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ORIGINAL RESEARCH

Arterial Stiffness in Heart-Healthy Indigenous Tsimane Forager-Horticulturalists

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BACKGROUND: Little is known about arterial stiffness in rural subsistence populations that experience few cardiovascular risk factors. We conducted a cross-sectional study comparing 3 arterial stiffness metrics among Tsimane forager-horticulturalists with 2 representative US cohorts.

METHODS: Arterial elasticity (the inverse of stiffness) markers C1 (large artery elasticity) and C2 (small artery elasticity) were measured using a tonometry device among 490 Tsimane adults (mean age, 51.2±10.1 years; 55% women), and compared with 6294 multiethnic US adults (mean age, 62.0±10.2 years; 52% women) from MESA (Multi-Ethnic Study of Atherosclerosis). Carotid-femoral pulse wave velocity was assessed using the foot-to-foot method in a smaller Tsimane sample (n=94) and compared with 3086 predominantly White US adults (mean age, 46.1±8.7 years; 54% women) from the FHS Gen3 (Framingham Heart Study Third Generation).

RESULTS: Tsimane participants exhibited superior arterial health compared with US cohorts, with higher elasticity (C1/C2) and lower stiffness (carotid-femoral pulse wave velocity). Their C1 (mean 22.8±12.2 mL/mm Hg×10) and C2 (mean 7.5±4.0 mL/mm Hg×100) were 47.3% and 35.7% higher than MESA participants by age 40 years, respectively, and differences remained sustained throughout adulthood. Compared with participants in FHS Gen3, the carotid-femoral pulse wave velocity in Tsimane participants (mean 6.2±1.2 m/s) was 33.9% lower and showed a minimal age-related increase, with carotid-femoral pulse wave velocity only higher by age 70+ (β=1.74±0.38; reference <40 years). Tsimane participants with ≥2 comorbidities (hypertension, obesity, and diabetes) had ≈25% higher arterial elasticity than healthy Americans with no comorbidities.

CONCLUSIONS: Tsimane forager-farmers of the Bolivian Amazon demonstrate substantially lower arterial stiffness throughout adulthood than more urbanized and sedentary populations, and the differences are only partially explained by conventional cardiometabolic risk factors.

Key Words: arterial stiffness ■ cardiovascular health ■ indigenous health ■ vascular aging

Arterial stiffening appears to be a universal feature of human aging. It reflects structural changes in the properties of the arterial wall, including a reduction in elastin and increase in collagen fibers, resulting in compromised arterial expansion and contraction in relation to pressure changes.[1] The stiffening of arteries often parallels other aspects of cardiovascular aging, which involve endothelial dysfunction, vascular remodeling, and loss of arterial distensibility, leading to increased vessel wall stiffness and elevated arterial pressure.[2]

Understanding the conditions affecting arterial stiffness and its age-related increase is of clinical

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CLINICAL PERSPECTIVE

What Is New?

- Tsimane individuals exhibit substantially lower arterial stiffness throughout adulthood than more urbanized and sedentary populations, which was partially explained by conventional cardiometabolic risk factors.
- Arterial stiffness advances with age among tested US ethnic groups, while Tsimane individuals show limited progression until age 70+ years, exemplifying healthy arterial aging.

What Are the Clinical Implications?

- A physically active lifestyle and a lean high-fiber diet, combined with persistently low blood pressure and low-density lipoprotein cholesterol may delay, if not prevent, arterial aging and age-related cardiovascular diseases.

Nonstandard Abbreviations and Acronyms

C1	large artery elasticity
C2	small artery elasticity
cfPWV	carotid-femoral pulse wave velocity
DBP	diastolic blood pressure
FHS	Framingham Heart Study
FHS Gen3	Framingham Heart Study Third Generation
MESA	Multi-Ethnic Study of Atherosclerosis
SBP	systolic blood pressure
SUPERNOVA	super normal vascular aging
THLHP	Tsimane Health and Life History Project

importance. Since its first direct measurement in the 1920s, arterial stiffness has emerged as a vital subclinical marker of cardiovascular disease (CVD).[3] Large-scale prospective studies and meta-analyses have demonstrated that arterial stiffness predicts the risk of major CVD outcomes, such as stroke, coronary artery disease, and death related to cardiovascular causes.[4,5] In many of these studies, arterial stiffness contributes substantially to further cardiovascular risk stratification beyond conventional risk factors.[6]

Multiple metrics have been used to assess arterial stiffness noninvasively.[7] The current "gold standard" for measuring arterial stiffness is carotid-femoral pulse wave velocity (cfPWV), defined as the transit time of the pressure wave from the carotid to the femoral artery.[7] Numerous disease-specific and community-based cohort studies have shown that elevated cfPWV is associated with increased risk for major CVD outcomes in various populations, independently of other risk factors.[4,6] Less commonly assessed measures reflect arterial elasticity, the inverse of stiffness. C1 (large artery elasticity) and C2 (small artery elasticity) are functional markers for large and small arteries, respectively, derived from the third-order Windkessel model, with higher values indicating greater elasticity (and lower stiffness). C1 is primarily associated with the decay of pressure during early diastole, representing the distensibility of the aorta and other major arteries in response to pressure changes.[8] C2 reflects the ability to diminish pressure oscillations from late systole to mitral valve closure and was found to decrease when small vessel dilation is inhibited.[9] In MESA (Multi-Ethnic Study of Atherosclerosis), C2 outperformed other tested arterial markers in predicting risk of hypertension, and was independently associated with future CVD outcomes.[10,11]

While age-related increases in blood pressure (BP) and arterial stiffness have been extensively identified worldwide, rural subsistence-oriented populations have shown distinct trajectories of vascular health. The absence of age-related, cross-sectional BP increase among groups such as the Yanomamo and island-dwelling Kuna[12,13] inspired the notion of "super normal" vascular aging (SUPERNOVA), whereby certain groups of individuals may be protected from age-related cardiovascular worsening and exhibit exceptionally low arterial stiffness with age.[14] Subsistence populations provide a rare opportunity to discover conditions that protect against cardiometabolic risks, providing compelling case studies that diverge from the sole emphasis on disease management while focusing on health promotion and preservation.

Here, we evaluate measures of arterial stiffness/elasticity (stiffness: cfPWV; elasticity: C1 and C2) among Indigenous Tsimane forager-horticulturalists. Prior research among the Tsimane has revealed the lowest levels of coronary atherosclerosis ever reported, minimal peripheral arterial disease, low age-related increase in BP, minimal atrial fibrillation, and robust maximum oxygen consumption.[15–19] Tsimane individuals are physically active throughout adulthood, eat a complex carbohydrate–rich diet low in saturated fat, and showed minimal obesity or diabetes during the period of study. Their main cardiometabolic risk factors include high inflammation from repeated acute and chronic infections and low high-density lipoprotein cholesterol (HDL-C) levels. While Tsimane have low CVD risk, it is unknown whether they also show preserved arterial distensibility with age. Arterial stiffening has been argued to be an inevitable aspect of cardiovascular aging. To date, the only study of arterial stiffness in a nonindustrialized subsistence population reported low cfPWV and no age differences in cfPWV

among Cameroonian hunter-gatherers, but higher cfPWV among older neighboring farmers.[20] However, the sample size of this study was small (n=20).

We compared 3 metrics of arterial health among Tsimane participants with 2 urbanized US samples (MESA cohort and FHS [Framingham Heart Study]), and explored whether population differences in cardiometabolic comorbidity can explain population differences. We first assessed the level of arterial stiffness, then explored its association with age and other cardiometabolic risk factors. Given their heart-healthy status, we expected to find evidence of low arterial stiffness among Tsimane, but stiffer arteries (relative to other Tsimane) among those with cardiometabolic conditions, such as hypertension. A positive association of arterial stiffness with age (but in the absence of other cardiovascular morbidity) would be consistent with the notion of universal age-related arteriosclerosis.[2]

METHODS

Ethics Statement

Informed consent was obtained for all protocols at three levels: 1) Gran Consejo Tsimane, the local Tsimane government organization that represents Tsimane interests and oversees all projects, 2) community officials and participants in village meetings, and 3) individual consent during medical visits and before each procedure. After explanation of a formal protocol by bilingual Tsimane assistants, consent forms were signed for literate participants, and verbal approval with fingerprint signature given for non-literate participants. Our consent procedures have been approved by the Institutional Review Boards at the University of California, Santa Barbara, University of New Mexico, and Universidad San Simon Mayor, Cochabamba Bolivia. Tsimane data that support the findings of this study are available from the corresponding author (M.G.) on reasonable request.

MESA and FHS Gen3 (Framingham Heart Study Third Generation) cohort data used in this study were obtained from the National Heart, Lung, and Blood Institute data repository (Biologic Specimen and Data Repositories Information Coordinating Center) at https://biolincc.nhlbi.nih.gov/studies/mesa/ and https://biolincc.nhlbi.nih.gov/studies/gen3/.

Study Samples

Tsimane Health and Life History Project

The aims and design of the THLHP (Tsimane Health and Life History Project) have been thoroughly described.[21] In brief, the THLHP is a multidisciplinary study of health and aging among Indigenous Tsimane of Bolivia that began in 2002. Tsimane are lowland forager-horticulturalists subsisting by slash-and-burn farming, hunting, fishing, and gathering. During the period of arterial health measurements from 2010 to 2012, cash income from wages, cash crop farming, and other activities were modest. Tsimane occupied >80 villages, with an estimated total population of 12 000 during that time.[15] The THLHP makes regularly scheduled visits to Tsimane villages, during which clinical examinations are performed and blood samples are collected.

MESA and FHS Gen3

MESA is a multicenter cohort study conducted between July 2000 and August 2002.[22] A total of 6814 men and women aged 45 to 84 years and free of clinically apparent CVD were recruited from 6 US sites, including ≈38% White, 28% Black, 22% Hispanic, and 11% Asian American (predominantly Chinese descendants) participants. We use data from the MESA Exam 1, which includes C1 and C2 measurements.

FHS is a long-term, multigenerational study initiated in 1948 in Framingham, Massachusetts. The FHS Gen3 is the third generation of the original cohort.[23] Briefly, it was established between 2002 and 2005, enrolling 4095 adults (almost all of whom self-reported as White) who were grandchildren of the original participants. This study uses cfPWV data from the FHS Gen3 Exam 2, including 3086 unique individuals after excluding those with a history of CVD (n=164).

Arterial Stiffness Measurements

Tonometry data and resting 12-lead ECGs that were used for the calculation of C1, C2, and cfPWV were collected by a trained Bolivian physician (E.C.L.). Individual waveforms and ECGs were reviewed by a collaborating cardiologist (D.D.) who gave adjudication scores from 1 to 4 based on a subjective evaluation of the shape and consistency of the visual image (1=excellent in waveform quality and 4=unacceptable). All individuals with a waveform of adjudication score 4 were excluded from this study (n=59).

C1 and C2

Tsimane C1 and C2 were obtained using an HDI CR-2000 tonometry device (Hypertension Diagnostics). Briefly, a tonometer was placed over the radial artery of the dominant arm. After achieving a stable measurement, a 30-second analog tracing of the waveform was digitized at 200 samples per second. Measurements of C1 and C2 were produced by the device from the diastolic portion of the waveform modeled as a decaying exponential function plus a sinusoidal function diminished by a decaying exponential.[11] C1/C2 were measured at least twice among 97% of the studied Tsimane

participants (C1: Cronbach α=0.91 [95% CI, 0.89–0.93]; C2: Cronbach α=0.92 [95% CI, 0.89–0.94]). The mean value was used for analysis. MESA C1 and C2 were obtained using the same device following a similar protocol.[11]

Carotid-Femoral PWV

The cfPWV of Tsimane participants was obtained based on sequentially collected pulse waves at the common carotid and femoral arteries and the simultaneously recorded ECG.[7] cfPWV (m/s) was estimated as distance (d) divided by transit time (Δt). Distance was calculated as 0.8 times the tape-measured straight distance between the carotid and femoral sites. Transit time was obtained using the R wave on the ECG qRs complex as a common reference and subtracting the time between the ECG and carotid pulse from the time between the ECG and femoral pulse. We measured Δt by calculating the time difference from the peak of the R wave to the "foot" of the carotid/femoral pulse contour. The foot was identified at the intersection of 2 lines: (1) a horizontal line tangent to the lowest point of the waveform following the ECG complex, and (2) an extension of the line derived from the mean square deviation of points representing the initial ascending phase of the waveform. Two independent cfPWV calculations were performed by trained researchers (Cronbach α=0.93 [95% CI, 0.83–0.95]). The mean value was used for analysis.

FHS cfPWV was calculated using a similar method.[5] However, the transit distance was calculated by subtracting the distance of the suprasternal notch to the femoral site from the distance of the suprasternal notch to the carotid site. The FHS transit distance was standardized to the direct method used in Tsimane using the following equation, with d indicating transit distance: $d_{direct}=0.45\times d_{subtracted}+0.21\times height+0.08$ (m).[24]

Covariates

Clinical and anthropometric data were collected by the THLHP mobile medical team, consisting of trained researchers and physicians. Height was collected using a Seca 213 portable stadiometer, and weight was obtained with a Tanita BF-572 scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Systolic BP (SBP) and diastolic BP (DBP) were measured from the right arm using a Welch Allyn Tycos Aneroid 5090 sphygmomanometer (with Littman stethoscope) after participants had been seated for at least 20 minutes in quiet surroundings. All BP measurements were repeated after ≥30 minutes following the same procedures. The mean value was used. Serum was separated and frozen in liquid nitrogen after an overnight fast. Blood testing, including lipids and glucose, were measured (Stat Fax 1908, Awareness Technology) in the THLHP's laboratory in San Borja, Beni, Bolivia. We defined hypertension as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, or use of antihypertensive medication. Obesity was defined as a BMI ≥30. Diabetes was defined as a fasting blood glucose ≥126 mg/dL or use of diabetic medication.

Age estimates were determined using a multifaceted approach, including known ages from documented records, relative age lists, significant dated events, missionary records, and photo comparisons of individuals with established ages.[25] Cross-validation was conducted through independent interviews with kin. When multiple estimates provided birth dates within a 3-year range, the average was used.

Statistical Analysis

Sample characteristics of the study population were summarized by ethnicity for THLHP and the MESA cohort, and by study cohort for THLHP and FHS Gen3. We used multivariable linear regression models to examine associations between age and arterial markers. For analysis of C1 and C2, model 1 was the unadjusted model. Model 2 was adjusted for sex, height, BMI, heart rate, and SBP, while model 3 additionally adjusted for lipid markers including triglycerides, low-density lipoprotein cholesterol, HDL-C, and fasting glucose. For cfPWV analysis, model 1 was unadjusted, and model 2 was adjusted for sex, height, BMI, heart rate, SBP, and DBP. For each regression model, we assessed the assumptions of normality, homoscedasticity, and multicollinearity. The log-transformed–dependent C1, C2, and cfPWV were used to account for skewness in their distributions. We added an interaction term between age group (10-year intervals) and ethnicity/cohort to account for potential differences in how age is associated with arterial stiffness among populations. Adjusted values of C1, C2, and cfPWV are stratified by age intervals and ethnicity/cohort. Estimated age coefficients (beta) are extracted from separate analyses of each ethnicity and cohort.

We examined the levels of C1 and C2 among adverse cardiometabolic conditions using adjusted multivariable linear regression models. The hypertension models excluded SBP and DBP, the obesity model excluded BMI, and the diabetes model excluded fasting glucose. The diabetes model was not tested among the Tsimane due to the limited number of cases but was tested in the MESA cohort. We further analyzed the association between arterial markers and comorbidity burden (hypertension, diabetes, and obesity). Participants were grouped based on the number of comorbid conditions (0, 1, or ≥2). Multivariable linear regression models were used to predict C1 and C2

values for each group with covariables from model 3 excluding SBP, DBP, BMI, and fasting glucose.

We assessed Pearson correlation coefficients (*r*) between the 3 arterial stiffness measures, and with other covariates. The proportion of variance explained by each model in each cohort subset was calculated using the "relaimpo" package in R (The proportion of variance was calculated using the Lindeman, Merenda, and Gold method, which decomposes the model's total R^2 by averaging the sequential contribution of each predictor among all possible orderings. We conducted 2 sensitivity analyses: (1) to account for age differences between the THLHP and MESA samples, we used propensity score matching with the "MatchIt" package in R, matching on age and sex using nearest-neighbor matching with a caliper of 0.05; and (2) to account for the potential confounding of smoking status, we excluded all cases of smoking, including past and current smokers, in the MESA and FHS Gen3 cohort.

All analyses were conducted using R software, version 4.4.0 (http://www.R-project.org/). A *P* value <0.05 was considered statistically significant. This study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies.

RESULTS

Descriptives

Our analysis of C1 and C2 compares 490 Tsimane participants with 6294 participants from the MESA cohort, including 1710 Black, 770 Chinese American, 1429 Hispanic, and 2385 White participants (Figure S1). Our analysis of cfPWV compares 94 Tsimane participants with 3086 predominantly White participants from the FHS Gen3 cohort (Figure S2).

Sample characteristics of the study populations are presented in Table 1. In the C1/C2 data set, Tsimane participants (mean age, 51.2±10.1 years; 55.1% women) were younger, shorter, had lower BMI, SBP, DBP, triglycerides, fasting glucose, low-density lipoprotein cholesterol, HDL-C, systemic vascular resistance, total vascular impedance, cardiac output, and stroke volume, as well as a lower prevalence of hypertension, obesity, and diabetes, but a higher ejection time and heart rate compared with the MESA participants (mean age, 62.2±10.1 years; 52.3% women) (Table 1, Tables S1 and S2). Approximately 17% and 1% of Tsimane and MESA participants, respectively, were missing data on blood lipids (Table S3). In the cfPWV data set, Tsimane participants (mean age, 49.9±14.7 years; 51.1% women) had lower mean height, BMI, SBP, DBP, and prevalence of hypertension and obesity, but higher age and heart rate than the FHS Gen3 group (mean age, 46.1±8.7 years; 54% women).

Tsimane participants exhibited higher C1 and C2 compared with the MESA participants (C1: 22.8±12.2 versus 13.3±5.6 mL/mm Hg×10; C2: 7.5±4.0 versus 4.5±2.8 mL/mm Hg×100, respectively). Similar findings were observed in age-matched comparisons (Tables S4 and S5). Also consistent with lower arterial stiffness, cfPWV in Tsimane participants was lower than that of the FHS Gen3 participants, at 6.2±1.2 versus 8.3±1.5 m/s. Compared with previously reported values from literature review, Tsimane participants show markedly higher C1 and C2 and lower cfPWV than other global populations, indicating a healthier status in terms of arterial stiffness (Table S6, Figure S3).

No prior studies have studied C1, C2, and cfPWV together in the same population. In a small Tsimane subset with all 3 measures evaluated (n=38; results not shown), C2 was associated with cfPWV (Pearson *r*=−0.41, *P*=0.01), while C1 was not (*r*=−0.24, *P*=0.15), but C1 was related to C2 (*r*=0.38, *P*=0.02).

Arterial Stiffness and Age

Figure 1 shows the adjusted estimates of C1, C2, and cfPWV among ethnic groups/cohorts, stratified by age groups. Overall, all tested populations showed lower C1 and C2 and higher cfPWV with advancing age. For C1 and C2, Tsimane participants exhibited higher elasticities compared with other populations, although the differences diminish with age. In contrast, Tsimane participants had lower cfPWV compared with the FHS Gen3 cohort among all age groups and this difference was greater with age. Tsimane participants' cfPWV was relatively constant until around age 70 years, whereas FHS Gen3 participants showed a notable cross-sectional increase of cfPWV with age. A similar finding was observed after excluding ever-smokers (current or past smokers) in MESA and FHS Gen3 (Figure S4).

The estimated age coefficient in models with C1 and C2 as the dependent variable was similar among ethnicities, but Tsimane participants showed a markedly slower rate of cfPWV increase compared with FHS Gen3 participants (Figure 2). For C1, model 2 adjustments reduced the age coefficient by ≈30% among all groups (versus the unadjusted model), with β values ranging from −0.11 (95% CI, −0.13 to −0.08) in White individuals to −0.17 (95% CI, −0.28 to −0.07) in Tsimane individuals. Further adjustments for lipid markers increased the coefficient by 20% in Tsimane participants, with minimal changes in MESA participants. For C2, model 2 reduced the age coefficient by 20%, with the smallest adjusted β in Black individuals (−0.07 [95% CI, [−0.08 to −0.06]) and the largest in Tsimane individuals (−0.11 [95% CI, −0.14 to −0.08]). Lipid adjustments had little impact on C2. For cfPWV, model 2 adjustments reduced the age coefficient by 17.5% in Tsimane participants (to 0.03 [95% CI, 0.02–0.05]) and

Table 1. Characteristics of Study Samples

	C1–C2 data set*					cfPWV data set†	
	Tsimane	Black	Chinese American	Hispanic	White	THLHP (Tsimane)	FHS Gen3
No.	490	1710	770	1429	2385	94	3086
Demographics							
Age, y	51.2 (10.1)	61.9 (10.0)	62.2 (10.3)	61.3 (10.3)	62.5 (10.3)	49.9 (14.7)	46.1 (8.7)
Women, %	55	55	51	51	51	51	54
Physiology							
Height, cm	155.4 (7.8)	168.5 (9.6)	161.6 (8.5)	161.9 (9.2)	169.2 (9.7)	156.3 (7.8)	169.8 (9.4)
Body mass index, kg/m^2	24.7 (4.2)	30.1 (5.8)	23.9 (3.2)	29.4 (5.0)	27.8 (5.0)	24.3 (2.9)	27.7 (5.5)
SBP, mm Hg	118.9 (13.7)	131.7 (21.5)	124.2 (21.2)	126.7 (21.8)	123.4 (20.2)	110.5 (11.5)	115.6 (13.8)
DBP, mm Hg	67.3 (7.7)	74.7 (10.2)	71.9 (10.4)	71.6 (10.1)	70.3 (10.0)	69.1 (8.9)	74.1 (9.3)
Mean arterial pressure, mm Hg	84.5 (9.3)	93.7 (12.5)	89.4 (12.6)	90.0 (12.5)	88.0 (12.0)	82.9 (9.1)	87.9 (10.0)
Heart rate, beats per min	64.2 (7.4)	63.1 (10.2)	63.2 (8.6)	63.4 (9.5)	62.9 (9.6)	65.5 (6.4)	64.0 (9.8)
Lipids‡							
Triglycerides, mg/dL	101.5 (51.6)	104.6 (69.0)	142.5 (81.7)	156.8 (94.0)	133.0 (90.5)		
Fasting glucose, mg/dL	79.6 (16.5)	100.1 (32.4)	99.0 (28.7)	104.0 (39.6)	91.1 (20.6)		
LDL-C, mg/dL	65.6 (25.1)	116.5 (32.8)	114.9 (29.2)	119.6 (33.1)	117.1 (30.1)		
HDL-C, mg/dL	36.7 (11.0)	52.3 (15.1)	49.4 (12.6)	47.6 (13.1)	52.2 (15.5)		
Medical and medication§							
Antihypertensive medication, %	0‖	50	28	33	33	0‖	15
Hypertension, %	7.8	60	37	41	38	1.1	20
Obesity, %	8.6	45	3.8	38	28	2.3	28
Diabetes, %	0.6	18	13	18	5.8		
Arterial stiffness markers							
C1, mL/mm Hg×10	22.8 (12.2)	13.5 (5.8)	12.9 (5.4)	12.8 (5.2)	13.7 (5.7)		
C2, mL/mm Hg×100	7.5 (4.0)	4.2 (2.5)	4.1 (2.8)	4.4 (2.8)	4.9 (3.0)		
cfPWV, m/s						6.2 (1.2)	8.3 (1.5)

Data are presented as mean (SD) or median (IQR) for continuous variables and percentage for categorical variables. BMI indicates body mass index; C1, large artery elasticity; C2, small artery elasticity; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; FHS Gen3, Framingham Heart Study Third Generation; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; SBP, systolic blood pressure; and THLHP, Tsimane Health and Life History Project.

*C1–C2 data set includes THLHP (Tsimane) and MESA samples.

†cfPWV data set includes THLHP (Tsimane) and FHS Gen3 samples.

‡Conversion factors from mg/dL to mmol/L: for LDL-C and HDL-C, divide mg/dL by 38.67; triglycerides, divide mg/dL by 88.57; and glucose, divide mg/dL by 18.02.

§Hypertension was defined as an SBP of >140 mm Hg or a DBP of >90 mm Hg or use of antihypertensive medication. Obesity was defined as a BMI of >30 kg/m^2. Diabetes was defined as a fasting blood glucose of >126 mg/dL or use of diabetic medication.

‖No Tsimane individuals were using antihypertensive medication at the time this study was conducted.

by 13.5% in FHS Gen3 participants (to 0.08 [95% CI, 0.07–0.08]).

Arterial Stiffness Variance and Other Risk Factors

Table 2 shows the estimated coefficients from multivariable analysis with Tsimane C1, C2, and cfPWV as the dependent variables. Men showed higher mean C1 than women. Higher heart rate and SBP and lower DBP were associated with lower C1, while shorter height, lower BMI and higher DBP were associated with lower C2. Notably, HDL-C was negatively associated with both C1 and C2 in Tsimane participants, but no such associations were found in MESA participants (Tables S7 and S8). In Tsimane participants, heart rate was positively associated with cfPWV, which was also found in FHS Gen3 participants (Table S9).

Among all tested covariates, age explains the greatest variance in C2 among MESA (11.8%) and Tsimane (8.8%) participants, as well as in cfPWV among FHS Gen3 (22.1%) and Tsimane (19.5%) participants. However, SBP accounts for the most variance in C1 in MESA participants (8.4%), while HDL-C is the main

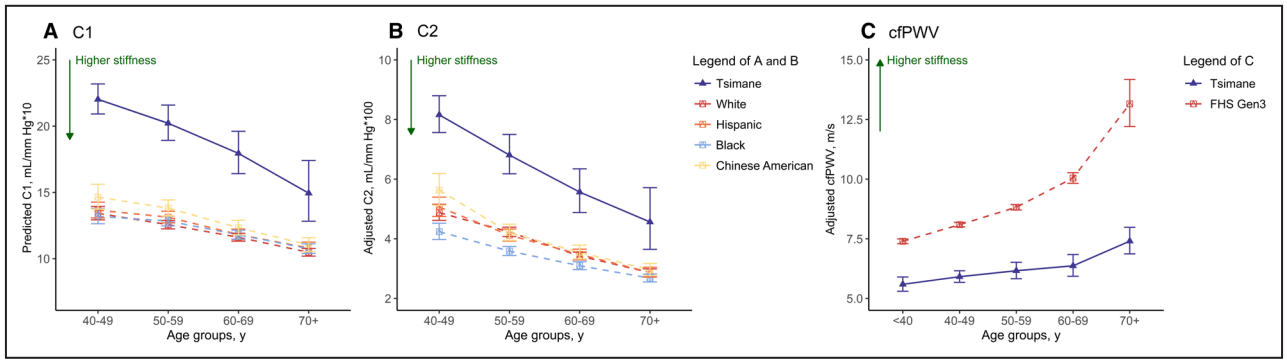

Figure 1. C1, C2, and cfPWV stiffness levels by age.
Shown are the adjusted C1 (**A**), C2 (**B**), and cfPWV (**C**) levels among age groups in 10-year intervals. Predicted values of C1 and C2 were obtained from multivariable linear regression models adjusting for sex, height, BMI, heart rate, SBP, DBP, fasting glucose, triglycerides, LDL-C, HDL-C, and an interaction term reflecting ethnicity × age group. Predicted cfPWV was obtained from a similar model adjusting for sex, height, BMI, heart rate, SBP, DBP, and an interaction term reflecting cohort × age group. Points are mean values, and error bars show 95% CIs. BMI indicates body mass index; C1, large artery elasticity; C2, small artery elasticity; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; FHS Gen3, Framingham Heart Study Third Generation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, sytolic blood pressure.

contributor to the variance in C1 in Tsimane participants (7.4%) (Table S10).

Arterial Stiffness Associations With Cardiometabolic Morbidity

Tsimane showed a substantially lower prevalence of cardiometabolic conditions, including hypertension, obesity, and diabetes, and they also have much lower rates of comorbidity (Figures S5 and S6). In Tsimane individuals, hypertension was associated with lower C2, but not C1. Obesity was associated with higher C1, whereas there was no statistical association with C2 (Table 2). In MESA, hypertension was associated with lower C1 and C2, while obesity was associated with higher C1 and C2 (Table S11).[10] Furthermore, in MESA, diabetes showed no significant association with C1, but was associated with lower C2.[26]

We next tallied the number of cardiometabolic comorbidities (range, 0 to 3; including hypertension, obesity, diabetes) for Tsimane and MESA participants. Participants with a higher comorbidity burden exhibited lower C1 and C2 levels compared with those with fewer or no comorbidities (Figure 3). Both C1 and C2 are the lowest among those with the highest number of comorbidities (2+ versus 1 versus 0). While the 4 MESA subgroups showed similar C1 and C2 levels at the same level of comorbidity status, Tsimane consistently

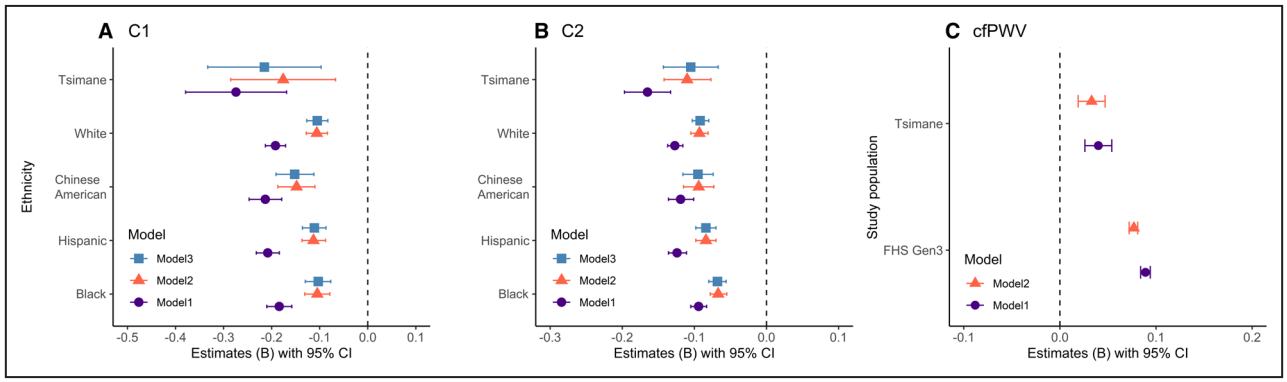

Figure 2. Association of age with C1, C2, and cfPWV.
Shown are the estimated effects (β value, difference in elasticity unit per year) of age on C1 (**A**), C2, (**B**), and cfPWV (**C**) in model 1, model 2, and model 3. Model 1 was the unadjusted model. Model 2 was adjusted for sex, height, BMI, heart rate, SBP, and DBP. Model 3 was further adjusted for fasting glucose, triglycerides, LDL-C, and HDL-C. Lipid data are missing in the cfPWV data set and thus were not analyzed. Points are estimated effect sizes (β value), and error bars show 95% CIs. The dashed vertical line indicates x=0. All R^2 values were highly significant (P<0.001). Units of β: C1 (mL/mm Hg×10), C2 (mL/mm Hg×100), and cfPWV (m/s). BMI indicates body mass index; C1, large artery elasticity; C2, small artery elasticity; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; FHS Gen3, Framingham Heart Study Third Generation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

Table 2. Multivariable Analysis of Tsimane C1, C2, and cfPWV

	C1		C2		cfPWV	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Demographics						
Age, y	−2.16 (0.61)	<0.001	−1.06 (0.19)	<0.001	0.48 (0.11)	<0.001
Sex (male vs female)	3.98 (1.63)	0.02	0.88 (0.52)	0.09	0.35 (0.24)	0.15
Physiology						
Height, cm	1.44 (0.80)	0.07	1.12 (0.26)	<0.001	0.06 (0.12)	0.59
BMI, kg/m^2	0.92 (0.56)	0.10	0.58 (0.18)	<0.001	0.05 (0.10)	0.63
Heart rate, beats per min	−2.24 (0.59)	<0.001	0.09 (0.19)	0.63	0.30 (0.10)	0.004
SBP, mm Hg	−2.02 (0.96)	0.03	−0.37 (0.30)	0.23	0.22 (0.14)	0.14
DBP, mm Hg	1.77 (0.97)	0.07	−1.00 (0.31)	<0.001	−0.11 (0.15)	0.46
Lipids						
Triglycerides, mg/dL	0.79 (0.57)	0.17	0.16 (0.18)	0.38		
Fasting glucose, mg/dl	0.41 (0.53)	0.45	−0.02 (0.17)	0.89		
LDL-C, mg/dL	0.77 (0.52)	0.14	−0.10 (0.17)	0.98		
HDL-C, mg/dL	−3.25 (0.55)	<0.001	−0.87 (0.18)	<0.001		
Cardiometabolic conditions						
Hypertension (yes vs no)	−1.60 (2.01)	0.43	−2.57 (0.62)	<0.001		
Obesity (yes vs no)	4.13 (1.89)	0.03	0.65 (0.57)	0.26		

Shown are the estimated coefficient (β) and SE of Tsimane C1, C2, and cfPWV as the dependent variables in multivariable regression models. For continuous variables, results are presented per SD increase. The estimated coefficients of cardiometabolic conditions (hypertension and obesity; as the independent variables) in relation to C1 and C2 were separately analyzed using multivariable linear regression adjusted for age, sex, height, heart rate, BMI, SBP, and DBP. The hypertension models excluded SBP and DBP, the obesity model excluded BMI, and the diabetes model was not tested due to the limited number of cases. BMI indicates body mass index; C1, large artery elasticity; C2, small artery elasticity; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

show the highest levels of C1 and C2. Notably, Tsimane participants with 2+ comorbidities maintained higher C1 and C2 than all MESA groups with no comorbidities. Tsimane with 2+ comorbidities have mean C1 that ranged from 25% higher (compared to healthy Black participants) to 35% higher (healthy Chinese Americans); their C2 values ranges from 14.4% (White participants) to 31.2% higher (Chinese Americans).

To assess whether differences in cardiometabolic comorbidity between groups can explain the large discrepancy in arterial stiffness measures, we used regression equations to estimate levels of C1, C2, and cfPWV

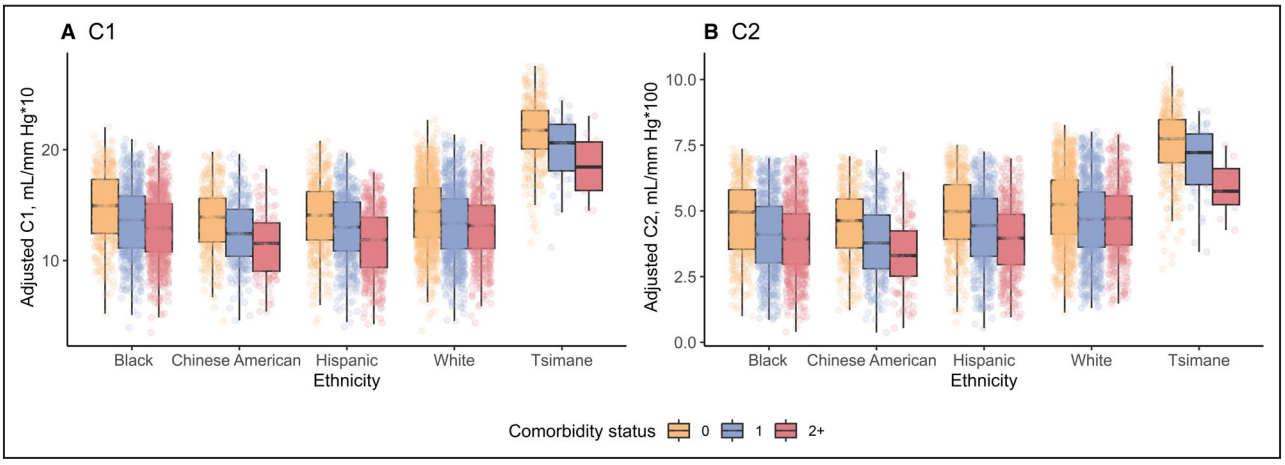

Figure 3. C1 and C2 levels by comorbidity status.
Shown are the levels of C1 (**A**) and C2 (**B**) across cardiometabolic comorbidity status in each ethnicity subset. Estimated C1 and C2 values were derived from multivariable linear regression models adjusted for age, sex, heart rate, triglyceride, LDL-C, and HDL-C. C1 indicates large artery elasticity; C2, small artery elasticity; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

of Tsimane individuals having US-level risk factors, and for US adults if they had Tsimane-level risk profiles (Figure S7). Tsimane with MESA-level risk factors and MESA participants with Tsimane-level risk factors converge for C2 and approach convergence for C1 only by age 70+ years. However, Tsimane with FHS Gen3–level risk factors have significantly lower cfPWV than FHS Gen3 participants with Tsimane-level risk factors.

DISCUSSION

Indigenous Tsimane of Bolivia show substantially lower levels of arterial stiffness than more urbanized and sedentary populations. The lower arterial stiffness of Tsimane individuals, compared with 2 US cohorts (MESA and FHS Gen3), was only partially explained by conventional cardiometabolic risk factors, underscoring the pivotal role of lifestyle and behavioral factors in modulating vascular health. Among community-based adults without a history of CVD, and from multiple ethnic backgrounds, advancing age is associated with higher arterial stiffness (lower C1 and C2; higher cfPWV). However, while C1 and C2 are consistently lower with age, cfPWV only appeared higher in Tsimane individuals after age 70 years.

The low arterial stiffness observed among Tsimane individuals supports prior observations of their superior vascular health.[15,16,18,19] In the age- and sex-matched subset, we find that Tsimane mean C1 and C2 are 33.3% and 32.0% higher, respectively; and their cfPWV is 33.9% lower than in healthy US populations. Population differences in C1 and C2 are evident by age 40 years, and mostly sustained throughout life. We found more convergence between Tsimane and US populations for C1 and C2 than for cfPWV. By age 70+, the differences in adjusted C1 and C2 between the Tsimane and MESA participants were approximately half of those observed at age 40 to 49 years. Conversely, the gap in cfPWV between Tsimane and FHS Gen3 participants widens with age, increasing from a 1.73-m/s difference in those younger than 40 years to 5.65 m/s in those aged 70+ years. By age 70+ years, mean cfPWV in the FHS Gen3 cohort exceeded 12 m/s, while cfPWV in Tsimane individuals remained <8 m/s. In fact, Tsimane cfPWV is consistently the lowest across each age stratum compared with other healthy populations, such as in those in Uruguay, Argentina, and Europe.[24,27,28]

Tsimane individuals exhibit a notably healthy vasculature in early-middle adulthood, which is sustained in later stages, particularly for central stiffness (cfPWV). The lower arterial stiffness of Tsimane might have contributed to their favorable cardiometabolic profile and comorbidity. Studies have shown that arterial stiffness precedes incident hypertension and is an early predictor of new-onset diabetes.[29–31] In addition, arterial stiffness in adolescence might be a causal factor of hyperinsulinemia and insulin resistance in adulthood and is bidirectionally associated with adiposity.[32,33] While cardiometabolic comorbidities (hypertension, obesity, diabetes) are rare in Tsimane, higher comorbidity burden is associated with lower C1 and C2, and both C2 and cfPWV are significantly associated with SBP, which aligns with previous findings.[10,29] It is also noteworthy that Tsimane with 2+ comorbidities still show much higher C1 and C2 than healthy Americans without those conditions. Such a vascular advantage corresponds with the very low prevalence of cardiovascular events and dementia among Tsimane, and dovetails with the notion of SUPERNOVA, characterized by exceptionally low arterial stiffness. In support, longitudinal evidence in Sweden demonstrates that cfPWV-defined SUPERNOVA was associated with a 41% reduction in the subsequent risk of CVD compared with normal vascular aging, while those with higher cfPWV given age (early vascular aging) was associated with a 170% increased risk.[34]

The disparities in arterial stiffness between Tsimane and urbanized cohorts can be attributed to their subsistence-oriented lifestyle and environmental context, which align with key metrics in cardiovascular health promotion, such as a lean diet, high physical activity, and consistently low blood glucose and blood pressure.[15,21,35,36] The combined effect of the aforementioned factors might promote optimal vascular health from early life and contribute to sustained cardiovascular well-being. In fact, Tsimane individuals lifestyle exemplifies many of the core principles outlined in the American Heart Association's Life's Essential 8 metrics, a framework that emphasizes proactive cardiovascular health improvement and preservation across the life course.[37] Based on that framework, the primary distinctions between Tsimane and their urbanized peers are diet and physical activity, the 2 criteria in which US adults scored the lowest among all 8 cardiovascular health metrics between 2013 and 2020.[38]

Tsimane individuals typically engage in high levels of low- and moderate-intensity activities year-round, despite seasonality of production tasks (Figure 4). Men and women typically engage in physical activity for 6 to 7 hours/day and 4 to 6 hours/day, respectively, averaging ≈17 000 steps daily. Activity levels remain relatively high throughout adulthood, though decline at late ages.[35] Studies have reported an attenuated age-related arterial stiffness increase in physically active populations.[39] A recent meta-analysis found that sustained aerobic exercise interventions reduce arterial stiffness, particularly measures of PWV.[40] The underlying mechanism involves improved vessel wall homeostasis through a combination of pathways, including decreased vascular oxidative stress,

Figure 4. A teenage girl sifts rice after pounding it to separate the husk from the grain (A), a group of men embark on a multiday hunting trip (B), 2 sisters and their children harvest sweet manioc roots with machetes and knives (C), and an older man chops firewood for cooking (D).
Photo credits: Michael Gurven.

increased endothelial nitric oxide bioavailability, and upregulation of vascular growth factors.[41] Moreover, the diet of Tsimane individuals is best characterized as high-carbohydrate, fiber-rich, and low-fat, with a high intake of micronutrients, such as potassium and magnesium.[36] This dietary pattern, centered on cultigens, freshwater fish, and wild game, closely resembles the recommended heart-healthy diet, with an emphasis on healthy fats, dietary fiber, whole grains, healthy-sourced proteins, and limited refined sugars and processed foods.[42] According to 24-hour dietary recall, the Tsimane average daily fat intake is an estimated 11 g of saturated fat, 14 g of monounsaturated fat, and 8 g of polyunsaturated fat, with negligible trans fat. Multiple randomized controlled trials have shown that a heart-healthy diet can significantly slow the progression of arterial stiffness, such as omega-3 fish oil supplement, which is abundant in Tsimane breastmilk, and likely their diet.[43–45]

More than 70% of Tsimane individuals showed HDL-C values conventionally "undesirable" based on a <40-mg/dL threshold, yet they still exhibit lower arterial stiffness than US peers with normal HDL-C levels. We found that HDL-C alone explains a considerable amount of variance in C1 and C2 among Tsimane, and higher levels are significantly associated with lower C1 and C2 values. Interestingly, higher HDL-C is also associated with higher levels of coronary artery calcium among Tsimane.[16] The surprising inverse relationship may be attributable to the Tsimane's high infectious burden, which can alter HDL composition and functionality. During acute infections, the inflammatory response can reduce the ability of HDL particles to promote cholesterol efflux, and transform HDL into a proinflammatory state.[46] Repeated exposure to infections and inflammation can result in long-term alterations in HDL functionality, undermining its otherwise vascular protective effects.[47] Among Tsimane, polyparasitism is prevalent, and respiratory and gastrointestinal illnesses are common, such that most morbidity and mortality is due to infections.[25,48] However, no significant association was found between (high-sensitivity C-reactive protein) and C1 or C2 in Tsimane, whereas higher hs-CRP levels were associated with lower C2 in MESA. This difference may be due to the predominantly "sterile" nature of chronic inflammation in the United States, while among Tsimane, inflammation may be more acute and accompanied by other

compensatory immune responses, such as the regulatory effects of helminth infections.[49]

Finally, we found a minimal and delayed age-related increase in cfPWV in Tsimane, whereas C1 and C2 were consistently lower with advancing age at similar rates among Tsimane and US ethnic groupings. The physiological mechanisms underlying these patterns merit further attention. We speculate that cfPWV better captures the structural alterations in the vasculature and reflects the cumulative impact of vascular dysfunction, while C1 and particularly C2, are more sensitive to short-term hemodynamic changes such as fluctuations in vascular tone and reactivity.[9] Thus, abnormal C1 and C2, but normal cfPWV, might suggest early adaptive changes in vascular tone rather than advanced vascular remodeling and reflect a healthy ventricular load, especially in the absence of CVD and with normal BP. Moreover, the magnitude and timing of pressure wave reflection are critical in the Windkessel model, which estimates C1/C2 values based on the shape of the composite waveform.[8] In stiffer arteries, premature wave reflection further alters the shape of the collected waveform and augments SBP. However, in Tsimane, the systolic upslope likely involves minimal wave reflection, while the later rolling motion in the waveform, represented by the diminished cosine terms in C1 and C2, may capture factors beyond elasticity alone.

PERSPECTIVES

Tsimane forager-farmers of the Bolivian Amazon demonstrate substantially lower levels of arterial stiffness throughout adulthood than more urbanized and sedentary populations. Population differences are partially explained by conventional cardiometabolic risk factors, but advancing arterial stiffness exists among all tested ethnic groups without a history of CVD. Our findings suggest that a physically active lifestyle combined with a lean diet low in saturated fat can preserve vascular health well into older age. While low arterial stiffness may contribute to the minimal atherosclerosis and dementia documented among Tsimane individuals, current changes in lifestyle amid increasing market integration and "modernization" may soon alter their epidemiological landscape.

LIMITATIONS

We note several study limitations. First, Tsimane cfPWV measurements were retrospectively calculated using ECG and waveform data, which may introduce potential bias and errors. However, efforts were made to ensure accuracy, and similar observed age-related patterns have been confirmed in ongoing data collection using a validated automated device. Second, we converted the cfPWV transit distance of FHS Gen3 into the direct distance between carotid and femoral sites, which might introduce variability despite using a recognized standard formula. In addition, lipid data were not available during the period of Tsimane cfPWV data collection, and thus were not included in the analysis. Nonetheless, our model performed well with the existing confounders, explaining 46.6% and 39.3% of cfPWV variance in the FHS Gen3 and THLHP cohorts, respectively, which is higher than the proportion of variance explained for C1 and C2 when lipid variables were included. Last, although cigarette smoking data were not available for Tsimane (the median Tsimane has smoked 0 pack-years),[16] our comparative results based on a smoke-free US subset were similar.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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