 0,8). Uit deze studie bleek tevens dat de TAPQOL, oorspronkelijk ontwikkeld voor kinderen vanaf één jaar, ook haalbaar en betrouwbaar is voor zuigelingen van 2-12 maanden.

Deel III: De associatie tussen astma-gerelateerde symptomen en gezondheidsgerelateerde kwaliteit van leven

Het derde deel van dit proefschrift presenteert drie studies die de associatie tussen astma-gerelateerde symptomen en gezondheidsgerelateerde kwaliteit van leven bij kinderen bestuderen, waarbij speciale aandacht uitgaat naar de gezondheidsgerelateerde kwaliteit van leven bij voorschoolse kinderen met astma-gerelateerde symptomen.

Hoofdstuk 5 evalueert de gezondheidsgerelateerde kwaliteit van leven bij adolescenten met aanvallen van piepende ademhaling op basis van zelfgerapporteerde gegevens. De *Child Health Questionnaire-Child Form* (CHQ-CF) werd gebruikt om gezondheidsgerelateerde kwaliteit van leven te meten. De frequentie van aanvallen van piepende ademhaling werd vastgesteld op basis van vragen geselecteerd uit de *International Studies of Asthma and Allergies in Childhood*. Vergeleken met de subgroep adolescenten zonder piepende ademhaling, hadden de subgroepen adolescenten met aanvallen van piepende ademhaling, significant lagere kwaliteit van leven scores op negen van de 10 CHQ-CF schalen. Behalve op de *Role Physical* en *Family Activities* schalen, werden relevante verschillen in kwaliteit van leven waargenomen op alle schalen onder adolescenten met minimaal vier aanvallen van piepende ademhaling in het afgelopen jaar. De grootste verschillen werden gevonden op de schalen *Bodily Pain* (d = 1,2), *General Health* (d = 0,9), *Self Esteem* (d = 0,8) en *Mental Health* (d = 0,8).

In multivariate lineaire regressiemodellen, gecorrigeerd voor karakteristieken van adolescenten en comorbiditeit bleven aanvallen van piepende ademhaling significant geassocieerd met kwaliteit van leven in negen van de 10 CHQ-CF schalen. Uit deze studie bleek dat aanvallen van piepende ademhaling geassocieerd zijn met vele dimensies van gezondheidsgerelateerde kwaliteit van leven bij adolescenten, met name onder adolescenten met minimaal vier aanvallen van piepende ademhaling in het afgelopen jaar.

Hoofdstuk 6 evalueert de gezondheidsgerelateerde kwaliteit van leven bij voorschoolse kinderen van 2-48 maanden, met piepende ademhaling of kortademigheid in een aselecte steekproef van de algemene bevolking in Nederland. De TAPQOL werd gebruikt om kwaliteit van leven te meten. Vergeleken met de subgroep voorschoolse kinderen zonder piepende ademhaling en kortademigheid, hadden de subgroepen voorschoolse kinderen met piepende ademhaling of kortademigheid significant lagere kwaliteit van leven scores voor verschillende TAPQOL schalen. Relevante verschillen in kwaliteit van leven tussen de subgroep met versus zonder piepende ademhaling en kortademigheid werden waargenomen voor *longproblemen* (d = 2,1) en *slapen* (d = 0,8). Voor de subgroep met òf piepende ademhaling òf kortademigheid werd een relevant verschil in kwaliteit van leven waargenomen voor *longproblemen* (d = 0,9).
In multivariate lineaire regressiemodellen, gecorrigeerd voor leeftijd en geslacht van het kind, bleven piepende ademhaling en kortademigheid significant geassocieerd met kwaliteit van leven voor *longproblemen*, *slapen*, *eetlust*, *communicatie* en *positieve stemming*. Deze studie toonde aan dat de gezondheidsgerelateerde kwaliteit van leven bij voorschoolse kinderen met piepende ademhaling en kortademigheid verminderd is, vooral onder diegenen met beide symptomen. Ongeacht de ernst van de symptomen laten de TAPQOL schalen die de lichamelijke gezondheid meten, significant lagere scores zien.

Hoofdstuk 7 evalueert de gezondheidsgerelateerde kwaliteit van leven op de leeftijd van 12 maanden bij zuigelingen met astma-achtige symptomen in het eerste levensjaar. Deze studie maakt deel uit van de Generation R studie. De ITQOL werd gebruikt om kwaliteit van leven te meten. Subgroepen kinderen met astma-achtige symptomen, zoals piepende ademhaling, kortademigheid, nachtelijk hoesten zonder verkoudheid en druk op de borst, hadden significant lagere kwaliteit van leven scores voor alle ITQOL schalen vergeleken met de subgroep zonder deze symptomen. Met uitzondering van de schalen *Family Cohesion* en *Physical Functioning*, waren relevante verschillen in kwaliteit van leven waarneembaar voor alle ITQOL schalen bij de subgroep met *ernstige* astma-achtige symptomen, met name voor *General Health* (d = 1,2), *Bodily Pain* (d = 0,9) en *Family Activities* (d = 0,8). De subgroep kinderen met *matige* symptomen had relevante verschillen in kwaliteit van leven voor *General Health* (d = 0,7), terwijl de subgroep met *milde* symptomen geen relevante verschillen in kwaliteit van leven vertoonde.

In multivariate lineaire regressiemodellen, gecorrigeerd voor diverse karakteristieken van kind en moeder, bleven astma-achtige symptomen significant geassocieerd met kwaliteit van leven voor de schalen *General Health*, *Family Activities*, *Bodily Pain*, *Parental Time*, *Temperament and Moods* en *Parental Emotional*.

Voor de schalen *General Health* en *Family Activities* was het risico op lage gezondheidsgerelateerde kwaliteit van leven drie keer hoger voor de subgroep met *ernstige* astma-achtige symptomen. Op populatieniveau is het risico op verminderde kwaliteit van leven vooral hoog voor *Family Activities* en *General Health* (gecorrigeerde populatie attributieve risico van respectievelijk 28% en 24%). Dit betekent dat één op de vier zuigelingen volgens hun ouders een geringe algemene gezondheid heeft ten gevolge van astma-achtige symptomen in het eerste levensjaar. Tevens wordt bij één op de vier zuigelingen volgens hun ouders de familieactiviteiten verstoord ten gevolge van astma-achtige symptomen in het eerste levensjaar.

Resultaten van het derde deel van dit proefschrift tonen aan dat astma-gerelateerde symptomen geassocieerd zijn met multipele dimensies van gezondheidsgerelateerde kwaliteit van leven bij kinderen.

In **hoofdstuk 8**, de algemene discussie, zijn de belangrijkste bevindingen van dit proefschrift geïntegreerd en geïnterpreteerd.
Ten eerste, is de prevalentie van astma bij voorschoolse kinderen moeilijk vast te stellen bij afwezigheid van een gouden standaard voor de diagnose. Zowel de betrouwbaarheid als validiteit van ouder-gerapporteerde symptomen zijn moeilijk vast te stellen. Wanneer piepende ademhaling of kortademigheid bij zuigelingen alleen aanwezig was volgens ouder-gerapporteerde gegevens in schriftelijke vragenlijsten, bestond de subgroep uit relatief veel zuigelingen met andere luchtwegaandoeningen. Wanneer piepende ademhaling of kortademigheid bij zuigelingen alleen door de arts gerapporteerd was uit het interview met ouders tijdens een regulier consult op het consultatiebureau, omvatte de subgroep relatief veel zuigelingen die anti-astma medicatie kreeg of een afwijkende longauscultatie had.

Ten tweede, het belangrijkste onderscheid in kwaliteit van leven vragenlijsten is tussen generieke en ziektespecifieke instrumenten. Generieke instrumenten kunnen alle dimensies van kwaliteit van leven meten en kunnen daardoor toegepast worden

bij zowel gezonde populaties als bij subpopulaties met astma of astma-gerelateerde symptomen. De gezondheidsgerelateerde kwaliteit van leven bij astmatische kinderen kan het beste geëvalueerd worden door een combinatie van generieke en astmaspecifieke metingen, en indien mogelijk, zou een combinatie van door ouders gerapporteerde en zelfgerapporteerde gegevens van het kind geëvalueerd moeten worden. Voorschoolse kinderen hebben niet het cognitieve vermogen om vragenlijsten zelf in te vullen. Bij afwezigheid van een astmaspecifieke vragenlijst voor de voorschoolse groep, is een combinatie van de ITQOL en TAPQOL waarschijnlijk het beste voor het beschrijven van gezondheidsgerelateerde kwaliteit van leven bij voorschoolse kinderen met astma-gerelateerde symptomen. De TAPQOL heeft het voordeel dat het twee schalen omvat die specifieke aspecten van kwaliteit van leven bij astmapatiënten beschrijft, namelijk *longproblemen* en *slapen*.

Ten derde, astma-gerelateerde symptomen zijn sterk geassocieerd met verschillende dimensies van gezondheidsgerelateerde kwaliteit van leven bij kinderen. Aanvallen van piepende ademhaling onder adolescenten zijn significant geassocieerd met verminderde gezondheidsgerelateerde kwaliteit van leven voor negen van de 10 CHQ-CF schalen. Piepende ademhaling of kortademigheid bij voorschoolse kinderen van 2-48 maanden zijn significant geassocieerd met verminderde gezondheidsgerelateerde kwaliteit van leven voor de TAPQOL schalen *longproblemen*, *slaap*, *eetlust*, *communicatie* en *positieve stemming*. Astma-achtige symptomen gedurende het eerste levensjaar zijn significant geassocieerd met verminderde gezondheidsgerelateerde kwaliteit van leven voor de ITQOL schalen *General Health*, *Family Activities*, *Bodily Pain*, *Parental Time*, *Temperament and Moods* en *Parental Emotional.*

We concluderen dat strategieën voor verbetering van de gezondheidsgerelateerde kwaliteit van leven bij kinderen met astma zowel primaire, secundaire en tertiaire preventie van astma in de eerste levensjaren moeten omvatten. Vroegtijdige opsporing van astma bij voorschoolse kinderen door artsen en verpleegkundigen van consultatiebureaus en het adequaat monitoren van astma-gerelateerde symptomen door huisartsen zou mogelijkerwijs tot verbetering kunnen leiden van de gezondheid en de gezondheidsgerelateerde kwaliteit van leven bij kinderen. Voorafgaand aan de invoering van systematische vroegtijdige opsporing van astma bij de consultatiebureaus, is het belangrijk te weten of het effectief is om astma vroegtijdig

op te sporen om zodoende vermindering van astma-gerelateerde symptomen en verbetering van de gezondheidsgerelateerde kwaliteit van leven te bewerkstelligen. We hebben aangetoond dat astma-gerelateerde symptomen en de gezondheidsgerelateerde kwaliteit van leven als uitkomstmaten gebruikt kunnen worden in een interventiestudie naar de vroegtijdige opsporing van astma bij voorschoolse kinderen. Een cluster gerandomiseerde gecontroleerde interventiestudie is ontwikkeld en geïmplementeerd om de effectiviteit van vroegtijdige opsporing van astma bij voorschoolse kinderen te evalueren. Deze interventiestudie maakt deel uit van de Rotterdamse kindercohort studie Generation R.

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Dankwoord

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Over de auteur

Over de auteur

Ashna Mohangoo is op 31 januari 1971 geboren te Wageningen in het District Nickerie in Suriname als dochter van Parmanand Mohangoo en Siromanie Mohangoo-Birdja en zusje van Dewin.

In 1989 behaalde zij het VWO diploma aan de Algemene Middelbare School in Paramaribo, Suriname. In hetzelfde jaar startte zij de opleiding Geneeskunde aan de Anton de Kom Universiteit van Suriname en behaalde in 1995 het doctoraal diploma. Tijdens haar medische opleiding werkte ze als assistent op de afdeling Histologie van de Faculteit der Medische Wetenschappen. Van 1996 tot 2000 werkte zij als wetenschappelijk medewerker aan de Faculteit der Medische Wetenschappen van de Anton de Kom Universiteit van Suriname en als docente Histologie bij de Stichting Jeugdtandverzorging in Paramaribo, Suriname.

In januari 2001 startte zij met de postdoctorale opleiding Epidemiologie aan het Instituut voor Extramuraal Geneeskundig Onderzoek (EMGO Instituut) van de Vrije Universiteit van Amsterdam en behaalde het diploma in juni 2002. Van oktober 2002 tot april 2003 werkte ze als junior onderzoeker bij het Nederlands Instituut voor Onderzoek in de Gezondheidszorg (NIVEL) in Utrecht onder begeleiding van prof.dr. F.G. Schellevis en dr. M.W. van der Linden.

Van april 2003 tot april 2007 is zij als onderzoeker verbonden geweest aan de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC, Universitair Medisch Centrum Rotterdam. Binnen de Generation R studie zette zij een gerandomiseerde gecontroleerde interventiestudie op naar de vroegtijdige opsporing van astma bij voorschoolse kinderen (begeleiders prof.dr. H.J. de Koning en dr. H. Raat). In augustus 2004 startte zij met de *Master of Public Health* opleiding aan de *Netherlands Institute for Health Sciences* (Nihes) in Rotterdam en behaalde het diploma in juni 2005.

Sinds juli 2007 is zij werkzaam als epidemioloog bij TNO Kwaliteit van Leven, Preventie en Zorg, afdeling Jeugd (hoofd dr. S.B. Detmar). Binnen de sector Verloskunde en Kraamzorg, voorheen Voortplanting en Perinatologie, werkt ze nauw samen met prof.dr. S.E. Buitendijk. Zij is onder andere als projectleider betrokken bij het monitoren van aangeboren afwijkingen in Nederland en het Euro-Peristat project. Zij is lid van de Euro-Peristat stuurgroep en van de door het Ministerie van Volksgezondheid, Welzijn en Sport ingestelde Commissie Registratie Aangeboren Afwijkingen.

Ashna Mohangoo is getrouwd met Danny Sukdeo.

About the Author

About the Author

Ashna Mohangoo is born on 31st of January 1971 at Wageningen in the District Nickerie of Surinam as daughter of Parmanand Mohangoo and Siromanie Mohangoo-Birdja and as sister of Dewin.

In 1989 she graduated from high school (*Algemene Middelbare School*) in Paramaribo, Surinam. In the same year she started her medical training at the Anton de Kom University of Surinam and obtained her doctoral degree in 1995. During her medical training she worked as an assistant in the Department of Histology of the Faculty of Medical Sciences. From 1996 to 2000 she worked as scientific staff member at the Faculty of Medical Sciences of the Anton de Kom University of Surinam and she also taught Histology at the *Opleiding voor Jeugdtandverzorging* (Training for Youth Dental Care) in Paramaribo, Surinam.

In January 2001 she started with the Postgraduate Epidemiology Program at the Institute for Research in Extramural Medicine (EMGO Institute) of the VU University of Amsterdam and obtained her diploma in June 2002. From October 2002 to April 2003 she worked as a junior researcher at the Netherlands Institute for Health Services Research (NIVEL) in Utrecht. Her supervisors were prof.dr. F.G. Schellevis and dr. M.W. van der Linden.

From April 2003 to April 2007 she worked as a researcher at the department of Public Health of the Erasmus MC, University Medical Center Rotterdam. Within the framework of the prospective child cohort study Generation R she set up a randomized controlled trial on early detection of asthma in preschool children (supervisors prof.dr. H.J. de Koning and dr. H. Raat). In August 2004 she started the Master of Public Health training at the Netherlands Institute for Health Sciences (Nihes) in Rotterdam and obtained her diploma in June 2005.

Since July 2007 she is employed as an epidemiologist at TNO Quality of Life, Prevention and Care, department Youth (head dr. S.B. Detmar). Within the section Maternal and Child Health, formerly Reproduction and Perinatology, she works with prof.dr. S.E. Buitendijk on several projects including monitoring congenital anomalies in the Netherlands and the Euro-Peristat project. She is a member of the Commission for Registration of Congenital Anomalies, established by the Ministry of Health, Welfare and Sports in the Netherlands. She is also member of the Euro-Peristat Steering Committee.

Ashna Mohangoo is married with Danny Sukdeo.

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- Mohangoo AD, de Koning HJ, Hafkamp-de Groen E, van der Wouden JC, Jaddoe VWV, Moll HA, Hofman A, Mackenbach JP, de Jongste JC, Raat H. A Comparison of Parent-Reported Wheezing or Shortness of Breath among Infants as Assessed by Questionnaire and Physician Interview: the Generation R Study. *Submitted*.
- Gissler M, Mohangoo AD, Blondel B, Chalmers J, Gaizauskiene A, Gatt M, Lack N, MacFarlane A, Sakkeus L, Zeitlin J. Challenges of Perinatal Health Monitoring in Europe: Results from the Euro-Peristat Project. *Submitted.*
- Van Dommelen P* and Mohangoo AD*, Verkerk PW, van der Ploeg CPB, van Straaten HLM. Risk Factors for Hearing Loss among Infants Treated in Neonatal Intensive Care Units. *Submitted.* *Both authors equally contributed.

PhD Portfolio

PhD Portfolio

Name PhD student: Ashna D. Mohangoo	PhD period: April 2003 - April 2007
Erasmus MC Department: Public Health/the Generation R Study	Promotor: H.J. (Harry) de Koning
Research school: Netherlands Institute for Health Sciences (Nihes)	Supervisor: Hein Raat

PhD training

	Year	Workload
Master of Public Health training at the Nihes	2004-2005	
Research skills: General courses at the Nihes		
Principles of Research in Medicine and Epidemiology	2004	40 hours
Methods of Public Health Research	2004	24 hours
Topics in Evidence-Based Medicine	2004	24 hours
Introduction to Public Health in the Changing Global Context	2004	24 hours
Methods of Health Services Research	2004	24 hours
Prevention Research	2004	24 hours
Study Design	2004	64 hours
Classical Methods for Data-analysis	2004	96 hours
Principles of Epidemiologic Data-Analysis	2005	40 hours
Modern Statistical Methods	2005	64 hours
Research skills: Specific courses at the Nihes		
Planning and Evaluation of Screening	2003	40 hours
Public Health Research: Analysis of Population Health	2004	32 hours
Public Health Research: Analysis of Determinants	2004	32 hours
Public Health Research: Intervention Development and Evaluation	2004	32 hours
International Health System Comparison	2004	32 hours
Maternal and Child Health	2005	24 hours
Health Status Measurement	2005	24 hours
Research skills: Other courses at the Nihes		
Discussion Meeting Research Proposal	2005	8 hours
Site visit to Municipal Health Service in Rotterdam	2005	8 hours
Integration Module	2005	8 hours
Seminars and workshops		
Attending Seminars at the Department of Public Health	2003-2007	140 hours
Attending Generation R Research Meetings	2003-2007	140 hours
Attending Lunch Meetings at the Department of Epidemiology	2003-2007	40 hours
Workshop Gezondheidsgerelateerde kwaliteit van Leven bij kinderen in de praktijk en onderzoek van de kindergeneeskunde, huisartsgeneeskunde en de jeugdgezondheidszorg. Rotterdam, the Netherlands. June 24, 2003.	2003	8 hours
Workshop Ondersteuning van de jeugdgezondheidszorg door internetgestuurde gezondheidsbevordering bij adolescenten. Rotterdam, the Netherlands. November 6, 2003.	2003	8 hours
Workshop Health-Related Quality of Life in Children and Youth. Prague, Czech Republic. November 12, 2003.	2003	4 hours

Workshop Evaluating Changes in Health-Related Quality of Life Measures. Prague, Czech Republic. November 12, 2003.	2003	4 hours
Seminar Evidence Based JGZ 0-19 Jaar. Rotterdam, the Netherlands. February 13, 2006.	2006	8 hours
Presentations		
A Randomized Controlled Trial for Early Detection of Asthma-Related Symptoms in Preschool Children at Preventive Child Health Centers: Study Design. *Generation R Research Meeting.* Rotterdam, the Netherlands. October 9, 2003.	2003	16 hours
The Impact of Wheezing and Dyspnea on Health-Related Quality of Life in a Random General Population Sample of Preschool Children. *10th Annual Conference of the International Society for Quality of Life Research (ISOQOL).* Prague, Czech Republic. November 13, 2003.	2003	24 hours
A Randomized Controlled Trial for Early Detection of Asthma-Related Symptoms in Preschool Children at Preventive Child Health Centers: First Results. *Discipline Meeting Consultatiebureau Ouder en Kind (OEK).* Rotterdam, the Netherlands. November 14, 2005.	2005	16 hours
A Randomized Controlled Trial for Early Detection of Asthma-Related Symptoms in Preschool Children at Preventive Child Health Centers in the Generation R Study: Study Design and Preliminary Results. *Landelijke Retraite van de Werkgemeenschap Jeugd en Gezondheid.* Soesterberg, the Netherlands. January 21, 2006.	2006	8 hours
A Randomized Controlled Trial for Early Detection of Asthma-Related Symptoms in Preschool Children at Preventive Child Health Centers in the Generation R Study: Study Design and Preliminary Results. *Klankbordgroep Zorg Meeting.* Rotterdam, the Netherlands. March 27, 2006.	2006	8 hours
A Randomized Controlled Trial for Early Detection of Asthma-Related Symptoms in Preschool Children at Preventive Child Health Centers: Study Design and Preliminary Results. *Generation R Research Meeting.* Rotterdam, the Netherlands. June 27, 2006.	2006	8 hours
Asthma-Related Symptoms and Health-Related Quality of Life in Infants: the Generation R Study. *Landelijke Retraite van de Werkgemeenschap Jeugd en Gezondheid.* Soesterberg, the Netherlands. January 20, 2007.	2007	8 hours
A Comparison of Wheezing and Shortness of Breath as Assessed by Questionnaire and Physician Interview: the Generation R Study. *Generation R Research Meeting.* Rotterdam, the Netherlands. May 23, 2007.	2007	8 hours
Asthma-Related Symptoms and Health-Related Quality of Life in Infants: the Generation R Study. *Generation R Research Meeting*. Rotterdam, the Netherlands. May 23, 2007.	2007	8 hours

A Randomized Controlled Trial for Early Detection of Asthma-Related Symptoms in Preschool Children at Preventive Child Health Centers: Study Design and Preliminary Results*. TNO Quality of Life. Department Youth Meeting.* Leiden, the Netherlands. January 8, 2008.	2008	8 hours
A Comparison of Wheezing and Shortness of Breath as Assessed by Questionnaire and Physician Interview: the Generation R Study. *Retraite Landelijk Netwerk Onderzoek Jeugd & Gezondheid.* Soesterberg, the Netherlands. January 16, 2009.	2009	8 hours
Conferences		
10th Annual Conference of the International Society for Quality of Life (ISOQOL) Research. Prague, Czech Republic. November 12-15, 2003.	2003	36 hours
Landelijke Retraite van de Werkgemeenschap Jeugd en Gezondheid. Soesterberg, the Netherlands. January 21-22, 2006.	2006	16 hours
Landelijke Retraite van de Werkgemeenschap Jeugd en Gezondheid. Soesterberg, the Netherlands. January 20, 2007.	2007	12 hours
Joint Meeting of the Society for Social Medicine and the International Epidemiological Association: SSM/IEA Conference. Cork, Ireland. September 12-14, 2007.	2007	32 hours
Retraite Landelijk Netwerk Onderzoek Jeugd & Gezondheid. Soesterberg, the Netherlands. January 16, 2009.	2009	12 hours
Abstracts		
Measuring the Prevalence of Asthma and COPD by Self-Report or from Routine General Practice Care: What's the Difference? *11th Annual EUPHA Conference.* Rome, Italy. November 20-22, 2003.	2003	8 hours
Comparison of the Infant and Toddler Quality of Life Questionnaire (ITQOL) and the TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL). *13th Annual Conference of the International Society for Quality of Life (ISOQOL) Research.* Lisbon, Portugal. October 10-14, 2006.	2006	8 hours
The Association between Smoking Status and Health-Related Quality of Life in a Population of Adolescents (13-17 years) as Measured by the Child Health Questionnaire (CHQ-CF87). *14th Annual Conference of the International Society for Quality of Life (ISOQOL) Research.* Toronto, Canada. October 10-13, 2007.	2007	8 hours
Asthma-Related Symptoms in the First Year of Life and Health-Related Quality of Life at Age Twelve Months: the Generation R Study. *15th Annual Conference of the International Society for Quality of Life (ISOQOL) Research.* Montevideo, Uruguay. October 22-25, 2008.	2008	8 hours