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The correlation between age, blood pressure variability and estimated pulse wave velocity

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Studies have separately compared the association of age with blood pressure variability (BPV) or pulse wave velocity (PWV). We aimed to establish the association between age and metrics of short-term BPV and PWV in the same sample. 508 under 60 years (< 60) and 141 in their sixties (≥ 60) measured blood pressure (OBP), and PWV using the oscillometric technique (br-PWV). They recorded an ambulatory BP monitoring (ABPM) to obtain variables for systolic (SBPV) and diastolic BPV (DBPV). We also estimated PWV using formulas. We calculated the Pearson correlation coefficient (r) and determination coefficient (R^2) of all parameters with age. The correlation between age and PWV was very strong (br-PWV; r = 0.901; p < 0.001). It was poor for SBPV, 24-h weighted SD r = 0.492; p < 0.001, and not significant for DBPV, 24-h weighted SD r = 0.220; p < 0.001. The correlation and determination values were generally better in the group comprising ≥ 60-years, with R^2 values robust for PWV (br-PWV = 0.812) weaker for SBPV (24-h weighted SD = 0.243) and deemed irrelevant for DBPV (24-h weighted SD = 0.048). Our study shows that PWV metrics are firmly and significantly more influenced by age than short-term BPV.

Keywords Age, Pulse wave velocity, Blood pressure variability, Blood pressure

The prevalence of hypertension among adults aged 30–79 worldwide is estimated to be around 33%. That number takes into consideration that hypertensive individuals present systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or use medication for hypertension[1]. Hypertension is commonly associated with cardiocerebrovascular diseases, kidney diseases, and cardiovascular mortality. This relation starts at ≥ 110–115 mmHg of SBP. The main hypertension guidelines worldwide do not incorporate this value into their recommendations for treating individuals diseases. In 2019, the high systolic level was the world's leading risk factor for mortality and could have prevented 10.8 million deaths (19%) if it had been controlled[2]. Analysis of individual records from 83 health examination surveys in 52 countries indicates that between the ages of 30 and 64, SBP increases by 1.7 to 11.6 mm Hg per decade of age[3]. Moreover, data from the National Health and Nutrition Examination Survey (2007–2012) indicates that 70% of American elderly adults (> 65 years old) have hypertension, against only 32% of adults aged 40–59[4]. The high prevalence of hypertension in older people is related to vascular aging (VA), a process of vascular degeneration. Its main features are the deterioration in arterial structure and function over time, including a substantial range of alterations affecting the functional and structural components of the arterial wall regardless of size. As a consequence, the vessel wall changes lead to an increase in arterial stiffness (AS)[5]. Stiffening of the great arteries amplifies the pulsatility of blood pressure. It responds to many other issues, including elevated pulse pressure (PP) and isolated systolic hypertension. Premature wave reflections reach the central aorta sooner, leading to the amplification of PP. The higher the AS, the greater the transmission velocity of both forward and reflected waves from peripheral to large arteries[6].

In the last twenty years, AS has emerged among many biological risk markers as one of the most valuable, distinctive, and independent predictors of cardiovascular events, based on a solid set of evidence from many studies showing carotid-femoral pulse wave velocity (cf-PWV) as an independent predictor of total mortality and cardiovascular (CV) events[7,8].

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Many invasive and non-invasive techniques have been introduced within the past decades to measure AS. The carotid-femoral PWV is currently the gold standard for arterial stiffness assessment. However, many other methods can be employed for that purpose. Some devices estimate PWV by recording signals at peripheral arteries using brachial cuffs. The Mobil-O-Graph, for instance, is one of them. It is an automated oscillometric brachial cuff-based ambulatory BP monitoring device that measure PWV (br-PWV) using a proprietary algorithm[9]. Even regression equations built from the database of Reference Values for Arterial Stiffness Collaboration using age and MBP can estimated PWV (e-PWV)[10,11]. The correlation between AS and age is well-established and documented for cf-PWV and many other PWV measures. All such measures increase, non-linearly, with age, with more notable changes visible in > 50-year-olds. However, for e-PWV and br-PWV, the relationship has yet to be the objective of studies[12]. Other biomarkers beyond blood pressure and arterial stiffness have demonstrated prognostic cardiovascular risks, including blood pressure variability (BPV). It reports to higher mortality outcomes regardless of mean blood pressure or baseline risk of CV events[13,14].

Blood pressure variability (BPV) includes a wide range of BP variations, which are separated into different groups based on time intervals for measurement. The short-term BPV is that occurring within 24 h. BP values from a non-invasive, intermittent 24-h ambulatory blood pressure monitoring (ABPM) allows for the calculation of some short-term BP variations, as 24-h BP. Calculating 24-h BP standard deviation (SD), is the simplest and most objective way to determine short-term BPV. The degree of day-night BP reduction strongly influences these indices. Average real variability (ARV) and weighted—24 h BP SD avoid the interference of day–night BP fluctuations in calculating short-term BPV measures[15,16].

Evidence from basic and clinical sciences proposes that BPV could be a plausible marker of aging. However, studies for quantifying age association with short-time BPV variables still need to be included. Several explanations have been offered regarding the associations between BPV and aging[17]. On that matter, the short-time BPV independently demonstrated a linear positive and moderate relation to aortic stiffness measured by cf-PWV and br-PWV, and some short-time BPV variables demonstrated an independent prediction for PWV[18,19]. Considering that age, short-time BPV, and arterial stiffness have an interdependent relationship. We aimed to establish, compare, and quantify the association between age and some short-time BPV and PWV metrics (oscillometric and estimated) in younger and older subjects.

Methods

This study is a secondary analysis conducted from a database collected from another cross-sectional research performed at a specialized center in Brazil to diagnose and treat non-communicable diseases. It included individuals older than 18 with a suspected hypertension diagnosis, individuals under treatment who were referred to record twenty-four hours of ABPM either to confirm a hypertension diagnosis or evaluate uncontrolled hypertension[19]. Between May 2016 and April 2019, we invited subjects referred to the clinic to carry out an ABPM and consecutively included those who were eligible and agreed to participate in the research.

All individuals included in this research signed an informed consent form. A trained nurse collected demographic and clinical data, including any previous reports of clinical cardiovascular disease (CVD), acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, transient ischemic attack, aortic aneurysm, peripheral artery disease, and severe chronic kidney disease (CKD). We not included any subjects with or suspected have a secondary hypertension. In addition, all subjects had their BP, weight, height, waist circumference measured and their body mass index (BMI) calculated. We considered a cut-off value of ≥ 140 and/or 90 mmHg to define elevated and uncontrolled BP; body obesity for BMI values ≥ 30 kg/m^{2}and an increased waist circumference > 102 cm in males and > 88 cm in females[20].

Blood pressure measurement and ambulatory blood pressure monitoring

The nurse assistant used a Microlife device model BP3AC1-1PC device (Onbo Electronic Co, Shenzhen, China) to conduct attended BP measurements (OBP) in a clinical setting. The equipment automatically recorded a set of 3 measurements with a 15-s interval between them and displays the average of the three readings. We applied a correct measurement technique and a consistent approach to BP measurement for each patient. All participants had their BP measured after 5 min of rest, avoided stimulants (caffeine, tobacco) for at least 30 min, and emptied their bladder beforehand. Measurements were taken while participants were seated with their backs supported and legs uncrossed. BP was measured on the supported, non-dominant, bare arm using an appropriately sized cuff[21].. The subjects underwent twenty-four hours of ABPM using a Dyna-Mapa / Mobil-O-Graph-NG monitor (Cardios, São Paulo, Brazil), appropriately attached with a cuff on their non-dominant arm. During the day, the device recorded readings every 20 min, and every 30 min during the night, encompassing the period between going to bed and waking up. Daytime and night-time intervals were defined using sleeping times reported in participants' diary cards (awake and asleep periods). We excluded from analysis individuals who did not complete the required data, those with 24-h recordings presenting less than 70% of the expected measurements, fewer than 20 valid awake or seven valid sleeping measurements, or fewer than two valid daytime and one valid night-time measurement per hour[22].

Pulse wave analyses

Soon after the BP measurements were taken, participants rested for 10 min in a supine position in a quiet room. Then, they performed the pulse wave analyzes (PWA) using the Mobil-O-Graph (I.E.M., Stolberg, Germany). They completed four sequential measurements of PWV following the protocols recommended by the Expert Consensus Document on measuring Aortic Stiffness in 2012. We calculate br-PWV as the average of the four PWV measurements[23,24].

Short-term BPV metrics

One of the BPV measures derived directly from mean systolic and diastolic BP from ABPM is the standard deviation (SD) of twenty hours BP (24-h BP), which is strongly influenced by the number of day-night BP changes. Thus being, we calculated two additional (weighted SD and average real variability) and more specific indices of short-term BPV in order to minimize the contribution of nocturnal BP falls to overall variance. The weighted SD of 24 h-BP is the mean of daytime and nighttime SD, weighted by the duration (in hours) of day and nighttime. We computed the wake and sleep hours from all AMBP records to calculate it. Then, a mathematical formula was employed: 24 h-BP SD weighted = awake SD x awake hours + sleep SD x sleep hours / total hours[25]. The average real variability (ARV) calculates the average of absolute changes between consecutive BP readings: ARV = 1N-1Σk = 1 N-1(BPk + 1-BPk), where N indicates the number of valid BP measurements, and k is the order of measures[26]. Additionally, we calculated the coefficient of variability for the 24-h BP average (CV 24-h), which results from a ratio of 24-h SD by 24-h BP average[27].

Calculation of estimated pulse wave velocity

The e-PWV was calculated using the Eq. 1derived from the Reference Values for Arterial Stiffness Collaboration, incorporating age and mean BP (MBP). MBP was calculated as DBP + 0.4 (SBP-DBP)[10,11].

Eq. 1:

$$9.58748315543126 - 0.402467539733184 * age + 4.56020798207263 * 10 - 3 * age2 - 2.6207705511664 * 10 - 5 * age2 * MBP + 3.1762450559276 * 10 - 3 * age * MBP - 1.83\,2150382185 * 10 - 2 * MBP \quad (1)$$

We calculated e1-PWV_{OBP} utilizing MBP from OBP (MBP_{OBP}) and e1-$PWV_{24\text{-}hBP}$ with MBP of twenty hours BP average ($MBP_{24\text{-}hBP}$)[28].

Statistical analysis

The cut-off age is a reference point for elderly individuals in many countries, for it is when they become eligible for old-age social benefits. We followed the Brazilian legal criteria and considered the World Health Organization's guideline to divide the total sample into two groups based on age: individuals under 60 years old (< 60 years), and those aged 60 or older (≥ 60 years)[29]. The database was built using Microsoft Excel, and statistical analysis was performed using the MedCalc software. The values of the categorical variables are presented as both number and proportions. The values of the continuous variables are presented as the mean and the SD. The variables were checked for normality.

We employed chi-squared statistics to compare proportions, while t-tests were used to compare means. The unadjusted Pearson correlation coefficient (r) between age and all parameters of PWV, systolic, and diastolic BPV was calculated for the total sample, as well as for the groups under 60 years and 60 years or older. Additionally, we calculated the partial correlation coefficient adjusted for gender, race, OBP, 24-h BP, treated hypertension, uncontrolled hypertension, elevated BP (non-treated), clinical CVD and CKD, diabetes, dyslipidemia, body obesity, and BMI (kg/m2). The z-test on Fisher z-transformed correlation coefficients compared the values of unadjusted and adjusted coefficients in the two groups. To quantify to what extent age influences the variance of systolic and diastolic BPV as well as estimated PWV variables, a multiple linear regression model utilizing age alone calculated the coefficient of determination (R^2) for all of them. In this model, no adjustments were made for any others clinical or demographic variables such as gender, race, treated hypertension, uncontrolled hypertension, elevated BP (non-treated), systolic BP, diastolic BP, diabetes, dyslipidemia, smoking, obesity, or BMI. The Forkman test compared the R^2 of the groups.

The Human Research Ethics Committee of the university provided ethical approval for data collection under protocol number 61985316.9.0000.5154. The research followed all recommendations of the Declaration of Helsinki for medical research involving human participants.

Results

We analyzed data from 649 subjects; 508 were under 60 years of age, and 141 were 60 or older. Table 1 shows the entire sample and the main clinical and demographic characteristics of the groups. The individuals in the ≥ 60 years group have a significantly higher prevalence of white individuals, females, treated hypertension, uncontrolled hypertension, clinical CVD and CKD, diabetes, and dyslipidemia, $p < 0.001$ for all of them. On the other hand, elevated non-treated BP, $p < 0.001$, and body obesity, $p = 0.005$, are comparatively more prevalent in individuals under 60. In addition, they display a higher BMI; $p = 0.006$. There were no differences between the abdominal waist average, $p = 0.92$, and smoking, $p = 0.21$.

Table 2 displays all values of office BP, 24-h BP, BP variability and PWV values both in the entire sample and in the groups. The participants in the ≥ 60 years group had a higher systolic OBP of 140 ± 17.9 vs. 133 ± 15.6, 24-h systolic BP SD 14.4 ± 3.4 vs. 12.5 ± 3.1, weighted systolic 24-h BP SD 11.7 ± 3.3 vs. 10.8 ± 2.8, systolic 24-h BP ARV 9.9 ± 2.7 vs. 8.6 ± 2.2, systolic CV 24-h 10.2 ± 2.3 vs 11.5 ± 2.4, br-PWV 10.00 ± 1.3 vs. 6.86 ± 1.1, e1-PWV_{OBP} 11.39 ± 1.5 vs. 8.27 ± 1.2, e1-$PWV_{24\text{-}hBP}$ 10.57 ± 1.5 vs. 7.63 ± 1.1, with $p < 0.01$ for all of them. Although diastolic OBP 88 ± 10.5 vs. 82 ± 11.9; $p < 0.01$, diastolic 24-h BP 79 ± 10.1 vs. 74 ± 10.6; $p < 0.01$ and $MBP_{24\text{-}hBP}$ 97 ± 10.2 vs. 95 ± 10.8; $p = 0.04$ were significantly higher in < 60-year group. There were no differences in diastolic BPV variables in both groups: 24-h diastolic BP SD 11.4 ± 3.8 vs. 11.0 ± 2.7; weighted diastolic 24-h BP SD 9.4 ± 2.2 vs. 9.5 ± 2.1; $p = 0.62$, diastolic 24-h BP ARV 7.7 ± 1.7 vs. 7.9 ± 1.9; $p = 0.22$, diastolic CV 24-h 14.5 ± 5.3 vs 15.0 ± 3.6; $p = 0.19$.

	Total	< 60 years	≥ 60 years	
Number of participants	649	508	141	
Variable				**P value**
Clinical characteristic				
Age (yr)	47.7 ± 14.2	42.1 ± 10.3	67.7 ± 6.3	< 0.001
White	440 (68.2)	323 (63.6)	117 (83.0)	< 0.001
Female sex	320 (49.4)	233 (45.9)	87 (61.7)	< 0.001
Treated Hypertension	221 (34.1)	130 (25.6)	91 (64.5)	< 0.001
Uncontrolled Hypertension	113 (17.4)	66 (13.0)	47 (33.3)	< 0.001
Elevated BP (non-treated)	214 (33.0)	187 (36.8)	27 (19.1)	< 0.001
Clinical CVD and CKD	47 (7.3)	19 (3.7)	28 (19.9)	< 0.001
Diabetes	69 (10.6)	35 (6.9)	34 (24.1)	< 0.001
Dyslipidemia	188 (29.0)	124 (24.4)	64 (45.4)	< 0.001
Body obesity	245 (37.8)	206 (40.6)	39 (27.7)	0.005
Smoking	48 (7.4)	41 (8.1)	7 (5.0)	0.21
BMI (kg/m^2)	28.8 ± 5.8	29.1 ± 6.1	27.6 ± 4.3	0.006
Abdominal waist (cm)	95.5 ± 11.5	95.5 ± 11.7	95.6 ± 10.7	0.92

Table 1. The main clinical and demographic characteristics for the entire sample, individuals under 60 years, and those in the 60 years group. The P values refer to chi-squared statistics and t-tests for < 60 and ≥ 60 years comparisons. Data demonstrated as mean ± standard deviation (SD) or absolute number (n) and proportion (%). CVD, cardiovascular disease; CKD, severe chronic kidney disease; BMI, body mass index.

Figure 1 displays the unadjusted Pearson correlation coefficient for age with systolic BPV variables in the whole sample. A poor correlation for 24-h BP SD (A), r = 0.286, 24-h BP ARV (C), r = 0.264, and CV 24-h (D), r = 0.270; p < 0.0001 for all. Even though weighted 24-h BP SD (B), r = 0.305 showed a moderate correlation; p < 0.0001.

r—Pearson's correlation coefficient; BP, blood pressure; SD – standard deviation; 24-hBP, 24-h ambulatory blood pressure average; ARV, average real variability; CV 24-h, coefficient of variability of 24-h BP average; CI—95% confidence interval.

Additionally, Fig. 2 shows the correlation between age and diastolic BPV variables. In the entire sample, none of the variables appeared to have a correlation with age: 24-h BP SD (A), r = −0.069; p 0.07, weighted 24-h BP SD (B), r = 0.063; p = 0.10, 24-h BP ARV (C), r = 0.035; p = 0.37, and CV 24-h (D), r = 0.002; p = 0.95.

r—Pearson's correlation coefficient; BP, blood pressure; SD – standard deviation; 24-hBP, 24-h ambulatory blood pressure average; ARV, average real variability; CV 24-h, coefficient of variability of 24-h BP average; CI—95% confidence interval.

Figure 3, in turn, shows the r values for the association between age and PWV measurements for all the individuals. The correlation was very strong for all of them. The r value for br-PWV was (A), r = 0.924, e1-PWV$_{OBP}$ (B), e1-PWV$_{24\text{-}hBP}$ (C), r = 0.871; p < 0.0001 for all of them. The r values of e1-PWV$_{24\text{-}hBP}$ were significantly lower than br-PWV.

r—Pearson's correlation coefficient; OBP, office blood pressure; 24-hBP, 24-h ambulatory blood pressure average; br-PWV, oscillometric brachial cuff-based pulse wave velocity; e1-PWV, estimated pulse wave velocity from Eq. 1; CI—95% confidence interval.

Table 3 presents the unadjusted Pearson coefficient of pulse wave velocity and BP variability (24-h BP SD, weighted 24-h BP SD, and 24-h ARV, CV 24-h) with age, in the two groups that were studied. For the systolic BP variability parameters in the < 60 years group, the correlation with age was poor, 0.124, 0.130, 0.122, and 0.107 respectively; p > 0.05. However, in the ≥ 60 years group, all systolic BP variables presented a fair correlation of 0.419, 0.492, 0.332, 0.388 respectively, p < 0.01. The correlation with age was significantly more robust in the group of ≥ 60 years individuals than the other group; p < 0.05. Conversely, for diastolic BP variability, the 24-h BP weighted SD 0.250 and CV 24-h 0.228 showed a poor correlation with age among the subjects who were ≥ 60 years old; p < 0.05. The remaining variables did not demonstrate any correlation, 24-h BP SD 0.131and 24-h ARV 0.091, p > 0.05 for all of them. The same can be observed in the group of individuals < 60 years old: −0.042, −0.010, 0.017, −0.075 respectively, p > 0.05 for all of them. The r values were significantly higher for weighted 24-h BP SD in the ≥ 60-year individuals, p < 0.011, and for CV 24-h, p = 0.001. The r values for PWV parameters showed a moderate correlation between e1-PWV$_{OBP}$ 0.759 and e1-PWV$_{24\text{-}hBP}$ 0.745 in the group < 60 years, and a strong correlation for br-PWV 0.850. In the group aged ≥ 60 years, e1-PWV$_{OBP}$ maintained a moderate correlation 0.787, while br-PWV 0.901, e1-PWV$_{24\text{-}hBP}$ 0.824 exhibited a very strong correlation. The r values for br-PWV and e1-PWV$_{24\text{-}hBP}$ in the group of ≥ 60-year-olds were higher than the r values found in the other group.

Table 4 presents the adjusted r values. For systolic BP variability (24-h BP SD, weighted 24-h BP SD, 24-h ARV and CV 24-h) no correlations were observed in the < 60 years group, with r values of 0.058, 0.049, 0.064 and 0.0615, and respectively; p > 0.05 for all. Within the group of subjects older than ≥ 60 years, correlations persisted, 0.353, 0.430; p < 0.001 for both, 0.281; p 0.05, and 0.394; p < 0.001, respectively. Comparing both groups, all variables showed significantly higher values in the ≥ 60 years group; p < 0.021 for all. No correlations were found for diastolic BP in the < 60 years group, with values of −0.080, −0.055, −0.0056 and −0.077, p > 0.005

	Total	< 60 years	≥ 60 years	
Participants	649	508	141	
Variable				**P Student or x^2**
BP values				
Systolic OBP	135 ± 16.4	133 ± 15.6	140 ± 17.9	< 0.01
Diastolic OBP	87 ± 10.9	88 ± 10.5	82 ± 11.9	< 0.01
MBP_{OBP}	101 ± 11.9	106 ± 12.3	106 ± 12.3	1.0
Systolic 24-h BP	123 ± 12.3	122 ± 11.8	125 ± 13.7	0.08
Diastolic 24-h BP	78 ± 10.4	79 ± 10.1	74 ± 10.6	< 0.01
$MBP_{24\text{-}hBP}$	96 ± 10.4	97 ± 10.2	95 ± 10.8	0.04
BP variability (mmHg)				
SD of 24-h SBP	12.9 ± 3.3	12.5 ± 3.1	14.4 ± 3.4	< 0.01
SD of 24-h DBP	11.3 ± 3.6	11.4 ± 3.8	11.0 ± 2.7	0.24
Weighted SD of 24-h SBP	11.2 ± 3.0	10.8 ± 2.8	11.7 ± 3.3	< 0.01
Weighted SD of 24-h DBP	9.4 ± 2.2	9.4 ± 2.2	9.5 ± 2.1	0,62
ARV of 24-h SBP	8.9 ± 2.4	8.6 ± 2.2	9.9 ± 2.7	< 0.01
ARV of 24-h DBP	7.7 ± 1.7	7.7 ± 1.7	7.9 ± 1.9	0.22
CV of 24-h SBP	10.5 ± 2.3	10.2 ± 2.3	11.5 ± 2.4	< 0.01
CV of 24-h DBP	14.5 ± 3.3	14.5 ± 5.3	15.0 ± 3.6	0.19
Pulse Wave Velocity (m/s)				
br-PWV	7.54 ± 1.7	6.86 ± 1.1	10.00 ± 1.3	< 0.01
$e1\text{-}PWV_{OBP}$	8.95 ± 1.8	8.27 ± 1.2	11.39 ± 1.5	< 0.01
$e1\text{-}PWV_{24\text{-}hBP}$	8.27 ± 1.7	7.63 ± 1.1	10.57 ± 1.5	< 0.01

Table 2. The values of BP, BP variability and pulse wave velocity parameters, for the entire sample, individuals under 60 years, and those in the 60 years group. The P values refer to t-tests for < 60 and ≥ 60 years comparisons. OBP, office blood pressure; MBPOBP, mean blood pressure of office blood pressure; 24-hBP, 24-h ambulatory blood pressure average; MBP24hBP, mean 24-h ambulatory blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; ARV, average real variability; CV 24-h, coefficient of variability of 24-h BP average; br-PWV, oscillometric brachial cuff-based pulse wave velocity; e1-PWV, estimated pulse wave velocity from Eq. 1.

for all, respectively. However, a correlation was found in the ≥ 60 years group, 24-h BP SD; 0.174, weighted 24-h BP SD; 0.211, CV 24-h 0.283; $p < 0.05$ for all, while 24-h ARV; 0.102; $p > 0.05$, still presents no correlation. Except for diastolic 24-h ARV; $p = 0.09$, all partial correlation coefficients were higher in the ≥ 60 years group. Partial r values for all PWV measurements (br-PWV, $e1\text{-}PWV_{OBP}$ and $e1\text{-}PWV_{24\text{-}hBP}$) maintained a correlation with age in both groups. The r values for participants under 60 years were 0.859, 0.924, and 0.913; $p < 0.001$, respectively. In the other group, the r values were 0.898, 0.926, and 0.963; $p < 0.001$, respectively. Only $e1\text{-}PWV_{24\text{-}hBP}$ showed a higher correlation in the ≥ 60 years compared to the < 60 years group; $p = 0.0009$.

Table 5 presents the R2 values, demonstrating how age influences the variation among individuals in terms of BP variability (24-h BP SD, weighted 24-h BP SD, 24-h ARV, and CV 24-h), and PWV (br-PWV, $e1\text{-}PWV_{OBP}$ and $e1\text{-}PWV_{24\text{-}hBP}$). For systolic BPV, in the < 60 years group age accounts for 1.5%, 1.7%, 1.4%, and 1.1% of the variation, respectively; $p < 0.05$ for all. For diastolic BP, variability was not significant: 0.1%, 0.01% , 0.03%, and 0.5%| respectively; $p > 0.05$. for all. Conversely, age explains a substantial portion of all the PWV variables: 72.3%, 57.6%, and 55.5%, respectively; $p < 0.001$ for all of them. In the ≥ 60 years group, age explains a substantial variance of 17.5%, 24.3%; $p < 0.001$ for both, 11.0%; $p < 0.05$, and 15%; $p < 0.001$ respectively. For diastolic BPV, significant R^2 results were observed for weighted 24-h SD 4.8%, and CV 24-h 5.2%; $p < 0.05$ for both, despite insignificant results for 24-h BP SD 1.7% and 24 h-BP ARV 0.8%, $p > 0.11$ for all of them. Similarly, for these individuals, age explains a significant portion of all the PWV variables: 81.2%, 62.0%, and 67.9%, respectively; $p < 0.001$ for all. The comparisons of R^2 for BPV resulted in expressive differences between the groups; $p < 0.0001$ for all. However, except for $e1\text{-}PWV_{24\text{-}Hbp}$, $p = 0.02$, there was no observable difference for PWV variables with $p > 0.24$. Age also exhibits a stronger association with PWV than with BPV; $p < 0.0001$ for all comparisons.

Discussion

Basic, epidemiological, and clinical research provide the foundation of knowledge regarding the close association among elevated BP prevalence, aging, arterial stiffness, and BP variability, all recognized biological markers of cardiovascular events[4,12,17]. At least two studies have established a fair association between arterial stiffness metrics and short-time BPV[18,19]. Each of those publications had different aims compared to the present study. We evaluated how closely age, PWV metrics (oscillometric and estimated) and short-time BPV metrics could be associated, and quantified to what extent age has an influence on each variable.

The main finding of this study is that, despite age significantly explaining a higher proportion of all PWV values (br-PWV, $e1\text{-}PWV_{OBP}$, and $e1\text{-}PWV_{24\text{-}hBP}$) than BPV, there is no difference in the determination coefficient

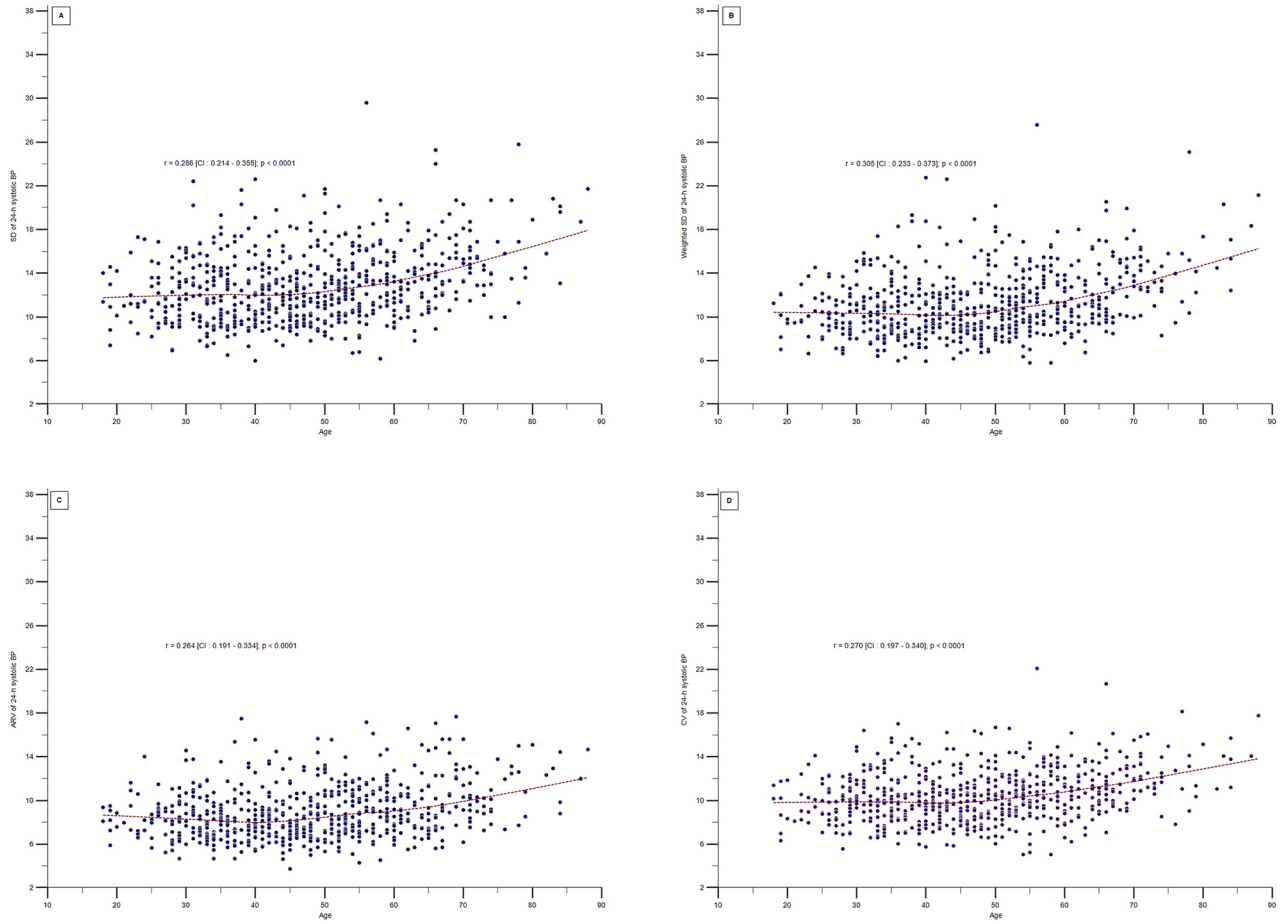

Fig. 1. Scatter diagram of undjusted correlation between age with systolic short-term BPV measures.

to all PWV metrics between the two groups. Nevertheless, age explains the variance of systolic BPV better in ≥ 60 years than in < 60 years group. Even if age explains only a maximum of 5.2% of diastolic BPV among 60-year-olds, this result is markedly higher than 0.1% for individuals < 60 years. Additionally, other results are worth mentioning. We observed a robust correlation between all metrics of PWV and age; in general, there are no differences between the groups. Unlike in the adjusted model, systolic and diastolic BPV do not show a correlation with age in younger subjects. In the older group, systolic BPV demonstrated a fair association with age, whereas diastolic BPV showed a poor one.

The high coefficients observed with all PWV metrics report to the methods used to measure and calculate PWV. Evidence from at least one study has already demonstrated that all of them strongly rely on age. Like our study data suggest, age explains around 75% of estimated PWV[28,30]. The result is high, and there is no significant difference in the correlation and determination coefficients of PWV metrics between the groups. This is attributed to data from the Reference Values for Arterial Stiffness Collaboration, which shows that PWV increases gradually with age in a large European population[10,31]. Therefore, the correlation is expected to be high in any age group analyzed.

It is also worth mentioning the correlation and determination coefficient results of BPV by age. Systolic BPV showed a poor correlation and great differences in proportion between the groups; in the group of older individuals, it reached a considerable age determination of around 25%. It is also important to highlight that in the adjusted analysis, all systolic BPV variables lost their correlation with age in the younger group, which did not occur in the older group. Diastolic BPV displayed an irrelevant 5.2% of determination by age in younger group. Interpreting this kind of data can be challenging due to the need for studies associating age and BPV in large populations. BPV has been described as an event associated with some circumstances related to age. Considering it in young people, BPV may occur in response to routine activities. In older individuals, nonetheless, high rates of BPV have commonly been correlated with some specific conditions, such as an impaired baroreflex function and increased arterial stiffness[17]. Data from the Dublin Outcome Study supports this evidence[32]. Comparing data of systolic BPV between the age range under 50 years and 50 to 65 years showed expressive differences across all BPV metrics, with the results remaining in the ranges above the aforementioned. However, diastolic BPV variables do not exhibit differences between the groups, except for diastolic SD of daytime BP. Similarly, we found an association between age and diastolic BPV in the ≥ 60 years group only for weighted SD 24-h.

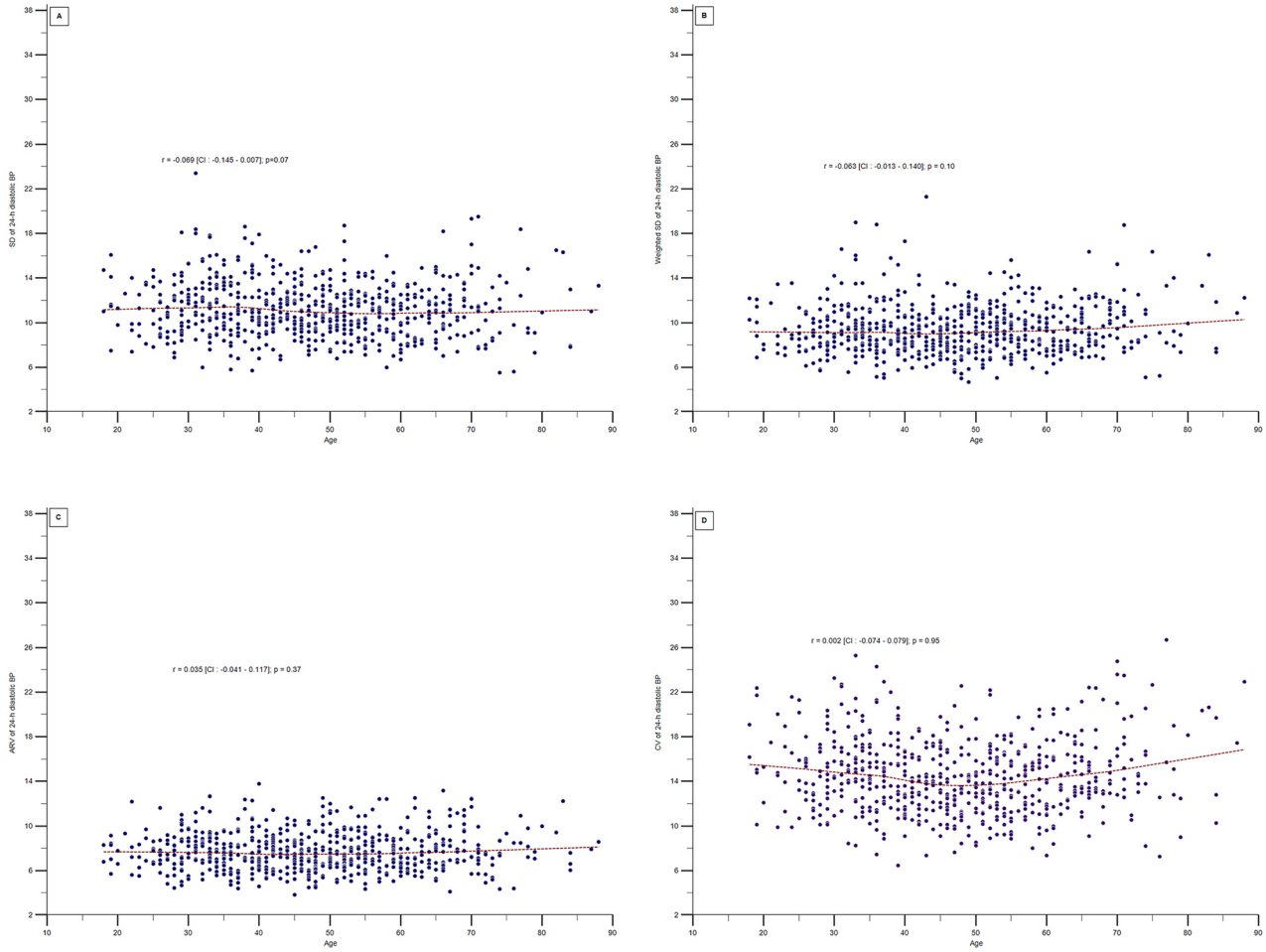

Fig. 2. Scatter diagram of unadjusted correlation between age with diastolic short-term BPV measures.

It has long been known that there is a relation between aging and arterial stiffness. Along the last decade, many studies have confirmed that PWV increases with age[10,31]. In spite of this finding, there are few published studies available for comparison with our results regarding the correlation and determination of estimated PWV with age[28,30]. Schwartz et al., in a sample from the Masked Hypertension Study using Mobil-O-Graph and SphygmoCor devices, demonstrated that age accounted for 75% of the total variation of oscillometric PWV (Mobil-O-Graph). We found 72.3%, and 81.2% for br-PWV in individuals < 60 years and ≥ 60 years, respectively. In addition, they demonstrated that using a model with age and systolic BP accounted for 40.2% of the variance in cf-PWV (SphygmoCor), leaving 60% unexplained by these variables, values significantly higher than the PWV provided by Mobil-O-Graph[30]. Furthermore, Salvi et al. demonstrated in Marfan syndrome subjects that cf-PWV was only weakly affected by age (21%). On the contrary, br-PWV measured by Mobil-O-Graph was strongly determined by age (86%), as well as e1-PWV (57%) and e2-PWV (68%). Thus, it acts alone accounts for less than 20% of the variation when utilizing a gold standard method such as cf-PWV[33]. Our results for oscillometric and estimated PWV were very similar to theirs. Taking these data into account. At least in the oldest group, the differences in age coefficients of determination between PWV and BPV are overestimated by the PWV metrics we used in the study.

It is essential to emphasize that there is no evidence based on data for age-alone correlation and determination with short-term BPV, making it challenging to compare our results with other studies. Nevertheless, this challenge also strengthens our research, owing to its novelty. We would also highlight the quality of BP, ABPM, and PWV measurements as strengths of this study.

One limitation of our work is its cross-sectional design and the fact that it involved a secondary data analysis. The study population primarily consisted of individuals referred to a specialized center for AMBP. As a consequence, the generalizability of our findings to a general population may be limited. The main weakness was that there was no data on a gold standard method of cf-PWV in this sample. Thus, using a gold standard procedure, the age determination of AS and short-term BPV comparisons could become more precise and realistic.

It opens future perspectives for clinical research using metrics of cf-PWV and short-term BPV in both young and older adults to determine to which extent age explains each measure. Additionally, our findings reinforce

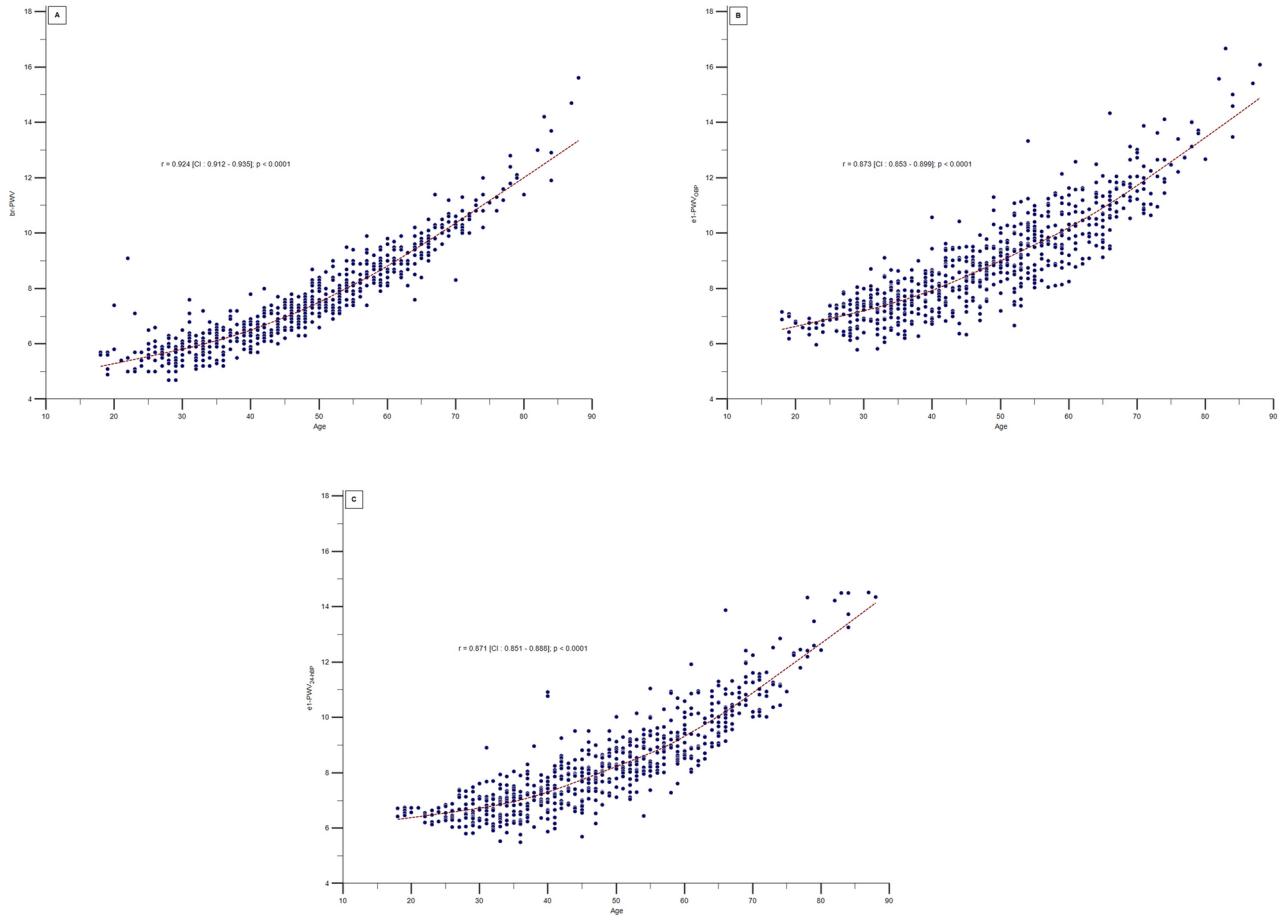

Fig. 3. Scatter diagram of unadjusted correlation between age with pulse wave velocity measurements.

some past evidence indicating that whatever measure estimated PWV is highly dependent on age, which has implications for both research and the clinical field.

Conclusion

In summary, our data demonstrate that all the PWV metrics here employed are strongly and significantly more determined by age than short-term BPV, while systolic BPV was only weakly and diastolic BPV was negligibly explained by age. Based on this study's data and results, the metrics used for PWV appear to be highly age-dependent, while systolic BPV is mainly associated with older age. Future research should better compare the absolute dependence of PWV and BPV using the cf-PWV metric, the gold standard for measuring arterial stiffness.

	Unadjusted Pearson correlation coefficient (r) [CI]		
	< 60 years	≥ 60 years	
Participants	508	141	P value
Systolic BP variability			
SD of 24-h SBP	0.124* [0.038 – 0.209]	0.419** [0.272 – 0.546]	0.0008
Weighted SD of 24-h SBP	0.130* [0.044 – 0.215]	0.492** [0.356 – 0.608]	< 0.0001
ARV of 24-h SBP	0.122* [0.035 – 0.206]	0.332** [0.177 – 0.472]	0.02
CV 24-h	0.107* [0.002 – 0.192]	0.388** [0.237 – 0.519]	0.001
Diastolic BP variability			
SD of 24-h DBP	−0.042 [−0.215 – 0.044]	0.131 [−0.034 – 0.290]	0.06
Weighted SD of 24-h DBP	−0.010 [−0.096 – 0.076]	0.220* [0.057 – 0.372]	0.010
ARV of 24-h DBP	−0.017 [−0.104 – 0.069]	0.091 [−0.074 – 0.253]	0.24
CV 24-h	−0.075 [−0.161 – 0.012]	0.228* [0.065 – 0.379]	0.001
Pulse Wave Velocity			
br-PWV	0.850** [0.824 – 0.873]	0.901** [0.865 – 0.928]	0.017
e1-PWV_{OBP}	0.759** [0.719 – 0.793]	0.787** [0.715 – 0.843]	0.45
e1-$PWV_{24\text{-}hBP}$	0.745** [0.704 – 0.781]	0.824** [0.763 – 0.871]	0.026

Table 3. Unadjusted correlation between age, measures of BP variability, and pulse wave velocity in the under 60 years and 60 + years groups. * $P < 0.05$; ** $P < 0.001$. The P values refer to z-test for < 60 and ≥ 60 years comparisons.CI—95% confidence interval; BP, blood pressure; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; OBP, office blood pressure; 24-hBP, 24-h ambulatory blood pressure average; ARV, average real variability; CV 24-h, coefficient of variability of 24-h BP average; br-PWV, oscillometric brachial cuff-based pulse wave velocity; e1-PWV, estimated pulse wave velocity from Eq. 1.

	Partial Pearson correlation coefficient (r) [CI]		
	< 60 years	≥ 60 years	
Participants	508	141	P value
Systolic BP variability			
SD of 24-h SBP	0.058 [−0.029 – 0.144]	0.353** [0.199 – 0.490]	0.001
Weighted SD of 24-h SBP	0.049 [−0.117 – 0.213]	0.430** [0.266 – 0.541]	< 0.0001
ARV of 24-h SBP	0.064 [−0.102 – 0.227]	0.281 * [0.121 – 0.427]	0.01
CV 24-h	0.061 [−0.105 – 0.224]	0.394** [0.245 – 0.525]	0.0002
Diastolic BP variability			
SD of 24-h DBP	−0.080 [−0.242 – 0.086]	0.174* [0.008 – 0.330]	0.007
Weighted SD of 24-h DBP	−0.055 [−0.218 – 0.111]	0.211* [0.047– 0.364]	0.005
ARV of 24-h DBP	−0.056 [−0.219 – 0.110]	0.102 [−0.064 – 0.263]	0.09
CV 24-h	−0.077 [−0.239 – 0.089]	0.283* [0.123– 0.428]	0.0001
Pulse Wave Velocity			
br-PWV	0.859** [0.808 – 0.897]	0.898** [0.860 – 0.926]	0.07
e1-PWV_{OBP}	0.924** [0.895 – 0.945]	0.926** [0.898 – 0.946]	0.88
e1-$PWV_{24\text{-}hBP}$	0.913** [0.881—0.937]	0.953** [0.935 – 0.966]	0.0009

Table 4. Adjusted correlation between age, measures of BP variability and pulse wave velocity in the under 60 years and 60 + years groups. * $P < 0.05$; ** $P < 0.001$. The P values refer to z-test for < 60 and ≥ 60 years comparisons. CI—95% confidence interval; BP, blood pressure; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; OBP, office blood pressure; 24-hBP, 24-h ambulatory blood pressure average; ARV, average real variability; CV 24-h, coefficient of variability of 24-h BP average; br-PWV, oscillometric brachial cuff-based pulse wave velocity; e1-PWV, estimated pulse wave velocity from Eq. 1.

	Coefficient of determination R^2		
	< 60 years	≥ 60 years	
Participants	508	141	P value
Systolic BP variability			
SD of 24-h SBP	0.015*	0.175**	< 0.0001
Weighted SD of 24-h SBP	0.017*	0.243**	< 0.0001
ARV of 24-h SBP	0.014*	0.110*	< 0.0001
CV-24 h	0.011*	0.150**	< 0.0001
Diastolic BP variability			
SD of 24-h DBP	0.001	0.017	< 0.0001
Weighted SD of 24-h DBP	0.0001	0.048*	< 0.0001
ARV of 24-h DBP	0.0003	0.008	< 0.0001
CV-24 h	0.005	0.052*	< 0.0001
Pulse Wave Velocity			
br-PWV	0.723**	0.812**	0.25
e1-PWV_{OBP}	0.576**	0.620**	0.39
e1-$PWV_{24\text{-}hBP}$	0.555**	0.679**	0.02

Table 5. Parameters of multiple linear regression model predicting measures of BP variability and pulse wave velocity from age among 649 participants. * $P < 0.05$; ** $P < 0.001$. The P values refer to Forkman test for < 60 and ≥ 60 year comparisons. BP, blood pressure; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; OBP, office blood pressure; 24-hBP, 24-h ambulatory blood pressure average; ARV, average real variability; CV 24-h, coefficient of variability of 24-h BP average; br-PWV, oscillometric brachial cuff-based pulse wave velocity; e1-PWV, estimated pulse wave velocity from Eq. 1.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request .

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Author contributions

MAVS: conceptualization, methodology development, formal analysis, resources provision, data curation management activities, writing—original draft preparation, writing—review & editing prep, visualization preparation, project administration management, final approval of the version to be submitted; ABBF, FI, RCLS, LMV, JRU, MJH, JCYT and LNCM: investigation conducting, data curation management activities, final approval of the version to be submitted, writing—original draft Preparation; JFVM : conceptualization, methodology development, writing—review & editing prep, supervision oversight and leadership responsibility, final approval of the version to be submitted. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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