



Effects of Arterial Stiffness and Carotid Intima-Media Thickness Progression on the Risk of Overweight/Obesity and Elevated Blood Pressure/Hypertension: a Cross-Lagged Cohort Study

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ABSTRACT: We examined the temporal longitudinal associations of carotid-femoral pulse wave velocity (cfPWV), a measure of arterial stiffness, and carotid intima-media thickness (cIMT) with the risk of overweight/obesity and elevated blood pressure (BP)/hypertension. We studied 3862 adolescents aged 17.7 years from the Avon Longitudinal Study of Parents and Children, followed-up for 7 years. cfPWV and cIMT were measured by ultrasound. Total and trunk fat mass and lean mass were assessed by dual-energy X-ray absorptiometry. Body mass index and BP were measured. Data were analyzed using logistic regression, linear mixed-effect, and cross-lagged structural equation models, with covariate adjustments. Among 1719 male and 2143 female participants, higher cfPWV at 17.7 years was associated with the risk of elevated systolic BP/hypertension (odds ratio, 1.20 [1.02–1.41]; $P=0.026$), elevated diastolic BP/hypertension (1.77 [1.32–2.38]; $P<0.0001$), body mass index-overweight/obesity (1.19 [1.01–1.41]; $P=0.041$), and trunk fat mass overweight/obesity (1.24 [1.03–1.49]; $P=0.023$) at 24.5 years. Higher cIMT at 17.7 years had no associations with obesity and elevated BP at follow-up. cfPWV progression was directly associated with 7-year increase in systolic BP (effect estimate 16 mmHg [9–24]; $P<0.0001$) and diastolic BP (28 mmHg [23–34]; $P<0.0001$). cIMT progression was directly associated with the 7-year increase of all adiposity measures and diastolic BP. In the temporal analysis, baseline cfPWV was directly associated with follow-up systolic and diastolic BP, however, baseline BP was unassociated with follow-up cfPWV. cfPWV but not cIMT was bidirectionally associated with adiposity. Obesity and hypertension prevention from adolescence may require developing novel approaches to mitigate arterial stiffness. (*Hypertension*. 2022;79:159–169. DOI: 10.1161/HYPERTENSIONAHA.121.18449.)

• Supplemental Material

Key Words: adolescent ■ atherosclerosis ■ blood pressure ■ body mass index ■ carotid-femoral pulse wave velocity ■ obesity ■ young adult

The global prevalence of obesity¹ and hypertension² in adolescence and young adulthood is on the rise. These twin risk factors of cardiovascular morbidity and mortality progress from childhood.^{1–6} Although obesity, elevated blood pressure (BP), and hypertension are well-established risk factors for arterial stiffness and carotid intima-media thickness (cIMT), surrogate markers of atherosclerotic cardiovascular diseases, a temporal or bidirectional

relationship remains unexamined among adolescents and young adults.^{3–5,7–13}

An American Heart Association's scientific statement recommended that future studies investigate the natural history of arterial stiffness, obesity, and BP in relation to the rate at which arterial stiffness and BP increase with age.⁴ Similarly, another American Heart Association's scientific statement just published recommended addressing the global burden of obesity hypertension

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Novelty and Significance

What Is New?

- The temporal longitudinal associations of repeatedly measured arterial stiffness (carotid-femoral pulse wave velocity) and carotid intima-media thickness with the risk of elevated blood pressure/hypertension and overweight/obesity risk among adolescents and young adults are unknown.

What Is Relevant?

- Adolescent arterial stiffness may be a precursor of hypertension and other metabolic risk factors in young adulthood rather than a consequence.

Summary

Persistently high carotid-femoral pulse wave velocity from adolescence through young adulthood was strongly associated with elevated blood pressure/hypertension and obesity, suggesting that obesity and hypertension prevention from adolescence may require developing novel approaches to mitigate arterial stiffness.

Nonstandard Abbreviations and Acronyms

ALSPAC	Avon Longitudinal Study of Parents and Children
BMI	body mass index
BP	blood pressure
cfPWV	carotid-femoral pulse wave velocity
cIMT	carotid intima-media thickness
OR	odds ratio

through a life-course strategy of prevention and control, especially from a young age.¹³ From a public health perspective, it is important to determine whether decreasing arterial stiffness and cIMT from adolescence could independently reduce overweight/obesity and elevated BP/incident hypertension in early adulthood because studies in the age group are lacking.^{4,13} Therefore, we examined the temporal and bidirectional longitudinal associations of cfPWV and cIMT with total fat mass, trunk fat mass, lean mass, body mass index (BMI), and BP among adolescents and young adults, using data from the ALSPAC (Avon Longitudinal Study of Parents and Children) birth cohort, England, United Kingdom.

METHODS

Data Availability Statement

The informed consent obtained from ALSPAC participants does not allow the data to be made freely available through any third-party maintained public repository. However, data used for this submission can be made available on request to the ALSPAC Executive. The ALSPAC data management plan describes in detail the policy regarding data sharing, which is through a system of managed open access. Full instructions for applying for data access can be found here: <http://www.bristol.ac.uk/alspac/researchers/access/>. Please note that the study website contains details of all the data that is available

through a fully searchable data dictionary and variable search tool: (<http://www.bristol.ac.uk/alspac/researchers/our-data/>).

Study Cohort

Descriptions of the ALSPAC birth cohort have been published earlier^{14–16} and detailed in the Appendix in the [Supplemental Material](#). Data were from the ALSPAC birth cohort, which investigates factors that influence childhood development and growth. Altogether, 14 541 pregnancies from women residing in Avon, southwestern England, United Kingdom, who had a total of 14 676 fetuses, were enrolled between April 1, 1991, and December 31, 1992. When the oldest children were ≈7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally resulting in 913 additional pregnancies. The total sample size for analyses using any data collected after 7 years of age is 15 454 pregnancies, resulting in 15 589 fetuses. Of these 14 901 were alive at 1 year of age. Regular clinic visits of the children commenced at 7 years of age and are still ongoing. For our analysis, we included participants who had both cfPWV and cIMT measurements at age 17.7 years (Figure S1 in the [Supplemental Material](#)). The demographic characteristics of excluded participants were similar to those included in this study (Table S1). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees and informed consent for the use of data was obtained from participants accordingly. Study data at 24.5 years were collected and managed using REDCap electronic data capture tools.¹⁷

All blood biochemical values were serially measured from fasting samples at 17.7 and 24.5 years, and body composition (total fat mass, trunk fat mass, and lean mass) was assessed using a dual-energy X-ray absorptiometry scanner.^{10–12} Details of the methods used for the measurement of weight, height, BP, fasting lipid, insulin, glucose levels, high-sensitivity C-reactive protein are contained in the Appendix in the [Supplemental Material](#). At age 17.7 years, cfPWV was computed from pressure waveforms obtained using the Vicorder device (Skidmore Medical, Bristol, United Kingdom), whereas cIMT was assessed by ultrasound using a linear 12-MHz transducer (Vivid7, GE Medical, Chicago, Illinois) as earlier reported. At 24.5 years, cfPWV was measured, 5 minutes after resting in a semiprone

position, using a Vicorder instrument (Skidmore Medical, Bristol, United Kingdom) with 2 BP measurement channels and 2 Velcro pressure sensor cuffs applied over each of the carotid and femoral arteries. The cfPWV measurement was repeated until three readings that were within 0.5 m/s of each other had been recorded. The right and left common carotid arteries at age 24.5 years were imaged using an ultrasound machine (CardioHealth Panasonic and a 13.5 MHz linear array broadband transducer; probe; center frequency 9.0 MHz). We calculated BMI by dividing weight by squared height. Participants at >75th percentile of total fat mass, trunk fat mass, or having >24.9 kg/m² of BMI were classified as overweight and obese while those below this cut points were classified as normal weight.¹⁸ A high lean mass category included participants having >75th percentile of lean mass while those below this threshold were considered having normal lean mass.¹⁸ Participants were categorized as normotensive if BP was <120/80 mm Hg and elevated BP/hypertension when BP was >120/80 mm Hg.¹⁹ Missing data were handled with multiple imputations.^{10,11,20,21} Questionnaire to assess smoking behavior were administered at the 17.7-year and 24.5-year clinic visits. At the 17.7-year clinic visit, participants were briefly asked about their personal and family (mother, father, and siblings) medical history, such as a history of hypertension, diabetes, high cholesterol, and vascular disease. Moderate to vigorous physical activity at age 15.5 years was assessed with ActiGraphTM accelerometer worn for 7 days,¹⁰ whereas at 24.5 years moderate to vigorous physical activity was assessed using ActiGraph GT3X+ accelerometer device worn for 4 consecutive days,²² ideally starting the day after the clinic visit (see [Supplemental Material](#) and Tables S2 through S10).

Statistical Analysis

Participants' descriptive characteristics were summarized as means and SD, medians, and interquartile ranges, or frequencies and percentages. We explored sex differences using Independent *t* tests, Mann-Whitney *U* tests, or χ^2 tests for normally distributed, skewed or dichotomous variables, respectively. We assessed the normality of variables and logarithmically or reciprocally transformed skewed variables before further analysis.

We investigated the separate longitudinal associations of cfPWV and cIMT (predictors) at 17.7 years with each of total fat mass, trunk fat mass, lean mass, BMI, systolic BP, and diastolic BP (outcomes) categories at 24.5 years using logistic regression ([Supplemental Methods](#)). We also examined the separate associations of the 7-year progression in cfPWV and cIMT with the longitudinal progression in each of the outcomes from ages 17.7 through 24.5 years using linear mixed-effect models for repeated measures. Analyses were adjusted for sex, age at 17.7 years, and covariates measured at 17.7 and 24.5 years, such as low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, fasting blood glucose, diastolic or systolic BP, and fat mass or lean mass depending on the outcome, smoking status, family history of hypertension/diabetes/high cholesterol/vascular disease, and moderate to vigorous physical activity at 15.5 and 24.5 years.

Lastly, we used structural equation modeling with autoregressive cross-lagged design²³ (detailed in the

[Supplemental Material](#)) to examine the separate temporal associations of cfPWV and cIMT with outcomes, adjusting for covariates listed above. All covariates were selected based on previous studies.^{10–12,18,24} We examined sex interactions and presented sex-stratified results and cross-sectional analysis results in Table S11. For sensitivity analyses, we examined the quartile categories (high, moderate-high, moderate-low, and low) of cfPWV and cIMT progression with the increase in body composition and BP and presented the result in Table S12. We considered differences and associations with a 2-sided $P < 0.05$ as statistically significant and made conclusions based on effect estimates and their 95% CI or SEs. Analyses involving 40% of a sample of 10 000 ALSPAC children at 0.8 statistical power, 0.05 alpha, and 2-sided *P* value would show a minimum detectable effect size of 0.049 SDs if they had relevant exposure for a normally distributed quantitative variable.²⁵ All statistical analyses were performed using SPSS statistics software, Version 27.0 (IBM Corp, Armonk, NY), and structural equation modeling was conducted using IBM AMOS version 27.0.

RESULTS

Study Population and Characteristics

Altogether, 14 901 children in the ALSPAC birth cohort were alive at 1 year of age, of whom 5217 adolescents participated in the 17.7-year follow-up clinic visit, whereas 4026 young adults participated in the 24.5-year follow-up clinic visit (Figure S1). Only 3862 participants who had complete cfPWV and cIMT measurements at age 17.7 years were included in the study. The prevalence of overweight/obesity at 17.7 and 24.5 years was 20% and 38%, respectively. The prevalence of elevated systolic BP/hypertension at 17.7 and 24.5 years was 26% and 33%, respectively. Other characteristics of our study participants are shown in Table 1 and Tables S7 through S10.

Longitudinal Associations of cfPWV and cIMT at 17.7 Years With Risk Categories of Obesity and Hypertension at Age 24.5 Years

A higher cfPWV at 17.7 years predicted elevated systolic BP/hypertension (odds ratio [OR], 1.20 [95% CI, 1.02–1.41]; $P=0.026$), elevated diastolic BP/hypertension (OR, 1.77 [95% CI, 1.32–2.38]; $P<0.0001$), BMI-overweight/obesity (OR, 1.19 [95% CI, 1.01–1.41]; $P=0.041$), trunk fat mass-obesity (OR, 1.24 [95% CI, 1.03–1.49]; $P=0.023$), and decreased high lean mass (OR, 0.73 [95% CI, 0.54–0.98]; $P=0.035$) at age 24.5 years, after adjusting for cardiometabolic and lifestyle factors (Table 2). Among males, a higher cfPWV at 17.7 years predicted elevated systolic BP/hypertension (OR, 1.31 [95% CI, 1.02–1.70]; $P=0.038$) and elevated diastolic BP/hypertension (OR, 2.18 [95% CI, 1.49–3.19]; $P<0.0001$) at 24.5 years but not among females (OR, 1.09 [95% CI, 0.83–1.42]; $P=0.542$) and (OR, 1.40

Table 1. Descriptive Characteristics of Cohort Participants

Variables	17.7 y					24.5 y				
	Male		Female		P value	Male		Female		P value
	N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)	
Anthropometry										
Age, y	1719	17.72 (0.32)	2143	17.72 (0.34)	0.753	954	24.58 (0.72)	1502	24.50 (0.74)	0.008
Height, m	1693	1.79 (0.07)	2112	1.65 (0.06)	<0.0001	949	1.80 (0.07)	1484	1.66 (0.06)	<0.0001
Weight, kg*	1696	69.40 (14.45)	2114	60.40 (13.50)	<0.0001	948	77.80 (17.65)	1484	64.65 (17.10)	<0.0001
Somatic maturation (n,%)	1600	1601 (100)	1927	1927 (100)	NA	NA				
Ethnicity–White (n,%)	1565	1498 (95.7)	1925	1848 (96.0)	0.670	NA				
Body composition										
Total fat mass, kg*	1675	10.28 (9.81)	2080	19.24 (10.44)	<0.0001	927	17.91 (10.35)	1436	22.12 (11.91)	<0.0001
Trunk fat mass, kg*	1675	5.30 (5.46)	2080	9.46 (5.63)	<0.0001	927	8.79 (6.50)	1436	9.91 (6.65)	<0.0001
Lean mass, kg	1675	54.83 (8.13)	2080	37.68 (5.16)	<0.0001	927	56.09 (10.07)	1436	40.82 (6.79)	<0.0001
Total fat mass index, kg/m ² *	1665	3.18 (3.09)	2072	7.03 (3.67)	<0.0001	925	5.57 (3.27)	1434	7.96 (4.33)	<0.0001
Trunk fat mass index, kg/m ² *	1664	1.64 (1.70)	2072	3.46 (2.00)	<0.0001	925	2.72 (2.00)	1434	3.60 (2.37)	<0.0001
Lean mass index, kg/m ² *	1664	17.11 (1.94)	2072	13.78 (1.52)	<0.0001	925	17.29 (2.44)	1434	14.76 (1.96)	<0.0001
Body mass index, kg/m ² *	1693	21.54 (4.05)	2112	21.95 (4.42)	<0.0001	948	23.98 (4.79)	1483	23.51 (5.70)	0.177
Metabolic profile										
Total cholesterol, mmol/L	1276	3.56 (0.62)	1310	3.94 (0.69)	<0.0001	839	4.34 (0.85)	1174	4.48 (0.82)	<0.0001
High-density lipoprotein, mmol/L	1276	1.19 (0.26)	1310	1.35 (0.32)	<0.0001	839	1.40 (0.37)	1174	1.66 (0.42)	<0.0001
Low-density lipoprotein, mmol/L	1276	2.00 (0.56)	1310	2.21 (0.63)	<0.0001	837	2.46 (0.79)	1174	2.40 (0.74)	0.071
Triglyceride, mmol/L*	1276	0.74 (0.34)	1310	0.76 (0.37)	0.096	838	0.87 (0.55)	1174	0.81 (0.47)	<0.0001
Glucose, mmol/L	1276	5.16 (0.69)	1310	4.91 (0.51)	<0.0001	839	5.46 (0.58)	1174	5.22 (0.63)	<0.0001
Insulin, mU/L*	1258	6.05 (4.19)	1285	7.33 (4.37)	<0.0001	839	6.92 (4.94)	1174	7.75 (5.56)	<0.0001
High-sensitivity C-reactive protein, mg/L*	1276	0.44 (0.68)	1310	0.67 (1.28)	<0.0001	752	0.63 (1.10)	1100	0.99 (2.13)	<0.0001
Vascular measures										
Pulse rate, bpm	1717	63 (9)	2138	68 (10)	<0.0001	952	64 (10)	1495	69 (10)	<0.0001
Systolic blood pressure, mmHg	1717	120 (9)	2138	110 (8)	<0.0001	952	122 (10)	1495	112 (10)	<0.0001
Diastolic blood pressure, mmHg	1717	63 (6)	2138	65 (6)	<0.0001	952	67 (8)	1495	66 (8)	0.004
Carotid-femoral PWV, m/s*	1719	6.03 (0.70)	2143	5.54 (0.62)	<0.0001	640	6.47 (1.21)	1012	5.90 (1.03)	<0.0001
Carotid IMT, mm*	1719	0.48 (0.05)	2143	0.47 (0.04)	<0.0001	532	0.47 (0.05)†	866	0.45 (0.05)†	<0.0001
Lifestyle factors										
Smoked cigarettes in the past 30 d, n (%)	1491	369 (21.5)	1853	542 (25.3)	0.004	674	171 (25.4)	1105	284 (25.7)	0.911
MVPA, mins/d	691	56 (31)	884	40 (23)	<0.0001	220	46 (43)	411	42 (35)	0.030
Family history of H-D-C-V, n (%)	1718	492 (28.6)	2140	670 (31.3)	0.072	NA				

The values are means (SDs) and median (interquartile range) except for maturation status and lifestyle factors in percentage. Differences between sexes were tested using Student *t* test for normally distributed continuous variables, Mann-Whitney *U* test for skewed continuous variables, and χ^2 test for dichotomous variable. A 2-sided $P < 0.05$ is considered statistically significant. *P* value for sex difference. cIMT indicates carotid intima-media thickness; H-D-C-V, hypertension/diabetes/high cholesterol/vascular disease; IMT, intima-media thickness; MVPA, moderate to vigorous physical activity; NA, not available/applicable; and PWV, pulse wave velocity.

*Median (interquartile range).

†Mean cIMT measurement at 24 y, whereas maximum cIMT measurement for males is 0.54 mm (0.09) and for females is 0.53 mm (0.08).

[95% CI, 0.91–2.16]; $P=0.122$), respectively. There were no sex differences in the associations of higher cfPWV with obesity indices at 24.5 years. A higher cIMT at 17.7 years was only associated with the risk of decreased high lean mass at 24.5 years (OR, 0.02 [95% CI, 0.00–0.61]; $P=0.026$). There were no sex differences in the associations of higher cIMT at 17.7 years with higher obesity indices, body composition, and elevated BP at 24.5 years.

Effect of cfPWV and cIMT Progression on Fat Mass, Lean Mass, and BP Progression From Ages 17.7 to 24.5 Years

A 7-year progression in cfPWV was directly associated with the 7-year increase in lean mass: (mean difference from baseline to follow-up 0.11 kg; [95% CI, 0.06–0.15; $P < 0.0001$]), systolic BP: 16 mmHg; (9–24; $P < 0.0001$), and diastolic BP: 28 mmHg; (23–34; P

Table 2. Carotid-Femoral Pulse Wave Velocity and Carotid Intima-Media Thickness at 17.7 y in Association With Risk Categories of Obesity and Hypertension at 24.5 y

	Total fat mass (n=449)		Trunk fat mass (n=450)		Lean mass (n=450)		Body mass index (n=685)		Systolic blood pressure (n=556)		Diastolic blood pressure (n=84)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Univariable analysis												
Carotid-femoral pulse wave velocity	1.194 (1.045–1.363)	0.010	1.219 (1.076–1.381)	0.002	0.735 (0.605–0.894)	0.002	1.151 (1.035–1.281)	0.009	1.280 (0.958–1.712)	0.092	1.154 (0.739–1.801)	0.513
Carotid intima-media thickness	0.137 (0.021–0.909)	0.040	0.116 (0.017–0.820)	0.031	0.004 (<0.0001–0.083)	0.001	2.426 (0.415–14.180)	0.324	5.378 (0.072–400.84)	0.430	0.967 (0.006–166.819)	0.989
Multivariable analysis												
Carotid-femoral pulse wave velocity	1.210 (0.991–1.478)	0.061	1.239 (1.031–1.490)	0.023	0.725 (0.538–0.977)	0.035	1.193 (1.007–1.413)	0.041	1.198 (1.022–1.405)	0.026	1.773 (1.321–2.378)	<0.0001
Carotid intima-media thickness	0.414 (0.022–7.611)	0.550	0.561 (0.029–11.018)	0.702	0.017 (<0.0001–0.609)	0.026	2.499 (0.171–36.543)	0.501	2.517 (0.169–37.520)	0.499	3.209 (0.029–354.24)	0.625

Univariable analysis was adjusted for sex. Multivariable analysis was adjusted for sex, age, low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, fasting blood glucose, diastolic or systolic blood pressure and fat mass or lean mass depending on the outcome, moderate to vigorous physical activity at 15.5 y, smoking status and family history of hypertension/diabetes/high cholesterol/vascular disease OR from multivariable logistic regression. Multiple imputations were used to account for missing cases. Lean mass at 24.5 y was reciprocally transformed before categorization. At 24.5 y, participants at >75th percentile of total and trunk fat mass or having >24.9 kg/m² body mass index (38% of the study population at 24.5 y) were classified as overweight and obese. A high lean mass category at 24.5 y included participants at >75th percentile. Participants with blood pressure >120/80 mmHg were grouped as elevated systolic (31% of the study population at 24.5 y) or diastolic (5% of the study population at 24.5 y) blood pressure/hypertension at 24.5 y. P value <0.05 was considered statistically significant. OR indicates odds ratio.

<0.0001) but negatively associated with trunk fat mass -0.19 kg (-0.35 to -0.02 ; $P<0.0001$) and BMI: -0.05 kg/m²; (-0.09 to -0.01 ; $P=0.026$), after adjustment for cardiometabolic and lifestyle factors (Table 3). The sex-stratified results were largely in consonance with the combined results (Table 3). Additional adjustments for light physical activity and sedentary time did not alter the results (data not shown). In the sensitivity analyses with the lowest quartile as the reference, the highest quartile of cfPWV progression from 17.7 through 24.5 years was directly associated with the 7-year increase in lean mass but negatively associated with the increase in total fat mass, trunk fat mass, and BMI (Table S12). In comparison with the lowest or reference category, the highest quartile of cfPWV progression was associated with the 7-year increase in systolic BP: 4 mm Hg; (3–5; $P<0.0001$) and diastolic BP: 3 mm Hg; (2–4; $P<0.0001$). The moderate-high cfPWV quartile was associated with the 7-year increase in systolic BP: 3 mm Hg; (1–4; $P<0.0001$) and diastolic BP: 2 mm Hg; (1–3; $P<0.0001$). The moderate-low cfPWV quartile was associated with the 7-year increase in systolic BP: 2 mm Hg; (1–3; $P=0.001$) and diastolic BP: 1 mm Hg (0.4–2; $P=0.002$; Table S12).

A 7-year cIMT progression was directly associated with the 7-year increase in total fat mass, trunk fat mass, BMI, lean mass, and diastolic BP but negatively associated with systolic BP after adjustment for cardiometabolic and lifestyle factors (Table 3). Among males, there were no associations between cIMT progression and increase in lean mass and systolic BP. However, among females, cIMT progression was not associated with trunk fat mass and diastolic BP (Table 3). In the sensitivity analyses with the lowest quartile as the reference, the highest quartile of cIMT progression from 17.7 through 24.5

years was directly associated with the 7-year increase in lean mass and systolic BP but not associated with the increase in total fat mass, trunk fat mass, BMI, and diastolic BP (Table S12)

Cross-Lagged Temporal Relationships of cfPWV and cIMT With Fat Mass, Lean Mass, and BP

cfPWV, total fat mass, trunk fat mass, BMI, lean mass, systolic, and diastolic BP at 17.7 years were directly associated with their individual variables at 24.5 years; however, cIMT at 17.7 years was inversely associated with cIMT at 24.5 years (Table 4). We observed bidirectional associations between cfPWV and all measures of body composition, whereas cIMT had bidirectional associations with lean mass but had no relationships with adiposity indices (Figure 1A and 1B and Table 4). Higher cfPWV at 17.7 years was associated with high systolic and diastolic BP at 24.5 years, but neither systolic nor diastolic BP at 17.7 years was associated with cfPWV at 24.5 years (Figure 2A and Table 4). cIMT at 17.7 years was unrelated to systolic and diastolic BP at 24.5 years, whereas only diastolic BP at 17.7 years was associated with cIMT at 24.5 years (Figure 2B and Table 4).

DISCUSSION

In a large longitudinal birth cohort, we showed for the first time that arterial stiffness, assessed by cfPWV, and cIMT during adolescence may be independent risk factors for obesity and incident hypertension in early adulthood. We thus conclude because first, we observed that cfPWV at 17.7 years independently predicted general and trunk obesity, decreased lean mass,

Table 3. Longitudinal Progression in Arterial Stiffness and Carotid Intima-Media Thickness in Relation to Progression in Fat Mass, Lean Mass, and Blood Pressure From Age 17.7 to 24.5 y

	Total fat mass (kg)		Trunk fat mass (kg)		Lean mass (kg)	
	Effect estimate (95% CI)	P value	Effect estimate (95% CI)	P value	Effect estimate (95% CI)	P value
All participants (n=3862)						
Carotid-femoral pulse wave velocity	-0.072 (-0.219 to 0.075)	0.338	-0.185 (-0.350 to -0.020)	0.028	0.106 (0.063 to 0.149)	<0.0001
Carotid intima-media thickness	0.095 (0.079 to 0.111)	<0.0001	0.061 (0.042 to 0.080)	<0.0001	0.024 (0.019 to 0.028)	<0.0001
Male participants (n=1719)						
Carotid-femoral pulse wave velocity	-0.121 (-0.382 to 0.141)	0.365	-0.212 (-0.486 to 0.062)	0.129	0.092 (0.034 to 0.151)	0.002
Carotid intima-media thickness	0.158 (0.131 to 0.185)	<0.0001	0.133 (0.102 to 0.163)	<0.0001	0.006 (-0.004 to 0.016)	0.243
Female participants (n=2143)						
Carotid-femoral pulse wave velocity	-0.008 (-0.159 to 0.144)	0.923	-0.139 (-0.323 to 0.045)	0.139	0.093 (0.035 to 0.152)	0.002
Carotid intima-media thickness	0.031 (0.014 to 0.049)	0.001	-0.006 (-0.027 to 0.016)	0.610	0.027 (0.020 to 0.034)	<0.0001

(Continued)

and elevated BP/incident hypertension at 24.5 years. Second, we reported that a 7-year increase in cfPWV was directly associated with the 7-year increase in systolic BP and diastolic BP, whereas the longitudinal progression of cIMT was directly associated with the 7-year increase in total fat mass, trunk fat mass, lean mass, and diastolic BP. Lastly, using cross-lagged temporal structural equation models, cfPWV was bidirectionally associated with total fat mass, trunk fat mass, and lean mass but temporally preceded systolic and diastolic BP. cIMT was bidirectionally associated with lean mass only.

Arterial Stiffness with Obesity, Lean Mass, and Incident Hypertension

We and others have shown that cumulative exposure to total fat mass from childhood was associated with cfPWV in adolescence¹¹ and in young adulthood.²⁴ These previous findings^{11,24} and a meta-analysis³ involving 2237 children/adolescents (1281 with obesity, 956 healthy BMI controls) between 5 and 24 years of age emphasize a unidirectional relationship in which obesity is a strong and independent risk factor for arterial stiffness. However, to the best of our knowledge, it remains unknown whether arterial stiffness precedes (temporal relationship) incident obesity among a healthy young population. Our prospective analysis revealed that cfPWV at 17.7 years was independently associated with $\approx 20\%$ increased risk of total and trunk fat mass overweight/obesity at age 24.5 years, although the 7-year increase in cfPWV was unrelated to the 7-year increase in total fat mass and trunk fat mass. Nonetheless, the cross-lagged findings showed that cfPWV had strong bidirectional associations with

all measures of adiposity, suggesting that cfPWV may be a cause and a consequence of altered fat metabolism and deposit since increased arterial stiffness leads to high-flow low-resistance microvascular organ damage in the liver, pancreas, etc.^{5,8} By contrast, we observed that a higher cfPWV in late adolescence predicted $\approx 25\%$ reduced lean mass in early adulthood. We have shown that higher lean mass from age 9 to 24 years may drive the increase in cfPWV from 17 to 24 years¹² and in tandem with the cross-lagged findings, bidirectional relationships likely exist between cfPWV and muscle mass. In adults, arterial stiffness has been related to decreased lean mass via the mechanism of aging-induced chronic inflammation, hormonal dysregulation, impaired glucose metabolism, and other comorbidities.²⁶

There is mounting evidence on the bidirectional relationship between arterial stiffness and BP and that arterial stiffness predates altered BP in the causal pathway.^{4,5,27} We have shown that BP is independently associated with higher cfPWV where a 15-year 1 mmHg rise in BP predicted a 0.013 m/s rise in cfPWV over a 7-year period.²⁴ For the first time, we found in a young population, across cross-sectional, longitudinal, and cross-lagged analyses that arterial stiffness, measured with cfPWV, is a strong and consistent independent predictor of elevated BP/incident systolic and diastolic hypertension. We observed that a 1 m/s increase in cfPWV from ages 17.7 to 24.5 years was associated with a 4 mmHg and 3 mmHg increase in systolic and diastolic BP, respectively, over 7 years among participants in the highest quartile of cfPWV. Importantly, the cross-lagged findings suggest that arterial stiffness in late adolescence precedes the increase in systolic and diastolic BP in early adulthood. Baseline cfPWV did not

Table 3. Continued

Body mass index (kg/m ²)		Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)	
Effect estimate (95% CI)	P value	Effect estimate (95% CI)	P value	Effect estimate (95% CI)	P value
−0.050 (−0.094 to −0.006)	0.026	16.160 (8.841 to 23.839)	<0.0001	28.151 (22.520 to 33.781)	<0.0001
0.018 (0.013 to 0.022)	<0.0001	−1.540 (−2.512 to −0.568)	0.002	1.099 (0.363 to 1.835)	0.003
−0.080 (−0.138 to −0.022)	0.007	12.628 (0.825 to 24.430)	0.036	28.880 (20.226 to 37.533)	<0.0001
0.020 (0.013 to 0.027)	<0.0001	−0.552 (−2.215 to 1.111)	0.514	2.966 (1.762 to 4.169)	<0.0001
−0.026 (−0.089 to 0.037)	0.417	18.140 (8.127 to 28.152)	<0.0001	27.968 (20.617 to 35.320)	<0.0001
0.015 (0.007 to 0.022)	<0.0001	−1.782 (−2.984 to −0.580)	0.004	0.153 (−0.784 to 1.091)	0.748

Multivariable analysis was adjusted for sex only in all participants' model, age at 17.7 y, and covariates at 17.7 and 24.5 y such as low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, fasting blood glucose, diastolic or systolic blood pressure and fat mass or lean mass depending on the outcome, moderate to vigorous physical activity at 15.5 y, smoking status, and family history of hypertension/diabetes/high cholesterol/vascular disease. Skewed variables were logarithmically transformed before analyses. Effect estimate was from linear mixed-model analyses for repeated measures. $P < 0.05$ was considered statistically significant.

predict elevated systolic and diastolic BP/hypertension at follow-up when controlled only for sex but was statistically significant after controlling for several potential confounders. This suggests that logistic regression analyses may be reported alongside path analysis or linear regression hierarchical models for the robustness of the results. Our findings, therefore, shed novel insights into the natural history of arterial stiffness and BP in relation to the rate at which arterial stiffness and BP increase with age, as identified as a research priority by the American Heart Association.^{4,13} Taken together, our finding buttress previous reports^{4,5,13} that arterial stiffness antedates and probably contribute to the pathogenesis of incident hypertension, independent of cardiometabolic, and lifestyle factors. The carotid-femoral artery has a thin collagenous adventitial layer, an elastin-laden medial layer, and a thin intimal layer.^{4,5,8,27} The elastic media layer enables arterial distensibility during systole and blood flow augmentation during diastole. Elastic fiber degradation or an increased collagen deposit reduces the energy storing capacity of the elastic fiber and decreases collagen fiber undulation, thereby occasioning stiffened arteries.^{4,5,8,27} Arterial stiffness may lead to the remodeling of small resistance arteries which are implicated in the early phases of prehypertension. Damage to these arteries results in an elevated BP via wave reflections and propagation and may progressively aggravate into a vicious loop of increased arterial stiffness and more pressure wave reflections.^{4,5,8,27} Arterial stiffening increases characteristic impedance leading to higher wave reflections and pulse pressure propagation. This reflected wave returns

earlier during ventricular contraction and increases late systolic BP.^{4,5,27}

Carotid Intima-Media Thickness with Obesity, Lean Mass, and Incident Hypertension

Recent reports among adolescents¹⁰ and young adults^{12,24} seem to challenge the previous notion that obesity measured by BMI predicts cIMT progression in a healthy young population.⁹ These reports,^{10,12,24} in a large healthy young population, emphasized that dual-energy X-ray absorptiometry-measured total fat mass or trunk fat mass may not associate with cIMT progression during early life. Nonetheless, evidence on whether cIMT has a temporal relationship with body fat is lacking. In the longitudinal analysis, higher cIMT at 17.7 years of age had no relationship with all measures of adiposity at 24.5 years, both in the logistic regression and cross-lagged analyses. However, a 7-year progression in cIMT was independently and directly associated with the 7-year increase in total and central adiposity, especially in males. As expected, males had lower body fat content in contrast to females; however, there was a significant accumulation of fat mass among males during the 7-year growth. The median 7-year increase in total fat mass and trunk fat mass among males was 7.63 kg and 3.49 kg, respectively, whereas females had 2.88 kg of total fat mass and 0.45 kg of trunk fat mass increase. This 3- to 8-fold increase in fat mass among males relative to females may be a simultaneous increase not in the causal pathway of cIMT progression since cIMT increase did not precede the fat mass increase in the cross-lagged analyses.

Table 4. Autoregressive Cross-Lagged Temporal Analyses of Carotid-Femoral Pulse Wave Velocity and Carotid Intima-Media Thickness With Fat Mass, Lean Mass, and Blood Pressure at 17.7 and 24.5 y of Age

Carotid-femoral pulse wave velocity					Carotid intima-media thickness				
Autoregressive	B	β	SE	P value		B	β	SE	P value
Participants (3862)									
Systolic BP T1 \longleftrightarrow systolic BP T2	0.505	0.429	0.023	<0.0001	Systolic BP T1 \longleftrightarrow systolic BP T2	0.517	0.439	0.023	<0.0001
Diastolic BP T1 \longleftrightarrow diastolic T2	0.405	0.324	0.026	<0.0001	Diastolic BP T1 \longleftrightarrow diastolic T2	0.455	0.364	0.024	<0.0001
cfPWV T1 \longleftrightarrow cfPWV T2	0.497	0.356	0.033	<0.0001	cIMT T1 \longleftrightarrow cIMT T2	-0.096	-0.055	0.041	0.019
Total fat mass T1 \longleftrightarrow total fat mass T2	0.576	0.800	0.014	<0.0001	Total fat mass T1 \longleftrightarrow total fat mass T2	0.573	0.796	0.014	<0.0001
Trunk fat mass T1 \longleftrightarrow trunk fat mass T2	0.645	0.788	0.016	<0.0001	Trunk fat mass T1 \longleftrightarrow trunk fat mass T2	0.642	0.784	0.016	<0.0001
BMI T1 \longleftrightarrow BMI T2	0.911	0.799	0.019	<0.0001	BMI T1 \longleftrightarrow BMI T2	0.904	0.793	0.019	<0.0001
Lean mass T1 \longleftrightarrow lean mass T2	0.836	0.879	0.014	<0.0001	Lean mass T1 \longleftrightarrow lean mass T2	0.838	0.880	0.014	<0.0001
Cross-lagged									
Systolic BP T1 \longleftrightarrow cfPWV T2	0.000	-0.039	0.000	0.168	Systolic BP T1 \longleftrightarrow cIMT T2	0.000	0.054	0.000	0.063
cfPWV T1 \longleftrightarrow systolic BP T2	11.910	0.054	3.761	0.002	cIMT T1 \longleftrightarrow systolic BP T2	5.132	0.018	4.412	0.245
Diastolic BP T1 \longleftrightarrow cfPWV T2	0.000	-0.003	0.000	0.899	Diastolic BP T1 \longleftrightarrow cIMT T2	0.001	0.099	0.000	<0.001
cfPWV T1 \longleftrightarrow diastolic BP T2	20.678	0.137	3.075	<0.0001	cIMT T1 \longleftrightarrow diastolic BP T2	3.943	0.021	3.392	0.245
Total fat mass T1 \longleftrightarrow cfPWV T2	0.022	0.079	0.009	0.010	Total fat mass T1 \longleftrightarrow cIMT T2	0.013	0.045	0.009	0.162
cfPWV T1 \longleftrightarrow total fat mass T2	0.172	0.048	0.053	0.001	cIMT T1 \longleftrightarrow total fat mass T2	-0.083	-0.018	0.063	0.187
Trunk fat mass T1 \longleftrightarrow cfPWV T2	0.020	0.075	0.008	0.013	Trunk fat mass T1 \longleftrightarrow cIMT T2	0.011	0.041	0.008	0.195
cfPWV T1 \longleftrightarrow trunk fat mass T2	0.164	0.038	0.066	0.013	cIMT T1 \longleftrightarrow trunk fat mass T2	-0.138	-0.026	0.077	0.074
BMI T1 \longleftrightarrow cfPWV T2	0.070	0.066	0.030	0.021	BMI T1 \longleftrightarrow cIMT T2	0.019	0.018	0.032	0.560
cfPWV T1 \longleftrightarrow BMI T2	0.070	0.047	0.021	<0.0001	cIMT T1 \longleftrightarrow BMI T2	-0.010	-0.005	0.025	0.700
Lean mass T1 \longleftrightarrow cfPWV T2	0.109	0.143	0.036	0.002	Lean mass T1 \longleftrightarrow cIMT T2	0.156	0.204	0.038	<0.0001
cfPWV T1 \longleftrightarrow lean mass T2	0.049	0.028	0.013	<0.0001	cIMT T1 \longleftrightarrow lean mass T2	0.032	0.015	0.015	0.036

Autoregressive cross-lagged analyses were adjusted for sex, time in years between ages 17.7 and 24.5 y, and other covariates at 17 y such as age, low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, fasting blood glucose, diastolic or systolic blood pressure and fat mass or lean mass depending on the outcome, moderate to vigorous physical activity at 15.5 y, smoking status and family history of hypertension/diabetes/high cholesterol/vascular disease. Skewed variables were logarithmically transformed before analyses. B indicates unstandardized regression; BMI, body mass index; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; cIMT, carotid intima-media thickness; time T1, 17.7 y of age; time T2, 24.5 y; and β , standardized regression.

We observed that the 7-year progression in cIMT was directly associated with the increase in lean mass from ages 17.7–24.5 years in both males and females, consistent with cross-sectional and cross-lagged analysis. In adolescents¹⁰ and young adults,^{12,24} cumulative high exposure to a dual-energy X-ray absorptiometry-measured lean mass was directly associated with cIMT^{10,24} and cIMT progression,²⁴ but little is known regarding a reverse association (temporal association).²⁸ We have now shown that a bidirectional relationship exists between cIMT and lean mass in a young healthy population, although the relationship is stronger when lean mass is the predictor. This temporal relationship may be due to a physiological carotid wall adaptation in association with skeletal muscle growth during maturation.^{10,24,26} It is important to note that higher cIMT at 17.7 years predicted a slight decrease in lean mass at 24.5 years. Considering the age and health status of our study population, an optimal cIMT may facilitate, decreased reactive oxidant species, rapid oxygen supply, increased

myocyte proliferation, and increased production of anabolic hormones.^{9,26,28}

cIMT measured at 17.7 years was unrelated to systolic or diastolic BP at 24.5 years either via logistic regression or cross-lagged analyses. However, a 7-year cIMT progression was independently and directly associated with the 7-year increase in diastolic BP, particularly among males. Although cIMT maximally increased by 0.06 mm between ages 17.7–24.5 years, among males, it explained $\approx 18\%$ of the increase in diastolic BP during the observation period. This simultaneous rise in cIMT and intravascular pressure may suggest a compensatory nonatherosclerotic adaptation occurring between lumen diameter and cIMT via the maintenance of local wall shear stress.²⁹

Strengths and Limitations of the Study

The ALSPAC dataset based on a large birth cohort provides an extensive array of gold-standard and repeated

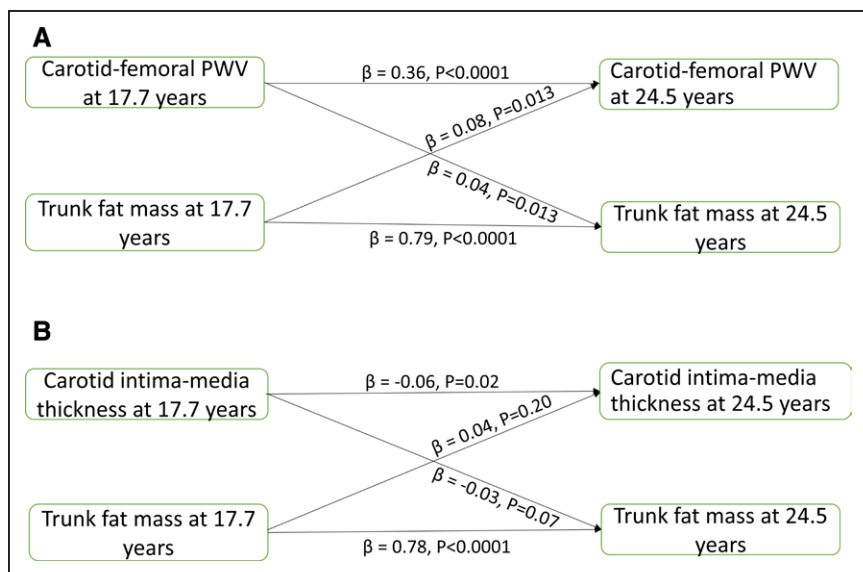


Figure 1. Temporal causal relationships between arterial measures and body fat.

Cross-lagged temporal analysis of arterial stiffness (A) and carotid intima-media thickness (B) progression with higher trunk fat mass among 3862 adolescents from the ALSPAC (Avon Longitudinal Study of Parents and Children) birth cohort. Analyses were adjusted for sex, time in years between ages 17.7 and 24.5 y, and other covariates at 17.7 y such as age, low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, fasting blood glucose, systolic blood pressure, lean mass, moderate to vigorous physical activity at 15.5 y, smoking status and family history of hypertension/diabetes/high cholesterol/vascular disease. Skewed variables were logarithmically transformed before analyses. β , standardized regression. PWV indicates pulse wave velocity

measures of variables during adolescence and young adulthood which allowed us to construct cross-lagged structural equation models to examine temporal and bidirectional associations. We could not adjust for diet as the variable was unavailable at 17.7- and 24.5-year follow-up clinic visits, nonetheless, participants' body composition and metabolic state which we controlled for may reflect their diets. The absolute time in moderate to vigorous physical activity was a relatively small proportion of the day, although within the expected range.^{13,22} Therefore, we additionally controlled for sedentary time and light physical activity but the findings remained unchanged. We cannot exclude unmeasured or residual confounders, for instance, adiponectin has been associated with arterial stiffness progression.³⁰ Although we could not control for the effect of adiponectin because the variable was measured only in childhood, we controlled for high-sensitivity

C-reactive protein, another inflammatory marker associated with arterial stiffness progression.⁵ There were no regional differences in our study population as all were from the Avon area of England and were mostly White participants; therefore, we are unable to generalize our findings to other populations with different ethnicities. Lastly, the observational nature of our study may not establish causality; however, a temporal longitudinal path in the associations of cfPWV and cIMT with obesity and hypertension is a critical step in the causal pathway.

PERSPECTIVES

Adolescence arterial stiffness independently predicted trunk fat overweight/obesity, elevated BP/incident hypertension, and a decreased lean mass in early adulthood. Arterial stiffness appears to precede the increase in systolic and

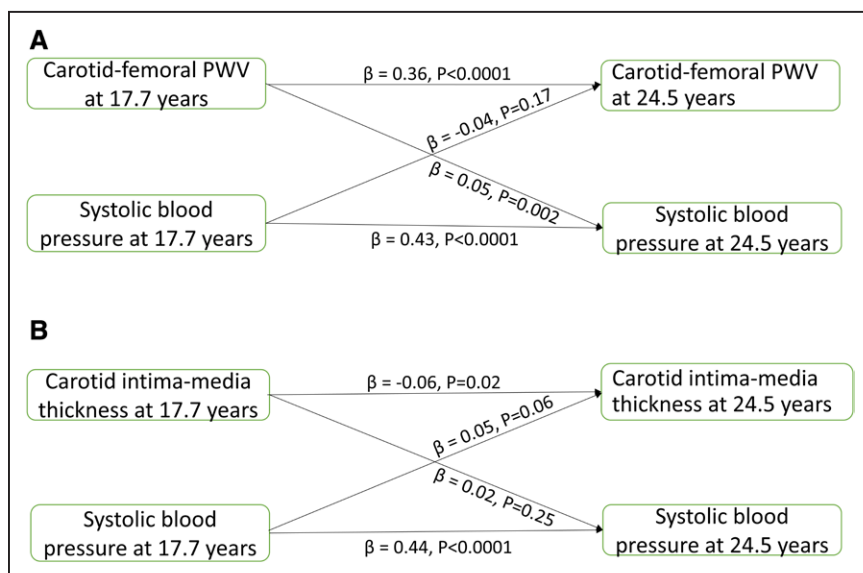


Figure 2. Temporal causal relationships between arterial measures and blood pressure.

Cross-lagged temporal analysis of arterial stiffness (A) and carotid intima-media thickness (B) progression with higher systolic blood pressure in 3862 participants from the ALSPAC (Avon Longitudinal Study of Parents and Children) birth cohort. Analyses were adjusted for sex, time in years between ages 17.7 and 24.5 y, and other covariates at 17.7 y such as age, low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, fasting blood glucose, fat mass, lean mass, moderate to vigorous physical activity at 15.5 y, smoking status and family history of hypertension/diabetes/high cholesterol/vascular disease. Skewed variables were logarithmically transformed before analyses. β indicates standardized regression; and PWV indicates pulse wave velocity.

diastolic BP but the relationship with adiposity may be more complex and bidirectional. Increased cIMT at 17.7 years was associated with decreased lean mass at 24.5 years. A 7-year arterial stiffness progression, that is, persistently high cfPWV from 17.7 through 24.5 years, was strongly associated with the increase in systolic and diastolic BP, whereas cIMT progression was associated with the increase in all measures of adiposity at the end of the observation period. Reducing arterial stiffness and cIMT from adolescence may be effective in preventing elevated BP/hypertension and overweight/obesity risks in early adulthood. Nonetheless, future temporal longitudinal investigations of cfPWV and cIMT in mediating obesity and hypertension risk are warranted in a large multiethnic adolescent population.

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Disclosures

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