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ORIGINAL RESEARCH

Biological Pathways in Adolescent Aortic Stiffness

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BACKGROUND: Aortic stiffening begins in youth and antedates future hypertension. In adults, excess weight, systemic inflammation, dyslipidemia, insulin resistance, neurohormonal activation, and altered adipokines are implicated in the pathogenesis of increased aortic stiffness. In adolescents, we assessed the relations of comprehensive measures of aortic stiffness with body mass index (BMI) and related but distinct circulating biomarkers.

METHODS AND RESULTS: A convenience sample of 246 adolescents (mean age, 16±2 years; 45% female, 24% Black, and 43% Hispanic) attending primary care or preventive cardiology clinics at 2 tertiary hospitals was grouped as normal weight (N=98) or excess weight (N=148, defined as BMI ≥age- and sex-referenced 85th percentile). After an overnight fast, participants underwent anthropometry, noninvasive arterial tonometry, and assays for serum lipids, CRP (C-reactive protein), glucose, insulin, renin, aldosterone, and leptin. We used multivariable linear regression to relate arterial stiffness markers (including carotid-femoral pulse wave velocity) to BMI *z* score and a biomarker panel. Carotid-femoral pulse wave velocity was higher in excess weight compared with normal weight group (5.0±0.7 versus 4.6±0.6 m/s; $P<0.01$). After multivariable adjustment, carotid-femoral pulse wave velocity was associated with BMI *z* score (0.09 [95% CI, 0.01–0.18]; $P=0.04$) and with low-density lipoprotein cholesterol (0.26 [95% CI, 0.03–0.50]; $P=0.03$).

CONCLUSIONS: Higher BMI and low-density lipoprotein cholesterol were associated with greater aortic stiffness in adolescents. Maintaining optimal BMI and lipid levels may mitigate aortic stiffness.

Key Words: adipokines ■ arterial stiffness ■ cholesterol ■ hypertension ■ inflammation ■ obesity ■ pediatric

High blood pressure (BP) in childhood predicts future cardiovascular disease events and mortality, even after adjusting for BP in adulthood.[1–3] Because pediatric hypertension tracks into adulthood, targeting interventions to children with biophysical and biochemical antecedents of hypertension may reduce cardiovascular disease risk over the life course.[4,5] Pediatric obesity tracks into adulthood and triples the risk of elevated BP.[6,7] Yet, nearly 45% of youth with elevated BP have normal weight (NW), suggesting factors beyond obesity may be implicated in the pathogenesis of high BP in this group.[7]

Aortic stiffness is a key antecedent of hypertension.[8,9] Longitudinal studies in adults have established that higher carotid-femoral pulse wave velocity (CFPWV), a marker of aortic wall stiffness, predicts risk of developing hypertension.[8,10] Other concomitants of aortic stiffness (such as central pulse pressure [PP], forward pulse wave [FPW] amplitude, and characteristic impedance [Zc]) that reflect the interactions of pulsatile flow and aortic size also predict hypertension, aging-related vascular remodeling, and future cardiovascular disease events.[11–14] Of note, a wide PP is present in >90% of youth with elevated BP.[9,15]

Previous work on mechanisms underlying hypertension has implicated several biological pathways involved in the pathogenesis of aortic stiffness, including excess weight (EW), insulin resistance, lifestyle and genetic disorders, altered adipokine profile, inflammation, and neurohormones.[16–19] Many

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CLINICAL PERSPECTIVE

What Is New?

- In adolescents, higher body mass index was associated directly with worse large and small artery wall stiffness measures but inversely related to arterial measures sensitive to aortic root size.
- After body mass index adjustment, serum lipid concentrations and systemic inflammation were associated with vascular stiffness measures dependent on large artery wall properties; leptin and low-density lipoprotein cholesterol concentrations were inversely associated with vascular measures dependent on arterial size and flow, and contrary to previous reports, insulin resistance was primarily related to small artery function.

What Are the Clinical Implications?

- Presence of these blood markers may signal adolescents at risk of large or small artery remodeling.

Nonstandard Abbreviations and Acronyms

CFPWV	carotid-femoral pulse wave velocity
cPP	central pulse pressure
EW	excess weight
FPW	forward pulse wave
NW	normal weight
PP	pulse pressure
Zc	characteristic impedance

of these pathways are interrelated and associated with obesity. Likewise, aortic stiffness results from the interactions between aortic wall stiffness, flow, size, and downstream resistance vessels, implicating additional distinct determinants.[11,20,21] However, obesity and obesity-related circulating biomarkers have not been related to a comprehensive set of vascular measures in adolescents. In the present analysis, after adjusting for weight status, we examined the association between several key measures of aortic stiffness and a panel of biomarkers (including lipids, systemic inflammation, neurohormonal activation, leptin, and insulin resistance).

METHODS

A convenience sample of 246 patients, aged 13 to 21 years, from primary care and Preventive Cardiology practices centered within tertiary care pediatric hospital systems in metropolitan Boston, MA, and Houston, TX, was recruited to participate in the present investigation. Deidentified data, analytic methods, and study materials are available on request to the corresponding author per transparency and openness promotion guidelines. Inclusion criteria included both sexes, any race or ethnicity, and any weight but with special focus on recruiting twice as many EW participants as NW participants. EW participants were defined as at or above the age- and sex-referenced 85th percentile.[22] Exclusion criteria included cardiac condition affecting outflow tracts or great arteries and physician diagnoses of any of the following conditions: diabetes mellitus or use of diabetic medications, treated hypertension or use of antihypertensive medications, use of lipid-lowering medications, chronic renal disease or use of renal replacement therapy, systemic inflammatory conditions or current use of oral corticosteroid therapy, or other disease-modifying anti-inflammatory therapies. Adolescents with fever or infectious illness within the previous 2 weeks, current menstruation, pregnancy, and chronic disease preventing maintaining supine posture for at least 30 minutes, and those who were not able to fast for at least 6 hours were also excluded. The study was approved by ethics review boards at both hospitals. Written informed consent was obtained from participants aged >18 years; for those aged <18 years, parental consent and participant assent were obtained. Recruited participants fasted overnight before the research visits.

Study Visit

At a research study visit conducted at a single central location in each hospital, participants had verification of inclusion criteria, exclusion criteria, and overnight fasting status. Anthropometric measurements were performed by a trained research assistant with the participants wearing only underwear and a hospital gown. Weight was measured to the nearest 0.1 kg twice with an electronic scale, and the readings were averaged. Height was measured to the nearest 0.1 cm twice using a standing stadiometer and averaged. Waist circumference was measured at the level of the anterior superior iliac spine using a nonelastic measuring tape twice, and the 2 measurements were averaged. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2) and then referenced to age- and sex-referenced Centers for Disease Control and Prevention normative values to estimate the respective age and sex strata *z* scores and percentiles.[22] Phlebotomy, a targeted ad hoc lifestyle survey constructed for this study, and hemodynamic assessment were also performed. Participants were allowed to self-report overlapping

Hispanic ethnicity, and identify as White, Black, Asian, or other/mixed race.

Biochemical Assays

At the time of the research visit, venous blood draw was obtained and sent for analysis without freeze-thaw cycles. Clinical Laboratory Improvement Amendments–certified laboratories at each hospital were contracted to perform standardized assays, including fasting lipid panel with total cholesterol, high-density lipoprotein cholesterol, and triglycerides; leptin; aldosterone; plasma renin activity; CRP (C-reactive protein); glucose; and insulin. Homeostatic model assessment of insulin resistance was calculated as the product of blood glucose and insulin concentrations in mg/dL divided by 405. Aldosterone was divided by renin to derive the aldosterone/renin ratio. We calculated low-density lipoprotein cholesterol (LDL-C) with use of the Freidewald formula for participants with fasting triglycerides <400 mg/dL.

Hemodynamic Assessment

Hemodynamic assessments were performed after 3 minutes of supine rest using the NIHem hemodynamic workstation (Cardiovascular Engineering, Inc, Norwood, MA) combined with Philips IE33 echocardiogram system (Philips Healthcare, Andover, MA). The NIHem workstation has been previously validated, demonstrating reproducibility and validity compared with invasive measurement.[13,23,24] In the parasternal long axis view, left ventricular outflow tract diameter and Doppler interrogation of aortic flow over >10 heart beats was acquired, signal averaged, and integrated to estimate the aortic flow volume. After recording the 2-dimensional echocardiographic and Doppler flow data, the NIHem hemodynamic workstation used a special BP cuff with an integrated audio microphone to record the Korotkoff sounds and the oscillometric BP waveform for measurement of brachial BP. Then, a noninvasive micromanometer was placed on the skin overlying an artery to measure pressure waveforms at the brachial, carotid, and femoral arteries. The brachial artery waveform was calibrated by using systolic and diastolic BP measured at the same site and was then integrated to calculate mean arterial pressure (MAP). The carotid and femoral pressure waveforms were calibrated to the same mean and diastolic BP. By referencing the simultaneously acquired ECG rhythm strip, the time between R wave and onset of pulse at carotid and femoral sites could be calculated. An external body caliper was used to measure distance from the suprasternal notch to the site of carotid measurement and to the site of femoral measurement. To account for parallel transmission up to the carotid and around the arch, the difference in notch-femoral distance and notch-carotid distance was divided by the difference of R wave-femoral pulse onset and R wave-carotid pulse onset to calculate the CFPWV. The NIHem system automatically used the carotid pressure tracing to calculate central PP (cPP) as the difference between maximum systolic and diastolic BP. Left ventricular outflow tract flow was assessed by using a signal averaged spectral analysis. The leading edge of the flow spectrum was used to extract the flow waveform, which was multiplied by left ventricular outflow tract area to convert the flow velocity to volumetric flow rate. Then, to eliminate the temporal lag between flow and pressure, the echocardiographic flow waveform was matched in an automated manner by the workstation to the carotid tonometry pressure waveform by aligning the foot of the respective signal averaged waveforms.[23] The point at which flow reaches 95% of its peak was identified. The corresponding pressure change during the interval between foot of the flow waveform and 95% of its peak was automatically determined. Zc was calculated as the ratio of change in pressure/change in flow in the time period from the foot of the waveform to 95% of its peak. Forward and backward pressure waves were separated in the time domain, as previously described.[25] FPW was calculated as the difference in wave peak minus trough of the forward pressure wave before the arrival of the reflected wave. All hemodynamic data were analyzed in batches in a blinded, deidentified manner by a single reader (J.P.Z.).

Statistical Analysis

We compared anthropometric measures, hemodynamic measurements, and biomarker concentrations between NW and EW participants. Categorical variables were compared between groups with the Fisher exact analysis. Continuous variables were compared with the Student *t* test.

Linear regression models were constructed separately for each of the hemodynamic measures of interest (dependent variables in statistical modeling): CFPWV, cPP, Zc, FPW, and MAP. Because of nonnormal distributions, cPP, Zc, FPW, and biomarkers were natural logarithmically transformed. The stepwise regression models adjusted for covariates known to influence aortic stiffness.[26] Step 1 treats BMI *z* score as a continuous primary independent variable, with covariates of age (in years) and sex. In step 2, step 1 variables were combined with continuous averaged height (cm), resting heart rate (beats per minute), and distending pressure as MAP (mm Hg). Step 3 added (to step 2) a block of biomarkers (lntriglycerides, lnLDL-C, lnHOMA, lnCRP, lnleptin, and lnaldosterone/renin ratio). In Step 4, backward elimination was

Table 1. Baseline Characteristics

Characteristics	NW Group	EW Group	*P* Value
No.	98	148	
Demographics			
Female sex	45 (46)	67 (45)	1
Age, y	16±2	16±2	0.68
White	28 (28)	30 (20)	1
Non-Hispanic Black	23 (23)	30 (20)	0.88
Non-Black Hispanic	26 (27)	72 (49)	<0.001
Asian	9 (9)	2 (1)	0.005
Native American/Pacific Islander	3 (3)	3 (2)	0.61
Multirace/unknown	9 (9)	11 (7)	0.62
Anthropometric measures			
Height, m	1.64±0.10	1.67±0.09	0.01
Weight, kg	57±11	92±21	<0.001
Waist circumference, cm	74.3±9.2	103.0±13.6	<0.001
BMI, kg/m^2	20.9±2.7	32.9±6.6	<0.001
BMI age-sex percentile, %	51.2±24.7	93.5±10.7	<0.001
Lifestyle factors			
Secondhand smoking exposure	5 (5)	19 (13)	0.049
Daily soda	11 (11)	12 (8)	0.42
Daily fruit juice	27 (28)	20 (14)	0.006
Daily sports drinks	11 (11)	10 (7)	0.43
Breakfasts per week	5.0±2.1	4.1±2.5	0.006
Days with ≥30 min of activity	4.4±2.1	3.8±2.1	0.02
Television hours per day	1.8±1.4	2.3±1.4	0.006
Biomarkers			
Total cholesterol, mg/dL	160±39	176±40	0.001
HDL-C, mg/dL	55±14	42±12	<0.001
Triglycerides, mg/dL	80±47	132±75	<0.001
LDL-C, mg/dL	89±33	106±36	<0.001
CRP, mg/L	0.7±0.8	1.3±2.0	<0.001
Glucose, mg/dL	84±6	83±7	0.87
Insulin, μIU/mL	11.5±16.1	20.6±17.2	<0.001
HOMA-IR	2.5±3.7	4.3±3.7	<0.001
Plasma renin activity, ng/mL per h	1.7±1.2	1.7±1.4	0.75
Aldosterone, ng/dL	6.4±4.4	7.2±6.5	0.53
Aldosterone/renin ratio	5.3±5.3	5.4±4.3	0.45
Leptin, ng/mL	5.0±7.0	15.5±11.9	<0.001

Data are given as number (percentage) or mean±SD. BMI indicates body mass index; CRP, C-reactive protein; EW, excess weight; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; and NW, normal weight.

performed with variables significantly associated with the arterial stiffness measures (P<0.05) retained in the model. Models with MAP as an outcome did not include MAP as a covariate. In an additional analysis, we added race/ethnicity as a covariate in step 2. SAS 9.4 (SAS Institute Inc, Cary, NC) was used for data analysis. Multicollinearity analysis revealed variance inflation factors of <2.5 for all analyses. As this was a hypothesis-generating study, both nominal P<0.05 and Bonferroni-corrected P values (0.05/[6 outcomes×12 variables] ≈0.001) are reported.

RESULTS

The NW (n=98) and EW (n=148) groups were similar in terms of age and sex distributions (Table 1). Compared with the NW group, the EW group was significantly heavier and had larger waist circumference (by definition), was less likely to be of Asian race, was more likely to be Hispanic, and was taller. With respect to lifestyle habits, the EW group reported eating breakfast fewer times per week, reported higher secondhand cigarette smoke exposure, had fewer days with physical activity, and watched more television per day, but they were less likely to drink fruit juice daily. The groups were similar in their daily intake of soda or sports drinks. The EW group had significantly higher concentrations of blood total cholesterol, triglycerides, LDL-C, CRP, insulin, homeostatic model assessment of insulin resistance, and leptin than the NW group. Concentrations of glucose, aldosterone, renin, and the aldosterone/renin ratio were similar between the 2 groups.

With respect to hemodynamic variables, the EW group had higher heart rate, higher systolic, diastolic, and brachial BP, higher systolic and diastolic central BP, and higher values of CFPWV, cPP, and MAP (Table 2). In the subgroup with echocardiographic

Table 2. Hemodynamic Results Comparing EW With NW Group

Variable	NW Group	EW Group	*P* Value
No.	98	148	
Heart rate, beats per minute	64±10	68±10	0.002
Brachial systolic pressure, mm Hg	114±11	124±13	<0.001
Central systolic pressure, mm Hg	103±14	114±18	<0.001
Diastolic pressure, mm Hg	52±8	59±10	<0.001
Carotid-femoral pulse wave velocity, m/s	4.6±0.6	5.0±0.7	<0.001
Central pulse pressure, mm Hg	51±15	56±17	0.035
Mean arterial pressure, mm Hg	72±9	80±11	<0.001
Echocardiographic subgroup No.	82	119	
Forward pressure wave amplitude, mm Hg	50±14	54±17	0.09
Left ventricular outflow tract diameter, cm	2.0±0.2	2.1±0.2	0.002
Characteristic impedance, dynes×s/cm^5	301±122	281±138	0.045
Peripheral resistance, dynes×s/cm^5	2148±860	1867±809	0.003

Data are given as mean±SD. EW indicates excess weight; and NW, normal weight.

Table 3. Correlations Between Hemodynamic Variables

Variable	CFPWV	cPP	Zc	FPW	MAP
CFPWV R^2	1	0.15	0.03	0.15	0.30
P		0.02	0.66	0.04	<0.0001
cPP R^2		1	0.56	0.98	0.30
P			<0.0001	<0.0001	<0.001
Zc R^2			1	0.58	0.14
P				<0.0001	0.04
FPW R^2				1	0.28
P					<0.001
MAP R^2					1

Data are given as Pearson correlation *R* and the *P* value. CFPWV indicates carotid-femoral pulse wave velocity; cPP, central pulse pressure; FPW, forward pulse wave; MAP, mean arterial pressure; and Zc, characteristic impedance.

data, FPW trended toward a higher value in EW group, whereas Zc was lower compared with the NW group. Correlations between hemodynamic variables demonstrated that MAP was mild to moderately correlated with each large artery stiffness measure (Table 3). CFPWV was modestly positively correlated with cPP and FPW. cPP was highly correlated with FPW in this young cohort, and it was moderately correlated with Zc. FPW was positively correlated with Zc.

In multivariable-adjusted stepwise models, higher BMI was nominally associated with higher CFPWV, cPP, FPW, and MAP, and with lower Zc (Table 4). Race/ethnicity was not associated with hemodynamic measures (data not shown). After adjustment for BMI, age, sex, height, pulse, MAP, and biomarkers as a group, higher blood leptin concentration was associated with lower cPP and FPW; higher LDL-C was nominally associated with higher CFPWV and lower Zc but not at the multiple testing comparison *P*-value threshold; and higher CRP was associated with higher cPP. Homeostatic model assessment of insulin resistance was associated with MAP but not large artery stiffness measures. Aldosterone/renin ratio was not associated with any outcome after adjustment for BMI and MAP. The total proportion of variance explained by covariates for each vascular stiffness measure ranged between 13% and 34%.

DISCUSSION

In this cross-sectional analysis of a convenience sample of adolescents, we identified several key associations between aortic stiffness and circulating biomarkers. Generally, aortic stiffness was higher in EW compared with NW participants, consistent with previous reports (including stiffness measured by cardiac magnetic resonance imaging).[27] EW participants had worse blood cholesterol, insulin resistance, inflammation, and leptin concentrations. Divergent association patterns emerged on multivariable regression analyses, suggesting that higher BMI was associated positively with worse large and small artery wall stiffness measures but was inversely related to other measures sensitive to aortic root size. After adjustment for BMI, blood lipid concentrations and systemic inflammation were associated with vascular stiffness measures that are strongly dependent on large artery wall properties. Blood adipokine leptin and LDL-C concentrations were inversely associated with vascular measures dependent on arterial flow and size. Contrary to previous reports, insulin resistance was primarily related to small artery function, which in turn was associated with aortic stiffness.[28] Overall regression models accounted

Table 4. Linear Regression Results for Hemodynamic Outcome Variables

Variable	CFPWV	cPP	Zc	FPW	MAP
BMI	0.09 (0.01 to 0.18)	0.06 (0.01 to 0.11)	−0.07 (−0.13 to −0.01)	0.07 (0.01 to 0.13)	3.52 (2.16 to 4.88)
P value	0.04	0.03	0.01	0.02	<0.001
LDL-C	0.26 (0.03 to 0.50)		−0.21 (−0.36 to −0.06)		
P value	0.03		0.007		
CRP		0.06 (0.05 to 0.06)			
P value		0.02			
Leptin		−0.09 (−0.14 to −0.04)		−0.09 (−0.15 to −0.04)	
P value		<0.001		0.002	
HOMA-IR					2.25 (0.35 to 4.15)
P value					0.02
Model R^2	0.18	0.24	0.13	0.19	0.34

Reported as regression coefficient (95% CI) and the *P* value. All biomarkers and outcomes (cPP, Zc, and FPW) are natural logarithm transformed for nonnormal distributions. Only biomarkers with $P<0.05$ for a given outcome are reported. Model R^2 indicates the proportion of variance in the respective hemodynamic outcome accounted for by the significant covariates and biomarkers. Adjustment covariates forced into the model are age, sex, height, heart rate, MAP, and BMI *z* score. BMI indicates body mass index (age- and sex-referenced *z* score); CFPWV, carotid-femoral pulse wave velocity; cPP, central pulse pressure; CRP, C-reactive protein; FPW, forward pulse wave; HOMA-IR, homeostatic assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; and Zc, characteristic impedance.

Triglycerides and aldosterone/renin ratio were not associated with these vascular stiffness measures.

for a modest proportion of the interindividual variance in aortic stiffness measures, indicating there are additional drivers of adolescent arterial stiffness that were not captured in the present analyses.

Higher LDL-C and triglyceride levels are demonstrated in our sample to be associated with greater large artery stiffness. Previous studies in adults and youth demonstrate positive cross-sectional associations between CFPWV and LDL-C and triglyceride concentrations.[18,24,29–32] In longitudinal studies of adolescents, LDL-C has also been shown to predict arterial remodeling in adults, including stiffness and intimal medial thickening.[33–35] LDL-C is associated positively with aortic stiffness in youth with genetic hyperlipidemia.[36] Our longitudinal data in adults as well as other studies in children have shown that changes in blood lipids predicted future changes in arterial wall stiffness or wall thickness.[18,33] Mechanisms for lipid-associated aortic stiffening could include generalized lipid deposition in the subendothelial layer of the artery, localized atheromatous plaque progression, or oxidization of lipid fractions.[37,38] The association between higher low-density lipoprotein and lower Zc could be consistent with the lower Zc observed in EW compared with NW. LDL-C–associated arterial remodeling may lead to arterial dilation (the Glagov phenomenon) or wall stiffening. If arterial dilation predominates compared with wall stiffening, the expected net effect would be a decline in Zc. EW can lead to increased higher aortic flow and larger aortic size.[39,40] The association between higher CRP and higher PP is consistent with previous reports in adults.[16] Inflammatory effects on arterial stiffness could be caused by either neurohormonal activation or concomitant early atherosclerosis.[41,42] Insulin resistance has been associated with aortic stiffness in adolescent cohorts previously.[28] Our work demonstrates that insulin resistance is associated with small artery function, which in turn is associated with several large artery vascular function measures. It is conceivable that prior published associations may have conflated small artery versus large artery effects of insulin resistance.

Circulating leptin concentration was associated with lower cPP and FPW. Leptin is elaborated by adipose tissue and is linked to BMI.[43] Higher leptin has been described in youth, young adults, and older adults to be associated with higher aortic stiffness.[17,44] In contrast, we have reported previously that in adults, higher leptin was associated with lower aortic stiffness and higher small artery stiffness, after adjustment for weight.[17] The current findings in growing adolescents link higher blood leptin concentrations to lower PP. Mechanistically, PP and FPW reflect the interaction between aortic wall stiffness, pulsatile flow, and aortic size.[11,20] Given that blood leptin levels were not associated with CFPWV, it may be inferred that leptin concentrations are related to pulsatile flow or to aortic remodeling, presumably to accommodate the increased flow associated with EW. Blood volume and flow are higher in obese youth.[15,40,45] Leptin acts in the central nervous system to stimulate aldosterone, which could in turn cause fluid retention.[46] Leptin receptors are present on vascular cells, suggesting a direct role for leptin in vascular physiological features.[47] Leptin increases renal sympathetic activation, which can increase pressure pulsatility.[48] Leptin is a key long-term energy homeostasis signal with energy replete status being signaled through higher leptin levels.[49,50] "Leptin resistance" can occur in obesity, wherein circulating leptin levels are elevated because of altered leptin receptor signal transduction in target tissues, which could then lead to excess leptin signaling in "off-target" tissues, such as the vasculature.[43,51] Consistent with our previous work in adults, the current findings signal a potentially salutary role for leptin on vascular stiffness after adjusting for obesity. Aldosterone/renin ratio was not associated with aortic stiffness in our sample, in contrast to previous reports in adult cohorts.[16] The intravascular fluid regulation and direct vascular tissue effects of the renin-angiotensin-aldosterone system make it a plausible mechanistic mediator of vascular remodeling. The lack of association of aldosterone/renin ratio with aortic stiffness measures in our sample likely may reflect the well-documented variability of circulating aldosterone levels in relation to pubertal stage, which was not assessed in our study.[52]

The present investigation has several strengths, including the racial/ethnic diversity in an adolescent cohort (which enhances generalizability); statistical modeling to ensure parsimonious variable selection; deep phenotyping, including integrated pressure and flow hemodynamics, defining the intercorrelations among the arterial measures in adolescents; and extending the associations of previously recognized drivers of aortic stiffness in adults to children. Limitations include its cross-sectional design, which precludes causal inferences. Our sample size may limit power to detect more modest associations. The echocardiographic assessment of flow is an estimate and, therefore, the indexes dependent on echocardiographic assessment are also estimates. Aortic stiffness, measured by tonometry, may not be capturing other large artery characteristics compared with other modalities, such as magnetic resonance imaging. As with any observational study, unmeasured confounders may have affected the results reported. For example, pubertal stage was not assessed and may have affected variance of the aldosterone/renin ratio. Therefore, our findings should be considered hypothesis generating.

In conclusion, in this diverse sample of adolescents, higher BMI was related to worse large and

small artery stiffness measures but inversely with other measures sensitive to aortic size. Blood lipid concentrations and systemic inflammation were associated with vascular measures driven by artery wall tissue characteristics. Blood leptin and LDL-C levels were inversely associated with arterial flow and size-dependent vascular function measures. These associations of select biomarker pathways with vascular stiffness may represent avenues for future studies to mitigate arterial stiffness and its downstream consequences over the life course.

ARTICLE INFORMATION

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Disclosures

None.

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