Asthma and physical activity in childhood

ASTHMA AND PHYSICAL ACTIVITY IN CHILDHOOD

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Chapter 1

General introduction

General introduction

This thesis is aimed to look into asthma and physical activity in childhood. In this general introduction we will focus on the background, pathophysiology and development of asthma, followed by the background of physical activity and its measurement. The link between asthma and physical activity will be elaborated, complemented with the role of other possible risk factors, such as obesity.

Asthma

Background

Asthma is one of the most common chronic illnesses in childhood. More than 330 million people worldwide suffer from this breathtaking disease.[1] In the last decades of the twentieth century, a steep increase in asthma prevalence was observed, which stabilised around the change of the century (Figure 1.1). Valuable epidemiological information on global childhood asthma prevalence has been gathered since the nineties by the International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Phase I (1993-95), repeated in Phase III (2001-03) identified that the prevalence of asthma symptoms in school-aged children was rising in especially low-income and middle-income countries.[2] The Global Asthma Network (GAN) continued the global surveillance of asthma prevalence in GAN Phase I (2015-20), and showed that about one in ten children had asthma symptoms, of whom almost half had severe symptoms.

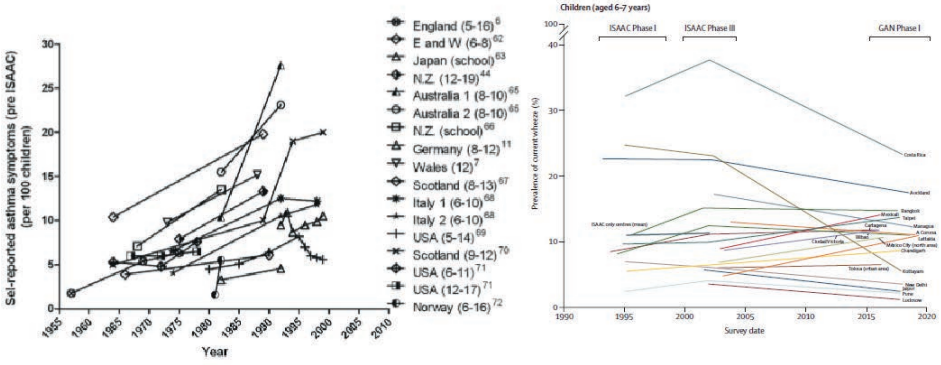

Figure 1.1: Change over time in prevalence of asthma symptoms in childhood. Left: survey date ranging from 1955 to 2000 reported by different questionnaires pre-ISAAC. Right: survey date ranging from 1995 to 2020 reported by uniform questionnaires in ISAAC phase I, phase III and GAN Phase I. (adapted from Chawla et al, Pediatric Pulmonology 2012 (left) and Asher et al, Lancet 2021 (right)).

Asthma has a rich history. Already in ancient Chinese and Egyptian scriptures symptoms of breathlessness and respiratory distress were mentioned.[3] The word 'asthma' is

probably derived from the ancient Greek *α'ιω* meaning 'to blow'. Homerus used the word *άσθμα* to describe severe breathlessness of his mythological heroes in the Ilias, around 800 before Christ. It was not before 400 years later, that Hippocrates used the term asthma to describe a condition of laboured breathing and noticed a seasonal relation to autumn.[4] Nowadays, asthma is defined as a disease "characterized by recurrent attacks of breathlessness and wheezing" (World Health Organization, WHO).[1] The Global Initiative for Asthma (GINA) describes asthma as "a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation".[5]

Asthma pathophysiology

Asthma pathophysiology consists of two key components: (1) airway hyperresponsiveness and (2) inflammation. Both mechanisms lead to narrowing of the airway, which causes shortness of breath. Airway hyperresponsiveness is an exaggerated bronchoconstrictor response, due to different stimuli. In childhood, the vast majority of asthma consists of allergic asthma, caused by inhalation allergens.[6] In allergic asthma sensitization of IgE antibodies to environmental triggers (such as dust, house mite, pollen) plays an important role. These IgE antibodies bind to mast cells and basophils, which in case of inhalation of the environmental trigger, release cytokines such as histamine, prostaglandins, and leukotrienes. These cytokines contract the smooth muscle and cause airway tightening. T helper (Th)2 lymphocytes produce several interleukins (IL-4, IL-5, IL-13), which promote inflammation. IL-13 contributes to remodelling, fibrosis, and hyperplasia. Within hours after the start of an asthma exacerbation, eosinophils, basophils, neutrophils, and helper and memory T-cells direct to the lungs, and lead to bronchoconstriction and ongoing inflammation. All of these mechanisms together change the compliance of the lungs slightly to increase the work of breathing, eventually leading to airway remodelling.[7]

Asthma development

Asthma has a multifactorial origin and is caused by a complex combination of genetic and environmental factors.[8] Children with positive family history of asthma have a 2 to 3 times higher chance to develop asthma.[9] Genetic studies showed that no single gene can be held responsible for this genetic susceptibility. More than hundred different genes have been associated with asthma. Asthma is considered a polygenic disease in which many genetic variants determine small changes in the immune response or airway responsiveness to the environment.[10,11] Asthma seems to develop as a result of environmental exposures in genetic susceptible individuals.[12] Environmental factors that are identified[13] are for example exposure to tobacco smoke,[14] air pollution such as

traffic pollution[15], open fire cooking,[16] residential exposure to dampness and moulds,[17] antibiotic use early in life,[18] exposure to viral infections (especially hospitalization for respiratory syncytial virus (RSV) infection),[19] and fast food intake.[20] Possible protective factors are fresh fruit and vegetable intake,[20] living in a farm environment,[21] and breastfeeding.[22] Lifestyle factors are important to identify, because these are potentially modifiable.

Physical activity

Background

"The exercise boom is not just a fad; it is a return to 'natural' activity – the kind for which our bodies are engineered and which facilitates the proper function of our biochemistry and physiology. Viewed through the perspective of evolutionary time, sedentary existence, possible for great numbers of people only during the last century, represents a transient, unnatural aberration." (Eaton, Shostak, Konner 1988, p. 168)[23]

In prehistoric times physical activity played an important role in everyday life, not only as necessity for survival, but as integral component of religious, social, and cultural expression.[24] The ancient Greeks knew the importance of physical activity and viewed great athletic achievement as representing both spiritual and physical strength rivalling that of the gods, reflected in the classical Olympic Games.[25] The Greek physicians Herodicus (around 480 BC) and later Hippocrates (around 460 BC) already propagated the health benefits of physical activity. Much later, in the 16th century, sedentary behaviour was described to be associated with disease. The English physician Thomas Cogan (The Haven of Health, 1584) observed that sedentary people appeared to suffer from more maladies than active people. From the 19th century more attention was spent on physical education, which was not only focused on exercise, but also bathing, fresh air, among other topics.[24] Since the middle of the 20th century the first recommendations for physical activity to achieve health benefits occurred, leading to the current World Health Organization's Global Recommendations for Physical Activity and Sedentary Behaviour. The most recent recommendations (WHO, 2020) state that children should participate in moderate-to-vigorous physical activity (MVPA) for at least 60 minutes per day on average.[26] Physical activity has been associated with multiple beneficial health outcomes, such as cardiorespiratory fitness, muscular fitness, bone health, cardiometabolic health, and mental health.[27]

Children have become less active during the past decades: global trend studies showed that active transportation, organised sports, and physical education lessons at school have declined since the second half of the twentieth century.[28] Overall physical activity, as measured by motion sensors, has declined further in the last 20 years, both in adults

and in children, especially in adolescents.[29] Worldwide, fewer than 20% of all adolescents met the WHO recommendations for physical activity in 2016.[30]
It is important to realise that sedentary behaviour is not merely the absence of physical activity.[31] Sedentary behaviour is defined as activities with an energy expenditure of ≤1.5 MET (metabolic equivalent of a task) during wake time, while in sitting, reclining of lying posture. Sedentary behaviour in high doses (i.e. more than 6 to 8 hours per day during wake time) is shown to be associated with an increased long term mortality risk.[32] On the other hand, physical inactivity is usually defined as not meeting the WHO global recommendations on physical activity. In theory, it is possible that a person meets the physical activity recommendations while also engaging in sedentary behaviour during a large part of the day.

Measuring physical activity

Habitual physical activity is difficult to quantify because it consists of a complex set of behaviours. The nature of (especially young) children makes their activity patterns highly variable, sporadic and omnidirectional.[33] In epidemiological studies, physical activity is most often measured via questionnaires. Proxy measurements may be useful in measuring physical activity patterns in childhood. Time spent outdoors seems to be strongly predictive of physical activity level in children.[34] Involvement in community sports programs may also be a useful proxy measurement.[33] A few validated questionnaires are available, such as the Physical Activity Questionnaire (PAQ), which is developed in paediatric version (PAQ-C Physical Activity Questionnaire for children) and adolescent version (PAQ-A Physical Activity Questionnaire for adolescents). Validity studies on these questionnaires found contrasting results, varying from good reliability with moderate validity to acceptable/good reliability and validity.[35-37] Recently, a large systematic review assessed all available questionnaires on childhood physical activity and judged that none of the included questionnaires had conclusive evidence for both acceptable validity and reliability.[38]

A possible alternative for questionnaires is direct monitoring of physical activity levels through behavioural observation, physiological measurements (such as direct and indirect calorimetry, doubly labelled water in order to calculate the energy expenditure), or electronical devices (such as motion sensors). Most of these options are limited by their high costs and are time consuming, and therefore not suited for large scale epidemiological studies. Motion sensors (i.e. pedometer or accelerometer) are relatively affordable and can be used in larger epidemiological studies. The most important advantage of accelerometry over questionnaires in children is the ability to quantify the frequent bursts of activity that (young) children tend to show. It has been shown that accelerometry data are strongly correlated with energy expenditure.[39] Moreover, objective measurements are not subject to reporting bias or recall bias that can be associated with parent reported data. An important disadvantage of using

accelerometry is that it usually measures a relatively short period in time (e.g. 3 days or 1 week), while it is known that activity patterns change over time, for example due to weather or seasonal influences.[40] Moreover, most accelerometers tend to underreport physical activity during bicycling and cannot be worn during swimming. It has been suggested to combine the questionnaire based data with objectively measured data to get a more comprehensive description of children's activity patterns.[41]

Asthma and physical activity

Earlier studies have suggested that individuals with asthma are less physically active compared to those without asthma, both in adulthood[42,43] and in childhood.[44] Several explanations are possible: especially vigorous physical activity is a known trigger for asthma symptoms,[45] and can cause exercise induced bronchoconstriction, a distinct form of bronchial hyperresponsiveness defined as acute, transient narrowing of the airways during exercise.[46] Children with exercise induced bronchoconstriction show less habitual physical activity compared to asthmatic children without this feature.[47] Besides this, other environmental triggers that play a role when exercising (such as cold air, pollen, traffic pollutants) can induce an asthma exacerbation.[48] Whether asthma is well controlled (for example by medication) plays an important role in physical activity levels in asthmatics.[49] Poorly controlled asthma may result in exercise intolerance and fear of asthma symptoms.[50] Sometimes, parents restrict their asthmatic children in being physically active because of their fear of an asthma exacerbation.[51] Children with low physical fitness are more prone to experience symptoms of breathlessness, that can be misinterpreted as asthma symptoms.[52]

Asthma organisations all around the world (e.g. Longfonds,[53] Asthma UK,[54] American Lung Association[55]) promote children with asthma to engage in normal physical activity levels. Physical activity is believed to improve asthma control,[56] due to improving cardiorespiratory fitness, helping to maintain a healthy weight, and improving mental health status which in turn can improve asthma control.[54] Exercise training programs for individuals with asthma are described to improve asthma control and lung function.[57-59]

While the link between asthma influencing physical activity has prevailed for a long time, more recently the hypothesis evolved that physical activity might protect against asthma development, possibly through immunological factors: exercise training has proven systemic anti-inflammatory effects,[60,61] while airway inflammation is a known principal feature of asthma. Increased habitual physical activity in daily life was found to be associated with lower systemic inflammation in patients with severe asthma, although no association with eosinophilic airway inflammation was found.[62] In animal

studies, aerobic exercise was shown to decrease eosinophilic airway inflammation and airway modelling.[63-66]

Asthma and obesity

The link between asthma and obesity has been studied extensively in the last decades. In 1999, Camargo et al.[67] was one of the first to describe obesity as a risk factor for developing asthma in adult women. Since then numerous studies have demonstrated a relation between obesity and asthma, in adults as well as in children.[68-71] Cross-sectional studies have consistently showed that asthmatics are more often obese than their non-asthmatic peers.[72,73] Longitudinal studies have found that obesity is an independent risk factor for developing asthma: obese children have a 30-50% higher risk of developing asthma.[74,75] The pathophysiology of the obesity-asthma link is not fully understood yet. Mechanical, genetic, environmental, and immune factors are hypothesised to influence this association.[76] Obesity and asthma are both linked to lifestyle factors, such as diet and physical activity.[77] Poor diet has been associated with both increased risk of obesity and poor asthma control. High fat intake has been linked to increased airway inflammation. Fruit and vegetable intake are both negatively associated with prevalent asthma.[78] Obese asthmatic patients are described to have a higher burden of symptoms, more severe disease, poorer lung function, more frequent exacerbations, and are less prone to respond to standard treatments, such as beta-2 agonists and inhaled corticosteroids. Treating obesity, by weight loss, exercise, and pulmonary rehabilitation, is the most important treatment for the obese asthma phenotype.[76]

It is not clear what the role of physical activity is in the association between obesity and asthma. The association between physical activity and obesity, as well as between obesity and asthma has been established, but the physical activity-asthma link is still subject to debate (Figure 1.2). A possible route is that children with low physical activity become obese, and subsequently develop asthma. Or alternatively it could be that obese children engage less in physical activity and then develop asthma. Leinaar et al published a systematic review on the relationship between asthma and overweight in children, and the role of physical activity in this relation.[79] They postulated that physical activity is likely to mediate the relationship between asthma and overweight. However, their conclusions are based upon mostly cross-sectional studies and a few studies with asthma preceding overweight, which makes it difficult to determine a causal relation.

To unravel all these possible interactions and relations, it is very important that longitudinal data from cohort studies are available with clear information on physical activity and asthmatic symptoms.

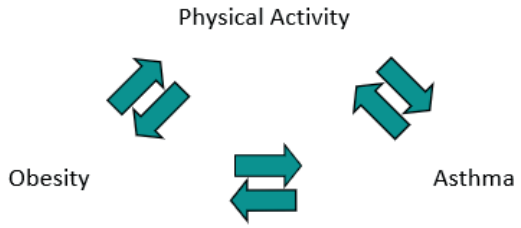

Figure 1.2: Visual representation of possible associations between physical activity, obesity, and asthma.

Aim of this thesis

The aim of this thesis is to investigate the relation between asthma and physical activity, with special attention to causality and direction of the possible associations.

Outline of this thesis

Chapter 2 describes a study we performed on the validity of parent reported physician diagnosed asthma, compared to medical information provided by their general practitioner.
Chapter 3 describes the relation between asthmatic symptoms in the first two years of life and subsequent physical activity levels at age 4 to 5 years.
Chapter 4 presents an overview of the available literature on asthma and physical activity, in adults as well as children, based on a broad literature review and meta-analysis.
Chapter 5 looks into physical activity at age 4 to 5 years as exposure, and asthma development at age 6 to 7 years.
Chapter 6 describes a large collaborative study that we conducted in 26 European cohorts, on physical activity and asthma in childhood.
Finally, in **chapter 7** the main results of this thesis are discussed and placed in a bigger picture. **Chapter 8** describes the scientific and societal impact of this thesis.

KOALA Birth Cohort

Data for this thesis were mainly derived from the KOALA Birth Cohort Study (acronym (in Dutch) for Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg; (in English) child, parents and health: lifestyle and genetic constitution). In this birth cohort study more than 2500 children born between 2001 and 2003 are followed from pregnancy into adulthood. The main focus of the cohort is allergy and asthma, growth and development. A unique feature of the KOALA cohort is the enrichment with families with alternative lifestyles, often inspired by anthroposophical philosophy. This leads to a broader spectrum of behaviours such as playing outdoors, breast feeding, healthy diets etc.[80,81]

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Chapter 2

Comparison of parent reported physician diagnosed asthma and general practitioner registration

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Abstract

Objective
To compare parent reported physician diagnosed asthma from questionnaires for epidemiological purposes, to general practitioner (GP) recorded childhood asthma.

Methods
This study was embedded in the KOALA Birth Cohort Study with regular follow-up by ISAAC core questions on asthma in 2834 children in two different recruitment groups, with 'conventional' lifestyles or 'alternative' lifestyles. At age 11-13 years these data were linked to data extracted from GP records. We compared parent reported physician diagnosed asthma, asthma medication use, and current asthma with GP recorded asthma diagnosis and asthma medication. Two different combinations of questions were used to define current asthma (i.e. ISAAC and MeDALL based definition).

Results
Among 958 children with information provided both by the parents and GPs, 98 children (10.2%) had parent reported physician diagnosed asthma, and 115 children (12.0%) had a GP recorded asthma diagnosis (Cohen's kappa 0.49; 95% CI 0.40 to 0.57). Discrepant cases showed that asthma symptoms at an early age led to different labeling between parents and GP. The agreement between the ISAAC based definition and MeDALL based definition was excellent (Cohen's kappa 0.82; 95% CI 0.74 to 0.88).

Conclusion
Parent reported physician diagnosed asthma and GP recorded childhood asthma had only moderate agreement, and is possibly influenced by labeling early transient wheeze as asthma diagnosis. It is important that parent reported physician diagnosed asthma is combined with additional questions such as current asthma symptoms and asthma medication use, as used in ISAAC or MeDALL based current asthma, in order to obtain reliable information for epidemiological research.

Introduction

Asthma is a heterogeneous disease with symptoms of wheeze and shortness of breath that are highly variable in time.[1] Asthma is a clinical diagnosis, based on a combination of recurrent clinical symptoms and signs in patient history and physical examination, combined with a reversible airflow obstruction in spirometry.[2] Ideally, spirometry is performed at the time that clinical symptoms of an asthma exacerbation are present. For epidemiological research, it is important to use a uniform and reliable asthma definition that is feasible to perform in large study populations. In most epidemiological studies, asthma is defined through questionnaires instead of spirometry or clinical assessment due to advantages in data collection, costs and time efficiency.[3] The most comprehensive international study on asthma prevalence in children is the International Study of Asthma and Allergies in Childhood (ISAAC).[4] This collaborative research project developed and validated questionnaires for measuring prevalence of asthma in childhood. Common core ISAAC questions on asthma are: "Did a physician ever diagnose asthma in your child?" and "Has your child ever had asthma". Although ISAAC has contributed greatly to uniform and valid asthma measurement, a standardized operational asthma definition for epidemiological studies is lacking.[5] The MeDALL collaboration (Mechanisms of the Development of Allergy) aimed to further harmonize information on asthma in epidemiological studies and made proposals for definitions of current asthma, eczema and rhinitis.[6,7]

The main goal of this study is to compare questionnaire based parent reported physician diagnosed asthma and parent reported use of asthma medication with GP reported asthma diagnosis and asthma medication in children. We will also describe the discrepancies between parent reported physician diagnosed asthma and GP records.

We compared parent reported physician diagnosed asthma, GP recorded asthma diagnosis, asthma medication use, and commonly used combinations of questions to define current asthma in order to determine which gives the most accurate information on the presence of asthma. Our hypothesis is that parent reported physician diagnosed asthma corresponds well to GP reported asthma diagnosis. This is important for the use of parent based questionnaires in epidemiological research, but also useful for clinical practice, as the parents are the spokesperson for their child and it is important that clinicians know whether a parent reported physician diagnosed asthma is indicative of a GP reported asthma diagnosis.

Materials and methods

Study design

This study is an agreement study comparing parent reported physician diagnosed asthma and asthma medication use with GP recorded asthma diagnosis and asthma medication.

Study population

This study was embedded in the KOALA Birth Cohort Study of 2834 children born between 2001 and 2003 (KOALA is an acronym [in Dutch] for Child, Parent, and Health: Lifestyle and Genetic Constitution). The study consists of 2 recruitment groups, families with "alternative" and "conventional" lifestyles.[8] Families with alternative lifestyles with regard to child rearing practices, dietary habits, vaccination schemes and/or use of antibiotics, were recruited through organic food shops, anthroposophical doctors and midwives. Healthy pregnant women with conventional lifestyles were recruited from an ongoing study on pregnancy-related pelvic girdle pain.[9] Parents were asked to fill out written questionnaires on asthma symptoms and asthma diagnosis at several ages (i.e. 3 and 7 months, 1 year, 2 years, 4 to 5 years, 6 to 7 years, 6 to 8 years, 7 to 9 years, 8 to 10 years, and 8 to 11 years). ISAAC core questions on physician diagnosed asthma and asthma medication use were used: "Did a physician ever diagnose asthma in your child?" and "Did your child use medication for asthma or wheezing in the last 12 months?", "Which medication and how often did your child use medication in the last 12 months for asthma or wheezing?".

Asthma care pathway

In the Netherlands the general practitioner (GP) is the central person in the patient's healthcare, and acts as a gatekeeper for the patient's health and that of their family. In general, asthma is diagnosed by the general practitioner or pediatrician by clinical observation of recurrent episodes of dyspnea and wheeze, preferably supported by a spirometry with reversible bronchoconstriction. In general, mild asthma with only on demand bronchodilators or stable with normal dosage of inhaled corticosteroids, is treated by the general practitioner. Moderate or severe asthma is treated by the pediatrician. The pediatrician will inform the general practitioner of the diagnosis and treatment with regular correspondence, as the general practitioner is the gatekeeper of the patient's health in general.[10]

Operational asthma definitions

In the KOALA cohort we defined current asthma using the following combination of ISAAC questions: physician diagnosed asthma combined with symptoms of dyspnea or wheeze in the last 12 months and/or regular use of asthma medication in the last 12 months (i.e. daily use of corticosteroids or bronchodilators or use of bronchodilators during exercise).[11] For this study, we also used the MeDALL based definition of current asthma, which is defined as presence of at least two out of the next three criteria: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, and (3) use of asthma medication in the last 12 months.[7]

Data collection

In 2008 (when the children were around age 6-7 years), the parents were asked informed consent to approach their GP for their child's medical information. In 2014 (when the children were around age 11-13), GPs of participating children were asked to fill out a written questionnaire on several diagnoses (i.e. asthma, eczema, hay fever, attention deficit hyperactive disease (ADHD), chronic intestinal disorders) and medication use. Children with available information from their GP and follow-up at least until the age of 8 to 10 years were included in this study.

Written informed consent was obtained from the parents of participating children. Ethical approval was obtained from the Medical Ethical Review Committee of Maastricht University Medical Centre+ (approval number MEC 08-4-016.4, 2008).

Statistical analysis

Data were analyzed using SPSS 23.0 for Windows (SPSS Inc, Chicago, IL). We used Cohen's kappa statistic with 95% confidence intervals (CI) to quantify agreement. A kappa over 0.81 was considered as excellent, a kappa of 0.61 to 0.80 was considered good, 0.41 to 0.60 moderate, 0.21 to 0.40 fair, and lower than 0.20 poor.[12]

Because the last follow-up by parental questionnaire was around one year before the extraction of GP data, we restricted GP reported asthma medication to the period up to the questionnaire date.

The main analysis was aimed to quantify agreement between parent reported physician diagnosed asthma and GP recorded asthma diagnosis. Secondly, we compared parent reported asthma medication use with asthma medication reported by the GP. Thirdly, we compared two different sets of combined questions to define current asthma (i.e. ISAAC and MeDALL based definition of current asthma) with physician diagnosed asthma reported by the parents or GP. In addition, we provided insight into causes of

discrepancies between parent reported information and GP records. We performed additional analyses with stratification for recruitment group because we hypothesized that parents in the alternative lifestyle recruitment group could possibly be more restrictive in seeking medical care for asthmatic symptoms and asthma medication use.

Results

In total, parents of 1795 children consented to approaching the GP for medical information. Those with incomplete information or no possibility to link to the GP data were excluded from analysis (missing or unreadable GP address (n=15), incomplete form (n=35), discontinued or unknown GP practice (n=82)).

Valid GP addresses were available for 1663 children from 744 different GP practices (420 practices with one child; the others with two up to nineteen children per practice). These GPs were sent a short questionnaire, to which 529 (71% of 744 GP practices) responded by returning the questionnaire for one or more children, totaling 1172 children. Of the returned questionnaires 1061 questionnaires were valid. The remainder indicated that the child was no longer a patient (n=95), or refused to fill out the questionnaire (n=16), for example because of lack of time. We excluded twins (n=16) to prevent accidental mix-ups by their parents or GP.

Finally, 966 of the remaining 1045 children had information on either parent reported asthma diagnosis or asthma medication at age 8-10 or 8-11 years, and were included in this study. Table 2.1 shows the characteristics of the base population, the children whose parents gave informed consent for linkage with the GP record, and the children with available GP record.

Physician diagnosed asthma

Physician diagnosed asthma was reported by the parents in 98 children (10.2% of 958 children with information on parent reported physician diagnosed asthma), compared to 115 children (12.0%) according to the GP record (Table 2.2). The agreement between parent reported physician diagnosed asthma and GP recorded asthma diagnosis was moderate, with a Cohen's kappa of 0.49 (95% CI 0.40 to 0.57).

We zoomed in on the cases in which there was no agreement between parental and GP provided information. In 40 cases, the parents indicated that the child had been diagnosed with asthma by a physician while the GP did not. From these 40 discrepant cases it was striking that 36 children (90%) were reported by the parents as having an asthma diagnosis set by a physician before the age of 6 (often 0 to 2 years). Of these

children with a reported asthma diagnosis at an early age, only 6 children (15%) were still using asthma medication according to the parents, and 5 according to the GP record (13%). When the more strict definition of current asthma was applied to these 36 cases, only 8 (22%) met the ISAAC based definition, compared to 6 (17%) when using the MeDALL based definition of current asthma.

Table 2.1: Characteristics of participants of the KOALA Birth Cohort Study, Netherlands.

Characteristic	Participants with follow-up on parent reported asthma diagnosis or medication (n=1886), n (%)	Participants with informed consent for linking with GP record (n=1580), n (%)	Participants with valid linked GP record (n=966), n (%)
Sex			
Boy	967 (51)	787 (50)	485 (50)
Girl	919 (49)	793 (50)	481 (50)
Lifestyle			
Regular	1532 (81)	1284 (81)	783 (81)
Alternative	354 (19)	296 (19)	183 (19)
Maternal education level			
Lower	163 (9)	135 (9)	78 (8)
Middle	703 (37)	577 (37)	349 (36)
Higher vocational	666 (35)	577 (37)	358 (37)
Academic	286 (15)	242 (15)	150 (16)
Other	68 (4)	49 (3)	31 (3)
Parental asthma [a]			
No	1524 (81)	1277 (81)	771 (80)
Yes	356 (19)	274 (17)	174 (18)
Unknown	34 (2)	23 (2)	17 (2)
Missing	6	6	4
Parental atopy [b]			
No	758 (41)	632 (41)	389 (41)
Yes	1099 (59)	928 (60)	564 (59)
Missing	29	20	13
Older siblings with atopy [c]			
No older siblings	818 (44)	690 (44)	407 (42)
No	748 (40)	628 (40)	389 (40)
Yes	299 (16)	250 (16)	162 (17)
Unknown	15 (1)	6 (0)	4 (0)
Missing	6	6	4
Wheeze at age 0 to 2 years [d]			
No	1262 (67)	1054 (67)	646 (67)
Yes	615 (33)	518 (33)	315 (33)
Missing	9	8	5
Eczema at age 0 to 2 years [e]			
No	1440 (77)	1215 (77)	752 (78)
Yes	421 (22)	349 (22)	203 (21)
Missing	25	16	11

[a] Father and/or mother history of asthma; [b] Father and/or mother history of asthma, eczema or allergy; [c] One or more older siblings history of asthma, eczema or allergy; [d] Parent reported wheeze at age 0 to 2 years; [e] Parent reported eczema at age 0 to 2 years.

Table 2.2: Parent reported physician diagnosed asthma compared to GP record.

Parent reported physician diagnosed asthma	GP recorded asthma diagnosis		Total (n)
	No asthma (n)	Asthma (n)	
No asthma (n)	803	57	860
Asthma (n)	40	58	98
Total (n)	843	115	958
Cohen's kappa 0.49 (95% CI 0.40 to 0.57)			

Agreement of parent reported physician diagnosed asthma, as reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to GP recorded childhood asthma diagnosis. 958 children had information on parent reported physician diagnosed asthma (the difference with the total included group of 966 children is caused by 8 missings, which did have information on asthma medication use and therefore were included for this study). 95% CI: 95% confidence interval.

On the other side, in 57 cases the GP record showed an asthma diagnosis, while the parents did not report this in the last two follow-up questionnaires (ages 8 to 10 years and 8 to 11 years). From these 57 discrepant cases, 4 were diagnosed only recently (after the last follow-up questionnaire) and thus could not have been indicated as diagnosed asthma by the parents yet. From the remaining 53 discrepant cases, 31 children (59%) were diagnosed at an early age according to the GP record (before 6 years), from which 23 (74% of 31 children) had no symptoms or medication use anymore at age 8 to 11 years according to the parents. In 11 cases (21%), parents seemed to have forgotten an earlier asthma diagnosis: in earlier questionnaires (at ages 6 to 7 years, 6 to 8 years, or 7 to 9 years) the parents did fill out an asthma diagnosis, while they did not in the last two follow-up questionnaires at ages 8 to 10 years and 8 to 11 years. In total, only 8 of the 31 discrepant cases with an early diagnosis met the ISAAC based definition of current asthma (26%), while 4 met the MeDALL based definition (13%). See Figure 2.1 for a visual representation of agreement and discrepancies of parent reported physician diagnosed asthma compared to GP recorded asthma.

Physician diagnosed asthma compared to current asthma

The agreement between parent reported physician diagnosed asthma and current asthma was moderate for both definitions: Cohen's kappa 0.59 (95% CI 0.49 to 0.68) for ISAAC based current asthma, Cohen's kappa 0.57 (95% CI 0.47 to 0.67) for MeDALL based current asthma. The agreement between GP recorded asthma diagnosis and current asthma was somewhat lower: Cohen's kappa 0.53 (95% CI 0.44 to 0.63) for ISAAC based current asthma, and Cohen's kappa 0.48 (95% CI 0.37 to 0.56) for MeDALL based current asthma. (More details in appendix).

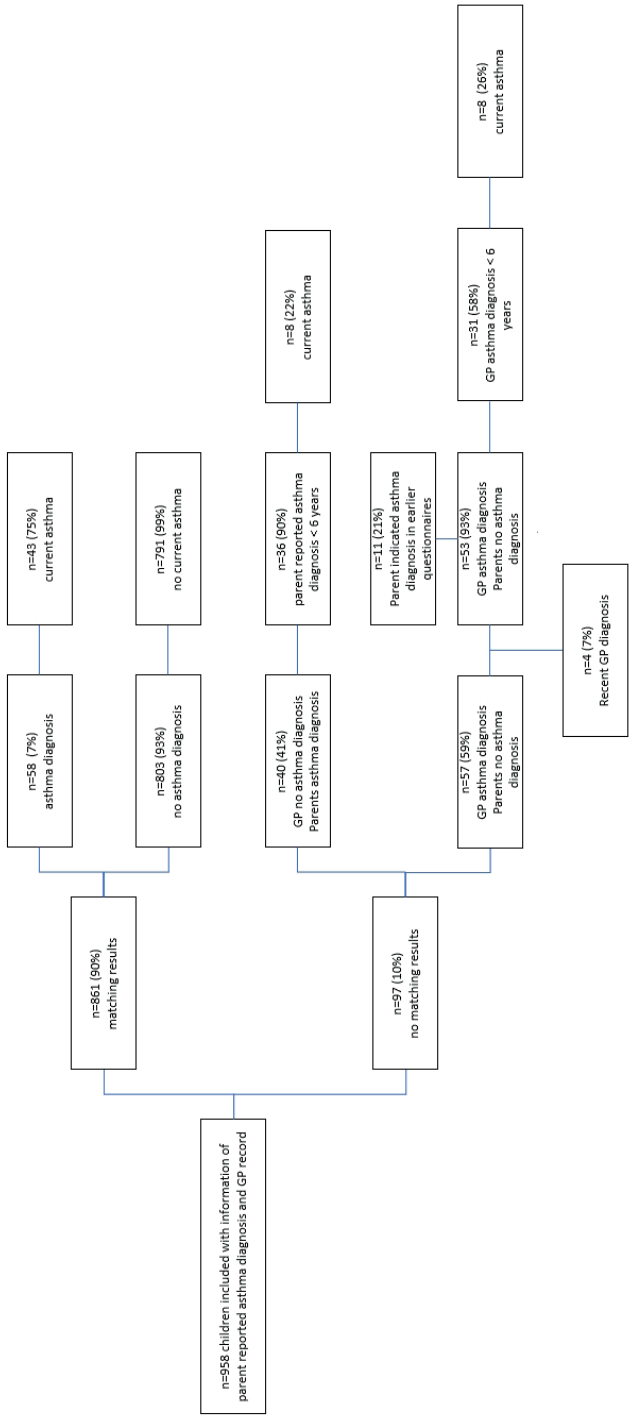

Figure 2.1: Visual representation of agreement and discrepancies of parent reported physician diagnosed asthma ever reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to GP recorded asthma diagnosis. Current asthma either by ISAAC or MeDALL based definition. ISAAC based current asthma is defined as ((1) physician diagnosed asthma and (2) asthma symptoms (dyspnea or wheeze) in the last 12 months) and/or (3) regular use of asthma medication in the last 12 months. MeDALL based current asthma was defined as presence of two out of the next three criteria: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, and (3) use of asthma medication in the last 12 months.

Asthma medication

The recent use of asthma medication was reported in 78 (8.1% of 965) children by the parents, compared to 63 (6.5%) children in the GP records (Table 2.3). The agreement between parent reported asthma medication use in the last 12 months and GP recorded asthma medication around the same time period was moderate, with a Cohen's kappa of 0.56 (95% CI 0.45 to 0.66).

Table 2.3: Parent reported asthma medication compared to GP record.

Parent reported asthma medication	GP registered asthma medication		Total (n)
	No (n)	Yes (n)	
No (n)	866	21	887
Yes (n)	36	42	78
Total (n)	902	63	965
Cohen's kappa 0.56 (95% CI 0.45 to 0.66)			

Agreement of parent reported asthma medication, as reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to GP registered asthma medication. 965 children had information on parent reported asthma medication (the difference with the total included group of 966 children is caused by 1 missing, which did have information on physician diagnosed asthma and therefore was included for this study). 95% CI: 95% confidence interval.

We focused on the discrepancies: in 21 cases asthma medication was prescribed by the GP recently, while the parents did not report this. In 6 of these cases (29%) parents reported physician diagnosed asthma, compared to 7 asthma diagnoses (33%) in the GP records. Only a few cases met the definitions for current asthma (n=2 for ISAAC based definition, and n=1 for MeDALL based definition). In 36 cases parents did report recent asthma medication use, while there was no record of this in the GP record. In 21 cases (58%) parents reported a physician diagnosed asthma, and in 22 cases there was an asthma diagnosis in the GP record (61%). A notable number of 32 cases (89%) met the ISAAC based definition of current asthma, and 28 (78%) met the MeDALL based definition.

Current asthma

In total, 75 children (7.8%) met the ISAAC based definition of current asthma, as reported by the parents, compared to 58 children (6.0%) defined by the MeDALL based definition of current asthma (Table 2.4). The agreement between the ISAAC based definition and MeDALL based definition was (as expected) excellent, with a Cohen's kappa of 0.82 (95% CI 0.74 to 0.88).

In 3 cases, the child met the MeDALL definition of current asthma, but not the ISAAC based definition. In 20 cases, the child met the ISAAC based definition but did not meet the MeDALL based definition. See Figure 2.2 for a visual representation and explanation of the differences between the ISAAC and MeDALL based definitions.

Table 2.4: ISAAC and MeDALL based definition of current asthma.

Current asthma according to ISAAC based definition	Current asthma according to MeDALL based definition		Total (n)
	No asthma (n)	Asthma (n)	
No asthma (n)	888	3	891
Asthma (n)	20	55	75
Total (n)	908	58	966
Cohen's kappa 0.82 (95% CI 0.74 to 0.88)			

Agreement of ISAAC and MeDALL based definition of current asthma, both reported in follow-up questionnaires at age 8 to 10 years or 8 to 11 years. ISAAC based current asthma is defined as ((1) physician diagnosed asthma and (2) asthma symptoms (dyspnea or wheeze) in the last 12 months) and/or (3) regular use of asthma medication in the last 12 months. MeDALL based current asthma was defined as presence of two out of the next three criteria: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, and (3) use of asthma medication in the last 12 months. 95% CI: 95% confidence interval.

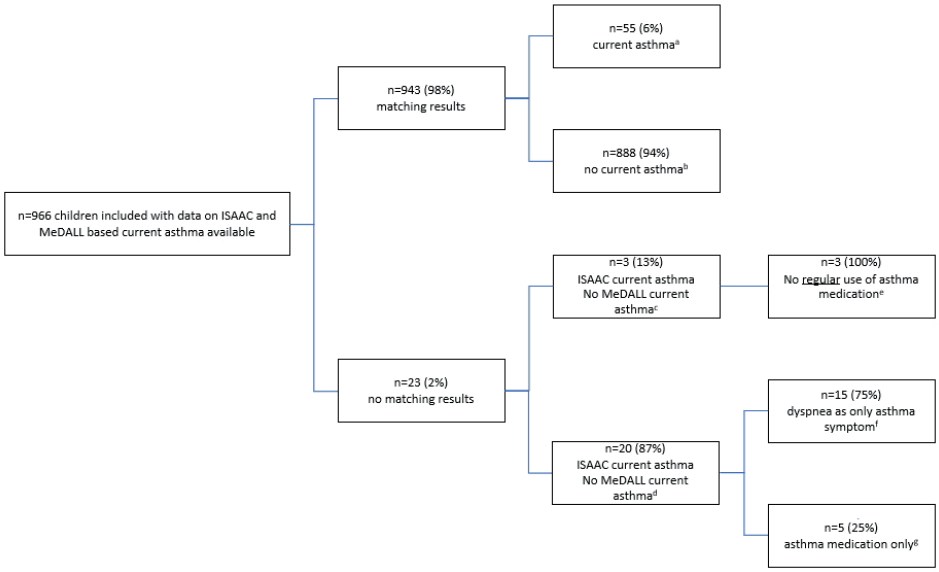

Figure 2.2: Visual representation of agreement and discrepancies of ISAAC based current asthma and MeDALL based current asthma, both reported in follow-up questionnaires at age 8 to 10 years or 8 to 11 years. ISAAC based current asthma was defined as ((1) physician diagnosed asthma and (2) asthma symptoms (dyspnea or wheeze) in the last 12 months) and/or (3) regular use of asthma medication in the last 12 months. MeDALL based current asthma was defined as presence of two out of the next three criteria: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, and (3) use of asthma medication in the last 12 months.
[a] Current asthma according to both ISAAC and MeDALL based definition; [b] No current asthma according to both ISAAC and MeDALL based definition; [c] Current asthma according to MeDALL based definition, but not according to ISAAC based definition; [d] Current asthma according to ISAAC based definition, but not according to MeDALL based definition; [e] Any use of asthma medication but not meeting the requirements for regular asthma medication use according to ISAAC based definition (i.e. daily use of corticosteroids or bronchodilators or use of bronchodilators during exercise); [f] Dyspnea as only asthma symptom which meets the asthma symptoms according to ISAAC based definition (i.e. dyspnea or wheeze) but not MeDALL based definition (i.e. wheeze); [g] Regular use of asthma medication but no physician diagnosed asthma or recent asthma symptoms. ISAAC based definition required the logical rule of (physician diagnosed asthma AND asthma symptoms) OR (asthma medication use), while MeDALL required 2 out of 3 criteria.

Lifestyle

Of the total study population, 783 children (81%) were from families in the conventional recruitment group, while 183 children (9%) were born into families in the alternative lifestyle recruitment group. Parents of children from the alternative recruitment group less often reported a physician diagnosed asthma (6.6% compared to 11.1%), as did their GP (8.2% compared to 12.9%). Medication use was also slightly lower in the alternative recruitment group (parent reported 6.6% vs. 8.4%; GP reported 6.0% vs. 6.6%). The agreement of the parent reported physician diagnosed asthma and GP recorded asthma diagnosis was comparable, while the agreement of asthma medication use was higher in the conventional recruitment group (results in appendix).

Discussion

This study shows that there is moderate agreement between parent reported physician diagnosed asthma and GP reported childhood asthma. The discrepant cases revealed several difficulties in reporting physician diagnosed asthma, for example because of a recent diagnosis, or because they were still in the diagnostic process at the time of reporting. But the most striking discrepancies were noted in children where an asthma diagnosis was set at an early age: both parent reports and GP records had difficulties when reporting these cases. Several explanations are possible: it is possible that parents don't remember an early asthma diagnosis (especially when the child does not have any asthma symptoms anymore: recall bias), or that the GP did not look back far enough in the medical chart. An important reason could also be misclassification of transient early wheeze as asthma diagnosis. Several parents reported their struggle with the words used by their physician. One parent quoted: "I don't know if the doctor called it asthma, but [my child] wheezed at the age of 2 years, for which he was prescribed puffs". It was noteworthy that in case of transient wheeze at a young age, a part of the parents did put down "was ever diagnosed with asthma by a physician", while others did not, or left the question open. One parent noticed: "my family doctor does not make a diagnosis of asthma before the age of 6 years". This shows that it is very important that physicians speak the same language in describing (viral induced) wheeze and asthma. In this study, we noticed that also GPs struggled with asthma diagnoses at an early age. It has to be noted that these asthma diagnoses were set more than ten years ago, and possibly due to new developments and schooling in childhood asthma would have been recorded as early transient or preschool wheeze nowadays.

The differences in the asthma medication reported by the parents compared to the GP can be caused by different issues: it is possible that medication was requested by the parents but not used in absence of asthma symptoms, or that the timing of the parent reported asthma medication use and GP records did not match completely. In other

cases where the parents reported asthma medication use while the GP did not, it is possible that the asthma medication was prescribed by another physician than the GP, especially when there were asthma symptoms or current asthma. It is plausible that these children were referred to a pediatrician who prescribed the asthma medication (and the GP was not notified, the notification letter was not entered in the GP's record, or was not reported in the GP's questionnaire).

Earlier studies showed an increasing agreement between parent reported wheezing and GP recorded asthma diagnosis with increasing age, with a Cohen's kappa of 0.57 at age 7, and 0.61 at age 11.[13] Other studies compared parent reported asthma or wheeze with clinical assessment of asthma. Hansen et al. found a good agreement (kappa 0.80) between parent reported asthma diagnosis ever in school children compared to clinical assessment, consisting of a standardized interview, a clinical examination, skin prick tests, blood samples, spirometry, exercise treadmill test, and measurement of exhaled nitrogen oxide.[14] Hederos et al compared parent reported physician diagnosed asthma and symptoms in preschool children with hospital records of admissions and visits to the outpatient clinic, and concluded that only half of the individual patients identified as asthmatic by questionnaires were the same as those identified clinically.[15] When comparing parent reported physician diagnosed asthma with health care registry data, agreement was moderate to good (Cohen's kappa 0.57) in a Swedish study.[16] The combination of ISAAC questions of recent wheeze and use of asthma medication in the last 12 months was highly comparable with the Finnish registration of medication reimbursement.[17] What this study adds, is an insight of the discrepancies between parent reported physician diagnosed asthma and asthma medication use compared to GP records. This study shows that the discrepant cases are often caused by early transient wheeze that can be prematurely labeled as an asthma diagnosis. This could lead to an overestimation of asthma prevalence when using (parent reported) physician diagnosed asthma. This issue can be solved by using the definition current asthma, built up from a combination of asthma questions, such as ISAAC or MeDALL based definition. In this study, we found only minor differences between how these two definitions classified the children. Both definitions of current asthma were able to differentiate between early transient wheeze and asthma, while (parent reported) physician diagnosed asthma could not. This suggests that (parent reported) physician diagnosed asthma is better not used as stand-alone question for determining asthma prevalence in epidemiological studies.

The most important strength of this study is the repeated and detailed information on parent reported asthma questions, prospectively from birth onwards, which allowed this study to elaborate on the discrepancies between the parent reported data and GP recorded data.

Limitations of this study are that the timing of the questionnaire sent to the GP was not exactly at the same time as the questionnaires were sent to the parents; this could implicate that a very recent asthma diagnosis was not yet known at the time of filling

out the questionnaire by the parents. It is also possible that the information in the GP record was not complete, or that the GP did not look far enough in the medical record. This appeared to be the case especially for the asthma medication. We assumed that the GP would have all the available information on asthma diagnosis and medication, but it is thinkable that when a child is referred to a pediatrician that the GP does not have complete information. It is also possible that the parents and child changed their GP without handing-over of the medical record, so that we missed part of the medical history.

Conclusions

In conclusion, this study showed only moderate agreement between parent reported physician diagnosed asthma and GP recorded childhood asthma and demonstrated some difficulties in classifying physician diagnosed asthma. When using (parent reported) physician diagnosed asthma for epidemiological research, it is important to be informed on the timing of the diagnosis, and especially whether the asthma symptoms were transient or still present. Preferably, combined questions on current asthma are used in order to define asthma in epidemiological studies. Both ISAAC based and MeDALL based definitions of current asthma give valuable information on asthma symptoms and medication use, and are more accurate than merely an asthma diagnosis ever.

Appendix

Table 2.A: Parent reported physician diagnosed asthma compared to ISAAC based current asthma.

Parent reported physician diagnosed asthma	Asthma according to ISAAC defintion		Total (n)
	No asthma (n)	Asthma (n)	
No asthma (n)	840	20	860
Asthma (n)	44	54	98
Total (n)	884	74	958

Agreement of parent reported physician diagnosed asthma, as reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to ISAAC based current asthma. ISAAC based current asthma is defined as ((1) physician diagnosed asthma and (2) asthma symptoms (dyspnea or wheeze) in the last 12 months) and/or (3) regular use of asthma medication in the last 12 months. 958 children had information on parent reported physician diagnosed asthma (the difference with the total included group of 966 children is caused by 8 missings, which did have information on asthma medication use and therefore were included for this study).

Table 2.B: Parent reported physician diagnosed asthma compared to MeDALL based current asthma.

Parent reported physician diagnosed asthma	Asthma according to MeDALL defintion		Total (n)
	No asthma (n)	Asthma (n)	
No asthma (n)	850	10	860
Asthma (n)	51	47	98
Total (n)	901	57	958

Agreement of parent reported physician diagnosed asthma, as reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to MeDALL based current asthma. MeDALL based current asthma was defined as presence of two out of the next three criteria: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, and (3) use of asthma medication in the last 12 months. 958 children had information on parent reported physician diagnosed asthma (the difference with the total included group of 966 children is caused by 8 missings, which did have information on asthma medication use and therefore were included for this study).

Table 2.C: GP recorded asthma diagnosis compared to ISAAC based current asthma.

GP recorded asthma diagnosis	Asthma according to MeDALL defintion		Total (n)
	No asthma (n)	Asthma (n)	
No asthma (n)	830	20	850
Asthma (n)	61	55	116
Total (n)	891	75	966

Agreement of GP recorded asthma diagnosis, compared to ISAAC based current asthma. ISAAC based current asthma is defined as ((1) physician diagnosed asthma and (2) asthma symptoms (dyspnea or wheeze) in the last 12 months) and/or (3) regular use of asthma medication in the last 12 months.

Table 2.D: GP recorded asthma diagnosis compared to MeDALL based current asthma.

GP recorded asthma diagnosis	Asthma according to MeDALL defintion		Total (n)
	No asthma (n)	Asthma (n)	
No asthma (n)	837	13	850
Asthma (n)	71	45	116
Total (n)	908	58	966

Agreement of GP recorded asthma diagnosis, compared to MeDALL based current asthma. MeDALL based current asthma was defined as presence of two out of the next three criteria: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, and (3) use of asthma medication in the last 12 months.

Table 2.E: Stratification for lifestyle – parent reported physician diagnosed asthma compared to GP record.

Lifestyle recruitment group			GP recorded asthma diagnosis		Total (n)
			No asthma (n)	Asthma (n)	
Conventional	**Parent reported physician diagnosed asthma**	No asthma (n)	642	49	691
		Asthma (n)	35	51	86
		Total (n)	677	100	777
Cohen's kappa 0.49 (95% CI 0.39 to 0.58)					
Alternative	**Parent reported physician diagnosed asthma**	No asthma (n)	161	8	169
		Asthma (n)	5	7	12
		Total (n)	166	15	181
Cohen's kappa 0.48 (95% CI 0.18 to 0.70)					

Agreement of parent reported physician diagnosed asthma, as reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to GP recorded childhood asthma diagnosis, stratified for lifestyle.
958 children had information on parent reported physician diagnosed asthma (the difference with the total included group of 966 children is caused by 8 missings (6 in the conventional group, 2 in the alternative group), which did have information on asthma medication use and therefore were included for this study).
95% CI: 95% confidence interval.

Table 2.F: Stratification for lifestyle – parent reported asthma medication compared to GP registered asthma medication.

Lifestyle recruitment group			GP registered asthma medication		Total (n)
			No (n)	Yes (n)	
Conventional	**Parent reported asthma medication**	No (n)	700	16	716
		Yes (n)	30	36	66
		Total (n)	730	52	782
Cohen's kappa 0.58 (95% CI 0.46 to 0.69)					
Alternative	**Parent reported asthma medication**	No (n)	166	5	171
		Yes (n)	6	6	12
		Total (n)	172	11	183
Cohen's kappa 0.49 (95% CI 0.24 to 0.72)					

Agreement of parent reported asthma medication, as reported in follow-up questionnaires at ages 8 to 10 years or 8 to 11 years, compared to GP registered asthma medication, stratified for lifestyle.
965 children had information on parent reported asthma medication (the difference with the total included group of 966 children is caused by 1 missing (in the conventional group), which did have information on physician diagnosed asthma and therefore was included for this study). 95% CI: 95% confidence interval.

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Chapter 3

Asthmatic symptoms, physical activity, and overweight in young children

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Abstract

Objective

Prevalence of asthma and overweight has increased simultaneously during the past decades. Several studies have reported an association between these two health problems, but it is unclear whether this relation is causal. We hypothesize that children with asthmatic symptoms are less physically active, which may contribute to the development of overweight.

Patients and methods

The study included children from the KOALA Birth Cohort Study who were invited at 4 to 5 years of age to wear an Actigraph accelerometer for 5 days (n=305; 152 boys). Information on wheezing was gathered by repeated questionnaires completed by parents at child ages 7 months and 1, 2, and 4 to 5 years. Questionnaires on physical activity were completed at child age 4 to 5 years, and height, weight, and abdominal circumference were measured. Accelerometer data were expressed as mean counts per minute, minutes per day performing vigorous activity, and moderate-to-vigorous physical activity during ≥1 minute.

Results

Children who had wheezed in the last 12 months showed very similar activity levels compared with children who had never wheezed. By contrast, boys who had wheezed at least once but not in the last 12 months were more physically active than boys who had never wheezed (geometric mean: 694 vs. 625 cpm; adjusted geometric mean ratio: 1.11). This was not found for girls. Similar results were found in parent-reported physical activity data. No association was found between wheezing at any age and overweight at the age of 4 to 5 years.

Conclusions

These results do not support our hypothesis and previous studies that showed that wheezing children are less physically active. Our data provide no evidence that asthmatic symptoms induce a lower physical activity level and more overweight. Additional research could concentrate on the effect of physical activity and overweight on the development of asthmatic symptoms.

Introduction

There has been an increase in the prevalence of asthma.[1-4] Studies have shown that the prevalence of asthma is highest in Western countries. The United Kingdom and the United States have especially high asthma prevalence, at 15.3% and 10.9% of the population, respectively. Although asthma prevalence in developing countries was low, it is rising with increasing Westernization.[4] An explanation for the increasing asthma prevalence could be found in changes in environmental factors, such as air pollution, exposure to infectious diseases, use of antibiotics, breastfeeding, family size, diet, and smoking.

Another Western health concern is overweight, the prevalence of which has increased dramatically as well.[5-7] Although trends in overweight could not explain the increase in asthma, overweight might be a marker of recent lifestyle changes associated with both asthma and overweight.[8]

The available evidence suggests an association between asthma and overweight, in adults as well as in children,[9-14] although it is not yet clear whether overweight causes asthma or vice versa. The prevailing hypothesis for this association is that overweight is a cause of asthma. Prospective studies with healthy, nonasthmatic participants showed that a gain in weight increased the risk of asthma in adults and adolescents.[15,16] Flaherman and Rutherford[17] found that a BMI above the 85th centile in childhood increases the risk of asthma in adulthood by 50%. Several explanations have been suggested, such as mechanical effects of overweight, increased perception of symptoms in obese persons, gastroesophageal reflux, changes in inflammatory responses, and influence of hormones.[18,19] However, the evidence does not rule out the possibility that the causal direction is reversed. In this study, we hypothesize that asthmatic children engage in less physical activity, which subsequently can lead to overweight. Possible reasons for this self-restriction in wheezing children could be overprotective parents or because these children may easily get out of breath when physically active. The results from cross-sectional studies on the association between childhood asthma and physical activity have been inconclusive. A number of studies showed that children who wheezed were less physically active than children who did not wheeze.[20-22] By contrast, others did not find such association[9] or even found the reverse.[23] Because these studies were cross-sectional in design, they provide no information about the direction of the association. Moreover, all of the studies were based on self-reported physical activity. Substantial differences in physical activity level have been reported between self-reported data and data obtained with accelerometers.[24] Firrincieli et al.[25] used accelerometers to assess the physical activity level of asthmatic and nonasthmatic children. In their cross-sectional study, they found that a lower level of physical activity was associated with a higher risk of asthma.

The aim of the current, prospective study was to evaluate whether wheezing in the first 2 years of life results in a lower physical activity level at the age of 5 years. In addition, the relation among wheezing, a lower physical activity level, and a subsequent rise in BMI was evaluated. To our knowledge, this is the first study that combines repeated measurements of wheezing symptoms early in life with the use of both accelerometers and self-reported data to assess physical activity later in life.

Patients and methods

This prospective study was embedded in the KOALA (Child, Parent and Health: Lifestyle and Genetic Constitution [in Dutch]) Birth Cohort Study in the Netherlands,[26] which aims to identify factors that influence the clinical expression of atopic disease and overweight. The study consists of 2 recruitment groups, women with “alternative” and “conventional” lifestyles. Healthy pregnant women with conventional lifestyles were recruited from an ongoing study on pregnancy-related pelvic girdle pain.[27] Inclusion criteria were being well versed in the Dutch language and ≥18 years old. In total, 2539 pregnant women were included and completed a questionnaire at 34 weeks' gestation. Information about wheezing during infancy among the children born from these pregnancies was gathered by questionnaire at the ages of 7 months and 1 and 2 years.

For the present study, 929 children were selected from the KOALA cohort who had reached the age of 4 years in or before 2006 and were able to complete a questionnaire in the child's first year of life (either at 7 months or at 1 year) and at the age of 2 years. In addition, the parents had to live within 20 km from the communal building in 1 of the following cities: Maastricht, Geleen, Heerlen, Roermond, Eindhoven, or Tilburg, Netherlands. Children were excluded from the study if they were born with congenital defects, born before 34 weeks' gestational age, or had used growth hormones.

Parents and children were invited to a communal building in 1 of the above-mentioned cities in which height, weight, and abdominal circumference of the children were measured. They also were asked to wear an Actigraph accelerometer for ≥5 days. Furthermore, the parents were asked to complete a questionnaire including questions about wheezing and physical activity level of their child during the last 4 weeks.

All of the participants gave written informed consent. Ethical approval was obtained from the medical ethics committee of the University of Maastricht and Academic Hospital of Maastricht.

Questionnaires

In the questionnaires at 7 months and 1, 2, and 4 to 5 years of age, the International Study of Asthma and Allergies in Childhood (ISAAC) questions[28] on wheezing were phrased as follows: “Did your child experience wheezing in the last period?” Asthma medication use and physician's diagnosis of asthma were asked as follows: “Did your child use asthma medication prescribed by a physician in the last 12 months?” and “Did a physician ever diagnose asthma in your child?” which all could be answered by “yes” or “no.” Children were classified into 3 groups: children who wheezed in the last 12 months (recent wheeze), children who wheezed at any moment in the first 2 years of life but not in the last 12 months (past wheeze), and children who never wheezed (never wheeze).

In the questionnaire at 4 to 5 years of age, parents were also asked about the physical activity level of their child during the last 4 weeks: “How many times a week does your child exercise in school or a sports club?” and “How many days a week does your child play outside?” These could be answered by “never or less than 1 day a week,” “1 day a week,” “2 days a week,” “3 days a week,” “4 days a week,” and “5 days a week or more.” Furthermore, the duration of these activities was asked. From these answers, the number of hours of physical activity per week was calculated.

The following potential confounders were addressed in the questionnaires, based on a priori expectations from the literature: breastfeeding, maternal smoking during pregnancy, exposure to environmental tobacco smoke during the first 2 years of life and at 4 to 5 years, a positive family history for asthma, educational level of the parents, obesity of the parents, and birth weight of the child.

Measurements

The Actigraph accelerometer (Actigraph, Fort Walton Beach, FL) is the most studied one-dimensional motion sensor in children and gives a good reproducibility, validity, and feasibility.[29] Children were instructed to wear the accelerometer on the right hip during daytime for ≥5 days. The accelerometer was only removed when water was involved, as in swimming, showering, and bathing. Data were collected with period lengths of 15 seconds, because young children engage in physical activity in frequent bursts of short duration.[30]

Four levels of activity were distinguished, that is, sedentary, light, moderate, and vigorous physical activity, using count cutoffs for 4-year-old children established and validated by Sirard[31]: 0 to 363 counts per 15 seconds for sedentary activity, 364 to 811 counts per 15 seconds for light physical activity, 812 to 1234 counts per 15 seconds for moderate physical activity, and >1234 counts per 15 seconds for vigorous physical activity. The number of minutes per day was summed within each of these categories. Moreover, the mean counts per minute per day were determined.

Outcome measures

The primary outcome was the amount of physical activity at the age of 4 to 5 years. This was presented as the mean counts per minute and the number of minutes that the children were practicing vigorous activity per day. In addition, we measured the number of episodes of moderate-to-vigorous physical activity by counting the number of times the activity level was reaching or exceeding moderate intensity (MVPA) for ≥1 minute. Participants were included in the analysis when the accelerometer was worn for ≥3 weekdays and 1 weekend day during ≥400 minutes per day. The amount of physical activity obtained by the questionnaires was presented as the number of reported hours of physical activity per week.

Other outcomes were BMI (weight/length^2 [kg/m^2]) and abdominal circumference at 4 to 5 years. Children were classified into weight groups, namely, underweight, normal weight, overweight, and obesity, using international reference standards based on age- and gender-specific values.[32] This corresponds with BMI values for overweight and obesity at the age of 5 years of 17.42 and 19.30 kg/m^2 for boys and 17.15 and 19.17 kg/m^2 for girls.

Statistical analysis

Data were analyzed by using SPSS 13.0 for Windows (SPSS Inc, Chicago, IL), using linear regression for the association between wheezing and parent-reported physical activity and wheezing and objectively measured physical activity and between parent-reported and objectively measured physical activity and overweight. Continuous outcome variables were the number of reported hours of physical activity per week, counts per minute, vigorous activity, and MVPA of ≥1 minute. Differences in activity levels between groups were estimated by linear regression analysis by including categories as dummy variables, and models were adjusted by including all of the potential confounders simultaneously. Because activity levels were not normally distributed, logarithmic transformation was performed. Levels within groups are expressed as geometric means (GMs), and differences between groups are expressed as GM ratios (GMR), with 95% confidence intervals (CIs). The GMR is equivalent to the logarithmic ratio of the group means on the untransformed scale. For the association between wheezing and physical activity, separate analyses were performed for boys and girls because of known gender differences from the literature on wheezing[33,34] and physical activity.[35,36] Logistic regression analysis was used for exploring the association between wheezing and overweight. Pearson correlation (r) was used for exploring the correlation between physical activity measured by accelerometer (in counts per minute) and reported hours of physical activity.

Results

Of the 929 children who were invited for the present study, 363 children (39.1%) participated. Three children refused to wear the accelerometer, and 1 accelerometer got lost while worn by the child. Eight accelerometers did not record any data. In 44 children, the wearing time was <3 weekdays and 1 weekend day for ≥400 minutes a day. In 1 child, the measurement date registered by the accelerometer differed from the date that the accelerometer was worn. Finally, the questionnaire of 1 child was not returned. These data were excluded. Statistical analysis was conducted on the remaining data (n = 305). Participant characteristics are summarized in Table 3.1. There were no striking differences between the total cohort and the participating group on the variables considered. Mean age was 4.9 years (range: 4.1–5.6 years).

Table 3.1: Characteristics of children in the total cohort, children invited for this study, and participants: KOALA Birth Cohort Study, Netherlands.

Variable	Total Cohort (n=2539), n (%)	Invited Group (n=929), n (%)	Participating Group (n=305), n (%)
Gender			
Male	1229 (51)	468 (50)	152 (50)
Female	1240 (49)	461 (50)	153 (50)
Parental history of asthma			
Blank	2105 (83)	774 (83)	260 (85)
Positive (one or both parents)	434 (17)	155 (17)	45 (15)
Obesity of parents			
No obesity of parents	2365 (93)	867 (93)	284 (93)
Obesity of one or both parents	174 (7)	62 (7)	21 (7)
Birth weight			
<2500 g	41 (2)	19 (2)	6 (2)
2500-4000 g	2157 (85)	811 (87)	264 (87)
>4000 g	341 (13)	99 (11)	35 (12)
Smoking during pregnancy			
Yes	170 (7)	85 (9)	15 (5)
No	2369 (93)	844 (91)	290 (95)
Parental smoking near child at 2 y			
Yes	268 (11)	130 (14)	31 (10)
No	2271 (90)	899 (86)	274 (90)
Breastfeeding			
Yes, until 6 mo	1032 (41)	281 (30)	101 (33)
Yes, but stopped before 6 mo	1026 (40)	395 (43)	134 (44)
Never	381 (15)	194 (21)	50 (16)
Unknown	100 (4)	59 (6)	20 (7)
Educational level of mother			
Low	244 (10	102 (11)	25 (8)
Moderate	1071 (42)	422 (45)	118 (39)
High	1224 (48)	405 (44)	162 (53)
Wheeze			
Never	1779 (70)	648 (70)	221 (73)
At least once in first 2 y of life	760 (30)	281 (30)	84 (28)

At the age of 4 to 5 years, 18 boys (12%) and 11 girls (7%) had recent wheeze, and 54 boys (36%) and 36 girls (24%) had past wheeze. Boys showed a mean physical activity level of 650 cpm, were on average 5.4 minutes per day active at the vigorous activity level, and performed on average 3.0 episodes of MVPA for ≥1 minute per day. For girls, these values were 606 cpm, 5.7 minutes, and 2.6 episodes per day, respectively.

We found an almost similar physical activity level in 4- to 5-year-old children with recent wheeze compared with children who had never wheezed, both for boys and for girls (Table 3.2). For boys with past wheeze, we found a slightly higher activity level compared with boys who had never wheezed. For girls, no such differences were apparent.

Thirty-three children (9.1%) had used asthma medication in the last 12 months, and 22 children (6.1%) had ever been diagnosed with asthma by a physician. These children showed very similar physical activity levels compared with children without an asthma diagnosis and asthma medication use (results not shown).

Children with overweight at the age of 4 to 5 years showed similar physical activity levels compared with children with a normal weight in all 3 of the physical activity variables (Table 3.3). Obese children (n = 6) showed significantly less vigorous activity and less MVPA for ≥1 minute than normal weight children. Wheezing at any age was not associated with overweight or obesity at the age of 4 to 5 years (in recent wheeze, adjusted OR: 0.51, 95% CI: 0.06–4.32 for overweight and adjusted OR: 3.34, 95% CI: 0.27–40.93 for obesity, and in past wheeze, adjusted OR: 0.80, 95% CI: 0.26–2.46 for overweight and adjusted OR: 0.27, 95% CI: 0.02–3.93 for obesity, respectively).

A weak correlation was found between physical activity measured by accelerometer and the number of hours of physical activity reported by the parents in the questionnaire (r=0.20; P=.01). Using the parent-reported data, we found similar results as in analyses with accelerometer data: the number of reported hours of physical activity in children with recent wheeze was comparable to children who had never wheezed. The reported physical activity was slightly higher in boys with past wheeze than in boys who had never wheezed, but this was not statistically significant. Likewise, obese children showed a tendency to report less physical activity than normal weight children, but this was not statistically significant. Children with overweight were reported by their parents to have very similar physical activity levels compared with normal weight children (results not shown).

Table 3.2: Wheezing in the first 5 years of life.

Wheeze Category	n		Total Activity, cpm		Vigorous Activity, Minutes >1234 Counts per 15 s			MVPA, No. of Times >812 Counts per 15 s for ≥1 min		
		GM	GMR (95% CI)	Adjusted GMR (95% CI)[a]	GM	GMR (95% CI)	Adjusted GMR (95% CI)[a]	GM	GMR (95% CI)	Adjusted GMR (95% CI)[a]
Boys										
Recent wheeze	18	635	1.02 (0.90–1.14)	1.06 (0.94–1.20)	5.0	1.03 (0.68–1.56)	1.17 (0.76–1.81)	2.8	1.07 (0.68–1.67)	1.28 (0.81–2.01)
Past wheeze	54	694	1.11 (1.02–1.20)[b]	1.11 (1.02–1.20)[b]	6.5	1.35 (1.02–1.78)[b]	1.38 (1.03–1.85)[b]	3.8	1.43 (1.05–1.93)[b]	1.38 (1.01–1.88)[b]
Never wheeze	80	625	1.00 (Reference)	1.00 (Reference)	4.8	1.00 (Reference)	1.00 (Reference)	2.6	1.00 (Reference)	1.00 (Reference)
Girls										
Recent wheeze	11	596	0.98 (0.85–1.13)	0.99 (0.85–1.14)	5.2	0.90 (0.59–1.40)	0.95 (0.61–1.48)	2.9	1.15 (0.65–2.03)	1.19 (0.67–2.11)
Past wheeze	36	606	1.00 (0.92–1.09)	1.02 (0.93–1.12)	5.6	0.98 (0.75–1.28)	0.99 (0.74–1.32)	2.7	1.09 (0.77–1.54)	1.17 (0.80–1.70)
Never wheeze	106	607	1.00 (Reference)	1.00 (Reference)	5.7	1.00 (Reference)	1.00 (Reference)	2.5	1.00 (Reference)	1.00 (Reference)

Physical activity was measured by Actigraph accelerometer at the age of 4 to 5 years. Recent wheeze indicates wheeze in the last 12 months (measured by the questionnaire at 4 to 5 years of age); past wheeze indicates wheeze in the past (measured by the questionnaire at 7 months and 1 and 2 years of age), but not in the last 12 months.

[a] Adjusted GMR indicates GMR adjusted for parental asthma, parental obesity, birth weight, smoking during pregnancy, environmental tobacco smoke exposure during the first 2 years of life, environmental tobacco smoke exposure at 4 to 5 years, breastfeeding in the first 6 months, education of the mother, and season of measurement.\; [b] The P value was <0.05 for comparison with the reference group (linear regression analysis); the associations between wheezing and physical activity were not statistically significantly different between boys and girls (test of interaction in the linear regression analyses: P>0.05).

Table 3.3: Overweight and Physical Activity, measured by Actigraph Accelerometer, both at age 4 to 5 years

Weight Category	n		Total Activity, cpm		Vigorous Activity, Minutes >1234 Counts per 15 s			MVPA, No. of Times >812 Counts per 15 s for ≥1 min		
		GM	GMR (95% CI)	Adjusted GMR (95% CI)[a]	GM	GMR (95% CI)	Adjusted GMR (95% CI)[a]	GM	GMR (95% CI)	Adjusted GMR (95% CI)[a]
Underweight	35	609	0.97 (0.89–1.05)	0.98 (0.90–1.07)	4.8	0.84 (0.64–1.09)	0.89 (0.68–1.17)	2.8	0.98 (0.72–1.35)	1.07 (0.77–1.47)
Normal weight	242	629	1.00 (Reference)	1.00 (Reference)	5.7	1.00 (Reference)	1.00 (Reference)	2.8	1.00 (Reference)	1.00 (Reference)
Overweight	22	655	1.04 (0.94–1.15)	1.03 (0.93–1.14)	5.7	1.01 (0.73–1.40)	0.92 (0.66–1.28)	3.0	1.07 (0.72–1.57)	0.99 (0.67–1.47)
Obesity	6	576	0.91 (0.76–1.10)	0.88 (0.73–1.06)	3.6	0.63 (0.34–1.16)	0.49 (0.26–0.92)[b]	1.2	0.41 (0.20–0.85)[b]	0.35 (0.17–0.74)[b]

[a] Adjusted GMR indicates GMR adjusted for gender, parental asthma, parental obesity, birth weight, smoking during pregnancy, environmental tobacco smoke exposure during the first 2 years of life, environmental tobacco smoke exposure at 4 to 5 years, breastfeeding in the first 6 months, education of the mother, and season of measurement; [b] The P value was <0.05 for comparison with the reference group (linear regression analysis).

Discussion

Our results indicate that 4- to 5-year-old children with recent wheeze have very similar physical activity levels compared with children who had never wheezed. We also found that boys with past wheeze were more physically active than boys who had never wheezed, whereas such a difference was not apparent in girls. We found a weak association between physical activity measured by accelerometer and obesity; there was a tendency in obese children to be less vigorously active and to show less MVPA for ≥1 minute. Comparable results were found in parent-reported data. We did not find an association between wheezing at any age and overweight or obesity.

The results do not confirm our working hypothesis, in which we postulated that wheezing children are hampered in physical activity because of their wheezing symptoms. This contradicts results from a similar study from Firrincieli et al.[25] They found that wheezing children are less physically active, although most outcome variables were not statistically significant. Only prolonged activity, defined as activity of >1000 cpm for ≥10 minutes, was statistically significantly decreased in wheezing children compared with nonwheezing children in the study from Firrincieli et al.[25] However, this cannot completely be compared with our study where MVPA for >1 minute was used, defined as >3248 cpm for ≥1 minute. Moreover, Firrincieli et al.[25] performed measurements in only 54 children, compared with 305 children in the present study. To our knowledge, no other study used objective activity measurements for exploring the association between wheezing and physical activity. All of the other studies used questionnaires to assess the physical activity level.

In our study, boys showed more physical activity and more wheezing symptoms than girls. This is in line with literature which describes that prevalences of asthma and wheezing are higher in boys than in girls until adolescence[33,34] and that boys tend to be more active than girls from an early age.[35,36] The higher physical activity level in boys with past wheeze compared with boys who had never wheezed could be explained by stimulation in physical activity. In the Netherlands, many physicians emphasize the importance of a normal level of physical activity in wheezing children, and they have to meet the same standard of health-enhancing physical activity as their healthy pears.[37] Several studies[38-40] have shown that, in asthmatic subjects, physical activity decreases symptoms and improves the quality of life. This could explain why these children do not wheeze anymore at age 4 to 5 years and still have a similar or even higher physical activity level than children who had never wheezed. Another explanation for the higher physical activity level in children with past wheeze could be that children who are more physically active at the age of 4 to 5 years were also more active in the first 2 years of life (eg, because of their temperament). Nystad[41] showed that children who are more physically active seem to report symptoms of wheezing more often. It is not clear

whether being more physically active increases the risk for developing asthma or whether breathlessness is experienced more often, which could be misinterpreted as wheezing. This higher physical activity level in children with past wheeze was only clear in boys, which could be explained by a gender difference in airway structure, which favors girls. It seems that girls exhibit a better lung function than boys, although lungs in females are smaller. An explanation for this is that large lungs have longer and narrower airways than small lungs.[33] It is possible that physically active boys are more prone to be troubled with (transient) wheeze because of these anatomic differences. Unfortunately, we have no accelerometer data in the first 2 years of life to examine this possible explanation. In our data we did not find a significant gender difference in wheezing or physical activity.

Our results indicate that 4- to 5-year-old children with recent wheeze were not different from children who had never wheezed in terms of physical activity. This is an important finding, because it rules out the explanation that wheezing children are hampered in physical activity through overprotective parents or self-imposed restrictions. It also makes it less plausible that overweight in wheezing children is caused by a lower level of physical activity, at least until the age of 5 years. In line with this, we found no relation between wheezing and overweight, but it must be remarked that the CIs were very wide because of the small number of children with combined wheezing and overweight in our population. Several studies have shown that there is a positive relationship between overweight or obesity and asthmatic symptoms, in which overweight mostly precedes wheezing.[9-17] Our prospective results show no evidence that wheeze precedes overweight or that they occur at the same moment at age 4 to 5 years. It is possible that overweight in wheezing children does not occur until later. However, this is not expected, because our results show normal physical activity levels in wheezing children, which would exclude physical activity as an intermediate factor between asthma and overweight. We did find an indication of lower physical activity in the small group of obese children. It is possible that these less physically active children are more likely to develop both obesity and asthma later in life, as has been described in the literature before.[42,43] Additional research is needed to explore this association.

A limitation of this study was the response, which was not very high (only 39%), likely because of the efforts that the parents had to make to come to the communal building twice. The questionnaires until 2 years of age (all sent by mail) had a very high response rate: >87%.[26] However, relevant background characteristics of the participating children were similar to those in the total cohort. Furthermore, the invitation was strongly focused on physical activity and overweight and did not mention wheezing or asthma. This makes it unlikely that bias occurred through a higher response of wheezing children.

Important strengths of this study compared with previous studies were the prospective design, the large number of participants, and the use of accelerometers. Another strength was the simultaneous use of questionnaires and accelerometers to determine the child's physical activity level. We found a weak correlation between questionnaire-derived information and accelerometer data, which corresponds with earlier literature.[24] Although it seems that the use of accelerometers is more objective and more reliable than the use of questionnaires, disadvantages should be considered too. Accelerometers tend to underreport physical activity during cycling and cannot be worn during swimming. In addition, the season and weather conditions have a large effect on the activity level in children. The multivariable analyses corrected for seasonal influences, and no measurements were conducted in the summer holiday to avoid periods when children swim a lot. Another disadvantage of accelerometers is the short duration in time, which only covered 5 days. To counterbalance these disadvantages, we also used the information from questionnaires. Herewith, we found similar results compared with accelerometer data.

Conclusions

We found no difference in the physical activity level between children with recent wheeze and children who had never wheezed. Boys with past wheeze showed higher physical activity levels than boys who never wheezed. The results did not confirm our hypothesis of wheezing causing overweight through lower levels of physical activity. Additional research could concentrate on the effect of physical activity and overweight on the development and severity of asthmatic symptoms.

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Chapter 4

Physical activity and asthma: a systematic review and meta-analysis

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Abstract

Introduction

This review aims to give an overview of available published evidence concerning the association between physical activity and asthma in children, adolescents and adults.

Methods

We included all original articles in which both physical activity and asthma were assessed in case-control, cross-sectional or longitudinal (cohort) studies. Excluded were studies concerning physical fitness, studies in athletes, therapeutic or rehabilitation intervention studies such as physical training or exercise in asthma patients. Methodological quality of the included articles was assessed according to the Newcastle-Ottawa Scale (NOS).

Results

A literature search was performed until June 2011 and resulted in 6,951 publications derived from PubMed and 1,978 publications from EMBASE. In total, 39 studies met the inclusion criteria: 5 longitudinal studies (total number of subjects n=85,117) with physical activity at baseline as exposure, and asthma incidence as outcome. Thirty-four cross-sectional studies (n=661,222) were included. Pooling of the longitudinal studies showed that subjects with higher physical activity levels had lower incidence of asthma (odds ratio 0.88 (95% CI: 0.77-1.01)). When restricting pooling to the 4 prospective studies with moderate to good study quality (defined as NOS ≥5) the pooled odds ratio only changed slightly (0.87 (95% CI: 0.77-0.99)). In the cross-sectional studies, due to large clinical variability and heterogeneity, further statistical analysis was not possible.

Conclusions

The available evidence indicates that physical activity is a possible protective factor against asthma development. The heterogeneity suggests that possible relevant effects remain hidden in critical age periods, sex differences, or extremes of levels of physical activity (e.g. sedentary). Future longitudinal studies should address these issues.

Introduction

The prevalence of asthma has increased significantly during the past decades.[1] Concurrently, the prevalence of overweight has increased, while physical activity levels have decreased substantially.[2,3] In 2005, less than half (49.1%) of US adults met the CDC/ACSM (Centers for Disease Control and Prevention/American College of Sports Medicine) physical activity recommendation (at least 30 minutes of moderately intense activity on five days per week or vigorously intense activity for a minimum of 20 minutes on three days each week).[4] Physical inactivity is an important risk factor, because it is potentially modifiable and therefore an opportunity for prevention. Several studies have shown that training improves cardiopulmonary fitness, asthma symptoms and quality of life in asthmatic subjects.[5] This evidence suggests that training and high levels of physical activity play a role in the course and severity of asthma. Besides this, an etiological relation between physical activity levels and development of incident asthma might also be possible. Different hypotheses have been suggested to explain the possible protective character of physical activity against asthma development such as reducing airway inflammation, a central feature of asthma.[6] Another explanation is that physical activity could positively influence the patency of bronchioles: poor mucociliary clearance from decreased epithelial stimulation secondary to decreased activity can cause excess mucus and airway edema. Decreased deep inspiration and sigh rate during physical inactivity could lead to smooth muscle latching and subsequent increased risk of asthmatic symptoms.[7]

We performed a systematic literature review to evaluate the potential causal relation between physical (in)activity and asthma development, and a pooled analysis to estimate the effect size.

Methods

Search strategy

We conducted an electronic search in PubMed (US National Library of Medicine) and EMBASE to obtain all publications on studies that reported on physical activity and asthma published until June 2011. The PubMed search used the Medical Subject Headings (MeSH) terms “motor activity” or text word terms “activity”, “physical activity”, “physical exercise” or “sedentary”, as well as the MeSH term “asthma” or text word terms “asthma”, “asthmatic”, “wheeze” or “wheezing”. The EMBASE search used the MeSH terms “motor activity” or “physical activity” or text word terms “physical activity”, “physical exercise”, “sedentary”, as well as the MeSH terms “asthma” or “wheezing” or the text word terms “asthma”, “asthmatic”, “wheeze” or “wheezing”.

These terms were searched using limits that included all articles published in the English language. There were no age restrictions.

We conformed to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines for reporting[8] and PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[9]

Inclusion

Our primary research question concerned the role of habitual physical activity in the development of incident asthma. Therefore, we searched for longitudinal studies in which the exposure (physical activity) precedes the outcome (onset of asthma). In addition, we included studies that looked into asthma prevalence in different physical activity levels. For this goal, we searched cross-sectional studies that investigated physical activity levels in subjects with asthma compared to controls. For maximal sensitivity, a broad inclusion strategy was used. Inclusion criteria were: original articles in which physical activity as well as asthma was studied, and a control group consisting of healthy subjects or general population. Excluded were studies that did not concern habitual physical activity such as studies in athletes, physical fitness, therapeutic or rehabilitation intervention studies such as physical training in asthma patients. Two investigators (ME, MM) independently assessed whether articles met the inclusion criteria. In case of disagreement, consensus was reached through discussion.

Quality assessment and data extraction

Methodological quality of included articles was assessed according to the Newcastle-Ottawa Scale (NOS). This instrument was developed to assess the quality of nonrandomized studies. Its content validity and inter-rater reliability has been established.[10] The NOS gives predefined criteria, some of which have to be further specified for the specific topic. We specified these criteria in a consensus meeting with all authors (criteria are presented in Figure S4.4.A and S4.4.B in the appendix) before assessing the studies. In short, longitudinal studies were assessed for quality of selection (representativeness, selection of controls, ascertainment of exposure, no asthma at start of study); comparability (confounding); and outcome (assessment of outcome, length and adequacy of follow-up). Gender, weight, and smoking were identified as important confounders. Studies could be awarded a maximum score of 9 points. Studies with scores of 5 points or more were considered to be of moderate to good study quality. However, all studies were used for analysis, irrespective of NOS score. Quality assessment was done by all five authors using the NOS. Each single article was assessed by at least three authors independently. In case of disagreement the other two authors were consulted. Quality assessment was completed before data extraction was started. Data were extracted from the full text article. Quantitative

results were extracted from text and tables, choosing preferably those adjusted for important confounders (gender, weight, and smoking). Data-extraction in the longitudinal studies was performed independently by two authors (ME, CT). If essential data were lacking in the original studies, their authors were contacted.

Statistical analysis

Analyses were performed using the statistical software Review Manager version 5.[11] Heterogeneity among studies was assessed using the chi-square test (significant at $p<0.05$) and the Higgins I^2 test.[12] A random effects model with the Mantel–Haenszel method was used for pooling the results of different studies. Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated for the longitudinal studies and a subgroup of the cross-sectional studies, namely those studies that used a motion sensor for measuring physical activity levels. We decided to refrain from statistical pooling of the other cross-sectional studies because of substantial clinical and methodological heterogeneity.

Results

Literature search

The search resulted in 6,951 publications derived from PubMed, and 1,978 studies from EMBASE. Based on titles and abstracts, 8,790 articles were excluded at first screening because they did not meet the eligibility criteria, such as experimental studies with intermediate outcomes (such as inflammatory markers) but no asthma as clinical outcome, case reports and studies with case series without control group, and studies of exercise induced asthma in athletes. Full-text copies of the remaining 139 potentially relevant studies were obtained. Ninety-five studies were excluded because they did not meet the inclusion criteria. Four were excluded because they were duplicate publications of the same studies. One study was not available in full-text. The remaining 39 studies were included for this systematic review. Five studies were longitudinal studies and 34 were cross-sectional in design (Figure 4.1).

Study quality

All 39 studies were assessed using the adjusted NOS scale (see appendix Figure S4.4.A and S4.4.B for the adjusted NOS scales), of which the majority (79%) scored 5 points or more, indicating a moderate to good study quality (appendix Table 4.A and 4.B). When grouped by study quality, we could not detect a clear pattern in study results or study characteristics (Tables 4.1 and 4.2). The authors of 4 articles[13-16] were contacted to obtain essential data that were lacking in the original studies, of which 3 replied.[14-16]

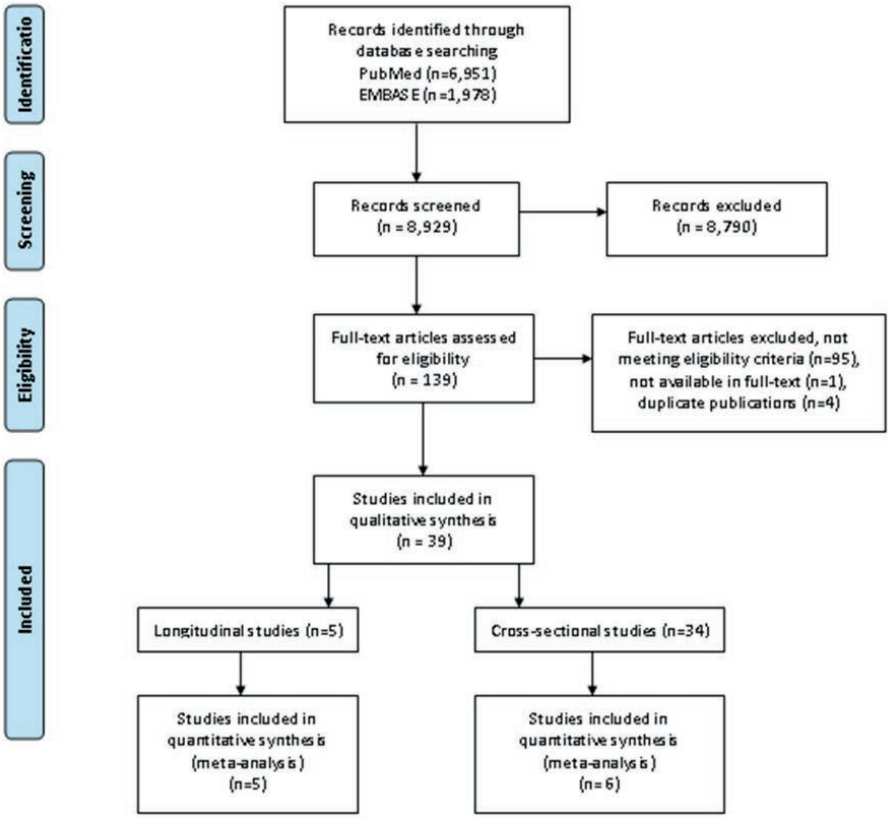

Figure 4.1: Flow diagram of study inclusion.

Longitudinal studies

Study characteristics and odds ratios of the longitudinal studies[14; 17-20] are summarized in Table 4.1. All 5 studies looked into physical activity levels of subjects at baseline and incident asthma during follow up. Follow up duration ranged between 5 and 10 years. Physical activity was assessed by questionnaires. Different reference categories, subgroups and confounders were used (Table 4.1). Asthma diagnosis was defined as doctor's diagnosis, either through self-report or linkage to an insurance registry.

Table 4.1: Overview of longitudinal studies on physical activity at baseline and incident asthma.

Study basics					Physical activity	Asthma	Confounders	Follow up (yrs)	NOS	Odds ratio (95% CI)	Reference
Reference	*Country*	*n*	*Age*	*Population*	*Measurement*	*Diagnosis*					
Beckett 2001	US	4,547	18-30	African American and white adults	Questionnaire #c	Asthma medication or doctor's diagnosis (self-reported)	Gender, other #h	10	7	2nd quintile: aHR 0.81 (0.57-1.15) 3rd quintile: aHR 0.84 (0.59-1.20) 4th quintile: aHR 0.94 (0.66-1.35) 5th quintile: aHR 1.08 (0.75-1.55)	Highest quintile PA
Benet 2011	France	51,080	40-65	Women	Questionnaire #d	Asthma attacks and doctor's diagnosis (self-reported)	Weight, smoking, other #i	9	7	2nd tertile: aHR 1.03 (0.83-1.27) 3rd tertile: aHR 1.00 (0.81-1.24)	Lowest tertile PA
Huovinen 2003	Finland	9,671	25-52	Twins#b	Questionnaire #e	Doctor's diagnosis (insurance register)	Gender, weight, smoking, other #j	9	7	Men: Occasional: aOR 0.86 (0.41-1.81) Conditioning: aOR 0.54 (0.22-1.33) Women: Occasional: aOR 1.83 (0.74-4.51) Conditioning: aOR 1.42 (0.51-3.93)	Sedentary
Lucke 2007 #a	Australia	19,021	18-75	Women	Questionnaire #f	Doctor's diagnosis (self-reported)	None stated	5-7	6	Older (age 70-75): Nil/low PA: OR 1.15 (0.92-1.47) Mid-aged (age 45-50): Nil/low PA: OR 1.28 (1.09-1.56) * Younger (age 18-23): Nil/low PA: OR 1.12 (0.82-1.54)	Moderate/ high PA
Thomsen 2006	Denmark	798	12-41	Discordant twin pairs	Questionnaire #g	Asthma (self-reported)	None stated	8	3	Dizygotic twin pairs: High PA: OR 1.48 (0.84-2.61) Monozygotic twin pairs: High PA: OR 0.35 (0.13-0.91) *	Low PA

Overview of study characteristics, study quality based on the Newcastle-Ottawa Scale (NOS) and odds ratios of longitudinal studies on physical activity and asthma incidence. Note that Beckett and Lucke use high physical activity levels as reference category, while Benet, Huovinen and Thomsen use low physical activity levels as reference category.CI; confidence interval, PA; physical activity, aHR; adjusted hazard ratio, aOR; adjusted odds ratio, OR; odds ratio. * P<0.05.#a Data provided by the authors; #b Analyses did not account for the correlation between twin pairs but twins were considered unrelated subjects; #c PA assessed through questionnaires using the Physical Activity History Score (validated); categorized in five equal levels (quintiles); #d PA defined as time spent in household and leisure time PA, converted to metabolic equivalents (METs); categorized in three equal levels (tertiles); #e Three categories of PA: Sedentary: Respondents estimating their own leisure time physical activity as practically non-existent; Conditioning: Respondents who exercised at least 6 times per month for at least 30min with a mean intensity corresponding to walking; Occasional: Respondents who did not meet the criteria of sedentary or conditioning. #f Two categories of PA: Nil/low PA: <600 METs (metabolic equivalents) per week (this reflects 30 minutes of moderate activity on five days each week). Moderate/high PA: > 600 METs per week; #g Two categories of PA: Low PA: <2 hours per week of light leisure time exercise activities. High PA: >2 hours per week of light leisure time exercise activities. #h other confounders: age, race, centre, and maximal education; #i other confounders: menopausal status, education level, working status, and co-morbidities; #j other confounders: age, atopy, and respiratory symptoms.

Statistical analysis and pooling

Data of the 5 longitudinal studies were pooled using a random effects model (Figure 4.2). Data on studies with more than two groups of different physical activity levels were converted into two groups, namely low physical activity and high physical activity, of which low physical activity was used as reference category. In case of an uneven number of groups, the reference category consisted of the lowest physical activity levels including the middle group.

Pooled odds ratio was 0.88 (95% CI: 0.77-1.01). Chi-square test for heterogeneity was borderline significant (p=0.07). Higgins I^2 index was 45%, indicating moderate inconsistency. These results are not adjusted for potential confounders as the majority of studies did not provide adjusted results. When we restricted analysis to the studies with moderate to good study quality, identified by NOS scores of 5 or higher, 4 studies remained.[14,17-19] Sensitivity analysis showed a consistent result: the pooled odds ratio did not change much (0.87 (95% CI: 0.77-0.99)) but did reach statistical significance.

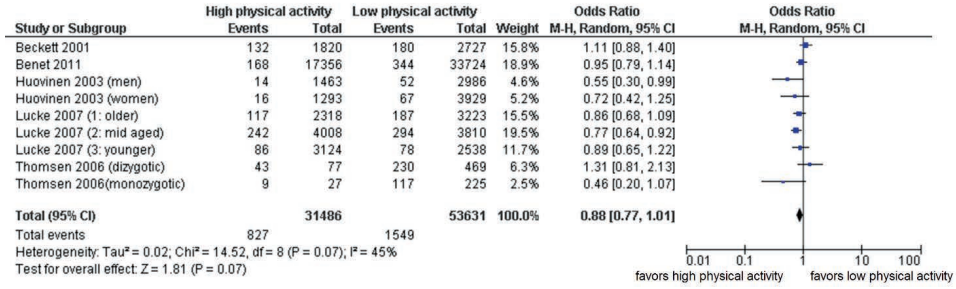

Figure 4.2: Pooling of longitudinal data on physical activity and risk of asthma incidence.
M-H; Mantel-Haenszel method, Random effects, CI; confidence interval. Not adjusted for potential confounders. Low physical activity used as reference category. Note that odds ratios are different of those in table 4.1 because reference categories were reversed and/or the number of categories was converted into two categories per study. For example Beckett et al. and Lucke et al. use high physical activity as reference category; in our meta-analysis we standardized low physical activity as reference category. In studies were more than two categories of physical activity were used (such as Beckett et al. who used 5 levels of physical activity), these were converted into two categories (in case of Becket et al. we converted the highest two levels into high physical activity, and the lowest three levels into low physical activity).

Cross-sectional studies

Study characteristics and results of the 34 cross-sectional studies[13,15,16,21-52] are summarized in Table 4.2. The vast majority (25 studies) examined children of different age spans, 8 studies included only adults, and one study included both children (12 years and older) and adults (Table 4.2).

Table 4.2: Overview of cross-sectional studies on physical activity and asthma prevalence.

Study basics				Physical activity	Asthma	Confounders	NOS	Odds ratio (95% CI)	Reference	Author's conclusions
Reference	*Country*	*n*	*Age*	*Measurement*	*Diagnosis*					
Adults										
Questionnaire										
Chen 2001	Canada	16,813	>12	Questionnaire #c	Doctor's diagnosis (self-reported)	Weight, smoking, other	6			It was concluded that asthmatics were not consistently inactive compared with non-asthmatics.
Dogra 2008	Canada	21,636	65-79	Questionnaire #f	Doctor's diagnosis (self-reported)	Gender, weight, other	5			Older asthmatics were less active than their non-asthmatic peers.
Ford 2003	U.S.	165,123	>18	Questionnaire #bdf	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	8			Participants with current asthma were significantly more often considered to be inactive and had significantly lower estimated energy expenditure compared with respondents who never had asthma.
Kilpeläinen 2006	Finland	10,667	18-25	Questionnaire #a	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	7	Men: Moderate PA: aOR 0.62 (0.42–0.92)* Vigorous PA: aOR 0.77 (0.56-1.07) Women: Moderate PA: aOR 0.77 (0.56-1.07) Vigorous PA: aOR 1.19 (0.88-1.60)	low PA	Moderate leisure time physical activity was associated with lower risk of asthma in men, but not among women
Mälkiä 1998	Finland	7,193	>30	Questionnaire #d	Doctor's diagnosis (self-reported) and spirometry	Gender	7			The intensity of physical activity was lower in the asthmatic subjects than in those who were not asthmatic.
Ritz 2010	U.S.	40	21-38	Questionnaire #a	Doctor's diagnosis	Other	2			No differences were found between asthma and controls in physical activity.
Strine 2007	U.S.	354,025	>18	Questionnaire #f	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	7	No leisure time PA in past 30 days: aOR 1.2 (1.1-1.2)*	Leisure time PA in past 30 days	Moreover, persons who (…) were physically inactive were slightly more likely to have asthma than those without (…) these behaviors.
Teramoto 2011	U.S.	3,840	>18	Questionnaire #bf	Doctor's diagnosis (self-reported)	Gender, weight	6	No regular PA: aOR 3.01 (1.63–5.55)*** No leisure time PA in past 30 days: aOR 2.17 (1.40–3.37)***	Regular PA in past 30 days	It was found that asthmatic people spent significantly less time on moderate and vigorous physical activity than their nonasthmatic counterparts.

Table 4.2: (continued)

Study basics				Physical activity	Asthma	Confounders	NOS	Odds ratio (95% CI)	Reference	Author's conclusions
Reference	***Country***	***n***	***Age***	***Measurement***	***Diagnosis***					
Vogt 2008	U.S.	4,925	> 18	Questionnaire #b	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	7			[No significant relation between physical activity and asthma diagnosis.]
Children										
Questionnaire										
Bener 1996	United Arab Emirates	729	6-14	Questionnaire #f	Asthma symptoms (self-reported)	None stated	3			Environmental risk factors associated with asthma were (…) physical exercise. (…)
Cheng 2010	China	232	7-14	Questionnaire #a	Doctor's diagnosis and spirometry	Gender	4			Asthmatic children took part in less exercise than their healthy peers.
Chiang 2006	China	429	9-11	Questionnaire #ab	Doctor's diagnosis	Gender, weight, other	5	MVPA >90 min/week: Healthy controls: OR 1.24 (0.57-2.71) VPA >60min/week: Healthy controls: OR 2.03 (1.31-3.15)**	Diagnosed asthma	Asthma interferes with children's ability to participate in vigorous physical activity but not in moderate-to-vigorous physical activity.
Corbo 2008	Italy	20,016	6-7	Questionnaire #ae	Asthma symptoms (self-reported)	Gender, weight, smoking, other	7	Rarely PA: aOR 1.05 (0.85-1.29) 1-2 times/week: aOR 1.13 (0.93-1.38) >3 times/week: aOR 1.33 (0.99-1.77)	No PA	Our data support the hypothesis that (…) spending a lot of time watching television (…) increases the risk of asthma symptoms in children. Wheeze or asthma was not associated with regular sports activity.
Gannotti 2007	U.S.	15,300	9	Questionnaire #ae	Doctor's diagnosis (self-reported)	None stated	5			For children with asthma (…), the most frequent perception of parents was that their children were as active as their peers. Days per week of aerobic activity, number of structured activities per week, and playing sports with parents three times a week or more did not vary significantly between children with and without disabilities [including asthma].

Table 4.2: (continued)

Study basics				Physical activity	Asthma	Confounders	NOS	Odds ratio (95% CI)	Reference	Author's conclusions
Reference	*Country*	*n*	*Age*	*Measurement*	*Diagnosis*					
Glazebrook 2006	U.K.	117	7-14	Questionnaire #a	Doctor's diagnosis and Peak Flow variability	Gender, weight, other	2			We found that children attending a hospital clinic for asthma (…) were significantly less active than a comparison group with other medical conditions.
Jones 2006	U.S.	13,222	high school (grades 9-12)	Questionnaire #bef	Doctor's diagnosis (self-reported)	Gender, other	6	Sufficient VPA: Current asthma: OR 1.1 (1.0-1.3) Sufficient MPA: Current asthma: OR 1.1 (0.9-1.3)	No asthma	No significant differences were found for participation in sufficient vigorous or moderate physical activity or strengthening exercises among students with and without current asthma.
Kitsantas 2000	U.S.	135	14-18	Questionnaire #a	Doctor's diagnosis	Gender (only girls included)	6			It was found that asthmatic girls (…) participated less often in vigorous activities than nonasthmatic girls.
Lang 2004	U.S.	243	6-12	Questionnaire #af	Doctor's diagnosis (self-reported)	None stated	4			Children with asthma were less active than their peers.
Children										
Questionnaire (continued)										
Nystad 1997	Norway	4,585	7-16	Questionnaire #a	Doctor's diagnosis (self-reported)	Gender, other	5	PA 1-3 times/week: aOR 0.9 (0.5-1.4) PA >3 times/week: aOR 1.1 (0.6-1.9)	PA <3 times/month	The data suggest that asthmatic children are as physically active as their peers.
Ownby 2007	U.S.	636	8-10	Questionnaire #d	Doctor's diagnosis (self-reported)	Gender, other	7			Higher levels of physical activity were related to more diagnosed asthma.
Priftis 2007	Greece	700	10-12	Questionnaire #ade	Asthma symptoms (self-reported)	Gender, weight, other	7	Not participating in any PA: Asthmatic boys: aOR 2.17 (1.34-3.54)* Asthmatic girls: aOR 1.63 (0.86-3.11)	No asthma	Multiple logistic regression analysis revealed that (…) sedentary lifestyle is associated with asthma symptoms only in boys.
Romieu 2004	U.S.	7,851	2-16	Questionnaire #e	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	7	Television watching >4 hours/day: aOR 2.67 (0.97-7.31)	Television watching <3 hours/day	[No significant relation between physical activity and and asthma diagnosis.]

Table 4.2: (continued)

Study basics				Physical activity	Asthma	Confounders	NOS	Odds ratio (95% CI)	Reference	Author's conclusions
Reference	*Country*	*n*	*Age*	*Measurement*	*Diagnosis*					
Tsai 2007	China	2,218	11-12	Questionnaire #ae	Doctor's diagnosis (self-reported)	Gender, weight, other	6	Boys: PA 1-2 times/week: aOR 0.74 (0.42-1.32) PA > 3 times/week: aOR 0.55 (0.30-1.03) PA every day: aOR 0.76 (0.43-1.35) Girls: PA 1-2 times/week: aOR 1.63 (0.69-3.84) PA > 3 times/week: aOR 2.27 (0.92-5.59) PA every day: aOR 1.74 (0.67-4.47)	PA low (<1 time/ week)	Results of the present study suggest that sedentary life is associated with increased risk of respiratory symptoms. [No significant relation between physical activity and asthma diagnosis.]
Tsai 2009	China	1,287	11-12	Questionnaire #ae	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	7	PA > 30 min, times/week: aOR 1.02 (0.96-1.09)	PA <30min times/ week	The number of respiratory symptoms was positively correlated with (...) self-reported sedentary time per weekend-day in girls. [No significant relation between physical activity and asthma diagnosis.]
Vlaski 2008	Macedonia	3,026	13-14	Questionnaire #ae	Doctor's diagnosis (self-reported)	Gender, weight, smoking, other	7	VPA 1-2 times/week: aOR 1.84 (0.94-3.60) VPA >3 times/week: aOR 1.13 (0.40-3.23)	VPA occasionally/never	The findings support the aggravating role of sedentary regimen and poor physical fitness on asthma symptoms. [No significant relation between physical activity and asthma diagnosis.]
Vogelberg 2007	Germany	2,910	16-18	Questionnaire #ae	Asthma symptoms (self-reported)	Gender, weight, smoking, other	6	Sport > 3 times/week: aOR 0.8 (0.5-1.3)	Sport <1 time/ month	In the bivariate analyses, exercising more than once per week (...) was inversely related to new onset of wheeze. The association between physical activity and new onset of wheeze disappeared when active smoking was taken into account.
Weston 1989	New Zealand	408	11-13	Questionnaire #a	Doctor's diagnosis (self-reported)	None stated	4			Asthmatic children were significantly more active than nonasthmatic children for all activities and for school activities.

Table 4.2: (continued)

Study basics				Physical activity	Asthma	Confounders	NOS	Odds ratio (95% CI)	Reference	Author's conclusions
Reference	*Country*	*n*	*Age*	*Measurement*	*Diagnosis*					
Children										
Motion sensor										
Berntsen 2009	Norway	174	13-14	Accelero-meter SenseWear #ac	Doctor's diagnosis (self-reported)	Gender, other	7			Neither aerobic fitness, total energy expenditure nor hours in moderate to very vigorous intensity physical activity during week and weekend differed between adolescents with and without asthma.
Eijkemans 2008	The Nether lands	305	4-5	Accelero-meter Actigraph and Questionnaire #a	Asthma symptoms (self-reported)	Smoking, other	6	Total activity (counts/minute) Boys: Recent wheeze: aGMR 1.06 (0.94-1.20) Girls: Recent wheeze: aGMR 0.99 (0.85-1.14)	Never wheeze	Our data provide no evidence that asthmatic symptoms induce a lower physical activity level.
Firrincieli 2005	U.S.	54	3-5	Accelero-meter Actiwatch #a	Asthma symptoms (self-reported)	None stated	5			Physical activity measured with the motion sensor was decreased among children with a history of wheezing.
Rundle 2009	U.S.	437	4	Accelero-meter Actiwatch #ae	Doctor's diagnosis or wheeze (both self-reported)	Weight, other	5	Quartile of mean activity counts/minute Quartile 2: aOR 0.85 (0.45-1.63) Quartile 3: aOR 1.03 (0.54-1.96) Quartile 4: aOR 0.91 (0.46-1.80)	Quartile 1 (lowest PA)	In cross-sectional analyses (…) asthma symptoms were not associated with physical activity in this age group.
Vahlkvist 2009	Denma rk	214	6-14	Accelero-meter RT3 #ad	Asthma symptoms (self-reported) and FEV variability	None stated	4			No statistically significant differences were found between the two groups [asthma vs no asthma] in overall daily activity, time spent in high or vigorous activity (…)
Van Gent 2007	The Nether lands	1,614	7-10	Accelero-meter PAM and Questionnaire #a	Doctor's diagnosis (self-reported) and FEV variability	None stated	6			Childhood asthma does not appear to be associated with a decreased level of daily physical activity in our study population.

Table 4.2: (continued)

Study basics				Physical activity	Asthma	Confounders	NOS	Odds ratio (95% CI)	Reference	Author's conclusions
Reference	*Country*	*n*	*Age*	*Measurement*	*Diagnosis*					
Walders-Abramson 2009	U.S.	118	10-16	Pedometer Omron #a	Doctor's diagnosis (self-reported) and asthma medication	None stated	7			We found similar rates of objectively measured physical activity among youth with well controlled asthma and controls.

Overview of study characteristics, study quality based on the Newcastle-Ottawa Scale (NOS), odds ratios and author's conclusions of cross-sectional studies on physical activity and asthma prevalence. Odds ratios are noted here only if odds ratios or equivalents with 95% confidence intervals are specified in the article. Author's conclusions are noted only if the author mentions a conclusion on the relation between physical activity and asthma prevalence. If not, a conclusion was drawn based on the data in the article. In this case the conclusion is noted between [ ]. CI; confidence interval, PA; physical activity, aOR; adjusted odds ratio, aHR; adjusted hazard ratio, OR; odds ratio, aGMR; adjusted geometric mean ratio, MVPA; moderate to vigorous physical activity, VPA; vigorous physical activity. * P<0.05; ** P<0.01; *** P<0.001; #a frequency of physical activity (PA); #b participation of enough PA to meet the recommendations for PA; #c Energy Expenditure (EE); #d Metabolic Equivalent of Task (MET); #e physical inactivity (e.g. TV watching, computer play); #f physically active vs. physically not active group.

Physical activity was assessed by motion sensors in 7 studies[13,16,22,28,42,48,49], all examining children (n=2916). In these studies, asthma was defined as self-reported doctor's diagnosis or asthma symptoms. Two studies[48,49] combined self-reported asthma diagnosis with spirometry. Not enough data were available for pooling in one study (i.e. standard deviations were missing despite contacting the authors).[13] Data of the other 6 studies using motion sensors were pooled: standard mean difference -0.19 (95% CI -0.69; +0.32) (Figure 4.3). Testing for heterogeneity showed a highly significant result (p<0.00001) and high inconsistency (I^2=94%).

The other 27 studies used only questionnaires to assess physical activity levels. Methods were diverse (Table 4.2): the majority focused on activity by counting frequency and duration of activity per time unit (month, week, day).[15,24-26,30,31,33-35,37,39,40,46,47,50,52] Others looked into the proportion of subjects that was physically active[21,27,29,32,35,43,44] or met the physical activity recommendation.[25,29,32,44,51] A relatively small number of studies focused on energy expenditure per day[23] or metabolic equivalent of task (MET).[29,36,38,39] Besides physical activity, inactivity (television watching, sedentary time) was also investigated by 9 studies.[15,26,30,32,39,41,46,47,50] Asthma was defined as self-reported doctor's diagnosis or asthma symptoms. Only three studies combined questionnaire based asthma diagnosis with spirometry.[24,31,36]

We decided to refrain from statistical pooling due to heterogeneity of study designs, populations, and measurement methods for both physical activity and asthma outcome.
In total, 13 studies (564,394 subjects in total) reported a statistically significant association between high physical activity levels and lower asthma prevalence.[13,24,25,27,29,31,33-36,39,43,44] In contrast, 3 studies (total of 1,773 subjects) found a statistically significant association between high physical activity levels and higher asthma prevalence.[21,38,52] Eighteen studies (95,055 subjects) obtained no significant results.[15,16,22,23,26,28,30,32,37,40-42,46-51]

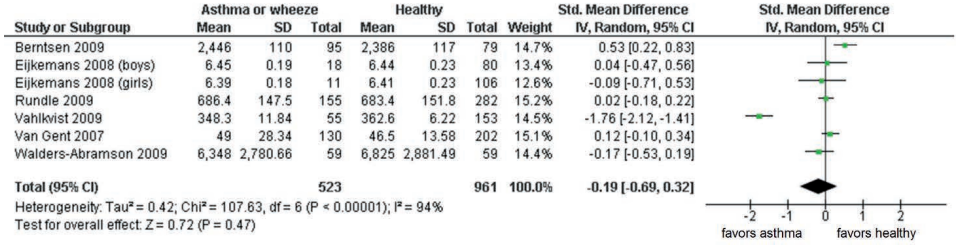

Figure 4.3: Pooling of cross-sectional data using motion sensors: physical activity and asthma.
Figure 4.3. pooling of cross-sectional data using motion sensors: physical activity measured by motion sensors and asthma prevalence. Random effects, CI; confidence interval. Not adjusted for potential confounders. Low physical activity used as reference category.

Discussion

This systematic review gives an overview of the published evidence concerning the association between physical activity and asthma. Our primary research question was aimed at the etiological association between different physical activity levels and subsequent asthma incidence. In an extensive search, we only found 5 longitudinal studies that met the inclusion criteria and could be of use in answering this question. Although the number of longitudinal studies was small, the total accrued number of subjects was considerable (n=85,117). Pooling showed that subjects with higher physical activity levels might have lower risk of developing asthma.

Thirty-four studies were cross-sectional in design. Due to large clinical variability and heterogeneity we had to refrain from further statistical analysis, except for a small group of studies using a motion sensor to measure physical activity. Despite this limitation, however, we can draw some conclusions: a substantial number of included cross-sectional studies, with the largest total study population, did find an association between high physical activity levels and low asthma prevalence. This seems consistent with physical activity being protective against asthma. However, we can not rule out publication bias. Moreover, cross-sectional studies are not suited to give insight into the causal relation between physical activity and subsequent asthma incidence. Besides the hypothesis that subjects with higher physical activity levels have a lower risk of developing asthma (protective), reverse causality is also possible. There are several hypotheses why asthma patients (with asthma as exposure) could have lower physical activity levels (outcome), such as fear for symptoms of shortness of breath, wrongful education, or by asthma that is not well regulated.

In contrast to the studies that were cross-sectional in design, this reverse causality does not play a role in interpreting the results of the 5 longitudinal studies. In all 5 studies physical activity levels were measured before asthma was diagnosed. However, the results could be influenced by protopathic bias (e.g. physical activity restricted by respiratory complaints that precede an asthma diagnosis) or earlier diagnosis of asthma through exercise-induced symptoms. The first would lead to overestimation of the true association between low physical activity levels and subsequent asthma development; whereas the second would lead to an underestimation. Unfortunately, none of the longitudinal studies addressed these biases.

Limitations

It is important to realize that there are several limitations to this review. First of all, due to the fact that this research is based on published material, publication bias is an important factor. Furthermore, studies showed substantial heterogeneity in different

areas such as population (number, age, gender, race, duration of follow-up), exposure variables (physical activity measured by questionnaires, whether or not validated, or measured by motion sensors) and outcome variables (asthma diagnosis as self-reported doctor's diagnosis, asthma symptoms or spirometry). Analysis showed borderline statistical heterogeneity. The small number of longitudinal studies prevented us from performing meta-regression or subgroup analysis. Confounding is an important issue, because other risk factors (such as smoking and obesity) could be associated with both low habitual physical activity as well as asthma development. First and second-hand cigarette smoke exposure is already established as an independent risk factor for developing asthma.[53] It is suggested that obesity is a risk factor for asthma development.[54] In our meta-analysis of longitudinal studies, pooling of results adjusted for confounders was not sensible because only three studies presented such results. However, adjusted odds ratios were never lower than unadjusted odds ratios (see appendix Table 4.C), so that a pooled effect for the adjusted results would be higher than the odds ratio of 0.88 (95% CI: 0.77-1.01) found for the unadjusted result.

Another limitation might be the fact that the validity of the NOS score recently has been questioned by Stang who believes that the NOS provides a quality score that has unknown validity at best.[55] We noted that some methodological pitfalls were not well represented in the NOS scale: reverse causation and protopathic bias or confounding by indication (e.g. advice to remain physically active for children with respiratory complaints).

Conclusion

In conclusion, the results of available published evidence indicate that high physical activity levels are a possible protective factor against asthma development. The heterogeneity suggests that possible relevant effects remain hidden in critical age periods, sex differences, or extremes of levels of physical activity (e.g. sedentary). Future longitudinal studies should address these issues.

Appendix

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES
Review: physical activity and asthma

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the general population ✸
   b) somewhat representative of the general population ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) use of accelerometer ✸
   b) validated questionnaire ✸
   c) not validated questionnaire or no validation is mentioned
   d) no description
4) Demonstration that outcome of interest was not present at start of study (no asthma at start of study)
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for gender ✸
   b) study controls for any smoking (eg. parental smoking, past smoking, smoking during pregnancy) AND weight (eg. BMI, overweight, obesity) ✸

Outcome

1) Assessment of outcome
   a) doctor's diagnosis (not self-reported doctor's diagnosis) OR objective measurements (eg. lungfunction) ✸
   b) parent/self-reported doctor's diagnosis OR use of asthma medication ✸
   c) parent/self-report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (majority of population at least 1 year) ✸
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost, proving a non-selective loss to follow up ✸
   c) follow up rate < 80% and no description of those lost, or a selective loss to follow up
   d) no statement

Figure 4.A: NOS scale physical activity and asthma longitudinal studies.
NOS: Newcastle-Ottawa Scale. Adjusted NOS scale for physical activity and asthma in longitudinal studies.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES
Review: physical activity and asthma

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection
1) Is the case definition (asthma) adequate?
   a) yes, with independent validation (eg. self-reported doctor's diagnosis, reference to primary record source) ✸
   b) yes, based on self-reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases (random sample of cases) ✸
   b) potential for selection biases or not stated
3) Selection of Controls
   a) community controls (same community as cases)✸
   b) hospital controls
   c) no description
4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability
1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for gender ✸
   b) study controls for any smoking (eg. parental smoking, past smoking, smoking during pregnancy) AND weight (eg. BMI, overweight, obesity) ✸

Exposure
1) Ascertainment of exposure
   a) use of accelerometer ✸
   b) validated questionnaire ✸
   c) not validated questionnaire or no validation is mentioned
   d) written self-report
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no
3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

Figure 4.B: NOS scale physical activity and asthma cross-sectional studies.
NOS: Newcastle-Ottawa Scale. Adjusted NOS scale for physical activity and asthma in cross-sectional studies.

Table 4.A: NOS scores of longitudinal studies.

NOS scale	Beckett 2001	Benet 2011	Huovinen 2002	Lucke 2007	Thomsen 2006
A Selection (maximum 4)	4	3	3	3	2
1 Representativeness of the exposed cohort	1	0	1	1	0
2 Selection of the non-exposed cohort	1	1	1	1	1
3 Ascertainment of exposure	1	1	0	0	0
4 Demonstration that outcome of interest was not present at start of study	1	1	1	1	1
B Comparability (maximum 2)	1	2	2	1	0
1 Comparability of cohorts on the basis of the design of analysis	1	2	2	1	0
C Outcome (maximum 3)	2	2	2	2	1
1 Assessment of outcome	1	1	1	1	0
2 Was follow-up long enough for outcomes to occur	1	1	1	1	1
3 Adequacy of follow up of cohorts	0	0	0	0	0
Totaal (maximum 9)	7	7	7	6	3

NOS: Newcastle-Ottawa Scale. Result of quality assessment of longitudinal studies on physical activity and asthma using NOS scores. We refer to figure 4.A for the adjusted NOS for longitudinal studies, which was used as a scoring list.

Table 4.B: NOS scores of cross-sectional studies.

NOS scale	Bener 1996	Berntsen 2009	Chen 2001	Cheng 2010	Chiang 2006	Corbo 2008	Dogra 2008	Eijkemans 2008	Firrincieli 2005	Ford 2003	Gannotti 2007	Glazebrook 2006	Jones 2006	Kilpeläinen 2006	Kitsantas 2000	Lang 2004	Mälkiä 1998
A Selection (maximum 4)	2	4	3	2	2	4	3	3	3	4	4	1	4	4	4	2	4
1 Case definition adequate	0	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1
2 Representativeness of the cases	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	1
3 Selection of controls	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	1
4 Definition of controls	0	1	0	1	1	1	0	1	1	1	1	0	1	1	1	1	1
B Comparability (maximum 2)	0	1	2	1	1	2	1	1	0	2	0	0	1	2	1	0	1
1 Comparability of cohorts on the basis of the design of analysis	0	1	2	1	1	2	1	1	0	2	0	0	1	2	1	0	1
C Exposure (maximum 3)	1	2	1	1	2	1	1	2	2	2	1	1	1	1	1	2	2
1 Ascertainment of exposure	0	1	0	0	1	0	0	1	1	1	0	0	0	0	0	1	1
2 same method cases and controls?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3 non-response rate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Totaal (maximum 9)	3	7	6	4	5	7	5	6	5	8	5	2	6	7	6	4	7

Table 4.B: (continued)

NOS scale	Nystad 1997	Ownby 2007	Priftis 2007	Ritz 2010	Romieu 2004	Rundle 2009	Strine 2007	Teramoto 2011	Tsai 2007	Tsai 2009	Vahlkvist 2009	Van Gent 2007	Vlaski 2008	Vogelberg 2007	Vogt 2008	Walders-Abramson 2009	Weston 1989
A Selection (maximum 4)	3	4	4	1	4	3	4	4	4	4	2	4	4	3	4	3	3
1 Case definition adequate	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0
2 Representativeness of the cases	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	0	1
3 Selection of controls	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1
4 Definition of controls	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
B Comparability (maximum 2)	1	1	1	0	2	0	2	1	1	2	0	0	2	2	2	1	0
1 Comparability of cohorts on the basis of the design of analysis	1	1	1	0	2	0	2	1	1	2	0	0	2	2	2	1	0
C Exposure (maximum 3)	1	2	2	1	1	2	1	1	1	1	2	2	1	1	1	3	1
1 Ascertainment of exposure	0	1	1	0	0	1	0	0	0	0	1	1	0	0	0	1	0
2 same method cases and controls?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3 non-response rate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Totaal (maximum 9)	5	7	7	2	7	5	7	6	6	7	4	6	7	6	7	7	4

NOS: Newcastle-Ottawa Scale. Result of quality assessment of cross-sectional studies on physical activity and asthma using NOS scores. We refer to figure 4.B for the adjusted NOS for cross-sectional studies, which was used as a scoring list.

Table 4.C: data extraction of longitudinal studies.

Study	Unadjusted results			Adjusted results (95% CI)	
Beckett 2001		Not reported		aHR #1	
1st quintile (highest PA)				Reference	
2nd quintile				0.81 (0.57-1.15)	
3rd quintile #a				0.84 (0.59-1.20)	
4th quintile #a				0.94 (0.66-1.35)	
5th quintile (lowest PA) #a				1.08 (0.75-1.55)	
Benet 2011		Not reported		aHR #2	
1st tertile (lowest PA) #a				Reference	
2nd tertile #a				1.03 (0.83-1.27)	
3rd tertile (highest PA)				1.00 (0.81-1.24)	
Huovinen 2003	OR			aOR #3	
	men	*women*		*men*	*women*
Sedentary #a	Reference	Reference		Reference	Reference
Occasional #a	0.82 (0.40-1.68)	1.71 (0.69-4.21)		0.86 (0.41-1.81)	1.83 (0.74-4.51)
Conditioning	0.47 (0.20-1.10)	1.22 (0.44-3.34)		0.54 (0.22-1.33)	1.42 (0.51-3.93)
Lucke 2007	RR				
	Younger cohort (age 18-23)	*Mid-aged cohort (age 45-50)*	*Older cohort (age 70-75)*	Not reported	
Moderate/high PA	Reference	Reference	Reference		
Nil/low PA #a	1.12 (0.82-1.54)	1.28 (1.09-1.56)*	1.15 (0.92-1.47)		
	OR				
Thomsen 2006	*Monozygotic twin pairs*	*Dizygotic twin pairs*		Not reported	
Low PA #a	Reference	Reference			
High PA	0.35 (0.13-0.91)*	1.48 (0.84-2.61)			

CI; confidence interval, PA; physical activity, aHR; adjusted hazard ratio, OR; odds ratio; aOR; adjusted odds ratio, BMI; body mass index. Data extraction of longitudinal studies concerning baseline physical activity and asthma incidence. * p<0.05; #a used as reference category for pooling in this review; #1 adjusted for age, race, sex, center, and maximal education; #2 adjusted for BMI, smoking status, menopausal status, education level, working status, co-morbidities; #3 adjusted for age, atopy, and respiratory symptoms.

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Chapter 5

Physical activity and asthma development in childhood

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Abstract

Background

Sedentary behavior and decreased physical activity are possible risk factors for developing asthma. This longitudinal study investigates the association between physical activity and subsequent asthma. We hypothesize that children with decreased physical activity at early school age, have higher risk of developing asthma.

Methods

1838 children from the KOALA Birth Cohort Study were analyzed. Children who were born prematurely or with congenital defects/diseases with possible influence on either physical activity or respiratory symptoms were excluded. Physical activity, sedentary behavior and screen time were measured at age 4 to 5 years by questionnaire and accelerometry in a subgroup (n=301). Primary outcome was asthma, assessed by repeated ISAAC questionnaires between age 6 to 10. Secondary outcome was lung function measured by spirometry in a subgroup (n=485, accelerometry subgroup n=62) (forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio) at age 6 to 7 years.

Results

Reported physical activity was not associated with reported asthma nor lung function. Accelerometry data showed that daily being one hour less physically active was associated with a lower FEV_1/FVC (z score Beta −0.65, 95% confidence interval −1.06 to −0.24).

Conclusions

Physical activity at early school age was not associated with reported asthma development later in life. However, lung function results showed that sedentary activity time was associated with lower FEV_1/FVC later in childhood. Since this is the first longitudinal study with objectively measured physical activity and lung function, and because the subgroup sample size was small, this result needs replication.

Introduction

Asthma is one of the most common chronic diseases in childhood and is associated with increased westernization.[1] Sedentary behavior and decreased physical activity are also associated with prosperity.[2] Physical activity has been identified as a possible protective factor in several chronic illnesses, such as diabetes, high blood pressure, heart disease and asthma.[3,4] The role of physical activity in asthma is subject to debate. Several studies have suggested that asthmatic children are less physically active than their healthy peers,[5,6] however other studies showed no difference.[7] Exercising induces a beneficial effect on allergic inflammation,[8] on quality of life and cardiopulmonary fitness in asthmatics, but it has no effect on lung function.[9] The role of physical activity in asthma prevention is still unclear. To establish a causal role of physical activity in asthma development there is a need for longitudinal studies. In adults, these longitudinal studies are not conclusive: some showed no association,[10,11] others designated low physical activity as potential risk factor for developing asthma,[12,13] and one study found a reverse association.[14] In children, only a few longitudinal studies were conducted on this subject: Byberg et al. showed that low physical activity at age 3-6 years was associated with asthma later in childhood.[15] Parents of 617 children were asked if their child was “not so active”, “active” or “very active”. Sherriff et al. showed that children who watched more TV at age 3 years had a higher risk of developing asthma at age 11.5 years.[16]

In this study, we aim to evaluate physical activity preceding asthma development in childhood. We measured physical activity at age 4 to 5 years, lung function at age 6 years, and asthma at several ages between 6 and 10 years. We hypothesize that low physical activity in childhood increases the risk of asthma development later in life. To our knowledge, this is the first longitudinal study in childhood on physical activity and asthma using questionnaires as well as objective measurements for both the exposure and the outcome (accelerometry and spirometry).

Materials and methods

This prospective study was embedded in the KOALA (Child, Parent and Health: Lifestyle and Genetic Constitution [in Dutch]) Birth Cohort Study,[17] which focuses on potential risk factors for atopy and asthma development in childhood. In total, 2834 pregnant women were recruited and completed a questionnaire at 34 weeks of gestation. The birth cohort consists of two recruitment groups, based on lifestyle (alternative and conventional). Children born to these mothers were followed at several ages (i.e. 3 and

7 months, 1 year, 2 years, 4 to 5 years, 6 to 7 years, 6 to 8 years, 7 to 9 years and 8 to 10 years).

Inclusion criteria for the present study were: all children for whom their parents completed a questionnaire on physical activity at age 4 to 5 years and at least one questionnaire at any age between 6 and 10 years on asthma symptoms. We excluded children born with congenital defects or diseases with possible influence on either physical activity or respiratory symptoms, such as for example cystic fibrosis, Down's syndrome or rheumatic disease (for the complete list, see Appendix 5). Other exclusion criteria were prematurity with a gestational age of less than 37 weeks, birth weight of less than 2000 grams, and use of growth hormone.

All parents gave written informed consent. Ethical approval was obtained from the medical ethics committee of Maastricht University and Academic Hospital of Maastricht, Netherlands.

Physical activity

Questionnaires

At age 4 to 5 years physical activity was assessed using questionnaires. Parents were asked about their child's frequency (days per week) and duration of activities (minutes per day) during the last four weeks: walking or cycling to school, school gymnastics, sports club, and playing outside. The total time that a child was physically active was added and converted in total physical activity in hours per day. Screen time was calculated by adding the frequency and duration of TV watching and playing computer games into one variable (screen time in hours per day).

Accelerometry

A subgroup of 4 to 5 year olds was invited to participate in accelerometry, based on the location of their home addresses (all children who lived within a range of 20 km from the communal building from where the accelerometers were distributed).[18] These children were instructed to wear an accelerometer (ActiGraph 7164, Fort Walton Beach, FL) on the right hip during daytime for at least five days. Children were instructed to only remove the accelerometer when water was involved, as in swimming or showering. Physical activity counts were registered in epochs of 15 seconds, for young children are known for their short and intermittent movement bursts.[19] This was transformed in counts per minute to express total activity. Four intensity-levels were distinguished: sedentary, light, moderate and vigorous physical activity, based on cut off values established by Evenson.[20,21] Time in these Physical Activity (PA) levels was expressed in hours per day, in order to make it comparable with PA from questionnaire data. Only accelerometer data with at least 400 minutes (i.e. 6.7 hours) of wear time

per day (during at least three weekdays and one weekend day) were included in analyses.[22] All analyses with accelerometry were adjusted for wear time.

Asthma

Questionnaires

Asthma was identified through parental questionnaires at several ages between 6 and 10 years. Asthma was defined according to the International Study of Asthma and Allergies in Childhood Questionnaire (ISAAC):[23] doctor's diagnosed asthma combined with clinical symptoms in the last 12 months (i.e. wheezing or shortness of breath) and/or if they used asthma medication in the last 12 months. Asthma medication was defined as regular use of short-acting bronchodilators or the use of inhaled corticosteroids. Regular use was defined as everyday use for a period of at least two months or use associated with physical activity of the child. Asthma at the age 6 to 10 years was considered present if at least one questionnaire in this age period met the asthma definition.

Lung function

In a subgroup children's lung function was assessed at age 6 to 7 years. Children were selected for this subgroup if their mothers participated in an earlier study in a subgroup for which they had to donate a blood sample at 34 weeks of pregnancy. Lung function was assessed using the handheld Medikro Spirostar USB spirometer (Medikro, Kuopio, Finland) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[24,25] This was assessed by trained research assistants during home visits. Lung function was performed after 10 minutes rest in an upright seated position. Each child performed forced expiration until three acceptable curves were achieved. Acceptable curves met the reproducibility criteria defined by the ATS/ERS. Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC) and Tiffeneau-Pinelli index (FEV_1/FVC) were transferred into z scores using the GLI-2012 (Global Lung Function Initiative) reference values for spirometry, corrected for the child's sex, age, and height.[26] We presented FEV_1/FVC as primary lung function outcome, because in children it gives a better indication of asthma severity than FEV_1, which can be normal even in severe persistent childhood asthma.[27]

Statistical analysis

Data were analyzed using SPSS 22.0 for Windows (SPSS Inc, Chicago, IL). The total number of missing values ranged from none (for e.g. sex, birth weight, environmental tobacco smoke exposure) up to 6.1% for Body Mass Index (BMI). In 10.8% of the children one or more variables were missing. Missing data were imputed using multiple imputation in SPSS, using the regression method with 5 iterations. The missing data

pattern was evaluated as random. The imputed variables were parent reported physical activity variables and all confounding variables. Logistic regression analysis was used for evaluating the association between physical activity, screen time and asthma. Linear regression analysis was used for evaluating the associations between physical activity, screen time and lung function. We adjusted for the following potential confounders: sex, atopic family history (father and/or mother history of asthma, eczema or allergy), maternal education level, maternal age, maternal BMI, smoking during pregnancy, birth weight, breast feeding (exclusively in first 3 months), environmental tobacco smoke in first 4 years of life, and recruitment group.[17] The accelerometry data were adjusted for wear time. Children's BMI measures were transferred into z scores adjusted for age and sex, using reference values from the Fourth Dutch Growth Study.[28] Protopathic bias is a major potential issue in longitudinal studies on this subject: it consists of the hypothesis that physical activity can be restricted by respiratory symptoms preceding asthma diagnosis. Sensitivity analyses were performed by comparing models without and with parent reported wheeze in the 12 months before exposure to evaluate protopathic bias. Possible effect modification was assessed by testing for interaction by wheeze and BMI. In order not to miss non-monotonous confounding or effect modification by BMI we also used BMI as a categorical variable (lower/normal/overweight based on lower and upper quartiles).

Results

In total, 1957 children met the inclusion criteria at the age of 4 to 5 years. Of these, 1838 children (94%) completed at least one questionnaire at any age between 6 and 10 years on asthma symptoms. Table 5.1 shows the characteristics of participants and their physical activity levels at age 4 to 5 years for the total group and for the subgroups of children that participated in accelerometry (n=301), lung function (n=485), and both measurements (n=62). There were no obvious differences between the total cohort and the subgroups. On average, children participated in physical activity 1.9 hours per day, and they were engaged in screen time 1.0 hour per day (questionnaire based). Boys were reported to be more physically active than girls (mean 2.0 hours per day vs 1.8 hours per day). Accelerometry data confirmed that there was a difference in physical activity between boys and girls (666 *vs.* 615 counts per minute). Table 5.2 shows the characteristics of accelerometry data. A weak correlation was found between parent reported physical activity and counts per minute in accelerometry ($r=0.20$, $p<0.01$), and also between parent reported sedentary activity and time spent in sedentary activity level in accelerometry ($r=0.05$, $p<0.05$).

Table 5.1 Characteristics of participants of the KOALA Birth Cohort Study, Netherlands.

Characteristic	All Participants (n=1838), n (%)	Participants who had accelerometry (n=301), n (%)	Participants who had lung function (n=485), n (%)	Participants who had accelerometry and lung function (n=62), n (%)
Sex				
Boy	939 (51)	146 (49)	230 (47)	31 (50)
Girl	899 (49)	155 (52)	255 (53)	31 (50)
Atopic family history[a]				
Yes	1100 (60)	190 (63)	316 (65)	43 (69)
No	738 (40)	111 (37)	169 (35)	19 (31)
Maternal education level				
Low	156 (8)	25 (8)	35 (7)	5 (8)
Moderate	675 (37)	100 (33)	183 (38)	15 (24)
High	1007 (55)	176 (58)	267 (55)	42 (68)
Smoking during pregnancy				
Yes	87 (5)	13 (4)	18 (4)	1 (2)
No	1751 (95)	288 (96)	467 (96)	61 (98)
Birth weight				
2000 – 3000 grams	177 (10)	23 (8)	51 (11)	3 (5)
3000 – 4000 grams	1353 (74)	226 (75)	361 (74)	47 (76)
> 4000 grams	308 (17)	52 (17)	73 (15)	12 (19)
Breastfeeding[b]				
Yes	991 (54)	122 (41)	221 (46)	24 (39)
No	847 (46)	179 (59)	264 (54)	38 (61)
Environmental tobacco smoke				
Yes	310 (17)	58 (19)	70 (14)	13 (21)
No	1528 (83)	243 (81)	415 (86)	49 (79)
Physical Activity (parent reported)				
Physical activity (hours/day)[c]	1.9 (0.9)	1.7 (0.8)	1.9 (0.9)	1.6 (0.8)
Screen time (hours/day)[d]	1.0 (0.7)	1.1 (0.6)	0.9 (0.6)	1.0 (0.6)
Wheeze at time of exposure				
Yes	181 (9.9)	31 (10.3)	55 (11.4)	6 (9.7)
No	1648 (90.1)	269 (89.7)	426 (88.6)	56 (90.3)
Missing	9 (0.5)	1 (0.3)	4 (0.8)	0 (0.0)
Asthma at age 6 to 10 years				
Yes	186 (10.1)	26 (8.6)	66 (13.6)	7 (11.3)
No	1652 (89.9)	275 (91.4)	419 (86.3)	55 (88.7)

Characteristics of participants of the KOALA Birth Cohort Study, with an overview of all participants, participants who had accelerometry, participants who had lung function, participants who had accelerometry and lung function. [a] Father and/or mother history of asthma, eczema or allergy; [b] Exclusively breastfeeding in first 3 months; [c] Hours per week engaging in physical activity: walking or cycling to school, school gymnastics, sports club, and playing outside; [d] Hours per week watching television or playing computer games.

Asthma

A number of 186 children (10.1%) met the ISAAC definition of asthma between the age of 6 and 10. The majority of these children (n=101, 56%) had already wheezed at the age of 4 to 5 years.

We found no association between physical activity and asthma (Table 5.3). Sensitivity analyses for wheeze showed no difference between the children that had already wheezed at age 4 to 5 years and the children that had not wheezed at that age in relation to physical activity and asthma. BMI z scores or categories (under/normal/overweight) did not affect the relation between physical activity and asthma either.

Table 5.2: Descriptive information on physical activity derived from accelerometry at age 4-5.

	% of wear time[d]	Mean (SD)	Range	Median	25th percentile	75th percentile
Wear time (hours/day)		11.0 (0.8)	5.4	11.0	10.4	11.5
Total activity (cpm)[a]		640 (153)	916	617	521	728
Time in activity level in hours/day[b]						
Sedentary PA	47	5.2 (0.7)	4.5	5.2	4.7	5.6
Light PA	45	5.0 (0.7)	3.6	5.0	4.5	5.4
Moderate PA	6	0.6 (0.2)	0.9	0.6	0.5	0.7
Vigorous PA	2	0.2 (0.1)	0.8	0.2	0.1	0.3
MVPA[c]	8	0.8 (0.3)	1.6	0.8	0.6	1.0

Descriptive information on physical activity derived from accelerometry at age 4-5 years (n=301). [a] Total activity measured by accelerometry in average daily counts per minute (cpm); [b] Time in Physical Activity (PA) levels, converted to hours per day for reasons of comparability; [c] Moderate to vigorous physical activity (MVPA) (sum of time in moderate physical activity and time in vigorous physical activity in hours per day); [d] Time in Physical Activity (PA) levels, calculated in percentage of total wear time.

Table 5.3: Asthma and FEV_1/FVC in relation to physical activity earlier in childhood.

	Asthma		FEV_1/FVC	
	OR (95% CI)	Adjusted OR (95% CI)[#]	B (95% CI)	Adjusted B (95% CI)[#]
Questionnaires	n=1838		n=485	
Physical Activity[a]	1.13 (0.95 to 1.34)	1.07 (0.90 to 1.27)	-0.08 (-0.16 to 0.00)	-0.08 (-0.16 to 0.01)
Screen time[b]	1.10 (0.99 to 1.23)	0.98 (0.77 to 1.23)	-0.07 (-0.20 to 0.05)	-0.09 (-0.22 to 0.05)
Accelerometry	n=301		n=62	
Total activity (cpm)[c]	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Time in sedentary PA[d]	0.72 (0.39 to 1.32)	0.75 (0.37 to 1.52)	-0.32 (-0.64 to 0.00)	-0.65 (-1.06 to -0.24)
Time in MVPA[e]	0.87 (0.22 to 3.51)	1.11 (0.25 to 4.98)	-0.03 (-0.90 to 0.83)	0.10 (-0.91 to 1.11)

Odds ratios (OR) and 95% confidence intervals for asthma in relation to physical activity (PA) earlier in childhood. Beta's (B) and 95% confidence intervals for FEV_1/FVC (in z-scores) in relation to physical activity.
[#] Adjusted for sex, birth weight, smoking during pregnancy, environmental tobacco smoke, atopic family history, maternal education level, maternal age, maternal BMI, breastfeeding, recruitment group, wear time (in accelerometry data). (Sensibility analyses for wheeze and BMI did not show significant differences, results not shown). [a] Hours per day engaging in physical activity: walking or cycling to school, school gymnastics, sports club, and playing outside; [b] Hours per day watching television or playing computer games; [c] Total activity measured by accelerometry in average daily counts per minute (cpm); [d] Time in activity level sedentary physical activity, converted to hours per day for reasons of comparability; [e] Time in activity levels moderate and vigorous physical activity (MVPA) (sum of time in moderate physical activity and time in vigorous physical activity), converted to hours per day for reasons of comparability.

Lung function

There was no association between parent reported physical activity and FEV_1 or FVC (results in supplement) or FEV_1/FVC (Table 5.3). A small subgroup (n=62) participated in accelerometry as well as lung function. Accelerometry data in this group showed a significant association between sedentary time and lung function on follow-up: children who had spent more time being physically inactive (i.e. in physical activity level sedentary) at age 4 to 5 years had a lower FEV_1/FVC at age 6 to 7 years (Table 5.3). In a sensitivity analysis we evaluated whether protopathic bias could explain this association, by repeating the analyses with and without wheeze at age 4 to 5 years as co-variable in the model. This did not influence the association between sedentary time and FEV_1/FVC. BMI did not influence the association either. There was no association between sedentary time and FEV_1 or FVC separately (results in appendix Table 5.A). Total activity (counts per minute) and time spent in moderate to vigorous physical activity (MVPA) were not associated with lung function.

Discussion

This study did not confirm an association between lower physical activity levels and asthma development in childhood. Sedentary time as measured by accelerometry, however, was associated with lower FEV_1/FVC.

Physical activity and asthma is subject of an ongoing debate and numerous studies looked into this subject. However, no convincing evidence was shown yet. In 2012, we performed a systematic review and meta-analysis on physical activity and asthma.[5] We identified 34 cross-sectional studies, of which a large portion showed a significant association between physical activity and asthma. Unfortunately, due to large clinical and statistical heterogeneity, it was not possible to perform a pooled analysis. Five longitudinal studies were identified and these showed that adults with high physical activity levels had lower asthma incidence in follow-up. No high quality longitudinal studies in children were identified at that time.

Since then, two systematic reviews on physical activity and childhood asthma were published, both in 2016. Lochte et al.[6] identified 8 cross-sectional studies, which were considered too heterogenous for pooling. Three longitudinal studies were identified and pooled, which showed a positive association of low physical activity and new-onset asthma.

Cassim et al.[7] focused on accelerometry studies and found no difference in physical activity and childhood asthma in 10 cross-sectional, 1 case-control, and 1 cohort study.

No longitudinal studies with physical activity as exposure were identified in this meta-analysis. A very recent publication by Pike et al.[29] showed no association between MVPA in accelerometry and asthma status in their cross-sectional analysis. No longitudinal analysis was reported in this publication.

The most important strength of this study is that it is a longitudinal study with physical activity as exposure preceding the outcome measurement of asthma and lung function. A longitudinal study design is necessary to ensure that cause (physical activity) precedes effect (asthma development). Another strength of this study is the use of objective measures for assessing physical activity and asthma in a subgroup.

This study has several limitations. An important issue in the debate is reverse causation and protopathic bias: is asthma caused by low physical activity or is the child less physically active because of its asthmatic symptoms? Asthma is often preceded by wheeze symptoms in early childhood. However, asthma can be difficult to diagnose before the age of 6 years because spirometry is often not possible before this age. Children that wheeze at a young age and eventually develop asthma are sometimes difficult to distinguish from the children with viral induced wheeze: children that wheeze due to respiratory infections in combination with small airways but who outgrow it and do not develop asthma.[30] In this study, 72% of the children with asthma diagnosis at the age of 6 to 10 years had already wheezed at the age of 4 to 5 years. On the other hand, 44% of the children that had wheezed at age 4 to 5 years did not meet the ISAAC definition of asthma at the age of 6 to 10 years. To evaluate protopathic bias, we performed sensitivity analysis by adding and removing the variable wheeze at the age of exposure in all analyses. This did not show any relevant influence on the results. A recent study on this subject performed bidirectional longitudinal analyses and found no association between high physical activity levels and asthma development in childhood.[31] Unfortunately, we have no objective data on long function at time of exposure, because children were too young to perform spirometry at that time (i.e. 4-5 years). It is possible that children with lower lung function capacities are (subsequently) becoming less physically active. Therefore, some level of reverse causation is not ruled out.

Another limitation of this study is that although the accelerometer used (ActiGraph 7164) has established validity and reliability for assessing physical activity,[33] it is less suited for measuring sedentary activity. The accelerometer underestimates activities such as bicycling, because of its uniaxial measurement. Moreover, it is not possible to measure the posture of the child (sitting, lying, standing up). More recent literature advises to use triaxial accelerometers worn on the thigh for assessing sedentary behavior.[34]

To our knowledge, the finding of an association between sedentary activity and FEV_1/FVC later in childhood has not been reported before. In cross-sectional studies, no association between physical activity and lung function was found in non-asthmatic children,[35] nor in exercise studies in asthmatic children.[9] Most studies focused on physical activity levels and asthma found no significant association.[7,31] It could be possible that contrasting results are caused by different methods to measure physical activity. This study suggests that sedentary activity possibly is a more important factor in developing asthma than high physical activity levels, which is consistent with earlier studies on sedentary activity.[16,32] It should be noted that our results were based only on a small sample (n=62) from the whole cohort with both accelerometry and lung function measurements available, warranting replication in larger groups.

For future research, it is important to focus on physical activity and especially sedentary behavior and subsequent asthma and lung function development in (larger) longitudinal studies, taking into account protopathic bias, in order to prove causality.

Appendix

Table 5.A: FEV_1 and FVC in relation to physical activity earlier in childhood.

	FEV_1		**FVC**	
	B (95% CI)	**Adjusted B (95% CI)[#]**	**B (95% CI)**	**Adjusted B (95% CI)[#]**
Questionnaires	n=485		n=485	
Physical Activity[a]	-0.03 (-0.12 to 0.07)	-0.02 (-0.12 to 0.07)	0.03 (-0.02 to 0.07)	0.03 (-0.06 to 0.12)
Screen time[b]	-0.12 (-0.26 to 0.02)	-0.11 (-0.26 to 0.04)	-0.08 (-0.21 to 0.04)	-0.07 (-0.21 to 0.07)
Accelerometry	n=62		n=62	
Total activity (cpm)[c]	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)	0.00 (-0.00 to 0.00)
Time in sedentary PA[d]	-0.29 (-0.59 to 0.02)	-0.29 (-0.71 to 0.14)	-0.09 (-0.37 to 0.19)	0.63 (-0.33 to 0.45)
Time in MVPA[e]	0.34 (-0.48 to 1.17)	0.46 (-0.51 to 1.42)	0.32 (-0.40 to 1.04)	0.39 (-0.48 to 1.26)

Beta's (B) and 95% confidence intervals for FEV_1 and FVC (in z-scores) in relation to physical activity (PA) earlier in childhood. [#] Adjusted for sex, birth weight, smoking during pregnancy, environmental tobacco smoke, atopic family history, maternal education level, maternal age, maternal BMI, breastfeeding, recruitment group. (Sensibility analyses for wheeze and BMI did not show significant differences, results not shown); [a] Hours per day engaging in physical activity: walking or cycling to school, school gymnastics, sports club, and playing outside; [b] Hours per day watching television or playing computer games; [c] Total activity measured by accelerometry in average daily counts per minute (cpm); [d] Time in activity level sedentary physical activity, converted to hours per day for reasons of comparability; [e] Time in activity levels moderate and vigorous physical activity (MVPA) (sum of time in moderate physical activity and time in vigorous physical activity), converted to hours per day for reasons of comparability.

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Chapter 6

Physical activity, sedentary behaviour, and childhood asthma in Europe

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Submitted

Chapter 7

General discussion

General discussion

This thesis aimed to investigate the relation of asthma and physical activity. We performed four different studies on asthma and physical activity in different directions: chapter 3 is aimed at asthma symptoms preceding physical activity, chapter 4 gives an overview of cross-sectional and longitudinal studies with physical activity preceding asthma outcome, and chapter 5 and 6 are looking into physical activity preceding asthma development in childhood.
Investigating the relation between asthma and physical activity in both directions poses us for several methodological challenges. These challenges will be discussed one by one:

1. Defining paediatric asthma in epidemiological studies
2. Confounding and mediation
3. Time sequence

Defining paediatric asthma in epidemiological studies

Asthma diagnosis in young children is difficult: asthma is a clinical diagnosis based on recurrent episodes of wheezing and breathlessness, reversible with bronchodilatating medication such as beta 2 mimetics. In the Netherlands, and most other Western countries, asthma is usually not diagnosed before the age of 5 or 6 years. Around the age of 6, children are capable of performing a lung function test, which can support a clinical asthma diagnosis. Besides this, asthmatic symptoms at a young age are difficult to distinguish from viral induced wheeze, which is usually transient. The vast majority (66.8% in the PIAMA birth cohort) of wheezing children before the age of 3 to 4 years turns out to have transient early wheeze, of which only 3.6% had an asthma diagnosis at age 8.[1] The pathophysiology of viral induced wheeze is believed to be caused by the relatively small airways of young children. A viral infection causes narrowing of the airway, caused by inflammation, oedema, and mucus. This narrowing of the airway has little noticeable effect on the airflow of an older child or adult, but due to the small airway diameter of the young child, slight narrowing leads to a proportionally larger restriction in airflow. This is explained by Poiseuille's law describing that (airway) resistance is inversely proportional to the radius of the pipe to the power of 4. Until now, no test can distinguish the early transient wheezers from the children who will develop asthma later in life, although reaction to multiple triggers (such as pollen, pets, smoke), positive family history of atopy and aero-allergic sensitization can be clues of clinical asthma in development – but this is not enough for an asthma diagnosis.

This means that asthma is best *not* diagnosed before the age of 5 to 6 years. But even after this age, asthma diagnosis can be difficult, because of the variability of symptoms over time. In most asthmatic children, lung function parameters (such as FEV_1,

FEV_1/FVC) will be normal unless the child has an asthma exacerbation at that moment. If the clinical suspicion of asthma remains, repeated lung function tests are needed to demonstrate obstruction and reversibility. The more invasive airway hyperresponsiveness test for asthma diagnosis is more reliable, but not often used in clinical practice.

In epidemiological studies, various asthma definitions are used. The International Study of Asthma and Allergies in Childhood (ISAAC) is an international collaboration of more than 300 research centres in 105 countries that contributed immensely to asthma research for over 20 years.[2] The main goal of the ISAAC study group was global disease monitoring and development of environmental measures for future interventions to reduce the burden of asthma and allergies. This global project led to another important step in epidemiologic asthma research: the group has laid the foundation for uniformity of asthma definition by developing ISAAC core questionnaires. The ISAAC question 'Asthma ever' ("Has your child ever had asthma?") is probably the most used question in asthma research. This question has its limitations due to culturally differing terminology and beliefs on asthma. For example, viral induced wheeze in young children is in some countries labelled as asthma, while in others asthma is only diagnosed after the age of 6. More accurate but less specific is the ISAAC question 'Wheeze ever' ("Has your child ever had wheezing or whistling in the chest at any time in the past?"). This question is used for the ISAAC prevalence studies. It is the question with the highest sensitivity (80.6% in adolescents) for the diagnosis of asthma, but also the lowest specificity (74.9%) compared to other ISAAC questions. This can lead to false positive identification of asthma cases.[3] There are also cross-cultural objections: it is believed that the term "wheeze" is not easy to translate in some languages, despite of validated questionnaires in several languages. Some state that this could be the reason that the English speaking countries have the highest wheeze prevalence of the world.[4] 'Current asthma' is defined by a combination of ISAAC questions that together implicate that the child has present asthma. In our studies, we used a common combination of physician diagnosed asthma in combination with asthma symptoms in the last 12 months (wheeze or breathlessness), or regular use of asthma medication in the last 12 months (i.e. daily corticosteroids or bronchodilators or during exercise). With this definition of current asthma the asthma prevalence in the KOALA birth cohort was 7.0%, which is comparable to other birth cohorts in Europe (chapter 6).

Although the ISAAC studies laid the foundation for uniformity of asthma definition in epidemiological research, there is still a large variation in how these questions are combined to define asthma. Sá-Sousa et al. revealed that operational definitions of asthma used in prevalence studies are inconsistent: they found 29 different ways to define current asthma in published asthma studies, which caused substantial differences in prevalence rates. Depending on which definition was used current

asthma prevalence ranged between 1.1% and 17.2%.[5] Combined questions on asthma symptoms, diagnosis and medication use are recommended in order to achieve the best asthma definition. [5,6]

In 2010 a collaboration called Mechanisms of the Development of Allergy (MeDALL) was started, aiming at generating novel knowledge on the mechanisms of allergy and asthma. One of their goals was to further harmonise asthma definition in epidemiologic studies.[7,8] Current asthma according to MeDALL is defined as presence of at least two of following: (1) physician diagnosed asthma, (2) wheeze in the last 12 months, or (3) asthma medication use in the last 12 months. In **chapter 2** we compared our ISAAC based definition of current asthma with the MeDALL based definition, and found excellent agreement between these definitions. In our study, asthma prevalence was slightly higher with the ISAAC based definition compared to the MeDALL based definition (7.8% vs. 6.0%). This can be explained by a slightly broader inclusion of asthma symptoms in the ISAAC based definition, which considered both breathlessness and wheeze as asthma symptoms, while MeDALL only included wheeze as asthma symptom. Moreover, the combination of the three components of the definition is slightly different: ISAAC based definition required the logical rule "(physician diagnosed asthma and asthma symptoms) or asthma medication use", while MeDALL defined asthma as 2 out 3 criteria. This works out differently for children whose parents only report asthma medication (i.e. current asthma according to ISAAC based definition, but no current asthma according to MeDALL based definition). Our ISAAC based definition assumes that asthma medication requires an asthma diagnosis (justified in the Netherlands since asthma medication can only be obtained on medical prescription) and allows that a child need not have current asthma symptoms, due to asthma medication being effective. Both definitions (ISAAC and MeDALL) represent current asthma and could be used interchangeably. However, in order to pursue uniformity in reporting asthma prevalence worldwide it is advisable to comply to the MeDALL based definition.

In **chapter 2** we also compared parent reported physician diagnosed asthma and asthma diagnosis according to information provided by their general practitioner (GP), and found only moderate agreement. Especially cases where an asthma diagnosis was reported to be set by a physician at an early age (i.e. before 6 years) showed large discrepancies between the parent reported data and the GP. It is possible that early transient wheeze was (prematurely or wrongly) labelled as asthma diagnosis. This can be a pitfall for reporting asthma prevalence in epidemiological research: when only reporting the question physician diagnosed asthma, it can lead to an overestimation of asthma prevalence. This strengthens the importance of using a combination of questions in a uniform manner, such as using the MeDALL definition of current asthma. In the studies described in this thesis, we chose for the combined use of different

asthma questions to report on asthma prevalence (i.e. ISAAC based current asthma in chapter 4 and 5 and both ISAAC and MeDALL based current asthma in chapter 2 and 6).

Confounding and mediation

Asthma development is believed to have a multifactorial origin. An ISAAC phase III study examined the combined effect of five modifiable lifestyle factors on asthma (i.e. no parental smoking, child's adherence to Mediterranean diet, child's healthy BMI, high physical activity and non-sedentary behaviour) and found that each additional healthy lifestyle factor attributed to a reduced risk of current wheeze.[9] However, this study was cross-sectional in design, and therefore gives no insight in causality and possible interactions.

In order to comprehend the possible association between physical activity and asthma and its possible interactions we designed a directed acyclic graph (DAG) with known or potential confounders and mediators (figure 7.1).

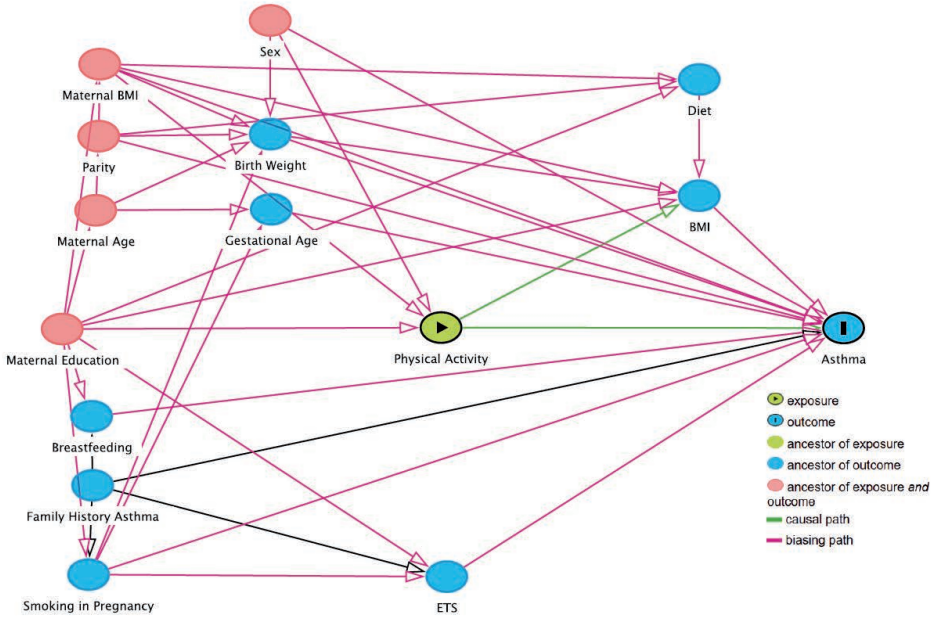

Figure 7.1: Directed Acyclic Graph (DAG) of possible covariables on the association between physical activity and asthma. Minimal dataset was identified as sex, maternal education, and maternal BMI.

This DAG is a schematic tool to give insight into the possible interactions and confounders that are described in the literature on physical activity and asthma development. We used it in our European study (chapter 6) in order to select the most important confounders to be adjusted for in the analyses. However, while identified confounders can be adjusted for (if measured), what remains is residual and unmeasured confounding.

A relatively new technique for taking into account residual confounding is Mendelian randomisation.[10] This is an analytical method that uses genetic variants as instrumental variables for studying modifiable risk factors on health outcomes. For valid research, it is important that there is a known genetic variant (or set of genetic markers) that meets these criteria: (1) association with the risk factor (relevance assumption), (2) no common cause with the outcome (independence assumption), and (3) no influence on the outcome except through the risk factor (exclusion restriction assumption).[10] Very recently, Ha et al. looked into the causal effects of a broad range of risk factors on asthma using Mendelian randomisation.[11] They examined 69 risk factors that are described in the literature as possibly related to asthma, among which physical activity and obesity. For all these factors, genetic variants were identified in the UK Biobank with genome-wide association analysis. No causal relation between physical activity and asthma was found. BMI did causally affect the development of asthma, both in children and in adults. The causal relation was found to be the strongest in adult-onset, moderate-to-severe asthma, especially in females. Although this study was methodologically sound, there were some important limitations: the study was limited by the availability of genetic variants in the UK Biobank, as well as the quality of the corresponding phenotypes. Physical activity was assessed by self-reported questionnaires, which is an important limitation. In chapter 1 we described the disadvantages and the lack of validated questionnaires for physical activity in childhood.

Time sequence

In order to understand causality and direction of the relation between asthma and physical activity, it is important that exposure and outcome are really separated in time and that the exposure precedes the outcome. Both for asthma as for physical activity this poses a major challenge.

Asthma is almost always preceded by (multiple) periods of wheezing. As discussed earlier, in children a new asthma diagnosis will not often be set before 6 years, while in the majority of cases (72% in KOALA data) the child has wheezed already at a younger age. Presence of symptoms, not (yet) diagnosed as asthma, can influence physical activity of the child because of protopathic bias: wheeze or asthmatic symptoms

causing children to participate less in physical activity, for example because their symptoms of breathlessness are holding them back or because they are afraid of getting out of breath. In our studies on physical activity preceding asthma (chapter 5 and 6), we evaluated protopathic bias by performing sensitivity analyses: the analyses were repeated with adding the co-variable 'wheeze at exposure' (i.e. the time period of physical activity preceding asthma) to the model. This did not influence the association between physical activity and asthma. We also performed additional analyses after exclusion of all children who wheezed at the age of exposure, therefore creating a "wheeze-free" population. Also in these children, we found no association between physical activity and subsequent asthma development. This makes protopathic bias unlikely.

Physical activity is also difficult to pinpoint in time, as physical activity is always present, but not always measured. It is important to realise that one measurement in time has to be interpreted with caution when there is no information on earlier or later physical activity. This one measurement in time may or may not reflect long term physical activity. Not much is known about the course of physical activity in childhood. On average, physical activity tends to decrease when children grow older,[12] but individual changes throughout childhood can be difficult to measure. Studies in this area show that there is a low to moderate stability of physical activity levels during the life span, with women showing lower stability than men.[13] In early childhood there is more intra-individual variability over time.[13] In **Chapter 3** we addressed the influence of early wheeze (i.e. in the first 2 years of life) on physical activity patterns and overweight at age 4 to 5 years within the KOALA birth cohort study and found that wheezing boys were more physically active later in childhood. As we had no information on physical activity levels between 0 to 2 years, it is possible that children in our study who were defined as being physically active at age 4 to 5 years (outcome), were already more active in their first years of life. This could mean that the longitudinal (possible causal) relation that was found in this study was in fact not causal or possibly even reversed, with physical activity as exposure and asthmatic symptoms as outcome. Unfortunately, in the studies presented in this thesis we do not have repeated measurements of physical activity.

Studies on the influence of asthma on physical activity

Several researchers described the physical activity levels of asthmatic children compared to their non-asthmatic peers. A systematic review published in 2016 focused on the effect of asthma or wheeze on physical activity measured by accelerometry.[14] The authors identified ten cross-sectional, one case control, and one cohort study (which was our 2008 study as described in chapter 3). The review showed that there was no difference in objectively measured physical activity level between asthmatic and non-asthmatic children (cross-sectionally, as well as longitudinally with asthmatic

symptoms as exposure). The longitudinal design of the study presented in chapter 3 was repeated recently by the group of Cassim et al.:[15] wheeze and asthma were evaluated at age 4 and 6 years via questionnaires and physical activity level was assessed at the age of 6 by accelerometry. The investigators found no association between early asthma symptoms and subsequent physical activity levels. To our knowledge, this is the only other longitudinal study on asthmatic symptoms in young children and effect on physical activity.

Several large cross-sectional studies on this subject have been published, and in general no difference in physical activity levels in asthmatic children compared to their healthy peers was found.[16-18] Some even found a higher physical activity level in asthmatic children.[19,20] This might be explained by the current advice to encourage asthmatics to engage in physical activity as a strategy for improving respiratory function and asthma control, or by experiencing more exercise induced bronchoconstriction due to engaging more in vigorous activity. In 2021, two systematic reviews with meta-analyses on physical activity levels in asthmatic children were published: Vasconcello-Castillo et al. focused on physical activity measured by subjective measurements (e.g. questionnaire) or objective measurements (e.g. accelerometry).[21] They included 28 studies and found no difference in MVPA, steps per day and sedentary time in asthmatics compared to healthy controls. Mackintosh et al. focused on device-assessed physical activity levels in children with and without asthma.[22] They identified 15 studies on physical activity time and five studies on sedentary time, and found that asthmatic children were equally physically active as their healthy peers and spent marginally less time in sedentary behaviour. It is noticeable that while there is no clear difference in physical activity levels in asthmatic children, asthmatic adults did show to be less active than healthy controls.[23]

In subgroups, such as children with severe asthma or poorly controlled asthma, it is clear that there is a negative impact of asthma on physical activity levels and fitness.[24,25] For example, children who were recently hospitalised for their asthma showed lower physical activity levels than other asthmatic children.[16]

Studies on the influence of physical activity on asthma development

In 2012 we published a systematic review and meta-analysis on the (at that time) available literature with focus on physical activity as exposure and asthma as outcome (**chapter 4**). No longitudinal studies in children with physical activity measurement preceding asthma were available at that time. In adults, the available evidence from longitudinal studies indicated that higher physical activity levels might be protective for asthma development (chapter 4). This lack of longitudinal studies in childhood was the motivation for performing two original, longitudinal studies with physical activity as exposure and asthma development in children as the outcome, as described in chapter

5 and 6. Since our systematic literature review in 2012 on physical activity and asthma, several new studies on physical activity and asthma have been published, leading to new systematic reviews. In 2019, a systematic review on cohort studies in children with physical activity measurement preceding asthma and lung function outcomes concluded that there was insufficient evidence to determine the longitudinal effect of physical activity on subsequent asthma and lung function outcomes in children, due to the highly inconsistent results.[26] In 2020, we published a study on the association between physical activity and sedentary behaviour at age 4 to 5 years (exposure) and asthma and lung function at age 6 to 10 years assessed in the KOALA birth cohort (**chapter 5**). In this study, we found no association between physical activity and subsequent asthma development. In a small subgroup for which both accelerometry and lung function data were available, sedentary behaviour was associated with lower FEV_1/FVC ratio. We replicated this study design on larger scale in a collaborative study in 26 European cohorts with information on physical activity preceding asthma measured at different ages between birth and 18 years (**chapter 6**). No longitudinal associations between physical activity and subsequent asthma or lung function were found. Sedentary behaviour was not associated with asthma development either, while the lung function results were inconsistent. The possible association between sedentary behaviour and lower FEV_1/FVC ratio was not confirmed in the other cohorts. In a very recent study, Lu et al. studied the association of moderate-to-vigorous physical activity (MVPA) and subsequent asthma in 542,486 previously healthy children in a large retrospective cohort.[27] They found that in children with a (very) low MVPA level at baseline (age 2-17 years), an increase in MVPA was associated with lower asthma risk, while the opposite was found in children who were already physically active: an increase in MVPA in these children was associated with a slightly higher asthma risk. The effect sizes were very small, and comparable to the effect sizes found in the studies described in this thesis (chapter 5 and 6), but due to the large study size it just reached statistical significance. The mean MVPA level of children in chapter 5 was comparable with this study (see Table 5.2, MVPA levels in hours per day) when converted into hours per week: 5.6 hours per week compared to 5.4 hours per week in the study of Lu et al. but the standard deviation was smaller (2.1 hours per week vs, 4.4 hours per week), which implies that there were fewer children with a very low MVPA level in our study, in which Lu et al. found the possible association with asthma. In the European collaboration study in chapter 6, MVPA levels were higher. A possible U-shaped dose-response relation between physical activity and asthma could be suggested from the study of Lu et al. And although the effect sizes are small, an increase of MVPA level in children who are very inactive could be protective against asthma development.

Studies on the bidirectional relation between asthma and physical activity

In 2018, the group of Cassim et al. performed a very interesting bidirectional longitudinal study on this subject: they used cross-lagged generalised structural equational modelling (GSEM) in a large cohort of children followed biennially from the age of 6 until 14 years for physical activity and asthma (Figure 7.2).[28] It showed that there was no association in either direction: current asthma did not influence time spent in physical activity; and physical activity did not influence incident nor current asthma. The investigators had no information on the influence of wheeze or asthmatic symptoms before the age of 6 on physical activity later in life. They only reported incident asthma as new onset physician diagnosed asthma after the age of 6, and they did not adjust for wheeze before the age of 6. The researchers concluded that in school aged children (i.e. 6 years and older), no association between physical activity and asthma exists, in neither direction.

We considered using this interesting technique for the European collaborative study, but unfortunately this was not possible because of large heterogeneity in both the physical activity data as the asthma data. The included cohorts provided information on physical activity and asthma at different ages and these could not be aggregated because of substantive differences. This means that there were not enough repeated measurements of comparable periods of exposure and outcome to perform cross-lagged analyses. Instead, we used sensitivity analyses on wheeze at age of exposure to evaluate protopathic bias and reverse causality. Our study confirmed what Cassim et al. found in their bidirectional analysis: there was no association between physical activity and asthma in either direction.

Bedard et al. performed a comparable study in adult women, but also looked into obesity in this relation.[29] The prevailing hypothesis was that the role of obesity in adult asthma could partially be attributed to an underlying role of physical activity (lack of physical activity could possibly enhance the risk of obesity and asthma). They calculated the independent causal effects of body mass index (BMI) and physical activity on current asthma using marginal structural models (MSMs) in three time periods. While they found a strong and positive dose-response relationship between BMI and current asthma, no causal effect of physical activity on current asthma was found.

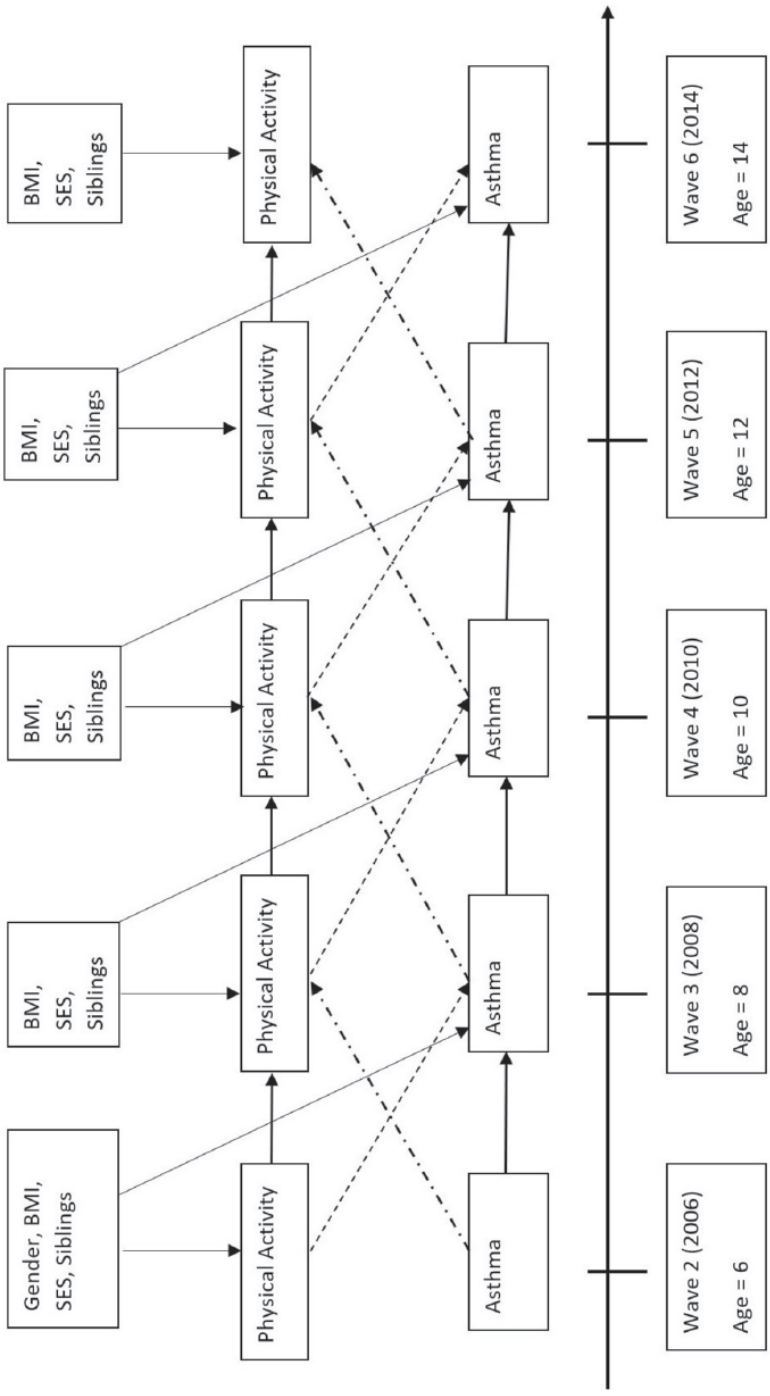

Figure 7.2: schematic representation of the cross-lagged generalised structural equation model with physical activity and asthma. BMI: body mass index. SES: socioeconomic status. (Cassim et al., J Epidemiol Community Health, 2018).

Conclusion

In conclusion, it is justified to state that physical activity does not play a large role in asthma development. Of course, in specific cases there is an association between asthma and physical activity: severe asthmatics can be held back because of their symptoms in case of insufficient asthma control. And vice versa: athletes performing in top sports are described to experience more exercise induced asthma symptoms. But in the general population there is no convincing evidence that habitual physical activity and asthma are related. However, physical activity is a major part of a healthy lifestyle that in combination does affect asthma and health status in general. There is overwhelming evidence that physical activity is important for numerous other health outcomes, and therefore this thesis should not distract from adherence to global or national physical activity guidelines.

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Chapter 8

Impact

Impact

This chapter describes the scientific and societal impact of this thesis.

Impact on research

This thesis was aimed to investigate the association between asthma and physical activity, and gave a comprehensive overview of the possible association, both based on original studies and a systematic review of the existing literature, supplemented with new insights from the literature that have been published in the last years. Due to the thoroughness of the research and consistency of the results, it is safe to state that asthma and physical activity are not clearly related. Clear answers in the scientific field are necessary to prevent researchers to continue to do new studies on the same subject. This thesis clarifies that it is not necessary to continue to focus on the association between asthma and physical activity in childhood. For specific groups, for example very young children (under the age of 2) it has to be said that this conclusion is not clear yet, especially because of the lack of validated measurements of physical activity at this age. This thesis helps researchers to focus on the subjects where answers are not clear yet.

The validation of asthma questions is of great value for the proper interpretation of the results of epidemiological research. Chapter 2 describes an important subject for future epidemiological research on asthma. The commonly used asthma definition 'parent reported physician diagnosed asthma' showed only moderate agreement with general practitioner (GP) recorded asthma diagnosis. Especially children with early transient wheeze can be mislabelled as having an asthma diagnosis. This could lead to overestimation of the true asthma prevalence in epidemiological studies. In this thesis we showed that it is advisable to use a combination of asthma questions, preferably a uniform definition such as MeDALL definition of current asthma. To improve collaboration with other cohorts in Europe and globally it would be helpful to use the same definition of current asthma, as suggested by the MeDALL group.[1,2]

Chapter 6 describes a large European collaboration study. During analysing and writing this study, the input of all these different European researchers was immense and gave an extensive representation of different European cohorts. It brings asthma research, and research in general, closer together and brought this study to a higher level. For future research such collaborations are of great importance. It increases the study size and gives a broader representation of types of behaviour and environments. Another positive effect of these collaborations is that it leads to a decrease of research waste: possibly interesting research questions are not investigated because it is not possible to study and publish all possible associations in a birth cohort. Moreover, it decreases the

risk of publication bias: analyses of smaller cohorts have often less statistical power and are less likely to make an impact in scientific journals. By combining the results of several cohorts, the statistical power will increase and thereby the chances of publication of important results. The experiences gained by organising this collaborative study have taught us the importance of data harmonisation beforehand and legal implications, such as data safety. For future research, it would improve the quality and progress if collaborations become more aligned. A good example is the LifeCycle Project, which is a collaboration of European birth cohort studies that is working on bringing all the data together in one virtual database: the EU Child Cohort Network (figure 8.1).[3,4] Especially the organisation with all data of all participating cohorts in one virtual database, without individual issues on legal and ethical aspects of data sharing and data safety is a huge step forward from the current collaborations that are already present.

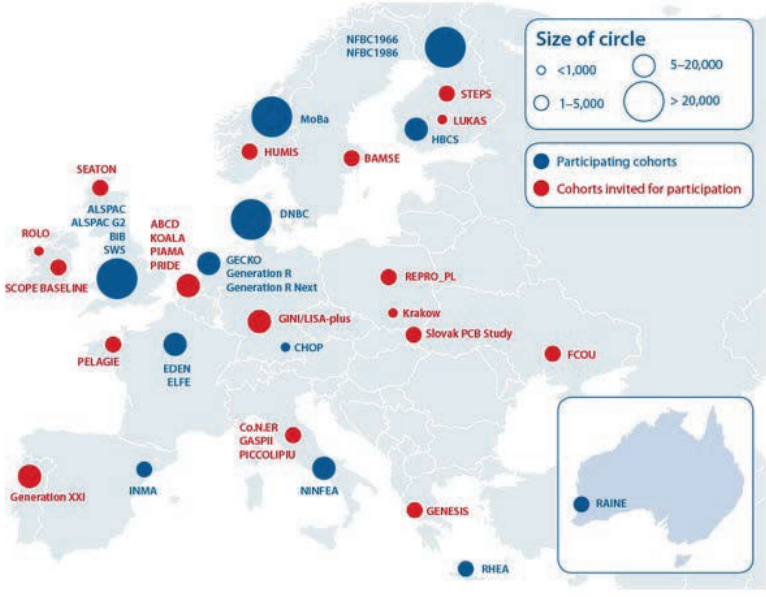

Figure 8.1: the LifeCycle Project and the EU Child Cohort Network (adapted from https://lifecycle-project.eu/for-scientists/the-eu-child-cohort-network/).

Impact on public health and health care

The societal impact of this thesis is especially supportive for counselling and management of physical activity in the general population and children who are prone to developing asthma. The results are relevant for all health care workers that are involved in community medicine for children (in the Netherlands organised as the

'jeugdgezondheidszorg' (JGZ)), family doctors and paediatricians. For asthma patients and their parents it is important to realise that it is safe to exercise and this should be encouraged for several health benefits. It is important for all children to adhere a healthy lifestyle. For physical activity the current advice is according to the 2020 global WHO recommendation: at least 60 minutes of moderate-to-vigorous physical activity (MVPA) per day on average.[5] For children who are prone to developing asthma, or who have asthmatic symptoms, this advice is the same. This thesis shows physical activity does not increase the risk of developing asthma. From other literature, described in this thesis, we know that physical activity improves quality of life and asthma control in children with asthma.[6,7] Therefore, it is important that children who show the first signs of asthma are stimulated to stay active.

While the physical activity recommendations are general, the management and counselling should be tailor made. Children (and parents) should not be hesitant in using bronchodilatating medication in order to be able to be physically active without asthmatic symptoms. Another important reason to adopt a healthy lifestyle, is the obvious relation of obesity and subsequent increased risk of developing (or worsening of existing) asthma. Children who have a healthy weight status, are less prone to develop asthma. As physical activity provides a major contribution to a healthy lifestyle (together with a healthy diet), we should continue to advice all children (and adults) to adhere to the WHO or national guidelines of physical activity.

Another aspect of this thesis with societal impact on health care is the difference between parent reported physician diagnosed asthma and GP recorded asthma diagnosis in childhood. Chapter 2 shows that there are large differences in the way parents experience an asthma diagnosis set by a physician compared to their GP, especially when it concerns asthma diagnosis in very young children. For clinical practice, it is important for physicians to use the correct wordings when explaining (preschool) wheeze to parents and that parents and physicians work together in shared decisions concerning the health of the child.

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Summary

Summary

Asthma is one of the most common chronic diseases in children in the world. Asthma is caused by multiple factors, both genetic and environmental. Known environmental factors for developing asthma are exposure to cigarette smoke, air pollution, open fire cooking, antibiotic use early in life, diet and obesity. Low levels of physical activity are also considered as possible risk factor for developing asthma. Since the second half of the twentieth century, children (and adults) have been participating less in physical activity. The WHO Global Recommendations for Physical Activity and Sedentary Behaviour (2020) advises children to participate in moderate-to-vigorous physical activity for at least 60 minutes per day on average. Currently, only 20% of all adolescents globally meet this recommendation.

Asthma and physical activity are possibly associated: earlier studies have shown that individuals with asthma are less physically active compared to individuals without asthma. Possible explanations can be found in vigorous activity acting as a trigger for asthma symptoms (especially in exercise-induced asthma), or by poorly controlled asthma or fear of an asthma attack. As a consequence, children who engage less in physical activity become deconditioned and a vicious circle arises with shortness of breath when exercising. Physical training improves asthma control and possibly lung function in asthmatics. Asthma organisations and doctors advise asthmatic patients to stay physically active.

The aim of this thesis is to investigate the relation between asthma and physical activity.

Chapter 2 describes a validation study in which we evaluated whether physician diagnosed asthma as reported by the parents corresponds to the medical information recorded by their general practitioner (GP). This showed only moderate agreement. In studies that use questionnaires to define asthma, the advice is not only to ask for physician diagnosed asthma, but to use a combination of questions, such as medication use and current asthma symptoms. Preferably, a uniformly applicable asthma definition is used, as proposed by the Mechanisms of the Development of Allergy (MeDALL) collaboration, which consists of a combination of asthma diagnosis, recent medication use and/or symptoms of wheezing (2 out of 3 criteria).

In the following chapters we describe 4 studies on asthma and physical activity in different directions: Chapter 3 describes asthma symptoms prior to physical activity, Chapter 4 provides an overview of the literature of cross-sectional and longitudinal studies with physical activity as a risk factor for developing asthma in children and

adults. Chapters 5 and 6 describe original studies with physical activity as a risk factor for childhood asthma.

Chapter 3 addresses the influence of early wheeze (before the age of 2) on physical activity patterns and overweight (at age 4 to 5 years) within the KOALA birth cohort study. Physical activity was measured with motion sensors. Boys were physically more active if they had experienced wheezing before the age of 2 but had outgrown it, compared with boys who had never experienced wheezing. No difference was found in girls. Children aged 4 to 5 who had experienced wheezing in the past year were equally physically active compared to children who did not wheezed. There was no relation between wheezing and overweight or physical activity and overweight.

Chapter 4 provides an overview of the available literature on asthma and physical activity. At the time of this study (2012), no longitudinal studies in children with physical activity as exposure and asthma as outcome were available. In adults, the available evidence in longitudinal studies indicated that higher physical activity levels might be protective for asthma development. Cross-sectional studies in childhood showed conflicting results. This lack of longitudinal studies in childhood was the motivation for performing two original, longitudinal studies with physical activity as exposure and asthma development in children, as described in chapter 5 and 6. **Chapter 5** describes an original study within the KOALA birth cohort on physical activity and sedentary behaviour (measured with motion sensors and questionnaires) at the age of 4 to 5 years and asthma and lung function between 6 and 10 years. No association between physical activity or sedentary behaviour and subsequent asthma development was found. In a small subgroup for which both accelerometry and lung function data were available, sedentary behaviour was associated with lower FEV_1/FVC ratio. **Chapter 6** describes a large collaborative study that we initiated, in which we brought together information from 26 European cohorts on physical activity, sedentary behaviour and the development of asthma and lung function between birth and 18 years. Again, no association was found between physical activity, sedentary behaviour and the development of asthma. We found no confirmation of our previous finding of a possible association between sedentary behaviour and lung function.

Finally, in **chapter 7** the results of this thesis are discussed in relation to the existing literature and considerations. In **chapter 8** the results of this thesis are placed in a bigger picture, with attention to the societal impact.

In conclusion, this thesis shows that physical activity does not play a large role in asthma development. Prevention programs should focus on broader lifestyle advice, in particular the prevention of cigarette smoke exposure, a healthy diet, and the prevention of obesity.

Samenvatting

Samenvatting

Astma is één van de meest voorkomende chronische ziekten bij kinderen in de wereld. Astma wordt veroorzaakt door meerdere factoren, zowel door genetische factoren als omgevingsfactoren. Bekende omgevingsfactoren voor het ontwikkelen van astma zijn blootstelling aan sigarettenrook, luchtvervuiling, koken op open vuur, antibiotica-gebruik vroeg in het leven, voeding en overgewicht. Gebrek aan beweging wordt ook als mogelijke risicofactor voor het ontwikkelen van astma gezien. Sinds halverwege de vorige eeuw bewegen kinderen (en volwassenen) steeds minder. De internationale WHO richtlijn voor beweging (2020) adviseert kinderen om tenminste gemiddeld 60 minuten per dag matig tot intensief te bewegen. Op dit moment haalt slechts 20% van de adolescenten wereldwijd deze beweegrichtlijn.

Astma en beweging zijn mogelijk geassocieerd: eerdere studies hebben aangetoond dat personen met astma minder bewegen dan personen zonder astma. Mogelijke verklaringen hiervoor zijn het uitlokken van een astma-aanval door intensief bewegen (vooral bij inspanningsgebonden astma), matig gecontroleerd astma en angst voor kortademigheid. Doordat kinderen weinig bewegen ontstaat er een vicieuze cirkel met een matige conditie waardoor er sneller kortademigheid ontstaat bij bewegen. Fysieke training verbetert de astma-controle en mogelijk longfunctie van astmapatiënten. Astma-organisaties en artsen adviseren astmatische patiënten om in beweging te blijven.

Het doel van dit proefschrift is om de relatie tussen astma en beweging te onderzoeken.

Hoofdstuk 2 beschrijft een validatiestudie waarin we onderzocht hebben of een arts diagnose astma die door ouders gerapporteerd wordt overeenkomt met de medische gegevens die hun huisarts genoteerd heeft. Hieruit blijkt dat dit maar matig overeenkomt. Het advies is om in studies waarin gebruikt gemaakt wordt van vragenlijsten om astma te definiëren niet alleen te vragen naar een astma diagnose maar dit te combineren met andere vragen, zoals medicatiegebruik en huidige klachten. Bij voorkeur wordt gebruik gemaakt van een uniform toepasbare astma definitie zoals voorgesteld door het samenwerkingsverband Mechanisms of the Development of Allergy (MeDALL), die bestaat uit een combinatie van astma diagnose, recent medicatiegebruik en/of klachten van een piepende ademhaling (2 van de 3 criteria).

In de volgende hoofdstukken beschrijven we 4 studies over astma en bewegen in verschillende richtingen: hoofdstuk 3 beschrijft astma symptomen voorafgaand aan beweging, hoofdstuk 4 geeft een overzicht over de literatuur van cross-sectionele en

longitudinale studies met beweging als risicofactor voor het ontwikkelen van astma bij kinderen en volwassenen. Hoofdstuk 5 en 6 beschrijven originele studies met beweging als risicofactor voor het ontwikkelen van astma op kinderleeftijd.

Hoofdstuk 3 beschrijft een studie binnen het KOALA geboortecohort naar het effect van een piepende ademhaling op jonge leeftijd (voor 2 jaar) op het beweegpatroon en overgewicht op latere leeftijd (4 tot 5 jaar). Beweging werd met beweegmeters gemeten. Jongens bewogen meer als zij een piepende ademhaling hadden gehad voor de leeftijd van 2 jaar maar daar overheen gegroeid waren, vergeleken met jongens die nooit last hadden gehad van een piepende ademhaling. Bij meisjes werd geen verschil gevonden. Kinderen van 4 tot 5 jaar die het afgelopen jaar last hadden gehad van een piepende ademhaling bewogen niet meer of minder dan kinderen die geen piepende ademhaling hadden. Er was geen relatie tussen piepende ademhaling en overgewicht of bewegen en overgewicht.

Hoofdstuk 4 geeft een overzicht van de beschikbare literatuur over astma en bewegen. Ten tijde van deze studie (2012) was er geen literatuur beschikbaar over longitudinale studies met een meting van bewegen voorafgaand aan astma bij kinderen. Bij volwassenen werd een mogelijk beschermend effect van bewegen op het ontwikkelen van astma gevonden. Er werden veel cross-sectionele studies gevonden die tegenstrijdige uitkomsten toonden. Dit was de aanleiding om twee vervolgstudies te doen, gericht op het onderzoeken van de invloed van beweging op het ontstaan van astma, beschreven in hoofdstuk 5 en 6. **Hoofdstuk 5** beschrijft een originele studie binnen het KOALA geboortecohort naar beweging en sedentair gedrag (gemeten met beweegmeters en vragenlijsten) op de leeftijd van 4 tot 5 jaar en astma en longfunctie tussen 6 en 10 jaar. Er werd geen verband gevonden tussen bewegen of sedentair gedrag en het ontstaan van astma. In een kleine subgroep waar zowel beweegmetingen als longfunctie beschikbaar waren werd een mogelijk verband gevonden tussen sedentair gedrag en een lagere longfunctiewaarde FEV_1/FVC. **Hoofdstuk 6** beschrijft een grote studie die we in Europees samenwerkingsverband gedaan hebben, waarbij we informatie uit 26 Europese cohorten bij elkaar gebracht hebben over beweging, sedentair gedrag en het ontstaan van astma en longfunctie tussen geboorte en 18 jaar. Ook hier werd geen verband gevonden tussen bewegen, sedentair gedrag en het ontstaan van astma. We vonden geen bevestiging van onze eerdere bevinding van een verband tussen sedentair gedrag en longfunctie.

Tenslotte worden in **hoofdstuk 7** de resultaten van dit proefschrift besproken in relatie tot de bestaande literatuur en overwegingen. In **hoofdstuk 8** worden de resultaten van dit proefschrift in een groter geheel geplaatst, met aandacht voor het maatschappelijke belang.

Concluderend toont dit proefschrift aan dat beweging geen duidelijke rol speelt in het ontstaan van astma. Preventieprogramma's zouden gericht moeten zijn op een breder leefstijladvies, met name het voorkomen van blootstelling aan sigarettenrook, een gezond dieet en het voorkomen van overgewicht.

Dankwoord

Dankwoord

Om te beginnen wil ik graag alle KOALA kinderen en hun ouders bedanken. Zonder hun bereidwilligheid om vanaf de geboorte gevolgd te worden en een bijdrage te leveren aan de wetenschap was dit proefschrift niet mogelijk geweest.

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Curriculum vitae

Curriculum vitae

Marianne Eijkemans is op 20 september 1983 geboren in Veghel. Zij groeide op met haar ouders en broer en zus in Sint-Michielsgestel. Ze slaagde Cum Laude voor het Gymnasium Beekvliet te Sint-Michielsgestel en verhuisde naar Maastricht om Geneeskunde te studeren. In 2006 voldeed ze haar wetenschapsstage bij de vakgroep Epidemiologie binnen de KOALA studie, onder begeleiding van Monique Mommers en Carel Thijs. Aansluitend ging ze voor haar laatste coschap (GEZP stage) naar Nuevo Hospital El Milagro in Salta, Argentinië waar ze stage liep op de afdeling neonatologie. Hier rondde ze het eerste artikel van dit proefschrift af. Na haar studie werkte ze als ANIOS kindergeneeskunde in het Radboudumc, waar ze in 2009 werd aangenomen voor de opleiding tot kinderarts. Hierbij voldeed ze het perifere deel van de opleiding in het MMC Veldhoven, onder begeleiding van dr. Martin de Kleine, en het academische deel in het Radboudumc met als opleider dr. Jos Draaisma. Na haar opleiding werkte ze 6 maanden in de Gelderse Vallei in Ede als waarnemend kinderarts, voor ze in 2014 haar droombaan vond in het Catharina Ziekenhuis in Eindhoven. Hier is zij algemeen kinderarts met bijzondere aandacht voor de neonatologie en maag-darm-leverziekten. Daarnaast is zij co-assistentenopleider en vakgroepvoorzitter. Tijdens haar opleiding tot kinderarts en naast haar werk als kinderarts voltooide ze in haar vrije tijd dit proefschrift.

Marianne is getrouwd met Bas, samen hebben zij 3 kinderen: Guus (2012), Tom (2013) en Eva (2016). Zij wonen in Vught.