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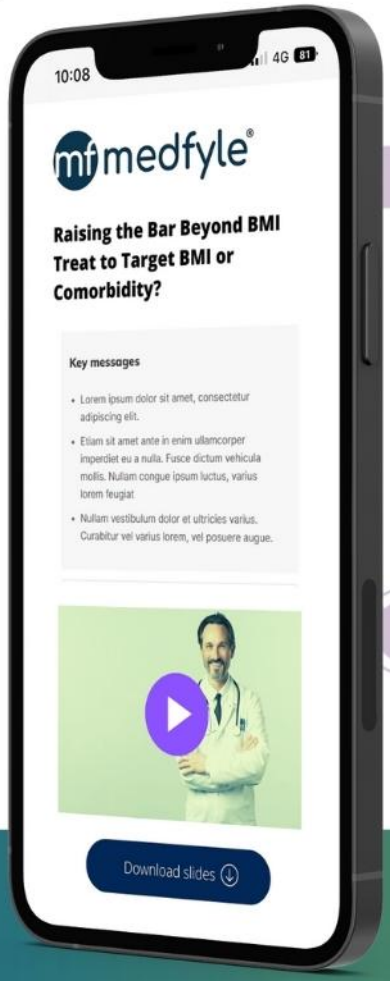

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ORIGINAL ARTICLE

Epidemiology/Genetics

Infant weight growth patterns, childhood BMI, and arterial health at age 10 years

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Abstract

Objective: Associations of obesity with cardiovascular disease may originate in childhood. This study examined critical periods for BMI in relation to arterial health at school age.

Methods: Among 4,731 children from a prospective cohort study, associations of infant peak weight velocity, both age and BMI at adiposity peak, and BMI trajectories with carotid artery intima-media thickness and carotid artery distensibility at 10 years were examined.

Results: A 1-standard deviation score (SDS) higher peak weight velocity and BMI at adiposity peak were associated with higher intima-media thickness (0.10 SDS; 95% CI: 0.06 to 0.13 and 0.08 SDS; 95% CI: 0.05 to 0.12) and lower distensibility (−0.07 SDS; 95% CI: −0.10 to −0.03 and −0.07 SDS; 95% CI: −0.11 to −0.03) at 10 years. For distensibility, current BMI explained these associations. Children within the highest BMI tertile at ages 2 and 10 years had the lowest distensibility ($p < 0.05$), but similar intima-media thickness, compared with children constantly within the middle tertile.

Conclusions: Infant weight growth patterns and childhood BMI are associated with subtle differences in carotid intima-media thickness and carotid distensibility at school age. For distensibility, current BMI seems critical. Follow-up is needed to determine whether these associations lead to adult cardiovascular disease.

INTRODUCTION

Obesity is a major risk factor for atherosclerotic cardiovascular disease in adults (1,2). Childhood adiposity, which tracks into adulthood, also is associated with cardiovascular risk factors and disease in adulthood (3-7). Carotid intima-media thickness and distensibility are two measures of arterial structure and function, respectively. These markers for arterial health could be used to assess cardiovascular risk in children (8,9). Previous cross-sectional and prospective observational studies reported associations of higher BMI with higher carotid intima-media thickness from school age onward and lower carotid distensibility from school age to adulthood (5,10-14). Furthermore, one study among 1,811 Australian adolescents reported that cumulative exposure to a high BMI from age 2 years onward was associated with higher carotid intima-media thickness at age 12 years (15). Another study among 500 Finnish adolescents reported that participants with relatively low brachial or aortic distensibility during adolescence had higher BMI from infancy onward than those with high distensibility (16). In the same cohort as the current study, we have previously shown that higher peak weight velocity and BMI at adiposity peak are strongly associated with an increased risk of childhood overweight and obesity, as well as with cardiovascular outcomes at school age (17-20). These studies have strongly suggested that early-life weight growth patterns affect cardiovascular health in later life. Still, it is not yet known whether infant weight growth patterns or body mass trajectories across childhood are associated with higher carotid intima-media thickness and lower carotid distensibility at age 10 years. Identification of such associations is important from an etiologic perspective.

We hypothesized that higher BMI from infancy across school age is associated with carotid intima-media thickness and carotid distensibility. In a population-based cohort study among 4,731 children, we examined the associations of infant weight growth patterns and BMI trajectories from age 2 to 10 years with carotid intima-media thickness and carotid distensibility in children aged 10 years.

Study Importance

What is already known?

► The association of obesity with cardiovascular disease in adulthood may originate in early life.

What does this study add?

► Infant peak weight velocity and BMI at adiposity peak were associated with carotid intima-media thickness in healthy children aged 10 years, independent of current BMI.
► Associations of infant weight growth patterns with carotid distensibility were explained by current BMI.
► Compared with children with normal weight, those with underweight had lower carotid intima-media thickness, whereas those with overweight had lower carotid distensibility at 10 years.

How might these results change the direction of research or the focus of clinical practice?

► Our findings are important from an etiological perspective, as they suggest that both infant and childhood weight might be important for arterial health at school age.

METHODS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward in Rotterdam, the Netherlands (21). The Medical Ethical Committee of Erasmus Medical Center approved the study (MEC 198.782/2001/31). Pregnant women with an expected delivery date between April 2002 and January 2006 who were living in Rotterdam were eligible to participate. In this study, we included 4,731 singleton children with data on infant weight growth velocity patterns and/or BMI across childhood and carotid intima-media thickness or carotid distensibility measured at the median age of 9.7 years (95% CI: 9.4-10.5). Written informed consent was provided by their parents. Supporting Information Figure S1 shows a flowchart of participants.

Growth measurements

We obtained information on repeated infant and preschool (age 0-4 years) length and weight measurements from community health centers (21). At ages 6 and 10 years, we invited children to our research facility for detailed measurements. We measured height and weight without shoes and/or heavy clothing, from which we calculated BMI (weight in kilograms divided by height in meters squared) and, subsequently, sex- and age-adjusted standard deviation score (SDS) based on Dutch reference growth charts (Growth Analyzer 4.0, Dutch Growth Research Foundation) (22). From infant growth measures, we derived peak weight velocity, reflecting the greatest weight change in infancy, and both age and BMI reached at adiposity peak, as described previously (20,23). Peak weight velocity was derived by fitting the Reed1 model by sex on all weight measurements taken between birth and age 3 years (24). The first derivative of the fitted distance curve was taken to obtain the weight velocity curve. Peak weight velocity, reflecting the maximum rate of growth in infancy, was defined as the maximum of this curve. We obtained both age and BMI at adiposity peak by fitting a cubic mixed-effects model on log(BMI) from age 14 days to age 1.5 years, adjusted for sex (20). These measures refer to the age and BMI level, respectively, at which the infant reaches maximum BMI change. We categorized children at the median ages of 2.1 years (95% CI: 1.2-3.0), 6.0 years (95% CI: 5.6-7.3), and 9.7 years (95% CI: 9.3-10.5) years into BMI tertiles. Subsequently, to

examine body mass growth pattern, we created three variables combining BMI at ages 2 and 6 years, ages 6 and 10 years, and ages 2 and 10 years. Thus, these three variables each reflected nine different BMI combinations across a different age interval. At age 10 years, we also categorized BMI into underweight, normal weight, overweight, and obesity based on the International Obesity Task Force cutoffs (25).

Carotid intima-media thickness and carotid distensibility

When children visited the research facility at age 10 years, we measured intima-media thickness and distensibility three times at both common carotid arteries ($n = 5{,}746$) using the Logiq E9 device (GE Medical Systems, Wauwatosa, Wisconsin). Children were in the supine position, with the head tilted slightly away from the transducer. The common carotid artery was identified in a longitudinal plane, ~10 mm proximal from the carotid bifurcation. We obtained six recordings that ideally included multiple heart cycles. The analyses were performed offline and semiautomatically, using the application Carotid Studio (Cardiovascular Suite; Quipu srl, Pisa, Italy). For each recording, and at all R waves of the simultaneous electrocardiogram (ECG), carotid intima-media thickness was computed at the far wall as the average distance between lumen-intima and media-adventitia borders. The average carotid intima-media thickness of all frames of the acquired image sequence was computed. The distensibility coefficient, or distensibility, was defined as the relative change in lumen area during systole for a given peripheral pressure change. We assessed blood pressure at the right brachial artery four times with the validated automatic sphygmomanometer Datascope Accutorr Plus (Paramus, New Jersey) (26). The lumen diameter of the carotid artery was computed as the average distance between the far and near media-adventitia interfaces for each frame of the acquired image sequence. Distension was calculated as the difference between the maximal (diastolic) and minimal (systolic) lumen diameter of the carotid artery. Per recording, the average distension and diameter values were used to compute the average carotid distensibility. During these offline analyses, we excluded 516 and 704 children without any valid carotid intima-media thickness or carotid distensibility measurement, respectively; reasons included lack of appropriate recording, insufficient quality of the recording, recording of the heart only, or no blood pressure measurement available to calculate carotid distensibility. Further data processing for the remaining 5,230 and 5,042 children with carotid intima-media thickness and carotid distensibility data, respectively, was performed using R (The R Foundation, Vienna, Austria). We excluded nine children with unreliable low or high carotid distensibility values. We used the overall mean carotid intima-media thickness (millimeters) and carotid distensibility ($kPa^{-1} \times 10^{-3}$) as main outcomes of interest. In a reproducibility study among 47 participants, the interobserver and intraobserver intraclass correlation coefficients were >0.85.

Covariates

We constructed a directed acyclic diagram (Supporting Information Figure S2). Potential covariates were selected based on previous literature and by observing a >10% change in effect estimate. We obtained information on maternal age, educational level, prepregnancy BMI, parity, folic acid supplement use, smoking and alcohol consumption during pregnancy, child ethnicity, and breastfeeding from questionnaires (21). From midwife and hospital records, we obtained information on child sex and birth weight, for which we created a sex- and gestational-age-adjusted SDS (27). At ages 6 and 10 years, blood pressure was assessed at the right brachial artery four times with the Datascope Accutorr Plus. Mean systolic and diastolic blood pressure was calculated from the last three measurements (26). Subsequently, mean arterial pressure was calculated using the following formula:

$$\text{Diastolic Blood Pressure} + 1/3 \times (\text{Systolic Blood Pressure} - \text{Diastolic Blood Pressure}).$$

Gestational diabetes did not change the results; therefore, it was not included in the model.

Statistical analysis

First, we performed a nonresponse analysis by comparing characteristics of children with and without carotid artery ultrasound data using Student *t* tests, Mann–Whitney tests, and χ^2 tests. Second, we examined the associations of infant peak weight velocity, age at adiposity peak, and BMI at adiposity peak with carotid intima-media thickness and carotid distensibility using linear multivariable regression models. Third, to examine the associations of three BMI combinations across childhood (ages 2-6 years, ages 6-10 years, and ages 2-10 years) with carotid intima-media thickness and carotid distensibility, we used linear multivariable regression after adjustment for the age interval between exposure measurements. Fourth, we examined cross-sectional associations of BMI in categories with both outcomes. We examined trends using BMI continuously. Basic models were adjusted for sex and age at outcome measurement. Confounder models were considered as main models and additionally adjusted for ethnicity and birth weight SDS, maternal age, education, parity, BMI, folic acid supplementation, smoking and alcohol consumption during pregnancy, and breastfeeding. For analyses of infant growth, we further explored significant associations ($p < 0.05$) in the confounder model by examining whether they were independent of BMI at age 10 years after excluding multicollinearity as a threat to the validity of these models (variance inflation factors ≤ 2.5). As sensitivity analyses, we additionally adjusted confounder models for mean arterial pressure, which we considered to be a potential mediator. To compare effect estimates, we analyzed exposures and outcomes in SDS after natural-log transformation of carotid distensibility, which had a skewed distribution. Interaction terms between exposures and birth weight SDS or sex in relation to both outcomes were not significant in the basic models ($p_{interaction} > 0.05$).

TABLE 1 Participant characteristics after imputation of covariates ($n = 4,731$)[a]

	Value
Maternal characteristics	
Age (y)	30.9 (5.0)
Educational level	
None, primary, or secondary	2,442 (50.6%)
College or higher	2,289 (49.4%)
Parity	
Nulliparous	2,752 (58.2%)
Multiparous	1,979 (41.8%)
Prepregnancy BMI (kg/m^2)	22.8 (17.7-34.0)
Smoking	
Nonsmoker or smoked until pregnancy was known	4,016 (84.9%)
Smoked throughout pregnancy	715 (15.1%)
Alcohol consumption	
No consumption or consumption until pregnancy was known	2,719 (57.5%)
Sustained consumption	2,012 (42.5%)
Folic acid supplement use	
No	1,084 (22.9%)
From early pregnancy	1,502 (32.8%)
From preconception	2,145 (45.3%)
Birth and infant characteristics	
Gestational age (wk)	40.1 (35.4-42.3)
Birth weight (kg)	3.42 (0.57)
Sex	
Boy	2,348 (49.6%)
Girl	2,383 (50.4%)
Ethnicity	
European[b]	3,191 (67.4%)
Non-European	1,540 (32.6%)
Breastfeeding	
No	357 (7.5%)
Yes	4,375 (92.5%)
Childhood growth	
Age at peak weight velocity (mo)	0.79 (0.18)
Peak weight velocity (kg/y)	12.0 (8.6-16.8)
Age at adiposity peak (mo)	8.4 (7.8-9.6)
BMI at adiposity peak (kg/m^2)	17.6 (0.80)
Childhood characteristics	
At 2 years	
Age at visit (mo)	24.8 (23.4-28.2)
BMI (kg/m^2)	16.5 (14.1-19.6)
At 6 years	
Age at visit (y)	6.0 (5.6-7.6)
BMI (kg/m^2)	15.8 (13.6-20.9)
At 10 years	
Age at visit (y)	9.7 (9.4-10.5)
BMI[c] (kg/m^2)	17.0 (14.0-24.8)
Underweight	327 (6.9%)
Normal weight	3,537 (74.9%)
Overweight	678 (14.4%)
Obesity	179 (3.8%)
Common carotid artery intima-media thickness (mm)	0.46 (0.04)
Common carotid artery distensibility[d] ($kPa^{-1} \times 10^{-3}$)	55.8 (37.1-85.4)
Blood pressure (mm Hg)	
Systolic	103 (8)
Diastolic	59 (6)
Mean arterial pressure	74 (6)

[a]Exposures and outcomes were not imputed. Supporting Information Table S1 shows values based on observed, not imputed data. Values are median (95% CI), mean (SD), or *n* (%).

[b]A subgroup of 2,775 children were of Dutch ethnic background and used for exploratory sensitivity analyses.

[c]Categorized based on the International Obesity Task Force cutoffs (19).

[d]Values before natural-log transformation.

The interaction term between BMI at age 10 years and ethnicity was significant for carotid intima-media thickness. Therefore, exploratory analyses of BMI with this outcome were performed among children from a Dutch ethnic background, our largest subgroup ($n = 2,275$). We used multiple imputations for covariates with missing values using the Markov Chain Monte Carlo method. We created five data sets and reported pooled regression coefficients (28). We performed statistical analyses using SPSS Statistics version 25.0 (IBM Corp., Armonk, New York). As exposures were correlated, we did not correct for multiple testing or specify two-sided $p < 0.05$ and $p < 0.01$.

RESULTS

Participant characteristics

Table 1 and Supporting Information Table S1 show participant characteristics. At age 10 years, 74.9% of children had a normal BMI. The mean carotid intima-media thickness at this age was 0.46 (SD 0.04) mm, and the median carotid distensibility was 55.8 (95% CI: 37.3-85.4) $kPa^{-1} \times 10^{-3}$. Compared with mothers of children with carotid artery ultrasound data, the mothers of children without these data were younger, had lower levels of education, and were multiparous. They also smoked more often but consumed alcohol or used folic acid supplements less frequently (Supporting Information Table S2). Supporting Information Table S3 shows correlations between exposures and outcomes.

TABLE 2 Associations of infant growth measures with carotid intima-media thickness and carotid distensibility at age 10 years[a]

	SDS, regression coefficient (95% CI)			
	Common carotid artery intima-media thickness (n = 3,779)		Common carotid artery distensibility (n = 3,611)	
	Confounder model	BMI model	Confounder model	BMI model
Peak weight velocity (SDS)	0.10 (0.06 to 0.13)[b]	0.09 (0.05 to 0.13)[b]	−0.07 (−0.10 to −0.03)[b]	−0.02 (−0.06 to 0.02)
Age at adiposity peak (SDS)	0.02 (−0.01 to 0.05)	0.02 (−0.02 to 0.05)	−0.02 (−0.05 to 0.02)	−0.01 (−0.04 to 0.03)
BMI at adiposity peak (SDS)	0.08 (0.05 to 0.12)[b]	0.07 (0.03 to 0.11)[b]	−0.07 (−0.11 to −0.03)[b]	−0.01 (−0.05 to 0.03)

[a]Regression coefficients are linear multivariable regression coefficients based on SDS of carotid intima-media thickness and log-transformed carotid distensibility. Models were adjusted for child sex, age at outcome measurement, birth weight SDS, ethnicity, maternal age, education, parity, prepregnancy BMI, folic acid supplementation, smoking and alcohol consumption during pregnancy, and breastfeeding. BMI models were additionally adjusted for child BMI SDS at outcome measurement.

[b]$p < 0.01$.

Infant growth and markers of arterial health

Higher peak weight velocity and BMI at adiposity peak were both associated with higher carotid intima-media thickness (0.10 SDS; 95% CI: 0.06 to 0.13 and 0.08 SDS; 95% CI: 0.05 to 0.12, respectively, per SDS increase in growth measure) and lower carotid distensibility (−0.07 SDS; 95% CI: −0.10 to −0.03 and −0.07 SDS; 95% CI: −0.11 to −0.03, respectively, per SDS) at age 10 years. The associations for carotid distensibility were fully explained by BMI at age 10 years (Table 2). Age at adiposity peak was not associated with both outcomes. Basic models showed similar results (Supporting Information Table S4).

Childhood BMI and markers of arterial health

Stratified analyses showed that, compared with children in the middle BMI tertile at ages 2 and 10 years, children in the highest tertile at both ages had the lowest carotid distensibility (difference −0.26 SDS; 95% CI: −0.38 to −0.14; Table 3). No consistent associations were observed for carotid intima-media thickness. Compared with children within the middle BMI tertile at ages 2 and 10 years, those within the lowest tertile at both ages had the lowest carotid intima-media thickness and highest distensibility (differences −0.18 SDS; 95% CI: −0.30 to −0.06 and 0.17 SDS; 95% CI: 0.05 to 0.29, respectively; Table 3). Basic models showed similar results (Supporting Informaton Table S5). Patterns for BMI change between ages 2 and 6 years and ages 6 and 10 years were similar (Supporting Information Tables S6 and S7).

At age 10 years, higher BMI was associated with higher carotid intima-media thickness (0.05 SDS = 95% CI: 0.02 to 0.08, per SDS) and lower carotid distensibility (−0.16 SDS; 95% CI: −0.19 to −0.13, per SDS; Figure 1). Compared with children with normal weight at age 10 years, those with underweight had lower carotid intima-media thickness (difference −0.23 SDS; 95% CI: −0.31 to −0.09) and higher carotid distensibility (difference 0.33 SDS; 95% CI: 0.22 to 0.45), whereas those with overweight and obesity had only lower carotid distensibility (differences −0.26 SDS; 95% CI: −0.34 to −0.17 and −0.31 SDS; 95% CI: −0.46 to −0.15, respectively). Basic models showed similar results (Supporting Information Table S8).

Sensitivity analyses

The identified associations were largely similar after adjustment for mean arterial pressure (data not shown). Among Dutch children, we observed tendencies for similar associations with carotid intima-media thickness, although not significant, likely because of lower numbers (Supporting Information Tables S9 and S10).

DISCUSSION

In this large population-based cohort study of healthy children, we observed that both higher peak weight velocity and BMI at adiposity peak were associated with higher carotid intima-media thickness at age 10 years. Associations of these exposures with lower carotid distensibility were fully explained by BMI at outcome measurement. BMI across childhood was more consistently associated with carotid distensibility than with carotid intima-media thickness at age 10 years.

Early-life growth is associated with cardiovascular outcomes at school age and cardiovascular disease in adulthood (6,17,18,29). Previous observational studies in children have reported associations of higher BMI with higher carotid intima-media thickness and lower carotid or brachial distensibility from school age onward (5,10-12,14,30,31). Also, two previous studies have reported associations of repeated BMI measurements from infancy onward with either carotid intima-media thickness or carotid distensibility in adolescents (15,16). We hypothesized that BMI from infancy onward is associated with higher carotid intima-media thickness and lower carotid distensibility already at age 10 years. The identification of such associations is important from an etiological perspective.

TABLE 3 Associations of BMI patterns across childhood with carotid intima-media thickness and carotid distensibility at age 10 years[a]

	SDS, regression coefficient (95% CI)			
	BMI at 10 years			
	First tertile	Second tertile	Third tertile	p_{trend}
Common carotid artery intima-media thickness (n = 3,855)				
BMI at 2 years				
First tertile	−0.18 (−0.30 to −0.06)[b]	−0.06 (−0.20 to 0.07)	−0.07 (−0.23 to 0.09)	0.16
	(n = 694)	(n = 363)	(n = 228)	
Second tertile	−0.15 (−0.28 to −0.02)[c]	*Reference*	−0.08 (−0.21 to 0.06)	0.34
	(n = 421)	(n = 479)	(n = 385)	
Third tertile	−0.05 (−0.23 to 0.12)	0.07 (−0.06 to 0.20)	0.07 (−0.05 to 0.19)	0.94
	(n = 170)	(n = 443)	(n = 672)	
p_{trend}	0.25	0.03	0.09	
Common carotid artery distensibility (n = 3,684)				
BMI at 2 years				
First tertile	0.17 (0.05 to 0.29)[b]	−0.02 (−0.16 to 0.12)	−0.15 (−0.32 to 0.01)	<0.001
	(n = 659)	(n = 349)	(n = 219)	
Second tertile	0.13 (−0.01 to 0.26)	*Reference*	−0.22 (−0.36 to −0.08)[b]	<0.001
	(n = 402)	(n = 450)	(n = 368)	
Third tertile	0.01 (−0.17 to 0.19)	−0.15 (−0.28 to −0.01)[c]	−0.26 (−0.38 to −0.14)[b]	<0.001
	(n = 165)	(n = 424)	(n = 648)	
p_{trend}	0.11	0.09	0.15	

[a]Regression coefficients are linear multivariable regression coefficients based on SDS of carotid intima-media thickness and log-transformed carotid distensibility. Models were adjusted for child sex, age at outcome measurement, birth weight SDS, ethnicity, maternal age, education, parity, prepregnancy BMI, folic acid supplementation, smoking and alcohol consumption during pregnancy, and breastfeeding.

[b]$p < 0.01$.

[c]$p < 0.05$.

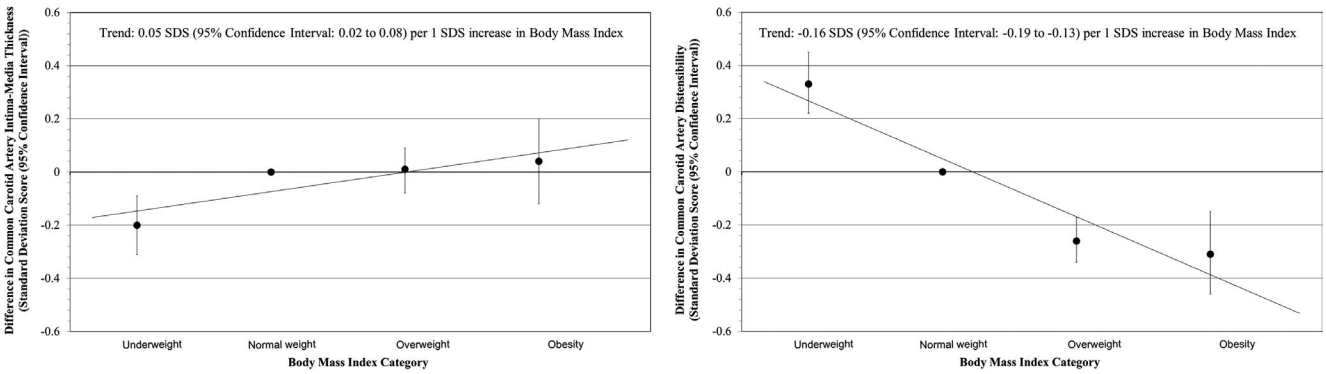

FIGURE 1 Associations of BMI with carotid intima-media thickness and carotid distensibility at age 10 years. Values are regression coefficients (95% CI) from linear multivariable regression models that reflect differences in childhood carotid intima-media thickness (left panel, n = 4,731) and log-transformed carotid distensibility (right panel, n = 4,554), in SDS, for each BMI category compared with the reference group (children with normal weight). Models were adjusted for child sex, age at outcome measurement, birth weight SDS, ethnicity, maternal age, education, parity, prepregnancy BMI, folic acid supplementation, smoking and alcohol consumption during pregnancy, and breastfeeding. *P* for linear trend <0.01. SDS, standard deviation score

Intima-media thickness may reflect early structural atherosclerotic changes within the intimal layer of arteries (32,33). Additionally, it may reflect physiological remodeling of the medial layer in response to growth (14,32). Higher intima-media thickness has been associated with cardiovascular disease in adults (34). We were the first study, to our knowledge, that reported on infant

weight growth velocity patterns in relation to carotid intima-media thickness. We observed positive associations of infant peak weight velocity and BMI at adiposity peak with this measure at age 10 years. We also observed some evidence that BMI across childhood is positively associated with carotid intima-media thickness at age 10 years, although this may be restricted to lean children. Our findings seem in line with those from previous cross-sectional studies in adolescents and, less often, in children (12-14,35,36). Of these, a large study among 3497 children aged 6 to 17 years from five worldwide population-based studies reported that children with overweight had higher carotid intima-media thickness than children with normal weight (13). One prospective study from Australia among 1,811 healthy adolescents reported associations of obesity but not overweight from age 2 years onward with higher carotid intima-media thickness at age 12 years (15). This smaller study among slightly older children, compared with our population, also reported that cumulative exposure to a high BMI from age 2 years onwards was associated with higher carotid intima-media thickness at age 12 years (15). Therefore, our large prospective study adds to previous studies by reporting associations of detailed infant growth indices and of childhood BMI with higher carotid intima-media thickness in lean children aged 10 years.

The distensibility coefficient reflects the elastic properties of arteries as hollow structures (37). It depends on the elastin-to-collagen-protein ratio in the extracellular matrix of the medial layer (16,38). Lower arterial distensibility has been associated with cardiovascular disease in adults (39). We observed that infant peak weight velocity and BMI at adiposity peak were inversely associated with carotid distensibility at age 10 years. These associations were explained by BMI at age 10 years, underscoring the importance of weight management across childhood. We also observed that body mass growth across childhood was inversely associated with carotid distensibility at age 10 years. In contrast to carotid intima-media thickness, this finding was not restricted to lean children. Our results suggest that suboptimal BMI in children may be associated with early functional changes of the carotids (33,38). Previous cross-sectional European studies, among 65 up to 838 children or adolescents, reported either null findings or findings in line with ours, i.e., inverse associations of BMI with distensibility (12,14,30,36). One prospective study among up to 500 Finnish healthy adolescents, with data on carotid and aortic distensibility measurements between ages 11 and 19 years, reported that adolescents with a mean arterial distensibility below the 20th percentile of the study population had higher BMI from infancy onward than adolescents with values above this cutoff (16). Contrary to this smaller study, we assessed school-aged children with data on infant weight growth velocity patterns and analyzed distensibility continuously after detailed adjustment for covariates. The Finnish study further reported an inverse association of repeated BMI measurements between ages 11 and 15 years with aortic, but not carotid, distensibility at these ages, whereas similar analyses between ages 15 and 19 years showed the converse (16). Thus, our findings in a larger sample suggest that associations of BMI with carotid distensibility are already present at age 10 years. Overall, we showed, for the first time, that BMI from infancy onward is negatively associated with carotid distensibility in healthy children aged 10 years.

The mechanisms underlying the observed associations are not known; therefore, we can only speculate about their interpretation (40). Moreover, we cannot distinguish whether subtle differences in carotid intima-media thickness and carotid distensibility in relation to BMI represent preclinical pathological changes or physiological adaptations in response to normal growth. Assuming pathological changes, it may be that metabolic complications associated with obesity, such as insulin resistance, inflammation, and higher blood pressure, mediate the identified associations. Also, adipose cells are metabolically active and produce leptin. This hormone regulates appetite and body weight and is involved in vascular physiology. It has angiogenetic activity, increases oxidative stress in endothelial cells, and promotes vascular cell calcification and smooth muscle cell proliferation and migration (41). Atherosclerosis and arterial stiffening are distinct but synergistic processes that often coexist and share risk factors (38). Arterial stiffening seems to activate pathophysiologic mechanisms involved in atherogenesis (16,38). Our findings were more consistent for carotid distensibility than for carotid intima-media thickness, suggesting that functional changes proceed structural changes (33). The observed associations may also be explained by normal growth. BMI is the sum of lean and fat mass index, but one cannot distinguish between these components. Lean mass is metabolically more active than fat mass and is the main determinant of resting energy expenditure (9). Thus, lean mass increases oxygen demand, which requires higher cardiac output and thereby increases blood pressure (32). Blood pressure has been linked to higher intima-media thickness and lower distensibility (11,16,30). Lean mass might be a stronger determinant of cardiovascular structure and function than BMI in children (14,32,42). Although more extreme values may be pathological, in healthy school-aged children, subtle differences in intima-media thickness and carotid distensibility may reflect adaptation to lean mass and blood pressure (14,32). This needs further study.

The effect estimates of the observed associations were small and may not be relevant at an individual level. Also, we observed that, compared with children with normal weight, those with overweight or obesity had lower carotid distensibility but similar carotid intima-media thickness. We did expect that overweight was associated with higher carotid intima-media thickness. Our findings suggest that the associations of BMI with measures of arterial health are complex and might be different for distensibility and intima-media thickness. The specific age at which BMI becomes associated with higher intima-media thickness should be further studied. Previously, childhood overweight that normalizes in adulthood has been associated with the same risk of cardiovascular risk factors in adulthood, compared with having a healthy BMI across life (5). Obesity also tracks from childhood to adulthood (3,4). Therefore, on a population-based level, our findings underline the importance of a healthy BMI from infancy onward.

Major strengths of this study are its population-based prospective design, repeated BMI measurements, and detailed outcome measurements. This study also had limitations. As included children were from an affluent background and predominantly lean, our findings may not be generalizable to the general population with higher prevalence of obesity. Also, we had no data on infant BMI rebound available because of infrequent measurements. This measure may also be associated with arterial health. Furthermore, although BMI is a common screening tool that has a high sensitivity to identify childhood adiposity, it has a moderate specificity (43). Therefore, some children in our population with normal BMI may, in fact, have excess adiposity. We calibrated carotid distensibility to brachial mean arterial pressure, which will have shifted the calculated distensibility to higher values (44). Although we demonstrated high reproducibility, we cannot exclude observer bias in the carotid measurements. Last, we had data on many covariates, but information on diet and physical activity was not available at all ages. Therefore, the observed associations were not adjusted for these potential time-varying confounders, and residual confounding might be an issue, as in any observational study.

CONCLUSION

Our findings suggest that, in predominantly lean children, infant weight growth patterns and BMI across childhood are associated with subtle differences in carotid intima-media thickness and carotid distensibility at age 10 years. Our findings also underscore the importance of weight management across childhood, as, for carotid distensibility, the associations were dependent on BMI at outcome measurement. Whether the observed associations predispose children to increased risk of cardiovascular disease in later life needs further study.O

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

GSM and VWVJ had full access to all the data in the study and take responsibility for its integrity and the data analysis. VWVJ was responsible for conceptualization and design of this study. GSM analyzed the data. GSM and VVWJ interpreted the data. GSM wrote the original draft of the manuscript under the supervision of VWVJ, and CCVS, SS, RG, RG, and JFF were major contributors. All authors read and contributed to the preparation of the final manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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