




ORIGINAL ARTICLE

Epidemiology/Genetics

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

Giulietta S. Monasso^{1,2} | Carolina C. V. Silva^{1,2} | Susana Santos^{1,2}  |
Romy Goncalvez^{1,3} | Romy Gaillard^{1,2}  | Janine F. Felix^{1,2} | Vincent W. V. Jaddoe^{1,2} 

¹The Generation R Study Group, Erasmus University Medical Center, Rotterdam, the Netherlands

²Department of Pediatrics, Erasmus University Medical Center, Rotterdam, the Netherlands

³Department of Obstetrics and Gynaecology, Erasmus University Medical Center, Rotterdam, the Netherlands

Correspondence

Vincent W. V. Jaddoe, The Generation R Study Group (Na 29 – 08), Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands.
Email: v.jaddoe@erasmusmc.nl

Funding information

The general design of the Generation R Study is made possible by financial support from the Erasmus University Medical Center; Erasmus University Rotterdam; the Netherlands Organization for Health Research and Development (ZonMw); the Netherlands Organization for Scientific Research (NWO); the Ministry of Health, Welfare and Sport; and the Ministry of Youth and Families. VVVJ received funding from the European Research Council (ERC-2014-CoG-648916). The project was supported by funding from the European Union's Horizon 2020 research and innovation program, under grant agreements no. 733206 (LifeCycle) and no. 874739 (LongITools), and from the European Joint Programming Initiative "A Healthy Diet for a Healthy Life" (JPI HDHL, NutriPROGRAM project, ZonMw no. 529051022; PREcisE project, ZonMw no. 529051023; and EndObesity, ZonMw no. 529051026). RG received funding of the Dutch Heart Foundation (grant no. 2017T013), the Dutch Diabetes Foundation (grant no. 2017.81.002), and ZonMw (NWO, ZonMw, grant no. 543003109).

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.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. Obesity published by Wiley Periodicals LLC on behalf of The Obesity Society (TOS).

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.

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.

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.

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 $\log(\text{BMI})$ 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 ($\text{kPa}^{-1} \times 10^{-3}$) 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 ($p_{\text{interaction}} > 0.05$).

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

	Value
<i>Maternal characteristics</i>	
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%)
<i>Birth and infant characteristics</i>	
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%)
<i>Childhood growth</i>	
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)
<i>Childhood characteristics</i>	
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)

TABLE 1 (Continued)

	Value
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	
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 × 10 ⁻³)	55.8 (37.1-85.4)
Blood pressure (mm Hg)	
Systolic	103 (8)
Diastolic	59 (6)
Mean arterial pressure	74 (6)

^aExposures 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 (%).

^bA subgroup of 2,775 children were of Dutch ethnic background and used for exploratory sensitivity analyses.

^cCategorized based on the International Obesity Task Force cutoffs (19).

^dValues 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 × 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)

^aRegression 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 Information 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	<i>P</i> _{trend}
Common carotid artery intima-media thickness (<i>n</i> = 3,855)				
BMI at 2 years				
First tertile	-0.18 (-0.30 to -0.06) ^b (<i>n</i> = 694)	-0.06 (-0.20 to 0.07) (<i>n</i> = 363)	-0.07 (-0.23 to 0.09) (<i>n</i> = 228)	0.16
Second tertile	-0.15 (-0.28 to -0.02) ^c (<i>n</i> = 421)	Reference (<i>n</i> = 479)	-0.08 (-0.21 to 0.06) (<i>n</i> = 385)	0.34
Third tertile	-0.05 (-0.23 to 0.12) (<i>n</i> = 170)	0.07 (-0.06 to 0.20) (<i>n</i> = 443)	0.07 (-0.05 to 0.19) (<i>n</i> = 672)	0.94
<i>p</i> _{trend}	0.25	0.03	0.09	
Common carotid artery distensibility (<i>n</i> = 3,684)				
BMI at 2 years				
First tertile	0.17 (0.05 to 0.29) ^b (<i>n</i> = 659)	-0.02 (-0.16 to 0.12) (<i>n</i> = 349)	-0.15 (-0.32 to 0.01) (<i>n</i> = 219)	<0.001
Second tertile	0.13 (-0.01 to 0.26) (<i>n</i> = 402)	Reference (<i>n</i> = 450)	-0.22 (-0.36 to -0.08) ^b (<i>n</i> = 368)	<0.001
Third tertile	0.01 (-0.17 to 0.19) (<i>n</i> = 165)	-0.15 (-0.28 to -0.01) ^c (<i>n</i> = 424)	-0.26 (-0.38 to -0.14) ^b (<i>n</i> = 648)	<0.001
<i>p</i> _{trend}	0.11	0.09	0.15	

^aRegression 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.

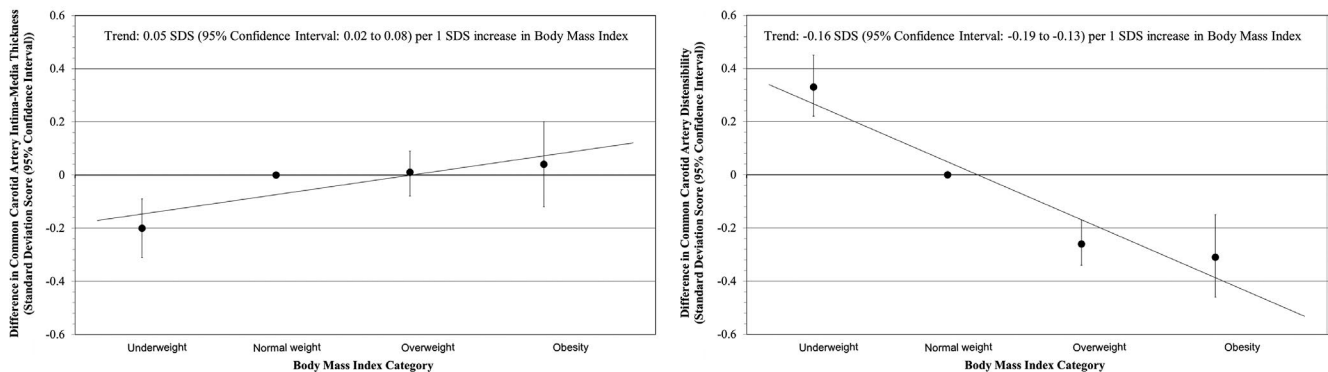


FIGURE 1 Associations of BMI with carotid intima-media thickness and carotid distensibility at age 10 years. Values are regression coefficients (95% CI) from linear multivariable regression models that reflect differences in childhood carotid intima-media thickness (left panel, *n* = 4,731) and log-transformed 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 angiogenic 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 precede 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. 

ACKNOWLEDGMENTS

The Generation R Study is conducted by the Erasmus University Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service of the Rotterdam area, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC). We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

GSM and VVWJ had full access to all the data in the study and take responsibility for its integrity and the data analysis. VVWJ 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 VVWJ,

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.

ORCID

Susana Santos  <https://orcid.org/0000-0003-0613-3181>

Romy Gaillard  <https://orcid.org/0000-0002-7967-4600>

Vincent W. V. Jaddoe  <https://orcid.org/0000-0003-2939-0041>

REFERENCES

1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377:13-27.
2. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67:968-977.
3. Ward ZJ, Long MW, Resch SC, et al. Simulation of growth trajectories of childhood obesity into adulthood. *N Engl J Med*. 2017;377:2145-2153.
4. Geserick M, Vogel M, Gausche R, et al. Acceleration of BMI in early childhood and risk of sustained obesity. *N Engl J Med*. 2018;379:1303-1312.
5. Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011;365:1876-1885.
6. Baker JL, Olsen LW, Sørensen TIA. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 2007;357:2329-2337.
7. Franks PW, Hanson RL, Knowler WC, et al. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med*. 2010;362:485-493.
8. Dalla Pozza R, Ehringer-Schetitska D, Fritsch P, et al. Intima media thickness measurement in children: a statement from the Association for European Paediatric Cardiology (AEPIC) Working Group on Cardiovascular Prevention endorsed by the Association for European Paediatric Cardiology. *Atherosclerosis*. 2015;238:380-387.
9. Doyon A, Kracht D, Bayazit AK, et al. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. *Hypertension*. 2013;62:550-556.
10. Li S, Chen W, Srinivasan SR, et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA*. 2003;290:2271-2276.
11. Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the cardiovascular risk in young Finns study. *JAMA*. 2003;290:2277-2283.
12. Urbina EM, Kimball TR, McCoy CE, et al. Youth with obesity and obesity-related type 2 diabetes mellitus demonstrate abnormalities in carotid structure and function. *Circulation*. 2009;119:2913-2919.
13. Zhao M, López-Bermejo A, Caserta CA, et al. Metabolically healthy obesity and high carotid intima-media thickness in children and adolescents: international childhood vascular structure evaluation consortium. *Diabetes Care*. 2019;42:119-125.
14. Sletner L, Mahon P, Crozier SR, et al. Childhood fat and lean mass: differing relations to vascular structure and function at age 8 to 9 years. *Arterioscler Thromb Vasc Biol*. 2018;38:2528-2537.
15. Lycett K, Juonala M, Magnussen CG, et al. Body mass index from early to late childhood and cardiometabolic measurements at 11 to 12 years. *Pediatrics*. 2020;146:e20193666. doi:10.1542/peds.2019-3666

16. Mikola H, Pahkala K, Niinikoski H, et al. Cardiometabolic determinants of carotid and aortic distensibility from childhood to early adulthood. *Hypertension*. 2017;70:452-460.
17. Marinkovic T, Toemen L, Kruihof CJ, et al. Early infant growth velocity patterns and cardiovascular and metabolic outcomes in childhood. *J Pediatr*. 2017;186:57-63.e54.
18. Toemen L, de Jonge LL, Gishti O, et al. Longitudinal growth during fetal life and infancy and cardiovascular outcomes at school-age. *J Hypertens*. 2016;34:1396-1406.
19. Kruihof CJ, Gishti O, Hofman A, Gaillard R, Jaddoe VW. Infant weight growth velocity patterns and general and abdominal adiposity in school-age children. The Generation R Study. *Eur J Clin Nutr*. 2016;70:1144-1150.
20. Mook-Kanamori DO, Durmuş B, Sovio U, et al. Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study. *Eur J Endocrinol*. 2011;165:623-630.
21. Kooijman MN, Kruihof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol*. 2016;31:1243-1264.
22. Fredriks AM, van Buuren S, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. *Arch Dis Child*. 2000;82:107-112.
23. Tzoulaki I, Sovio U, Pillas D, et al. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. *Am J Epidemiol*. 2010;171:989-998.
24. Berkey CS, Reed RB. A model for describing normal and abnormal growth in early childhood. *Hum Biol*. 1987;59:973-987.
25. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320:1240-1243.
26. Wong SN, Tz Sung RY, Leung LC. Validation of three oscillometric blood pressure devices against auscultatory mercury sphygmomanometer in children. *Blood Press Monit*. 2006;11:281-291.
27. Niklasson A, Ericson A, Fryer JG, et al. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand*. 1991;80:756-762.
28. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393
29. Barker DJP, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med*. 2005;353:1802-1809.
30. Whincup PH, Gilg JA, Donald AE, et al. Arterial Distensibility in Adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. *Circulation*. 2005;112:1789-1797.
31. Shah AS, Dolan LM, Khoury PR, et al. Severe obesity in adolescents and young adults is associated with subclinical cardiac and vascular changes. *J Clin Endocrinol Metab*. 2015;100:2751-2757.
32. Chiesa ST, Charakida M, Georgiopoulos G, et al. Determinants of intima-media thickness in the young: the ALSPAC study. *JACC Cardiovasc Imaging*. 2021;14:468-478.
33. Weberruß H, Pirzer R, Böhm B, et al. Intima-media thickness and arterial function in obese and non-obese children. *BMC Obes*. 2016;3:2.
34. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness. *Circulation*. 2007;115:459-467.
35. Park MH, Skow Á, De Matteis S, et al. Adiposity and carotid-intima media thickness in children and adolescents: a systematic review. *BMC Pediatr*. 2015;15:161.
36. Geerts CC, Evelein AMV, Bots ML, et al. Body fat distribution and early arterial changes in healthy 5-year-old children. *Ann Med*. 2012;44:350-359.
37. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588-2605.
38. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: pathophysiologic mechanisms and emerging clinical indications. *Vascul Pharmacol*. 2016;77:1-7.
39. Yuan C, Wang J, Ying M. Predictive value of carotid distensibility coefficient for cardiovascular diseases and all-cause mortality: a meta-analysis. *PLoS One*. 2016;11:e0152799. doi:10.1371/journal.pone.0152799
40. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444:875-880.
41. Singhal A, Farooqi IS, Cole TJ, et al. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? *Circulation*. 2002;106:1919-1924.
42. Toemen L, Santos S, Roest AA, et al. Body fat distribution, overweight, and cardiac structures in school-age children: a population-based cardiac magnetic resonance imaging study. *J Am Heart Assoc*. 2020;9:e014933. doi:10.1161/JAHA.119.014933
43. Javed A, Jumean M, Murad MH, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: a systematic review and meta-analysis. *Pediatric Obes*. 2015;10:234-244.
44. McEnery CM, Yasmin, McDonnell B, et al. Central pressure: variability and impact of cardiovascular risk factors. *Hypertension*. 2008;51:1476-1482.

SUPPORTING INFORMATION

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

How to cite this article: Monasso GS, Silva CCV, Santos S, et al. Infant weight growth patterns, childhood BMI, and arterial health at age 10 years. *Obesity (Silver Spring)*. 2022;30:770-778. doi:[10.1002/oby.23376](https://doi.org/10.1002/oby.23376)