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PEDIATRIC ORIGINAL ARTICLE

Overweight patterns throughout childhood and cardiometabolic markers in early adolescence

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BACKGROUND: Risk of cardiovascular and metabolic disease is higher in adults who were relatively thin at birth and had subsequent accelerated weight gain. This specific pattern of weight gain may relate to unfavorable cardiometabolic markers already in childhood. We prospectively assessed whether children with different patterns of overweight development from age 3 months to 11 years had distinct levels of cardiometabolic markers at age 12 years.

SUBJECTS/METHODS: We used data of 1500 children participating in the PIAMA birth cohort that started in 1996/1997. Parents reported height and weight during 10 waves of follow-up from age 3 months to 11 years. Four distinct overweight development patterns were derived using longitudinal latent class analysis; 'never'; 'early transient'; 'gradually developing' and 'persistent' overweight. Cardiometabolic markers (total-to-high-density lipoprotein cholesterol (TC/HDLC) ratio, blood pressure (BP), glycated hemoglobin (HbA1c)) were assessed at age 12 years in 1500 children.

RESULTS: Children who developed overweight gradually and children with persistent overweight throughout childhood, at age 12 years had a 2–3-fold higher risk of having high (>90th centile) TC/HDLC ratio, systolic and diastolic BP, compared with children who were never overweight. In children who gradually developed overweight, TC/HDLC ratio was 0.75 higher (95% confidence interval (CI) 0.54–0.96); systolic BP 4.90 mmHg higher (95% CI 2.45–7.36) and diastolic BP 1.78 mmHg higher (95% CI 0.07–3.49) than in children who never had overweight. Estimates for children with persistent overweight were similar.

CONCLUSIONS: Children with gradually developing overweight, and those with persistent overweight had unfavorable cholesterol and blood pressure levels already at age 12 years, whereas children with early transient overweight avoided these unfavorable outcomes. Our results support the hypothesis that specific overweight patterns predispose to an adverse cardiometabolic profile, which is already apparent in early adolescence before progressing to adult cardiometabolic disease.

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INTRODUCTION

Adults with coronary heart disease and diabetes more often experienced a specific pattern of weight gain, characterized by relative thinness at birth and subsequent accelerated weight gain during childhood, than adults who do not develop these diseases.[1–5] The observed association between growth in early life and disease many decades later raises the question whether this increased cardiometabolic risk already builds-up during childhood and adolescence. Prospective studies showed that children with accelerated weight gain have higher levels of cardiometabolic markers, such as blood pressure (BP) and cholesterol, than those who follow normal curves.[6,7] However, most of these studies focused on weight gain in infancy or in other specific periods and lacked repeated assessment of weight status with small time-intervals throughout childhood. A better understanding of how patterns of overweight in childhood contribute to an unfavorable cardiometabolic profile will help to determine which stages of childhood are crucial for overweight prevention.[8,7]

An important strength of the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is the availability of 10 assessments of body mass index (BMI) between birth and 11 years of age, and measurements of multiple cardiometabolic markers; cholesterol, BP and glycated hemoglobin (HbA1c) at age 12 years. In a previous study using data from this cohort,[9] we showed that four different patterns of overweight development exist from 3 months to 11 years. In the current study, we examined whether children following these patterns had distinct levels of cardiometabolic markers at age 12 years.

SUBJECTS AND METHODS

Study participants

We used the data from a population-based ongoing Dutch birth cohort study: the PIAMA study, with prenatal inclusion of 3963 children in 1996/1997. A detailed description of the study design was published previously.[10] At age 11 years, 3541 children (89%) were still in the study. At age 12 years, 3202 children were invited to a clinical assessment, and 1511 of them were willing to participate (response rate 47%). The study population for the current study consisted of 1500 children of whom data were available for at least four observations of BMI between the ages of 3 months to 11 years, and for any of the cardiometabolic markers at age 12 years. The study protocol was approved by the medical ethics

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committees of the participating institutes. All parents gave written informed consent for the general study and separately for the clinical assessment; in addition, children themselves gave written informed consent for the clinical assessment.

Assessment of childhood BMI between birth and 11 years

Parents reported child's height (in cm) and weight (in kg) at the age of 3 months, annually from age 1 to 8 years, and again at 11 years. Parents were asked to report child's weight and height measured by a medical professional during the regular scheduled visits to a youth health center, if this measurement was within the last 3 months. Otherwise parents were asked to measure child's weight and height themselves without shoes and heavy clothes. BMI was calculated as weight/height^2, and percentiles were calculated according to national growth curves, derived from the National Growth Study.[11] A child was considered overweight when BMI for age and sex was above the 90th percentile of the reference population. Previously we reported on the validity of self-reported versus measured height and weight, and found that BMI reported by the parents underestimates the absolute prevalence of overweight. As the difference between self-reported and measured BMI was systematic, the use of parental-reported height and weight is a valid method for identifying children in the highest decile for BMI.[12,13]

Patterns of overweight development

We previously used, longitudinal latent class analysis (LLCA) to identify patterns of overweight development from age 3 months to 11 years.[9] These patterns were included as independent variables in the current study. Four overweight patterns were derived from 90% of the population at baseline (3550/3963): never overweight, early transient overweight, gradually developing overweight and persistent overweight. Each pattern describes the risk of being overweight (that is, BMI $>$90th percentile) from the age of 3 months to 11 years. The patterns represent typical patterns of overweight development that exist in the population. They do not represent distinct groups of individual children: rather, individual children have a certain probability of belonging to each of the four patterns (posterior membership probabilities). The never-overweight pattern is characterized by a low probability of being overweight ($<5\%$) at every age (Supplementary Figure 1). The early transient overweight pattern is characterized by a relatively high probability (around 45%) of being overweight at age 3 months, followed by a decrease from age 2 years onwards, and reaching a probability near 0% around the age of 7 years. The gradually developing overweight pattern is characterized by a 10% probability of being overweight at age 3 months, gradually increasing to around 70% at the age of 11 years. The persistent overweight pattern is characterized by an already high (40%) probability of being overweight early in life that reaches a peak (about 80%) around the age of 7 years (see Supplementary Text S1 for further description of the overweight patterns).

Assessment of cardiometabolic markers at age 12 years

Clinical assessments around age 12 years (range 12–14 years) were performed by trained staff during home visits. Systolic and diastolic BP were measured according to the recommendations of the American Heart Association Council on High Blood Pressure Research.[14] BP readings were obtained from the non-dominant upper arm using an Omron M6 monitor while the child was seated. The first measurement was taken after $\geqslant$5 min of rest, without talking. Depending on arm circumference, 17–22 or 22–32 cm cuffs were used. BP was measured at least twice with 5 min intervals. If two consecutive measures differed by $>$5 mmHg, a third measurement was taken. The means of (2 or 3) systolic and diastolic measurements were used in analyses.

Blood was drawn for measurement of cholesterol and HbA1c. Serum total and high-density lipoprotein (HDL) cholesterol were determined enzymatically using Roche automated clinical chemistry analyzers (Roche Diagnostics, Indianapolis, IN, USA). The ratio between total and HDL cholesterol was calculated (TC/HDLC ratio). For analysis of HbA1c, erythrocytes from blood samples were stored, a 5-µl cell mass was lysated and HbA1c was measured by ion-exchange chromatography using the Adams A1c, HA-8160 HPLC Auto analyser (Menarini Diagnostics Benelux, Valkenswaard, The Netherlands). This analyzer was standardized on Diabetes Control and Complications Trial (DCCT) standards.

Characteristics of the study population

Characteristics that were used to describe the study population were child's sex, ethnicity, age, pubertal development, overweight, waist circumference, waist-to-height ratio, maternal weight gain during pregnancy, preterm birth, birth weight, breastfeeding, exposure to in-utero smoking and to second-hand smoking, maternal and paternal education and parental BMI. Child's weight, height and waist circumference were measured during the clinical assessment at age 12 years. Waist-to-height ratio and BMI for age and sex were calculated and overweight (including obesity) was defined based on international cutoff points.[15] Preterm birth was defined as gestational age $<$37 weeks. Breastfeeding was categorized as no breastfeeding, $\leqslant$16 weeks and $>$16 weeks. Ethnicity was based on country of birth of the child's parents, and was categorized as Dutch, Non-Dutch western and nonwestern. Mother's and father's educational levels were categorized as low (primary school, lower vocational or lower secondary education), intermediate (intermediate vocational education or intermediate/higher secondary education) and high (higher vocational education and university). Maternal smoking during pregnancy was defined as smoking during at least 4 weeks after onset of pregnancy. Exposure to second-hand smoking at home was defined as smoking within the child's home once a week or more. Mother's and father's BMI were calculated from reported weight and height and categorized as overweight (BMI $\geqslant$25 kg m^{-2}) or not overweight (BMI $<$25 kg m^{-2}). Pubertal development (Pubertal Development Scale; 1–4)[16] was reported by the child at age 11 years and used as a continuous variable in the analysis.

Statistical analyses

In order to describe children of the total study population and in each of the patterns separately we computed frequencies and means, weighted according to children's probability of belonging to each pattern. We examined the association of overweight patterns with cardiometabolic markers in two ways. First, we applied multiple linear regression analysis for each cardiometabolic marker separately, treating the never overweight pattern as reference. Posterior probabilities for three patterns (excluding the never-overweight pattern) were included as independent variables in the regression models. Second, besides the analysis with cardiometabolic markers as continuous outcome variables, we investigated associations of overweight patterns with the risk of having unfavorable levels of cardiometabolic markers. Using Poisson regression with robust error variance we estimated relative risks (RRs) of having unfavorable levels of cardiometabolic markers. We used $>$90th percentile ($<$10th percentile for HDLC) as cutoff value to indicate unfavorable levels. Cutoffs were: TC $>$4.9 mmol l^{-1}; HDLC $<$1.0 mmol l^{-1}; TC/HDLC ratio $>$4.2; systolic BP $>$127 mmHg; diastolic BP $>$75 mmHg; and HbA1c $>$35.5 mmol mol^{-1}. We assessed clustering of cardiometabolic markers to define children with the metabolic syndrome phenotype, as described and applied in previous studies.[17–19] We estimated RRs of having clustering of cardiometabolic markers; two or more of unfavorable cholesterol (TC, HDLC or TC/HDLC ratio); BP (systolic or diastolic BP); or HbA1c.

Factors that differed between overweight patterns (see Table 1) were examined for their role as potential confounders. The confounders included in the statistical analysis were sex, ethnicity, maternal and paternal education. We selected these confounders based on prior knowledge and their associations ($P<0.20$) with the outcome of interest or a change in effect estimate of more than 10%. Analyses with blood pressure were additionally adjusted for cuff size.

Overweight may cluster within families due to shared familial factors (genetics and environment). In addition, maternal overweight during pregnancy may predispose the child for overweight by intrauterine programming of the child's endocrine system.[20,21] Maternal prepregnancy BMI captures all of these aspects in one variable; therefore, we additionally adjusted for this variable in separate regression models. Sex has been shown to affect cardiovascular risk.[22,23] We therefore included interaction terms between sex and overweight pattern in the regression models to estimate associations between overweight patterns and cardiometabolic markers for boys and girls separately.

Childhood overweight is linked to earlier pubertal development in girls,[24] and possibly in boys,[25] and pubertal development affects levels of cardiometabolic markers.[24] We therefore considered pubertal development a potential mediator, hypothesizing that the gradually developing and persistent overweight patterns would be associated with advanced pubertal development at age 11 years, and that associations between these overweight patterns and cardiometabolic markers could be partly mediated by more advanced pubertal development. We investigated this in a sensitivity analysis by conducting path analysis (CALIS procedure

Table 1. Characteristics of the total study population and for each of the overweight patterns

	Total study population (n = 1500)		*Never-overweight pattern (n = 1220)*[a] *Weighted mean (s.d.) or weighted % (s.e.)*	*Early transient overweight pattern (n = 130)*[a] *Weighted mean (s.d.) or weighted % (s.e.)*	*Gradually increasing overweight pattern (n = 95)*[a] *Weighted mean (s.d.) or weighted % (s.e.)*	*Persistent overweight pattern (n = 55)*[a] *Weighted mean (s.d.) or weighted % (s.e.)*
	n/N	*Mean (s.d.) or %*				
Characteristics in childhood						
Boy (%)	734/1500	48.9	48.1 (1.4)	49.2 (3.2)	56.6 (3.7)	48.7 (6.0)
Firstborn (%)	778/1500	51.9	52.9 (1.4)	50.7 (3.2)	47.7 (3.8)	42.3 (5.9)
Preterm birth (< 37 weeks, %)	67/1498	4.5	4.7 (0.6)	3.7 (1.2)	5.2 (1.8)	0.8 (0.4)
Birth weight (kg)	1498	3532.3 (526.4)	3487.1 (463.0)	3670.8 (162.2)	3640.8 (151.2)	3848.9 (72.3)
No breastfeeding (%)	218/1497	14.6	13.4 (1.0)	18.0 (2.6)	21.5 (3.2)	14.3 (4.0)
Breastfeeding for more than 16 weeks (%)	595/1497	39.8	40.9 (1.4)	37.3 (3.1)	32.7 (3.5)	38.3 (5.8)
Maternal weight gain during pregnancy (kg)	1458	13.6 (4.8)	13.4 (4.2)	14.0 (1.6)	13.9 (1.4)	14.6 (1.1)
Maternal age at child's birth (years)	1485	31.3 (3.7)	31.3 (3.3)	31.4 (1.2)	31.3 (1.0)	31.9 (0.7)
Low maternal education (%)	261/1498	17.4	17.1 (1.1)	15.8 (2.3)	22.7 (3.2)	17.3 (4.5)
High maternal education (%)	618/1498	41.3	41.7 (1.4)	43.3 (3.2)	33.8 (3.5)	41.7 (5.9)
Low paternal education (%)	307/1488	20.6	20.1 (1.1)	17.9 (2.5)	27.9 (3.5)	24.4 (5.1)
High paternal education (%)	692/1488	46.5	48.8 (1.4)	43.9 (3.2)	30.4 (3.4)	39.9 (5.9)
Non-Dutch western ethnicity (%)	52/1479	3.5	3.4 (0.5)	5.7 (1.6)	2.0 (1.0)	4.0 (2.5)
Nonwestern ethnicity (%)	68/1479	4.6	4.5 (0.6)	5.1 (1.4)	5.6 (1.8)	2.8 (1.8)
Exposure to intrauterine smoking the first 4 weeks of pregnancy or longer (%)	212/1491	14.2	14.4 (1.0)	10.9 (1.9)	19.5 (3.1)	9.5 (3.3)
Exposure to second-hand smoking at home, age 11 (%)	162/1462	11.1	10.4 (0.9)	8.1 (1.7)	18.2 (3.1)	19.3 (4.8)
Maternal overweight before pregnancy (%)	250/1407	17.8	15.4 (1.1)	15.8 (2.5)	33.5 (3.8)	39.9 (6.2)
Maternal overweight child's age 1 (%)	324/1425	22.7	19.4 (1.1)	23.8 (2.9)	40.6 (3.9)	51.9 (6.1)
Maternal overweight child's age 8 (%)	445/1433	31.1	28.3 (1.3)	26.8 (3.0)	50.5 (3.9)	61.9 (5.9)
Paternal overweight child's age 8 (%)	671/1382	48.6	45.0 (1.5)	46.9 (3.4)	72.8 (3.4)	80.8 (4.8)
Age at clinical assessment (years)	1500	12.7 (0.4)	12.7 (0.3)	12.7 (0.1)	12.6 (0.1)	12.6 (0.1)
Pubertal Development Scale (1–4)	1456	1.5 (0.5)	1.5 (0.5)	1.5 (0.2)	1.7 (0.2)	1.6 (0.1)
Adiposity at age 12 years						
Overweight/obesity (%)	184/1497	12.3	5.8 (0.6)	5.1 (1.2)	59.5 (3.5)	68.1 (5.4)
Waist circumference (cm)	1494	66.4 (6.6)	65.0 (4.7)	66.6 (1.6)	75.2 (2.5)	76.4 (1.5)
Waist-to-height ratio	1494	0.4 (0.0)	0.4 (0.0)	0.4 (0.0)	0.5 (0.0)	0.5 (0.0)
Cardiometabolic markers at age 12 years						
Total cholesterol (mmol l^{-1})	1276	4.1 (0.6)	4.0 (0.6)	4.1 (0.2)	4.1 (0.2)	4.1 (0.1)
HDL cholesterol (mmol l^{-1})	1275	1.4 (0.3)	1.4 (0.3)	1.4 (0.1)	1.2 (0.1)	1.2 (0.1)
TC/HDLC ratio	1275	3.1 (0.8)	3.1 (0.7)	3.0 (0.2)	3.6 (0.3)	3.6 (0.2)
Systolic blood pressure (mmHg)	1460	115.1 (9.5)	115.0 (8.4)	114.5 (2.9)	115.8 (2.7)	116.3 (2.0)
Diastolic blood pressure (mmHg)	1460	66.7 (6.5)	66.6 (5.7)	66.3 (2.1)	66.9 (1.9)	68.4 (1.4)
HbA1c (mmol mol^{-1})	1261	32.4 (2.6)	32.4 (2.3)	32.4 (0.8)	32.4 (0.8)	32.3 (0.5)

Abbreviations: HbA1c, glycated hemoglobin; TC/HDLC, total-to-high-density lipoprotein cholesterol. [a]Based on children's highest posterior probability.

in SAS) using covariance matrices and the maximum-likelihood estimation method. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Based on pattern of the highest posterior probability, 81% of the total study population (1220/1500) belonged to the never-overweight pattern; 9% ($n = 130$) to the early transient overweight pattern; 6% ($n = 95$) to the gradually developing overweight pattern; and 4% ($n = 55$) to the persistent overweight pattern. The current prevalence of overweight at age 12 years was 12.3% in the total study population (Table 1). The prevalence of overweight at age 12 years was similar in the never-overweight pattern and the early transient overweight pattern (5.8% and 5.1%, respectively), and it was highest in the persistent overweight pattern (68.1%). Children in the gradually developing overweight pattern more often had lower educated parents, were more often boys, exposed to intra-uterine smoking, and of non-western ethnicity compared with those in the never-overweight pattern. Children in the persistent overweight pattern had the highest prevalence of parental overweight compared with those in the never-overweight pattern.

The levels of cardiometabolic markers in the early transient overweight pattern were similar to those in the never-overweight pattern (Table 2). In contrast, in both the gradually developing and persistent overweight patterns, levels of HDLC were lower, TC/HDLC ratios were higher and levels of systolic BP were higher than in the never-overweight pattern (Table 2). In the gradually developing overweight pattern, TC was 0.21 mmol l^{-1} higher (95% confidence interval (CI) 0.03; 0.39), HDLC was 0.21 mmol l^{-1} lower (95% CI −0.30; −0.13); TC/HDLC ratio 0.75 higher (95% CI 0.54; 0.96); systolic BP 4.90 mmHg higher (95% CI 2.45; 7.36) and diastolic BP 1.78 mmHg higher (95% CI 0.07; 3.49) than in the never-overweight pattern. Estimates for the persistent overweight pattern were similar to those for the gradually developing overweight pattern. HbA1c was similar in all of the overweight patterns.

Besides mean differences of absolute levels of cardiometabolic markers between patterns, we estimated RRs of having unfavorable levels of cardiometabolic markers. In both the gradually developing and persistent overweight patterns, RRs of unfavorable levels of HDLC, TC, TC/HDLC ratio, systolic and diastolic BP were increased and ranged between 2.04 and 3.32 (Table 3). The RR for clustering of two or more cardiometabolic markers was elevated in the gradually developing overweight pattern (RR 2.34 (95% CI 1.16–4.73)), and was increased but not statistically significant in the persistent overweight pattern (RR 1.96 (95% CI 0.82–4.66)).

Point estimates were somewhat larger in boys than in girls, although there was overlap of the 95% CIs for most cardiometabolic markers (Table 4). When we additionally adjusted for maternal prepregnancy BMI, associations remained statistically significant (Supplementaty Table 1). Children in the gradually developing and persistent overweight patterns had advanced pubertal development compared with those in the never-overweight pattern, but this mediated the associations with TC, HDLC, systolic and diastolic BP only slightly (Supplementary Table 2).

DISCUSSION

In our prospective study of 1500 children, we observed that already in early adolescence cardiometabolic profiles are unfavorable in children who develop overweight across childhood and in children with persistent overweight, compared with never-overweight children. These children had a 2–3-fold higher risk of being in the upper 10th percentile of TC/HDLC ratio and of systolic or diastolic BP. In children whose overweight gradually diminished in their preschool years, cardiometabolic profiles at

Table 2. Differences[a] in levels of cardiometabolic markers of three overweight patterns compared with a never-overweight pattern

	Never-overweight pattern *Absolute level (reference)*	*Early transient overweight pattern*		*Gradually developing overweight pattern*		*Persistent overweight pattern*	
		Difference[b]	P	*Difference*[b]	P	*Difference*[b]	P
Total cholesterol (mmol l^{-1})	4.4	0.01 (−0.13; 0.16)	0.86	**0.21 (0.03; 0.39)**	**0.02**	0.06 (−0.15; 0.27)	0.56
HDL cholesterol (mmol l^{-1})	1.5	0.05 (−0.02; 0.12)	0.14	**−0.21 (−0.30; −0.13)**	**< 0.0001**	**−0.17 (−0.26; −0.08)**	**< 0.001**
TC/HDLC ratio	3.0	−0.12 (−0.29; 0.06)	0.20	**0.75 (0.54; 0.96)**	**< 0.0001**	**0.55 (0.30; 0.79)**	**< 0.0001**
Systolic blood pressure (mmHg)[c]	118.9	−0.11 (−2.11; 1.88)	0.91	**4.90 (2.45; 7.36)**	**< 0.0001**	**4.30 (1.51; 7.09)**	**< 0.01**
Diastolic blood pressure (mmHg)[c]	69.3	−0.30 (−1.69; 1.09)	0.67	**1.78 (0.07; 3.49)**	**0.04**	**3.41 (1.46; 5.35)**	**< 0.01**
HbA1c (mmol mol^{-1})	33.1	−0.07 (−0.66; 0.52)	0.82	−0.21 (−0.93; 0.50)	0.56	−0.11 (−0.93; 0.72)	0.80

[a]Adjusted for sex, ethnicity, maternal education and paternal education, [b]Regression coefficients (95% confidence intervals) of the mean level of the cardiometabolic marker in each of the overweight patterns versus the mean level in the never-overweight pattern. [c]Additionally adjusted for cuff size. Associations with a significance level of $P < 0.05$ are boldfaced.

Table 3. Relative risks[a] of having high[b] (>90th centile) cardiometabolic markers for three overweight patterns compared with a never-overweight pattern

	Never-overweight pattern	*Early transient overweight pattern*	*Gradually developing overweight pattern*	*Persistent overweight pattern*
		RR (95% CI)	*RR (95% CI)*	*RR (95% CI)*
High total cholesterol	Ref.	1.15 (0.54–2.44)	**2.04 (1.02–4.09)**	0.93 (0.32–2.70)
Low HDL cholesterol (<10th centile)	Ref.	0.88 (0.42–1.86)	**2.58 (1.53–4.35)**	1.59 (0.71–3.56)
High total/HDL cholesterol ratio	Ref.	0.49 (0.17–1.35)	**3.32 (2.01–5.48)**	**2.85 (1.53–5.33)**
High systolic blood pressure[c]	Ref.	0.80 (0.38–1.71)	**3.16 (1.47–6.79)**	2.18 (0.85–5.62)
High diastolic blood pressure[c]	Ref.	0.58 (0.24–1.43)	1.99 (0.87–4.57)	**2.97 (1.42–6.21)**
High HbA1c	Ref.	1.05 (0.56–1.97)	1.11 (0.53–2.35)	0.87 (0.34–2.23)
Clustering of two or more cardiometabolic markers with high levels[d]	Ref.	0.66 (0.24–1.85)	**2.34 (1.16–4.73)**	1.96 (0.82–4.66)

[a]Adjusted for sex, ethnicity, maternal education and paternal education. [b]Cutoffs for >90th percentile (for HDLC <10th percentile) were as follows: TC >4.9 mmol l^{-1}; HDLC <1.0 mmol l^{-1}; TC/HDLC ratio >4.2; systolic BP >127 mmHg; diastolic BP >75 mmHg; and HbA1c >35.5 mmol mol^{-1}. [c]Additionally adjusted for cuff size. [d]Having two or more of HDLC <10th centile or TC >90th centile or TC/HDLC ratio >90th centile; systolic or diastolic BP >90th centile; and HbA1c >90th centile. Associations with a significance level of $P < 0.05$ are boldfaced.

age 12 years were comparable to those in children who never had overweight.

Our findings extend evidence from retrospective studies showing that adults with diabetes and cardiovascular disease more often have accelerated weight gain during childhood and suggest that an unfavorable cardiometabolic profile already builds-up during childhood. The pattern of gradually developing overweight reflects accelerated weight gain after being relatively thin in infancy. It is remarkable that children with this pattern had levels of cardiometabolic markers at age 12 years as high as for children with persistent overweight. As a potential mechanism to explain the increased cardiometabolic risk in individuals with early accelerated weight gain Barker[1] suggested that relative thinness at birth is associated with persistent reductions in muscle mass, and that subsequent accelerated weight gain may lead to a disproportionately high fat mass in relation to muscle mass. It has also been suggested that growth acceleration in childhood programs abnormal vascularization and endothelial dysfunction, signs of early atherosclerosis.[26] Singhal and Lucas called this the 'growth acceleration hypothesis' and stated that the adverse effects may not be exclusive to the infancy period or any specific time window.[26]

Three previous studies used a data-driven approach, such as LLCA, to identify distinct patterns of (over)weight development in the pediatric population and related these to cardiometabolic markers. Their findings were similar to ours, in that, in addition to persistent overweight, a pattern of gradually developing overweight was associated with higher BP at age 18 years,[27] insulin resistance at age 14 years[22] and multiple cardiometabolic markers in girls at age 15 years.[28] Extending previous findings, our study showed that unfavorable cardiometabolic markers were already present at the age of 12 years, and that there was clustering of cardiometabolic markers especially in children who gradually developed overweight. Our results also show that the cardiometabolic profile for those with early transient overweight is similar to those who were never overweight, as was previously observed for systolic BP[27] and insulin resistance[22] in adolescents. This is important because it may point toward potential benefits of interventions aimed at limiting excessive weight gain in children who start life with a relatively high BMI.

High birth weight is a strong risk factor for overweight later in childhood, but heavy infants are not necessarily predestined to become overweight children. In a substantial proportion (around 70%) of the heavier infants in our study population, overweight gradually diminished before the age of 7 years. These children, following the early transient overweight pattern, had levels of cardiometabolic markers at age 12 years that were similar to the levels of children who were never overweight. At the same time, low overweight risk in infancy is no guarantee that this risk will remain low throughout childhood. In a subgroup of children without overweight in infancy, overweight risk started to rise in the first year of life and continued to rise throughout childhood. These children, following the gradually developing overweight pattern, had similarly unfavorable cardiometabolic profiles at age 12 years as children with persistent overweight throughout childhood. Remarkably, the direction in which overweight risk will develop (that is, decreasing or increasing) seems to be established already in the first years of life, making this a particularly sensitive period for strategies aiming to prevent excessive weight gain and related unfavorable cardiometabolic markers.

Strengths of the study are the longitudinal design with 10 repeated assessments of height and weight, the large sample size and the availability of measurements of multiple cardiometabolic markers. We investigated the potential role of accelerated pubertal development by conducting a mediation analysis. A potential limitation may be that we cannot extend our results throughout young adulthood yet. Our study was restricted to children who had attended a clinical assessment at age 12 years. The prevalence of overweight in these children (12.3%) was similar to the Dutch countrywide prevalence among 13-year olds in 2009 (boys 12.0%, girls 12.5%).[29] Children with a lower socioeconomic position (as reflected by lower parental education) were underrepresented in the current study population, compared with the total study population. This implies that the gradually developing and persistent overweight patterns, which were more prevalent among children with parents of lower socioeconomic position, are likely to be even more prevalent in the general population than in our study. However, although socioeconomic disadvantage is strongly associated with adult cardiovascular disease, associations of overweight trajectories with cardiometabolic markers may be assumed to be in the same direction for children of lower or higher socioeconomic position.

CONCLUSION

Children with gradually developing risks of overweight during childhood, and those with persistent overweight had unfavorable levels of cholesterol and BP already at the age of 12 years, whereas children with early transient overweight avoided these unfavorable outcomes. Together with the findings from earlier studies that adults with diabetes and cardiovascular disease more often had accelerated weight gain after birth, our results support the hypothesis that specific overweight patterns predispose to an

Table 4. Differences[a] in levels of cardiometabolic markers of three overweight patterns compared with a never-overweight pattern, by sex

	Never-overweight pattern *Absolute level (reference)*	*Early transient overweight pattern*		*Gradually developing overweight pattern*		*Persistent overweight pattern*	
		Difference[b]	P	*Difference*[b]	P	*Difference*[b]	P
Girls							
Total cholesterol (mmol l^{-1})	4.0	0.03 (−0.19; 0.24)	0.80	−0.008 (−0.26; 0.25)[c]	0.95	−0.04 (−0.32; 0.24)[c]	0.76
HDL cholesterol (mmol l^{-1})	1.3	0.001 (−0.10; 0.10)	0.98	**−0.22 (−0.33; −0.09)**	**< 0.001**	**−0.18 (−0.30; −0.05)**	**0.01**
TC/HDLC ratio	3.2	−0.002 (−0.25; 0.25)	0.99	**0.54 (0.24; 0.83)** [c]	**< 0.001**	**0.56 (0.24; 0.88)**	**< 0.01**
Systolic blood pressure (mmHg)[d]	122.6	−0.26 (−3.25; 2.72)	0.86	**4.67 (0.84; 8.50)**	**0.02**	**4.11 (0.06; 8.15)**	**0.05**
Diastolic blood pressure (mmHg)[d]	70.0	−0.65 (−0.02; 4.84)	0.52	2.31 (−0.21; 4.84)	0.07	2.44 (−0.23; 5.10)	0.07
HbA1c (mmol mol^{-1})	32.7	0.22 (−0.70; 1.14)	0.65	−0.10 (−1.23; 1.04)	0.87	0.24 (−0.97; 1.44)	0.70
Boys							
Total cholesterol (mmol l^{-1})	4.0	0.03 (−0.17; 0.24)	0.75	**0.40 (0.15; 0.65)** [c]	**< 0.01**	0.23 (−0.08; 0.55)[c]	0.14
HDL cholesterol (mmol l^{-1})	1.4	0.09 (0.001; 0.19)	0.05	**−0.20 (−0.32; −0.09)**	**< 0.001**	**−0.16 (−0.30; −0.01)**	**0.03**
TC/HDLC ratio	3.1	−0.18 (−0.43; 0.07)	0.15	**0.92 (0.62; 1.22)** [c]	**< 0.0001**	**0.56 (0.19; 0.94)**	**< 0.01**
Systolic blood pressure (mmHg)[d]	122.0	0.12 (−2.56; 2.80)	0.93	**5.07 (1.89; 8.24)**	**< 0.01**	**4.57 (0.68; 8.46)**	**0.02**
Diastolic blood pressure (mmHg)[d]	70.6	−0.06 (−2.05; 1.93)	0.95	1.59 (−0.77; 3.94)	0.19	**4.47 (1.59; 7.36)**	**< 0.01**
HbA1c (mmol mol^{-1})	32.7	−0.29 (−1.04; 0.46)	0.44	−0.31 (−1.21; 0.60)	0.51	−0.45 (−1.59; 0.69)	0.44

Abbreviations: HbA1c, glycated hemoglobin; TC/HDLC, total-to-high-density lipoprotein cholesterol. [a]Adjusted for ethnicity, maternal education, and paternal education. [b]Regression coefficients (95% confidence intervals) of the mean level of the cardiometabolic marker in each of the overweight patterns versus the mean level in the never overweight pattern. [c]Statistically significant ($P < 0.15$) interaction with sex. [d]Additionally adjusted for cuff size. Associations with a significance level of $P < 0.05$ are boldfaced.

adverse cardiometabolic profile, which is already apparent in early adolescence before progressing to adult cardiometabolic disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Ms Berentzen and Dr van Rossem conceptualized and designed the study, carried out the initial analyses, drafted and revised the manuscript, and approved the final manuscript as submitted. Dr Smit and Dr Wijga conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. Drs Gehring, Koppelman, Postma and de Jongste critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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