Published in final edited form as:

J Hypertens. 2021 May 01; 39(5): 987–993. doi:10.1097/HJH.0000000000002731.

Longitudinal associations of blood pressure with aortic stiffness and pulsatility: the Atherosclerosis Risk in Communities Study

Patricia A. Metcalf[a], **Michelle L. Meyer**[b], **Hirofumi Tanaka**[c], **Sunil K. Agarwal**[d,e], **B. Gwen Windham**[f], **Susan Cheng**[g], **David Couper**[h], **Aaron R. Folsom**[i], **Gerardo Heiss**[j]

[a]University of Auckland, Auckland Mail Centre, Auckland, New Zealand [b]Department of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina [c]Department of Kinesiology and Health Education, University of Texas at Austin, Austin, Texas [d]Department of Epidemiology, Biostatistics, and Medicine, Johns Hopkins University, Baltimore, Maryland [e]Mount Sinai Hospital, New York, New York [f]Division of Geriatrics, Department of Medicine, University of Mississippi Medical Center, Mississippi [g]Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California [h]Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina [i]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota [j]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Abstract

Objective: To characterize the longitudinal relationships between blood pressure measured over 24 years and arterial stiffness in late life measured as pulse wave velocity (PWV).

Methods: Carotid–femoral (cf) and femoral–ankle (fa) PWV were measured in 4166 adults at the visit 5 Atherosclerosis Risk in Communities study cohort examination (2011–2013). Participants were categorized into tertiles of PWV measurements. Blood pressure measurements were made at baseline (1987–1989), three subsequent triennial examinations, and visit 5.

Results: Partial correlation coefficients between visit 5 cfPWV and SBP ranged from 0.13 for visit 1 SBP to 0.32 for visit 5 SBP. For visit 5 faPWV, correlations were ~0 for visits 1 to 4 SBP, but was 0.20 for visit 5 SBP. Over 24 years of follow-up, those with higher average SBP were more likely to fall in the middle and upper tertiles of visit 5 cfPWV. Average pulse pressure and mean arterial pressure over 24 years had similar but weaker associations with cfPWV tertiles. DBP had no clear association with cfPWV. Blood pressure measurements were positively associated with faPWV tertiles only cross-sectionally at visit 5.

Conclusion: Adult life-course measures of SBP, more so than mean arterial and pulse pressure, were associated with later life central arterial stiffness. By contrast, only contemporaneous measures of blood pressure were associated with peripheral arterial stiffness. Although arterial

Correspondence to Michelle L. Meyer, PhD, MPH, Department of Emergency Medicine, University of North Carolina Chapel Hill, 170 Manning Drive, Chapel Hill, NC 27599-7594, USA. Tel: +1 919 966 6539; fax: +1 919 966 3049; michelle_meyer@med.unc.edu.

Conflicts of interest

There are no conflicts of interest.

stiffness was only measured at later life, these results are consistent with the notion that elevated blood pressure over time is involved in the pathogenesis of arterial stiffening.

Keywords

arterial stiffness; blood pressure; longitudinal study; pulse pressure

INTRODUCTION

Pulse wave velocity (PWV) is a reliable measure of arterial stiffness that is associated with major adverse cardiovascular events and all-cause mortality in both clinical and population-based studies [1–4]. Carotid–femoral PWV (cfPWV) reflects central arterial stiffness and is considered to be the reference standard measure of arterial stiffness in research studies [5,6]. Femoral–ankle PWV (faPWV) measures peripheral arterial stiffness instead. Central elastic arteries are reported to stiffen progressively with age primarily as a result of tissue remodelling, whereas stiffness of the muscular peripheral arteries changes little with age [7,8].

Cross-sectional [9,10] and longitudinal [11–15] studies have consistently reported that blood pressure exerts a strong influence on central arterial stiffness, whereas others reported conversely that central artery stiffness is a determinant of the longitudinal increase in blood pressure [16–19]. It is also possible that the relation between elevated blood pressure and arterial stiffening is bidirectional [20,21]. Controversy exists about the relative contributions of systolic, diastolic and mean arterial pressures to central artery stiffening [11,12,20,22]. Few studies have addressed the temporal relation between elevated blood pressure and central artery stiffness based on repeated tonometric measures [23,24] but suggest that greater arterial stiffness predates elevated blood pressure.

Although a long-term association between cardiovascular risk factors measured in adolescence and carotid artery distensibility in adulthood has been described [22], the temporal relationship between blood pressure recorded over the course of adult life and aortic stiffness and pulsatility late in life has not been established. Additionally, there has yet to be a study addressing this question for segment-specific arterial stiffness. The aim of this study was to characterize the longitudinal relationships between sitting blood pressure measured over 24 years since mid-life and arterial stiffness and pulsatility measurements in later life among older adults in the Atherosclerosis Risk in Communities (ARIC) Study cohort. Understanding this relationship would inform on potential modifiable long-term effects of blood pressure on vascular stiffening and associated endorgan damage.

METHODS

Study population

The ARIC study is a population-based prospective study of the natural history and etiology of atherosclerotic disease and of cardiovascular disease events. ARIC is a predominantly biracial cohort that was selected as a probability sample of 15 792 men and women aged 45–64 years from four US communities (Forsyth County, North Carolina; Jackson, Mississippi;

Minneapolis, Minnesota; and Washington County, Maryland). The study objectives, design, sampling scheme, and cohort examination procedures have been described [25]. Participants provided written informed consent, and the study protocol was approved by the Institutional Review Boards of all field centers, the coordinating center, central laboratories, and reading centers.

Eligible participants were interviewed at home and then invited to a baseline clinical examination (visit 1) between 1987 and 1989. Participants returned for three triennial follow-up clinical examinations in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4) and 15 years later for visit 5 (2011–2013). Before each examination, participants were asked to fast for 12 h and refrain from using tobacco and participating in vigorous physical activity after midnight prior to the clinic visit, or for 8 h prior to the visit. Participants also brought to the examination all medications they had taken in the preceding 2 weeks.

A total of 5683 participants of the 5986 ARIC participants who completed at least part of the visit 5 visit had PWV measurements. Of these, to preserve PWV data quality, participants were excluded from these analyses if at visit 5 they had a BMI of 40 kg/m^2 or greater; major cardiac arrhythmias on a 12-lead electrocardiogram (Minnesota codes of 8.1.3, 8.3.1, or 8.3.2); self-reported aortic revascularization surgery, peripheral revascularization, aortic aneurysm, aortic stenosis, or aortic regurgitation; or had cfPWV greater than 2319 cm/s (>3 SD from the mean); or faPWV greater than 1665 cm/s (>3 SD from the mean); were of Asian or Native American race, or African American in Minnesota or Washington county (because of small numbers); had missing SBP or DBP measurements; or had prevalent coronary heart disease at visit 1. After exclusions, the final analytic sample constituted 4166 participants. Prevalent coronary heart disease was defined as myocardial infarction (MI) from adjudicated visit 1 electrocardiogram data, self-reported history of MI, heart or arterial surgery, coronary bypass, balloon angioplasty or angioplasty of coronary arteries. Study numbers vary because of missing information on some measurements.

Measurements

At each visit, sitting blood pressure was measured three times after a 5-minute seated rest, following a standardized protocol (https://www2.cscc.unc.edu/aric/cohort-manuals). Random-zero Hawksley manometers were used in visits 1–4, and digital automatic blood pressure monitors (Omron HEM-907 XL; Omron Co. Ltd., Kyoto, Japan) at visit 5 and these two methodologies yielded similar results [26]. The average of the last two of three readings was used at each examination visit, except at visit 4 when two readings were obtained and averaged. Pulse pressure was calculated as the difference between SBP and DBP at each visit and mean arterial pressure as DBP with 1/3 times pulse pressure.

Body weight was measured to the nearest (whole) pound at visits 1–4 and to the nearest 0.1 pound at the later visit and converted to kilograms, and height was recorded to the nearest centimeter. Waist circumference was measured in centimeters twice using standardized anatomical reference points. Diabetes was defined as fasting glucose at least 126 mg/dl, nonfasting glucose at least 200 mg/dl, antidiabetic medication use, or self-reported physician diagnosis of diabetes. Blood samples at visit 5 were obtained following a standardized

venipuncture protocol and shipped weekly to ARIC central laboratories where assays for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose were performed. Low-density lipoprotein (LDL) was calculated using the Friedewald equation. Glycated hemoglobin (HbA_{1c}) was measured in EDTA whole blood on the Tosoh Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, California, USA) using an automated high-performance liquid chromatography method calibrated with standard values derived by the National Glycohemoglobin Standardization Program.

PWV was measured by tonometry using the VP-1000 Plus system (Omron Co. Ltd). PWV measurements included cfPWV, brachial–ankle (baPWV), and faPWV. A minimum of two measurements were taken per participant and the last two nonzero values were averaged. To calculate pulse transit time, arterial waveforms were passed through a low-frequency and band-pass filter. The lowest down-sloping point was then taken as 'foot' of the systolic upstroke in the arterial waveform. Pulse transit time was then calculated as the time delay between the proximal and distal 'foot' waveforms. Path length (cm) for cfPWV was calculated as the distance between the carotid to femoral distance minus the suprasternal notch to carotid distance. Path lengths for baPWV and faPWV were calculated by the VP-1000 Plus using height-based formulas, as previously described [27]. Tertiles for cfPWV were 1009 and 1243 cm/s, tertiles for faPWV were 1017 and 1159 cm/s, and tertiles for baPWV were 1585 and 1846 cm/s. Lower and upper bounds for PWV measurements, after exclusions, were (in cm/s): 301 and 2299.5 for cfPWV; 611 and 2784.5 for faPWV; and 442 and 3721 for baPWV. Repeat visits were conducted for a subset of participants at each field center approximately 4–8 weeks later ($n = 79$; mean age 75.7 years; 46 women). The intra-class correlation coefficients and 95% confidence intervals (95% CIs) were 0.70 (0.59–0.81) for cfPWV, 0.84 (0.78–0.90) for baPWV, and 0.69 (0.59–0.79) for faPWV [28]. Results for the baPWV are shown in the Supplementary file, http://links.lww.com/HJH/B515, as baPWV is a composite measure of central and peripheral stiffness that is widely used in Asian countries.

Statistical methods

We used linear mixed models to investigate the time course of blood and pulse pressure measurements from visits 1 to 5 on PWV at visit 5. This method adjusts for the correlation between repeated observations on the same participant and allows for varying numbers and unequally spaced observations. In all mixed model analyses, an unstructured correlation structure was assumed. All models were adjusted for sex, race, center, heart rate, current smoking, blood pressure-lowering medication use at visit 5 and the inverse of Mill's ratio [4,29,30]. Age and heart rate were treated as time-varying covariates. Statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and results were plotted using the R statistical package.

In order to correct for possible attrition bias at visit 5, a two-stage Heckman model was used [31]. At the first stage, the probability of being selected at visit 5 was calculated based on covariates from visit 1, the inverse of the Mill's ratio was calculated from these probabilities and in stage 2, this was used as an adjustment variable for correlations and for mean levels calculated for the trajectory plots. Candidate covariate variables were initially chosen based

on covariation documented in the literature or if they were statistically associated with attrition. If the Mill's ratio was missing, it was replaced with the mean level of 0.50882. Candidate covariate variables were initially chosen if they were putatively or statistically associated with missing values.

RESULTS

At visit 5, the mean age of participants was 75 years, mean BMI was 28 kg/m^2, mean SBP and DBP were 130 and 66 mmHg, respectively, and mean cfPWV and faPWV were 1158 and 1077 cm/s, respectively (Table 1).

Cross-sectional and cross-temporal associations between SBP and pulse wave pressure

The Spearman partial correlation coefficients of SBP measurements with pulse wave velocity were higher for cfPWV than for faPWV (Table 2). Cross-sectional partial correlation coefficients between SBP and cfPWV were higher at visit 5 compared with blood pressure readings prior to visit 5 (cross-temporal). The correlations did not change appreciably after adjusting for age, sex, race, heart rate, and the inverse of the Mill's ratio. For faPWV, the partial correlation coefficients with SBP were positive and a greater magnitude when measured concurrently with faPWV (cross-sectional at visit 5), but were positive and a smaller magnitude when SBP was measured earlier in life (cross-temporal; visits 1–4) and lower than those observed between cfPWV and SBP. Partial correlation coefficients between baPWV (an indirect index of central arterial stiffness) and SBP were lower and are shown in the Supplementary file (Supplemental Table 1, http://links.lww.com/HJH/B515).

Cross-temporal association between blood pressure measurements and pulse wave velocity

The mean for blood pressure measurements (systolic, diastolic, mean arterial, and pulse pressure) were higher at each subsequent visit in all cfPWV tertiles, adjusted for age, sex, race, and heart rate (Table 3), apart from SBP in tertile 2 at visit 1. Results did not change after additional adjustment for blood pressure-lowering medication use and the inverse of the Mill's ratio to correct for possible attrition bias between visit 1 and visit 5 (data not shown).

SBP and pulse pressure levels were significantly higher over 24 years in the upper tertile of cfPWV compared with the lower tertile at all visits ($P < 0.0001$; Fig. 1; panels a and g). There was no consistent pattern of mean DBP and mean arterial pressure over 24 years with cfPWV tertiles (Fig. 1; panels c and e).

In contrast, blood pressure measurements were associated with faPWV tertiles only cross-sectionally at visit 5, but the middle tertiles for systolic, diastolic, and mean arterial blood pressure measures at visit 5 were slightly lower than at visit 4 (9 years), (Fig. 1; panels b, d, and f). Pulse pressure was not associated with faPWV tertiles at visit 5 (Fig. 1, panel h), although there was a generally increasing relationship over time.

The temporal patterns of blood pressure levels across baPWVtertiles are shown in the Supplementary file, Figure 1, http://links.lww.com/HJH/B515.

DISCUSSION

Aging is associated with progressive loss of arterial compliance followed by overt stiffening. Left ventricular afterload is increased when there is central artery stiffening [6], and is associated with impaired coronary perfusion [32,33] and left ventricular hypertrophy [34,35]. Our analysis showed that greater cfPWV was associated with higher systolic and mean arterial blood pressure and with pulse pressure over the course of 24 years. This suggests that blood pressure-related remodeling of the central elastic arteries may be cumulative over a long period of time resulting in vascular stiffening. These results are also consistent with the notion that gradual elevations in blood pressure over time contribute to arterial stiffening later in life.

Our cross-temporal results on SBP and cfPWV apply to physiologically relevant differences in mean levels of central arterial stiffness. In contrast, only blood pressure measured at visit 5, and not antecedent blood pressures, were associated with faPWV. faPWV measurements reflect the muscular nature of the lower extremity arteries, whereas aortic and carotid stiffness measures speak to predominantly elastic arteries [36]. Studies have shown conflicting associations between cardiovascular risk factors and faPWV [37–39]. For example, age is an established risk factor for arterial stiffening and is not associated with peripheral stiffness [40,41], but is strongly associated with cfPWV [9]. In this study, we did not observe an association between PP and faPWV. DBP decreases in the fifth to sixth decade of life, which would correspond to an increase in PP with age [42]. However, tertile 3 of faPWV showed an increase in DBP over time. As PP is DBP SBP, the concurrent increase in DBP and SBP in T3 with concurrent decrease in DBP and SBP in T2 could have attenuated associations between PP and tertiles of faPWV.

Longitudinal data suitable to assess the temporality of the blood pressure–arterial stiffness association are scarce. An alternative approach is to make use of existing prospective studies without the benefit of repeated observations of arterial PWV, and to examine the associations between measures of pressure and stiffness using both historical and cross sectional data. In this analysis, initial values in aortic stiffness were not taken into account (as the data were not collected), but it does have the advantage of making use of long-term follow-up and repeated measures of blood pressure that may provide insights into the pathophysiology of stiffening.

Two relatively short-term longitudinal studies of cfPWV conducted prospectively did not find SBP to be an independent predictor of the longitudinal changes in PWV [2,23]. Other studies have reported that arterial stiffening precedes and contributes to accelerated longitudinal increases in SBP, although different measures of stiffness were used in some studies [16–19]. In contrast, other studies report that blood pressure exerts a strong influence on arterial stiffening [11–15].

Our findings do not confirm those of a previous review that pulse pressure increases significantly after the fifth decade of life, suggesting stiffening of the large arteries occurs predominantly in later life [43]. Although we observed a lack of an association between cfPWV and DBP, which has been previously reported [11], these results suggest that SBP

could be the dominant hemodynamic factor associated with cfPWV at later life. The life course pattern of blood pressure measurements across baPWV tertiles showed similar relationships to cfPWV (Fig. 1 and Supplementary file, Figure 1, http://links.lww.com/HJH/B515) as has been reported previously [27].

The interpretation of our results should consider several limitations. Our analyses are limited to those participants with complete data on PWV at visit 5 and blood pressure measurements at all five visits. Participants who attended visit 5 had a more favorable cardiovascular risk profile than those who did not, suggesting the possibility of a 'healthy survivor effect'. We took this possibility into account by using Heckman's two-stage analytic method to correct for this but we may still have underestimated the strength of the associations of blood pressure measurements with PWV. Not only the blood pressure levels but also the observed change over time may not correspond to contemporaneous patterns of blood pressure change over the life course [44,45]. Although we have adjusted the analyses for several potential confounders, we cannot exclude the possibility of some residual confounding. Finally, as PWV was measured at visit 5 only, we cannot rule out the possibility of reverse causality. It is possible that arterial stiffness and vascular remodelling preceded changes in blood pressure over the life course.

In summary, higher cfPWV, a measure of central arterial stiffness, was associated with higher SBP levels over time preceding the cfPWV measurements. This was not observed for DBP or mean arterial pressure, and only weakly with pulse pressure, which uses DBP in its calculation. In contrast, faPWV, a measure of peripheral arterial stiffness, was associated only with blood pressure levels cross-sectionally at visit 5. If replicated, these results suggest the testable proposition that lowering SBP may retard progression of aortic stiffness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors thank the staff and participants of the ARIC study for their important contributions.

Sources of support: The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN 268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). The work was supported by R01AG053938. M.L.M. was supported by the UNC BIRCWH K12HD001441.

Abbreviations:

ARIC	the Atherosclerosis Risk in Communities study
baPWV	brachial–ankle (BA) pulse wave velocity
cfPWV	carotid–femoral (CF) pulse wave velocity
faPWV	femoral–ankle (FA) pulse wave velocity
HbA1c	glycated hemoglobin

HDL	high-density lipoprotein
LDL	low-density lipoprotein
MAP	mean arterial pressure
MI	myocardial infarction
PP	pulse pressure
PWV	pulse wave velocity
SD	standard deviation

REFERENCES

1. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010; 55:1318–1327. [PubMed: 20338492]
2. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001; 37:1236–1241. [PubMed: 11358934]
3. Sutton-Tyrrell K, Najjar A, Boudreau R, Venkitachalam L, Kupelian V, Sinmonsick E, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well functioning older adults. Circulation 2005; 111:3384–3390. [PubMed: 15967850]
4. Sa Cunha R, Pannier B, Benetos A, Siche J-P, London G, Mallion J, Safar ME. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. J Hypertens 1997; 15:1423–1430. [PubMed: 9431848]
5. Townsend R. Arterial stiffness: recommendations and standardization. Pulse 2016; 4 (Suppl 1):3–7. [PubMed: 28275588]
6. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert concensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27:2588–2605. [PubMed: 17000623]
7. Greenwald S. Ageing of the conduit arteries. J Path 2007; 211:157–172. [PubMed: 17200940]
8. Stehouwer C, Henry R, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome. A pathway to cardiovascular disease. Diabetologia 2008; 51:527–539. [PubMed: 18239908]
9. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 2009; 54:1328–1336. [PubMed: 19884567]
10. Mitchell G, Guo C, Benjamin E, Larson M, Keyes M, Vita J, et al. Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. Circulation 2007; 115:2638–2636.
11. McEniery C, Spratt M, Munnery M, Yarnell J, Lowe G, Rumley A, et al. An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly Prospective Study. Hypertension 2010; 56:36–43. [PubMed: 20530296]
12. Johansen N, Vistisen D, Brunner E, Tabák A, Shipley M, Wilkinson I, et al. Determinants of aortic stiffness: 16-year follow-up of the Whitehall II study. PloS One 2012; 7:e37165. [PubMed: 22629363]
13. Ohyama Y, Teixido-Tura G, Ambale-Venkatesh B, Noda C, Chugh A, Liu C-Y, et al. Ten-year longitudinal change in aortic stiffness assessed by cardiac MRI in the second half of the human lifespan: the Multi-Ethnic Study of Atherosclerosis. Eur Heart J Cardiovasc Imaging 2016; 17:1044–1053. [PubMed: 26758407]

14. AlGhatrif M, Strait J, Morrell C, Canepa M, Wright J, Elango P, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. Hypertension 2013; 62:934–941. [PubMed: 24001897]
15. Lin L-Y, Liao Y-C, Lin H-F, Lee Y-S, lin R-T, Hsu C. Determinants of arterial stiffness progression in a han-chinese population in Taiwan: a 4-year longitudinal follow-up. BMC Cardiovasc Disord 2015; 15:100. [PubMed: 26376690]
16. Najjar A, Scuteri A, Shetty V, Wright J, Muller D, Fleg J, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. J Am Coll Cardiol 2008; 51:1377–1383. [PubMed: 18387440]
17. El Khoudary S, Barinas-Mitchell E, White J, Sutton-Tyrell K, Kuller L, Curb J, et al. Adiponectin, systolic blood pressure, and alcohol consumption are associated with more stiffness progression among apparently healthy men. Atherosclerosis 2012; 225:475–480. [PubMed: 23040831]
18. Liao D, Arnett D, Tyroler H, Riley W, Chambless L, Szklo M, et al. Arterial stiffness and the development of hypertension. Hypertension 1999; 34:201–205. [PubMed: 10454441]
19. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension 2005; 45:426–431. [PubMed: 15710784]
20. Franklin S. Arterial stiffness and hypertension: a two-way street. Hypertension 2005; 45:349–351. [PubMed: 15710783]
21. Mitchell G. Arterial stiffness and hypertension chicken or egg? Hypertension 2014; 64:210–214. [PubMed: 24799614]
22. Ferreira I, van de Laar R, Prins M, Twisk J, Stehouwer C. Carotid stiffness in young adults: a life-course analysis of its early determinants: the Amsterdam Growth and Health Longitudinal Study. Hypertension 2012; 59:54–61. [PubMed: 22068867]
23. Kaess B, Rong J, Larson M, Hamburg N, Vita J, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA 2012; 308:875–881. [PubMed: 22948697]
24. Brunner E, Shipley M, Ahmadi-Abhari S, Tabak A, McEniery C, Wilkinson I, et al. Adiposity, obesity, and arterial aging longitudinal study of aortic stiffness in the Whitehall II cohort. Hypertension 2015; 66:294–300. [PubMed: 26056335]
25. Investigators ARIC. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol 1989; 129:687–702. [PubMed: 2646917]
26. Ostchega Y, Nwankwo T, Sorlie P, Wolz M, Zipf G. Assessing the validity of the omron hem-907×l oscillometric blood pressure measurement device in a national survey environment. J Clin Hypertens (Greenwich) 2010; 12:22–28. [PubMed: 20047626]
27. Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, et al. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens 2009; 27:2022–2027. [PubMed: 19550355]
28. Snyder M, Tanaka H, Palta P, Patel M, Camplain R, Couper D, et al. Repeatability of central and peripheral pulse wave velocity measures: the Atherosclerosis Risk in Communities (ARIC) study. Am J Hypertens 2016; 29:470–475. [PubMed: 26232036]
29. Lantelme S, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. Hypertension 2002; 39:1083–1087. [PubMed: 12052846]
30. Millasseau S, Stewart A, Patel S, Redwood S, Chowienczyk P. Evaluation of carotid-femoral pulse wave velocity: influence of timing algorithm and heart rate. Hypertension 2005; 45:222–226. [PubMed: 15642772]
31. Heckman J. Sample selection bias as a specification error. Econometrcia 1979; 47:153–161.
32. O'Rourke MF. How stiffening of the aorta and elastic arteries leads to compromised coronary flow. Heart 2008; 94:690–691. [PubMed: 18480345]
33. Saito M, Okayama H, Nishimura K, Ogimoto A, Ohtsuka T, Inoue K, et al. Possible link between large artery stiffness and coronary flow velocity reserve. Heart 2008; 94:e20. [PubMed: 17947361]
34. Chung CM, Lin YS, Chu CM, Chang ST, Cheng HW, Yang TY, et al. Arterial stiffness is the independent factor of left ventricular hypertrophy determined by electrocardiogram. Am J Med Sci 2012; 344:190–193. [PubMed: 22270392]

35. Watabe D, Hashimoto J, Hatanaka R, Hanazawa T, Ohba H, Ohkubo T, et al. Electrocardiographic left ventricular hypertrophy and arterial stiffness: The Ohasama study. Am J Hypertens 2006; 19:1199–1205. [PubMed: 17161763]

36. van der Heijden-Spek J, Staessen J, Fagard R, Hoeks A, Boudier H, van Bortel L. Effect of age on brachial artery artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension 2000; 35:637–642. [PubMed: 10679510]

37. Tillin T, Chambers J, Malik I, Coady E, Byrd S, Mayet J, et al. Measurement of pulse wave velocity: site matters. J Hypertens 2007; 25:383–389. [PubMed: 17211245]

38. Choo J, Shin C, Barinas-Mitchell E, Masaki K, Willcox BJ, Seto TB, et al. Regional pulse wave velocities and their cardiovascular risk factors among healthy middle-aged men: a cross-sectional population-based study. BMC Cardiovasc Disord 2014; 14:5. [PubMed: 24410766]

39. Tsuchikura S, Shoji T, Kimoto E, Shinohara K, Hatsuda S, Koyama H, et al. Brachial-ankle pulse wave velocity as an index of central arterial stiffness. J Atheroscler Thromb 2010; 17:658–665. [PubMed: 20467192]

40. Benetos A, Laurent S, Hoeks AP, Boutouyrie PH, Safar ME. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. Arterioscler Thromb 1993; 13:90–97. [PubMed: 8422344]

41. van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension 2000; 35:637–642. [PubMed: 10679510]

42. Franklin SS, Gustin Wt. Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997; 96:308–315. [PubMed: 9236450]

43. McEniery C, Wilkinson I, Avolio A. Age, hypertension and arterial function. Clin Exp Pharmacol Physiol 2007; 34:665–671. [PubMed: 17581227]

44. Wills A, Lawlor D, Matthews F, Sayer A, Bakra E, Ben-Shlomo Y, et al. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. PloS Med 2011; 8:e1000440. [PubMed: 21695075]

45. Hulman A, Tabak A, Nyari T, Vistisen D, Kivimake M, Brunner E, et al. Effect of secular trends on age-related trajectories of cardiovascular risk factors: the Whitehall II longitudinal study. IJE 1985-2009; 2014:866–877.

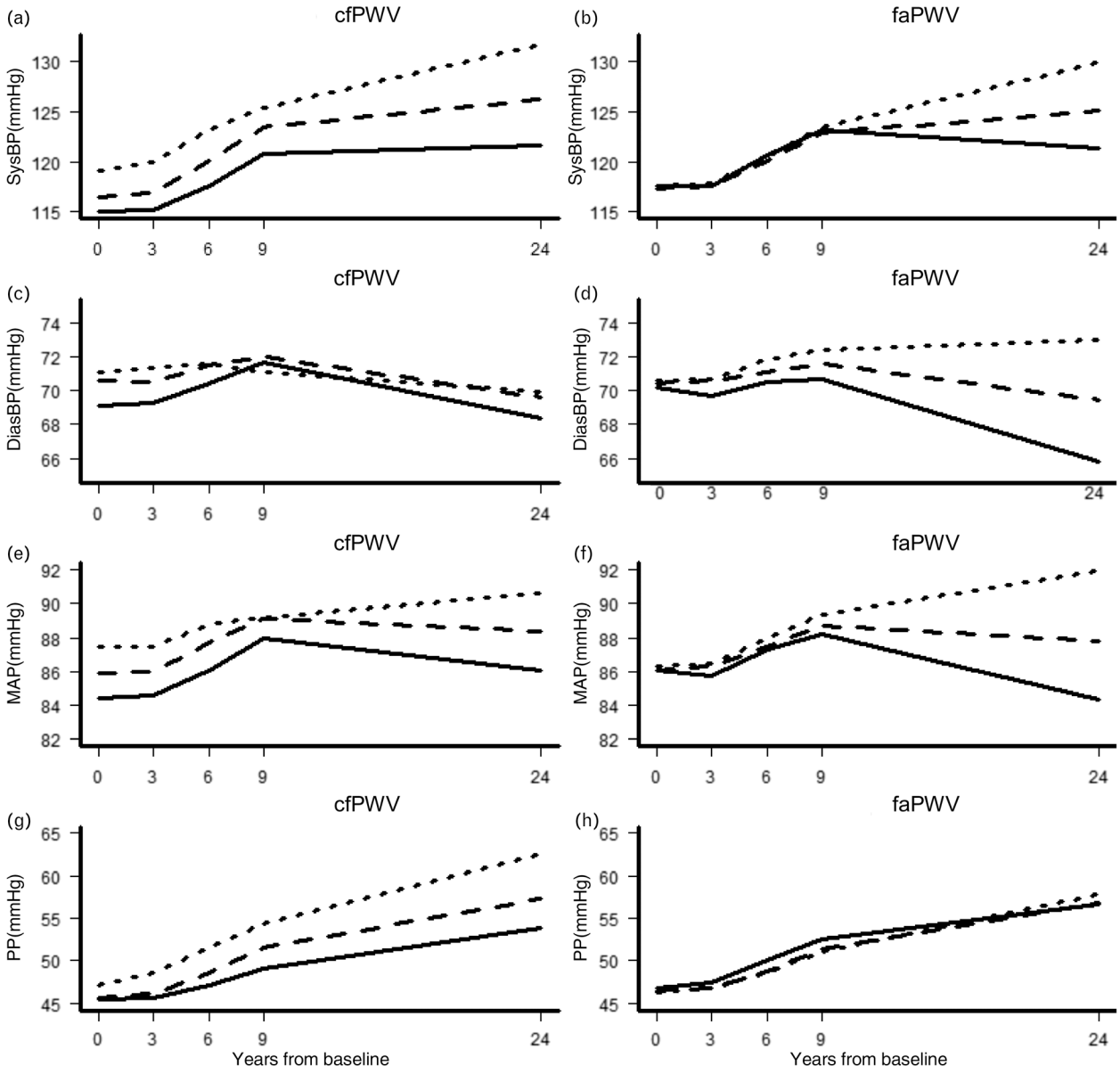

FIGURE 1.

Twenty-four-year life course of blood pressure and pulse pressure by tertiles of carotid–femoral (cf) and femoral–ankle (fa) pulse wave velocity (PWV) measured at an average age of 74 years. Least squares mean values adjusted for age, sex, race, center, smoking, heart rate, blood pressure-lowering medication use at time of PWV measurement, and the inverse of Mill's ratio. Stiffer arteries, that is, highest tertile, T1, black line less than 1009 cm/s; T2, long dashed line 1009–1243 cm/s; lowest tertile; T3, short dashed line greater than 1243 cm/s. SysBP, systolic blood pressure (a and b); DiasBP, diastolic blood pressure (c, d); MAP, mean arterial pressure (e and f), and PP, pulse pressure (g and h).

TABLE 1.

Mean (standard deviation) or percentage for characteristics of the the Atherosclerosis Risk in Communities Study cohort at Examination Visit 5 (2011–2013)

Variable	Overall	Men	Women
N	4166	1672	2494
Age (years)	75.4 (5.03)	75.6 (5.05)	75.2 (5.01)
BMI (kg/m^2)	27.8 (4.44)	28.0 (3.90)	27.7 (4.76)
Waist circumference (cm)	99.0 (12.24)	102.9 (10.41)	96.5 (12.69)
Waist-to-hip ratio	0.93 (0.08)	0.98 (0.05)	0.90 (0.08)
Smoker (current) (%)	5.5	5.9	5.2
SBP (mmHg)	130 (17)	129 (17)	131 (18)
DBP (mmHg)	66 (10)	67 (10)	66 (10)
Mean blood pressure (mmHg)	88 (11)	87 (11)	88 (11)]
Pulse pressure (mmHg)	64 (14)	62 (13)	65 (15)
Heart rate (bpm)	65 (12)	63 (11)	66 (11)
Total cholesterol (mmol/l)	4.77 (1.08)	4.39 (1.02)	5.02 (1.04)
HDL cholesterol (mmol/l)	1.37 (0.37)	1.20 (0.29)	1.49 (0.36)
LDL cholesterol (mmol/l)	2.75 (0.89)	2.54 (0.87)	2.88 (0.88)
Insulin (μu/ml)	13.0 (11.4)	13.5 (9.6)	12.8 (12.5)
HbA_{1c} (%)	5.9 (0.8)	5.9 (0.9)	5.9 (0.7)
Diabetes (%)	29.3	32.8	26.9
Carotid–femoral PWV (cm/s)	1158 (301)	1177 (304)	1145 (298)
Femoral–ankle PWV (cm/s)	1077 (201)	1079 (211)	1076 (195)

HbA_{1C}, haemoglobin A1c; PWV, pulse wave velocity.

TABLE 2.

Spearman correlation coefficients between pulse wave velocity and SBP unadjusted and adjusted partial correlation coefficients at each visit

Correlations	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Carotid–femoral PWV (n = 4116)					
Unadjusted	0.20**	0.21**	0.23**	0.20**	0.33**
Adjusted for age, sex, race	0.14**	0.16**	0.17**	0.14**	0.30**
Plus heart rate and smoking	0.14**	0.16**	0.17**	0.15**	0.31**
Plus IMR	0.13**	0.15**	0.16**	0.14**	0.32**
Right femoral–ankle PWV (n = 4120)					
Unadjusted	−0.04*	−0.03	−0.03	−0.02	0.18**
Adjusted for age, sex, race	−0.02	−0.02	−0.01	0.00	0.19**
Plus heart rate and smoking	−0.02	−0.02	−0.01	0.00	0.20**
Plus IMR	0.00	0.00	0.01	0.01	0.20**

PWV, pulse wave velocity; IMR, inverse of the Mill's ratio.

*0.01 less than P less than 0.0001.

**P less than 0.0001.

TABLE 3.

Mean (standard error) pressure levels of the study population (n = 4116) at each visit by tertiles of carotid–femoral pulse wave velocity and femoral–ankle pulse wave velocity measured at visit 5

	Group	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
cfPWV						
Systolic pressure (mmHg)	T1	115.9 (0.52)	115.6 (0.48)	117.5 (0.45)	120.1 (0.44)	118.6 (0.67)
	T2	118.1 (0.49)	117.9 (0.45)	120.5 (0.43)	123.5 (0.44)	124.0 (0.70)
	T3	121.0 (0.46)	121.3 (0.43)	124.0 (0.44)	125.8 (0.44)	129.9 (0.75)
Diastolic pressure (mmHg)	T1	68.9 (0.35)	69.2 (0.29)	70.4 (0.26)	71.7 (0.25)	69.1 (0.49)
	T2	70.3 (0.33)	70.4 (0.28)	71.4 (0.25)	72.0 (0.24)	70.2 (0.51)
	T3	71.4 (0.33)	71.2 (0.27)	71.6 (0.25)	71.3 (0.25)	70.7 (0.52)
Mean pressure (mmHg)	T1	84.1 (0.38)	84.4 (0.32)	86.1 (0.29)	88.0 (0.27)	86.8 (0.54)
	T2	85.6 (0.36)	85.8 (0.31)	87.6 (0.28)	89.2 (0.27)	89.1 (0.56)
	T3	87.3 (0.35)	87.4 (0.31)	88.8 (0.28)	89.4 (0.27)	91.3 (0.58)
Pulse pressure (mmHg)	T1	45.4 (0.40)	45.6 (0.35)	47.0 (0.32)	49.0 (0.33)	54.0 (0.61)
	T2	45.6 (0.38)	46.1 (0.33)	48.5 (0.32)	51.5 (0.33)	57.4 (0.63)
	T3	47.1 (0.38)	48.5 (0.32)	51.4 (0.31)	54.3 (0.33)	62.7 (0.65)
faPWV						
Systolic pressure (mmHg)	T1	117.3 (0.56)	117.3 (0.49)	120.6 (0.44)	123.1 (0.43)	121.8 (0.86)
	T2	117.0 (0.54)	117.4 (0.47)	119.9 (0.43)	122.9 (0.43)	125.8 (0.87)
	T3	117.2 (0.54)	117.6 (0.47)	120.4 (0.42)	123.4 (0.43)	130.6 (0.89)
Diastolic pressure (mmHg)	T1	70.1 (0.35)	69.7 (0.29)	70.5 (0.26)	70.7 (0.25)	65.9 (0.50)
	T2	70.3 (0.34)	70.5 (0.28)	71.2 (0.26)	71.7 (0.25)	69.6 (0.51)
	T3	70.5 (0.33)	70.6 (0.28)	71.7 (0.26)	72.4 (0.25)	73.1 (0.52)
Mean pressure (mmHg)	T1	86.0 (0.38)	85.6 (0.33)	87.2 (0.29)	88.1 (0.27)	84.4 (0.55)
	T2	86.0 (0.37)	86.2 (0.32)	87.5 (0.29)	88.7 (0.27)	88.1 (0.56)
	T3	86.1 (0.36)	86.3 (0.31)	87.9 (0.28)	89.4 (0.27)	92.1 (0.57)
Pulse pressure (mmHg)	T1	46.6 (0.41)	47.3 (0.35)	49.9 (0.33)	52.4 (0.34)	56.9 (0.64)
	T2	46.2 (0.39)	46.5 (0.34)	48.6 (0.32)	51.2 (0.34)	57.0 (0.65)
	T3	46.2 (0.39)	46.6 (0.33)	48.5 (0.32)	51.0 (0.34)	58.3 (0.66)

Multivariate model adjusted for sex, race, center, age, and heart rate at each visit. Also adjusted for selection bias (the inverse of the Mill's ratio), smoking habit and blood pressure lowering medication use at visit 5. Tertiles for cfPWV were 1009 and 1243cm/s. cfPWV, carotid–femoral pulse wave velocity; faPWV, femoral–ankle pulse wave velocity.