Hypertension

ORIGINAL ARTICLE

Relation of Pulse Wave Velocity to Contemporaneous and Historical Blood Pressure in Female Twins

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BACKGROUND: An association between blood pressure and aortic stiffness is well known, but ambiguity remains as to whether one precedes the other. This study aimed to investigate the association of aortic stiffness with contemporaneous versus historic blood pressure and direction of causality between aortic stiffening and hypertension in female twins.

METHODS: Aortic stiffness, measured by carotid-femoral pulse wave velocity (PWV), and mean arterial pressure (MAP) was recorded in 2037 female TwinsUK participants (mean age: 62.4±9.7 years) at a single time point. A subset of 947 participants had repeat PWV and MAP measures (mean interval 5.5±1.7 years) with additional historic MAP (mean interval 6.6±3.3 years before baseline).

RESULTS: Cross-sectional multivariable linear regression analysis confirmed PWV significantly associated with age and MAP. In longitudinal analysis, annual progression of PWV was not associated with historic MAP (standardized beta coefficient [β]=-0.02, P=0.698), weakly associated with baseline MAP (β=0.09, P=0.049) but strongly associated with progression (from baseline to most recent measurement) of MAP (β= 0.26, P<0.001). Progression of MAP associated with both baseline and progression of PWV (β=0.13, P=0.003 and β=0.24, P<0.001, respectively).

CONCLUSIONS: Progression of aortic stiffness associates more strongly with contemporaneous MAP compared with historic MAP. In contrast, progression of MAP is associated with prior arterial stiffness. These findings suggest a bidirectional relationship between arterial stiffness and blood pressure, and that lowering blood pressure may prevent a cycle of arterial stiffening and hypertension. **(*Hypertension*. 2023;80:361–369. DOI: 10.1161/HYPERTENSIONAHA.122.19311.)**
• **Supplemental Material**

Key Words: blood pressure ■ carotid-femoral pulse wave velocity ■ hypertension ■ longitudinal studies ■ vascular stiffness

Carotid-femoral pulse wave velocity (PWV), a measure of aortic and large artery stiffness, is an independent predictor of cardiovascular morbidity and mortality.[1] Many potential risk factors have been identified for increased PWV,[2–4] but only age and blood pressure (BP) have consistently and independently been found to be associated with PWV.[5] Although the association with BP is well documented, ambiguity remains about the association of aortic stiffness to historic or contemporaneous BP. Several studies suggest baseline or historical BP to be a significant predictor of progression in aortic stiffness,[2–4,6] but such studies were limited by lack of adjustment for baseline aortic stiffness, which would inherently bias the effect estimate of baseline BP. Furthermore, there may be a bidirectional association between aortic stiffness and BP with BP being a predictor of aortic stiffening through its effect on wall distension and aortic stiffening driving high BP and development of hypertension through reduced pressure buffering capacity.[7,8]

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

Examination of the longitudinal relationship between arterial stiffness and blood pressure (BP), by investigating the association between pulse wave velocity (PWV) and BP in both directions and by assessing the influence of baseline as well as older historical BP on progression of PWV.

Use of several iterations of regression model showing how factors associated with progression of PWV vary when other baseline and/ or follow-up factors are included, allowing comparison to other studies with more limited models.

What Is Relevant?

Historical BP is of little relevance for progression of PWV compared with the influence of progression of BP.

Progression of BP is, by contrast, dependent on prior arterial stiffness.

A bidirectional relationship may exist between PWV and BP and this may change with age.

Clinical/Pathophysiological Implications?

Treating hypertension at any stage would have a beneficial effect on reducing arterial stiffness, but early intervention may still be advantageous.

Early intervention in slowing arterial stiffening would also have a significant effect on BP.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
MAP	mean arterial pressure
PP	pulse pressure
PWV	pulse wave velocity

The present study aims to investigate the associations between arterial stiffness with historic and contemporaneous BP in the TwinsUK cohort. We investigate the effect of BP on progression of aortic stiffness compared with the effect of aortic stiffness on the progression of BP.

METHODS

Data Availability

The data used in the present study are held by the Department of Twin Research at King's College London. The data can be released to bonafide researchers using our normal procedures overseen by the Wellcome Trust and its guidelines as part of our core funding (https://twinsuk.ac.uk/resources-for-researchers/access-our-data).

Study Participants and Visits

The present study included participants from the UK Adult Twin Registry (TwinsUK),[9] a prospective observational investigation of adult twins across the whole of the United Kingdom. As part of the TwinsUK research programme, cardiovascular assessments were periodically offered to all subjects in TwinsUK with no exclusion criteria. Data collected included participant demographics, medical history, menopause status, BP and PWV. As shown in Figure 1, a total of 2670 participants attended St Thomas Hospital between 2006 and 2016 for one or more cardiovascular assessments. After exclusion of male subjects (n=294) and visits with missing PWV or BP data (n=339), the study group comprised 2037 subjects who had complete data for one or more visits for cross-sectional data analysis. In cases where measurements were made on > 1 occasion (947 out of 2037 subjects), data from the last visit was used in cross-sectional analysis. A longitudinal cohort (n =947) comprised subjects from the study group who attended on at least 2 occasions for measures of PWV. First visits were designated as "baseline" assessments, and final visits were designated as "follow-up visits." Intermediate measurements of PWV (in 152 subjects) between these timepoints were not used. Due to the longitudinal nature of the TwinsUK Registry,[9,10] many participants had attended for measurements of office BP before their baseline PWV visit. These participants formed a subset of the longitudinal cohort in which "historical BP" but not PWV was available 1 to 15 years before the baseline PWV (n=892). Of these, 248 had only 1 measurement of historical BP within this timeframe. Where subjects had 2 measurements of historical BP (n=644), a BP recorded 2 to 5 years prior to baseline PWV was selected. No participants had > 2 historical BPs prior to the baseline PWV.

Male subjects were excluded from this analysis due to the disproportion of males and females in the group (294 males versus 2406 females in original 2670 attendees). This was due to TwinsUK initially including only female participants; male subjects were recruited in later years. The group was predominantly comprised of twin pairs, but subjects were also included if their twin was unwilling or unavailable to participate in the research study (singletons). Paired twins accounted for 92% of the cross-sectional cohort and 88% of the longitudinal cohort. Ethical approval for the study was granted by the St Thomas Hospital Research Ethics Committee, and written informed consent was obtained from all participants.

Anthropometric and Biochemical Measurements

Height and weight, smoking status, use of antihypertensive and lipid-lowering medication, menopause status, and medical

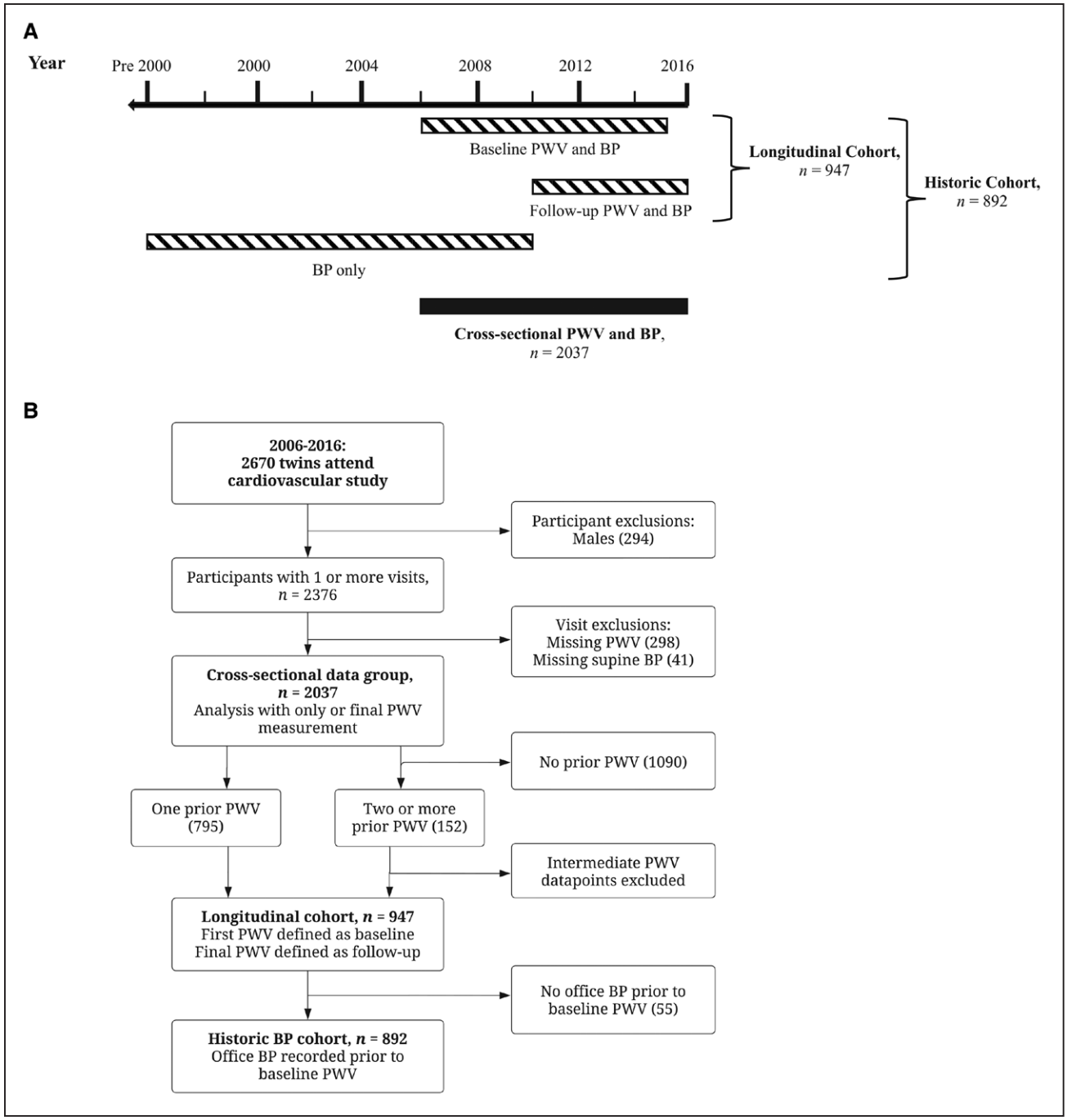

Figure 1. Schema for study design.
A, Timelines for recruitment. **B**, Flow diagram of subject inclusion and exclusion for the longitudinal cohorts and cross-sectional group. BP indicates blood pressure; and PWV, pulse wave velocity.

history were recorded at baseline and follow-up. Menopause was self-defined as premenopausal, perimenopausal, or postmenopausal. Fasting blood samples were measured in a subsample of 1519 (75%) of the cross-sectional study participants and 755 (80%) of the longitudinal participants. Total cholesterol, HDL (high-density lipoprotein) cholesterol, triglycerides, and plasma glucose were measured by colorimetric assay. LDL (low-density lipoprotein) cholesterol was estimated with the Friedewald equation. All assays were performed in an accredited laboratory at St Thomas Hospital.

PWV and BP

PWV was measured by sequential ECG-referenced carotid and femoral artery tonometry recordings, using the SphygmoCor system (AtCor Medical, Australia) with the participant supine in a quiet temperature controlled room as previously described.[11] Path length was estimated from surface distance measurement from the sternal notch to the femoral artery at the point of applanation. This protocol was used from the start of the TwinsUK cardiovascular visits in 2006, before the current guidelines for standardization of the technique

were published.[12] To ensure comparability of longitudinal data, the method was kept consistent throughout the duration of the TwinsUK cardiovascular study.

Systolic BP, diastolic BP, and heart rate were obtained at the time of PWV measurement by an oscillometric device (Omron 705IT, Japan). Measurements of PWV and supine BP were obtained in triplicate and mean PWV and BP were used for statistical analysis. Brachial pulse pressure (PP) was calculated as the difference between systolic BP and diastolic BP and mean arterial pressure (MAP) as diastolic BP+⅓PP. Historical blood pressures were obtained in triplicate after a period of rest by an oscillometric device with the participant seated. The average of the last 2 measurements as recorded in the subject notes was used in statistical analysis. The Omron Marshal MB02 x7 and Omron MX3PlusX3 were used from 2004 to 2012, and the Omron HEM-907 was used from 2013 to 2016 (Omron, Kyoto, Japan).

Statistical Analysis

Data analysis was performed using SPSS v24.0 (SPSS, Chicago, IL). Baseline and follow-up measurements were compared using Student's *t* test for continuous data and McNemar's test for categorical data. Results are presented as mean±SD unless otherwise specified. Univariable linear regression analysis was performed using an enter method to examine the association of PWV to BP and cardiovascular risk factors. Plasma concentrations of triglycerides were logarithmically transformed before analysis. Significantly associated variables ($P<0.10$) were then entered into multivariable analysis. For longitudinal analysis, annual progression (AP) was calculated for continuous variables (according to the difference divided by the time between visits). Baseline and annual progression of continuous variables, and baseline and follow-up categorical variables were entered into multivariable analysis. Variables measured at baseline are denoted by the subscript "B" while annual progression of variables is denoted by subscript "AP." Outcome and independent variables were standardized into *z*-scores before entering into linear regression models. Standardized regression coefficients are presented, with 95% CIs. Collinearity between independent variables was checked by examining variance inflation factors (VIFs) for each multivariable regression model. As the maximum VIF was 2.0, well below a commonly accepted threshold of 10,[13] all variables were retained in regression models.

We examined the effect of family relatedness in our models by performing sensitivity analyses in which only unrelated subjects were included in the sample (singletons and one twin from each pair). Beta coefficients were not significantly altered, but CIs for the beta coefficient were wider. One author (L.K.) had full access to all the data in the study and takes responsibility for its integrity and data analysis.

RESULTS

Participant Characteristics

Characteristics of the total cohort and the cohort followed longitudinally are shown in Table 1. In the total cohort, mean age of participants was 62.9±9.7 years. Mean PWV, MAP, and PP were 9.8±2.2 m/s, 92.9±10.7 mmHg and 54.5±13.5 mmHg respectively. Of these participants, 26% were taking antihypertensive medication, 19% were taking lipid-lowering therapy, 3% were taking medication for diabetes and 7% were current smokers. Subjects predominantly described themselves as post-menopausal (73%), rather than pre-menopausal (10%) or perimenopausal (14%).

Cross-sectional Association of Arterial Stiffness with Blood Pressure and Cardiovascular Risk Factors

Table 2 shows univariate and multivariable regression investigating the associations between PWV, BP and cardiovascular risk factors. When considered independently (in univariate analysis), all risk factors except LDL and HDL demonstrated some association with PWV. PWV associated with age, MAP, heart rate, height, weight, presence of diabetes, current smoking, triglyceride and glucose levels, with the strongest associations seen with age and MAP.

In multivariable regression analysis, PWV remained positively associated with age, MAP, heart rate, height, and diabetes in the absence of biochemistry data (Table 2). Including biochemical data, PWV additionally associated to current smoking, triglyceride level, and blood glucose level, but presence of diabetes no longer remained significantly associated. MAP remained highly associated with PWV when blood biochemistry was included in the model. Adjustment for menopausal status (reducing the sample size, $n=1974$) did not significantly change the associations with other variables.

Longitudinal Progression of Arterial Stiffness and the Association With Blood Pressure and Cardiovascular Risk Factors

Longitudinal data were available for 947 participants (Figure 1). Participant characteristics at the cardiovascular baseline and at follow-up visits are shown in Table 1. The median time between visits was 5.6 years (interquartile range, 2.3 years). Participant age at baseline was 57.8±8.8 years. The proportion of post-menopausal subjects increased from 44% at baseline to 80% at follow-up ($P<0.001$). Over the follow-up period, systolic BP increased by 4.8±14.5 mmHg, diastolic BP increased by 2.3±8.3 mmHg, PP increased by 2.5±10.5 mmHg, and MAP increased by 3.2±9.5 mmHg. Use of antihypertensive medication increased from 17% to 26% ($P<0.001$). Overall rate of PWV change was 0.14±0.34 m/s per year. PWV progression varied according to age, even when adjusted for MAP and heart rate at the time of each measurement (Figure 2). Aging was associated with higher trajectories of PWV progression with acceleration of stiffening occurring from the sixth or seventh decade of life. In the youngest quintile of treatment-naive subjects

Table 1. Subject Characteristics in the Cross-Sectional Group and in the Longitudinal Cohort

Variable	Cross-sectional group	Longitudinal cohort			
			PWV Visits		
		Historic BP	Baseline	Follow-up	*P* Value*
n	2037	892	947	947	
Age, y	62.9±9.7	52.0±8.7	57.9±8.8	63.4±8.7	<0.001
Height, cm	161.2±6.2	…	161.9±6.2	160.8±6.3	<0.001
Weight, kg	68.5±13.0	…	67.8±11.7	67.9±12.4	0.615
BMI, kg/m^2	26.4±4.8	…	25.9±4.3	26.3±4.6	0.936
Menopause					
Pre-menopause, n (%)	210 (10)	…	186 (21)	59 (6)	<0.001
Perimenopause, n (%)	272 (14)	…	292 (31)	105 (11)	<0.001
Post-menopause, n (%)	1480 (73)	…	413 (44)	759 (80)	<0.001
Total cholesterol, mmol/L	5.61±1.0	…	5.62±1.0	5.70±1.1	0.090
LDL-cholesterol, mmol/L	3.1±1.0	…	3.3±0.9	3.2±1.0	0.063
HDL-cholesterol, mmol/L	2.0±0.5	…	1.9±0.5	2.0±0.5	<0.001
Triglycerides, mmol/L	1.1±0.6	…	1.0±0.5	1.1±0.6	0.237
Glucose, mmol/L	4.9±0.8	…	5.1±0.6	4.9±0.6	<0.001
Diabetes, n (%)	57 (3)	…	7 (1)	20 (2)	<0.001
Antihypertensive therapy, n (%)	533 (26)	…	163 (17)	244 (26)	<0.001
Lipid-lowering therapy, n (%)	382 (19)	…	100 (11)	179 (19)	<0.001
Current smoker, n (%)	143 (7)	…	70 (7)	46 (5)	<0.001
Heart rate, bpm	63.5±10.2	…	62.5±9.7	63.7±10.0	<0.001
PWV, m/s	9.8±2.2	…	9.0±1.8	9.8±2.1	<0.001
Systolic BP, mmHg	129.1±17.6	121.1±15.1†	124.3±16.7	129.1±17.1	<0.001
Diastolic BP, mmHg	74.8±8.8	76.7±9.9 †	72.6±8.5	74.9±8.7	<0.001
MAP, mmHg	92.9±10.7	91.5±11.1†	89.8±10.4	93.0±10.5	<0.001
PP, mmHg	54.5±13.5	44.5±10.1†	51.7±12.2	54.2±13.0	<0.001

Data for the cross-sectional analysis and the subset at follow-up reflect the same timepoint. Baseline data for the longitudinal subset was recorded 5.5±1.7 years prior to this (median, 5.6 years, IQR: 2.3years). Values are mean±SD or *n* (%). BMI indicates body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; and PWV, pulse wave velocity.

*P Value refers to comparison of time-points in longitudinal cohort.

†BPs obtained in seated position not supine. Seated BPs are not included in *t* test comparison.

(mean age 43.8±4.3 years at baseline), PWV increased by 0.07 m/s/year, whereas in the oldest quintile of treatment-naive subjects (mean age 68.0±3.5 years at baseline), PWV increased by 0.19m/s per year (Figure 2).

Figure 3 shows the association between annual progression of PWV (PWV_{AP}) with baseline and follow-up measures. When considering only baseline factors but not baseline PWV (PWV_B), PWV_{AP} significantly associated with age_B and MAP_B (Figure 3A). When PWV_B was included in the model, the association of PWV_{AP} with MAP_B was no longer significant (Figure 3B).

When considering baseline and follow-up measures together, without PWV_B, PWV_{AP} associated with age_B, MAP_{AP}, HR_{AP}, and $height_{AP}$ (Figure 3C). When PWV_B was included in the model, these associations remained unchanged, with additional moderate associations with MAP_B and $height_B$. (Figure 3D). Model details and corresponding beta coefficients are listed in Table S1.

Longitudinal Progression of Arterial Stiffness and Its Association With Historic Blood Pressure

Long-term historical BP was recorded on average 6.6±3.3 years before the baseline measurements, and 12.0±3.5 years before the follow-up PWV. When historical MAP was included in multivariable regression, PWV_{AP} was significantly associated with MAP_{AP} (β=0.26 [CI, 0.19–0.33]; $P \leq 0.001$) and MAP_B (β=0.09, [CI, 0.00–0.17]; $P=0.049$). There was no significant association between PWV_{AP} and historical MAP (β=−0.02 [CI, −0.09 to 0.06]; $P=0.698$; Table 3). Findings were similar when PP was used in the model in place of MAP (data not shown). A full list of variables entered into this model and their associations with PWV_{AP} are shown in Table S2. This multivariable regression model was repeated with adjustment for menopausal data (reducing the sample size, $n=824$). Menopausal status was not associated with

Table 2. Cross-Sectional Univariable and Multivariable Linear Regressions Examining the Association of Pulse Wave Velocity to Blood Pressure and Cardiovascular Risk Factors

	Univariable			Multivariable					
	n=2037			n=1510			n=2021		
Variable	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
Age, y	0.55	0.52–0.59	<0.001	0.43	0.39–0.47	<0.001	0.45	0.41–0.49	<0.001
Heart rate, bpm	0.33	0.29–0.37	<0.001	0.24	0.20–0.27	<0.001	0.21	0.18–0.24	<0.001
MAP, mmHg	0.46	0.42–0.50	<0.001	0.32	0.28–0.35	<0.001	0.32	0.28–0.35	<0.001
Height, cm	−0.09	−0.13–−0.04	<0.001	0.08	0.04–0.12	<0.001	0.07	0.04–0.11	<0.001
Weight, kg	0.07	0.03–0.12	0.001	0.01	−0.03–0.05	0.718	0.02	−0.01–0.06	0.172
Diabetes	0.10	0.05–0.14	<0.001	0.01	−0.03–0.05	0.668	0.05	0.02–0.08	0.004
Current smoker	−0.09	−0.13–0.04	<0.001	−0.05	−0.08–−0.10	0.012	−0.02	−0.05–0.01	0.237
LDL, mmol/L	−0.03	−0.08–0.02	0.187	–	–	–	–	–	–
HDL, mmol/L	0.00	−0.05–0.06	0.861	–	–	–	–	–	–
TG, mmol/L*	0.17	0.12–0.22	<0.001	0.06	0.02–0.10	0.004	–	–	–
Glucose, mmol/L	0.18	0.13–0.22	<0.001	0.04	−0.01–0.08	0.09	–	–	–

Both univariate and multivariable analyses were performed using the enter method. Multivariable analyses were adjusted for antihypertensive and lipid-lowering therapy. Multivariable analysis has been performed excluding blood biochemistry variables (n=2021) and including blood biochemistry variables (n=1510). β is the standardised regression coefficient. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; and TG, triglyceride.

*TG data have been log-transformed.

PWV_{AP}; and inclusion of this data did not significantly change any associations with other variables.

Association of Longitudinal Progression of Blood Pressure With Arterial Stiffness and Cardiovascular Risk Factors

MAP_{AP} negatively associated with MAP_B (β=−0.42 [CI, −0.49 to −0.35]; P<0.001) and age_B (β=−0.09 [CI, −0.16 to −0.01]; P=0.034), and positively with PWV_B (β=0.13 [CI, 0.05 to 0.22]; P=0.003) and PWV_{AP} (β=0.24 [CI, 0.18 to 0.30]; P<0.001; Table 3). A full list of variables entered into these models and their associations with MAP_{AP} is shown in Table S3.

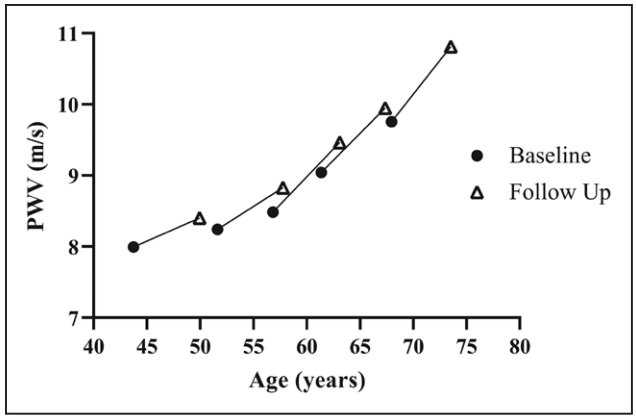

Figure 2. Trajectories of pulse wave velocity (PWV) progression for quintiles of age at baseline.
Baseline PWV estimates adjusted for mean arterial pressure and heart rate at baseline; follow-up estimates are adjusted for mean arterial pressure and heart rate at follow-up and time between measurements. Markers represent mean age of the quintile at each timepoint.

DISCUSSION

While the association between arterial stiffness and BP is well established, uncertainty exists on the impact of acute and past exposure to BP on arterial stiffness, association to pulsatile and steady BP components and direction of causality between arterial stiffness and BP. These questions remain largely unexplored due to limitations of cross-sectional study design and limited availability of longitudinal data. The present study examined the association between progression of arterial stiffness to contemporaneous and historic BP and the relation of arterial stiffness to BP progression over a 10-year period. The main finding is that, in longitudinal follow-up, progression of arterial stiffness most closely associated with progression of MAP and hence with contemporaneous BP rather than historical BP. By contrast, progression in MAP strongly associated with both baseline PWV and the progression of PWV.

Previous studies, including Caerphilly, Whitehall II, Bogalusa Heart Study and Malmo Diet & Cancer Study, investigating the influence of prior BP on arterial stiffness progression have reported prior BP to be a predictor of accelerated arterial stiffening.[2–4,6] However, these studies were limited by lack of a measure of baseline arterial stiffness and thus the association between baseline BP and future arterial stiffness could be explained by baseline BP acting as a surrogate for baseline arterial stiffness. The present study confirmed the importance of adjusting for baseline PWV: an association between progression in arterial stiffness and BP was seen when no adjustment was made for baseline PWV. However, following adjustment for baseline PWV, this association no longer persisted.

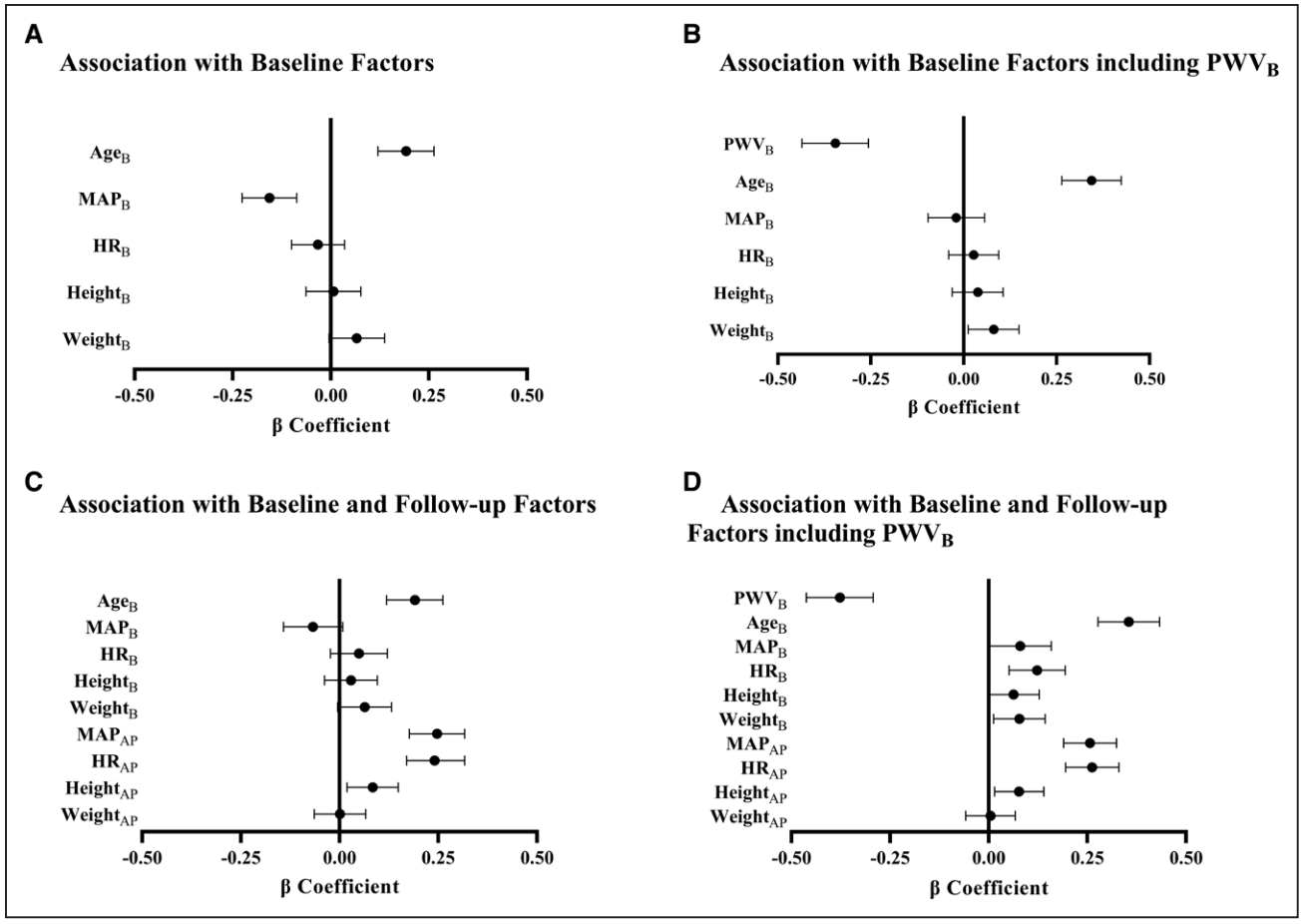

Figure 3. Forest plots of linear regression models examining how the associations of annual progression in pulse wave velocity (PWV$_{AP}$) to baseline and/or progression of blood pressure (BP) changes with inclusion of baseline PWV (PWV$_B$), and baseline and progression of cardiovascular risk factors.

A, Association of PWV$_{AP}$ to baseline BP and cardiovascular risk factors. **B**, Association of PWV$_{AP}$to baseline BP and cardiovascular risk factors and PWV$_B$. **C**, Association of PWV$_{AP}$ to baseline and progression of BP and cardiovascular risk factors. **D**, Association of PWV$_{AP}$ to baseline and progression of BP and cardiovascular risk factors and PWV$_B$. Plots show standardized beta coefficients and 95% CIs for association of follow-up pulse wave velocity with baseline (B) and annual progression (AP) of potential explanatory variables. Multivariable analyses were performed using the enter method. Models shown in **A** and **B** were additionally adjusted for use of antihypertensive therapy at baseline, use of lipid-lowering therapy at baseline, diabetes at baseline, current smoking at baseline, and time between baseline and follow-up PWV. Models in **C** and **D** were additionally adjusted for use of antihypertensive therapy at baseline and follow-up, use of lipid-lowering therapy at baseline and follow-up, diabetes at baseline and follow-up and current smoking at baseline and follow-up. Age$_B$ indicates age at baseline; HR$_{AP}$, annual progression in heart rate; HR$_B$, baseline heart rate; height$_{AP}$, annual progression in height; height$_B$, baseline height; MAP$_{AP}$, annual progression in mean arterial pressure; MAP$_B$, baseline mean arterial pressure; weight$_{AP}$, annual progression in weight; and weight$_B$, baseline weight

This is consistent with findings from other smaller studies that have included baseline PWV.[7,14] Our findings persisted when BP measured an average of 12years prior to follow-up were included and when pulsatile, instead of steady, BP components were considered in the model.

The interrelationship between BP and arterial stiffness is complex, and a common interpretation of their association is that steady BP components increase functional stiffening through arterial wall distension, which may lead to structural stiffening over time through distension. Alternatively, or in addition, pulsatile BP components may lead to elastin fragmentation and stiffening. Furthermore, arterial wall stiffening is a hemodynamic determinant of pulsatile BP components, often used as a surrogate measure of arterial stiffness. Thus, the direction of causality between arterial stiffness and BP is likely to be bidirectional and may change over time. Understanding these complex relationships is vital for identifying potential treatments with optimal times for intervention. Our findings of a more prominent association of stiffness with contemporaneous BP, compared with historic/baseline BP, suggest that in this predominantly normotensive cohort, PWV was largely dependent on distending pressure, rather than on underlying structural change as a result of longstanding hypertension.[15] This dependence on contemporaneous MAP indicates that blood pressure lowering at any stage is likely to have a clear beneficial effect on reducing arterial stiffness. Nonetheless, there was a significant, yet much weaker, association between arterial stiffness and baseline MAP so early intervention could still be advantageous.

When looking at determinants of BP progression, our finding of a strong association of BP progression to

Table 3. Associations Between Annual Progressions of PWV and MAP and Factors Measured at Baseline and Follow-Up

	PWV_{AP}			MAP_{AP}		
Variable	β	95% CI	*P* Value	β	95% CI	*P* Value
PWV_B, m/s	−0.38	−0.46–0.29	<0.001	0.13	0.05–0.22	0.003
Age_B, y	0.36	0.28–0.43	<0.001	−0.09	−0.16– −0.01	0.034
MAP_B, mm Hg	0.09	0.00–0.17	0.049	−0.42	−0.49– −0.35	<0.001
HR_B, bpm	0.12	0.05–0.19	0.001	0.02	−0.05–0.09	0.524
PWV_{AP}, m/s	–	–	–	0.24	0.18–0.30	<0.001
MAP_{AP}, mm Hg	0.26	0.19–0.33	<0.001	–	–	–
HR_{AP}, bpm	0.26	0.20–0.33	<0.001	−0.07	−0.13–0.00	0.057
Historic MAP, mm Hg*	−0.02	−0.09–0.06	0.698	–	–	–

Analyses were adjusted for baseline height, baseline weight, diabetes at baseline, lipid-lowering therapy at baseline, baseline smoking status, use of antihypertensive therapy at baseline, annual progression in height, annual progression in weight, diabetes at follow-up, use of lipid-lowering therapy at follow-up, smoking status at follow-up and use of antihypertensive therapy at follow-up. Multivariable analysis was performed using the enter method. β=standardized regression coefficient. Age_B indicates age at baseline; HR_{AP}, annual progression in heart rate; HR_B, baseline heart rate; MAP_{AP}, annual progression in MAP; MAP_B, baseline mean arterial pressure; PWV_{AP}, annual progression in pulse wave velocity; and PWV_B, baseline pulse wave velocity.

*Historic MAP only entered into regression model for PWV_{AP}.

baseline and future values of PWV suggests that early intervention in slowing arterial stiffening would have a significant effect on BP progression. These findings are consistent with animal models of arterial stiffening where a stiffening phenotype precedes development of hypertension.[16] Similarly, children with Williams syndrome, a congenital disorder caused by deletion of the elastin gene, demonstrate increased arterial stiffness and elevated BP compared with age-matched controls.[17] A commonly accepted explanation is that loss of elastin transfers pressure to stiffer collagen fibres increasing arterial stiffening which increases PP and causes isolated systolic hypertension.[18] Several longitudinal cohort studies confirm arterial stiffening to predict development of hypertension.[7,19–23] These findings indicate that a bi-directional relationship is likely to exist between arterial stiffness and BP and is consistent with our recent findings of a bidirectional association using Mendelian randomisation techniques.[8,24] Importantly, as arterial stiffening increases with age, particularly after mid-life,[25,26] this may indicate an optimal time for earlier treatment intervention for blood pressure regulation. Our findings confirm a nonlinear association between PWV and age in women, with a steepening of the PWV trajectory occurring around the 60th year of age.

Limitations

This study is limited to female participants and the findings may not be generalizable to men. However, this cohort has been shown to be representative of the general female population in the United Kingdom.[27] In a female cohort of this age, menopause may be a confounding factor for PWV progression. We did not demonstrate any significant associations between progression of arterial stiffness and menopause status but acknowledge this may be because menopause status was self defined. Historic BP was measured with a slightly different protocol to the BP on the PWV visit with the subject seated in an office environment whereas subsequent BP measurements were recorded supine. However, we found a high correlation between seated and supine pressures taken on the same day (R=0.70; P<0.001 in 1673 subjects), suggesting that historical seated pressures are a reasonable surrogate for previous supine BP in our regression models.

Perspectives

We present evidence that progression in aortic stiffness more strongly associates with contemporaneous BP compared with historic BP. Findings persisted when pulsatile, instead of steady, BP components were considered in our models. In contrast, progression of BP associated with both baseline and progression of arterial stiffness. The prominent association between PWV and contemporaneous BP compared with historic/baseline BP suggests that blood pressure lowering at any stage is likely to have a beneficial effect on reducing arterial stiffness, but early intervention may still be advantageous. Similarly, the strong association of both baseline and progression values of PWV to BP progression suggest that an early intervention in slowing arterial stiffening would also have a significant effect on BP. These findings indicate a bidirectional relationship between arterial stiffness and BP which may change with age.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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