HHS Public Access

Author manuscript

J Hum Hypertens. Author manuscript; available in PMC 2022 March 20.

Published in final edited form as:

J Hum Hypertens. 2022 March ; 36(3): 263–270. doi:10.1038/s41371-021-00506-7.

Physical Activity is Associated with Lower Pulsatile Stress but not Carotid Stiffness in Children

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Abstract

The cardiovascular disease (CVD) process may begin early in life when accompanied by atherosclerotic risk factors. CVD risk factors in children are associated with stiffening of the large elastic arteries, a reflection of subclinical atherosclerosis. Physical activity is a preventative lifestyle strategy that may benefit arterial stiffness by attenuating the hemodynamic stress on the artery wall. This study examined the relations between physical activity, carotid pulsatile stress, and carotid stiffness in children. One hundred and forty children (9-11 yrs; 50.0% male, 57.9% African American, 42.10% Caucasian, body mass index (BMI) 20.1±4.7 kg/m^2) participated in this study. Physical activity counts were measured using a wrist-worn accelerometer and averaged over 7 days. Carotid artery β-stiffness and pulse pressure (calibrated to brachial mean and diastolic pressure) were assessed as via ultrasound and tonometry, respectively. Pulsatile stress was calculated as the product of carotid pulse pressure and heart rate. Physical activity counts were correlated with pulsatile stress (r= -0.27), and BMI (r= -0.23), but were unrelated to carotid stiffness. In multivariate models, associations between physical activity counts and pulsatile stress remained (B= -1.3 [95%CI, -2.4, -0.2], β= -0.20, $p<0.05$) after covariate adjustment for age, race, sex, pubertal stage and BMI. Carotid pulsatile stress was related to regional carotid stiffness (r=0.45, $p<0.05$). These data suggest that higher levels of physical activity at young age are associated with lower hemodynamic stress in the carotid artery. Findings are discussed in the context of an inverse relationship between hemodynamic pulsatile stress and carotid stiffness in children.

Keywords

Physical activity; children; central hemodynamics; arterial stiffness

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We have no conflicts of interest to disclose.

Introduction

The pathological origins of cardiovascular disease (CVD) develop in the arteries early in life when coupled with CVD risk factors[1,2] and can manifest as subclinical changes in arterial stiffness. The stiffness of the large, elastic arteries (e.g. the carotid artery) increases naturally during childhood growth and maturation[3,4] but is modulated by behaviors like physical activity and its concomitant impact on CVD risk factors. Indeed, obesity,[5–8] type 2 Diabetes,[9] and low levels of physical activity[10–12] are associated with greater carotid artery stiffness in children. While it is difficult to differentiate the impact of growth/maturation versus CVD risk factors on arterial stiffness in children,[6] it remains recommended as part of a comprehensive assessment of subclinical atherosclerosis in children.[13] Indeed, carotid artery stiffness in childhood is linked with subclinical markers of end-organ health including cerebral blood flow pulsatility,[14] left ventricular mass,[15] and carotid intima media thickness (IMT).[16] As such, there is great interest in identifying hemodynamic and behavioral determinants of carotid artery stiffness in children.[17]

CVD risk factors in childhood appear to prime the arteries for accelerated stiffening in adulthood.[18–20] It is currently unclear, however, what hemodynamic factors modify how the arteries stiffen during childhood. In adulthood, pulsatile stress has emerged as a potentially modifiable contributor to increases in artery stiffness. Pulsatile stress describes the repeated cyclic stress exerted by pulse pressure on the arterial wall with each cardiac contraction that can fatigue elastic wall elements over time and contribute to arterial stiffening in adults.[21,22] Whether pulsatile stress is related to artery stiffness in children is unknown, but may offer a potentially modifiable hemodynamic target to attenuate the impact of CVD risk factors on carotid artery stiffness in adulthood. Identifying early life behaviors that benefit hemodynamic contributors to carotid artery stiffening is an important initial step in understanding how childhood behaviors may inform future CVD risk factors in adulthood.

Physical activity has emerged as an important lifestyle behavior in the prevention of CVD.[23] Physical activity during childhood is inversely related to hypertension,[24] and predicts carotid artery stiffening[25] and atherosclerosis progression in adulthood.[26] As such, physical activity during childhood may be an important behavior to improve cardiovascular health and specifically attenuate carotid artery stiffening in adulthood.[25] Indeed, physical activity appears inversely related to carotid artery stiffening in children.[10] The mechanisms underlying this beneficial effect of physical activity on carotid artery stiffness in children is unclear but may involve hemodynamic contributors such as lower pulsatile stress. Therefore, the purpose of this study was to investigate the associations of physical activity, carotid pulsatile stress, and carotid artery stiffness in children 9-11 years of age. We hypothesized that children with higher levels of physical activity would present with lower carotid pulsatile stress and artery stiffness.

Methods

This analysis included a subset of children aged 9-11 years from the Syracuse City community as part of the larger Environmental Exposures and Child Health Outcomes (EECHO) study.[27,28] Participants included in this analysis were required to have physical

activity accelerometry data and undergo vascular measures. This resulted in a total of 140 children being included in our data set. Race was self-identified by the parents as either African American or Caucasian. All children were free of serious medical or developmental disabilities reported by the parent that would impede participation. Specific exclusion criteria has been described previously.[24] The study was approved by the institutional review board of Syracuse University. All guardians gave written consent and all participants gave assent before enrollment.

Participants underwent descriptive measures, vascular testing, and physical activity assessment. Descriptive and vascular measures were completed on the same day, between approximately 8:00AM and 12:00PM. Participants were instructed to arrive fasted and abstain from vasoactive medications (e.g. allergy, attention-deficit (hyperactive) disorder medications) the day of testing. All vascular testing was conducted in a dimly lit, temperature-controlled laboratory with the participant in the supine position. Vascular measures were obtained after 5-minutes of quiet rest. Visits were not standardized by menstrual cycle phase among regularly menstruating females (n=13).

Descriptive measures

Descriptive measures were assessed as previously described,[27] and included height, weight, socioeconomic status (calculated based on parental occupation, income, and education data), and pubertal stage (Peterson's Pubertal Development Scale).[29] Body mass index (BMI) was calculated as weight (kg)/height (m) ^{2}. Percent body fat was estimated by dividing the amount of body fat by total bodyweight using a hand-held A-mode ultrasound device (BodyMetrix, Intelametrix, Inc., Livermore, CA; triceps and calf sites) that is reliable in children.[30] Waist and hip circumferences were measured using a flexible tape measure at the level of the natural waist and widest portion of the hips/buttocks and used to derive the waist:hip ratio. BMI classification (underweight, healthy weight, overweight, obese) was determined using CDC data as we have previously described.[31]

Physical activity

Physical activity was measured using a wrist-worn accelerometer (MotionWatch 8®, CamNtech, Cambridge, UK) over an average of 8 ± 1 days. Participants were instructed to wear the device continuously unless bathing/swimming. All activity counts were summed across each day the device was worn and divided by the number of days worn to calculate the average physical activity counts per day.

Vascular and central hemodynamic measures

Brachial systolic (SP), and diastolic (DP) blood pressures were obtained using an automated oscillometric sphygmomanometer on the nondominant arm that has been validated for pediatric use (Mobil-O-Graph, I.E.M., Stolberg, Germany). Two measurements were taken and averaged. If values differed by more than 5 mmHg, a third set was taken and the two most similar measures were averaged for analysis. Brachial mean arterial pressure (MAP) was calculated as 1/3(SP) + 2/3(DP).

Carotid intima-media thickness (IMT), β-stiffness, and wave intensity were measured just proximal of the carotid bulb using ultrasound (ProSound α7; Aloka, Tokyo, Japan) and a 7.5-10.0 MHz linear-array probe. IMT was measured as the distance between the lumen-intima interface and media-adventitia interface over a 5 mm region of interest using semi-automated digital calipers during diastole (determined by the R-wave from simultaneous EKG gating). The distance between common carotid artery near and far wall were traced continuously via eTracking to create wall distension waveforms, as described previously.[32] Wall distension waveforms were calibrated to carotid systolic pressure (assessed via applanation tonometry (AtCor Medical Inc., Naperville, IL)) and brachial diastolic pressure. β-Stiffness was calculated as $\ln(P_{max}/P_{min})/[(D_{max}-D_{min})/D_{min}]$, where P and D are pressure and diameter respectively, and max and min correspond to maximum (systolic) and minimum (diastolic) values. Distension waveforms were combined with simultaneously measured carotid flow waveforms for wave intensity analyses (WIA), described in detail elsewhere.[33] In brief, wave intensity was calculated using time derivatives of blood pressure (P) and velocity (U), where wave intensity = (dP/dt x dU/dt) in order to assess complementary measures of pulsatile hemodynamics including forward wave intensity (W1) and reflection index (RIx; calculated as reflected wave energy (wave intensity negative area) divided by W1). All ultrasound analyses were conducted by a single trained investigator (WKL)

Carotid pressures were derived from tonometry waveforms and calibrated to brachial mean and diastolic pressure. Carotid pulsatile stress was calculated as carotid pulse pressure (carotid SP-DP) multiplied by heart rate. Pulse pressure amplification was calculated as brachial pulse pressure divided by carotid pulse pressure.

Statistical analyses

Statistical analysis was conducted using R Version 3.6.2: (Vienna, Austria 2019 https://www.R-project.org/ - author R core Team, organization – R Foundation for Statistical Computing). All data is presented as mean ± SD. Residual plots were examined to evaluate for non-random or non-normal distributions, outliers, and non-linearity. Physical activity measures were centered around the mean and counts analyzed in thousands. Pearson correlations were computed between carotid stiffness, pulsatile hemodynamics (e.g. pulsatile stress, wave dynamics/reflection) and structure (IMT), and physical activity counts, age, and BMI. Based on relationships observed using linear regression, we further explored the relation between carotid pulsatile stress and physical activity when covarying for age, BMI, race, sex, SES, and pubertal stage.

Results

Participant descriptive characteristics are shown in Table 1. The sample size consisted of 140 children, of which 70 (50.0%) were females. Of the total sample, 81 (57.9%) were African-American and 59 (42.1%) Caucasian. The majority of the sample were categorized as healthy weight (59.3%) and in the early to mid-pubertal stage (77.1% Peterson's stage 2-3). Table 2 displays the vascular and physical activity outcomes for the full sample.

Linear associations between physical activity and outcomes of interest are show in Table 3. Age was significantly and positively associated with BMI (r=0.30; p<0.001) and carotid pulse pressure (r=0.25; p<0.01). BMI was inversely associated with physical activity (r=−0.23; p<0.01), carotid wave reflection (RIx, r=−0.17, p<0.05), pulse pressure amplification (r=−0.24, p<0.01) but positively associated with carotid pulsatile stress (r=0.22; p<0.01), β-stiffness (r=0.29; p<0.01), and forward wave intensity (W1; r=0.29, p<0.01). Physical activity was inversely associated with heart rate (r=−0.24; p<0.01), carotid pulse pressure (r=−0.17; p=0.04), pulsatile stress (r=−0.27; p<0.01) (Figure 1B), mean pressure (r=−0.17, p=0.04), carotid W1 (r=−0.20, p=0.02). Carotid β-stiffness was not significantly associated with physical activity counts (r=−0.15, p=0.07; Figure 1A). Multiple regression revealed the inverse relationship between physical activity and pulsatile stress and remained significant (p=0.02) even when adjusted for confounding factors such as race, sex, SES, age, BMI, and pubertal stage (Model R^2= 0.11, F statistic = 2.321, p<0.05; Table 4).

Discussion

This study sought to examine the associations between physical activity, carotid pulsatile stress, and carotid stiffness in children. Our findings revealed that 1) carotid pulsatile stress was correlated with regional carotid stiffness in children and 2) although physical activity in middle-childhood was not directly associated with carotid stiffness, it was associated with carotid pulsatile stress. These data suggest greater levels of physical activity in children reduces pulsatile stress within the carotid artery, which is associated with lower carotid stiffness.

To date, our understanding of modifiers of artery stiffness in children remains limited. Data indicate that artery stiffness in children is related to CVD risk factors (e.g. blood pressure, BMI) that may be modifiable by physical activity. The concept of pulsatile stress is an important construct in artery stiffening in the context of early vascular aging among adults,[21,22,34] but its importance among children is unclear. Pulsatile stress could theoretically contribute to remodeling in children, particularly in combination with CVD risk factors.[26,35,36] To our knowledge, we are the first to identify carotid pulsatile stress is linearly associated with carotid stiffness among children. Although this is conceptually logical given the adult literature, the relationship between pulsatile stress and carotid stiffness observed herein could be inherently mathematical (i.e. both measures are derived using carotid pulse pressure). As such, it is possible that pulsatile stress as defined by the product of heart rate and pulse pressure is not directly related to artery stiffness in children, unlike its application in adults.[21,34,37] The natural growth/maturation process may enable the vasculature to accommodate greater hemodynamic stress without substantially burdening or further stiffening the vascular wall until maturity and the end of growth. However, our associations between carotid pulsatile stress and known contributors to target organ damage and vascular dysfunction (BMI, mean pressure, carotid stiffness, forward wave intensity, and pulse pressure amplification) raises the possibility that this hemodynamic force is related to detrimental vascular changes even at younger ages.

We observed higher levels of physical activity were associated with lower carotid pulsatile stress in children, suggesting a potential mechanism through which physical activity

improves hemodynamics that appear related to arterial stiffness. The inverse relation between physical activity and pulsatile stress likely reflects the inverse associations between physical activity and pulse pressure and heart rate. Greater physical activity may lower pulse pressure in part by reducing BMI,[38] thereby preventing the expansion of pulse pressure that occurs with larger body size.[35] In support of this, we noted significant inverse relations between physical activity and BMI, as well as BMI and pulse pressure. The effect of physical activity on pulse pressure may extend beyond the indirect effects of BMI and reflect changes in the central determinants of pulse pressure (e.g. aortic characteristic impedance, diameter, and proximal aortic stiffness). Indeed, we noted greater physical activity counts was associated with lower W1 and greater pulse pressure amplification (both proxy indicators of impedance/impedance-matching); however, more research is necessary to confirm these effects on central determinants of pulse pressure. We also noted that greater physical activity is associated with lower heart rate in our sample, an established marker of cardiovascular health in children.[36] This result may be driven by the effects of physical activity on autonomic function. Previous data indicate that greater physical activity is associated with greater heart rate recovery after an exercise bout[10] (a proxy of autonomic function).[39] In this setting, improved autonomic function among active children may increase parasympathetic tone and lower resting heart rate, thereby reducing pulsatile stress. Cumulatively these data suggest that physical activity may improve pulsatile stress in children through its beneficial effects on pulse pressure, BMI, and autonomic function. It should be noted that effect of physical activity on carotid pulsatile stress appears modest, with the fully adjusted model accounting for approximately 11% of the variation in pulsatile stress. Ultimately, our data support a role for physical activity influencing both components of carotid pulsatile stress (heart rate and pulse pressure). Heart rate may be an initial modifiable target in children since carotid pulse pressure was not elevated in this sample per se; however more research is needed to identify the efficacy of these potential targets of pulsatile stress.

We noted a weak, non-significant relationship between greater physical activity and carotid stiffness in children. Prior investigations in normal and overweight/obese children have identified statistically significant inverse associations between moderate intensity physical activity and carotid stiffness, however the strength of the relationship was actually similar ($r=-0.13$) to our data ($r=-0.15$).[40] This suggests that while carotid stiffness may be more sensitive to moderate intensity physical activity (particularly among predominantly overweight/obese samples),[40] the cross-sectional relationship in general remains rather modest. While the cross-sectional impact of physical activity on arterial stiffness in children appears tenuous, there is much stronger evidence behind physical activity and longitudinal changes in arterial stiffness. Indeed, greater physical activity during early childhood (3-5 years of age at baseline) is associated with slower longitudinal progression of carotid stiffening over 3 years[10] and physical activity in middle-childhood/adolescence are associated with lower carotid stiffness as adults.[25] Further research is necessary to confirm the hemodynamic mechanism behind longitudinal associations of physical activity and arterial stiffening.

Considerations and Limitations

This study is not without its limitations. We chose wrist-worn accelerometers to assess physical activity to maximize use and compliance among the children. This did, however, limit the fidelity of our physical activity data as we are unable to derive step count or minutes of moderate and vigorous physical activity. The wrist-worn accelerometry may have also contributed to the modest association between physical activity and pulsatile stress in our study (~11%). Indeed, the relationship between physical activity and vascular hemodynamics appears stronger when assessed with hip versus wrist-worn accelerometers.[41] As such, our data may be underestimating the beneficial relationship between pulsatile stress (and potentially arterial stiffness) and physical activity, which may be more robust when assessed with hip-worn accelerometry. Additional work is necessary using gold-standard hip-worn accelerometers to better quantify and describe the amount or type of physical activity necessary to improve hemodynamic contributors to arterial stiffness. Brachial blood pressure values presented herein are not intended to be used as normative values. Finally, this study was cross-sectional in nature and cannot determine causality. Future longitudinal and intervention studies should be conducted in children to verify cause and effect relationships between physical activity, pulsatile stress, and progression of clinically relevant measures of arterial stiffness throughout the growth and maturation process.

Conclusion

This study sought to examine the associations between physical activity, carotid stiffness, and pulsatile stress in children 9 - 11 years old. We found that greater physical activity is associated with lower pulsatile stress but not directly associated with carotid stiffness. Taken together, these data suggest that having higher levels of physical activity are associated with less hemodynamic stress (assessed as pulsatile stress) within the carotid artery, which is associated with lower carotid artery stiffness in children.

Acknowledgments

This study was funded by NIH NIEHS R01 ES023252 02 (PI: B.B. Gump). W.K. Lefferts was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number T32HL134634 during preparation of this manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We wish to express our gratitude to the participants and their families/guardians for their willingness to participate in this study, and to the Environmental Exposures and Child Health Outcomes (EECHO) research team for their help with logistics and data collection.

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Summary Table

What is known about the topic?

- Cardiovascular disease development begins early in life and may result in accelerated stiffening of the large elastic arteries (i.e. the carotid)
- Physical activity may attenuate early life increases in carotid stiffness by reducing the pulsatile stress exerted against the artery over time
- The relationship between physical activity, pulsatile stress, and carotid stiffness in children is unclear

What this study adds?

- Although physical activity was not cross-sectionally associated with carotid stiffness, it was inversely associated with pulsatile stress even after controlling for age, race, sex, socioeconomic status, pubertal stage, and body mass index.
- Higher levels of physical activity were associated with less pulsatile stress within the carotid artery, suggesting a potential hemodynamic mechanism through which physical activity may benefit carotid stiffness in children

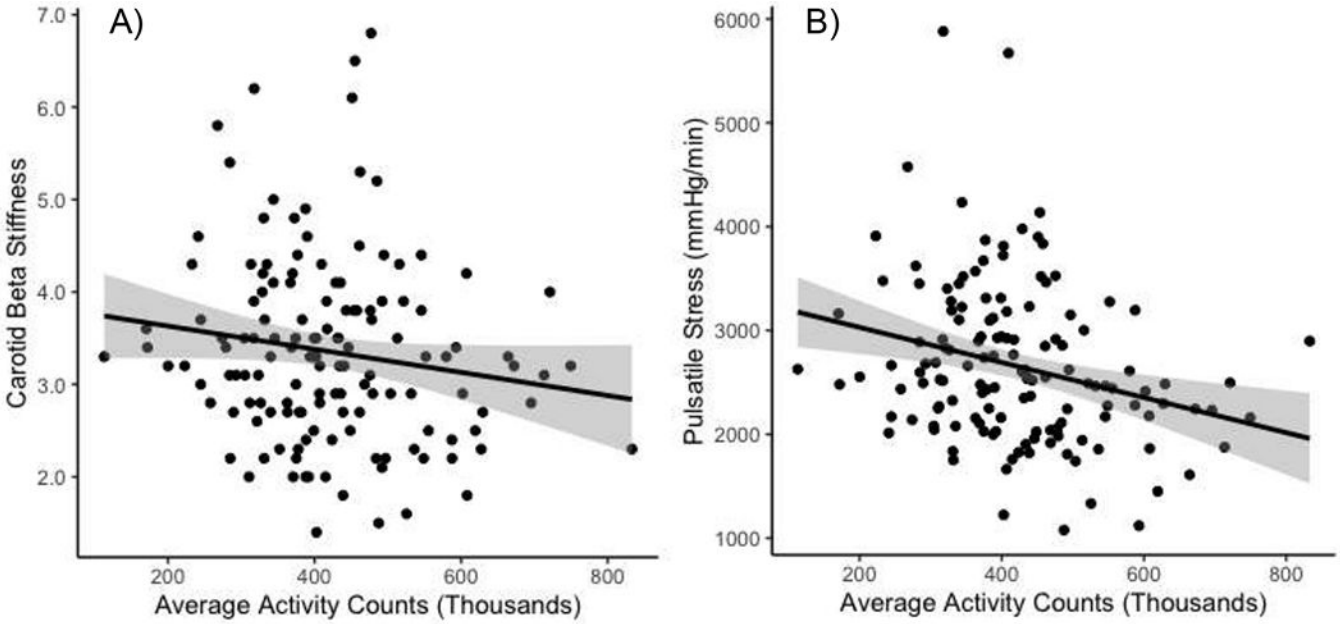

Figure 1:

Association between physical activity counts and carotid A) β-stiffness and B) pulsatile stress (mmHg/min) (n=140).

Table 1:

Descriptive characteristics of the full sample and by sex.

	Male (N=70)	Female (N=70)	Total (N=140)
Age (yrs)	10.4 (0.9)	10.5 (0.9)	10.5 (0.9)
Height (cm)	142.5 (9.0)	145.5 (9.2)	144.0 (9.2)
Weight (kg)	42.9 (13.9)	44.0 (12.6)	43.4 (13.2)
Waist Circumference (cm)	70.39 (12.51)	69.70 (16.27)	70.05 (14.47)
Hip Circumference (cm)	80.96 (11.09)	81.85 (13.13)	81.41 (12.12)
Waist-to-hip Ratio	0.87 (0.07)	0.85 (0.08)	0.86 (0.08)
Percent Body Fat (%)	24.68 (11.72)	26.40 (7.37)	25.54 (9.79)
Body Mass Index (kg/m^2)	20.4 (5.0)	19.9 (4.3)	20.1 (4.7)
Race, N(%)			
African-American	42 (60.0%)	39 (55.7%)	81 (57.9%)
Caucasian	28 (40.0%)	31 (44.3%)	59 (42.1%)
Socioeconomic Status	0.09 (0.87)	0.12 (0.88)	0.11 (0.87)
BMI Classification			
Underweight (<5th percentile)	2 (2.9%)	0 (0.0%)	2 (1.4%)
Healthy Weight (5-85th percentile)	37 (52.9%)	46 (65.7%)	83 (59.3%)
Overweight (85-<95th percentile)	7 (10.0%)	11 (15.7%)	18 (12.9%)
Obese (≥95th percentile)	24 (34.3%)	13 (18.6%)	37 (26.4%)
Pubertal Stage, N(%)			
Pre-pubertal	13 (18.6%)	3 (4.3%)	16 (11.4%)
Early puberty	34 (48.6%)	9 (12.9%)	43 (30.7%)
Mid-puberty	20 (28.6%)	45 (64.3%)	65 (46.4%)
Late puberty	3 (4.3%)	10 (14.3%)	13 (9.3%)
Post-pubertal	0 (0.0%)	3 (4.3%)	3 (2.1%)

Data presented as mean (SD), unless otherwise noted

Table 2:

Vascular outcomes and physical activity in the full sample and by sex (mean (SD).

	Male (N=70)	Female (N=70)	Total (N=140)
Brachial Systolic Pressure (mmHg)	112 (9)	115 (8)	114 (9)
Brachial Diastolic Pressure (mmHg)	67 (5)	68 (6)	68 (6)
Mean Arterial Pressure (mmHg)	82 (6)	84 (6)	83 (6)
Carotid Systolic Pressure (mmHg)	102 (11)	104 (8)	103 (10)
Carotid Pulse Pressure (mmHg)	35 (9)	36 (8)	35 (8)
Heart Rate (b/min)	74 (10)	76 (12)	75 (11)
Carotid Pulsatile Stress (mmHg/min)	2562 (787)	2750 (744)	2656 (769)
Physical Activity Counts ($x10^3$)	447.53 (122.21)	394.61 (118.22)	421.07 (122.71)
Physical Activity Days (count)	8 (1)	8 (1)	8 (1)
Carotid Intima Media Thickness (mm)	0.39 (0.05)	0.40 (0.07)	0.39 (0.06)
W1 ($mmHg/m/s^3$)	9.10 (4.72)	9.78 (6.31)	9.43 (5.55)
Negative Area ($mmHg/m/s^2$)	67.90 (39.09)	68.74 (62.80)	68.32 (51.95)
Reflection Index (au)	7.94 (3.17)	7.96 (6.72)	7.95 (5.21)
Carotid β-Stiffness (au)	3.30 (1.05)	3.41 (0.97)	3.35 (1.01)
Pulse Pressure Amplification (au)	1.36 (0.18)	1.33 (0.18)	1.34 (0.18)

Values presented as mean (SD); W1, forward wave intensity.

J Hum Hypertens. Author manuscript; available in PMC 2022 March 20.

Table 3:

Linear associations between physical activity, age, body size, and vascular outcomes of interest.

Variable	PA	Age	BMI	Heart Rate	cPP	cPS	MP	IMT	W1	RIx	β-Stiffness
Age	−0.16										
BMI	**−0.23**	**0.30**									
Heart Rate	**−0.25**	−0.11	−0.04								
cPP	**−0.17**	**0.25**	**0.29**	0.04							
cPS	**−0.27**	0.14	**0.22**	**0.58**	**0.83**						
MP	**−0.17**	0.02	0.01	**0.22**	**0.30**	**0.34**					
IMT	0.01	0.11	0.13	0.03	**0.17**	0.16	0.05				
W1	**−0.20**	0.07	**0.26**	0.17	**0.63**	**0.63**	0.10	0.09			
RIx	0.05	−0.09	**−0.17**	0.01	−0.01	−0.01	0.01	0.04	**−0.23**		
β-Stiffness	−0.15	0.14	**0.29**	0.11	**0.47**	**0.45**	0.01	0.16	**0.34**	−0.13	
PPA	**0.23**	**−0.29**	**−0.24**	−0.10	**−0.71**	**−0.63**	−0.12	−0.16	**−0.40**	0.03	**−0.22**

PA, physical activity counts; BMI, body mass index; cPP, carotid pulse pressure; cPS, carotid pulsatile stress; MP, mean pressure; IMT, carotid intima-media thickness; W1, forward wave intensity; RIx, reflection index; PPA, pulse pressure amplification. **Bold** indicates $p<0.05$.

J Hum Hypertens. Author manuscript; available in PMC 2022 March 20.

Table 4:

Predictors of carotid pulsatile stress (n=140)

Variable	B	95% CI Low	95% CI High	β	p value
Physical Activity (Centered)	−1.3	−2.4	−0.17	−0.20	0.02
Age	44.7	−106.8	196.21	0.05	0.56
Body Mass Index	25.3	−4.4	55.01	0.15	0.09
Race (Caucasian)	−32.3	−323.3	258.75	−0.02	0.83
Sex (Female)	105.3	−192.7	403.36	0.07	0.49
Socioeconomic Status	−14.4	−172.8	144.02	−0.02	0.86
Pubertal Stage	31.8	−145.3	208.98	0.04	0.72

Model R^2= 0.11, F statistic = 2.321, $p<0.05$. Standardized beta include categorical (factor) variables.