Overweight and respiratory and cardiovascular health in children

The PIAMA birth cohort study ~ Marga Bekkers

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Overweight and respiratory and cardiovascular health in children

The PIAMA birth cohort study

Overgewicht en respiratoire en cardiovasculaire gezondheid in kinderen

De PIAMA geboorte cohort studie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 15 mei 2012 des ochtends te 10.30 uur

door

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geboren op 20 oktober 1982 te Eindhoven

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Contents

Chapter 1

General introduction

General introduction

Today's children and adolescents have a much higher prevalence of overweight than the generation of their parents had in their childhood. The prevalence of asthma symptoms has also increased at the end of the last century and associations between overweight and asthma have been convincingly shown in previous research.[1] The increase in childhood and adolescent overweight prevalence may be expected to have consequences on the future health of the current child population. The increase in overweight might enhance the prevalence of cardiovascular diseases or earlier onset of cardiovascular disorders and the same can be hypothesized for lung diseases.
The children that were born and raised during the decades of a growing prevalence of overweight have not grown to maturity yet, therefore it will take decennia to understand the full extent of the overweight epidemic. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study does provide us with information to study associations between childhood overweight on the one hand and respiratory health and early indicators of cardiovascular health in adult life on the other hand.

Childhood overweight

The prevalence of overweight in children has increased rapidly over the past decades in most Western countries.[2,3] In the Netherlands, an increase in the overweight prevalence has been observed too (Figure 1). Although some recent studies suggest a stabilization of the prevalence of childhood overweight in specific countries[4,5], the percentage of children and adolescents that are overweight or obese still is high.[2,6] Therefore overweight in children remains a significant public health issue.

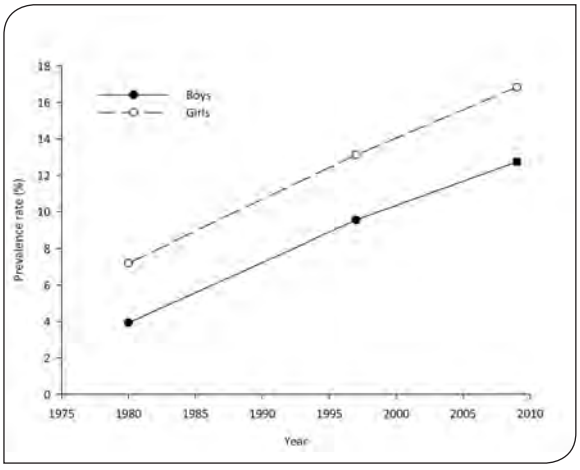

Figure 1
Prevalence of overweight and obesity in 4-to-8-year-old Dutch boys and girls according to international cut-off values.[7] This figure is reproduced from data of the Dutch National Growth Study.[8]

Overweight in childhood usually develops at an early age and tends to persist into adulthood.[9] In turn, adult overweight is a strong risk factor for several chronic diseases, e.g. type 2 diabetes mellitus and cardiovascular diseases. In addition, overweight in childhood and adolescence has consequences on premature mortality and morbidity in adulthood[6], these associations probably depend on the persistence of body mass index (BMI) from childhood into adult-

hood.[10] Adults with a history of childhood overweight might be at an even higher risk than adults who become overweight during adulthood. This may imply that the duration of overweight adds an increased risk to being overweight at the current moment.[11]

Cardiovascular risk factors

Cardiovascular diseases contribute substantially to mortality in Western countries, including the Netherlands.[12] These diseases typically become only manifest in adulthood. Well-known risk factors for cardiovascular diseases are an adverse lipid profile, hypertension, diabetes, smoking and overweight in adulthood.[13] During the last decades the prevalence of hypertension, smoking and adverse lipid profiles has decreased in Western countries.[14,15] This, together with improved medical treatment has led to a decrease in cardiovascular mortality in these countries.[16] However, mortality rates are still high. Besides lifestyle in adulthood, early-life determinants and childhood overweight may also contribute to the development of cardiovascular disease. For instance, higher blood pressure levels and elevated total and low density lipoprotein (LDL) blood cholesterol concentrations have been shown in overweight and obese children compared with normal weight children.[17-22] Also more frequently impaired glucose tolerance has been observed in obese children.[23] High blood pressure and cholesterol concentrations and other metabolic risk factors may persist over time and progress to adult dyslipidemias and hypertension.[24,25] The persistence and progression of child's high blood pressure and adverse cholesterol concentrations into adulthood may result in an increased burden of cardiovascular disease earlier in adulthood.

Respiratory factors

Normal lung development is characterized by growth of pulmonary function during childhood and adolescence until peak lung function is reached by age 18 to 20 years.[26] Lung function then plateaus and thereafter declines as a feature of normal ageing.[26] Children with asthma acquire a lung function deficit early in life which persists throughout childhood into adolescence.[26] Asthma is characterized by chronic inflammation of the airways, airway hyperresponsiveness, variable airflow limitation and recurrent respiratory symptoms, including wheeze, breathlessness, chest tightness, and coughing.[27] The prevalence of childhood asthma increased at the end of the last century[26] and this may affect the lung function and thereby respiratory health of the future adult population. Lung diseases contribute substantially to mortality in adulthood[28] and mortality from respiratory diseases may be expected to increase in the future in case respiratory health will decline. Childhood asthma is not the only potential determinant of adult lung function, as also overweight might influence lung function in adulthood. The effect of overweight on lung function has been clearly shown in adults[29-31], whereas in children the results on the relation between overweight and lung function are inconsistent so far. Summarizing, if lung development in childhood is negatively influenced by for instance asthma or overweight, children may reach a lower peak lung function, which increases the risk of respiratory disease in adulthood.

Measures of childhood overweight

The definition of overweight in epidemiologic studies is usually based on BMI, calculated as weight in kilograms divided by height in meters squared. In adults, a BMI ≥25kg/m^2 is defined as overweight and a BMI ≥30kg/m^2 as obese.[32] These definitions are based on the association between BMI and mortality.[32] In children, the definition of overweight is less straight forward, because BMI in children changes substantially with age.[7] Generally, the mean BMI increases from birth to one year of age, then decreases for five years and from the age of six years until adolescence the BMI increases. Cole et al. defined age- and sex-specific cutoff points for overweight and obesity per half year from 2 to 18 years of age.[7] To define these cutoff points they used BMI for age reference curves of six growth studies from different countries, including the Dutch National Growth Study of 1980.

The mean BMI differs at different ages during childhood, thereby complicating comparison of children's BMI at different ages. Therefore, BMI standard deviation scores (BMI SDS), also called z-scores, are commonly used to compare BMI of different genders and ages. These SDSs are calculated based on reference data of subjects with the same age and gender. In the Netherlands we commonly use the Dutch National Growth Study of 1997. Based on this reference population standard deviation scores can be calculated for the child's exact age and from the age of 2 weeks onwards. A BMI SDS of 0 means that the BMI of the individual is equal to the mean of subjects of the same age and gender in the reference population. A negative SDS corresponds to a BMI below the mean, and a positive SDS to a BMI above the mean. Standard deviation scores can also be calculated for weight for age, height for age, and weight for height.

BMI is generally used as measure of adiposity in epidemiologic studies, but has recognized shortcomings. For instance, BMI reflects total body mass which is influenced by bone mass and muscle mass besides fat mass. Waist circumference, on the other hand, more specifically reflects abdominal fat mass and is only to a minor extent influenced by muscle and bone mass. In epidemiologic studies, but also in clinical practice, not only the appropriateness of BMI and waist circumference indicating fat mass is of importance. Besides the utility as indicator of fat mass, different associations with health outcomes between BMI and waist circumference merit specific attention. The study of differences in associations with health outcomes between BMI and waist circumference may contribute to improved insights into the usefulness of BMI and waist circumference in both clinical practice and epidemiologic research. A more central deposition of fat, reflected by a large waist circumference, might be more strongly related to specific health outcomes, like higher blood pressure and less favorable lipid concentrations than fat in the extremities.[33,34] This would argue in favor of taking waist circumference into account in addition to the usual weight and height measurements. As previous studies have not been fully conclusive yet, we will study the relative importance of waist circumference and BMI in the associations with health outcomes.

In the studies described in this thesis, weight, height, and waist circumference were measured by professionals. However, most epidemiologic studies rely on self- or parent-reported data on weight and height to define overweight, because these data are easily obtained through questionnaires from large study populations. Studies in adults and in children showed that the prevalence of overweight based on self- or parent- reported data is lower than the prevalence based on measured weight and height.[35] In adults, waist circumference is generally underreported.[36-38] Whether this is true for children's waist circumference reported by their parents is not clear.

Prevention and Incidence of Asthma and Mite Allergy Study

In this thesis data from the 'Prevention and Incidence of Asthma and Mite Allergy' (PIAMA) study are analyzed. The PIAMA study is a prospective birth cohort study among children recruited from the general population. The initial objectives of the study were to evaluate the effectiveness of allergen reduction measures for the prevention of asthma and mite allergy in children of allergic mothers, and to investigate the natural history of childhood asthma and risk factors for the development of asthma. Later, the study aims were expanded to include early markers of cardiovascular disorders.

The study started with the recruitment of pregnant women via 52 prenatal health care clinics in the Netherlands in 1996 and 1997. A validated screening questionnaire on maternal allergy was used to ascertain maternal allergic status. In total, 10232 women completed the screening questionnaire (Figure 2). Based on this screening 7862 women (2779 allergic women and 5083 non-allergic women) were invited to participate in the study. Approximately 50% of the invited pregnant women agreed and gave written informed consent (n=4146). Of the baseline population of 4146 women, 183 were lost to follow-up before any data on the child had been obtained, so that the study started with 3963 newborn children. All children were born in 1996-1997 and followed up to the age of 8 years. At the age of 11 years the children and their parents were contacted again.

In the PIAMA study, data were mainly collected by postal questionnaires sent to the parents during pregnancy, 3 months after the child was born, and annually starting when the child was 1 year old to the age of 8 years. At the age of 11 years, a questionnaire was sent again to the parents. Additionally, the children received a questionnaire too. In all parental questionnaires the child's weight and height, asthma symptoms, diet, general health and medication was reported. The child questionnaire focused on respiratory and general health, medication and lifestyle factors.

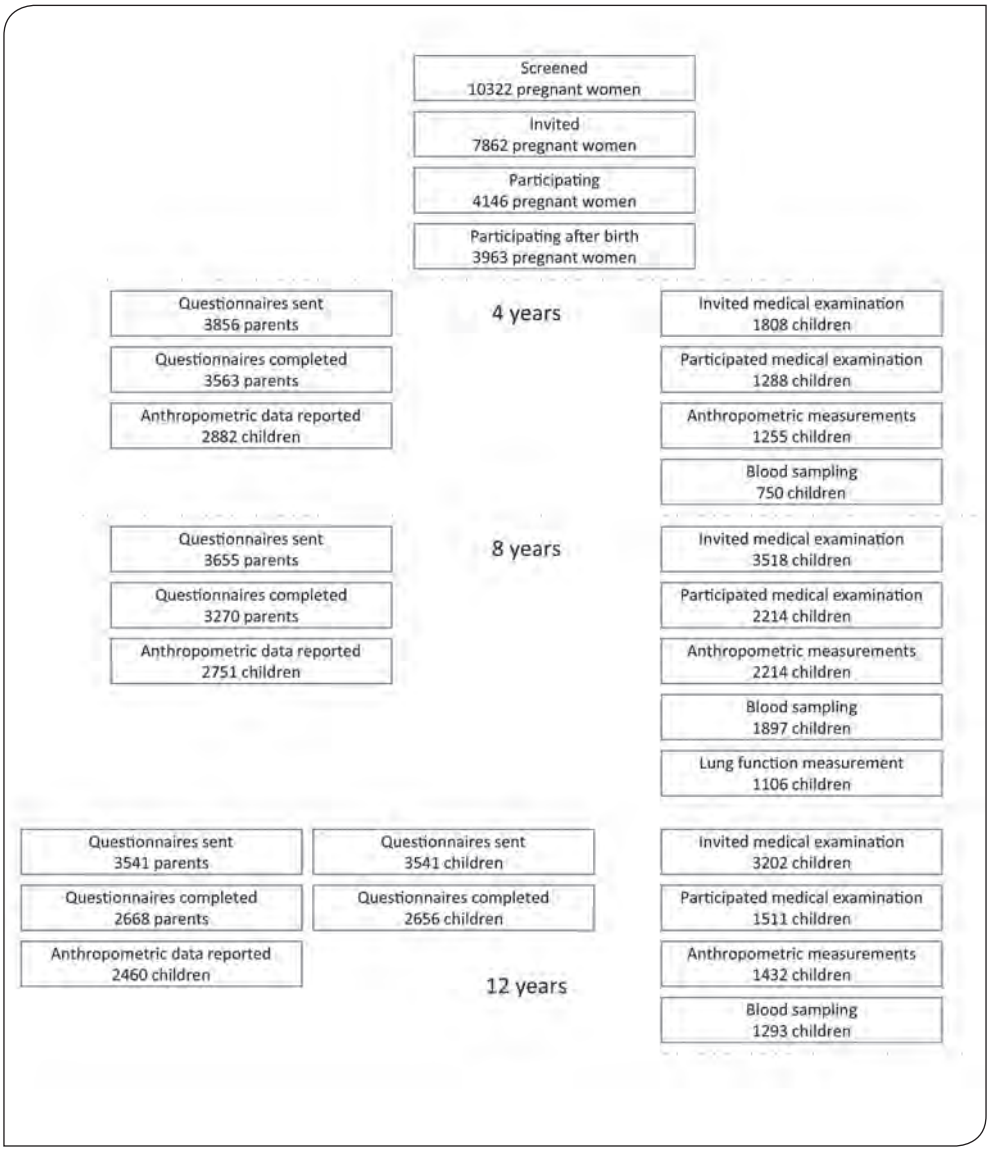

Figure 2

Flow chart of the PIAMA birth cohort study. Only ages at which medical examinations were performed are shown.

At 4, 8 and 12 years of age a medical examination was performed in 1288, 2214, and 1511 children respectively. Weight and height measures and blood sample collection were part of all three medical examinations. At 8 years of age waist circumference measurements and lung function testing were included. In the medical examination performed at age 12, additionally to the measurements at age 8 years, blood pressure was measured.

Aim & Outline of this thesis

The aim of this PhD research is to study aspects of cardiovascular and respiratory health in relation to childhood overweight and to study differences in associations with specific health determinants, using BMI or waist circumference as indicator of childhood overweight.

In Chapter 2, we investigate whether valid waist circumference data of school-aged children can be obtained by questionnaires. We study the agreement between waist circumference measured and reported by the parents and waist circumference measured by professionals. The agreement for waist circumference is compared with the agreement between BMI based on weight and height reported by the parents and BMI based on measured weight and height by professionals in 8-year-old children.

Chapter 3 studies possible early-life determinants of blood cholesterol concentrations in 8-year-old children and the role of the child's current BMI in these associations.

In Chapter 4, we examine the association between childhood overweight and asthma symptoms to get insight into potential underlying mechanisms. We do this by studying the association between overweight and asthma symptoms prospectively and by studying pro-inflammatory proteins as possible mechanism.

Besides asthma symptoms, we study other consequences of childhood overweight, by using objective markers of respiratory and cardiovascular health.

In Chapter 5 we study whether BMI and waist circumference in 8-year-old children are associated with lung function.

Chapter 6 investigates the relation between BMI and waist circumference in 8- and 12-year-old children on the one hand and blood pressure and cholesterol in 12-year-old children on the other hand.

The thesis concludes with a general discussion of the findings presented in this thesis.

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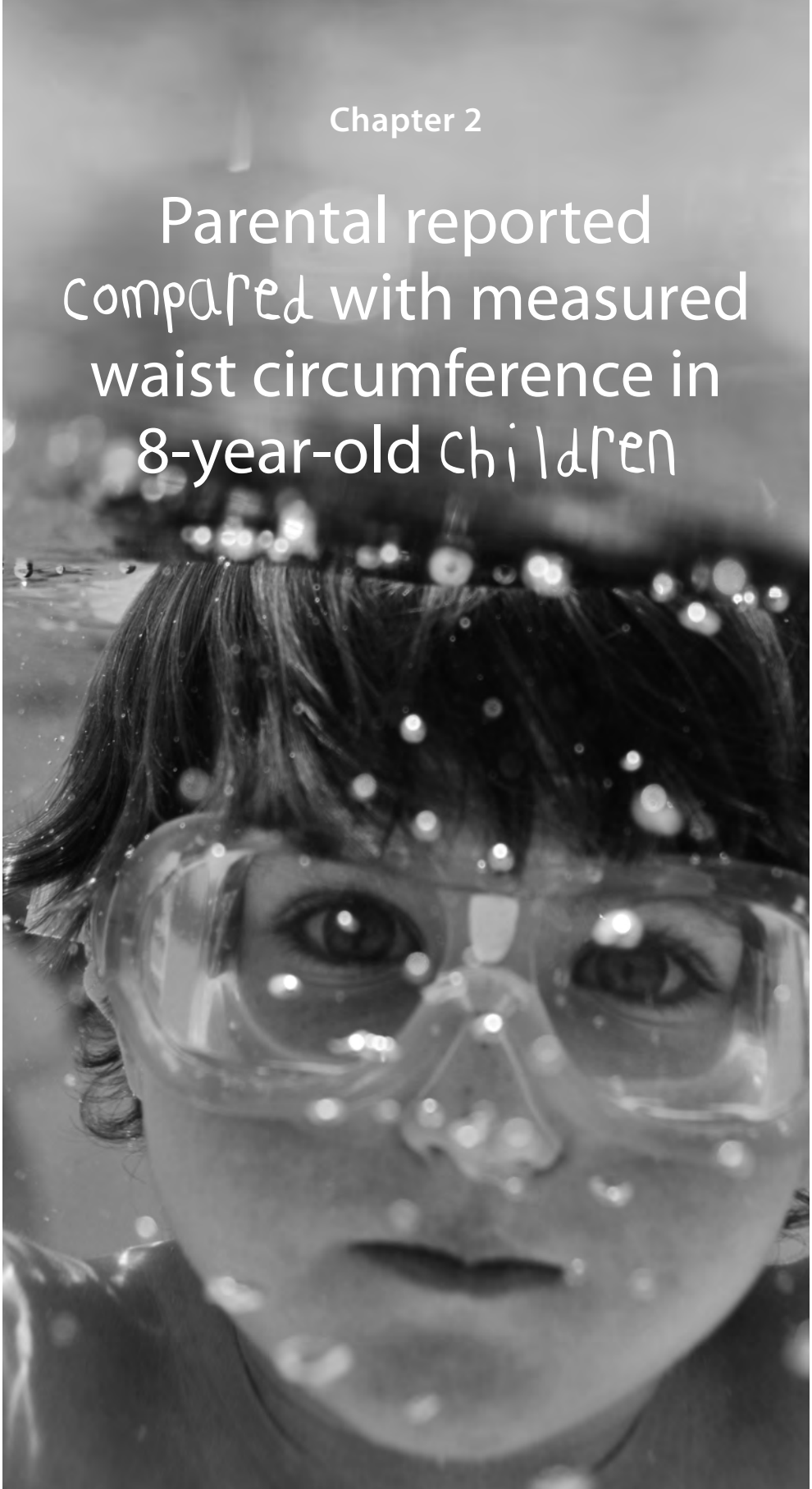
Chapter 2

Parental reported compared with measured waist circumference in 8-year-old children



Parental reported compared with measured waist circumference in 8-year-old children

Abstract

Most epidemiological, questionnaire-based studies collect data on body weight and height but not on waist circumference, although waist circumference is suggested to be clinically more relevant. It is unknown whether valid waist circumference data of school-aged children can be obtained by questionnaires. In this study the agreement between parental reported and measured waist circumference in 8-year-old children was investigated and compared with the agreement between parental reported and measured BMI. Data on body weight, height, and waist circumference of 1292 8-year-old Dutch children were collected by a medical examination and a questionnaire. Mean differences, correlations and misclassification based on parental reported values were calculated. Mean differences between parental reported and measured values were small. Pearson correlation coefficient for measured and reported waist circumference was 0.83 compared with 0.90 for measured and reported BMI. Parents of children with a high BMI tended to underreport their child's waist circumference and body weight. A total of 22.7% of overweight children were misclassified as being normal weight based on reported waist circumference compared with measured waist circumference. For BMI this applied to 23.7% of children. In conclusion, parental reported waist circumference corresponded well with measured values, indicating that reported waist circumference can be used to study associations between waist circumference and risk factors or health outcomes.

Based on manuscript

Bekkers MBM, Brunekreef B, Scholtens S, Kerkhof M, Smit HA, Wijga AH, Parental reported compared with measured waist circumference in 8-year-old children, International Journal of Pediatric Obesity, 2011;6:e78-e86

Introduction

Waist circumference may be clinically more relevant for assessing adiposity compared with BMI.[1-5] Consistent evidence exists that a greater central fat deposition increases the risk of metabolic complications, also in children.[6-14] BMI is only an indirect parameter of total body fat and does not reflect body fat distribution.[15,16] This might imply that BMI, compared with a measure taking waist circumference into account, might miss children with high abdominal adiposity [3]. Besides waist circumference, also waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) have been suggested as indicators of central adiposity in children.[1,2,5,17-19] However, waist circumference is widely considered as the preferred indicator in children.[2,20-23] Nevertheless in most epidemiologic studies, BMI is the main indicator for overweight related risks, and waist circumference is rarely used. BMI is often used because data on weight and height are easily obtained through questionnaires in epidemiologic studies. However, reported and measured data on body weight and height do not always correspond very well.[24-34] Self-reported waist circumference is investigated in only a few studies, and was underreported in four out of five studies.[35-39] As all these studies were performed in adults, information on the validity of reported waist circumference in children is crucial as epidemiologic studies often rely on reported data. Therefore, the aim of this study was to investigate the agreement between parental reported waist circumference, BMI based on parental reported body weight and height on the one hand, and waist circumference and BMI measured during a medical investigation on the other hand in 8-year-old Dutch children.

Methods

Study design

The children in this study are participants of the PIAMA birth cohort study and were born in 1996–1997. A detailed description of the study design has been published previously.[40] The mothers were recruited from the general population during pregnancy visiting one of 52 prenatal clinics. Postal questionnaires were sent to the parents during pregnancy, at the child's ages of 3 and 12 months, and yearly thereafter up to the age of 8 years. At the age of 8 years the children were invited for a medical examination. This medical examination took place in the hospital, in local health centers or during a home visit, in case the parents and the child were not able to visit the hospital or health centre. The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent.

Study population

At baseline the cohort consisted of 4146 pregnant women, of which 183 (5%) were lost to follow-up before any data of the child had been collected. Therefore the study started with 3963 newborns. At the age of 8 years 3658 (92.3% of 3963) children were still in the study and received a questionnaire. Questionnaires were returned by 3563 (89.9%) parents. Of 2889 (72.9%) children for whom the parents sent back the questionnaire, waist and hip circumference were reported. These numbers are similar to those for reported body weight (n=2883) and height (n=2872). For the medical examination 3518 children were invited, of which 2276 (57.4%) agreed to participate. Finally, the medical examination, including anthropometric measurements, was performed in 2214 children. In 795 children (61.5% of the final study population (1292 children)), the medical examination took place after the questionnaire was filled in.

For this study 545 of the 2214 children were excluded due to missing values for reported

waist circumference (n=286), hip circumference (n=285), body weight (n=339), or height (n=335). In addition, 354 children were excluded because of extremely unlikely dates for filling in the questionnaire (n=9), a time span of more than six months between the dates of the medical examination and the filling in of the questionnaire (n=326), or because of a difference larger than 60 days between the dates of reporting height and body weight (n=19). The latter exclusion criterion was included because body weight and height are needed for the calculation of BMI and therefore need to be measured around the same time to ensure proper interpretation. Although the parents were not given written records of their child's measured waist circumference, hip circumference, body weight, and height, another 17 children were excluded from the analyses because the parents copied the measured values in the questionnaire. The differences between reported and measured values did not differ between those who had the medical examination first and those who had the medical examination second. Finally six children with deviant ages at reported body weight and height (n=3) or extremely unlikely values for waist circumference were excluded (n=3). The final study population consisted of 1292 children.

Outcome variables

The measurements during the medical examination were performed by trained research staff using calibrated measuring equipment. Waist and hip circumference were measured twice and rounded to one decimal. In the analyses the mean of the two waist measurements was used. Body weight was measured to the nearest 0.1 kg and height (cm) was measured at one decimal. All anthropometric variables were measured while only wearing underwear.

Together with the questionnaire at 8 years of age, we sent a non-stretchable measuring tape to measure the waist and hip circumference. In the questionnaire we instructed the parents to measure their children while only wearing underpants, standing upright, facing the parent, and at the end of gentle expiration. They were instructed, by text and by an image, to measure the waist circumference midway between the lowest rib and the top of the iliac crest. Hip circumference had to be measured at the position where the circumference was the widest. These instructions where identical to those of the professionals. The values for waist and hip circumference were rounded to the nearest whole centimeter. Furthermore, the parents were asked to report their child ' s body weight and height the last time he or she was measured by a medical professional. In case these measures were taken more than a year ago, the parents were asked to measure their child themselves. Almost all parents (n=1076) measured their child's body weight and height themselves. The differences between measured and reported values did not vary between children measured by their parents, by someone else, or by a professional. They were instructed to measure their child's body weight and height without shoes and heavy clothes. For all measurements separately, the parents reported the date of the measurements and the person who performed the measurements (a medical professional, the parents or someone else).

Gender and age specific cut-off points for waist circumference to define abdominal overweight and obesity in children are based on cut-off points defined in a Dutch reference population.[2] The cut-off value for abdominal overweight was based on the 90th percentile and for abdominal obesity on the 99th percentile. BMI was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). Overweight and obesity were defined according to standard international definitions, specified for age and gender, based on adult overweight and obesity definitions.[41] The term overweight is equivalent to an adult BMI≥25 kg/m^2. Moderate

overweight corresponds to a BMI ≥25 kg/m^2 and <30kg/m^2 in adults, and the term obesity is equivalent to an adult BMI ≥30kg/m^2. The analyses were focused on waist circumference as this measure is suggested to be clinically more relevant compared with BMI. For completeness; however, the results on hip circumference, WHR and WHtR are also presented in the descriptive characteristics listed in Table 1.
In addition, in the questionnaires, data on the BMI and the educational level of the mother were collected. This was measured as the highest education completed and then divided into three categories; low, intermediate and high education.

Statistical analyses
For all the analyses conducted in this study SAS software version 9.1 (SAS Institute, Inc., Cary, NC) was used. As the date of medical examination and the date of reported measurements differed by up to 6 months, the measured waist and hip circumference, body weight, and height were standardized within the study population to the age of the child at the reported measurements using the average increase in waist and hip circumference, body weight, and height per day, separately for girls and boys. Baseline characteristics were compared between children participating in the medical examination and children whose parents filled in the questionnaire but did not participate in the medical examination. The difference between measured and parental reported values was calculated by subtracting the reported value from the measured value for each individual. This means that a positive difference reflects underreporting.
Agreement between parental reported and medical examination values was illustrated in Bland-Altman plots[42] in which the difference between parental reported and medical examination values is plotted against the mean of these two measurements. Limits of agreement were calculated as the mean difference ± 2 standard deviations (sd). The scales of the y-axes were adjusted to simplify comparison of the parameters.
Pearson correlation coefficients were calculated to examine whether ranking of children according to their waist circumference or BMI corresponded between parental reported and measured waist circumference body weight, height, and BMI. Although we recognise that the correlation coefficient may be misleading in identifying agreement, we calculated Pearson's correlation coefficient to allow comparison with the few studies already done in adults. Additionally, measured and parental reported waist circumference were plotted.
The highest 10% of waist circumference and BMI were studied to examine the correspondence between these two measures in ranking children according to their waist circumference or BMI. This illustrates whether BMI and waist circumference identify the same children as the highest 10%. The means of the measured values and the differences between the measured and the parental reported values were calculated separately for BMI and waist circumference quartiles, to study whether BMI and waist circumference are determinants of the difference between measured and parental reported values.
Univariate and multivariate regression were performed to study more determinants of the differences between parental reported and measured values i.e., the possible influence of the measured value, the child's gender, and BMI and education of the mother on the difference between measured and parental reported waist circumference, body weight, and height. *P*-values below 0.05 were considered to be statistically significant. The percentages of misclassified (abdominal) overweight children based on parental reported waist circumference and BMI were compared. This was to assess whether a difference exists between classifications based on parental reported waist circumference and parental reported BMI.

Results

The mean age in this study population was 8.1 years (sd=0.1) and the study population consisted of 49.1% of girls (n=634). Children included in this study did not differ from children whose parents completed the questionnaire but who did not participate in the medical examination with regard to child's gender, age, body weight, height, waist and hip circumference, the person who carried out the measurements, and BMI, age, and educational level of the mother. Measured waist circumference and measured BMI were strongly correlated (ρ=0.87, *P*<0.0001), but of the 129 children in the highest BMI decile, 30 children were not in the highest waist circumference decile. This indicates that the two measures do indeed classify children differently.

Table 1 shows the means for measured waist circumference, hip circumference, body weight, height, WHtR, WHR and BMI. Mean differences are close to zero.

Table 1

Mean (sd) measured waist circumference, hip circumference, weight, height, WHtR, WHR, and BMI and mean differences[1] between measured and reported values in 1292 8-year-old Dutch children

	Mean measured		Mean parent reported		Mean difference[1]	
Waist circumference (cm)	58.7	(5.2)	58.9	(4.9)	-0.02	(2.9)*
Hip circumference (cm)	67.6	(5.4)	67.1	(5.8)	0.4	(3.7)**
Weight (kg)	29.0	(4.8)	28.8	(4.7)	0.2	(1.4)**
Height (kg)	133.0	(5.4)	133.5	(5.6)	-0.5	(1.9)**
WHtR	0.44	(0.04)	0.44	(0.03)	-0.00	(0.02)
WHR	0.87	(0.04)	0.88	(0.05)	-0.01	(0.1)**
BMI (kg/m^2)	16.3	(2.0)	16.1	(2.0)	0.2	(0.9)**

Abbreviations: WHtR, waist-to-height ratio; WHR, waist-to-hip ratio

1 The difference was calculated by subtracting the parent-reported value from the measured value. Positive values reflect underreporting.

**P<0.05, **P<0.0001*

Agreement between measured and parental reported waist circumference, body weight and height is shown in Bland-Altman plots (Figure 1). These plots show that 95% of the parents reported their child's waist circumference between -6.1 cm and 5.7 cm from the measured waist circumference, and their child's body weight between -2.5 kg and 2.9 kg from the measured body weight. As for measured waist circumference the mean is 58.7cm and for measured body weight the mean is 29.0 kg, this means that for both waist circumference and body weight, 95% of the reported values were between about +10% and -10% of the mean measured value.

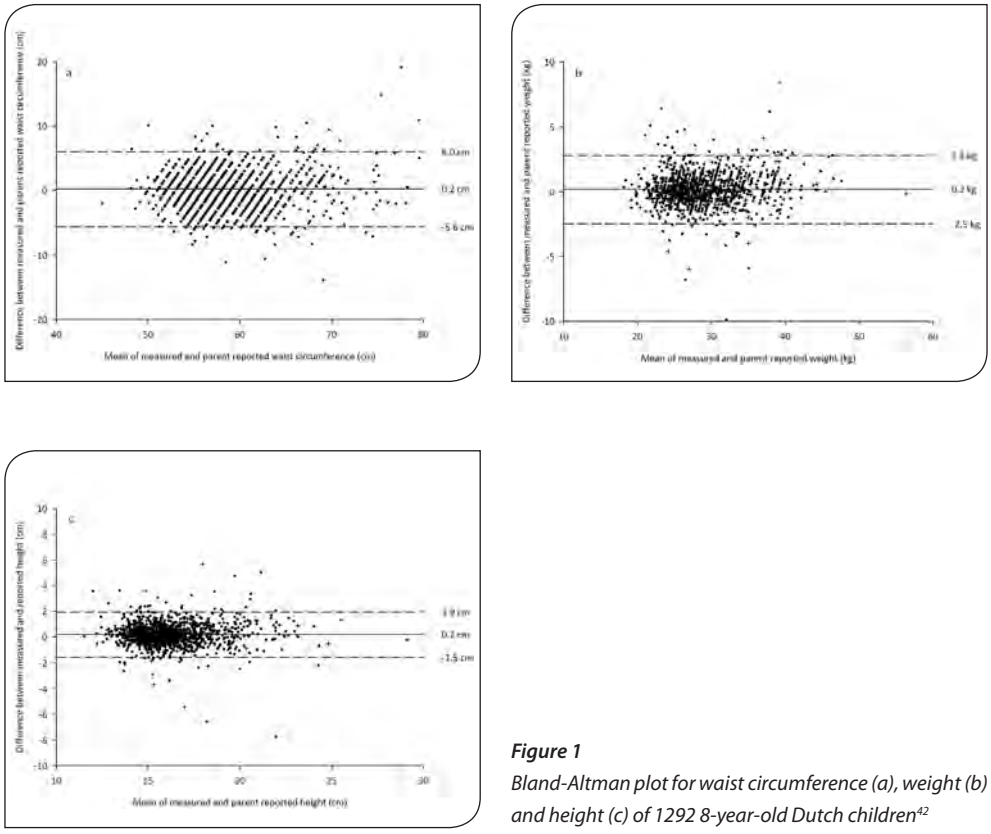


Figure 1

Bland-Altman plot for waist circumference (a), weight (b) and height (c) of 1292 8-year-old Dutch children[42]

Figure 2 shows the relationship between parental reported waist circumference and measured waist circumference. For measured and parental reported waist circumference the Pearson correlation coefficient was 0.83 ($P<0.0001$). Measured and parental reported body weight ($\rho=0.96$, $P<0.0001$) and height ($\rho=0.94$, $P<0.0001$) were strongly correlated, which resulted in a high Pearson correlation coefficient for BMI ($\rho=0.90$, $P<0.0001$).

Table 2 shows the mean differences and standard deviation of measured waist circumference, body weight, height, and BMI separately for waist circumference quartiles (Table 2a) and BMI quartiles (Table 2b), respectively. Although the average differences between measured and parental reported values overall were relatively small, the size and the direction of the difference between measured and parental reported data differed between measured waist circumference and BMI quartiles. In the lower quartiles of waist circumference and BMI parents tended to report a higher waist circumference and a higher body weight than were measured during medical examination. However, parents of children with a higher waist circumference or a higher BMI tended to underreport their child's waist circumference and body weight. This was the case both for boys and girls.

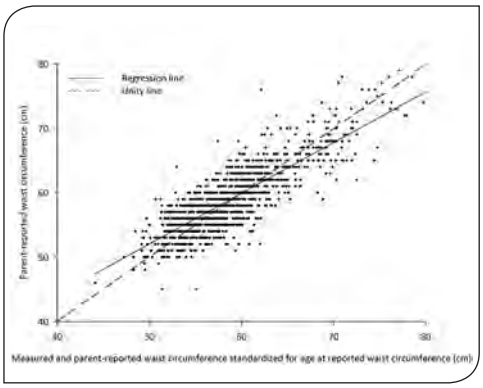


Figure 2
Measured and parent-reported waist circumference of 1292 8-year-old Dutch children

Table 2a
Mean differences (sd) between measured and reported values by measured standardized waist circumference quartiles in 1292 8-year-old Dutch children

	Waist circumference quartiles							
	1 (n=323)		2 (n=323)		3 (n=323)		4 (n=323)	
Range waist circumference	≤55.2		55.2-57.8		57.8-60.9		≥60.9	
Waist circumference (cm)	-1.41	(2.56)***	-0.53	(2.33)	0.11	(2.76)	1.06	(3.45)**
Weight (kg)	-0.17	(1.06)**	0.10	(1.34).	0.28	(1.23)**	0.27	(1.23)***
Height (cm)	-0.60	(1.86)**	-0.41	(1.88)**	-0.37	(1.75)***	-0.49	(2.24)***
BMI (kg/m^2)	0.03	(0.77)	0.15	(0.83)**	0.24	(0.80)***	0.35	(1.09)***

*The differences were calculated by subtracting the parent-reported value from the measured value. Positive values reflect underreporting. *P<0.05, **P<0.01, ***P<0.0001*

Regression analysis was used to investigate determinants of the difference between measured and parental reported values. In univariate regression analysis the difference between measured and parental reported waist circumference was significantly associated with measured waist circumference (β=0.21, *P*<0.0001). Including child's gender, and BMI and education of the mother in the model did not affect the association between parental reported and measured waist circumference. Parents of girls tended to underreport their child's waist circumference less (β=-0.4, *P*=0.02). The difference between measured and parental reported body weight was significantly associated with measured body weight (β=0.06, *P*<0.0001). Multivariate regression showed a significant association for gender (β=-0.2, *P*=0.008) and maternal BMI (β=-0.02, *P*=0.01). With regard to the difference between measured and reported height, a significant association was observed with measured height (β=0.03, *P*=0.003). Performing multivariate regression did not affect the association between the difference in measured and parental reported height and measured height.
The children were classified as normal weight, moderate abdominal overweight, or abdominal

obese based on measured and parental reported waist circumference waist circumference Based on parental reported waist circumference waist circumference a total of 149 children (11.5%) were misclassified compared with measured waist circumference (Table 3a).

Table 2b

Mean differences (sd) between measured and reported values by measured standardized BMI quartiles in 1292 8-year-old Dutch children

	BMI quartiles			
	1 (n=323)	2 (n=323)	3 (n=323)	4 (n=323)
Range BMI	≤14.9	14.9-16.0	16.0-17.3	≥17.3
Waist circumference (cm)	-0.88 (2.61)***	-0.26 (2.55)***	-0.20 (2.76)	0.56 (3.59)***
Weight (kg)	-0.19 (1.28)**	0.04 (1.25)	0.19 (1.18)***	0.59 (1.56)***
Height (cm)	-0.34 (1.79)***	-0.42 (1.95)**	-0.55 (1.74)**	-0.56 (2.25)**
BMI (kg/m2)	-0.04 (0.83)	0.11 (0.80)**	0.24 (0.75)***	0.45 (1.07)***

*The differences were calculated by subtracting the parent-reported value from the measured value. Positive values reflect underreporting. *P<0.05, **P<0.01, ***P<0.0001*

Table 3a

Classification of 1292 Dutch children in normal weight, moderate abdominal overweight, and abdominal obesity according to measured and reported waist circumference[2]

	Reported Waist Circumference				
Measured Waist Circumference	Normal weight	Moderate abdominal overweight	Abdominal Obesity	Total (%)	
Normal weight	1011	77	1	1089	(84.3%)
Moderate abdominal overweight	45	110	8	163	(12.6%)
Obesity	1	17	22	40	(3.1%)
Total (%)	1057 (81.8%)	204 (15.8%)	31 (2.4%)	1292	

Of the 203 abdominal overweight children (i.e., moderate abdominal overweight and obesity) identified using measured waist circumference, 46 (22.7%) were misclassified "normal weight" based on reported waist circumference. For BMI too, children were classified as normal weight, overweight or obese (Table 3b). The percentage of overweight children based on measured BMI misclassified "normal" using parental reported BMI was similar (n=42, 23.7%) to that of reported waist circumference. Based on parental reported BMI the prevalence of childhood overweight (11.9%) was underestimated compared with measured BMI (13.7%) (*P*=0.0027). Whereas, using parental reported waist circumference did not result in an underestimation of the childhood abdominal overweight prevalence compared with measured waist circumference (18.2% vs. 15.7%) (*P*=0.0052).

Table 3b

Classification of 1292 Dutch children in normal weight, moderate overweight, and obesity according to measured and reported BMI[41]

	Reported BMI			
Measured BMI	Normal weight	Moderate overweight	Obesity	Total (%)
Normal weight	1097	17	1	1115 (86.3%)
Moderate overweight	41	98	2	141 (10.9%)
Obesity	1	11	24	36 (2.8%)
Total (%)	1139 (88.2%)	126 (9.8%)	27 (2.1%)	1292

Discussion

Waist circumference, and BMI based on body weight and height reported by the parents of 8-year-old Dutch children corresponded well with the measured values in the present study. However, parents of children with a high waist circumference and/or BMI tended to underreport their child's waist circumference and body weight. Whereas parents of children with a low waist circumference and/or BMI tended to over report their child's waist circumference and body weight as well as their child's height. The ranking of measured and parental reported waist circumference correlated well suggesting that reported waist circumference could be used to represent waist circumference in epidemiologic studies aimed at studying associations with risk factors or health outcomes. Waist circumference was similar to BMI with respect to the response rate on the respective questions in the questionnaire, the correlation between measured and parental reported values, and the proportion of (abdominal) overweight children misclassified as normal weight. Whereas misclassification is the same for BMI and waist circumference overweight prevalence is slightly, but significantly underestimated by BMI, whereas slightly, but significantly, over estimated by waist circumference. This study showed that most parents who receive a measuring tape and written instructions with their questionnaire are willing and able to measure and report their child's waist and hip circumference.

To our knowledge, this large, population-based study was the first to examine the validity of parental reported waist circumference in children. Furthermore, we were able to compare the validity of the parental reported waist circumference with that of BMI, owing to the availability of data on parental

reported and measured body weight and height. Finally, we also studied the determinants of the difference between parental reported and measured waist circumference and BMI.
A limitation of this study was that the time between the medical examination and the dates of the reported measurements differed up to several months for some children. The mean time between measured and reported waist circumference was 72 days; for body weight and height this was 70 days. To take this time difference into account, children were excluded from the analyses if the dates of the measured and reported values were more than six months apart. Furthermore, measured waist circumference, hip circumference, body weight and height were standardized to the age of the child at the reported measurements, to take the average growth between the date of the medical examination and the date of the reported measurements into account.
Most studies on self-reported waist circumference in adults concluded that although waist circumference was underreported, it can be used to study associations in epidemiologic studies.[35-39] Dekkers et al.[36] concluded that despite over reporting of waist circumference in their overweight, adult population, there was a high concordance between measured and reported values.
Comparable with the studies in adults, in our childhood population, waist circumference and body weight were less underreported in girls than in boys. Furthermore underreporting was more frequent in adults and children with high waist circumference or BMI. Compared with previous studies in Dutch, British and Australian 8-year-old children that measured waist circumference[2,43,44], the mean waist circumference of children in the present study was up to 1-3 cm higher. This difference might be explained as those studies were performed 10 to 15 years ago, and waist circumference has increased during the last decade.[45]
The results on the agreement between parental reported and measured BMI in the present study were compared with the results of a similar study in the PIAMA cohort at the age of 4 years.[46] At both ages the mean differences between parental reported and measured body weight, height, and BMI were close to zero. Of the 4-year-old children, 13.5% were classified overweight, comparable with the present study where 13.7% of the 8-year-old children were classified overweight based on measured BMI. However, 45.7% of the overweight 4-year-old children based on measured BMI were misclassified as 'normal weight' using parental reported BMI. In 8-year-old overweight children, only 22.7% was misclassified as 'normal weight' based on parental reported BMI. At both ages body weight was about 0.5 kg underreported in the highest BMI quartile. This absolute difference is a larger proportion of the body weight of a 4-year-old child than for that of an 8-year-old child, which might explain the difference in misclassification of overweight children between both age groups.

Conclusion

Parent reported waist circumference corresponded well with measured values, indicating that reported waist circumference can be used to study associations between waist circumference and risk factors or health outcomes.

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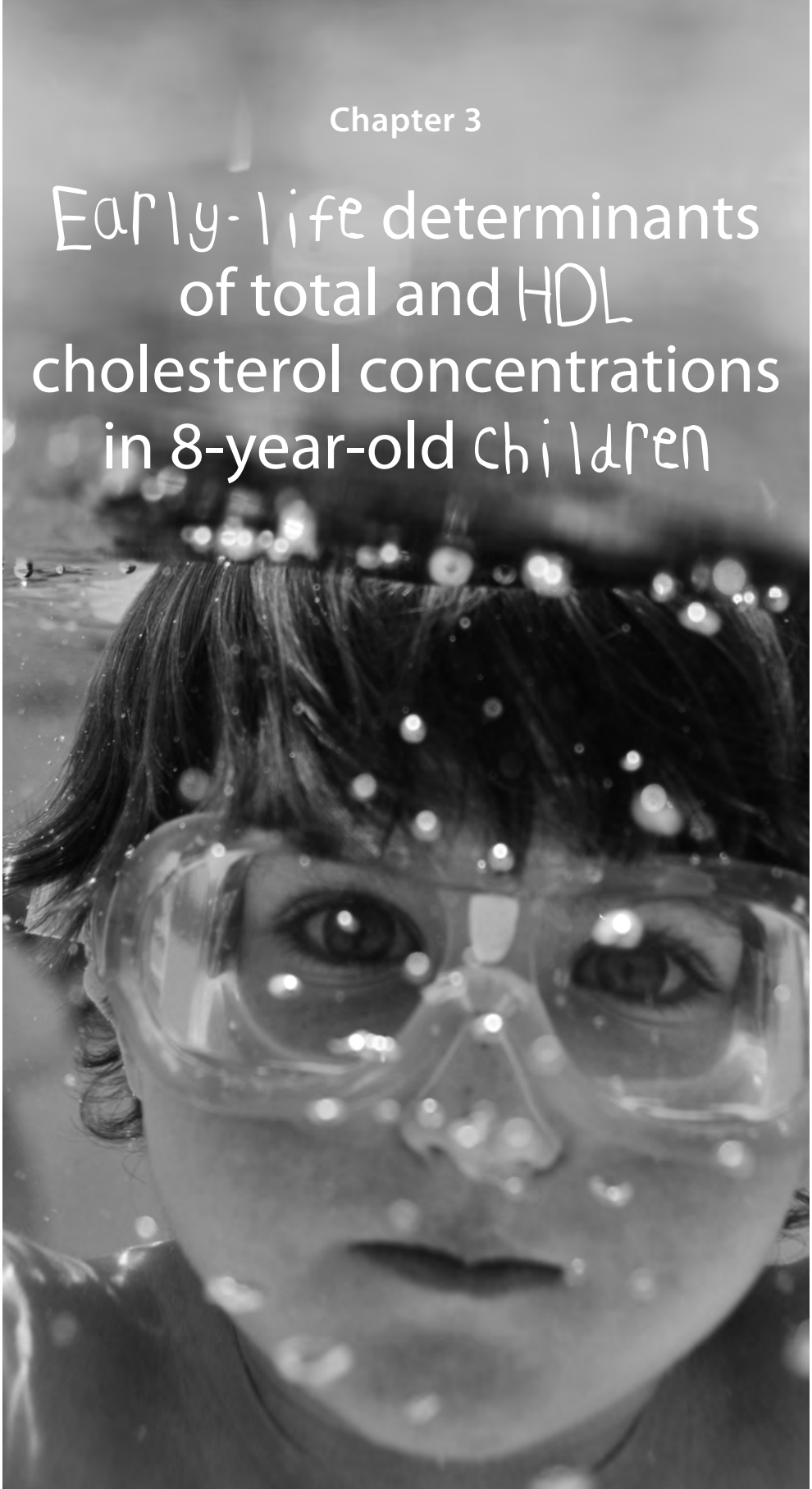
Chapter 3

Early-life determinants of total and HDL cholesterol concentrations in 8-year-old children



Early-life determinants of total and HDL cholesterol concentrations in 8-year-old children

Abstract

Adult cholesterol concentrations might be influenced by early-life factors, such as breastfeeding and birth weight, referred to as "early programming". How such early factors exert their influence over the life course is still poorly understood. Evidence from studies in children and adolescents is scarce and conflicting. We investigated the influence of six different perinatal risk factors on childhood total and HDL cholesterol concentrations and total-to-HDL cholesterol measured at 8 years of age, and additionally we studied the role of the child's current BMI. Anthropometric measures and blood plasma samples were collected during a medical examination in 751 8-year-old children participating in the prospective PIAMA birth cohort study. Linear and logistic regression were performed to estimate associations of total and HDL cholesterol concentrations with breastfeeding, birth weight, infant weight gain, maternal overweight before pregnancy, gestational diabetes and maternal smoking during pregnancy, taking into account the child's current BMI. We found an association between total-to-HDL cholesterol and maternal pre-pregnancy overweight (β=0.15, 95%CI 0.02, 0.28), rapid infant weight gain (β=0.13, 95%CI 0.01, 0.26), and maternal smoking during pregnancy (β=0.14, 95%CI 0.00, 0.29). These associations were partly mediated by the child's BMI. In conclusion, total-to-HDL cholesterol in 8-year-old children was positively associated with maternal pre-pregnancy overweight, maternal smoking during pregnancy and rapid infant weight gain.

Based on manuscript

Bekkers MBM, Brunekreef B, Smit HA, Kerkhof M, Koppelman GH, Oldenwening M, Wijga AH, Early-life Determinants of Total and HDL Cholesterol Concentrations in 8-year-old Children; The PIAMA Birth Cohort Study, *PlosOne*, 2011;6(9):e25533

Introduction

The risk of developing chronic disease later in life may be associated with prenatal and early postnatal factors, referred to as "early programming".[1] Several studies showed that increased adult total cholesterol concentrations were associated with exposure to risk factors early in life.[2,3] In a review Owen et al.[3] concluded that breastfeeding was associated with lower cholesterol concentrations in adulthood (age 17-79 years), whereas low birth weight has been associated with increased cholesterol concentrations measured at ages 17 to 76 years.[4-9]

It is of major interest whether childhood cholesterol concentrations are also associated with factors early in life, both from a public health perspective and for our understanding of the effects of early programming throughout the life course. However, only a limited number of studies have been performed on early-life factors and cholesterol concentrations in children, and their results are conflicting. Short-term breastfeeding (< 6 months) was associated with lower total cholesterol concentrations in one study[10], whereas others did not observe any difference between breastfed and non-breastfed children.[11] Higher total[12] and lower HDL cholesterol concentrations[13] were observed in low birth weight children, but this was not observed in two other studies.[14,15] In children of mothers having had gestational diabetes higher total cholesterol concentrations[16] and total-to-HDL cholesterol[16], and lower HDL cholesterol concentrations were observed.[16,17]

Leunissen et al. showed an inverse association between infant weight gain (first 3 months) and HDL cholesterol concentrations in young adults and a positive association with total-to-HDL cholesterol.[18]

We considered the joint effects of these early-life risk factors together with maternal smoking during pregnancy and maternal pre-pregnancy overweight, on childhood total and HDL cholesterol concentrations and total-to-HDL cholesterol in a prospective study. In addition, we studied the role of BMI in these associations.

Methods

Study design

The children in this study are participants of the PIAMA birth cohort study who were born in 1996-1997. A detailed description of the study design has been published previously.[19] The mothers were recruited from the general population during pregnancy visiting one of 52 prenatal clinics. Postal questionnaires were sent to the parents during pregnancy, at the child's ages of 3 and 12 months, and yearly thereafter up to the age of 8 years. At the age of 8 years a subgroup of children was invited for a hospital based medical examination.

Study population

At baseline the cohort consisted of 4146 pregnant women, of which 183 (5%) were lost to follow-up before any data of the child had been collected. Therefore the study started with 3963 newborns. When the medical examination of 8-year-olds was planned, 3655 children (92.2% of 3963) were still in the study. A subgroup of 1680 children was invited for a hospital based medical examination. Details of the subgroup selection were published before.[19] Briefly, this group consisted of 1076 children of allergic mothers and 604 children of non-allergic mothers. Parents of 1263 children (833 of allergic mothers and 430 of non allergic -mothers) gave informed consent for the child to participate in the medical examination and 1132 children (748 of allergic mothers and 384 of non-allergic mothers) attended the hospital

based medical examination. From 817 children (524 of allergic mothers and 293 of non allergic mothers) (non-fasted) a blood sample for cholesterol measurement was obtained and in 790 of these samples (505 of children of allergic mothers and 285 of children of non allergic mothers) cholesterol concentrations could be determined. For the present analyses 3 children were excluded because of missing data for gestational age. All children (n=36) with a gestational age of less than 37 weeks were excluded from the analysis to avoid possible confounding by prematurity. The final study population consisted of 751 children.
Children with missing data on infant weight gain (n=2), maternal BMI before pregnancy (n=51), gestational diabetes (n=12), or smoking of the mother during pregnancy (n=9) but with data on cholesterol concentrations, were not excluded from all analyses, but only from the analysis of the specific risk factor for which a value was missing.
No differences in total and HDL cholesterol concentrations and total-to-HDL cholesterol were observed between children with a missing value on one of the risk factors and children with complete data on all risk factors.

Exposure and outcome variables
Plasma total and HDL cholesterol concentrations were determined enzymatically using Roche automated clinical chemistry analyzers (Roche Diagnostics, Indianapolis).[20] Additionally the ratio between total and HDL cholesterol was calculated (total-to-HDL cholesterol).
The exposure variables birth weight, breastfeeding, BMI of the mother before pregnancy, infant weight gain, gestational diabetes of the mother during pregnancy of the index child, and smoking of the mother during pregnancy were reported by the parents in the questionnaires. To study both the effects of being born with a low or a high birth weight, birth weight categories were defined as low birth weight (<2,500g), birth weight ≥2,500g and <4,000g, and high birth weight (≥4,000g). Duration of breastfeeding was assessed by questions on infant feeding in the questionnaires at 3 months and 1 year of age. Breastfeeding was defined as any kind of breastfeeding, including partial breastfeeding. Total breastfeeding duration was categorized in no breastfeeding, breastfeeding 1 to 16 weeks, or ≥16 weeks of breastfeeding. Maternal BMI before pregnancy was calculated using pre-pregnancy body weight and height reported in the 1 year questionnaire, and overweight was defined based on international defined cut-off points, i.e. ≥25kg/m^2. Infant weight gain during the first year of life was calculated using data on body weight reported by the parents in the first year. The parents were asked to report the body weight as was measured by the health centre, which is visited regularly during the first years of life of a child. Infant weight gain was then divided into tertiles (slow <6.13kg/year, intermediate ≥6.14kg/year and <6.98kg/year and rapid ≥6.99kg/year weight gain). The child's BMI at age 8 years was calculated using body weight and height measured at the time of blood sampling. Body weight was measured at the nearest 0.1kg and height (cm) was measured at one decimal, both anthropometric variables were measured while only wearing underwear. BMI for age Standard Deviation Scores (SDS) were calculated using the reference growth curves of the Dutch Fourth Nation-wide Growth Study carried out in 1997.[21]

Statistical analyses
For all statistical analyses SAS software version 9.1 (SAS Institute, Inc., Cary, NC) was used. First means and standard deviations of total and HDL cholesterol concentrations, and total-to-HDL cholesterol were calculated. Bell et al.[22] suggested to consider children with total cholesterol concentrations higher than 5.9mmol/l, as well as children with HDL cholesterol concentrations

below 0.8mmol/l at risk of coronary heart diseases. As the prevalence of total cholesterol concentrations >5.9mmol/l in this study population was low, the cholesterol concentrations were divided into tertiles for the analyses.
Simple and multivariate linear regression were performed to estimate the associations of total and HDL cholesterol, and total-to-HDL cholesterol with the early life factors. Logistic regression was performed with total cholesterol concentrations or total-to-HDL cholesterol in the highest tertile of the distribution compared with the lowest tertile, and with HDL cholesterol concentrations in the lowest tertile of the distribution, compared to the highest tertile as binary outcome variables.
All analyses were performed with and without adjustment for potential confounders. A first model included age of the child (in days) at time of blood sampling and gender. A more detailed model was additionally adjusted for gestational age, maternal education (low, intermediate, high education), and the other exposure variables. Additionally, the child's BMI SDS was added to the model to investigate whether the child's BMI at the time of blood sampling was a mediating factor in the associations between early-life factors and cholesterol concentrations. Additionally the regression analyses were performed separately for boys and girls, and separately for children of allergic and non-allergic mothers to investigate the presence of effect modification by these variables.

Results

Maternal pre-pregnancy overweight and rapid infant weight gain were, in the fully adjusted models, associated with an increase in total-to-HDL cholesterol of 0.15 (95%CI 0.02, 0.28) and 0.13 (95%CI 0.01, 0.26) respectively (Table 1).

Table 1

Associations between total and HDL cholesterol, and total-to-HDL cholesterol and early life factors for 751 Dutch children[a]

	Total cholesterol		HDL cholesterol		Total-to-HDL cholesterol	
	β	95% CI	β	95% CI	β	95% CI
Birth weight <2500g						
Crude model	-0.02	(-0.33, 0.29)	-0.01	(-0.17, 0.15)	0.04	(-0.33, 0.40)
Adjusted model A b	-0.04	(-0.35, 0.27)	-0.01	(-0.16, 0.15)	0.02	(-0.34, 0.38)
Adjusted model B c	-0.05	(-0.38, 0.28)	-0.04	(-0.20, 0.12)	0.08	(-0.29, 0.46)
Birth weight >4000g						
Crude model	-0.06	(-0.17, 0.06)	-0.01	(-0.07, 0.04)	-0.02	(-0.15, 0.10)
Adjusted model A b	-0.04	(-0.15, 0.07)	-0.02	(-0.07, 0.04)	-0.00	(-0.12, 0.13)
Adjusted model B c	-0.00	(-0.13, 0.13)	0.01	(-0.05, 0.07)	-0.03	(-0.17, 0.07)
Breastfeeding 1-16wk						
Crude model	-0.01	(-0.13, 0.12)	-0.01	(-0.08, 0.05)	0.02	(-0.13, 0.16)
Adjusted model A b	-0.01	(-0.14, 0.12)	-0.01	(-0.08, 0.05)	0.01	(-0.13, 0.15)
Adjusted model B c	-0.01	(-0.15, 0.13)	-0.01	(-0.08, 0.06)	0.03	(-0.13, 0.18)
Breastfeeding ≥16wk						
Crude model	-0.03	(-0.17, 0.11)	-0.01	(-0.08, 0.06)	0.00	(-0.15, 0.16)
Adjusted model A b	-0.03	(-0.17, 0.10)	-0.01	(-0.08, 0.06)	-0.00	(-0.16, 0.15)
Adjusted model B c	0.003	(-0.15, 0.16)	-0.00	(-0.08, 0.07)	0.04	(-0.13, 0.22)
Maternal overweight before pregnancy						
Crude model	0.00	(-0.11, 0.12)	-0.04	(-0.10, 0.01)	0.13	(0.01, 0.26)*
Adjusted model A b	-0.01	(-0.11, 0.12)	-0.04	(-0.10, 0.01)	0.13	(0.01, 0.26)*
Adjusted model B c	0.01	(-0.10, 0.13)	-0.05	(-0.10, 0.01)	0.15	(0.02, 0.28)*
Gestational diabetes						
Crude model	-0.12	(-0.47, 0.24)	-0.01	(-0.18, 0.17)	-0.08	(-0.48, 0.31)
Adjusted model A b	-0.10	(-0.46, 0.25)	-0.01	(-0.18, 0.16)	-0.07	(-0.46, 0.32)
Adjusted model B c	-0.19	(-0.57, 0.19)	-0.06	(-0.24, 0.13)	-0.07	(-0.49, 0.35)
Smoking mother during pregnancy						
Crude model	0.04	(-0.09, 0.16)	-0.06	(-0.12, 0.00)	0.17	(0.02, 0.31)*
Adjusted model A b	0.02	(-0.10, 0.14)	-0.05	(-0.11, 0.01)	0.15	(0.01, 0.29)*
Adjusted model B c	0.01	(-0.13, 0.14)	-0.06	(-0.12, 0.01)	0.14	(-0.00, 0.29)
Slow infant weight gain						
Crude model	0.08	(-0.04, 0.19)	-0.00	(-0.06, 0.05)	0.09	(-0.04, 0.22)
Adjusted model A b	0.06	(-0.06, 0.17)	0.00	(-0.05, 0.06)	0.06	(-0.07, 0.18)
Adjusted model B c	0.06	(-0.07, 0.18)	0.01	(-0.05, 0.06)	0.07	(-0.07, 0.20)
Rapid infant weight gain						
Crude model	0.06	(-0.05, 0.18)	-0.01	(-0.07, 0.04)	0.11	(-0.01, 0.23)
Adjusted model A b	0.09	(-0.02, 0.20)	-0.02	(-0.08, 0.04)	0.15	(0.03, 0.27)*
Adjusted model B c	0.10	(-0.02, 0.22)	-0.01	(-0.07, 0.05)	0.13	(0.01, 0.26)*

** P< 0.05*

a) Results are presented as regression coefficients (β) with 95%CI

b) Regression model A is adjusted for age of the child at time of blood sampling and gender.

c) Regression model B is adjusted for age of the child at time of blood sampling, gender, gestational age, maternal education, and the other variables analyzed.

Maternal smoking was associated with an increase in total-to-HDL cholesterol of 0.14 (95%CI 0.00 to 0.29). In logistic regression no significant associations of the early-life risk factors with the tertiles of total and HDL cholesterol, and total-to-HDL cholesterol were found (Figure 1).

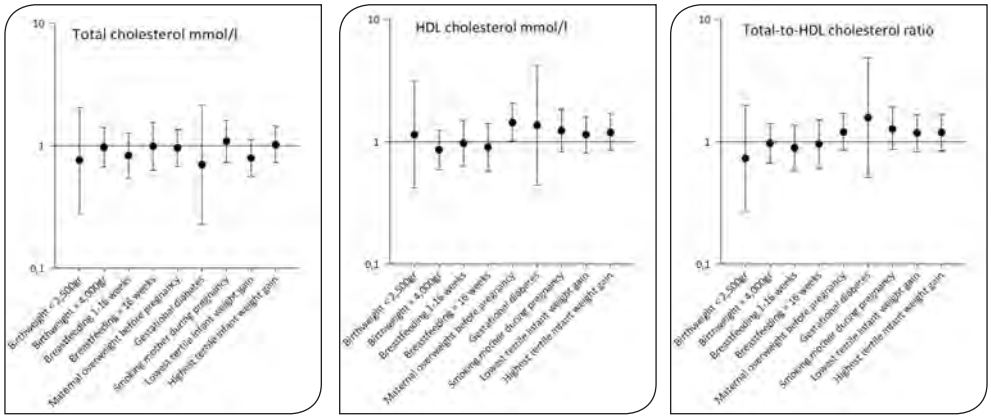


Figure 1

Adjusted odds ratios with 95% confidence intervals (Adjusted for age of the child at time of blood sampling, gender, gestational age, maternal education, and the other variables analyzed)

The total mean cholesterol concentration ranged from 2.37 to 6.32 mmol/L in girls and from 2.26 to 6.27 mmol/L in boys (Figure 2).

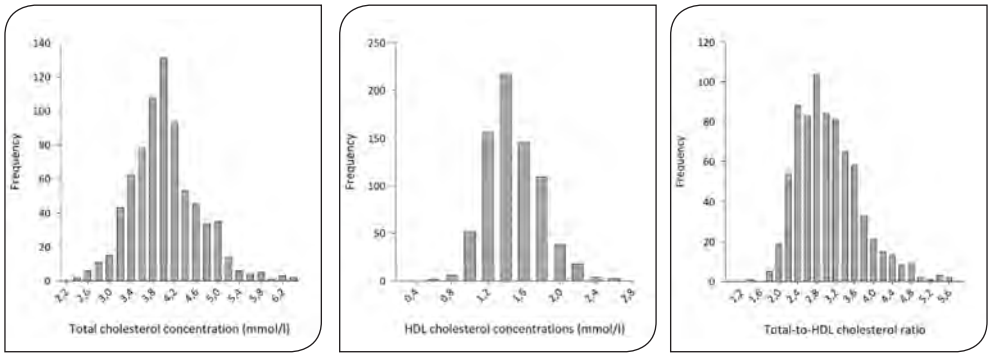


Figure 2

Distribution of cholesterol variables

Children of mothers with gestational diabetes had lower mean total cholesterol concentrations (3.81 vs. 3.93 mmol/L), but only 12 mothers (1.6%) had gestational diabetes and the association was non-significant (Table 2).

Table 2

Mean values and standard deviations (sd) of total and HDL cholesterol concentrations and total-to-HDL cholesterol

		Total cholesterol mmol/L	**HDL cholesterol** mmol/L	**Total-to-HDL cholesterol**
	n	Mean ± sd	Mean ± sd	Mean ± sd
Total Group	751	3.93 ± 0.62	1.38 ± 0.30	2.95 ± 0.70
Gender				
Boys	384	3.85 ±0.63*	1.40 ±0.31	2.85 ±0.64*
Girls	367	4.01 ±0.60	1.36 ±0.30	3.06 ±0.74
Breastfeeding				
None	112	3.95 ±0.58	1.39 ±0.31	2.95 ±0.69
< 16 weeks	349	3.94 ±0.60	1.38 ±0.29	2.96 ±0.67
≥ 16 weeks	290	3.92 ±0.65	1.38 ±0.31	2.95 ±0.73
Birth weight				
< 2,500g	15	3.92 ±0.62	1.37 ±0.28	3.00 ±0.96
≥ 2,500g and < 4,000g	587	3.94 ±0.61	1.38 ±0.31	2.96 ±0.70
≥ 4,000g	149	3.89 ±0.66	1.37 ±0.30	2.93 ±0.64
Infant weight gain (n=649)				
< 6.13 kg/year	216	3.94 ± 0.60	1.37 ± 0.28	2.97 ± 0.71
≥ 6.14 and <6.98kg/year	217	3.89 ± 0.61	1.39 ± 0.28	2.90 ± 0.65
≥ 6.99 kg/year	216	3.92 ± 0.62	1.39 ± 0.34	2.94 ± 0.68
Overweight mother before pregnancy				
Yes	143	3.93 ±0.63	1.35 ±0.30	3.06 ±0.88
No	557	3.93 ±0.63	1.39 ±0.30	2.92 ±0.64
Gestational diabetes				
Yes	12	3.81 ±0.58	1.38 ±0.34	2.87 ±0.53
No	727	3.93 ±0.62	1.38 ±0.30	2.95 ±0.70
Smoking mother during pregnancy				
Yes	114	3.96 ±0.67	1.33 ±0.30	3.10 ±0.78**
No	628	3.93 ±0.61	1.39 ±0.30	2.93 ±0.68

** P < 0.01, ** P < 0.05*

Children of mothers who were overweight, children of mothers who smoked during pregnancy, and children who gained weight rapidly during infancy all had higher BMI SDS at the age of 8 years than their counterparts. Higher BMI SDS values, in turn, were associated with higher total-to-HDL cholesterol. When BMI SDS was added to the regression models the effect estimates decreased to 0.09 (95%CI -0.04, 0.22) for maternal pre-pregnancy overweight, 0.12 (95%CI -0.02, 0.27) for maternal smoking during pregnancy, and 0.09 (95%CI -0.04, 0.22) for rapid infant weight gain. As a mediating factor current BMI thus partly, but not entirely, explained the association between total-to-HDL cholesterol and maternal overweight before pregnancy, maternal smoking during pregnancy, and rapid infant weight.
In stratified analyses no differences in associations between cholesterol concentrations and the exposure variables between boys and girls and between children of allergic and non-allergic mothers were found.

Discussion

Strengths and limitations

The results of the present study suggest an association between maternal pre-pregnancy overweight, maternal smoking during pregnancy and rapid infant weight gain and total-to-HDL cholesterol. These associations were attenuated after adjustment for BMI of the child at the time of blood sampling.
The strengths of our study are its prospective design, the possibility to study a range of perinatal and early life factors, the large size of the study population compared to most previous studies, the ability to adjust the different factors for each other and for BMI SDS at the time of the cholesterol measurement, and the availability of information on several confounding factors.
However, our study also has some limitations; the number of mothers having had gestational diabetes, and the number of children born *full term* with a low birth weight (<2,500g) were small, which may have limited the study's potential to detect associations with these factors. Data on the risk factors studied were obtained from parental reports and the possibility of reporting errors cannot be excluded. However, the data on the early life factors were obtained prospectively, consequently we do not expect recall bias. Furthermore, there is no indication that other types of misreporting in association with cholesterol explained our results. Only for a subset of the baseline population blood samples were available. There is no reason to assume that associations differ between children with and without data on cholesterol concentrations. In addition, children of allergic mothers were overrepresented, but no effect modification by maternal allergy was observed. Because of the design of the medical examination, it was not possible to take blood samples of children in the fasted state.

Findings of other studies

We compared the cholesterol concentrations measured in our study to those measured in other child populations. The total and HDL cholesterol concentrations in our study population were similar to those measured in comparable childhood populations[10, 14, 23], although only one study also showed significantly higher total cholesterol concentrations in girls.[10] Only one previous study reported the mean total-to-HDL cholesterol found in their childhood population.[24] The mean total-to-HDL cholesterol in our study population was somewhat higher compared to this recent study in 9-year-old UK children.
Studies on associations between cholesterol concentrations and early life risk factors in adults have mainly focused on breastfeeding and low birth weight. In a review including 17 original studies, slightly lower cholesterol concentrations were found in adults who had been

breastfed.[3-5,7,25,26] Low birth weight has only been associated with increased total cholesterol concentrations in men (age 17-76 years old).[2,4,5,7,9] In women (17-64 years old), no association between low birth weight and cholesterol concentrations has been reported.[5,27]
So far, there have been few studies on the association between breastfeeding and birth weight and cholesterol concentrations in children. Higher total cholesterol concentrations[12] and lower HDL cholesterol concentrations[13] were found in low birth weight children, but this was not found in two other studies (Table 3).[14,15] Bergstrom et al.[10] observed lower total cholesterol concentrations in breastfed children, whereas Fomon et al.[11] did not observe any difference between breastfed and non-breastfed children. Higher total cholesterol concentrations[16] and total-to-HDL cholesterol[16] and lower HDL cholesterol concentrations[16,17] were observed in children of mothers having had gestational diabetes. We were able to study the associations with other potential early life risk factors that were not studied earlier in adults or children.

Table 3

Studies on early factors influencing childhood cholesterol levels

Author	Year of publication	N	Study design	Age (years)	Number of girls	Early factors studied
Bergström	1995	405	→	14	201 (49.6%)	Breastfeeding < 6 months
Fomon	1984	469	→	8	188 (40.1%)	Any breastfeeding
Frontini	2004	1141	←	4-11	536 (47%)	Low birth weight
Leunissen	2008	297	←	18-24	181 (60.9%)	Low birth weight (birth weight sds)
Leunissen	2009	205	←	18-24	Nm	Weight gain first 3 months of life
Manderson	2002	118	←	5-11	65 (55.1%)	Gestational diabetes
Mortaz	2001	412	→	8-12	197 (47.8%)	Birth weight < 1,850g
Tenhola	2000	110	→	12	70 (63.6%)	Small for gestational age
Tam	2008	164	←	7-10	83 (50.6%)	Gestational diabetes

Legend: Nm=Not mentioned, r=correlation coefficient, NS=non-significant, SGA=small for gestational age, AGA=appropriate for gestational age, TC=total cholesterol, SES=socio-economic status, →=prospective, ←=retrospective

We observed associations between maternal pre-pregnancy overweight, rapid infant weight gain and maternal smoking during pregnancy and total-to-HDL cholesterol in our study. These associations attenuated after adjustment for the child's BMI SDS. The interpretation is not straightforward: early life risk factors apparently influence both BMI and cholesterol at age 8. The observed effects of the investigated early life risk factors are small, but relatively small changes in the cholesterol profile may have an impact on the burden of chronic diseases later in life.[28] If confirmed in future studies, these early-life factors might be a lead for prevention.

Conclusion

Total-to-HDL cholesterol in 8-year-old children was positively associated with maternal pre-pregnancy overweight, maternal smoking during pregnancy and rapid infant weight gain.

Adjustment for confounders	Total cholesterol	HDL cholesterol	Total-to-HDL cholesterol ratio
No	*r*=-0.07, P=0.057		
No	Males: *r*= 0.393 NS Females: *r*= 0.232 NS		
Age, race, sex		Lower mean HDL cholesterol (p=0.05)	
No	β=nm, *P*=ns	β=nm, *P*=ns	
Gestational age, sex, age, ses, height growth	β=-0.002, *P*=.89	β=-0.053, *P*=.005	β=0.052, *P*=.01
No	Diff non gestdiab-gestdiab: 0.27, *P*=0.03	Diff non gestdiab-gestdiab: -0.05, *P*=0.38	Diff non gestdiab-gestdiab: 0.33, *P*=0.03
No	β=nm, *P*=ns		
No	SGA higher TC concentration	NS diff between SGA and AGA children	
Age, sex		Lower HDL level (*P*=0.019)	

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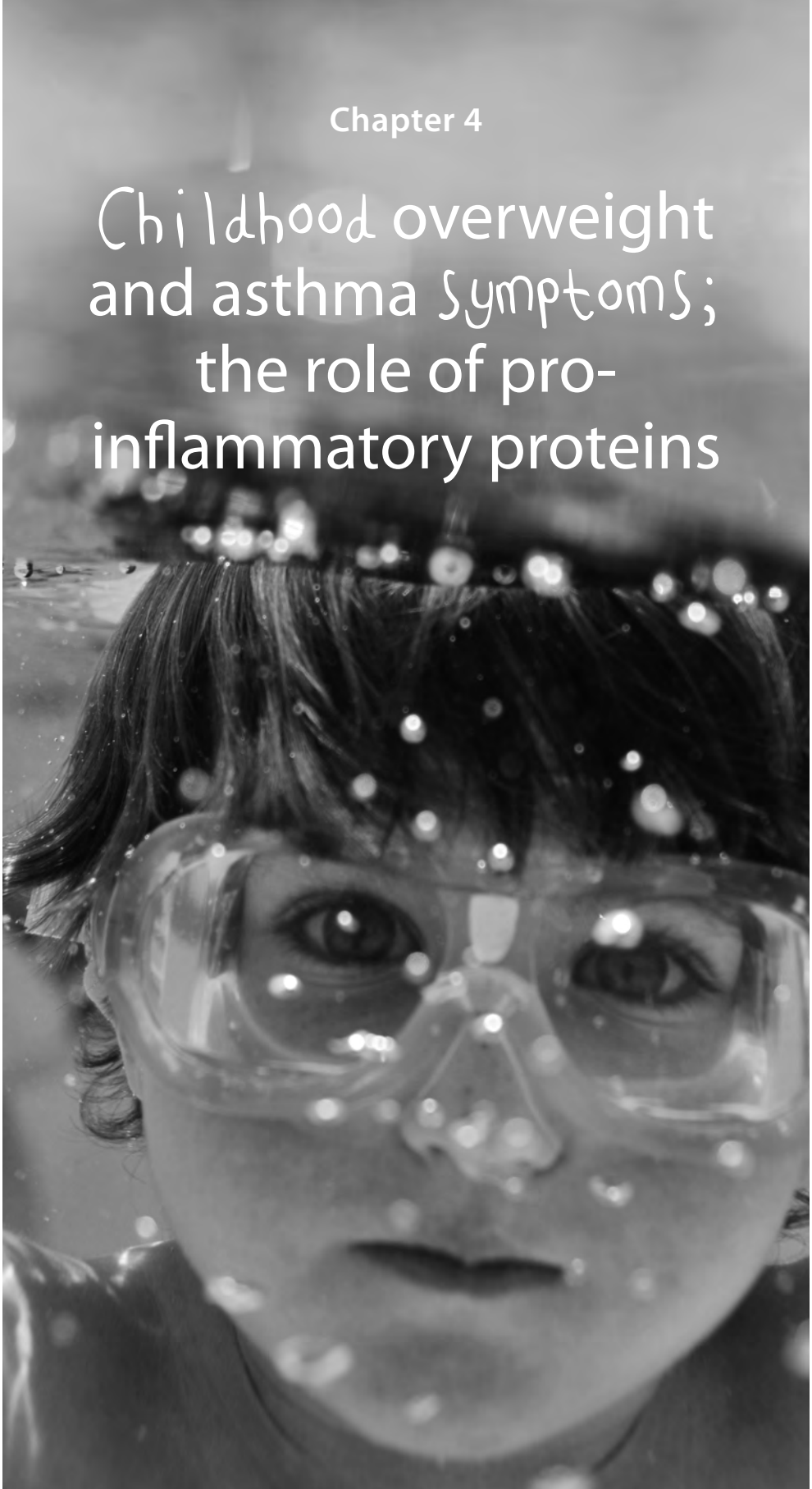
Chapter 4

Childhood overweight and asthma symptoms; the role of pro-inflammatory proteins



Childhood overweight and asthma symptoms; the role of pro-inflammatory proteins

Abstract

Systemic inflammation is suggested as a mechanism by which overweight might induce asthma. However, few studies have linked childhood overweight, inflammation and asthma. We aimed to study the association between BMI, asthma symptoms and pro-inflammatory proteins. High-Sensitivity C-Reactive Protein (hs-CRP), complement factor C3 and C4 concentrations, and body weight and height were available for 359 4-year-old children participating in the PIAMA birth cohort study. Data on asthma symptoms were obtained by yearly questionnaires. Logistic regression and Generalized Estimating Equations were used to analyse cross-sectional and prospective associations between BMI, asthma symptoms and pro-inflammatory proteins. BMI was associated with asthma symptoms (OR 1.43 (95%CI 1.08, 1.88) per BMI SDS). Inclusion of hs-CRP, C3 and C4 in the statistical models did not change this association. C3 was cross-sectionally associated with frequent asthma symptoms (OR per interquartile range of C3: 1.97 (95%CI 1.20, 3.24)), and prospectively with asthma symptoms (OR 1.48 (95%CI 1.04, 2.09)), independent of BMI SDS. In conclusion, we showed no evidence for a role of hs-CRP, C3 and C4 in the association between BMI and asthma symptoms. C3 concentrations were associated with (frequent) asthma symptoms, independent of BMI.

Based on manuscript

Bekkers MBM, Brunekreef B, de Jongste JC, Kerkhof M, Smit HA, Postma DS, Gehring U, Wijga AH, BMI and asthma symptoms; the role of pro-inflammatory proteins, *Clinical and Experimental Allergy*, 2012;42: 95-103

Introduction

Childhood asthma and overweight have reached high prevalence levels, each having a considerable public health impact.[1,2] Observational studies, including our own, have shown an increased risk of asthma in overweight adults[3] and children.[4-8] Suggested mechanisms for this relation include sedentary lifestyle, changes in immune function, insulin resistance, and airway narrowing.[9-12] Additionally, systemic inflammation is suggested as a mechanism by which overweight might induce asthma.[10,11] Previous studies showed increased serum concentrations of the pro-inflammatory proteins high sensitivity-C Reactive Protein (hs-CRP)[13-22], complement factor C3 (C3)[18,23-27], and complement factor C4 (C4)[18,24,27] with higher BMI in adults and adolescents. Few studies looked specifically at young children; Skinner et al.[28] found that obese children (age 3 to 5 years) were at increased risk of elevated (>1 mg/L) hs-CRP concentrations, and Cianflone et al.[29] showed increased C3 concentrations with increasing percentage of ideal body weight in 2-6-year-old children. Adipose tissue secretes C3 and activates the subsequent pathway.[30] Furthermore, adults and children with asthma have higher hs-CRP concentrations compared with non-asthmatic individuals.[14,16,17,31-33] The complement system is involved in the etiology of asthma.[34,35] These studies did not investigate whether the pro-inflammatory proteins mediate the association between BMI and asthma. To our knowledge, only one, recent, study linked overweight, asthma and inflammation in children, using CRP as a marker of inflammation.[16]

We studied the association between BMI, the pro-inflammatory proteins and asthma symptoms in four steps. In the first step we studied whether BMI measured at age 4 was associated with asthma symptoms measured at age 4 and with asthma symptoms at age 5-8. In the second, we studied the association between BMI and the pro-inflammatory proteins. In the third step, we studied the association between the pro-inflammatory proteins and asthma symptoms. In the last step, we studied the role of the pro-inflammatory proteins in the association between BMI and asthma symptoms.

Methods

Study design and study population

The children in this study participated in the PIAMA birth cohort study and were born in the Netherlands in 1996-1997. A detailed description of the study design has been published previously.[36] Mothers were recruited from the general population during pregnancy visiting one of 52 prenatal clinics. These prenatal clinics were spread over the Netherlands and were a representative sample of prenatal clinics. At baseline, the cohort consisted of 4146 pregnant women, of whom 183 (5%) were lost to follow-up before any data of the child had been collected (Figure 1). Therefore, the study started with 3963 newborns. Postal questionnaires were sent to the parents during pregnancy, at the child's ages of 3 and 12 months, and yearly thereafter up to the age of 8 years. At the age of 4 years, only a selected subsample (n=1808) of the PIAMA population was invited for a medical examination, i.e. all children of allergic mothers who were still in the study and a random sample of children of non-allergic mothers.[36] Only a limited number of the children participating in the medical examination (n=1288) were willing to provide a blood sample (n=750). For a group of children for whom aliquots were still left after IgE analysis, serum samples were analysed for pro-inflammatory proteins. Analyses were successful for 376 samples collected from children when they were 4 years old (see Figure 1 for details).

All children (n=11) with hs-CRP concentrations >10 mg/L reported fever at the day of the medical examination or in the last two weeks before the medical examination, or having a cold

at the day of the medical examination. Therefore these high levels of hs-CRP were considered to be due to the acute-phase response and these children were excluded from all analyses. Six children without information on either body weight or height or asthma symptoms were excluded from all analyses. Finally, the population under study consisted of 359 children. The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent.

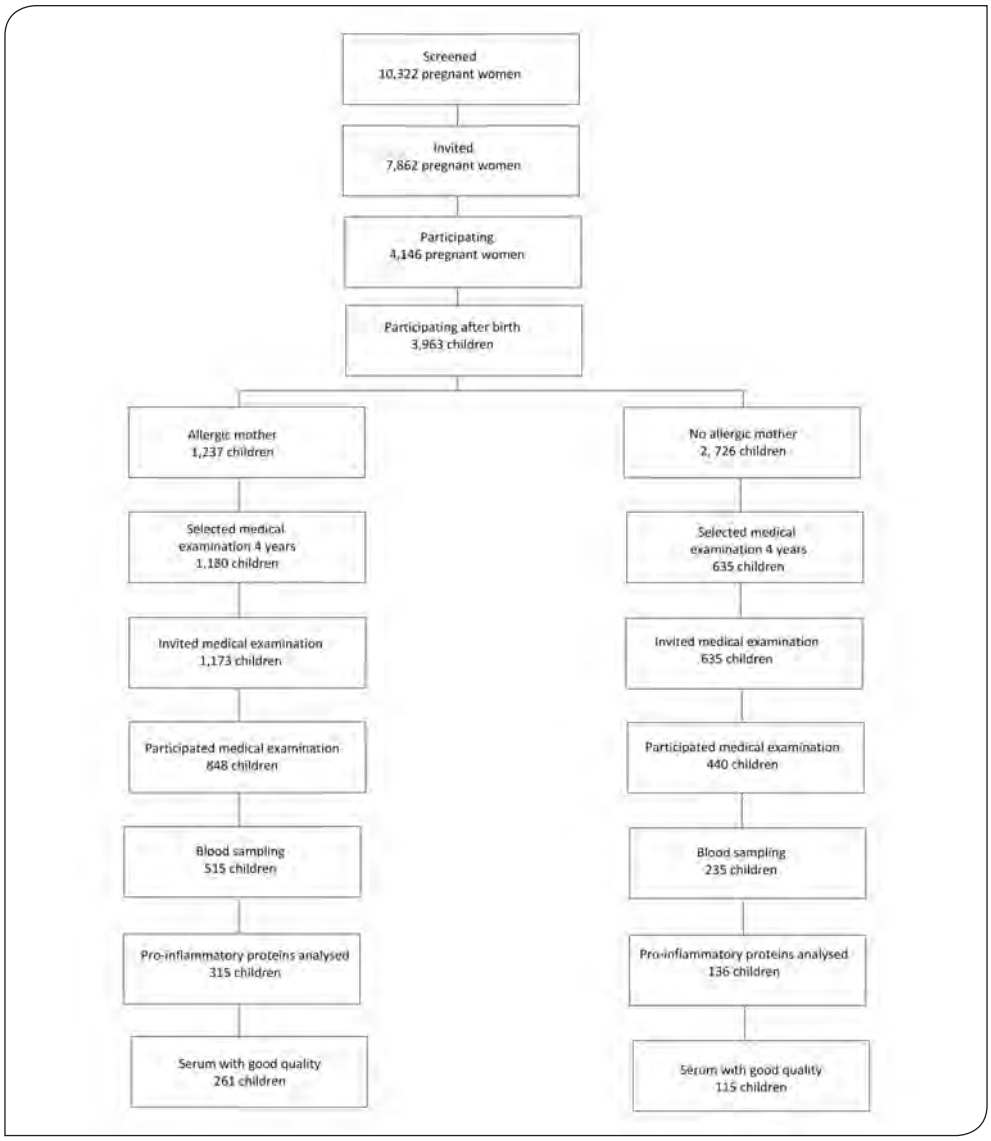


Figure 1

Recruitment scheme of children in the PIAMA birth cohort study

Outcome assessment

In the yearly questionnaires, parents reported whether their child had an attack of wheeze and/or an episode of dyspnea and/or a prescription of inhaled corticosteroids for respiratory or lung problems by a medical doctor in the preceding year. These questions were partly based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire[37]. In the PIAMA study, 'asthma symptoms' at ages 3-8 years are defined as at least one attack of wheeze, and/or at least one episode of dyspnea and/or a prescription of inhaled corticosteroids in the last 12 months. 'Frequent asthma symptoms' are defined as having asthma symptoms and ≥4 attacks of wheeze or ≥4 attacks of dyspnea in the last 12 months. Children with asthma symptoms and children with frequent asthma symptoms were compared with children with no asthma symptoms.

In the collected blood samples, specific IgE was determined on the following common inhalant allergens: house dust mite, cats, dogs, grass (*Dactylis glomerata*), birch pollen, and *Alternaria alternata*. Allergic asthma symptoms were defined as having asthma symptoms as well as a specific IgE concentration of ≥0.70IU/mL to at least one of the inhalant allergens. Children with allergic or non-allergic asthma symptoms were compared with children with no asthma symptoms.

Anthropometric measures

Anthropometric measurements were performed by professionals during the medical examination. Body weight, only wearing underwear, was measured to the nearest 0.1kg and height (cm) was measured to the nearest millimetre. BMI was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). Standard deviation scores (SDS) of BMI for age and sex were calculated by using the reference growth curves of the Dutch Fourth nationwide Growth Study.[38]

Assessment of pro-inflammatory proteins

Pro-inflammatory protein concentrations were determined in non-fasting serum samples (Synchron LX20-Pro, Beckman Coulter, Woerden, The Netherlands), using an immuno-turbidimetric assessment. These measurements are not affected by fasting/non-fasting states.[39] The assay could detect a minimal hs-CRP concentration of 0.2mg/L and values below this level were classified as below the detection limit. Minimal concentrations of 100mg/L C3 and 50mg/L C4 could be detected.

Assessment of effect modifiers and confounders

Maternal allergy was reported in a validated questionnaire during pregnancy and defined as current allergy to house dust mite or pets, or ever asthma, or current hay fever.[40] In the questionnaires, the parents reported maternal education, maternal smoking during pregnancy, smoking in the house by anyone when the child was 4 years old, and gender. Maternal education was measured as the highest education completed and then divided into 3 categories (low, intermediate, and high education). Data on TV-hours per day were collected by a yearly questionnaire and for the first time in the 5-year questionnaire.

Statistical analyses

In the first step, we studied the association between BMI SDS and asthma symptoms cross-sectionally and prospectively. The cross-sectional associations between BMI SDS measured at

age 4 and the prevalence of asthma symptoms at age 4 were studied using logistic regression. The prospective associations between BMI SDS measured at age 4 and asthma symptoms at the ages 5-8 years were studied using Generalized Estimating Equations (GEE), taking into account the serial correlations between repeated measurements in the same individual. As correlations between repeated measurements can be expected to depend on the time lag between two measurements, a three-dependent correlation matrix was modelled. The interaction of BMI SDS with age was included in the GEE model, allowing associations to vary with age.

Gender, age, maternal allergy, maternal education, maternal smoking during pregnancy, smoking by anyone in the house when the child was 4 years old and TV-hours, as indicator of physical inactivity, were considered as potential confounders. Effect modification by maternal allergy, maternal education, gender and allergic sensitization was tested.

In addition, allergic and non-allergic asthma symptoms were analyzed separately in association with BMI SDS. To study the possibility of a U-shaped association between BMI and the outcome variables, the association between BMI SDS quintiles and the asthma outcomes was assessed.

Secondly, we studied the associations between BMI SDS and the pro-inflammatory proteins, both measured at age 4 years, in linear regression models.

In the third step, we studied the associations of hs-CRP, C3 and C4 measured at age 4 with asthma symptoms measured at age 4 in logistic regression models. We used GEE models to study the prospective associations between the pro-inflammatory proteins and asthma symptoms at age 5-8 years. The lowest hs-CRP group (reference, n=117) consisted of all children with an hs-CRP concentration below the detection limit. The children with an hs-CRP concentration above the detection limit were distributed equally in the two other groups (hs-CRP concentrations 0.20-0.59mg/L and hs-CRP concentrations 0.61-9.89mg/L). No children had an hs-CRP concentration of 0.60mg/L. C3 and C4 were included in the model as continuous variables and effect estimates were calculated per interquartile range (IQR) (C3: IQR=2663 mg/L; C4: IQR=71.6mg/L).

Three different models were used to study these associations: a crude model, a model with adjustment for potential confounders, and a model with additional adjustment for BMI SDS.

Finally, in the fourth step, we added the pro-inflammatory proteins to the statistical models of BMI SDS and asthma symptoms to observe whether the associations between BMI SDS and asthma symptoms were attenuated. Data analysis was conducted using SAS software version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Eighteen percent of the children (n=65) were overweight (including obesity) according to the International Obesity Task Force (IOTF) standards[41], and 26.0% (n=91) of the children had asthma symptoms at age 4 (Table 1). The parents of the children in our analyses were more highly educated (39.7%) compared with the original PIAMA population (35.0%). Furthermore, the children in our analyses differed from the original PIAMA population in the prevalence of maternal allergy. 68.5% of the children in our analyses had a mother with allergy, whereas in the original PIAMA population, 31.2% of the children had an allergic mother. This is related to decisions made about which subgroups to invite for medical examination at age 4 as explained in the *'Methods'*.

Table 1

General characteristics of the 4-year-old study population, n (%)

General characteristics		**4-year-old children (n=359)**	
		n	*(%)*
Girls		152	(42.3%)
Maternal allergy		246	(68.5%)
Maternal education;	low	61	(17.2%)
	intermediate	153	(43.1%)
	high	141	(39.7%)
Maternal smoking during pregnancy		54	(15.1%)
Asthma symptoms		91	(26.0%)
Frequent asthma symptoms		30	(10.5%)
Wheeze		59	(17.0%)
Dyspnea		61	(17.4%)
Corticosteroid medication use		39	(11.4%)
Allergic asthma symptoms		26	(7.2%)
Overweight (including obesity) †		65	(18.2%)
Obesity †		15	(4.2%)
Hs-CRP concentration below detection limit		117	(32.6%)
		mean	*(sd)*
BMI (kg/m^2)		16.4	(1.37)
BMI SDS		0.54	(0.91)
Hs-CRP concentration mg/L ‡		0.78	(1.36)
C3 concentration g/L		1.43	(0.21)
C4 concentration g/L		0.22	(0.07)

BMI: body mass index, SDS: standard deviation score, Hs-CRP: high sensitivity C-reactive protein, C3 and C4: complement factor 3 and 4,† Defined according to the International Obesity Task Force (IOTF) standards[41],

‡ Geometric mean (geometric standard deviation) of the children with a hs-CRP concentration > detection limit (0.2mg/L)

Body mass index standard deviation scores and asthma symptoms

In the first step; at age 4, BMI SDS was significantly associated with the presence of asthma symptoms in the last 12 months; OR 1.43 (95%CI 1.08, 1.88) per BMI SDS and with frequent asthma symptoms (OR 1.74 (95%CI 1.12, 2.71)) per BMI SDS (Table 2). The association between BMI SDS and asthma outcomes was linear; no U-shaped association was detected.

Adjustment for maternal allergy, maternal education, and maternal smoking during pregnancy did not change this association. Effect modification by gender, maternal allergy, maternal education and allergic sensitization was not shown as interaction terms with gender, maternal allergy and allergic sensitization were not significant. Hours spent watching TV did not confound the association between BMI SDS and asthma.

Associations between BMI SDS at age 4 and asthma outcomes at ages 5-8 were also positive but failed to reach statistical significance (Table 2).

The cross-sectional association between BMI SDS and non allergic asthma symptoms was stronger (OR 1.62 (95%CI 1.16, 2.26)) than the association between BMI SDS and allergic asthma symptoms (OR 1.08 (95%CI 0.70, 1.69)).

Table 2

Associations (OR (95%CI)) between BMI SDS and asthma symptoms, frequent asthma symptoms, wheeze, dyspnea, and use of corticosteroids, n=359

	Asthma symptoms	Frequent asthma symptoms	Wheeze	Dyspnea	Corticosteroid use
Cross-sectional *association between BMI SDS (age 4) and asthma symptoms (age 4)*					
BMI SDS †	**1.43 (1.08, 1.88)**	**1.75 (1.13, 2.71)**	1.18 (0.86, 1.61)	1.53 (1.11, 2.10)	1.51 (1.03, 2.21)
Prospective ‡ *association between BMI SDS (age 4) and asthma symptoms (age 5 to 8)*					
BMI SDS †	1.15 (0.88, 1.52)	1.37 (0.91, 2.07)	1.31 (0.87, 1.96)	1.26 (0.92, 1.74)	1.25 (0.86, 1.83)

BMI SDS: body mass index standard deviation score

Odds ratio per 1 SDS increase in BMI

Asthma symptoms: ≥ 1 attack of wheeze, and/or ≥ 1 episode of dyspnea and/or a prescription of inhaled corticosteroids in the last 12 months (reference: no asthma symptoms); Frequent asthma symptoms: having asthma symptoms and ≥ 4 attacks of wheeze or ≥ 4 attacks of dyspnea in the last 12 months (reference: no asthma symptoms).

† Model adjusted for maternal allergy, maternal education, and maternal smoking during pregnancy

‡ The presented OR is the overall OR from the General Estimating Equations Model

Body mass index standard deviation scores and pro-inflammatory proteins

Second, we studied whether BMI SDS was associated with increased concentrations of the pro-inflammatory proteins. No clear association of BMI SDS and the pro-inflammatory proteins was shown in linear regression analyses; hs-CRP: β=0.01, *P*=0.96; C3: β=-1.29, *P*=0.91; C4: β=-3.65, *P*=0.34.

Pro-inflammatory proteins and asthma

In the third step, we studied whether the pro-inflammatory proteins were associated with asthma symptoms. The correlation (*r*) between hs-CRP and C3 and C4 was 0.27 and 0.37 respectively and *r* was 0.46 for the correlation between C3 and C4. Therefore, we performed logistic regression analyses with separate models for hs-CRP, C3 and C4 each. C3, but not hs-CRP and C4, was consistently associated with increased risk of (frequent) asthma symptoms both cross-sectionally and prospectively and independent of BMI SDS (Table 3). C4 was significantly associated with frequent asthma symptoms only prospectively and after adjustment for BMI (OR 1.42 (95%CI 1.00, 2.01) (Table 3). The associations between hs-CRP 0.20-0.59mg/L and asthma symptoms tended to be negative. Hs-CRP concentrations from 0.61 to 9.89mg/L were consistently, but not significantly, associated with wheeze, and cross-sectionally also with dyspnea (Table 3). Overall, no clear association between hs-CRP concentrations and asthma symptoms was observed.

We repeated the analyses with the pro-inflammatory proteins together in one model. The effect estimates of C3 and C4 did not change; those of hs-CRP did. Possibly, this is due to multicolinearity.

The associations of allergic asthma with hs-CRP, C3 and C4 were positive (hs-CRP 0.20-0.59mg/L: 1.35 (95%CI 0.48, 3.83), hs-CRP 0.61-9.89mg/L: 1.58 (95%CI 0.57, 4.37), C3: 1.68 (95%CI 1.00,

2.82), C4: 1.26 (95%CI 0.86, 1.84)), and were stronger than the associations between the pro-inflammatory proteins and non-allergic asthma (hs-CRP 0.20- 0.59mg/L: 1.08 (95%CI 0.55, 2.15), hs-CRP 0.61-9.89mg/L: 1.10 95%CI (0.55, 2.15), C3: 1.16 (95%CI 0.82, 1.65), C4: 0.87 (95%CI 0.63, 1.19)), but not significant.

Table 3

Associations (OR (95%CI)) between hs-CRP, C3 and C4 asthma symptoms, frequent asthma symptoms, wheeze, dyspnea, and use of corticosteroids, n=359

	Asthma symptoms	**Frequent asthma symptoms**	**Wheeze**	**Dyspnea**	**Corticosteroid use**
Cross-sectional *association between the pro-inflammatory proteins (age 4) and asthma symptoms (age 4)*					
Hs-CRP 0.20-0.59 mg/L †	1.11 (0.61, 2.04)	1.11 (0.43, 2.89)	1.56 (0.76, 3.20)	0.90 (0.44, 1.85)	0.81 (0.34, 1.93)
Hs-CRP 0.61-9.89 mg/L †	1.19 (0.65, 2.19)	1.35 (0.53, 3.46)	1.43 (0.68, 2.98)	1.51 (0.77, 2.98)	1.24 (0.54, 2.83)
C3 †	1.30 (0.95, 1.78)	**1.97 (1.20, 3.24)**	**1.58 (1.10, 2.28)**	1.38 (0.96, 1.96)	**1.90 (1.23, 2.93)**
C4 †	0.99 (0.76, 1.29)	1.21 (0.83, 1.77)	1.18 (0.87, 1.59)	0.98 (0.72, 1.32)	1.18 (0.83, 1.67)
Hs-CRP 0.20-0.59 mg/L ‡	0.94 (0.50, 1.75)	0.86 (0.32, 2.32)	1.42 (0.68, 2.97)	0.75 (0.36, 1.58)	0.67 (0.28, 1.64)
Hs-CRP 0.61-9.89 mg/L ‡	1.13 (0.61, 2.10)	1.24 (0.48, 3.24)	1.40 (0.67, 2.93)	1.42 (0.71, 2.84)	1.13 (0.49, 2.63)
C3 ‡	1.33 (0.96, 1.82)	**1.92 (1.16, 3.19)**	**1.64 (1.13, 2.37)**	1.37 (0.95, 1.96)	**1.91 (1.23, 2.95)**
C4 ‡	1.03 (0.79, 1.35)	1.27 (0.86, 1.88)	1.22 (0.90, 1.66)	1.00 (0.73, 1.36)	1.23 (0.86, 1.76)
Prospective *association between the pro-inflammatory proteins (age 4) and asthma symptoms (age 5-8)*					
Hs-CRP 0.20-0.59 mg/L †	0.82 (0.42, 1.61)	0.72 (0.27, 1.94)	0.66 (0.24, 1.77)	0.74 (0.35, 1.58)	0.87 (0.34, 2.24)
Hs-CRP 0.61-9.89 mg/L †	1.01 (0.53, 1.94)	0.84 (0.33, 2.13)	1.46 (0.62, 3.42)	0.85 (0.41, 1.76)	1.02 (0.41, 2.52)
C3 †	**1.48 (1.04, 2.09)**	1.18 (0.74, 1.86)	**1.65 (1.04, 2.61)**	1.38 (0.93, 2.05)	**1.84 (1.15, 2.94)**
C4†	1.26 (0.96, 1.66)	1.39 (0.98, 1.97)	1.31 (0.97, 1.76)	1.31 (0.97, 1.76)	1.44 (1.03, 2.04)
Hs-CRP 0.20-0.59 mg/L ‡	0.80 (0.41, 1.59)	0.64 (0.22, 1.81)	0.63 (0.33, 1.73)	0.71 (0.33, 1.54)	0.82 (0.31, 2.12)
Hs-CRP 0.61-9.89 mg/L ‡	0.99 (0.52, 1.91)	0.79 (0.31, 2.01)	1.42 (0.60, 3.35)	0.84 (0.41, 1.73)	0.98 (0.39, 2.43)
C3 ‡	**1.47 (1.04, 2.07)**	1.16 (0.73, 1.83)	**1.64 (1.04, 2.60)**	1.37 (0.92, 2.04)	**1.83 (1.14, 1.94)**
C4 ‡	1.27 (0.97, 1.67)	**1.42 (1.00, 2.01)**	1.32 (0.98, 1.78)	1.32 (0.98, 1.78)	**1.47 (1.04, 2.07)**

Asthma symptoms: ≥ 1 attack of wheeze, and/or ≥ 1 episode of dyspnea and/or a prescription of inhaled corticosteroids in the last 12 months (reference: no asthma symptoms); Frequent asthma symptoms: having asthma symptoms and ≥ 4 attacks of wheeze or ≥ 4 attacks of dyspnea in the last 12 months (reference: no asthma symptoms).

The reference category for hs-CRP was the group of children with hs-CRP concentrations below the detection limit. Results of C3 and C4 are displayed per interquartile range.

† Model adjusted for maternal allergy, maternal education, and maternal smoking during pregnancy

‡ Model additionally adjusted for BMI SDS

Pro-inflammatory proteins in the association between body mass index standard deviation scores and asthma symptoms

The inclusion of hs-CRP, C3 and C4 concentrations in the regression models did not attenuate the cross-sectional association between BMI SDS and asthma symptoms or the prospective association between BMI SDS at age 4 and asthma symptoms in the following years (i.e. 5-8) (See Table 4 in comparison with Table 2). This was also the case for the cross-sectional and prospective associations between BMI SDS and frequent asthma symptoms, wheeze, dyspnea and use of corticosteroids (Table 4).

Table 4

Associations (OR (95%CI)) between BMI SDS and asthma symptoms, frequent asthma symptoms, wheeze, dyspnea, and use of corticosteroids, additionally adjusted for the pro-inflammatory proteins, n=359

	Asthma symptoms	**Frequent asthma symptoms**	**Wheeze**	**Dyspnea**	**Corticosteroid use**
Cross-sectional *association between BMI SDS (age 4) and asthma symptoms (age 4)*					
BMI SDS §	**1.43 (1.08, 1.91)**	**1.71 (1.10, 2.65)**	1.17 (0.85, 1.60)	**1.57 (1.13, 2.18)**	**1.57 (1.07, 2.31)**
Prospective *association between BMI SDS (age 4) and asthma symptoms (age 5 to 8)*					
BMI SDS §	1.21 (0.92, 1.59)	1.45 (0.97, 2.16)	1.41 (0.94, 2.12)	1.36 (0.99, 1.88)	1.30 (0.92, 1.84)

Asthma symptoms: ≥ 1 attack of wheeze, and/or ≥ 1 episode of dyspnea and/or a prescription of inhaled corticosteroids in the last 12 months (reference: no asthma symptoms); Frequent asthma symptoms: having asthma symptoms and ≥ 4 attacks of wheeze or ≥ 4 attacks of dyspnea in the last 12 months (reference: no asthma symptoms).

BMI SDS: body mass index standard deviation score

Odds ratio per 1 SDS increase in BMI, § Model adjusted for maternal allergy, maternal education, maternal smoking during pregnancy, hs-CRP, C3, C4

Discussion

We found a significant cross-sectional association between BMI SDS and asthma symptoms in 4-year-old children that was not attenuated by adjustment for pro-inflammatory markers. This suggests that the association between BMI SDS and asthma symptoms was not explained by these pro-inflammatory proteins in this age group. We also found, for the first time, that, independent of BMI SDS, C3 was associated with asthma symptom prevalence in young children.

We were able to study the association between BMI SDS and asthma symptoms in a prospective birth cohort, using body weight and height measured by trained investigators. Information on asthma symptoms and the use of corticosteroids was available for each year, and in addition, we measured sensitization. In contrast to previous studies, we were able to study the role of C3 and C4 in addition to hs-CRP, and we were able to adjust for potential confounders like maternal smoking and maternal allergy during pregnancy, and maternal education reported at age 1 year of the child.

The definition of asthma symptoms in the PIAMA birth cohort study was based on wheeze, dyspnea and prescription of inhaled corticosteroids reported by the parents. Although these factors are important indicators for asthma in children, wheeze and dyspnea are also common symptoms of respiratory infections in children and some misclassification cannot be excluded. Therefore, we also used the definition of frequent asthma symptoms, which is more stringent by only including children who, in addition to having asthma symptoms according to our definition, also had four or more attacks of wheeze or dyspnea in the past 12 months. A limitation of this study was that serum pro-inflammatory protein concentrations were only available for a subset of children. This resulted in differences between the children in our study and the original PIAMA birth cohort with regard to maternal educational level and percentage of children with an allergic mother. Because effect modification by these variables was not present, we assume that selective serum sample availability has not affected the generalizability of our findings. The prevalence of obesity was only 4%; this is representative of the 4-year-old population in the Netherlands.[42] Besides, systemic inflammation may be more marked in obese compared with overweight children; however, already in overweight children, inflammation processes are going on.[43]

Recently, in line with our observations, Michelson et al.[16] showed, in a relatively young population (< 20 years old), that high BMI SDS was cross-sectionally associated with an increased risk of asthma. They additionally found that children with increased CRP levels were at a higher risk of having asthma, whereas we did not find an association between hs-CRP concentrations and asthma symptoms. The associations between BMI SDS and asthma and between CRP levels and asthma found in their study were independent of each other. Unfortunately, they did not report the association between BMI SDS and asthma without adjustment for CRP levels; therefore no conclusions on attenuation of the association between BMI SDS and asthma after adjustment for CRP can be drawn. The association between CRP levels and asthma they found was specifically in the severe asthmatics, which may explain our different findings, as we were not able to differentiate between three degrees of severity of asthma.
In contrast to previous studies reporting higher hs-CRP concentrations in overweight[14,19-21,28] and asthmatic[14,32,33] children, we did not find associations between hs-CRP and BMI and asthma. The children in the present study were young compared with the previous studies; possibly, a longer period of overweight is needed to cause systemic inflammation.[28] C4 has not been studied in children before. Two previous studies, one in adults[25] and one in children, showed higher C3 concentrations with increasing BMI or waist circumference, whereas we did not show increased C3 concentrations with increasing BMI SDS. This association may only be visible at a later stage in life or only in the very obese. On the basis of experimental models of asthma in animals, it is well established that the complement system plays a role in the pathophysiology of asthma.[34,35] In contrast to previous studies in adults showing an association of hs-CRP with non-allergic asthma, and not with allergic asthma[13,17] we did not observe associations between hs-CRP and allergic asthma symptoms and non-allergic asthma symptoms.

Some studies suggest that the impact of overweight on asthma is partly mediated by (chronic) systemic inflammation.[10,11] Our data do not support this for 4-year-old children as the associations we observed between BMI SDS and asthma outcomes were completely insensitive to adjustment for the inflammation markers we used in the present study. This implies that the association between BMI and asthma may be explained by pro-inflammatory

markers other than used in the present study, or as mentioned before, that a longer period of being overweight is needed to cause systemic inflammation; possibly, the effect of systemic inflammation is only present at a later age. In this context, Skinner et al.[28] found that at the age of 3-5 years only being very obese was associated with an increased risk of abnormal CRP values, whereas in 15-17-year-old children, this association was also found in overweight children.

Conclusion

The associations between BMI SDS and asthma symptoms in this study were not affected by adjustment for the inflammation markers hs-CRP, C3 and C4. C3 concentrations were associated with (frequent) asthma symptoms, independent of BMI SDS.

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Chapter 5

Waist circumference, body mass index and lung function in 8-year-old children

Waist circumference, body mass index and lung function in 8-year-old children

Abstract

BMI and waist circumference may be associated with lung function in children, as observed in adults. Height, weight, waist circumference and lung function (FVC and FEV_1) were measured during a medical examination in 1058 8-year-old children participating in the PIAMA birth cohort study. After adjusting for height, age and other potential confounders large waist circumference or high BMI (> 90th percentile) were not associated with forced expiratory volume in 1 second (FEV_1) or forced vital capacity (FVC). In girls only, large waist circumference was, independent of BMI, associated with 3.5% (95%CI -6.4, -0.6) lower FEV_1/FVC ratio in the model including waist circumference and BMI. Girls with low BMI (<10th percentile) had 4.6% lower FEV_1 (95%CI -8.4, -0.6) and 5.1% lower FVC (95%CI -8.8, -1.2) than girls with normal BMI. In boys we did not observe associations between low or high BMI and lung function independent of waist circumference, or between small or large waist circumference and lung function after adjustment for BMI. In conclusion, at 8 years of age, a high BMI or large waist circumference are not yet associated with FEV_1 and FVC, indicating that this association may change over the course of life from childhood to adulthood.

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Introduction

Being overweight, measured by BMI, is associated with reduced lung function in adults.[1-5] Additionally, an increased waist circumference is associated with reduced lung function in adults.[1-4,6,7] Some[3,6], but not all studies[1,2,4,7] showed that waist circumference is even more strongly related to lung function than BMI. This may be due to greater abdominal fat mass in those with large waist circumference, whereas BMI reflects total body mass and does not reflect fat distribution.[2,8] In children, results are inconsistent, but, in contrast to studies in adults, most seem to suggest a positive association[9-12] rather than a negative association between BMI and lung function.[13] Only two studies examined waist circumference in children in relation to lung function and showed a positive association with lung function.[14,15] Most studies investigating childhood BMI and waist circumference assumed a linear association with lung function, disregarding a possible inverse U-shaped association with reduced lung function in both underweight and overweight children.

Our aim was to study the association between waist circumference and BMI on one hand and lung function on the other hand in a group of 8-year-old children. With the current worldwide overweight epidemic, the health consequences of childhood overweight rank high on the public health agenda. The focus of our study is therefore on adiposity, and especially on abdominal adiposity (large waist circumference) in relation to lung function. In addition, we assessed the association between lung function and BMI and waist circumference at the lower end of the distribution, in order to gain a more complete understanding of the relationship of BMI and waist circumference with lung function.

Methods

Study design and population

The children in this study are participants of the PIAMA birth cohort study and were born in 1996-1997. The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent. A detailed description of the study design has been published previously.[16] At baseline, the cohort consisted of 4146 pregnant women, 183 being lost to follow-up before any data of the child had been collected, so that the study started with 3963 newborns. At the age of 8 years 3655 children (92.2%) were still in the study and 3270 questionnaires were completed. For the medical examination, 1680 children were invited. Due to the design of the PIAMA study children of allergic mothers were overrepresented in this sub sample (n=1078). 1263 children agreed to participate. Finally, the medical examination, including anthropometric measurements and lung function tests, was performed in 1106 children. In 1058 children the lung function tests succeeded.

Lung function, height, weight and waist circumference

The measurements during the medical examination were performed by trained research staff using calibrated measuring equipment. Waist and hip circumference (cm) were measured twice and rounded at one decimal, the mean of the two waist measurements being used in analyses. Weight was measured at the nearest 0.1kg and height (cm) was measured at one decimal. All anthropometric variables were measured while the children were wearing underwear only. BMI was calculated as weight in kilograms divided by height squared in meters (kg/m^2). We divided the children in three categories in our analyses, separately for waist circumference and BMI, and for girls and boys; 1) below the 10^{th} percentile, 2) above the 90^{th} percentile and 3) between the 10^{th} and 90^{th} percentile, which we call 'normal'.

A Jaeger pneumotachograph (Viasys Healthcare, USA) was used for lung function testing. The machines were calibrated every day the medical examination took place. FVC and FEV_1 were measured in sitting position, while wearing a nose clip, according to the ATS/ERS guidelines.[17] For each child, at least three acceptable maneuvers had to be obtained. Additionally, the ratio between FEV_1 and FVC (FEV_1/FVC ratio) was used as outcome measure.
Data on covariates were collected during the medical examination and in the yearly questionnaires. In the questionnaires, data on the BMI and the educational level of the mother were collected. The latter was measured as the highest education completed and divided into three categories; low, intermediate and high education. During the medical examination including the lung function test, the parents were interviewed on their child's current health complaints and medication use, and blood sampling of the children was performed for measurement of specific IgE concentrations. Sensitization to allergens was defined as having a specific IgE concentration of ≥0.70IU per ml against one or more of the following allergens: house dust mite, cat, dog, grass (*Dactylis glomerata*), birch pollen, *Alternaria alternata,* milk or egg.

Statistical analyses
In the analyses of the association of waist circumference and BMI with FVC, $FEV1_1$ and FEV_1/FVC ratio the natural logarithm of the lung function testing variables and of height and age were used to capture the complex and non-linear association between these variables.[18] The analyses were stratified by gender because lungs develop differently in boys and girls.[19] Maternal educational level, use of asthma medication within 48 hours before the lung function measurement, having a cold during the lung function measurement, hour of the day of the medical examination, sensitization to specific allergens, and wheezing in the past year changed the association between BMI, waist circumference and lung function >10% and were included in the adjusted models. We also considered TV-hours, indicator of sedentary behavior, as potential confounder but this did not change the association between waist circumference or BMI and the lung function testing variables.
The associations between waist circumference, and BMI on one hand and FVC, FEV_1, and FEV_1/FVC ratio on the other hand were first explored graphically using local regression (Loess), separately for boys and girls. The associations were adjusted for confounders and those with waist circumference were adjusted for BMI and *vice versa*. This resulted in smooth lines following the data without adjusting to a certain shape or predefined statistical model.
In linear regression analyses the associations between a small or large waist circumference and a low or high BMI and FVC, FEV_1 and FEV_1/FVC ratio were examined, separately for boys and girls. Statistical model: Ln (lung function testing variable) = constant + ln (height) + ln (age) + waist circumference$_{<10th\ percentile}$ + waist circumference$_{>90th\ percentile}$ + 'error'. The result is the percent difference in lung function in children in the lowest and highest 10% of waist circumference compared with lung function in children with 'normal' waist circumference. These analyses were repeated with BMI$_{<10th\ percentile}$ and BMI$_{>90th\ percentile}$ as exposure variable and with adjustment for confounders. Finally, one regression model was run including both waist circumference and BMI to assess the association between waist circumference and lung function conditionally on BMI, and *vice versa*. The categories of waist circumference and BMI are correlated but a test for multi colinearity did not show any indication of too high correlations between the two anthropometric measures (Tolerance (1/variance inflation factor) ranged from 0.54 to 0.61). Stratified analyses for maternal allergy were performed. Analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Mean age of the children was 8 years (range: 7.4 to 9.2 years). Mean (standard deviation) waist circumference was 58.6cm (5.4) in girls and 58.5cm (4.9) in boys. Mean BMI was 16.5 (2.0) and 16.2 (1.9) kg/m^2 in girls and boys respectively. Characteristics of the study population are given in Table 1. The prevalence of maternal allergy in the study population was 66% and the prevalence of asthma was 17%, compared to 30% and 13% respectively in the total PIAMA population of 8-year-olds, the difference being due to oversampling of children of allergic mothers in the subgroup selected for the medical examination as described in the method section. Characteristics of the few children (n=48) in whom the lung function tests did not succeed were comparable to those of children with successful lung function tests.

Table 1

Baseline characteristics of the study population, separately for girls and boys

	Girls n=533		**Boys n=525**	
	Mean (sd)		*Mean (sd)*	
Age (year)	8.08	(0.30)	8.07	(0.29)
Waist circumference (cm)	58.6	(5.4)	58.5	(4.9)
BMI (kg/m^2) *	16.5	(2.0)	16.2	(1.9)
Height (cm) *	132.4	(5.6)	133.3	(5.6)
FEV1 (L) *	1.76	(0.24)	1.84	(0.25)
FVC (L) *	1.95	(0.29)	2.07	(0.30)
FEV$_1$/FVC ratio *	0.91	(0.003)	0.89	(0.003)
	n (%)		*n (%)*	
Asthma symptoms † *	78	(14.9)	102	(19.8)
Frequent asthma symptoms ‡	20	(4.0)	23	(4.7)
Atopy*	121	(27.1)	180	(39.7)
Allergic mother	340	(63.8)	359	(68.4)
Overweight *	84	(15.8)	58	(11.1)
Obesity	16	(3.0)	11	(2.1)
Maternal educational level				
Low	100	(18.8)	103	(19.7)
Intermediate	232	(43.7)	213	(40.7)
High	199	(37.5)	208	(39.7)
Use of asthma medication within 48 hours before lung function measurement	14	(2.7)	15	(2.9)
Having a cold during lung function measurement	46	(8.6)	37	(7.1)
Wheezing in the past year	40	(7.6)	55	(10.7)

** P<.05 difference between boys and girls*

† In the PIAMA study, 'asthma symptoms' are defined as at least 1 attack of wheeze, and/or at least 1 episode of dyspnoea and/or a prescription of inhaled corticosteroids in the last 12 months.

‡ In the PIAMA study, 'frequent asthma symptoms' are defined as having asthma symptoms and ≥4 attacks of wheeze or ≥4 attacks of dyspnoea in the last 12 months. Overweight and obesity were defined according to standard international definitions, specified for age and gender.[20]

The figures show that FEV_1 and FVC increase with increasing waist circumference (Figure 1) and BMI (Figure 2). The FEV_1/FVC ratio decreases with increasing waist circumference and BMI in both boys and girls. Furthermore Figure 1 shows that FEV_1 and FVC start to reach a plateau at the upper end of the waist circumference distribution in boys and girls. Figure 2 shows that FEV_1 and FVC start to reach a plateau at the upper end of the BMI distribution in girls only, and that in boys FEV_1 and FVC increase with increasing BMI over the whole range of BMI.
Table 2 shows the distribution of children when classified by the 10th and 90th percentile of waist circumference and BMI. Some children were classified differently according to waist circumference than to BMI. All children with a BMI >90th percentile were overweight according to the IOTF overweight definition.[20]

Table 2

Number of children in the different categories of waist circumference and body mass index; separately for girls and boys.

	BMI							
	Girls				Boys			
Waist circumference	10th percentile	'Normal' BMI	10th percentile	Total	10th percentile	'Normal' BMI	10th percentile	Total
	BMI		*BMI*		*BMI*		*BMI*	
10th percentile WC	31	27	0	58	24	32	0	56
'Normal' WC	23	382	15	420	28	369	18	415
90th percentile WC	0	17	38	55	0	19	35	54
Total	54	426	53	533	52	420	53	525

Girls: 10th percentile of waist circumference ≤52.50cm, 90th percentile of waist circumference ≥66.50cm; 10th percentile of BMI ≤14.30kg/m², 90th percentile of BMI ≥19.40kg/m²
Boys: 10th percentile of waist circumference ≤53.30cm, 90th percentile of waist circumference ≥64.50cm; 10th percentile of BMI ≤14.20kg/m², 90th percentile of BMI ≥18.57kg/m²

No statistically significant association existed between large waist circumference or high BMI and FVC or FEV_1 in boys and girls, after adjustment for confounders (Table 3). Boys with a high BMI had a significantly lower FEV_1/FVC ratio (-2.5% (95%CI -4.7, -0.3)), whereas no such association was observed in girls.
Also after mutual adjustment for waist circumference and BMI, no associations between large waist circumference or high BMI and FEV_1 and FVC were found. In these analyses, girls with a large waist circumference given their BMI had a reduced FEV_1/FVC ratio (-3.5% (95%CI -6.4, -0.6)), in boys this association was not found. We observed no associations between high BMI and FEV_1/FVC ratio in both sexes. With regard to BMI, adjustment for waist circumference in the models resulted in attenuation of the associations in boys, but in girls the estimates changed considerably possibly indicating multi colinearity, although a test for colinearity did not indicate that (*Methods section*).
Girls with a small waist circumference had a 4.1% (95%CI -7.4, -0.7) lower FVC compared with girls with a 'normal' waist circumference in adjusted analyses. Similarly, girls with a low BMI had a 5.8% (95%CI -8.9, -2.6) lower FVC compared with girls with a 'normal' BMI, and they also had a lower FEV_1 (-5.1% (95%CI -8.3, -1.8). No significant associations were found for small

waist circumference or low BMI in boys. After including both waist circumference and BMI in the model the associations in girls attenuated, especially the associations with low waist circumference. Only the associations between low BMI and FEV_1 and FVC remained significant (-4.6% (95%CI -8.4, -0.6) and -5.1% (95%CI -8.8, -1.2) respectively). Again no associations were found in boys of small waist circumference or low BMI with lung function. Stratified analyses by maternal allergy yielded similar non-significant results (data not shown).

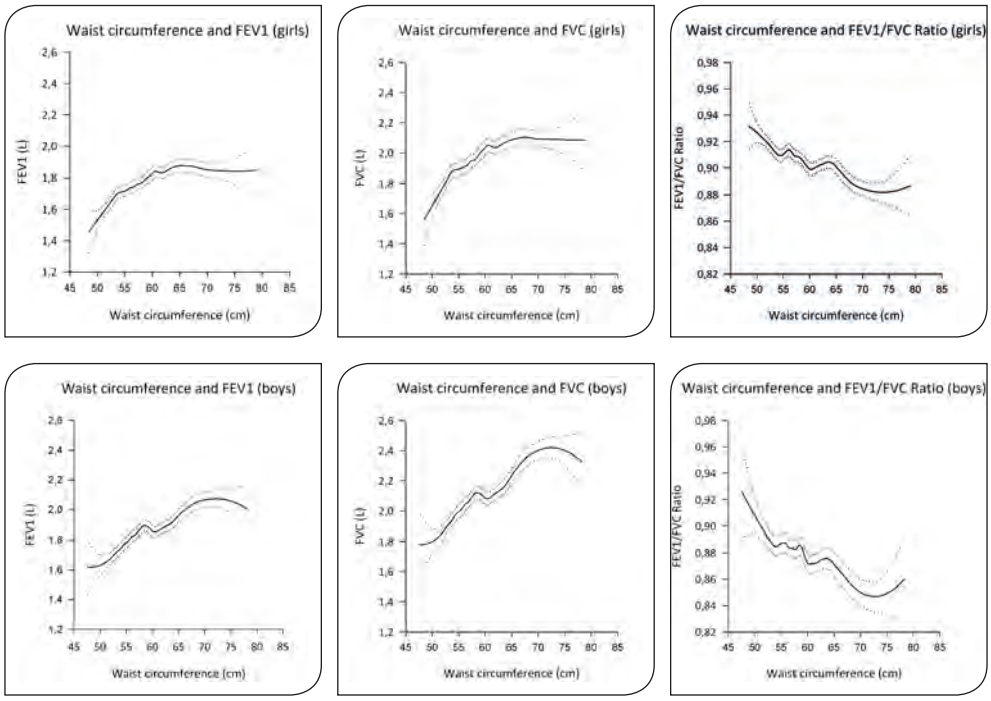


Figure 1

FEV_1, FVC and FEV_1/FVC ratio by waist circumference, separately for girls and boys. The lung outcomes were adjusted for BMI, maternal educational level, use of bronchodilating medication within 48 hours before the lung function measurement, having a cold during the lung function measurement, the hour of the day of the medical examination, sensitization to specific allergens, and wheezing in the past year at age 8.

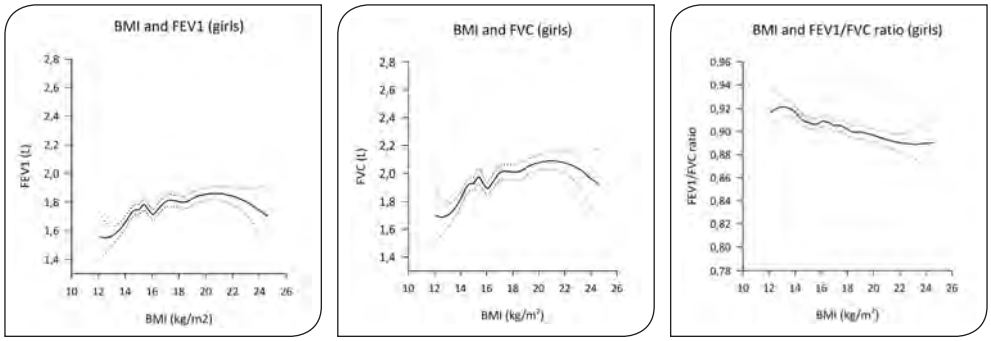


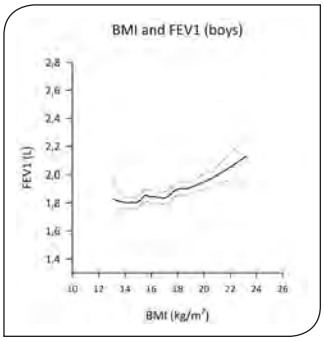
Figure 2

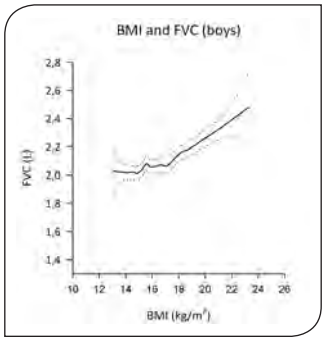
FEV_1, FVC and FEV_1/FVC ratio by BMI, separately for girls and boys. The lung outcomes were adjusted for waist circumference, maternal educational level, use of bronchodilating medication within 48 hours before the lung function measurement, having a cold during the lung function measurement, the hour of the day of the medical examination, sensitization to specific allergens, and wheezing in the past year at age 8.

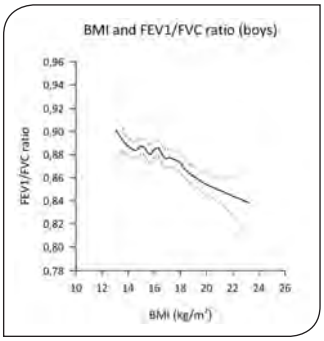
Table 3

Associations between waist circumference (WC) and BMI and the Lung Function Testing Variables FEV_1, FVC and FEV_1/FVC ratio separately for girls and boys. The results are a percent difference in the lung function testing variables of the children in the lowest en the highest 10% of waist circumference and BMI, compared with children who have a waist circumference or BMI between the 10th and 90th percentile. All analyses were adjusted for the child's height and age.

	FEV1					
	Girls		Boys		Girls	
	% difference (95%CI)		% difference (95%CI)		% difference (95%CI)	
<10th percentile WC	**-3.3**	**(-6.3, -0.3)**	-2.2	(-5.0, 0.8)	**-3.8**	**(-6.7, -0.8)**
>90th percentile WC	-1.3	(-4.3, 1.8)	0.4	(-2.7, 3.4)	-0.0	(-3.0, 3.1)
<10th percentile BMI	**-4.0**	**(-6.9, -1.0)**	-1.9	(-4.7, 1.1)	**-4.7**	**(-7.5, -1.8)**
>90th percentile BMI	0.5	(-2.6, 3.7)	0.2	(-2.7, 3.2)	0.8	(-2.3, 3.9)
Adjusted for confounders						
<10th percentile WC	-3.3	(-6.7, 0.2)	-1.5	(-4.7, 1.8)	**-4.1**	**(-7.4, -0.7)**
>90th percentile WC	-1.9	(-5.3, 1.6)	1.1	(-2.1, 4.4)	0.1	(-3.3, 3.6)
Adjusted for confounders						
<10th percentile BMI	**-5.1**	**(-8.3, -1.8)**	0.1	(-3.2, 3.4)	**-5.8**	**(-8.9, -2.6)**
>90th percentile BMI	-0.4	(-3.8, 3.1)	0.0	(-3.0, 3.2)	-0.2	(-3.5, 3.2)
Model with WC and BMI, adjusted for confounders						
<10th percentile WC	-1.3	(-5.2, 2.9)	-2.1	(-5.5, 1.4)	-1.6	(-5.5, 2.5)
>90th percentile WC	-2.6	(-7.2, 2.3)	2.0	(-2.1, 6.3)	1.0	(-3.7, 6.0)
<10th percentile BMI	**-4.6**	**(-8.4, -0.6)**	0.6	(-2.9, 4.3)	**-5.1**	**(-8.8, -1.2)**
>90th percentile BMI	1.6	(-3.1, 6.5)	-1.3	(-5.1, 2.7)	-0.6	(-5.1, 4.2)







BMI: body mass index, WC: waist circumference, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity. Confounders: maternal educational level, use of asthma medication within 48 hours before the lung function measurement, having a cold during the lung function measurement, the hour of the day of the medical examination, sensitization to specific allergens, and wheezing in the past year at age 8. Associations of P<.05 are given in bold.

FVC				**FEV1/FVC ratio**	
Boys		Girls		Boys	
% difference (95%CI)		% difference (95%CI)		% difference (95%CI)	
-3.5	**(-6.4, -0.5)**	0.4	(-1.5, 2.4)	1.4	(-0.8, 3.5)
2.5	(-0.7, 5.8)	-1.3	(-3.1, 0.6)	-2.1	(-4.2, 0.1)
-1.9	(-4.8, 1.2)	0.8	(-1.1, 2.7)	0.0	(-2.1, 2.1)
3.4	**(0.3, 6.6)**	-0.2	(-2.1, 1.7)	**-3.1**	**(-5.1, -1.0)**
-3.0	(-6.3, 0.4)	0.8	(-1.4, 3.1)	1.6	(-0.8, 4.0)
3.3	(-0.1, 6.9)	-2.0	(-4.1, 0.1)	-2.1	(-4.4, 0.2)
-1.0	(-4.4, 2.6)	0.7	(-1.4, 2.9)	1.1	(-1.4, 3.5)
2.6	(-0.7, 6.0)	-0.2	(-2.3, 2.0)	**-2.5**	**(-4.7, -0.3)**
-3.1	(-6.6, 0.6)	0.3	(-2.2, 2.9)	1.0	(-1.5, 3.5)
2.6	(-1.8, 7.2)	**-3.5**	**(-6.4, -0.6)**	-0.6	(-3.4, 2.4)
0.1	(-3.6, 3.9)	0.6	(-2.0, 3.2)	0.5	(-2.0, 3.1)
0.8	(-3.4, 5.0)	2.2	(-0.8, 5.2)	-2.0	(-4.7, 0.7)

Table 4

Characteristics of previous studies in children on lung function and BMI and waist circumference

Study	n	Age (years)	Gender	Study population	Lung function testing variables
Li, 2003[22]	64	7-18	Mixed	100% obese	(FVC, FEV_1, FEV_1/FVC, FEF_{25-75})% predicted
Chen, 2009[14]	718	6-17	Mixed		(FVC, FEV_1, FEV_1/FVC)%
Perez-Padilla, 2006[12]	6784	8-20	Separate	Separately for each 1-year age category	(FVC, FEV_1, FEV_1/FVC)%
Chu, 2009[10]	14654	Mean 14.30 m 14.21 f	Separate		FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, PEF
Consilvio, 2010[24]	118	IQR 6-8	Mixed	Children obesity clinic, paediatric allergy and respiratory clinic Pre-pubertal	(FVC, FEV_1,FEV_1/FVC, FEF_{25-75}) z-score
Spathopoulos *et al.*, 2009[13]	853	6-11	Mixed	Selected overweight and normal weight/ control group 75% obese	(FVC, FEV_1, FEF_{25-75}, FEV_1/FVC) L, % predicted, z-scores
He, 2009[11]	2179	8-13	Separate		FVC, FEV_1, FEF_{25}, FEF_{75}, FEF_{25-75}
Chow, 2009[9]	55	6-18	Mixed	Paediatric clinics 50% obese, 50% asthmatic	(FEV_1, FVC, FEV_1/FVC, FEF_{25}, FEF_{50}, FEF_{75}, PEF)% predicted
Musaad, 2009[15]	1123 (482 WC)	5-18	Mixed	Outpatient allergy/ immunology clinics	FEV_1

† Other possible confounders included in the studies were not mentioned here.

Statistical model	**Correction model (height, weight, age and gender) †**
Spearman correlation BMI z-score	ln (spirometric index)=$\alpha + \beta$ * ln (height)[23]
Multivariate multiple linear regression BMI and WC	1: spirometric index= $\alpha + \beta_1$ * WC + β_2 * sex + β_3 * age + β_4 * height 2: spirometric index= $\alpha + \beta_1$ * WC + β_2 * sex + β_3 * age + β_4 * height + β_5 * height^2 3: spirometric index= $\alpha + \beta_1$ WC + β_2 * sex + β_3 * age + β_4 * height + β_5 * weight
Linear regression BMI SDS, BMI SDS^2	Predicted spirometric index= $\alpha + \beta_1$ * height + β_2 * height^2
t-test,1-way Anova normal weight (ref), overweight, obesity	None
Kruskal-Wallis test Obese-asthmatic, normal weight-asthmatic, obese-non asthmatic, normal weight-non asthmatic	Age and height
Multivariate stepwise linear regression Normal weight (ref), overweight, obesity	ln (spirometric index)=$\alpha + \beta$ * ln (height)
Multivariate linear regression Normal weight (ref), overweight, obesity	Spirometric index= $\alpha + \beta_1$ * overweight + β_2 * obesity + β_3 * age + β_4 * height
Spearman correlation BMI, weight-for-height z-score	ln (spirometric index)=$\alpha + \beta$ * ln (height)[23]
BMI percentiles, WC	FEV_1= $\alpha + \beta_1$ * BMI percentiles + β_2 * sex + β_3 * age group

Discussion

In a population of 8-year-old children, we examined the association of waist circumference and BMI on the one hand and lung function on the other hand. We did not observe a significant association between abdominal or total adiposity and FEV_1 or FVC. Girls with abdominal adiposity (large waist circumference) had a significantly lower FEV_1/FVC ratio than 'normal weight' girls. Girls with a low BMI, and to a smaller extent a low waist circumference had a lower lung function than 'normal weight' girls.

Compared with previous studies in children investigating the association of waist circumference or BMI with lung function, the present study had several strengths. Our study population was relatively large, enabling stratification for gender, and consisted of pre-pubertal 8-year-olds with a narrow age range. Weight, height and waist circumference were measured by professionals. We studied both waist circumference and BMI in relation to lung function and also examined the association between waist circumference and lung function, conditional on BMI and vice versa. We studied associations with high and low BMI and with large and small waist circumference and lung function, without presupposing a linear relationship.

The PIAMA birth cohort is a large cohort with almost 4000 participating children. A drawback of our study is that only a specific subgroup was invited for the medical examination in the hospital at age 8. Due to the selection of this subgroup, most children in our study population were children of allergic mothers. However, analyses excluding children of allergic mothers did not yield different results, indicating no major implications for the generalisability of our results. The prevalence of obesity in our study population was only 5%, (as it is in the general population of 8-year-olds in the Netherlands[21]), which may have limited our possibilities to gain insight in the lung function of obese children.

Several previous studies have examined the association between BMI, waist circumference and lung function, but considerable differences exist between the reports in study populations, methods used and definitions of the outcomes studied (Table 4). BMI has been more extensively studied than waist circumference in association with lung function in children. In contrast to the evidence of a negative relation between BMI and lung function in adults, some of these childhood studies observed no associations[14,22] and some even reported positive associations between BMI and lung function.[9-12] Only one study showed reduced lung function in overweight or obese children, but this was in a selected study population with an obesity prevalence of 75%.[13] Two previous studies examined the association between waist circumference and lung function in children (Table 4).[14,15] Chen et al.[14] concluded that waist circumference and BMI were positively associated with FVC and FEV_1 and Musaad et al.[15] showed a significant positive association of waist circumference and BMI with FEV_1 in asthmatic children with non-allergic rhinitis. Both these studies assumed a linear association between BMI, waist circumference, and lung function, and therefore their results may not correctly reflect the associations between a high BMI or a large waist circumference and lung function. When we analyzed our own data linearly like Chen et al. did, we also found positive associations; significant for FVC but non-significant for FEV_1.

We found a significantly lower FEV_1/FVC ratio in girls with a large waist circumference, in concordance with the figures showing a decrease in the FEV_1/FVC ratio with increasing waist circumference or BMI in girls and boys. This observation is in line with the findings of Chen for waist circumference, and of others regarding BMI[10,12,13] and may indicate that in overweight children the FEV_1 is affected more than the FVC, suggesting obstruction of the airways.

Taking together the evidence from our own study and previous studies, we hypothesize that

during childhood two mechanisms influence the association between lung function and body size: growth increases lung volume and increasing adiposity decreases lung volume. Positive associations between BMI or waist circumference and lung function based on the assumption of a linear relationship may misleadingly suggest that (abdominal) adiposity may beneficially influence lung volume. The results of our study support earlier evidence from studies in children for a positive association between BMI, waist circumference and FEV_1 and FVC, but only for the lower part, and not for the higher part of the BMI and waist circumference distribution. Plots of the lung function testing variables against waist circumference and BMI (Figures 1 and 2) show that at the upper end of the waist circumference and BMI distribution FEV_1 and FVC no longer increase with increasing waist circumference (boys and girls) or BMI (girls only). Probably only in obese children, and not in moderately overweight children, the decrease in lung volume due to a high fat mass cancels out the increase of lung function with increasing BMI. During adulthood, only adiposity plays a role, leading to reduced lung volume. This might explain the reduced lung volume with increasing BMI in adulthood and the increase of lung volume with increasing BMI over most of the BMI distribution in childhood.

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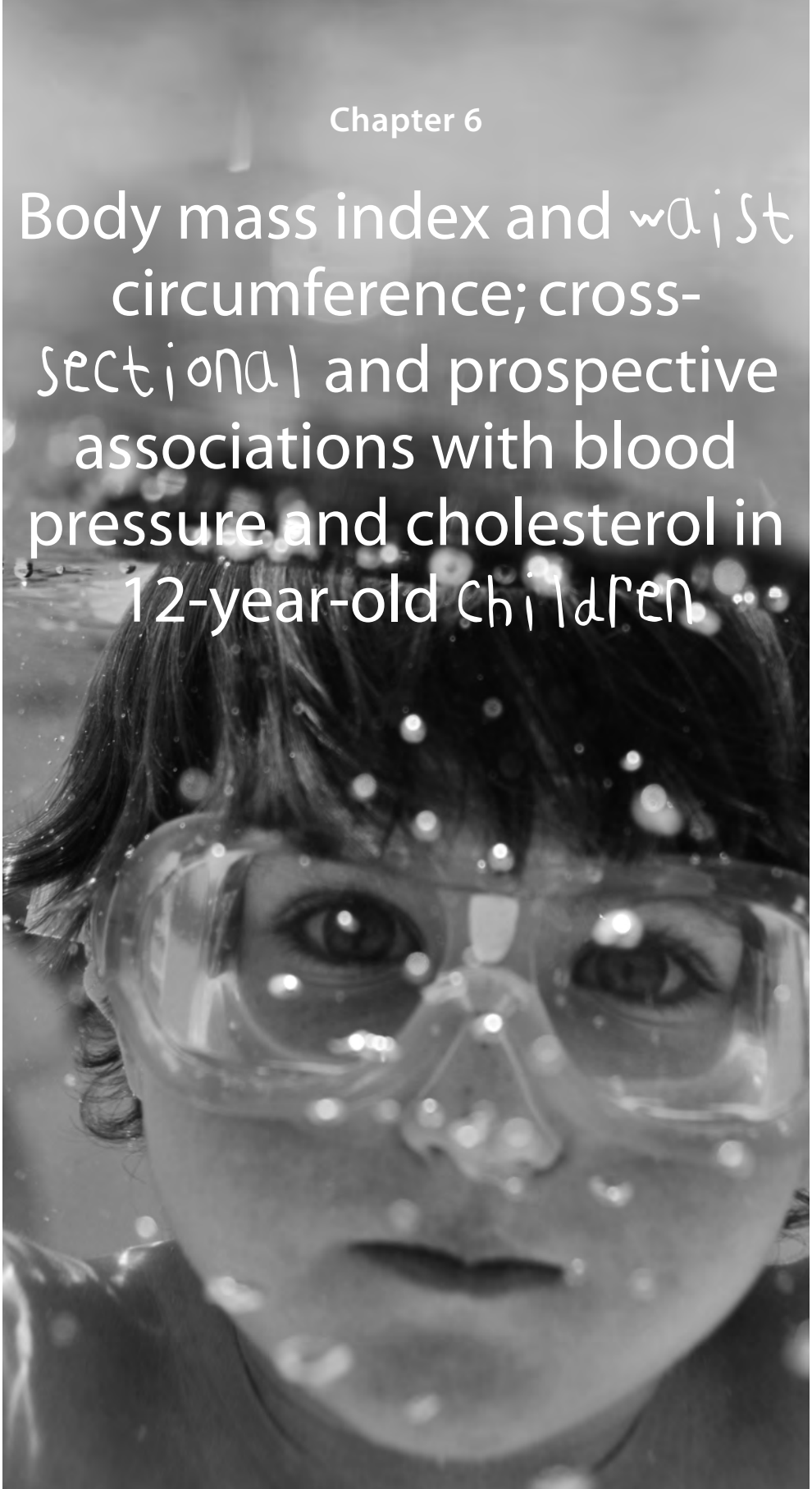
Chapter 6

Body mass index and waist circumference; cross-sectional and prospective associations with blood pressure and cholesterol in 12-year-old children



Body mass index and waist circumference; cross-sectional and prospective associations with blood pressure and cholesterol in 12-year-old children

Abstract

Childhood and adolescent overweight, defined by BMI, are associated with an increased risk of cardiovascular disease in later life. Abdominal adiposity may be more important in associations with cardiovascular diseases but waist circumference has been rarely studied in children. We studied associations between BMI and waist circumference and blood pressure and cholesterol in 12-year-old children and prospectively changes in BMI or waist circumference status between age 8 and 12 years and blood pressure and cholesterol at age 12. Weight, height, waist circumference, blood pressure and cholesterol concentrations were measured in 1432 children at age 12 years. Linear regression was used to study the associations between the highest 10% of the BMI and waist circumference distribution and blood pressure and cholesterol. Systolic blood pressure was 5.7 mmHg higher (95%CI 3.1, 8.3) in girls and 3.6mmHg (95%CI 1.3, 6.0) in boys with a high BMI. Large waist circumference was also associated with higher systolic blood pressure in girls (4.1mmHg (95%CI 1.7, 6.5)) and boys (3.9mmHg (95%CI 1.6, 6.2)). Diastolic blood pressure and cholesterol concentrations were significantly associated with high BMI and large waist circumference too. Waist circumference was more strongly associated with cholesterol than BMI in prospective analyses. Normal weight children with a history of overweight did not have higher blood pressure levels or adverse cholesterol concentrations than children that were normal weight at both ages. In conclusion, a high BMI and large waist circumference were associated with higher blood pressure levels and adverse cholesterol concentrations. Waist circumference should be taken into account when examining cardiovascular risk factors in children.

Manuscript based on

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Introduction

Overweight during childhood increases the risk of cardiovascular diseases later in life.[1-4] This is probably be due to the persistence of childhood and adolescent obesity into adulthood.[5] Besides that, already in children, overweight is associated with higher blood pressure levels and adverse cholesterol concentrations.[6-12] Waist circumference might more specifically reflect adiposity than BMI which reflects both lean and fat mass[13], and in addition, fat distribution may be more important for cardiovascular diseases. However, the question whether waist circumference is more strongly associated with cardiovascular risk than BMI is still unresolved.[6,11,12,14] Previous studies mainly focused on cross-sectional relations between BMI and cardiovascular risk factors, whereas the effect of persistence or remission of overweight on levels of cardiovascular risk factors remained underexposed. We hypothesize that longer duration of overweight puts children at increased risk of overweight-related health outcomes, like in adults.[15] We examined the association between high BMI and large waist circumference on one hand and blood pressure and cholesterol concentrations on the other hand in 12-year-old children. We also compared the relative influence of BMI and waist circumference in the associations with blood pressure and cholesterol. Besides that, we also studied blood pressure and cholesterol at age 12 years in children who lost, gained or maintained a high BMI or large waist circumference between the ages of 8 and 12 years as compared to children with normal BMI or waist circumference at both ages.

Methods

Study design

The children in this study are participants of the PIAMA birth cohort study and were born in 1996-1997. A detailed description of the study design has been published previously.[16] The mothers were recruited from the general population during pregnancy visiting one of 52 prenatal clinics. Postal questionnaires were sent to the parents during pregnancy, at the child's ages of 3 and 12 months, and yearly thereafter up to the age of 8 years. At the child's age of 11 years the parents received a questionnaire and a separate questionnaire was sent to the children. A medical examination took place during a home visit at age 12 years. For the medical examination at the age of 8 years children were invited to the hospital, local health centres or a home visit. The study protocol was approved by the medical ethics committees of the participating institutes and all parents gave written informed consent.

Study population

At baseline, the cohort consisted of 4146 pregnant women, 183 being lost to follow-up before any data of the child had been collected, thus the study started with 3963 newborns. At the age of 11 years 3541 children were still in the study and received a questionnaire. Questionnaires were returned by 2656 children and 2668 parents. For the medical examination, 3202 children were invited. 1511 children agreed to participate. Finally, the medical examination, including anthropometric measurements and blood pressure measurements, was performed in 1432 children. Blood samples were taken from 1293 children, and cholesterol concentrations were available for 1285 children. Not everyone had all outcome measures available; this resulted in slightly different numbers of children in the analyses regarding blood pressure and cholesterol concentrations. One child was excluded from the analyses with cholesterol because of very unlikely total and HDL cholesterol concentrations.

1277 children participating in the medical examination at 12 years also participated in the medical examination of 8-year-olds. This resulted in 1156 children for the analyses of BMI and waist circumference at age 8 and 12 years with blood pressure, and 994 children for the analyses with cholesterol concentrations.

Exposure measures: weight, height and waist circumference
The measurements during the medical examination were performed by trained research staff using calibrated measuring equipment. Waist circumference (cm) was measured twice and rounded at one decimal, the mean of the two waist measurements being used in the analyses. Weight was measured at the nearest 0.1kg and height (cm) was measured at one decimal. All anthropometric variables were measured while the children were wearing underwear only. BMI was calculated as weight in kilograms divided by height squared in meters (kg/m^2).
Z-scores of BMI and waist circumference for age and gender were calculated by using the reference growth curves of the Dutch Fourth nationwide Growth Study.[17] We divided the children in two categories in our analyses, separately for waist circumference and BMI, and for girls and boys, based on the distribution of the BMI z-score and the waist circumference z-score; 1) above the 90th percentile (high BMI, large waist circumference) and 2) below the 90th percentile, which we call 'normal'.

Outcome measures: blood pressure and cholesterol concentrations
Blood pressure was measured using automatic blood pressure meters (Omron M6 (Omron Healthcare Europe BV, Hoofddorp, the Netherlands)). Cuff-sizes of either 15-22 (small) or 22-32 cm (normal) were used dependent on the mid-upper arm circumference. The cuff was placed at the non-dominant arm. Systolic and diastolic blood pressure was measured at least two times with 5 minutes intervals according to the standard protocol while the child was seated and with the arm resting on their legs. We used the mean of the measures.
Serum total and HDL cholesterol concentrations were determined enzymatically using Roche automated clinical chemistry analyzers (Roche Diagnostics, Indianapolis). Additionally the ratio between total and HDL cholesterol was calculated (total-to-HDL cholesterol ratio).

Potential confounders
Potential confounders considered included the child's height and exact age at the time of clinical examination, birth weight, maternal education (low, intermediate and high education), maternal overweight before pregnancy, maternal smoking during pregnancy, TV watching and computer time (times per week) reported in the child questionnaire around 11 years, and pubertal development scale (PDS) (assessed by child report[18]).

Statistical analyses
General characteristics of the study population were calculated for boys and girls separately. First, we performed linear regression analyses with exposure (BMI and waist circumference) and outcome (blood pressure and cholesterol) measures around the age of 12 years. A potential confounder was included in the regression analyses when it changed the association between the exposure and outcome measures >10%. Three models were used in the regression analyses: Model A: adjusted for cuff size (only in blood pressure analyses) and child's age at time of the medical examination and Model B: additional adjustment for PDS, maternal pre-pregnancy overweight and the child's height. In model C we adjusted the two exposure

measures for each other to examine whether one the two measures explained the associations most strongly. Thus, model C was one model including BMI and waist circumference and confounders. All analyses were stratified for gender. Because BMI and waist circumference are highly correlated we performed a test of colinearity by determining the variance inflation factor for BMI and waist circumference in model C. The variance inflation factors ranged from 1.6 to 2.0, suggesting no colinearity.

Second, linear regression analyses were performed with BMI and waist circumference at age 8 and 12 years and outcome measures at age 12 years. For this purpose subgroups were created; children with a high BMI or large waist circumference at both ages ('high-high'), children with a high BMI or large waist circumference at age 8 and a normal BMI or waist circumference at age 12 years ('high-normal') and children with a normal BMI/ waist circumference at age 8 and a high BMI or large waist circumference at age 12 years ('normal-high') were compared with children with a normal BMI or waist circumference at both ages ('normal-normal'). These analyses were equal to the analyses previously performed regarding stratification and adjustment. To study whether BMI or waist circumference had a larger role in the associations with blood pressure and cholesterol we used model C including both measures. We included the high-high, high-normal, and normal-high groups of BMI and of waist circumference in one model, together with the confounders. All analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

Results

The mean waist circumference z-score was 0.26 in girls and 0.08 in boys and the mean BMI z-score was 0.05 in girls and 0.19 in boys (Table 1). This means that on average, girls had larger waist circumference and similar BMI compared with the reference population and, in contrast, that boys had similar waist circumference and higher BMI than the reference population. Children who maintained their high BMI status had higher BMI at 12 years than children who changed from normal BMI at 8 years to high BMI at 12 years. For example, the mean BMI of girls in the 'high-high' BMI group was 25.4kg/m^2 compared with 23.9kg/m^2 in the 'normal-high' group, and in boys the mean BMI was 25.3kg/m^2 and 23.4kg/m^2 in the two groups respectively. Similar results were found with the waist circumference groups. The mean (standard deviation (std)) systolic blood pressure was 114mmHg (9.5) in girls and 115mmHg (8.9) in boys and the diastolic blood pressure was 67mmHg (6.3) in girls and 67mmHg (6.6) in boys.

Table 1

General characteristics of the study population, separately for girls and boys

	Girls		Boys	
	Mean (sd)		*Mean (sd)*	
Age (year)	12.7	(0.4)	12.7	(0.4)
Weight (kg)	48.9	(9.4)	47.5	(9.2)
Height (cm)	160.5	(7.2)	159.5	(8.2)
Waist circumference (cm)	66.1	(6.5)	66.8	(6.8)
BMI (kg/m^2)	18.9	(2.7)	18.6	(2.6)
Weight z-score	0.12	(1.0)	0.18	(1.0)
Height z-score	0.21	(1.0)	0.13	(1.0)
Weight for height z-score	-0.13	(1.0)	0.11	(1.1)
BMI z-score	0.05	(1.1)	0.19	(1.1)
WC z-score	0.26	(0.9)	0.08	(1.0)
Systolic blood pressure (mmHg)	114	(9.5)	115	(8.9)
Diastolic blood pressure (mmHg)	67	(6.3)	67	(6.6)
Puberty development scale	1.8	(0.6)	1.3	(0.3)
Total cholesterol (mmol)	4.1	(0.6)	4.0	(0.7)
HDL cholesterol (mmol)	1.4	(0.3)	1.4	(0.3)
Total-to-HDL cholesterol ratio	3.1	(0.7)	3.1	(0.8)
	n (%)		*n (%)*	
Overweight (including obesity)	80	(11.0)	79	(11.3)
Obesity	6	(0.8)	8	(1.2)
BMI category 8 and 12 years				
Normal-normal	550	(88.0)	505	(87.8)
High-normal	23	(3.7)	13	(2.3)
Normal-high	16	(2.6)	27	(4.7)
High-high	36	(5.8)	30	(5.2)
WC category 8 and 12 years				
Normal-normal	538	(86.1)	494	(85.9)
High-normal	29	(4.6)	21	(3.7)
Normal-high	24	(3.8)	23	(4.0)
High-high	34	(5.4)	37	(6.4)
Maternal overweight before pregnancy	113	(15.5)	122	(17.5)
Maternal education				
Low	122	(16.8)	120	(17.2)
Intermediate	316	(43.6)	276	(39.6)
High	287	(39.6)	301	(43.2)
Allergic mother	243	(33.4)	222	(31.9)
Region				
North	255	(35.1)	204	(29.3)
West	305	(42.0)	334	(47.9)
Middle	167	(23.0)	159	(22.8)

Overweight and obesity were defined according to standard international definitions, specified for age and gender.[19] The PDS ranges from 1 to 5 where a score of 1 indicates that puberty has not started yet and a score of 5 indicates that the puberty development seems complete.

BMI and waist circumference in relation to blood pressure

In linear regression analyses we observed statistically significant associations between high BMI and large waist circumference and blood pressure. Systolic blood pressure was 5.95mmHg (95%CI 3.38, 8.52) higher in girls and 2.74mmHg (95%CI 0.39, 5.09) higher in boys with a high BMI than in girls and boys with normal BMI (Model A). A large waist circumference was associated with 4.54mmHg (95%CI 2.17, 6.90) higher systolic blood pressure in girls and 4.00mmHg (95%CI 1.69, 6.32) higher systolic blood pressure in boys (Model A). These associations changed somewhat after adjustment for confounders in model B (Table 2). After adjustment for the other exposure (BMI or waist circumference) in model C all associations became weaker; no clear difference in strength of the associations with blood pressure between BMI and waist circumference was observed (Table 2).

Table 2

Associations between high BMI and large waist circumference and systolic and diastolic blood pressure in 1424 12-year-old girls and boys

Blood pressure	**Girls n=706**				**Boys n=669**			
	Systolic BP		*Diastolic BP*		*Systolic BP*		*Diastolic BP*	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
BMI 90th centile								
Model B	5.70	(3.11, 8.29)	2.60	(0.78, 4.42)	3.64	(1.33, 5.95)	2.77	(0.99, 4.55)
Model C	4.72	(1.54, 7.90)	1.84	(-0.39, 4.07)	1.90	(-1.08, 4.87)	0.29	(-1.98, 2.57)
WC 90th centile								
Model B	4.09	(1.69, 6.49)	2.20	(0.52, 3.88)	3.91	(1.63, 6.20)	4.06	(2.32, 5.81)
Model C	1.55	(-1.39, 4.49)	1.21	(-0.85, 3.27)	2.73	(-0.22, 5.67)	3.88	(1.63, 6.13)

BMI: body mass index, WC: waist circumference, BP: blood pressure

Model B: adjusted for cuff size, pre-pregnancy maternal overweight, puberty development scale, age at the time of the measurements, height

Model C: additionally adjusted for WC (in BMI analyses) and BMI (in WC analyses)

BMI and waist circumference in relation to cholesterol concentrations

We found only significantly higher total cholesterol concentrations in boys with a high BMI (0.40mmol (95%CI 0.22, 0.58)) and large waist circumference associations (0.51mmol (95%CI 0.34, 0.68)) (Model A). HDL cholesterol concentrations were significantly lower in boys and girls with a high BMI and large waist circumference after adjustment for confounders (Table 3). In line with these results, total-to-HDL cholesterol ratio was significantly higher in boys and girls with a high BMI or a large waist circumference in adjusted analyses in Model B (Table 3). Similarly to the associations with blood pressure, all associations between BMI and waist circumference and cholesterol measures became weaker after inclusion of waist circumference or BMI (Model C). The associations with waist circumference seemed to attenuate less after adjustment for BMI than the associations with BMI after adjustment for waist circumference.

Prospective analyses of BMI and waist circumference at ages 8 and 12 years

Children with a high-high BMI status had statistically significantly higher blood pressure levels than children with a normal-normal BMI status (Table 4). The blood pressure was also higher in

the high-high group than in the normal-high group. Similarly, children with a high-high waist circumference status had higher blood pressure levels than children with a normal-normal waist circumference status (Table 4). Children with a normal-high waist circumference status had higher systolic (girls only) and diastolic (boys and girls) blood pressure than children with a normal-normal waist circumference status. Children with a high-normal BMI or waist circumference status did not have higher blood pressure at 12 years of age than children who had a normal-normal BMI or waist circumference status. The analyses with BMI and waist circumference in the same model showed that the associations between a high-high BMI status and blood pressure remained strong in girls whereas the associations between a high-high waist circumference status and blood pressure remained strong in boys specifically.

Significantly higher total cholesterol concentrations (boys only) (0.56mmol (95%CI 0.31, 0.81)), higher total/HDL cholesterol ratio (boys: 0.95 (95%CI 0.63, 1.26); girls: 0.55 (95%CI 0.26, 0.84)), and lower HDL cholesterol concentrations (boys: -0.19mmol (95%CI -0.30, -0.07); girls: -0.20 (95%CI -0.31, -0.09)) were found with high-high BMI status in adjusted analyses (Model B) (Table 5). To a lesser extent and mainly in boys, these associations were also present in the normal-high group. Similar, but somewhat larger, estimates were found for the associations between high-high waist circumference status and cholesterol outcomes. Children with a high-normal BMI or waist circumference status did not have more adverse cholesterol concentrations at 12 years of age than children who had a normal-normal BMI or waist circumference status. After mutual adjustment for BMI and waist circumference, generally the associations with waist circumference did hold, whereas the associations with BMI attenuated substantially.

Table 3

Associations between high BMI and large waist circumference and total and HDL cholesterol concentrations and total-to-HDL cholesterol ratio in 1213 12-year-old girls and boys

Cholesterol			**Girls n=581**			
	Total cholesterol		*HDL cholesterol*		*Total-to-HDL cholesterol ratio*	
BMI 90th centile	β	95% CI	β	95% CI	β	95% CI
Model B	0.03	(-0.15, 0.22)	**-0.17**	**(-0.26, -0.08)**	**0.54**	**(0.31, 0.76)**
Model C	-0.09	(-0.32, 0.15)	-0.07	(-0.18, 0.04)	0.15	(-0.13, 0.43)
WC 90th centile						
Model B	0.14	(-0.03, 0.31)	**-0.19**	**(-0.27, -0.11)**	**0.67**	**(0.47, 0.87)**
Model C	0.19	(-0.03, 0.40)	-0.15	(-0.25, 0.05)	**0.59**	**(0.34, 0.84)**

BMI: body mass index, WC: waist circumference, HDL: high density lipoprotein

Model B: adjusted for pre-pregnancy maternal overweight, puberty development scale, age at the time of the measurements, height

Model C: additionally adjusted for WC (in BMI analyses) and BMI (in WC analyses)

Table 4

Associations between high BMI and large waist circumference of 8-and-12-year old children and systolic and diastolic blood pressure in 12-year-old girls and boys compared with girls and boys with a normal BMI or WC at both ages (NN)

		Girls n=606				Boys n=550			
		Systolic BP		*Diastolic BP*		*Systolic BP*		*Diastolic BP*	
		β	95% CI	β	95% CI	β	95% CI	B	95% CI
BMI									
B	HN	-1.14	(-4.90, 2.62)	-0.70	(-3.39, 2.00)	1.42	(-3.47, 6.32)	-2.83	(-6.58, 0.93)
	NH	2.84	(-1.65, 7.33)	2.23	(-0.98, 5.45)	3.08	(-0.44, 6.61)	**2.97**	**(0.27, 5.68)**
	HH	**6.56**	**(3.34, 9.78)**	**3.39**	**(1.09, 5.70)**	**5.07**	**(1.76, 8.38)**	**2.87**	**(0.33, 5.41)**
C	HN	-1.12	(-5.38, 3.15)	-0.90	(-3.95, 2.15)	-0.71	(-5.84, 4.42)	**-4.36**	**(-8.28, -0.44)**
	NH	1.90	(-3.03, 6.82)	1.42	(-2.10, 4.95)	1.42	(-2.51, 5.35)	0.81	(-2.19, 3.82)
	HH	**5.93**	**(1.20, 10.7)**	2.58	(-0.81, 5.97)	0.25	(-4.30, 4.81)	1.29	(-4.77, 2.20)
WC									
B	HN	0.94	(-2.47, 4.35)	0.55	(-1.88, 2.98)	0.89	(-3.06, 4.84)	-0.92	(-3.95, 2.12)
	NH	**4.49**	**(0.61, 8.39)**	**2.89**	**(0.11, 5.67)**	1.89	(-1.72, 5.50)	**3.32**	**(0.54, 6.09)**
	HH	**4.66**	**(1.32, 8.00)**	**2.73**	**(0.35, 5.11)**	**6.90**	**(3.83, 9.96)**	**4.58**	**(2.22, 6.93)**
C	HN	-0.33	(-4.34, 3.69)	0.14	(-2.73, 3.02)	1.02	(-3.08, 5.11)	-0.11	(-3.24, 3.02)
	NH	2.80	(-1.42, 7.02)	2.04	(-0.98, 5.06)	1.31	(-2.69, 5.31)	**3.06**	**(0.00, 6.12)**
	HH	0.68	(-4.13, 5.50)	0.96	(-2.48, 4.41)	**6.67**	**(2.35, 11.0)**	**5.67**	**(2.36, 8.97)**

BMI: body mass index, WC, waist circumference, BP: blood pressure

NN: normal-normal, HN: high-normal, NH: normal-high, HH: high-high, high: >90th percentile

Model B: adjusted for cuff size, pre-pregnancy maternal overweight, puberty development scale, age at the time of the measurements, height

Model C: additionally adjusted for WC (in BMI analyses) and BMI (in WC analyses)

Boys n=587					
Total cholesterol		*HDL cholesterol*		*Total-to-HDL cholesterol ratio*	
β	95% CI	β	95% CI	β	95% CI
0.45	**(0.28, 0.63)**	**-0.23**	**(-0.31, -0.15)**	**1.01**	**(0.80, 1.22)**
0.04	(-0.20, 0.27)	**-0.17**	**(-0.29, -0.06)**	**0.52**	**(0.24, 0.81)**
0.63	**(0.46, 0.81)**	**-0.20**	**(-0.28, -0.12)**	**1.07**	**(0.86, 1.28)**
0.61	**(0.38, 0.85)**	-0.08	(-0.19, 0.03)	**0.71**	**(0.43, 1.00)**

Discussion

We examined 1) the associations between BMI and waist circumference on the one hand and blood pressure and cholesterol on the other hand in 12-year-old children, 2) the relative importance of BMI and waist circumference in the associations with blood pressure and cholesterol and 3) whether associations between BMI and waist circumference and blood pressure and cholesterol were stronger if the child had a high BMI or large waist circumference (defined as >90th percentile) at both 8 and 12 years of age (high-high).

First, we found strong associations between a high BMI and systolic and diastolic blood pressure, and total and HDL cholesterol concentrations. We also found lower HDL cholesterol and higher systolic blood pressure, diastolic blood pressure and total cholesterol concentrations with increasing waist circumference. These results are in line with previous studies.[6-11, 20, 21]

Second, in our study waist circumference was more strongly associated with cholesterol than BMI. This observation was most notable when waist circumference at 8 years was taken into account. For blood pressure this was less clear; waist circumference tended to be more important in boys only, whereas BMI seemed to be more strongly associated with blood pressure in girls. Only a few studies have examined both BMI and waist circumference in relation to

Table 5

Associations between high BMI and large waist circumference of 8-and-12-year-old children and total and HDL cholesterol concentrations and total-to HDL cholesterol ratio in 12-year-old girls and boys compared with girls and boys with a normal BMI or WC at both ages (normal-normal)

	Girls n=505					
	Total cholesterol		*HDL cholesterol*		*Total-to-HDL cholesterol ratio*	
	β	95% CI	β	95% CI	β	95% CI
BMI						
B						
HN	0.19	(-0.11, 0.48)	-0.09	(-0.22, 0.05)	0.33	(-0.02, 0.68)
NH	0.25	(-0.10, 0.59)	-0.14	(-0.30, 0.02)	**0.60**	**(0.19, 1.01)**
HH	-0.08	(-0.32, 0.17)	**-0.20**	**(-0.31, -0.09)**	**0.55**	**(0.26, 0.84)**
C						
HN	0.04	(-0.30, 0.38)	-0.07	(-0.23, 0.08)	0.16	(-0.24, 0.56)
NH	0.06	(-0.33, 0.44)	-0.06	(-0.24, 0.12)	0.22	(-0.23, 0.67)
HH	-0.30	(-0.65, 0.06)	-0.10	(-0.26, 0.06)	0.09	(-0.33, 0.51)
WC						
B						
HN	0.15	(-0.09, 0.40)	-0.02	(-0.13, 0.09)	0.16	(-0.12, 0.43)
NH	**0.33**	**(0.05, 0.62)**	-0.11	(-0.24, 0.01)	**0.59**	**(0.26, 0.92)**
HH	0.03	(-0.22, 0.29)	**-0.25**	**(-0.37, -0.14)**	**0.72**	**(0.42, 0.92)**
C						
HN	0.23	(-0.06, 0.52)	0.03	(-0.10, 0.17)	0.12	(-0.22, 0.47)
NH	**0.38**	**(0.07, 0.69)**	-0.08	(-0.22, 0.07)	**0.55**	**(0.18, 0.92)**
HH	0.21	(-0.16, 0.58)	**-0.17**	**(-0.34, -0.05)**	**0.65**	**(0.22, 1.08)**

cardiovascular risk factors.[6,11,12] Although waist circumference is, on theoretical grounds[13], hypothesized to be more important for cardiovascular risk this has not been confirmed so far in children. Two studies in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study compared the magnitudes of the associations between BMI and waist circumference, respectively, and cardiovascular risk factors.[6,11] In the ALSPAC cohort study waist circumference did not seem to be more strongly associated with blood pressure and cholesterol than BMI.[6,11] Maximova et al. observed similar effects of BMI and waist circumference on changes in systolic blood pressure in 12- and 13-year-old US children.[12] In younger children (age 8-10 years) no superior ability of waist circumference to identify children with elevated systolic blood pressure was shown over BMI.[14] Previous studies showed as strong associations with waist circumference as with BMI, but not stronger. These studies, including the present one, show that it is worth to measure waist circumference besides weight and height. Waist circumference is rather easy to measure and is a valuable additional measure in studies on the association between adiposity and cardiometabolic risk factors and in preventive youth health care.

Third, our study suggests that normal weight children with a history of overweight are not at increased risk of higher blood pressure levels and adverse cholesterol concentrations.

BMI: body mass index, WC, waist circumference, HDL: high density lipoprotein
Model B: adjusted for pre-pregnancy maternal overweight, puberty development scale, age at the time of the measurements, height
Model C: additionally adjusted for WC (in BMI analyses) and BMI (in WC analyses)

Boys n=489					
Total cholesterol		*HDL cholesterol*		*Total-to-HDL cholesterol ratio*	
β	95% CI	β	95% CI	β	95% CI
0.05	(-0.33 , 0.42)	0.10	(-0.07, 0.27)	-0.17	(-0.63, 0.29)
0.31	**(0.04, 0.58)**	**-0.21**	**(-0.33, -0.09)**	**0.91**	**(0.58, 1.24)**
0.56	**(0.31, 0.81)**	**-0.19**	**(-0.30, -0.07)**	**0.95**	**(0.63, 1.26)**
-0.13	(-0.52, 0.25)	0.17	(-0.02, 0.35)	-0.53	(-1.00, -0.06)
-0.04	(-0.34, 0.27)	**-0.16**	**(-0.30, -0.02)**	**0.48**	**(0.12, 0.85)**
0.02	(-0.34, 0.38)	-0.04	(-0.21, 0.13)	0.04	(-0.40, 0.48)
0.19	(-0.09, 0.48)	-0.07	(-0.21, 0.07)	0.29	(-0.07, 0.65)
0.62	**(0.29, 0.95)**	-0.13	(-0.27, 0.00)	**0.84**	**(0.50, 1.19)**
0.76	**(0.46, 1.05)**	**-0.22**	**(-0.33, -0.11)**	**1.19**	**(0.90, 1.47)**
0.13	(-0.17, 0.44)	-0.09	(-0.23, 0.05)	0.37	(-0.00, 0.74)
0.59	**(0.27, 0.91)**	-0.05	(-0.20, 0.10)	**0.61**	**(0.22, 1.00)**
0.67	**(0.33, 1.01)**	**-0.19**	**(-0.35, -0.03)**	**1.15**	**(0.73, 1.56)**

Only two previous studies measured BMI at two time points.[11,22] Lawlor et al. observed this only in girls that a history of overweight did not put normal weight children at increased risk, boys who changed from overweight to normal weight showed risk factor profiles intermediate between those seen in boys who were normal weight at both ages or overweight at both ages.[11] These results suggest that the high-risk status of overweight children for adult cardiovascular disease is reversible.[23,24] In contrast, children with a persistently high BMI or waist circumference status were at increased risk of higher blood pressure and more adverse cholesterol concentrations than children with a normal-high BMI or waist circumference status.

Conclusion

This study focussed on the relative importance of waist circumference in the associations with blood pressure and cholesterol. We showed that waist circumference was especially important in the prospective associations with cholesterol. These findings merit more research on waist circumference as measure of fat mass in association with cardiovascular risk factors in children. In our study, normal weight children with a history of overweight did not have higher blood pressure levels or adverse cholesterol concentrations than children that were normal weight at both ages. This may imply that the effects of overweight on cardiovascular risk factors like blood pressure and cholesterol are reversible, and that changing from overweight to normal weight status is worthwhile. In addition, children who were overweight at both ages had higher blood pressure levels and more adverse cholesterol concentrations than overweight 12-year-old children without a history of overweight. This implies that the duration of overweight contributes substantially to the risk of adverse levels of cardiovascular markers in overweight children. We did not study the changes in blood pressure levels and cholesterol concentrations with regard to the results on history of overweight. Many childhood overweight reduction interventions have been performed so far, and it might be interesting to monitor also cardiovascular risk factors in these intervention groups.

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Chapter 7

General discussion

General discussion

Main findings

The aim of this thesis was to study aspects of respiratory and cardiovascular health in relation to childhood overweight. We studied children at the ages 4, 8 and 12 years. The main findings of this thesis are that overweight 12-year-old children had higher blood pressure levels and more adverse (high total and low HDL) serum cholesterol concentrations than their healthy weight counterparts. Furthermore, in 8-year-old children current overweight is not the only determinant of cholesterol concentrations. We also found the early-life determinants maternal pre-pregnancy overweight, maternal smoking during pregnancy and rapid infant weight gain to be associated with 8-year-olds' cholesterol concentrations. BMI was associated with current asthma symptoms, but a high BMI and large waist circumference were not associated with lower lung function, measured as FEV_1 and FVC, in 8-year-old children. Over the 4-8 age range, we prospectively studied the association between BMI and asthma symptoms to assess whether this association could be explained by pro-inflammatory proteins such as hs-CRP, C3 and C4. In our study, these proteins did not play a role in the association between BMI and asthma symptoms. Furthermore, waist circumference measured and reported by the parents corresponded well with the waist circumference measured by the professionals.

Cardiovascular health

Overweight children are at increased risk of adverse levels of cardiovascular markers. For instance, dyslipidemia has been observed in overweight children.[1-3] Also our studies performed in 8- and 12-year-old children of the PIAMA study showed that total cholesterol concentrations and total/HDL cholesterol ratios were higher in children with a higher BMI. Besides the influence of the child's current BMI on cholesterol concentrations also pre- and early postnatal determinants may play a role, referred to as 'early programming'.[4] In this thesis factors identified as early-life determinants of childhood cholesterol concentrations were maternal pre-pregnancy overweight, maternal smoking during pregnancy and rapid infant weight gain (1st year of life). These associations were partly mediated by the child's current BMI, thereby indicating that BMI plays a role in the development of early life risk factors to outcome. That is, children with these determinants more often have a higher BMI and a higher BMI generally is associated with adverse cholesterol concentrations. Other studies on early-life determinants of childhood cholesterol concentrations have produced inconsistent findings so far.[5-8] Different determinants of cholesterol concentrations have been identified in diverse studies, with cholesterol concentrations measured at different ages. The lack of agreement on relevant determinants hampers the possibility to use these early-life determinants as a lead for prevention.

In addition to dyslipidemia, hypertension[1,2,9-11], non-alcoholic fatty liver disease[12] and glucose-intolerance[13,14] have been shown in overweight and obese children. Our results on blood pressure in 12-year-olds are in line with the observations in previous studies. We observed that overweight children had higher blood pressure levels and more often adverse cholesterol concentrations than normal weight children, irrespective of their weight history. Furthermore, we observed higher blood pressure levels and more adverse cholesterol concentrations in overweight children with a history of overweight than in overweight children without a history of overweight. These observations suggest that duration of overweight may be an important

risk factor for adverse health outcomes. In this thesis, in the study of cardiovascular determinants the focus was on cholesterol and blood pressure. Other analyses in the PIAMA study examined HbA_{1c} and observed no associations of BMI and waist circumference measured at 8 and 12 years of age with HbA_{1c} in 8-and 12-year-old children or with the change in HbA_{1c} from age 8 to 12 years (unpublished results). Although previous studies have shown associations between overweight and HbA_{1c} in US and Jamaican children[15-17], also Shultis et al. observed similar HbA_{1c} levels in normal weight, overweight and obese children in their study in European children (ALSPAC).[18] BMI is acknowledged as an important risk factor for diabetes mellitus, with higher BMI resulting in insulin resistance and thereby in higher levels of glycemia.[19] However, so far the findings on HbA_{1c} concentrations in relation to body size or body composition in healthy children are not consistent.[15-18,20,21] All together, research in the PIAMA study adds evidence that several, but not all, cardiometabolic risk factors are elevated in overweight children. The study of cardiovascular risk factors in childhood is relevant because it has been shown that cardiovascular disease risk factors tend to persist from childhood into adulthood. This means that children with a particular rank relative to their peers in the risk factor distribution tend to retain that relative rank when reaching adulthood. Evidence comes from longitudinal studies like the Bogalusa Heart Study[22,23] showing that adverse cholesterol concentrations and blood pressure levels in childhood persist over time. Persistence of adverse cholesterol concentrations and elevated blood pressure levels put these children at increased risk of cardiovascular diseases as adults. Additionally, childhood obesity is assumed to be an independent risk factor for adult metabolic and cardiovascular diseases. However, a recent review including 11 studies indicated that the associations between childhood BMI and adult blood pressure, cholesterol concentrations and insulin levels were largely dependent on the persistence of a high BMI from childhood to adulthood.[24] Thus this review did not show evidence that the childhood BMI was independently associated with adult cholesterol concentrations and blood pressure levels. The persistence of adiposity from childhood to adulthood has been widely observed.[25,26] It is generally assumed that earlier onset and longer duration of obesity is associated with a greater cardiovascular risk. We showed that 12-year-old overweight children with a history of overweight had higher blood pressure levels and total cholesterol concentrations than overweight children without a history of overweight. Whereas normal weight children with a history of overweight did not have higher blood pressure levels or cholesterol concentrations compared with normal weight children without a history of overweight. These findings suggest that the high-risk status of overweight children for adult cardiovascular disease may be reversible. In addition, considering the negative effect of duration of overweight on childhood levels of cardiovascular risk factors, a need for prevention of childhood overweight exists, aiming at the development of a healthy lifestyle early in life. The approach of children's lifestyle should be considered within the family context as parental overweight is an important determinant of childhood obesity.[27]

Respiratory health

The association between childhood overweight and asthma symptoms has been examined in a number of studies in the PIAMA birth cohort. In this thesis we observed a clear and significant association between BMI and asthma symptoms at 4 years, but no association between BMI at 4 years and asthma symptoms at ages 5 to 8 years. Scholtens et al.[28] showed that children who had a persistently high BMI (BMI >85th percentile) during childhood or a high BMI at 6 to 7 years

had a significantly increased risk of asthma symptoms at 8 years. A high BMI at earlier ages was not related to an increased risk of asthma symptoms at 8 years if the child had become normal weight at 6 to 7 years. The association between childhood overweight and asthma symptoms has been shown previously in other studies.[29-33]

The mechanism underlying the increased risk of asthma symptoms in overweight children has not been completely understood yet. A suggested mechanism is certain immunological changes in overweight subjects. Body fat has been shown to be associated with markers of systemic and vascular inflammation.[34,35] These inflammatory factors may exert local effects in lung tissue, leading to subtle reduction in the airway diameter.[36] We studied whether the pro-inflammatory proteins hs-CRP, C3 and C4, measured when the children were 4 years old, played a role in the association between BMI and asthma symptoms. In our study hs-CRP, C3 and C4 did not explain the association between BMI and asthma symptoms, because the proteins were not associated with BMI. In previous studies higher concentrations of hs-CRP and C3 were found in overweight children.[34,37-40] In these studies the obesity prevalence was substantially higher than in the PIAMA cohort, with prevalences ranging from 17 to 100%. Additionally, in most of these studies, children were older than the children participating in our study[37,39,40], which might explain the diverging results. Possibly, the effect of systemic inflammation might only be present at later ages, indicating that more severe overweight or several years of being overweight may be needed to cause systemic inflammation.

In the PIAMA study, we did not observe differences in the association of BMI with asthma symptoms between boys and girls, but some studies have shown a stronger association in girls than in boys.[41,42] In childhood, more boys than girls have asthma symptoms and this reverses in adolescence whereupon asthma symptoms are more prevalent in girls than in boys.[43,44] Possibly, the association between BMI and asthma symptoms changes during puberty and inflammatory proteins and sex hormones might be involved.[45] Recently, stronger correlations between BMI and waist circumference and the pro-inflammatory protein hs-CRP have been shown in adult females than in males.[46] The entrance of the PIAMA children to puberty would be an exquisite opportunity to study the role of sex hormones and markers of low systemic inflammation in the association between BMI and asthma symptoms.

Besides systemic inflammation, the direct mechanical effect of fat mass on lung volume is another suggested mechanism underlying the association between overweight and respiratory complaints in children. The direct effect of fat mass is by impeding the descent of the diaphragm or the expansion and excursion of the rib cage.[36] The strong association between BMI and asthma symptoms, in particular with dyspnea, at 4 and 8 years shown in the PIAMA study and the lack of prospective associations between BMI and asthma symptoms are in favor of such an explanation. At the children's age of 8 years we studied the associations between BMI and waist circumference and lung function. For lung function we used FEV_1, FVC and the ratio between those two, as a lower FEV_1/FVC ratio indicates possible obstruction of the airways. Previous studies in children showed higher lung function with higher BMI when examining the association between BMI and lung function assuming a linear relationship.[47-53] We investigated the lung function of children with a BMI or waist circumference >90th percentile and we did not find significant associations between large waist circumference or high BMI and lung function, except for a lower FEV_1/FVC ratio in girls with a large waist circumference. The lower FEV_1/FVC ratio may indicate that in girls with a large waist circumference the FEV_1 is affected more than the FVC, suggesting obstruction of the airways. We observed that lung function increased with increasing BMI or waist circumference as long as BMI and waist circumference

were in the 'normal' range (10-90th percentile). At the upper end of the waist circumference and BMI distribution, lung function no longer increased with increasing waist circumference (boys and girls) and BMI (girls only). These results suggest that FEV_1 and FVC start to level off at the upper end of the BMI and waist circumference distribution.

Whereas we did not observe lower lung function in children with a high BMI or large waist circumference, this association has been clearly observed in adults.[36,54,55] Lung function normally increases during childhood with growth, and at the end of adolescence lung function reaches a plateau.[56] We did not yet observe differences in lung function between overweight and normal weight 8-year-old children. However, lung function in these children is still increasing and it is unknown how lung function development is affected in children with persistent overweight. The duration of overweight may have consequences for the maximal plateau of lung function to be reached. The prolongation of the PIAMA study in 12- and 15-year-old children offers opportunities to investigate the development of the lung function in normal weight and overweight adolescents and to test the hypothesis of an association between long term overweight and lower lung function.

Other suggested mechanisms, besides systemic inflammation and a direct mechanical effect, for the association between BMI and asthma symptoms are insulin resistance, changes in immune function and a less physically active lifestyle.[57, 58] However, in the PIAMA study we did not find results confirming the hypothesis that asthmatic children are less physically active than non-asthmatic children.[59] Summarizing, the findings on respiratory health presented in this thesis suggest reduced respiratory health, mainly asthma symptoms, in overweight children, but we cannot explain this association with the additional information we collected on e.g. physical activity and inflammation.

Body mass index and waist circumference

BMI has been used as an indicator of adiposity in clinical and epidemiological settings for many years. BMI is a marker of total body mass, not distinguishing between lean and fat mass. Waist circumference has been suggested to be a better indicator of total fat mass. Waist circumference reflects abdominal fat mass and research in adults on the distribution of body fat has shown that a more central distribution of fat is associated with adverse outcomes, for example the metabolic syndrome. In a recent meta-analysis, including over 300,000 adults from 31 studies, waist circumference was more strongly than BMI associated with cardiovascular risk factors such as hypertension, type-2 diabetes mellitus, dyslipidemia, and the metabolic syndrome.[60] Another recent meta-analysis concluded that measures of abdominal adiposity, for example waist circumference, but not BMI, were related to an increased risk of cardiovascular disease mortality.[61]

It is reasonable to assume that also in children abdominal fat mass is more important to assess cardiovascular risk. However, this has not been convincingly shown yet.[1,2,62] In this thesis, in the assessment of the aspects of respiratory and cardiovascular health in relation to childhood overweight we took waist circumference into account and assessed the relative importance of waist circumference and BMI in relation to cardiovascular and respiratory health outcomes. The results on the association with cholesterol concentrations in 12-year-old children suggested that waist circumference was more important than BMI. With regard to lung function, we observed a lower FEV_1/FVC ratio in 8-year-old girls with a large waist circumference after adjustment for BMI, whereas no significant associations with BMI after adjustment for waist

circumference were found. In association with blood pressure we did not observe differences in the strengths of associations with BMI or with waist circumference.
In the studies presented in this thesis the data on weight, height and waist circumference were measured by professionals. However, epidemiologic studies usually rely on self-reported data in questionnaires and self-reported weight, height and waist circumference in adults are not always accurate.[63,64] Previous research in the PIAMA study and also other studies have shown that this is also true for parent-reported weight and height of children; resulting in an underestimation of overweight prevalence rates in children.[65-67] We studied whether obtaining children's waist circumference through questionnaires is feasible. We showed that, like for BMI, parents of children with a large waist circumference tended to underreport their child's waist circumference and parents of children with a small waist circumference tended to over report their child's waist circumference. The over reporting of small waist circumferences and height and low weight and the underreporting of large waist circumferences and high weight result in a smaller range of waist circumference and BMI. Due to the smaller range of waist circumference and BMI when reported by the parents, quantitative estimates of the effects of a high BMI or waist circumference on pertinent health outcomes may be somewhat biased when using parent-reported BMI or waist circumference. But still, in our study, the ranking of measured and parent-reported waist circumference corresponded well, indicating that parent-reported waist circumference, can be used to study associations between waist circumference and health outcomes. This also applied to BMI based on parent-reported weight and height.
The discussion on the importance of waist circumference in addition to BMI in relation to health outcomes has not been solved by this thesis, but some interesting elements have been identified, indicating that waist circumference is an important indicator of adiposity in the associations with health outcomes. That is for example that waist circumference is at least as strongly associated with cholesterol and blood pressure as BMI is. Furthermore, we have shown that obtaining data on children's waist circumference by questionnaire is feasible in epidemiologic studies.

Methodological considerations

In this section the design and strengths and limitations will be discussed that are relevant for all chapters in this thesis and typical for epidemiologic studies. Strengths and limitations regarding the specific measures in this thesis are discussed in the '*Discussion section*' of the specific chapters.

Study design

The PIAMA study is a prospective birth cohort study with repeated measurements. Such studies are designed to investigate the development of diseases during childhood and have several advantages compared with retrospective or cross-sectional studies. In a prospective study, data on several exposures are simultaneously collected prior to the development of the disease of interest. Consequently, the reporting of the exposure is not influenced by the presence of the disease. The probability of coincidental findings is diminished in longitudinal studies because of the repeated measurements. Because the measures of exposure and outcome variables are obtained repeatedly, the study of the development of diseases is possible. In the PIAMA study questionnaires were sent to the parents every year from birth of their child until their child's eighth anniversary, and again at ages 11 and 15 years.

Nonetheless, a longitudinal design may also have disadvantages. Studies with a longitudinal design are expensive and it takes a long waiting time before certain outcomes occur and before research questions can be answered. Meanwhile, the world is changing and questions that were relevant at the start of the study may have become less relevant at the time the data have been collected and are available for analyses. On the other hand, in prospective birth cohort studies, as in the PIAMA study, new insights may develop later on, and additional study questions may be incorporated when the study has been going on for several years. For instance, the PIAMA study was originally designed to study the natural history of childhood asthma and risk factors for the development of asthma and allergy. In this light a range of environmental, dietary and lifestyle factors were assessed. With the rising prevalence of childhood overweight and the availability of the lifestyle factors and anthropometric measures assessed in the questionnaires and during the medical examinations the study became more and more of interest for answering questions on childhood overweight and its sequelae as well. Therefore, in the PIAMA study aspects of childhood overweight have been extensively studied, although this was not in the original aims at the start of the birth cohort. With a broadening of the study to other endpoints, it was possible to choose the endpoints of interest, for example cholesterol concentrations in 8-year-olds, but information on some early determinants of these additional endpoints was unavailable, like maternal cholesterol concentrations. Additionally, the study question on the pro-inflammatory proteins as a mechanism possibly explaining the association between overweight and asthma symptoms, emerged later on during the follow-up, and at that time, blood samples were not available anymore for all children, resulting in small groups of children for the analyses. At present, research has shown that pregnancy is an important period for the development of the child. With the current knowledge it would have been most interesting to have obtained much more information on the pregnancy period. If new questions or insights like these arise, new birth cohort studies are of added value. A major strength of the PIAMA study in comparison with other Dutch birth cohort studies however, is the successful follow-up of the children up to age 15 with 11 waves of data collection at consecutive ages. Younger cohort studies may have more detailed data than PIAMA on, for example, prenatal development, but still have a long way to go before their participants reach early adolescence. Cooperation of birth cohorts at a national and international level is of added value to optimally use strengths of the specific cohorts.

Selective participation

The children participating in the PIAMA birth cohort study originated from the general population. Pregnant women were recruited from more than fifty prenatal clinics in different regions of the Netherlands.[68] In the PIAMA study the participation rate at the start of the study was approximately 50%. Selective participation may occur at the start of the study and during follow-up. As in many demanding studies, such as follow-up studies, relying on healthy volunteers, participants of the PIAMA study were not completely representative of the general population. To be more specific; twice as many children in the PIAMA study had highly educated parents, whereas half as many had a 'non' Dutch ethnic origin or parents who smoked compared with the general Dutch population.[69,70] This may have resulted in a more than average health-conscious study population.

During follow-up, children of lower educated parents were more likely to be lost to follow-up. Because of this selective participation, prevalences of health outcomes related to education level, ethnic origin or health consciousness based on this population may not apply to the ge-

neral population. However, the prevalence of overweight as observed in the PIAMA study corresponds well to the overweight prevalence as observed in children of the Dutch nationality in the 4th and 5th Dutch National Growth studies.[71,72] Irrespective of the prevalences based on the PIAMA study population, the associations reported in this thesis probably can be generalized to the general population, because no effect modification by maternal education level was observed in the reported associations. In this thesis we mainly used objective outcome measures, and it is not likely that associations between overweight and for instance, blood pressure, are different in children of low educated parents compared with children of high educated parents. The results presented in this thesis are not expected to be different in a different study population, although effect estimates might have been more pronounced in a study population with a higher prevalence of obesity.

Besides selective participation, selection due to non-random missingness of data is a problem that might arise in follow-up studies. Many variables of interest in this thesis were collected by professionals during medical examinations, but still a major part of the variables collected in the PIAMA study were obtained by parent report in questionnaires. In this thesis, these variables are mostly used as confounding variables. In questionnaires, non response to specific questionnaires and missing data on specific variables occur. Diverse reasons are imaginable: no time to fill in the (whole) questionnaire; not willing to answer delicate questions, for example, in the PIAMA study we have relatively often missing data on the BMI of the parents; or, in case of the child's weight and height, not having the necessary equipment available. Non-random missingness of data may bias estimated prevalences and effects.

Information bias

In case of the child's weight and height, we emphatically asked the parents to weigh and measure their child themselves at the moment of the filling in of the questionnaire in case they did not have recent written records of their child's weight and height measurement at the health centre. The questions on weight and height are sensitive to public norms and resulting socially desirable answers, which may result in misclassification of the children according to their weight and height. In Chapter 2 we compared the overweight classification based on BMI calculated from parent-measured and reported weight and height with the overweight classification according to BMI calculated from professionally measured weight and height. These figures showed that around 24% of the children that were overweight according to the BMI based on the measured values by professionals, were classified normal weight based on parent-report reported weight and height. In this study, weight was about 0.5kg underreported in the highest BMI quartile, based on measured weight and height. This absolute difference seems to represent a slight underestimation of weight in children, but has a strong effect on the prevalence estimation of childhood overweight.

Confounding

Confounding results in a spurious association between determinant and outcome. In all analyses, we included important confounders for which data were available. These were selected based on literature and influence of the confounding variable on the association between determinant and outcome. Although we were able to adjust for many potential confounders, thanks to the longitudinal design and the comprehensive datasets, a common difficulty in all epidemiologic studies is the impossibility to obtain information on all environmental and lifestyle related factors that could possibly confound the association studied. In our study, a large

number of potential confounding variables were available, but maternal education level and maternal pre-pregnancy BMI accounted for the greatest attenuation in most analyses. The influence of maternal education level was stronger on the associations between cholesterol and the parent-reported early-life determinants than on for example the association of BMI with blood pressure. This difference in effect size of the same confounder in different associations suggests that mainly the associations with lifestyle related, parent-reported exposures were subject to confounding. This is illustrated by the confounding effect of maternal education level on the association between pre-pregnancy maternal BMI and maternal smoking during pregnancy on the one hand and childhood cholesterol concentrations on the other hand, and the lack of a confounding effect by maternal education level on the association between rapid infant weight gain and childhood cholesterol concentrations in the same study population. Although we adjusted for the most important confounders, we cannot exclude some residual confounding.

Objective exposure and outcome measures

Objective anthropometric measures are preferred to self-reported data. These measures are obtained by trained professionals who are not inclined towards socially desirable results. Besides the training of the professionals, they use standardized equipment for the assessment of weight and height. However, epidemiologic research usually relies on data obtained from questionnaires. In the PIAMA study we sent the parents a measuring tape to measure their child's waist and hip circumference. They were instructed by a picture where to measure and by text how to perform the measurement. From the results described in Chapter 2 it is clear that waist circumference measured and reported by the parents yields usable data.

In the studies described in this thesis we used objective outcome measures like cholesterol concentrations, blood pressure and lung function. Opposing to the advantage of the objective measures are some disadvantages. First, study populations with data based on medical examinations usually are smaller than those with questionnaire data (See for more information on the PIAMA study the flow chart on page 12). These smaller study populations may result from the lack of money to examine all children. That situation would allow randomization of the study population. Mostly however, the children that participate in the medical examinations are children of a selection of willing parents resulting in a more health conscious study population. Thus more selective participation may occur in medical examinations than in questionnaires, thereby possibly affecting the generalisability of the results based on objective measures. Second, fewer repeated measurements are available for medical examination obtained data than for questionnaire obtained data. Third, related to the smaller number of time points of data collection, the group of children with measurements obtained in a medical examination at more than one time point is smaller than the group of children with repeated data from questionnaires. These last two elements may hinder the study of the development of the objective measures.

At the moment, the wave of data collection through parent and child questionnaires at the child's age of 15 years is going on. Additionally, data collection in a medical examination has been planned. The medical examination however, will challenge the researchers in motivating the early adolescents to participate in a new round. The abovementioned disadvantages of the use of measures collected during medical examinations should be aimed to be prevented. Ideally, all children still in the study at age 11 will participate so that development of respiratory and cardiovascular determinants into puberty can be studied.

Concluding remarks

In the studies with cardiovascular and respiratory outcomes we assessed the relative importance of waist circumference and BMI in these associations. We have not demonstrated that children's waist circumference is always more important than BMI in associations with health outcomes. However, we have several findings indicating that waist circumference is at least as strongly, and in case of specific aspects of cardiovascular health possibly more strongly, associated with adverse health outcomes than BMI is.

The prevalence of overweight in the childhood population is increasing and already in childhood being overweight has adverse consequences. In this thesis we studied a population with a relatively low prevalence of obesity (as compared with the prevalence in for instance the UK and USA). However, we observed higher blood pressure levels, more adverse cholesterol concentrations and more asthma symptoms in overweight than in normal weight children. Furthermore, in the 12-year-old children we observed similar blood pressure and cholesterol levels in normal weight children with and without a history of overweight. This suggests that the effects of overweight on blood pressure and cholesterol might be reversible. Though we did not study the reversibility of the effects of overweight on cardiovascular outcomes, still this is a promising observation.

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Summary

The prevalence of childhood overweight has risen rapidly over the past decades. Overweight in childhood usually develops at an early age and often persists into adulthood. Adult overweight is a strong risk factor for several chronic diseases, and adults with a history of childhood overweight might be at an even higher risk than adults who become overweight during adulthood. Cardiovascular risk factors have been shown to be present already in overweight children.
The prevalence of asthma has also increased at the end of the last century and overweight and asthma have been shown to be associated.
BMI is generally used as measure of adiposity in epidemiologic studies, but has recognized limitations. BMI reflects total body mass, including bone and muscle mass, whereas waist circumference may be a better indicator of fat mass. Additionally, abdominal fat mass may be more strongly related to health outcomes than total fat mass.
In this thesis we aimed to study aspects of respiratory and cardiovascular health in relation to childhood overweight. Additionally, we studied differences in associations using BMI or waist circumference as indicators of childhood overweight. This study was performed in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study. The PIAMA study is a prospective birth cohort study of Dutch children from the general population followed from birth to 8 years of age and again at the age of 12 years. At the ages of 4, 8 and 12 years medical examinations were performed, in which weight, height and waist circumference were measured and blood samples were collected. Lung function (age 8 and 12 years) and blood pressure (age 12 years) were measured as well.

Most epidemiologic studies rely on reported data on weight and height to define overweight. The prevalence of overweight tends to be underestimated based on self- or parent-reported weight and height. Waist circumference in adults is generally underreported by respondents. Whether this is true for children's waist circumference reported by their parents is not clear. Our data on measured weight, height and waist circumference enabled us to study the agreement between waist circumference measured and reported by parents and waist circumference measured by professionals in **Chapter 2**. Parents of children with a high BMI or waist circumference tended to underreport their child's weight and waist circumference, whereas parents of children with a low BMI or waist circumference tended to over report their child's weight, height and waist circumference. However, the ranking of the children according to the parent-reported waist circumference corresponded well with the ranking based on the measured values of the professionals, indicating that reported waist circumference may be used to study associations between waist circumference and risk factors or health outcomes.

In **Chapter 3** we aimed to identify early-life determinants of blood cholesterol concentrations in 8-year-old children. We studied a range of early-life determinants and found maternal prepregnancy overweight, maternal smoking during pregnancy and rapid infant weight gain to be associated with the ratio between total and HDL cholesterol at the child's age of 8 years. These associations were partly mediated by the child's BMI, indicating that the child's BMI at age 8 years played a role in the development of early-life risk to outcome.
Chapter 4 describes the associations between BMI at age 4 and pro-inflammatory proteins measured in blood at 4 years of age, and asthma symptoms at ages 4 to 8 years. We studied hs-CRP, C3 and C4 to get insight in the mechanism underlying the association between BMI and

asthma symptoms. We found a strong cross-sectional association between BMI and asthma symptoms, but not prospectively with asthma symptoms at ages 5 to 8 years. We did not find evidence for a role of the measured pro-inflammatory proteins in the association between BMI and asthma symptoms. The association between BMI and asthma symptoms might be explained by pro-inflammatory proteins other than those examined in our study, or a longer period of being overweight might be needed to reach a state of low grade systemic inflammation.

The aim of the study described in **Chapter 5** was to study the association between waist circumference and BMI on the one hand and lung function, measured as FEV_1 and FVC, on the other hand. We compared children with a high BMI or large waist circumference (>90th percentile), and children with a low BMI or small waist circumference (<10th percentile), with children with a BMI or waist circumference in the normal range (≥10th to ≤90th percentile). Girls with a low BMI, and to a smaller extent girls with a small waist circumference, had a lower lung function than girls with a 'normal' BMI or waist circumference. In girls with a large waist circumference, we observed a lower FEV_1/FVC ratio than in girls with a 'normal' waist circumference, suggesting obstruction of the airways. In boys, we did not observe associations between BMI or waist circumference and lung function.

Chapter 6 describes the associations between BMI and waist circumference on the one hand and blood pressure and blood cholesterol on the other hand measured in 12-year-old children. We compared the children with a high BMI or large waist circumference (>90th percentile) with children with a 'normal' BMI or waist circumference (≤90th percentile). In line with previous studies we found strong associations between a high BMI and systolic and diastolic blood pressure and cholesterol concentrations. We also found lower HDL cholesterol, and higher total cholesterol and higher systolic and diastolic blood pressure in children with large waist circumference. Furthermore, this study showed that normal weight children with a history of overweight were not at an increased risk of higher blood pressure levels and adverse cholesterol concentrations as compared to children who were overweight at both ages.

Finally, in **Chapter 7** we discuss the main findings of this thesis and methodological issues. We have not demonstrated that children's waist circumference is always more important than BMI in associations with health outcomes. However, we have several findings indicating that waist circumference is at least as strongly, in case of specific aspects of cardiovascular health possibly more strongly, associated with adverse health outcomes than BMI is. The prevalence of childhood overweight is increasing and already in childhood being overweight has adverse consequences. In this thesis we studied a population with a relatively low prevalence of obesity (as compared with the prevalence in for instance the UK and USA). However, we already observed higher blood pressure levels, more adverse cholesterol concentrations and more asthma symptoms in overweight than in normal weight children.

Samenvatting

In de laatste decennia is het aantal kinderen met overgewicht sterk gestegen. Overgewicht ontwikkelt zich meestal op jonge leeftijd en vaak leidt dit ook tot overgewicht in de volwassenheid. Overgewicht bij volwassenen is een sterke risicofactor voor verschillende chronische ziekten. Volwassenen die in hun kindertijd al overgewicht hadden, lopen wellicht een nog groter risico op gezondheidsproblemen dan volwassenen die pas later overgewicht krijgen. Het is aangetoond dat risicofactoren voor hartvaatziekten, zoals hoge bloeddruk, al aanwezig zijn bij kinderen met overgewicht.
Het aantal mensen met astma is ook sterk gestegen aan het eind van de vorige eeuw. Kinderen en volwassenen met overgewicht hebben vaker astma dan mensen met een normaal gewicht. De meest gebruikte maat om te bepalen of mensen overgewicht hebben is BMI (body mass index=gewicht(kg)/lengte(m)^2). Over de validiteit van BMI als indicator voor overgewicht wordt nog altijd gediscussieerd. Middelomtrek is geopperd als maat die overgewicht beter weergeeft. Daarnaast zijn er aanwijzingen dat buikvet sterker geassocieerd is met gezondheidsuitkomsten dan de totale vetmassa in het lichaam.
Het doel van dit proefschrift is de samenhang tussen luchtwegproblemen en risicofactoren voor hartvaatziekten, en overgewicht bij kinderen nader te onderzoeken. Daarnaast hebben we bestudeerd of middelomtrek belangrijker is dan BMI voor deze gezondheidsuitkomsten bij kinderen. Deze studie is uitgevoerd in de Preventie en Incidentie van Astma en Mijt Allergie (PIAMA) studie. De PIAMA studie volgt sinds 1996 een groot aantal Nederlandse kinderen vanaf hun geboorte. Totdat de kinderen acht jaar waren, hebben de ouders jaarlijks vragenlijsten ingevuld, en daarna opnieuw op elfjarige leeftijd. Gewicht, lengte en middelomtrek zijn gemeten tijdens medische onderzoeken toen de kinderen vier, acht en twaalf jaar oud waren. Tijdens deze onderzoeken is ook bloed verzameld en in dit bloed zijn cholesterolconcentraties en ontstekingsmarkers gemeten. De longfunctie is gemeten op acht- en twaalfjarige leeftijd en bloeddruk is alleen op twaalfjarige leeftijd gemeten. Voor de onderzoeken in dit proefschrift is deels gebruik gemaakt van gegevens uit de vragenlijsten, maar hoofdzakelijk van gegevens die voortkwamen uit de medische onderzoeken.

De meeste epidemiologische studies in dit veld zijn gebaseerd op door de ouders of volwassenen zelf gerapporteerde gegevens over gewicht en lengte om te bepalen of deelnemers overgewicht hebben. Op basis van gerapporteerde gegevens over gewicht en lengte door de deelnemers zelf of door de ouders in het geval van kinderen wordt het vóórkomen van overgewicht doorgaans onderschat: dikke mensen (en ouders van dikke kinderen) rapporteren meestal een wat lager gewicht dan zij in werkelijkheid hebben. Dikke volwassenen onderschatten in het algemeen ook hun eigen middelomtrek, maar het is niet duidelijk of dit ook geldt voor de door de ouders gerapporteerde middelomtrek van hun kind. In de PIAMA studie zijn gewicht, lengte en middelomtrek van de kinderen ook gemeten door onderzoeksmedewerkers. Daardoor hadden wij de mogelijkheid om te onderzoeken of de door ouders gemeten en gerapporteerde middelomtrek overeenkomt met de door onderzoeksmedewerkers gemeten middelomtrek (**Hoofdstuk 2**). Ouders van kinderen met een hoge BMI of een grote middelomtrek waren geneigd om het gewicht en de middelomtrek van hun kind te onderrapporteren, terwijl ouders van kinderen met een lage BMI of kleine middelomtrek juist geneigd waren om het gewicht, en de lengte en middelomtrek van hun kind te overschatten. De samenhang tussen de middelomtrek gemeten en gerapporteerd door de ouders en de

door de onderzoeksmedewerkers gemeten middelomtrek was sterk. Dit betekent dat waar de ouders een grote middelomtrek rapporteerden ook de onderzoeksmedewerkers een grote middelomtrek maten. Dit duidt aan dat middelomtrek gebruikt kan worden om verbanden tussen middelomtrek en risicofactoren en gezondheidsuitkomsten te bestuderen.

In studies bij volwassenen is aangetoond dat factoren vroeg in het leven van invloed kunnen zijn op cholesterolconcentraties bij volwassenen. Het doel van **hoofdstuk 3** is om pre- en postnatale determinanten van cholesterolconcentraties bij achtjarige kinderen te identificeren. We hebben verschillende mogelijke determinanten onderzocht en overgewicht van de moeder voor de zwangerschap, roken van de moeder tijdens de zwangerschap en snelle gewichtstoename in het eerste levensjaar van het kind waren geassocieerd met een hoge verhouding tussen totaal en HDL (high density lipoprotein) cholesterol op achtjarige leeftijd. Een hoge totale cholesterolconcentratie ten opzichte van een lage HDL cholesterolconcentratie is ongunstig. Deze verbanden worden gedeeltelijk verklaard doordat kinderen met deze determinanten vaker een hoge BMI hebben en een hoge BMI vaak samengaat met ongunstige cholesterolconcentraties.

Hoofdstuk 4 beschrijft de verbanden tussen BMI op vierjarige leeftijd en ontstekingseiwitten gemeten op vierjarige leeftijd, en astmasymptomen van vier tot en met acht jaar. We hebben in bloedmonsters de ontstekingseiwitten hs-CRP, C3 en C4 bestudeerd om inzicht te krijgen in het mechanisme van het verband tussen BMI en astmasymptomen. We vonden een sterk cross-sectioneel verband van BMI met astmasymptomen, maar geen prospectieve verbanden met astmasymptomen op vijf- tot en met achtjarige leeftijd. We vonden geen aanwijzingen dat deze ontstekingseiwitten een rol spelen in het verband tussen BMI en astmasymptomen. Mogelijk wordt dit verband verklaard door andere ontstekingseiwitten dan die wij onderzocht hebben, of wellicht is er een langere tijd van overgewicht nodig om ontstekingsreacties in het lichaam te laten ontstaan.

In **hoofdstuk 5** beschrijven we het verband tussen middelomtrek en BMI enerzijds en longfunctie, gemeten als FEV_1 (forced expiratory volume in 1 second) en FVC (forced vital capacity), anderzijds. De FEV_1 en de FVC worden gemeten tijdens geforceerde uitademing na maximale inademing. De FEV_1 is de hoeveelheid lucht die de eerste seconde van de uitademing uitgeblazen wordt en de FVC is de totale hoeveelheid lucht die dan uitgeblazen wordt. We vergeleken kinderen met een hoge BMI of een grote middelomtrek (hoogste 10 procent), en kinderen met een lage BMI of kleine middelomtrek (laagste 10 procent), met kinderen met een BMI of middelomtrek in de normale range (de 80 procent ertussenin). Meisjes met een lage BMI, en in mindere mate meisjes met een kleine middelomtrek, hadden een lagere longfunctie dan meisjes met een 'normale' BMI of middelomtrek. Bij meisjes met een grote middelomtrek vonden we een lagere FEV_1/FVC ratio, dan bij meisjes met een 'normale' middelomtrek, hetgeen kan wijzen op obstructie van de luchtwegen. Door obstructie kunnen kinderen eerder benauwd raken. Bij jongens vonden we geen verband tussen BMI of middelomtrek en longfunctie.

Hoofdstuk 6 beschrijft de verbanden tussen middelomtrek en BMI enerzijds en bloeddruk en cholesterol anderzijds, gemeten bij twaalfjarige kinderen. We vergeleken nu de kinderen met een hoge BMI of grote middelomtrek (hoogste 10 procent) met kinderen met een 'normale' BMI of middelomtrek (de andere 90 procent). Zoals andere studies ook vaststelden vonden we

een hogere systolische en diastolische bloeddruk bij kinderen met een hoge BMI. We vonden ook meer ongunstige cholesterolconcentraties bij deze kinderen. Bij kinderen met een grote middelomtrek vonden we ook lagere HDL cholesterolconcentraties, en hogere totale cholesterolconcentraties en hogere systolische en diastolische bloeddruk. Daarnaast laat deze studie zien dat kinderen met een normaal gewicht die eerder in hun leven overgewicht hadden, geen verhoogd risico hebben op hogere bloeddrukniveaus en ongunstige cholesterolconcentraties.

Tot slot bediscussiëren we in **hoofdstuk 7** de belangrijkste bevindingen van dit proefschrift en enkele methodologische kwesties. In de verschillende studies hebben we niet aangetoond dat bij kinderen middelomtrek altijd belangrijker is dan BMI in verbanden met gezondheidsuitkomsten. We hebben wel een aantal bevindingen die er op wijzen dat middelomtrek minstens even sterk, en voor sommige aspecten van cardiovasculaire gezondheid mogelijk sterker, geassocieerd is met ongunstige gezondheidsuitkomsten dan BMI. Overgewicht komt steeds meer voor bij kinderen en al in de kindertijd heeft overgewicht nadelige gevolgen. In dit proefschrift toonden we, in een relatief gezonde groep kinderen, een hogere bloeddruk, meer ongunstige cholesterolconcentraties en vaker astmasymptomen aan bij kinderen met overgewicht dan bij kinderen met een gezond gewicht.

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Marga

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Marga Bekkers was born on October 20th 1982 in Eindhoven, the Netherlands. In 2001 she completed secondary school at Gymnasium Beekvliet in Sint-Michielsgestel. In the same year she started her study medicine at the Radboud University Nijmegen. Due to an increased interest in research and the prevention of diseases rather than the curative site she discontinued her medical studies and started her study Nutrition and Health in Wageningen in 2003. In 2008 she graduated with a major in Epidemiology and Public Health. As part of her study, she spent 4 months at the Institute of Environmental Medicine at the Karolinska Institutet in Stockholm, Sweden. In July 2008 she started the work described in this thesis at the Institute for Risk Assessment Sciences at Utrecht University. She was based at the Centre for Prevention and Health Services Research at the National Institute for Public Health and the Environment (RIVM). In 2012 she continues working at the RIVM, on the subject of work and health.

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