Cross-Sectional Study of Arterial Stiffness in Adolescents with Down Syndrome

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Objectives To test whether youth with Down syndrome have aortic stiffness indices, as measured by pulse wave velocity (PWV), that differ from youth without Down syndrome and to compare reference-based age-adjusted (age-PWV-Z) and height-adjusted (Ht-PWV-Z) in youth with and without Down syndrome.

Study design Cross-sectional study of PWV in 129 adolescents with Down syndrome and 97 youth of comparable age, sex, race/ethnicity, and body mass index (BMI). PWV, age-PWV-Z, and Ht-PWV-Z were compared. Regression models were developed to test for associations with PWV.

Results Youth with Down syndrome and controls were comparable in BMI-Z (1.4 [−1.5 to 2.8] vs 1.2 [−2.0 to 2.8], $P = .57$) but not Ht-Z (−2.3 [−4.7 to 0.8] vs 0.4 [−2.0 to 2.6], $P < .0001$). PWV (m/s, 5.0 [3.1-7.9] vs 5.0 [3.6-8.0], $P = .5$) and mean arterial pressure (MAP, mm Hg) (78 [61-102] vs 74 [64-97], $P = .09$) were not different between groups. In adjusted analyses confined to Down syndrome, PWV was associated only with BMI, but not age, black race, or MAP ($R^2 = 0.11$). In contrast, BMI, age, black race, and MAP were all positively associated with and better explained PWV in controls ($R^2 = 0.50$). PWV was not associated with height in youth with or without Down syndrome. Although age-PWV-Z was not different in Down syndrome (−0.36 [−2.93 to 3.49]) vs −0.15 [−2.32 to 3.22]), Ht-PWV-Z was greater in Down syndrome (0.32 [−2.28 to 4.07] vs −0.08 [−2.64 to 2.64], $P = .002$), and Ht-PWV-Z was greater than age-PWV-Z in Down syndrome ($P < .0001$).

Conclusions The lack of relationship of PWV, an independent predictor of adult cardiovascular events, with its traditional determinants including MAP suggests Down syndrome–specific phenomena may alter such relationships in this population. In youth with Down syndrome, Ht-adjusted PWV may overestimate aortic stiffness. *(J Pediatr 2019;212:79-86)*.

Trial Registration Clinicaltrials.gov: NCT01821300.

Survival among individuals with Down syndrome has improved dramatically, and median life expectancy is now reported as 58 years.[1] Despite improved survival, individuals with Down syndrome, particularly those with congenital heart defect (CHD), routinely are excluded from both population-based and disease-based cardiovascular disease (CVD) research. The sparsity of data is particularly problematic, given the tendency for overweight and obesity in individuals with Down syndrome.[2,3] Such data are important to inform future risk for CVD in this population.[4]

Arterial stiffening leads to decreased arterial distensibility and is a marker for future cardiovascular events in adults.[5,6] Pulse-wave velocity (PWV) is a noninvasive measure that quantitates arterial stiffness. Arterial stiffness has been identified in children with chronic kidney disease,[7] type 1 diabetes, type 2 diabetes, and obesity,[8-10] as well as in children with CHD such as coarctation of the aorta

BMI	Body mass index
BP	Blood pressure
CHD	Congenital heart defect
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
Ht	Height
MAP	Mean arterial pressure
MVPA	Moderate-to-vigorous physical activity
OSA	Obstructive sleep apnea
PWV	Pulse-wave velocity
SBP	Systolic blood pressure

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and single ventricle.[11-14] PWV may be useful for determining whether adolescents with Down syndrome demonstrate enhanced arterial stiffness as a marker for future CVD.

The purpose of this study was to assess PWV in a well-phenotyped cohort of adolescents with Down syndrome who were recruited to assess cardiometabolic status and to test the relationships of PWV with its potential determinants. Sex-specific age-adjusted PWV and height (Ht)-adjusted PWV reference data for several PWV devices in healthy children are now available,[15] but the extent to which these methods of adjustment can be used for children with Down syndrome, in whom significant Ht deficits are present, is not known. Therefore, a control group, without Down syndrome and matched for age, sex, and body mass index percentile (BMI-%ile), was recruited for comparison. We hypothesized that the relationships of PWV to age and Ht would be different in youth with Down syndrome vs control subjects (non-Down syndrome).

Methods

Adolescents with Down syndrome and typically developing youth of comparable age, sex, race, ethnicity, and BMI-%ile (non-Down syndrome) were recruited from 2012 to 2017 for a cross-sectional study examining body composition and cardiometabolic risk in youth with Down syndrome. The institutional review boards of both research sites (The Children's Hospital of Philadelphia and Children's National Health System) approved all procedures. Parental consent and participant consent or assent, when appropriate, were obtained.

Participants were male and female subjects aged 10-20 years. Exclusion criteria included major organ system illness not related to Down syndrome (except diabetes mellitus), current or previous oncologic process, pregnancy, genetic syndrome known to affect glucose tolerance, familial hypercholesterolemia, or current treatment with medications known to affect insulin sensitivity or lipids (other than diabetes agents in known diabetes mellitus). In addition, youth were excluded for established diagnoses of pulmonary hypertension, cyanotic CHD, or end-stage CHD (defined as inoperable disease due to pulmonary hypertension, singe-ventricle disease, or heart failure, as measured by left ventricular ejection fraction <50%); clinical data were reviewed by a pediatric cardiologist. As previously published, participants underwent echocardiography as part of the study protocol[16] and were subsequently excluded if pulmonary hypertension was identified (right ventricular pressure estimate >30 mm Hg if tricuspid regurgitation jet present or flattened septal position if tricuspid regurgitation not present). CHD history was collected from the electronic medical record and by parent report and classified as absent, nonsurgical, or surgically repaired.

The sample size for the parent study was based on the primary outcome non−high-density lipoprotein cholesterol, as it has been shown in multiple studies to be predictive of CVD.[17-20] With 97 youth without Down syndrome with an average PWV of 5.1 m/s, 129 youth with Down syndrome, and a common SD of 0.73, we had 80% power to detect an effect size of 0.28 (or a PWV difference of 0.2 m/s).

Weight (kilograms) was measured by digital electronic scale (ScaleTronix; Welch Allyn, Skaneateles Falls, New York), calibrated daily, and Ht (centimeters) was measured on a wall-mounted stadiometer (Holtain Ltd, Crymych, United Kingdom) with the participant in light clothing without shoes by trained research anthropometrists using standard techniques. Age- and sex-specific z scores were generated based on Centers for Disease Control and Prevention 2000 growth charts[21] for weight-Z, Ht-Z, and BMI-Z so that Down syndrome and non-Down syndrome groups were compared by the same reference. Overweight was defined as BMI ≥85th-%ile and obesity as BMI ≥95th%ile for age and sex.

Breast development in girls[22] and testicular volume in boys[23] were assessed by physical examination by a pediatric endocrinologist in all but a limited number of participants (n = 9 total, n = 3 with Down syndrome and n = 6 without Down syndrome) for whom a validated self-assessment measure was used.[24] Testicular volume was converted to pubertal stage 1 (1-3 cc), 2 (4-6 cc), 3 (8-10 cc), 4 (12-15 cc), 5 (>15 cc). For regression models, pubertal status was defined as prepubertal/early puberty if pubertal stage was 1 or 2 and pubertal if pubertal stage was 3-5.

Blood pressure (BP) was measured in triplicate in the subject after at least 5 minutes of rest in seated position on the right upper arm by automatic oscillometry (Dinamap, GE Healthcare, Chicago, Illinois) using methods consistent with American Heart Association recommendations.[25] A cuff with a bladder width of at least 40% of the arm circumference midway between olecranon and acromion and covering 80%-100% of the arm circumference was used.[25] The average of the second and third measurements was used to report systolic blood pressure (SBP) and diastolic blood pressure (DBP). To allow for comparisons, age-, and Ht-adjusted SD scores (SBP-Z and DBP-Z) were calculated using the Fourth report on the Diagnosis, Evaluation, and Treatment of High BP in Children and Adolescents.[26] Hypertension was defined as SBP or DBP ≥95%-ile for age, sex, and Ht.[25]

Arterial stiffness was assessed by carotid-femoral PWV measured via applanation tonometry using a SphygmoCor device (AtCor Medical, Inc, Sydney, Australia), software version 8.2. All operators were trained in the collection of PWV and were certified before collecting study data. Study data were evaluated for satisfaction of quality control measures by one investigator, who was blinded to both study site and presence or absence of Down syndrome.

PWV was collected in duplicate after participants rested in the supine position for a minimum of 5 minutes. Three electrocardiographic leads were attached. The right carotid artery was palpated and marked, and the distance between the carotid pulse site and the suprasternal notch was

measured twice to the nearest millimeter and recorded as the proximal site. The right femoral artery was then palpated, marked, and recorded as the distal site. The distance between the suprasternal notch and right femoral artery was measured indirectly with the measuring tape against the skin: suprasternal notch to umbilicus then umbilicus to right femoral artery. The travel distance was the notch-to-femoral distance minus the notch-to-carotid distance.[27] The pulse waveform was captured for 10 seconds at the proximal and distal sites using a Millar tonometer. The software reports the mean PWV ± SD. If the SD exceeded 15% of the mean PWV value, the study was repeated.

Sex-specific, age-adjusted (age-PWV-Z), and Ht-adjusted (Ht-PWV-Z) were generated using published pediatric reference data from more than 1000 children and adolescents aged 7-19 years with rounded Ht of 120-195 cm (males) and 115-180 cm (females).[15] For participants aged ≥20 years (n = 17), age 19 years was used for calculations.

Heart rate was recorded by the SphygmoCor device during tonometric acquisition of the carotid pulse during PWV. Mean arterial pressure (MAP) was determined using the SphygmoCor device using applanation tonometry of the radial pulse. MAP is determined by measuring the area under the radial pressure waveform curve, taking into account the length of the cardiac cycle calibrated by the SBP and DBP measurements. For participants lacking an available radial waveform (n = 18), MAP was estimated from the casual BP using the following formula: (DBP + [SBP – DBP]/3).

As previously described, participants were instructed to wear a SenseWear Mini accelerometer (Body Media, Pittsburgh, Pennsylvania) on the left arm halfway between the shoulder and elbow with the sensor over the triceps for ≥23 hours/day over 7 consecutive days, except during water activities. Proprietary algorithms incorporating sex, age, Ht, weight, and sensor data are used to estimate physical activity intensity, duration, and energy expenditure. Average daily moderate-to-vigorous physical activity (MVPA, defined as ≥3 METS) was included in these analyses if data were available for ≥20 h/d for ≥2 weekdays and ≥1 weekend day.

Continuous variables were summarized as median and minimum-maximum (min-max) and compared between subjects with Down syndrome and without Down syndrome using the 2-sample *t* test or Wilcoxon signed-rank test, as appropriate based on distribution. Categorical variables were compared using the χ^2 test. PWV, age-PWV-Z, and Ht-PWV-Z were visually examined using scatterplots and then compared by paired *t* test within the Down syndrome and controls groups separately. The relationships between PWV and age, Ht, BMI, and MAP were assessed with Spearman correlation for Down syndrome and controls separately. A similar approach was used for age-PWV-Z and Ht-PWV-Z.

Separate linear regression models were developed to determine whether covariates (age, Ht, BMI, black race, MAP,[28] and MVPA) were similarly related to PWV in youth with and without Down syndrome. Combined models were then used to determine if PWV differed for youth with and without Down syndrome after adjusting for covariates. The impact of CHD status in youth with Down syndrome also was examined. Final models were retested after exclusion of participants treated with BP-lowering medications. *P* value <.05 was considered statistically significant. Statistical analyses were performed with STATA (V15, Stata Corp, College Station, Texas).

Results

The parent study enrolled 154 youth with Down syndrome and 103 typically developing youth. PWV was available in 129 adolescents with Down syndrome (69 [53.4%] female) and 97 controls (56 [57.7%] female) of similar age (P = .82), BMI (P = .86), pubertal status distribution (P = .08), and obesity status (0.67). As expected, participants with Down syndrome were shorter (P < .0001), **Table I**. Of the Down syndrome group, 39 had a history of CHD that did not require surgical repair and 43 had surgically repaired CHD. Although BP was similar between youth with and without Down syndrome, SBP-Z, DBP-Z, and MAP were all greater in subjects with Down syndrome after we adjusted for stature. Unadjusted PWV was not different in youth with Down syndrome vs controls (P = .5). MVPA was available in only a subset of participants but was not different between the 2 subgroups (Down syndrome: n = 65; median [min-max]: 73.7 minutes [9.8-290]) vs non-Down syndrome: n = 53; 109 [5.5-339]), P = .12. PWV was unavailable in a subset because of challenges with maintaining a quiet, still state (Down syndrome: n = 17), issues with identification/amplification of wave form due to adiposity (Down syndrome: n = 7; non-Down syndrome: n = 5), or software error messages (Down syndrome: n = 1; non-Down syndrome: n = 1); as expected, BMI-Z tended to be greater in the subset in whom PWV was unavailable (median [min; max] Down syndrome: 1.93 [−0.25 to 2.5]; non-Down syndrome: 2.1 [1.53 to 2.71]).

As shown in **Figure 1**, PWV more strongly correlated with age (non-Down syndrome: rho = 0.36, P = .0005 vs Down syndrome: rho = 0.18, P = .05) and BMI (non-Down syndrome: rho = 0.45, P < .0001 vs non-Down syndrome: rho = 0.28, P = .002) in youth without Down syndrome than in youth with Down syndrome. Moreover, although PWV was positively correlated with MAP in adolescents without Down syndrome (rho = 0.36, P = .005), it correlated poorly with MAP in adolescents with Down syndrome (rho = 0.16, P = .07). PWV did not correlate with Ht in either group (non-Down syndrome: rho = 0.16, P = .14; Down syndrome: rho = 0.12, P = .19). PWV negatively correlated with MVPA in both groups (non-Down syndrome: rho = −0.47, P = .0003; Down syndrome: rho = −0.31, P = .011).

Group-specific linear regression models were developed. Age, MAP, black race, and BMI better explained the variance in PWV in controls (R^2 = 0.50) than in Down syndrome

Table I. Study participant demographics, anthropometrics, and PWV characteristics

	Down syndrome (n = 129)	Control (n = 97)	*P* value*
Age, y	14.8 (10.0-20.9)	14.8 (10.4-20.3)	.82
Sex, M/F	60/69	41/56	.52
Weight, kg	53.5 (21.5-107.1)	66.2 (27.2-120.4)	<.0001
Weight-Z	0.24 (−3.3 to 2.8)	1.3 (−2.2 to 3.6)	<.0001
Ht, cm	145 (116.7-170.3)	163.4 (134.8-186.7)	<.0001
Ht-Z	−2.3 (−4.7 to 0.8)	0.4 (−2.0 to 2.6)	<.0001
BMI, kg/m^2	25.4 (14.5-48.5)	24.8 (14.2-44.6)	.86
BMI-Z	1.4 (−1.5 to 2.8)	1.2 (−2.0 to 2.8)	.57
BMI percentile category, n (%)			.67
Obese	39 (31)	25 (26)	
Overweight	33 (30)	33 (34)	
Non-obese/non-overweight	40 (39)	39 (39)	
Black/non-black	23/106	22/75	.37
Hispanic/non-Hispanic	10/119	5/92	.44
SBP, mm Hg	115 (76-141)	115 (93-144)	.97
SBP-Z	0.95 (−2.37 to 3.48)	0.3 (−2.8 to 3.2)	.0016
SBP ≥95%-ile (yes/no)	27/102	8/89	.009
DBP, mm Hg	61 (36-93)	58 (51-81)	.005
DBP-Z	−0.2 (−2.32 to 2.7)	−0.6 (−2.3 to 1.8)	.0001
DBP ≥ 95%-ile (yes/no)	4/125	1/96	.30
MAP, mm Hg	78 (61-102)	75 (64 to −97)	.09
HR, bpm	73 (47-117)	75 (46-103)	.98
PWV, m/s	5.0 (3.1-7.9)	5.0 (3.6-8.0)	.5
PWV for M/F, m/s	5.1 (3.8-7.9)/4.9 (3.1-7.0)	5.0 (3.6-8.0)/5.1 (3.7-7.1)	.36/.08
Age-adjusted PWV-Z	−0.36 (−2.93 to 3.49)	−0.15 (−2.32 to 3.22)	.15
Ht-adjusted PWV-Z	0.32 (−2.28 to 4.07)	−0.08 (−2.64 to 2.64)	.002

F, female; *HR*, heart rate; *M*, male.
For continuous variables: median (min-max).
*Down syndrome vs control.

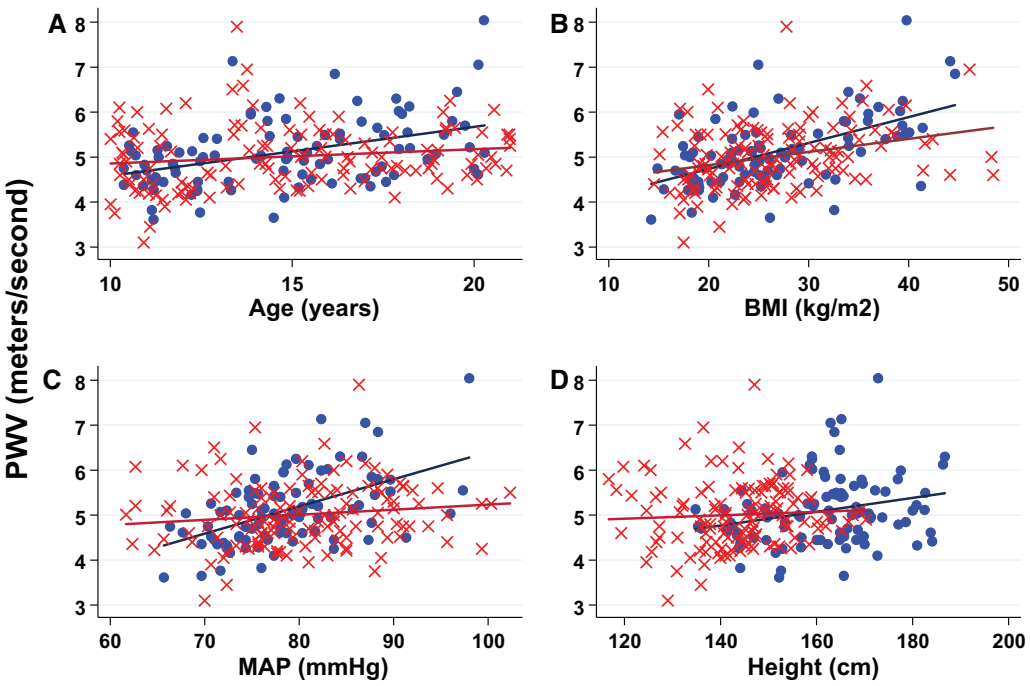

Figure 1. Relationships of PWV to potential determinants of PWV in adolescents with Down syndrome (*red* × *marks*) and typically developing matched-controls (*blue circles*). PWV more strongly correlated with **A,** age (non-Down syndrome: rho = 0.36, *P* = .0005 vs Down syndrome: rho = 0.18, *P* = .05), **B,** BMI (non-Down syndrome: rho = 0.45, *P* < .0001 vs Down syndrome: rho = 0.28, *P* = .002), and **C,** MAP in controls (non-Down syndrome: rho = 0.36, *P* = .005; Down syndrome: rho = 0.16, *P* = .07) compared with adolescents with Down syndrome. PWV did not correlate with **D,** Ht in either group (non-Down syndrome: rho = 0.16, *P* = .14; Down syndrome: rho = 0.12, *P* = .19). *Fitted lines* for Down syndrome (*red*) and controls (*blue*) also are shown.

Table II. Variance (R^2) and β coefficients (95% CI) from regression models of PWV (m/s) in adolescents with Down syndrome and typically developing matched controls

	Down syndrome (n = 129)	*P* value	Non-Down syndrome (n = 94)	*P* value
R^2	0.11		0.50	
Constant	3.49 (2.20-4.69)	<.0001	0.04 (−1.38 to 1.47)	.95
Age, y	−0.005 (−0.050 to 0.039)	.82	0.07 (0.02-0.11)	.004
Black	0.10 (−0.23 to 0.43)	.55	0.33 (0.02-0.63)	.002
MAP	0.01 (−0.01 to 0.03)	.17	0.04 (0.02-0.06)	<.0001
BMI	0.03 (0.01-0.05)	.005	0.03 (0.01-0.05)	.002

($R^2 = 0.11$) in whom only BMI was positively associated with PWV ($P = .005$), Table II. Ht, pubertal status, and MVPA were not significant in either Down syndrome or non-Down syndrome model and were not included in final model. Black youth without Down syndrome had greater PWV than non-black controls ($P = .002$), but this racial difference was not present in youth with Down syndrome ($P = .55$). Among individuals with Down syndrome, no differences in PWV were found by CHD-status (Figure 2; available at www.jpeds.com). In a combined age-, black race-, BMI-, and MAP-adjusted model, no difference in PWV was identified in Down syndrome (β-coefficient: −0.13 [95% CI −0.31 to 0.05]).

Age-adjusted PWV-Z ($P = .15$) was not different between Down syndrome and non-Down syndrome, Table I. However, Ht-adjusted PWV-Z was greater in youth with Down syndrome ($P = .002$), Table I. Moreover, Ht-adjusted PWV-Z was greater than age-adjusted PWV-Z in youth with Down syndrome ($P < .0001$) but not in non-Down syndrome youth ($P = .11$), Figure 3 (available at www.jpeds.com). Age-adjusted PWV-Z was negatively correlated with age in Down syndrome (r = −0.28, $P = .0015$) but not controls ($P = .77$). In contrast, Ht-adjusted PWV-Z was negatively correlated with Ht-Z in both youth with Down syndrome (r = −0.35, $P = .0001$) and controls (r = −0.34, $P = .0001$) (Figure 4).

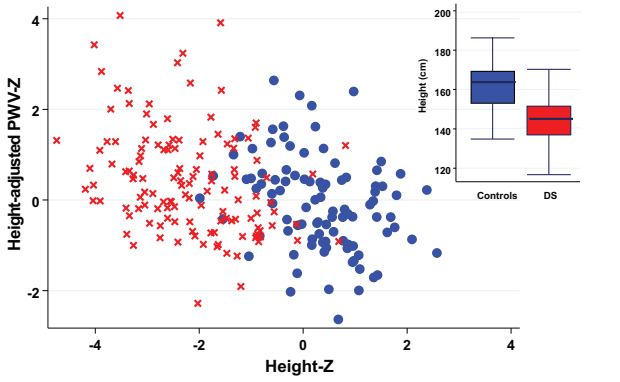

Figure 4. Relationships of Ht-adjusted-PWV to Ht-Z in adolescents with Down syndrome (*red* × *marks*) and typically developing matched-controls (*blue circles*). Ht-adjusted PWV-Z was greater in Down syndrome ($P = .012$) vs controls. Ht-adjusted PWV-Z was negatively correlated with Ht-Z in both Down syndrome (rho = −0.35, $P = .0001$) and controls (rho = −0.34, $P = .0006$). Ht was significantly lower in Down syndrome vs controls (*inset*, $P < .0001$).

Discussion

Arterial stiffness predicts cardiovascular events and mortality in both normotensive and hypertensive adults.[6,29] PWV is considered the "gold standard" for the noninvasive measure of arterial stiffness,[30] has been used to quantify arterial stiffness, and has been proposed as an important supplementary tool to guide management of elevated BP in clinical practice in adults.[31] Although PWV is greater in obese youth and youth with type 2 diabetes compared with lean controls,[8,32] evidence linking arterial stiffness to cardiovascular outcomes in youth is not as robust as it is in adults. Nonetheless, a large-scale study examining the evolution of BP, arterial stiffness, and target organ damage and potential genetic and epigenetic determinants is underway.[33]

Generally, MAP represents a loading characteristic on the aorta, and typically PWV is positively correlated to MAP, so much so that the recent American Heart Association Science Statement recommends controlling for MAP in analyses in which changes in PWV are the outcome.[30] MAP was similar in adolescents with Down syndrome and controls. Moreover, control subjects demonstrated the expected relationship between MAP and PWV (Figure 1 and Table II). However, subjects with Down syndrome showed a relatively flat relationship between MAP and PWV. In a study comparing PWV in subjects with Down syndrome vs age- and sex-matched control subjects spanning an age range of 13-42 years, investigators noted that unadjusted PWV was lower in Down syndrome compared with controls, consistent with a "younger" phenotype. When SBP was factored into the analyses, no differences in the PWV between groups were found, and both groups showed a positive relationship between SBP and PWV.[34] This previous report[34] had a much greater range of age, with a greater mean PWV in the control and Down syndrome groups (both were > 7.5 m/s), no matching for BMI (BMI was, on average, 4 kg/m^2 greater in Down syndrome than in controls), and no standardization of data with the use of z scores.

MAP is only one of several factors that affect PWV in humans, and we speculate that in adolescents with Down syndrome, other factors such as age and BMI are more important determinants of PWV in Down syndrome. Thus, the increasing BP dependency of PWV[35] in the aorta with aging in normal subjects may be delayed in adolescents with Down syndrome, whose aortic PWV appears less influenced by MAP in the narrow age range we examined in our study,

consistent with the "younger" phenotype of the aorta in previous studies.[34] A similar phenomenon has been proposed for atherogenesis in adults with Down syndrome, in whom typical predictors of atherosclerosis do not appear operative.[36]

PWV is considered a composite of vessel area, vessel wall thickness, and the vessel elastic modulus. Although atherosclerosis, due to plaque and lesions in the vessel intima, "obstructs" blood flow, arteriosclerosis, arising from repeated mechanical stress and biochemically induced derangements of the extracellular matrix, leads to reduced vessel wall elasticity and is thought to underlie both the increasing BP and the increase in PWV with aging.[37] Interestingly, low BP is recognized in adults with Down syndrome[38,39]; the extent to which this phenomenon arises from preservation of the medial wall and distensibility in Down syndrome is not known. Although systolic BPs were similar in our adolescents with Down syndrome and controls, age- and Ht-adjusted systolic BP-Z (the recommended approach to comparing BP among youth) was on average greater in Down syndrome (at nearly +1 SD); these results suggest that, at least in youth, enhanced elasticity is not present in Down syndrome. Importantly, 3 participants with Down syndrome were treated with daytime doses of angiotensin-converting enzyme inhibitors, these antihypertensive agents are thought to improve arterial stiffness beyond their simple BP-lowering effects.[40] Exclusion of participants treated with angiotensin-converting enzyme inhibitors did not alter results (data not shown).

Because PWV increases with age and perhaps Ht, reference equations have been developed to permit better comparisons of PWV across an age range and Ht.[15] PWV was not related to Ht in either our Down syndrome or non-Down syndrome population. Moreover, HT-adjusted PWV-Z was systematically greater than age-adjusted PWV-Z in our Down syndrome cohort whose average Ht-Z was −2.3 (equivalent to first percentile, ie, quite short). These findings suggest adjusting for this extreme short stature may overinflate estimates of Ht-adjusted estimates of arterial stiffness and that generalizing reference data from a typically developing population to youth with syndromic short stature may not be appropriate.

In children with end-stage renal disease, who also tend to have shorter stature (and also lower weight) compared with age matched controls, the selection of Ht-matched controls reveals the greater PWV in these children consistent with known enhanced cardiovascular risk in kidney disease.[41] Additional studies that include youth with syndromes and chronic health conditions characterized by shorter stature should provide further insight into whether this inflation is specific to Down syndrome (and perhaps real) or reflects the limitations of extending data from typically developing youth in whom shorter Hts are represented by younger instead of age-matched children.

A number of limitations in our study are present. First, our participants with and without Down syndrome may reflect a highly motivated group with a specific interest in cardiovascular health, and results may not be generalizable. Moreover, childhood cancer survivors, a group well-recognized to be at increased cardiovascular risk,[42,43] were excluded. This morbidity is particularly relevant for youth with Down syndrome, who are at increased risk of acute lymphoblastic leukemia. Independently of obesity, obstructive sleep apnea (OSA) is associated with increased CVD risk, including greater arterial stiffness.[44-51] Affecting 40%-80% in individuals with Down syndrome,[52-55] OSA is more common in adults with Down syndrome than in the general population. Polysomnography was not completed in our adolescent Down syndrome cohort, and potential contributions of OSA to arterial stiffness were not available in our study. Lower physical activity is associated with obesity and increased cardiometabolic risk,[56,57] and lower physical activity is well-recognized in youth with Down syndrome.[58-60] Unfortunately, MVPA could only be obtained in a subset of participants. Whether differences in arterial stiffness would have been unmasked by MVPA in the full complement of participants cannot be determined. In typically developing lean, obese, and adolescents and young adults with type 2 diabetes, average daily physical activity was not associated with PWV.[8] Finally, three 24-hour dietary recalls were obtained as part of this study, but data are not yet available.

Future studies of arterial stiffness in Down syndrome pursuing the disparate relationships of PWV with MAP, BMI, and Ht compared with appropriate controls may serve to extend our understanding of long-term cardiovascular outcomes in Down syndrome. ■

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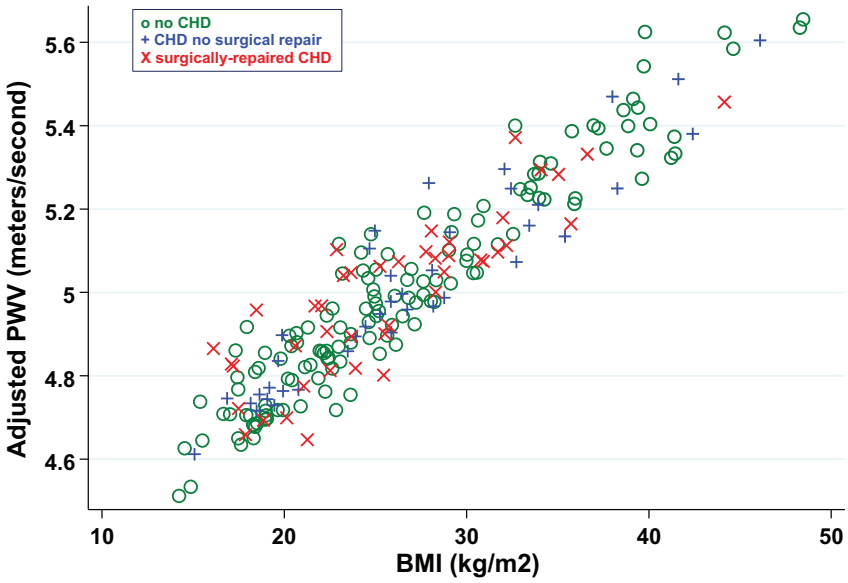

Figure 2. In adolescents with Down syndrome, PWV did not differ by CHD status (*green circles* indicate none, *blue plus signs* indicate present but not surgically managed, or *red* × *marks* indicate surgically repaired, $P = .27$). Surgically managed CHD included patent ductus arteriosus, atrial septal defect, ventricular septal defect, complete atrioventricular canal defect; CHD not managed with surgery included patent ductus arteriosus, atrial septal defect, ventricular septal defect, and bicuspid aortic valve.

Figure 3. Comparison of Ht-adjusted-PWV and age-adjusted-PWV in adolescents with Down syndrome (*red* × *marks*) and typically developing matched-controls (*blue circles*). Age-adjusted PWV-Z scores were not different in Down syndrome vs non-Down syndrome controls, ($P = .15$). However, Ht-adjusted PWV-Z was greater in Down syndrome ($P = .012$) vs controls, and Ht-adjusted PWV-Z was greater than age-adjusted PWV-Z in Down syndrome ($P < .0001$) but not controls ($P = .11$).