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Arterial stiffness and multiple organ damage: a longitudinal study in population

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Abstract

Aims—Previous cross-sectional observation identified arterial aging, indexed as pulse-wave velocity (PWV), as a key determinant of the simultaneous multiple organ damage (heart, carotid artery, and kidney). The aim of the present cohort study is to investigate trajectories of repeated measures of PWV and traditional CV risk factors in subjects who eventually presented clinical evidence of multiple organ damage in the SardiNIA study.

Methods and results—Organ damage was measured in the heart (left ventricular hypertrophy, LVH), the common carotid artery (intima–media thickness > 0.9 mm and/or plaque), and the kidney (eGFR < 60 ml/min/1.73 m^2) of 2130 men and women of a broad age range participating the SardiNIA study. SHATS was defined as the simultaneous occurrence of all the three-organ

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Conflict of interest No author has to disclose any conflict of interest that could have direct or potential influence or impart bias on the work.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

damages. Trajectory in traditional CV risk factors and PWV was analyzed retrospectively (four observations over 9 years) according to the number of organ damage (from 0 to 3). Compared to subjects with no organ damage, after controlling for traditional CV risk factors, each 1 m/s increase in baseline PWV was accompanied by a 93% higher odds of developing SHATS; and each 1 cm/s (0.01 m/s) annual increase in PWV by a 31% greater odds of developing SHATS.

Conclusions—Arterial stiffness, a proxy of arterial aging that can be measured clinically as PWV, is an integrated predictive marker of multiple age-associated organ damage recognized as clinical diseases.

Keywords

Arterial stiffness; Pulse-wave velocity; Left ventricular hypertrophy; Chronic kidney disease; Multiple organ damage; Longitudinal study

Introduction

Arterial stiffness, indexed as aortic PWV, has progressively emerged as a proxy of central arterial aging [1], from the early (accelerated) vascular aging (EVA) [2, 3] to the “lower than average” arterial aging, i.e., healthy vascular aging (HVA) [4]. Traditional CV risk factors remain significant determinants of PWV [5, 6], though the age-associated increase in arterial stiffening seems to be independent of CV risk factor levels [7], These considerations have led to the idea that high PWV may be regarded as an equivalent to target-organ damage [8], conferring greater individual odds of CV-related mortality and disability [9–11].

Organ damage is a key determinant of global CV risk, especially for the clinical management of hypertension [12, 13]. Hypertension is known to accelerate the progression in the CV continuum via a vicious cycle of hemodynamic stress and vascular wall response that has been recently conceptualized as systemic hemodynamic atherothrombotic syndrome (SHATS) [14]. We have shown that SHATS, operationally defined as the simultaneous damage in multiple organs and systems (heart, carotid artery, and kidney), has high prevalence in older subjects [15]. Of note, a high PWV informed on accelerated aging within the entire systemic vascular, emerging as a key determinant of multiple organ damage [15]. That study, however, was cross section in design and included mostly older hypertensive subjects. Validation of both the operational definition of SHATS and the link of high PWV and target-organ vascular damage requires a longitudinal study in a larger population of men and women of a broad age range.

The aim of the present study was to investigate trajectories of repeated measures of PWV and traditional CV risk factors in subjects who eventually presented clinical evidence of multiple organ damage and SHATS in the SardiNIA (PROGENIA) study.

Methods

Study population

The SardiNIA study investigates the genetics and epidemiology of complex traits/phenotypes, including CV risk factors and arterial properties, in a community-dwelling

Sardinian founder population [16]. The study population for the present analysis consisted in 2130 subjects with measurements of all the parameters required to define the future development of SHATS at their last visit. For each subjects, measurements were available at each of the previous three visits (mean follow-up time 9.4 years).

Variables measured

Blood pressure—Morning blood pressure was measured in both arms with a mercury sphygmomanometer using an appropriately sized cuff. Values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined by Korotkoff phases I and V, respectively. The average of the second and third measurements on both the right and left arms was used in the analysis. Pulse pressure was computed as PP = (SBP − DBP); mean BP was computed as MBP = DBP + (PP/3).

Anthropometry—Height, weight, and waist circumference were determined for all participants. Body mass index (BMI) was calculated as body weight (kg)/height (m^2).

Fasting plasma lipids—Blood samples were drawn from the antecubital vein between 7 and 8 AM after an overnight fast. Subjects were not allowed to smoke, engage in significant physical activity, or take medications prior to the collection of the samples. Plasma triglycerides and total cholesterol were determined by an enzymatic method (Abott Laboratories ABA-200 ATC BiochromaticAnalyzer, Irving, TX, 75015, USA). HDL cholesterol was determined by a dextran sulfate-magnesium precipitation. LDL-cholesterol concentrations were estimated by the Friedewald formula. Fasting plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments Inc., Fullerton, CA, 92634, USA).

Definition of the metabolic syndrome—Metabolic syndrome (MetS) was defined in accordance with the third report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (ATP III), as previously described [17], i.e., as an alteration in three or more of the following five components: abdominal obesity, high triglycerides, low HDL cholesterol, elevated blood pressure (systolic or diastolic), and elevated fasting glucose. The following cut-off values are used to define each altered component: waist circumference > 102 cm for men or > 88 cm for women, triglycerides ≥ 150 mg/dl HDL cholesterol < 40 mg/dl for men or < 50 mg/dl for women, blood pressure ≥ 130/≥ 85 mmHg, and fasting glucose ≥ 110 mg/dl.

Definition of SHATS

An SHATS score was defined as the sum of the affected target organs [15] leading to a score for 0 (none of the organs were damaged) to 3 (all three-organ systems exhibit damage). The presence of target-organ damage in the heart or the carotid artery or the kidney was scored as one point.

Assessment of target-organ damage

The following parameters were adapted to measure organ damage:

- Left ventricular hypertrophy (LVH) for the heart;
- Estimated glomerular filtration rate (eGFR) for the kidney;
- Thicker intimal-media layer and/or presence of plaque for the common carotid artery (CCA damage).

a. LVH

Echocardiograms (parasternal and apical views) were obtained (Agilent Sonos 5500®) at rest with the patients supine in the left lateral position. LV mass was estimated from the formula of Devereux et al. [18] and normalized for body surface area (BSA) (LVMI). The presence of LV hypertrophy was defined as an LVMI ≥ 115 g/m^2 for men or ≥ 95 g/m^2 for women [8].

b. Chronic kidney disease (CKD)

CKD stages were defined according to the International Classification of National Kidney Foundation as the presence of eGFR < 60 ml/min/1.73 m^2 (stage 3) [19].

c. CCA damage

High-resolution B-mode carotid ultrasonography was performed by use of a linear-array 5–7.5-MHz transducer. The subject lay in the supine position in a dark, quiet room. The stabilized BP after 15 min from the onset of testing was used for subsequent analyses. The right and left common and internal carotid arteries were examined with the head tilted slightly upward in the midline position. The right CCA IMT measurement was obtained from 5 contiguous sites at 1-mm intervals, and the average of the 5 measurements was used for analyses.

Carotid plaque was defined as focal encroachment of the arterial wall in any of the explored arterial segments (left and right CCA and bulb).

CCA damage was defined as a diastolic CCA IMT > 0.9 mm and/or the presence of CCA plaque [20].

Assessment of pulse-wave velocity (PWV)

Aortic stiffness was assessed non-invasively by the carotid-femoral PWV [16], using nondirectional transcu-taneous Doppler probes (Model 810A, 9–10-MHz probes, Parks Medical Electronics, Inc, Aloha, OR, USA) and adopting the subtraction method for estimating aorta length from the distance between carotid and femoral measurement sites. Accordingly, exaggerated stiff artery was defined as a PWV > 10 m/s [8].

The within day coefficient of variation for PWV was 7.8%. The between day correlation between repeated measurements was 0.902.

Statistical analysis

All analyses were performed using the R software [21], Data are presented as mean ± SD. Differences in mean values for the measured variables among subjects according to the number of altered SHATS components (SHATS score) at study entry and at their last visit

were compared by ANCOVA including Visit, SHATS score, and their interaction terms as covariates.

Longitudinal data changes were modeled with a single linear mixed-effects regression model [22], which easily accommodates unbalanced, unequally spaced observations and, consequently, is an ideal tool for analyzing both cross-sectional and longitudinal changes in data from this observational study. The fit of the mixed-effects models to the data are addressed by plots of the residuals and plots of observed vs. predicted values. To test the effect of SHATS (score) on longitudinal changes in CV risk factors and PWV, mixed-effects model included as covariates: age of entrance into the study, visit, SHATS score, and interaction terms of the last two variables.

To identify predictor of multiple organ damage, two sets of multinomial logistic regression models were constructed; the first model including established CV risk factors and PWV at baseline; the second model included also the annual rate of change in CV risk factors (calculated as the difference between last and first visit divided by the follow-up time) and PWV. Backwards elimination of non-significant factors led to the identification of the significant predictors of multiple organ damage.

A two-sided p value < 0.05 indicated statistical significance.

Results

Table 1 summarizes the characteristics of the 2130 participants at study entry and at the last visit. Among them, 1153 or 54.1% had no organ damage (SHATS score 0), 836 or 39.1% had a single organ damage (SHATS score 1), 124 or 5.4% had two organ damage (SHATS score 2), and only 17 or 0.8% had multiple organ damage (SHATS score 3 or SHATS). This uneven distribution may reflect the age structure of the study population. At their last visit, only 13.2% were older than 65 years—the age group with greater occurrence of multiple organ damage [15].

Women were less represented with increasing SHATS score (64.7%, 58.2%, 10.8%, and 7.2% from SHATS scores 0–3, i.e., from no organ damage to three-organ damages). Age, established CV risk factors, and MetS components' distribution all significantly differed by increasing SHATS score—as illustrated in Table 2.

BP levels and use of antihypertensive medications were all greater as SHATS score increased, but only BP levels over 9.4 years differed significantly by SHATS score (Supplemental Fig. 1). Notably, subjects with SHATS (SHATS score = 3) showed a dramatic decrease in SBP, DBP, and PP, possibly a consequence of the striking increase in antihypertensive medications use (Supplemental Fig. 1). BMI, waist circumference, abdominal obesity, and the number of altered components of MetS were all greater with increasing SHATS score and these trajectories significantly differed over 9.4 years by SHATS score (Supplemental Fig. 2). Of note, the occurrence of elevated fasting glucose dramatically increased in SHATS scores 2 and 3 after visit 1 (Supplemental Fig. 2). PWV—even when normalized for mean blood pressure (PWV/MBP)—was greater, as SHATS score increased, but did not significantly change over time (Fig. 1).

Backwards, elimination of non-significant factors led to the identification of male sex, BMI at baseline, MBP at baseline, PWV at baseline, as well as the rate of change of PWV as significant predictors of multiple organ damage (SHATS score). PWV showed an apparent effect in its association with a sort of dose-response as a predictor of multiple organ damage (Table 3). Compared to subjects with no organ damage, each 1 m/s increase in baseline PWV was accompanied by a monotonously increasing odds ratio (OR) of SHATS: there is a 30% higher odds of SHATS = 1,55% higher odds for SHATS = 2, and 103% for SHATS = 3. Similarly, for a 1 cm/s/year, increase in the rate of change in PWV leads to ORs of 7%, 22%, and 31% for SHATS scores 1, 2, and 3, respectively.

As illustrated in Table 4, both PWV at baseline and its rate of change over time were independently associated with greater odds of having each specific organ damage contributing to the SHATS and SHATS score, namely, left ventricular hypertrophy, chronic kidney disease, and CCA damage.

Discussion

This is the first longitudinal study aimed at identifying trajectories of simultaneous multiple target-organ damage (SHATS) risk factors. Both PWV at baseline and its rate of change over time were independently associated with greater odds of having each specific organ damage contributing to the SHATS, namely, left ventricular hypertrophy, chronic kidney disease, and CCA damage.

The occurrence of SHATS in the SardiNIA study was much lower than reported in a recent cross-sectional study [15]. However, the current study included a cohort of general population with a large proportion of younger subjects, whereas the previous study included mostly older hypertensive patients. These factors may explain the differences of SHATS occurrences in the two studies.

The dose-response such as associations of PWV (and its rate of change) with SHATS score may be interpreted as a facet of greater CV risk factors levels with increasing SHATS score. However, common trajectories of established CV risk factors did not universally differ with increasing SHATS score.

Average BP levels significantly decreased in subjects developing SHATS. These findings are consistent with the previous report that age-associated arterial stiffening is independent of blood pressure levels [7]. The concomitant greater use of antihypertensive medication in subjects with SHATS may not only explain the lower observed levels in BP. It may also remark the risk of inappropriate drug use with advancing age [23] as well as the detrimental consequence of decreasing BP levels in a stiffer arterial system [24]. Alternatively, the association between increasing PWV and multiple organ damages may be related to alteration in the coupling between the heart and the vasculature [1] and vascular remodeling [1], and/or microvascular damage related to a greater pulsatility in the arterial system, that eventually leads to a greater endothelial damage and arterial stiffness [25, 26], arterial damage [27, 28], and left ventricular load with progression to LVH [29]. Future studies will try to answer this question.

The present study has some limitations. The first and major is represented by the small number of subjects with SHATS (17 or 0.8%). This seems largely attributable to the nature of the study population (a cohort of predominantly healthy individuals) and its age structure (only 13.2% of the subjects were 65 years or older at the time of multiple organ damage assessment). In fact, our previous study, reporting a prevalence of SHATS about 20% [15], was conducted in a cohort of older hypertensive subjects, where both age and hypertension were major contributors to SHATS prevalence. The analytical approach focusing on the number of organ damage (i.e., SHATS score) may have reduced the potential bias deriving from the small number of subjects with multiple organ damage or SHATS.

In summary, our study further supports the idea that arterial stiffness, a proxy of arterial aging, clinically as PWV is an integrated diagnostic, predictive, and prognostic marker of multiple age-associated organ damage recognized as clinical diseases. Therapeutic interventions targeting PWV may effectively reduce our aging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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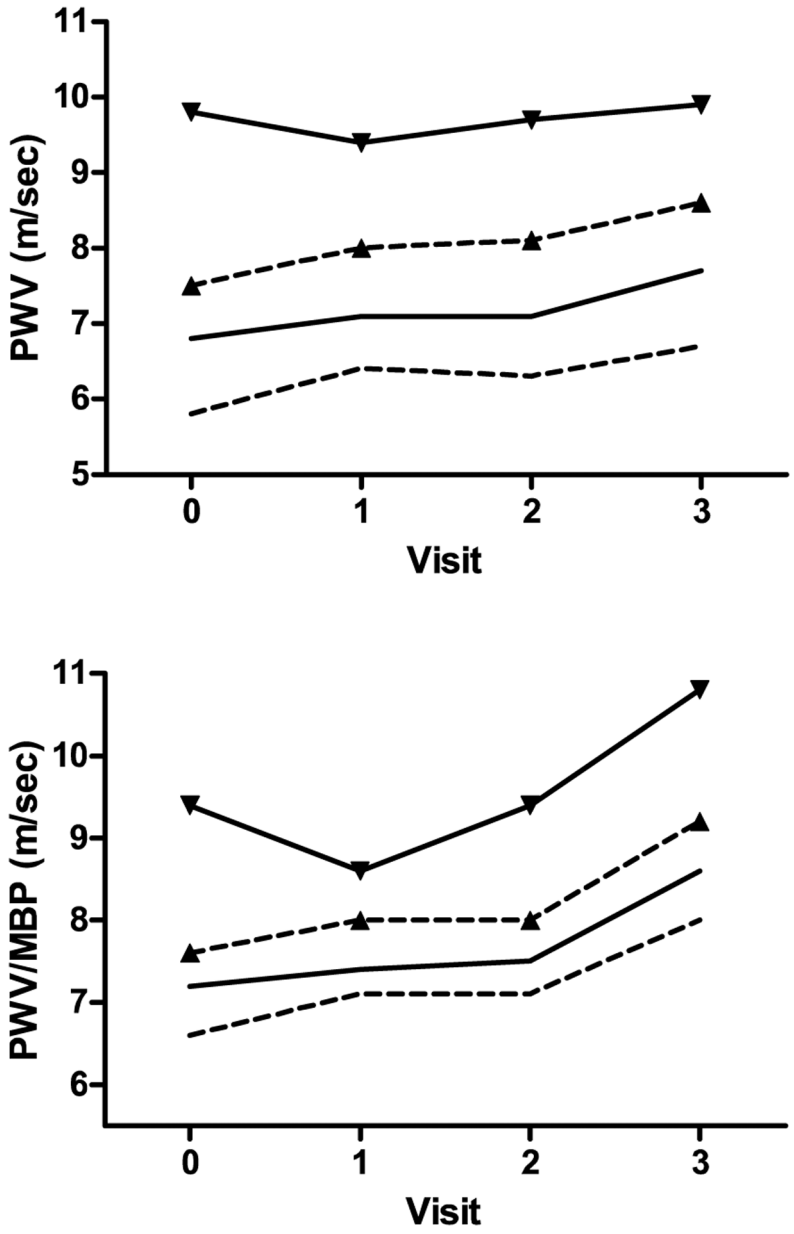

Fig-1.

Trends in PWV according to the SHATS score at last visit. Each line represents an SHATS score value: 0 (dashed line), 1 (continuous line), 2 (dashed line with triangle), and 3 (continuous line with triangle). PWV has been analyzed as “crude” values (top panel) or normalized for Mean Blood Pressure (MBP) to highlight BP-independent trends in PWV (bottom panel)

Table 1

Characteristics of study population at first and at last visit

	Baseline	Last visit
Age (years)	39.4 ± 13.5	48.2 ± 14.2
BMI (Kg/m^2)	24.6 ± 4.0	25.4 ± 4.3
Waist circumference (cm)	81.8 ± 11.4	87.4 ± 10.8
SBP (mmHg)	121.8 ± 15.7	119.1 ± 16.4
DBP (mmHg)	75.5 ± 10.2	73.6 ± 10.0
MBP (mmHg)	90.8 ± 11.2	88.6 ± 11.4
PP (mmHg)	46.4 ± 10.7	45.5 ± 10.6
Fasting glucose (mg/dl)	86.3 ± 16.3	95.2 ± 21.8
Total cholesterol (mg/dl)	207.4 ± 39.9	212.6 ± 41.6
LDL cholesterol (mg/dl)	126.0 ± 33.0	129.0 ± 35.6
HDL cholesterol (mg/dl)	64.9 ± 14.6	64.2 ± 14.5
Triglycerides (mg/dl)	80.8 ± 48.0	94.0 ± 52.3
Serum creatinine (mg/dl)	0.80 ± 0.19	0.85 ± 0.17
Uric acid (mg/dl)	4.0 ± 1.4	4.5 ± 1.4
Diabetes mellitus (%)	1.7	5.4
Obesity (%)	9.8	14.335.1
Overweight (%)	31.7	
PWV (m/s)	6.3 ± 1.9	7.3 ± 2.1
PWV > 10 m/s (%)	4.3	5.1
Antihypertensive (%)	4.5	10.6
Antidiabetic (%)	0.9	2.0
Statins (%)	1.2	6.5
Antiplatelet drugs (%)	0.8	4.9
Insulin therapy (%)	0.6	0.6
Diuretics (%)	1.8	3.6
Beta-blockers (%)	1.6	3.3
Alpha-blockers (%)	0.4	1.2
CCB (%)	1.0	1.5
CEI and/or ATI blockers (%)	2.5	4.3

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *PP* pulse pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PWV* pulse-wave velocity, *CCB* calcium channel blocker, *CEI* converting enzyme inhibitor, *ATI* angiotensin type 1 receptor

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Table 2

Characteristics of subjects at first and at last visit according to the number of altered components of SHATS (SHATS score) assessed at last visit

	First visit				Last visit				Visit	SHATS score	Visit* SHATS score
	0	1	2	3	0	1	2	3			
Age (years)	34.8 ± 11.9	43.5 ± 13.0	54.3 ± 11.2	65.3 ± 7.1	42.8 ± 12.6	53.2 ± 12.9	63.9 ± 11.3	75.4 ± 8.1			
BMI (Kg/m^2)	23.3 ± 3.5	26.0 ± 4.0	27.4 ± 3.2	28.1 ± 4.1	24.1 ± 3.8	26.8 ± 4.3	28.1 ± 3.5	27.7 ± 4.1	0.49	0.0001	0.54
Waist circumference (cm)	78.1 ± 10.4	85.3 ± 11.0	92.3 ± 9.1	94.7 ± 8.9	84.3 ± 10.1	90.5 ± 10.4	96.3 ± 8.8	97.6 ± 8.1	0.001	0.0001	0.13
SBP (mmHg)	118.1 ± 13.8	125.4 ± 16.4	132.8 ± 14.5	148.1 ± 18.3	114.8 ± 14.9	122.7 ± 16.5	133.1 ± 14.8	128.3 ± 13.1			0.01
DBP (mmHg)	73.2 ± 9.4	77.7 ± 10.4	82.5 ± 9.9	84.8 ± 9.9	71.3 ± 9.4	76.0 ± 10.1	78.3 ± 10.3	74.1 ± 9.3			0.05
MBP (mmHg)	88.0 ± 10.0	93.4 ± 11.5	99.1 ± 10.5	105.7 ± 11.8	85.7 ± 10.6	91.4 ± 11.5	96.4 ± 10.8	92.0 ± 9.9			0.05
PP (mmHg)	44.9 ± 9.9	47.7 ± 11.3	50.3 ± 10.9	63.3 ± 13.2	43.5 ± 9.8	46.7 ± 10.8	54.8 ± 10.9	54.2 ± 8.7			0.001
Fasting glucose (mg/dl)	84.4 ± 16.6	87.7 ± 15.5	95.1 ± 16.6	85.8 ± 10.6	91.8 ± 18.6	98.1 ± 24.5	107.1 ± 23.6	105.7 ± 18.9			0.05
Total cholesterol (mg/dl)	200.7 ± 39.7	213.9 ± 38.2	226.2 ± 37.2	229.6 ± 17.0	209.1 ± 41.5	217.4 ± 40.8	211.0 ± 44.2	222.5 ± 41.4			0.001
LDL cholesterol (mg/dl)	120.2 ± 32.0	131.7 ± 33.2	142.7 ± 30.8	141.1 ± 12.9	125.7 ± 35.6	133.3 ± 34.7	128.9 ± 37.9	141.5 ± 36.4			0.01
HDL cholesterol (mg/dl)	65.4 ± 14.5	64.6 ± 14.9	61.9 ± 13.7	67.5 ± 7.8	65.3 ± 14.7	63.5 ± 14.0	58.3 ± 12.6	61.1 ± 21.9	0.08	0.0001	0.28
Triglycerides (mg/dl)	73.8 ± 43.5	86.8 ± 50.2	108.0 ± 57.4	104.8 ± 56.4	88.6 ± 49.6	98.6 ± 52.9	113.7 ± 64.5	98.9 ± 40.9	0.06	0.0001	0.38
Serum creatinine (mg/dl)	0.78 ± 0.15	0.80 ± 0.20	0.93 ± 0.17	1.2 ± 0.9	0.83 ± 0.13	0.85 ± 0.18	1.05 ± 0.23	1.14 ± 0.18	0.01	0.0001	0.20
Uric acid (mg/dl)	3.8 ± 1.2	4.2 ± 1.4	5.2 ± 1.5	6.1 ± 1.4	4.3 ± 1.3	4.7 ± 1.3	5.6 ± 1.6	5.7 ± 1.2	0.18	0.0001	0.12
Diabetes mellitus (%)	1.1	1.9	6.7	0	3.3	6.7	13.1	28.5			0.001
Obesity (%)	4.9	15.1	18.1	30.0	8.2	20.8	26.2	28.5	0.43	0.0001	0.30
Overweight (%)	21.6	41.3	63.8	50.0	26.9	43.3	54.6	57.1	0.73	0.0001	0.14
PWV (m/s)	5.8± 1.4	6.7 ± 2.2	7.7 ± 2.0	9.2 ± 2.5	6.7 ± 1.8	7.7 ± 2.2	8.6 ± 2.5	9.9 ± 1.9	0.001	0.0001	0.81
PWV > 10 m/s (%)	1.6	6.5	10.3	30.0	2.5	7.4	11.5	35.7	0.81	0.0001	0.78

The column “Visit” indicates significance of differences in the variable between visits. The column “SHATS score” indicates significance of differences in the variable across SHATS score. The column with the interaction term “Visit*SHATS score” indicates that variable levels differ between visits according to the SHATS score

Table 3

Arterial stiffness (PWV at baseline and annual rate of change) as a predictors of multiple organ damage and SHATS, after controlling for established CV risk factors (BMI, LDL, and HDL cholesterol, fasting glucose, and MBP)

	SHATS score								
	1			**2**			**3**		
	OR	**95% CI**	***p*<**	**OR**	**95% CI**	***p*<**	**OR**	**95% CI**	***p*<**
PWV at baseline (per 1 m/s increase)	**1.30**	1.17–1.44	0.0001	**1.55**	1.29–1.87	0.0001	**2.03**	1.46–2.56	0.0001
Annual rate of change in PWV (per 0.1 m/s)	**1.07**	1.01–1.15	0.05	**1.22**	1.08–1.37	0.01	**1.31**	1.04–1.65	0.05
BMI at baseline (per 1 kg/m^2 unit increase)	**1.29**	0.88–1.07	0.48	**1.30**	1.11–1.20	0.0001	**1.18**	1.09–1.13	0.0001
MBP at baseline (per 10 mmHg increase)	**1.55**	0.78–3.08	0.20	**1.45**	1.06–1.98	0.05	**1.30**	1.10–1.54	0.001

Table 4

Arterial stiffness (PWV at baseline and annual rate of change) as a predictors of each organ damage contributing to SHATS, after controlling for established CV risk factors (BMI, LDL and HDL cholesterol, fasting glucose, and MBP)

	OR	95% Cl	*p*<
LVH			
PWV at baseline (per 1 m/s increase)	**1.28**	1.15–1.38	0.0001
Annual rate of change in PWV (per 0.1 m/s)	**1.07**	1.01–1.14	0.05
BMI at baseline (per 1 kg/m^2 Unit increase)	**1.13**	1.09–1.17	0.0001
MBP at baseline (per 10 mmHg increase)	**1.27**	1.08–1.49	0.01
CKD			
PWV at baseline (per 1 m/s increase)	**1.22**	1.07–1.39	0.01
Annual rate of change in PWV (per 0.1 m/s)	**1.10**	1.01–1.22	0.05
BMI at baseline (per 1 kg/m^2 Unit increase)	**1.10**	1.03–1.18	0.01
LDL cholesterol at baseline (per 10 mg/dl increase)	**1.12**	1.03–1.22	0.01
CCA damage			
PWV at baseline (per 1 m/s increase)	**1.40**	1.22–1.61	0.0001
Annual rate of change in PWV (per 0.1 m/s)	**1.24**	1.10–1.39	0.001
LDL cholesterol at baseline (per 10 mg/dl increase	**1.12**	1.03–1.22	0.01

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