Blood Vessels

Arterial Stiffness, Physical Function, and Functional Limitation
The Whitehall II Study


Abstract—Arterial stiffness has been proposed as an indicator of vascular aging. We aimed to examine this concept by analyzing associations of arterial stiffness with age, subjective and objective measures of physical functioning, and self-reported functional limitation. We measured aortic pulse wave velocity by applanation tonometry among 5392 men and women aged 55 to 78 years. Arterial stiffness was strongly associated with age (mean difference [SE] per decade: men, 1.37 m/s [0.06 m/s]; women: 1.39 m/s [0.10 m/s]). This association was robust to individual and combined adjustment for pulse pressure, mean arterial pressure, antihypertensive treatment, and chronic disease. Participants took an 8.00-ft (2.44-m) walking speed test, a spirometry lung function test, and completed health functioning and (instrumental) activities of daily living questionnaires. Associations of stiffness and blood pressure with physical function scores scaled to SD of 10 were compared. One-SD higher stiffness was associated with lower walking speed (coefficient [95% CI]: −0.96 [−1.29 to −0.64] m/s) and physical component summary score (−0.91 [−1.21 to −0.60]) and poorer lung function (−1.23 [−1.53 to −0.92] L) adjusted for age, sex, and ethnic group. Pulse pressure and mean arterial pressure were linked inversely only with lung function. Associations of stiffness with functional limitation were robust to multiple adjustment, including pulse pressure and chronic disease. In conclusion, the concept of vascular aging is reinforced by the observation that arterial stiffness is a robust correlate of physical functioning and functional limitation in early old age. The nature of the link between arterial stiffness and quality of life in older people merits attention. (Hypertension. 2011;57:1003-1009.) ● Online Data Supplement

Key Words: epidemiology ■ aging ■ physical function ■ functional limitation ■ arterial stiffness ■ pulse pressure

Arterial pulse wave velocity (PWV) predicts cardiovascular disease events and all-cause mortality.1 Clinical cardiovascular disease and death are clearly important outcomes, and variation in arterial stiffness, a measure of arteriosclerosis, is likely to be associated with other important morbidity, such as reduced physical functional capacity.2,3 Variation in arterial stiffening potentially has a causal role in the heterogeneity of age-related declines in health functioning and emergence of functional limitation. However, the associations of PWV with functional outcomes remain poorly described.

Arterial stiffness has been proposed as an indicator of vascular aging because it reflects both target organ damage and the underlying pathological process and potentially integrates the long-lasting effects of known and unknown vascular risk factors.4 Chronological age is important. Age is a surrogate for the number of heartbeats, and the number of expansion-relaxation cycles influences the rate of fatigue fracture of elastic elements within the aortic media.5 In addition, cumulative exposure to multiple vascular risk factors compared with no risk factors is linked, even in younger adults, with PWV difference of the order of 1 m/s.6 Aortic stiffening leads to a rise in systolic pressure and a fall in diastolic pressure such that pulse pressure widens. This has a number of detrimental consequences, including an increase in left ventricular afterload, increased pulsatility of pressure in fragile capillaries, and a fall in myocardial perfusion. Pathophysiological changes less directly connected to aortic function may follow, including adverse skeletal muscle microcirculation.7

There is some evidence to suggest that variation in arterial stiffness is related to several aspects of physical function.2,3 To extend this line of research, we present findings in 5392 men and women aged 55 to 78 years of age for the relations of PWV, measured by applanation tonometry, with objective and subjective measures of physical functioning, including walking speed, lung function, and the short form-36 physical component summary (PCS) score, and with self-reported functional limitation. Pulse pressure, mean arterial pressure (MAP), heart rate, chronic disease, and antihypertensive.
Methods

Study Sample
The Whitehall II Study is a longitudinal study of 10,308 male and female civil servants (initially aged 35 to 55 years) based in London and set up in 1985. The response rate was 73%.

Approval of the local ethics committee and written, informed consent from each participant have been obtained at each study phase.

The present study sample included those who attended the phase 9 clinical examination (N=5392), which was the target sample for PWV measurement, excluding by design 833 participants who were examined by nurses at home. Missing measurements of PWV and other covariates were imputed (see “Statistical Analysis”). Sensitivity analysis was conducted in 2 samples, the “observed PWV clinic sample” (N=4347) based on those who attended the clinic examination and provided a PWV measurement, and the “imputed PWV clinic and home sample” (N=6225) based on those who were screened in the clinic or at the participant’s home, using imputed values for those with missing PWV data.

Aortic PWV and Blood Pressure
At phase 9, with the participant in a supine position, blood pressure was measured twice after 10 minutes of rest. From the supine systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean blood pressure in millimeters of mercury was calculated as follows: DBP + 0.33(SBP−DBP). PWV was then assessed between the carotid and femoral sites using applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia). Path length was determined with a tape measure by subtracting the carotid-renal notch distance from the femoral-renal notch distance. In each participant, PWV was measured twice, and if the difference in velocity between the 2 measurements was larger than 0.5 m/s, a third measurement was taken. The average of all of the measurements was used in the analysis. PWV measurements were repeated in 125 study participants within 60 days to assess the short-term reproducibility. The median intraclass difference in PWV was 0.08 m/s (interquartile range: −0.68 to 0.93 m/s).

Physical Function
At phase 9, walking speed was measured by a trained nurse over a clearly marked 8-foot walking course using a standardized protocol.

Participants wore either low-heeled, close-fitting footwear or walked barefoot. Before the test, participants were shown the walking course and asked to “walk to the other end of the course at your usual walking pace, just as if you were walking down the street to go the shops. Walk all the way past the other end of the tape before you stop.” The starting position was standing with both feet together at the start of the course. Participants were asked to begin walking when properly positioned. The stopwatch was started as the participant’s foot hit the floor across the starting line. Nurses walked behind and to the side of the participant and stopped timing when the participant’s foot hit the floor after the end of the walking course. Three tests were conducted, and the fastest walk was used in the analysis. Pairwise correlations between measurements were between 0.92 and 0.95. Lung function was measured by portable flow spirometry. The highest of ≤5 measurements was used to define forced expiratory volume in 1 second. The United Kingdom version of the short form-36 questionnaire was administered by self-completion questionnaire. The PCS score combines 4 of the 8 scales, physical function, role limitations because of physical problems, pain, and general health perceptions. The PCS score is scaled 0 to 100, with 100 indicating high functioning.

Results
Characteristics of the phase 9 clinic sample are shown in Table 1. The proportion of missing values was nontrivial for functional limitation was measured at phases 8 (2006) and/or 9 using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales (please see the online Data Supplement at http://hyper.ahajournals.org). The ADL scale consists of 6 self-completed questions on the participant’s ability to carry out everyday tasks, such as dressing, walking, washing, and using the toilet. The IADL questions capture ability to live independently and involve cognitive and physical competences, including preparing a hot meal, taking medication, doing work around the house, and shopping for groceries. For both ADL and IADL, reporting 1 or more difficulty from the list of 6 items was taken as a functional limitation. Ninety-four percent of individuals in the clinic and home sample completed the ADL questionnaire at both phases 8 and 9. For these individuals, functional limitation was indicated if they reported ≥1 difficulty at either phase.

Vascular Disease, Diabetes Mellitus, and Antihypertensive Medication
Prevalent vascular disease status (myocardial infarction and/or stroke) was determined using self-report of doctor diagnosis and hospitalization with verification from medical charts where available. Prevalent diabetes mellitus was determined by self-report of doctor diagnosis and/or medication or oral glucose tolerance test.

Statistical Analysis
The baseline sample for the analyses was the 5392 participants attending the phase 9 clinic. We used multiple imputation to assign values for variables with missing data. The purpose was to maximize the number of participants in the analyses and to check for potential selection bias because of exclusion of those with missing values by comparing analyses performed with and without imputation. In addition, PWV values were imputed for participants examined at home (see “Study Sample” above). The multiple imputation creates a number of copies of the data (10 copies in this case), each of which has values imputed for the missing data with an appropriate level of randomness. The variables used for the imputation include all of the analysis variables together with other variables thought to predict missingness. We used the improved strategy of multiple imputation and then deletion, which resets the imputed values for outcome variables (eg, walking speed) back to missing.

The associations of PWV, blood pressure measures, and chronic disease with age and physical function score outcomes were estimated using linear least-squares regression, whereas logistic regression was used for the self-reported limitations outcomes. In the latter analyses, we additionally adjusted for the possible difference in detection of limited functioning by including a variable to indicate whether individuals responded to the ADL questionnaire at one or both of phases 8 and 9. To compare the associations between PWV and the other blood pressure predictors we standardized these measures, separately in men and women, to have a mean of 0 and SD of 1. In addition, to allow comparison across the different physical function score outcomes, we standardized these scores, separately in men and women, to have an SD of 10. The estimates from these regressions in the 10 imputed data sets were averaged using Rubin’s rules, which take into account the uncertainty in the imputation, as well as the uncertainty attributed to random variation, as in all multivariable analyses.

Two sets of sensitivity analyses were conducted to examine the stability of the aortic stiffness-functioning associations under differing definitions of the study sample. The first repeated the analyses in the sample of 4347 participants in whom PWV was measured (the observed PWV clinic sample), and the second repeated the analyses in the sample of all 6225 participants in the clinic or home samples (the imputed PWV clinic and home sample).
PWV (men: 17.9%; women: 23.4%) and maximum forced expiratory volume in 1 second (men: 22.8%; women: 17.9%). The proportions with prevalent cardiovascular disease and diabetes mellitus were, respectively, 39% in 30 and 1 in 7. Approximately one third of participants reported that they were taking antihypertensive medication. Mean short form-36 PCS score was close to the midpoint of the scale. One or more were taking antihypertensive medication. Mean short form-36 summary score demonstrated simultaneous links between aortic stiffness and performance measures of lower limb function and lung function; secon, a subjective reported composite measure of general health; and, third, limitations in conduct of everyday activities, such as washing and dressing, and in competences needed for independent living, such as shopping for groceries. The PWV-functional limitation associations were robust to adjustment for blood pressure measures, heart rate, and chronic disease.

**Sensitivity Analysis**

The main analyses were repeated in 2 samples, those in whom PWV was measured, not using imputation (observed PWV clinic sample, maximum N=4347), and those who were screened in the clinic or at home, using imputation for unmeasured PWV (imputed PWV clinic and home sample, maximum N=6225). In the observed PWV clinic sample, the regression coefficients for functioning were similar in relative size according to PWV, blood pressure measures, and chronic disease (Table S1, available in the online Data Supplement at http://hyper.ahajournals.org). For lung function, the coefficients tended to be smaller compared with the full imputed clinic sample (Table 3). In the imputed PWV clinic and home sample, coefficients for functioning tended to be larger. The odds ratios for ADL and IADL functional limitation in the observed PWV clinic sample and imputed PWV clinic and home sample (Table S2) were similar to those in the full imputed clinic sample (Table 4).

**Discussion**

Arterial stiffness exhibited a strong and robust association with poorer physical functioning and functional limitation in this relatively healthy sample of approximately 65 years of age. These findings contrast with the weak or absent links of measures based on blood pressure with the same set of functioning indices. The age-adjusted PWV-functioning associations were weakened no more than modestly when adjusted for the combination of pulse pressure, MAP, antihypertensive treatment, and chronic disease. Thus, the study demonstrates simultaneous links between aortic stiffness and several aspects of physical functioning, first, objective performance measures of lower limb function and lung function; second, a subjective reported composite measure of general physical health; and, third, limitations in conduct of everyday activities, such as washing and dressing, and in competences needed for independent living, such as shopping for groceries.

Our findings expand the evidence supporting the concept of vascular aging in relation to arterial stiffness.4,8,18 As...
expected, there was a clear age trend in aortic stiffness, assessed here by means of applanation tonometry PWV. In addition, aortic stiffness was associated with all indices of functioning after adjusting for chronological age. This observation is consistent with perspectives on heterogeneity in effective biological age involving multiple molecular and environmental mechanisms. Importantly, the vascular aging effect captured by PWV was not attributable to increasing age-related prevalence of overt vascular disease, including diabetes mellitus. First, prevalence of these conditions is, as yet, low in our cohort, and, second, there was little attenuation of the aortic stiffness-functioning associations on adjustment chronic disease status.

The vascular aging concept is emerging both in basic science and clinical applications. In biomedical science, vascular aging as distinct from subclinical vascular disease describes age-related changes in structure and physiological functioning of the vasculature, including conduit arteries. Mechanisms leading to increased stiffness of the abdominal aorta may include progressive collagen cross-linkage induced by dietary and endogenous production of advanced glycation end products, reduced elastic fiber content, calcification, and increased muscle tone because of endothelial cell senescence induced by oxidative stress. In clinical applications, the aim has been to develop “vascular age” as an intuitive risk communication message to convey an individual’s absolute risk of a cardiovascular event, estimated from a multivariable risk prediction function. Vascular age is, in this context, defined as the chronological age of a person of the same sex with the same predicted risk but all risk factors absent or at achievable low levels. More recently, Nilsson et al proposed PWV measurement as a means to identify and monitor interventions to slow early vascular aging. A similar concept has been applied in a commercial setting to calculate “heart health” on open access Web pages (https://www.heartagecalculator.com/HeartHealth/HeartAgeCalculator.aspx). Our findings suggest that vascular age, indexed by PWV, is relevant to age-related quality of life, as well as to risks of vascular morbidity and mortality.

Table 3. Association of Pulse Wave Velocity, Blood Pressure Measures, and Chronic Disease With Standardized Physical Function Scores in Those Seen at the Clinical Examination

<table>
<thead>
<tr>
<th>Independent Measures</th>
<th>Walking Speed (N=5286)</th>
<th>SF-36 Physical Component Summary Score (N=5227)</th>
<th>Lung Function (N=4234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95% CI)*</td>
<td>P</td>
<td>Coefficient (95% CI)*</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>−0.96 (−1.29 to −0.64)</td>
<td>&lt;0.001</td>
<td>−0.91 (−1.21 to −0.60)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>−0.08 (−0.37 to 0.21)</td>
<td>0.58</td>
<td>0.25 (−0.05 to 0.55)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>−0.20 (−0.47 to 0.08)</td>
<td>0.16</td>
<td>0.26 (−0.02 to 0.55)</td>
</tr>
<tr>
<td>Antihypertensive treatment (yes vs no)</td>
<td>−1.96 (−2.53 to −1.39)</td>
<td>&lt;0.001</td>
<td>−3.27 (−3.85 to −2.68)</td>
</tr>
<tr>
<td>Chronic disease†</td>
<td>−1.80 (−2.50 to −1.10)</td>
<td>&lt;0.001</td>
<td>−3.10 (−3.83 to −2.37)</td>
</tr>
<tr>
<td>Pulse wave velocity, fully adjusted†</td>
<td>−0.67 (−1.06 to −0.24)</td>
<td>&lt;0.001</td>
<td>−0.70 (−1.09 to −0.31)</td>
</tr>
</tbody>
</table>

*Regression coefficients of functioning scores were scaled to SD=10, per 1-SD change in pulse wave velocity, pulse pressure, and mean arterial pressure.
†Chronic disease was defined as prevalent stroke, myocardial infarction, or diabetes mellitus.
‡Fully adjusted model is adjusted for age, sex, ethnic group, pulse pressure, mean arterial pressure, heart rate, antihypertensive treatment, and chronic disease.
between PWV and hypertension is likely to be bidirectional, with rheumatoid arthritis who were free of overt arterial disability, was observed among patients and functional limitations, based on Stanford Health Assessment Questionnaire disability, was observed among patients and present smoking habit. A link between augmentation index association did not appear to be accounted for by past or study. Recent prospective analyses, including one in the Chinese community in China showed that the age-related rate of stiffening. The strong association with higher sodium excretion, higher mean blood pressure, increase in aortic PWV was faster in the urban community and greater hypertension prevalence. The strong association between arterial changes and blood pressure disturbances. Although the influence of other vascular risk factors on the speed of arterial stiffening may be relatively small, it was the case that the rate of stiffening differed markedly within strata of MAP in the Chinese study. The strong association between PWV and hypertension is likely to be bidirectional, the product of a vicious cycle of arterial changes and blood pressure disturbances. Although not community based, the study has been carried out in the largest healthy population-scale sample to date with a gold-standard PWV measurement. Crucially, we used multiple imputation to verify that missing PWV values, among some 20% of the clinic sample and, by design, among all of those examined at home, did not distort the associations of interest. Multiple imputation is designed to reduce the effect of selection bias on analytic findings, but imputed results may mislead if applied inappropriately. A key assumption is that the imputed variable is missing completely at random in the model. Here we have imputed missing PWV values using a range of variables that predict these missing values, including demographic variables, body mass index, and vascular risk factors shown to predict PWV in the study sample. All of the functioning measures of interest were included in the imputation model and imputed values subsequently set to missing in the computation of the effects reported. Sensitivity analyses with the pulse pressure variable suggested that the missing-at-random assumption was reasonable. Pulse pressure measurements were set to missing among participants without a PWV measurement who attended the clinic. PWV-functioning associations in the full clinic sample based on imputed pulse pressure values among those without a PWV measurement were close to the effects obtained when all of the observed pulse pressure values were used (data not shown).

Previous Studies
There are few previous studies of arterial stiffness and physical functioning and, to our knowledge, none of arterial stiffness and functional limitations in a general population sample. Based on a 20-metre timed test, the Health, Aging and Body Composition study found a similar relation to that observed here between walking speed and PWV and at mean age 74 years and also did not observe an association with pulse pressure. Among Welsh men at mean age 74 years, PWV and lung function were associated, using the same methods of measurement as in our study. Notably, this association did not appear to be accounted for by past or present smoking habit. A link between augmentation index and functional limitations, based on Stanford Health Assessment Questionnaire disability, was observed among patients with rheumatoid arthritis who were free of overt arterial disease.

The effect of aging on elasticity of the large arteries has been known and measured for many decades, and it is clear that the chronological age effect is not invariant. Blood pressure is a key risk factor implicated in the variation of the age effect. An early study comparing a rural and an urban community in China showed that the age-related rate of increase in aortic PWV was faster in the urban community with higher sodium excretion, higher mean blood pressure, and greater hypertension prevalence. The strong association between PWV and hypertension is likely to be bidirectional, the product of a vicious cycle of arterial changes and blood pressure disturbances. Although the influence of other vascular risk factors on the speed of arterial stiffening may be relatively small, it was the case that the rate of stiffening differed markedly within strata of MAP in the Chinese study. Recent prospective analyses, including one in the present cohort (data not shown), suggest that central obesity, raised serum triglycerides, and low-grade inflammation may be among the important non-blood-pressure risk factors responsible for variation in age-related heterogeneity in arterial stiffening.

Strengths and Limitations
Although not community based, the study has been carried out in the largest healthy population-scale sample to date with a gold-standard PWV measurement. Crucially, we used multiple imputation to verify that missing PWV values, among some 20% of the clinic sample and, by design, among all of those examined at home, did not distort the associations of interest. Multiple imputation is designed to reduce the effect of selection bias on analytic findings, but imputed results may mislead if applied inappropriately. A key assumption is that the imputed variable is missing completely at random in the model. Here we have imputed missing PWV values using a range of variables that predict these missing values, including demographic variables, body mass index, and vascular risk factors shown to predict PWV in the study sample. All of the functioning measures of interest were included in the imputation model and imputed values subsequently set to missing in the computation of the effects reported. Sensitivity analyses with the pulse pressure variable suggested that the missing-at-random assumption was reasonable. Pulse pressure measurements were set to missing among participants without a PWV measurement who attended the clinic. PWV-functioning associations in the full clinic sample based on imputed pulse pressure values among those without a PWV measurement were close to the effects obtained when all of the observed pulse pressure values were used (data not shown).

We restricted the analytic sample to participants who attended our clinic, because this was the group targeted for the PWV measurement. The main analyses were additionally carried out with imputation of PWV values for all of the participants in the study phase, including those seen by a nurse at home and, for comparison, a complete cases analysis without imputation (Tables S1 and S2). These analyses show considerable stability of effects in absolute and relative terms across the 3 analytic approaches. This baseline cross-sectional study cannot address the nature of associations between aortic stiffness and physical function. One causal interpretation leads from declining

Table 4. Association of Pulse Wave Velocity, Blood Pressure Measures, and Chronic Disease With Self-Reported Functional Limitation in Those Seen at the Clinical Examination

<table>
<thead>
<tr>
<th>Independent Measures</th>
<th>ADL (N=5380)</th>
<th>IADL (N=5380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse wave velocity</td>
<td>1.23 (1.12 to 1.35)</td>
<td>1.18 (1.07 to 1.31)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.93 (0.84 to 1.02)</td>
<td>0.94 (0.84 to 1.05)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.95 (0.87 to 1.04)</td>
<td>0.90 (0.81 to 0.99)</td>
</tr>
<tr>
<td>Antihypertensive treatment (yes vs no)</td>
<td>1.58 (1.32 to 1.88)</td>
<td>1.29 (1.05 to 1.59)</td>
</tr>
<tr>
<td>Chronic disease†</td>
<td>1.42 (1.15 to 1.74)</td>
<td>1.48 (1.17 to 1.87)</td>
</tr>
<tr>
<td>Pulse wave velocity, fully adjusted‡</td>
<td>1.20 (1.08 to 1.34)</td>
<td>1.21 (1.06 to 1.37)</td>
</tr>
</tbody>
</table>

ADL indicates Activities of Daily Living; IADL, Instrumental Activities of Daily Living. All of the models are adjusted for age, sex, and ethnic group. Analytic samples were restricted to those with observed physical function outcomes.

*Data show the odds ratios of having one or more ADL or IADL disability per 1-SD change in pulse wave velocity, pulse pressure, and mean arterial pressure.

†Chronic disease was defined as prevalent stroke, myocardial infarction, or diabetes mellitus.
‡Fully adjusted model is adjusted for age, sex, ethnic group, pulse pressure, mean arterial pressure, heart rate, antihypertensive treatment, and chronic disease.
cardiovascular function, indexed by aortic stiffness, to declining physical functioning. It is also plausible that poor physical functioning may be the factor driving the association. For example, poor lung function may be a precursor of aortic stiffness, and in the present study lung function is associated with pulse pressure, as well as PWV, whereas other functional measures are associated only with PWV. A third possibility is that long-term influences, behavioral and genetic, may generate the observed associations by accelerating or delaying aging processes. A further possibility is that the associations are bidirectional in nature. With respect to cardiac function, stroke volume was not assessed in the study, and so any impact of this parameter on the observed associations could not be quantified. Stroke volume may influence PWV indirectly via MAP, which we have adjusted for in the models. Resting heart rate was measured and included among the variables in the fully adjusted models.

**Implications**

Our analysis suggests that aortic stiffness is a useful marker of poor present and future physical function, and, because functional limitation is a precursor of disability, aortic stiffness in the young old may be a risk factor for incident disability. Against the set of functioning measures analyzed here, measurement of PWV by applanation tonometry is a more precise and powerful method for evaluating aortic stiffness than measurement of pulse pressure, which was associated only with lung function. Additional follow-up of the cohort with a second measurement of PWV will be valuable in evaluating the causal roles that variation in and progression of arterial stiffness may have in the heterogeneity of aging processes and in establishing whether arterial stiffness may be a useful target for clinical strategies designed to promote healthy aging.

We add to the scant evidence that aortic stiffness is associated with aging outcomes and for the first time demonstrate a relation with functional limitation in a healthy sample. Our observations reinforce the concept of vascular aging, in showing that aortic stiffness remained robustly associated with several ageing outcomes after taking account of chronological age, MAP, pulse pressure, heart rate, and chronic disease status.

**Perspectives**

Arterial stiffness based on PWV has been proposed as an indicator of vascular aging. We found associations of stiffness with walking speed, lung function, short-form-36 PCS score, and ADL/IADL functional limitation to be largely unchanged after multiple adjustment, including pulse pressure and chronic disease. Our results reinforce the concept of vascular aging. Carotid-femoral PWV based on applanation tonometry may be a sensitive tool for assessing the rate of progression of vascular stiffness in early old age in research and clinical practice.

**Acknowledgments**

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**Disclosures**

None.

**References**


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Arterial stiffness, physical function and functional limitation: the Whitehall II study

ONLINE SUPPLEMENT

Eric J Brunner, Martin J Shipley, Daniel R Witte, Archana Singh-Manoux, Annie R Britton,
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Short title: Arterial stiffness and functioning

4 tables, 1 figure
Online supplement

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1. **Functional limitation questionnaire**

Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales administered at Whitehall II Phase 8 (2006) and Phase 9 (2008-09).

2. **Main tables based on alternate definitions of the study sample**

Tables S1 and S2 are based on two alternate definitions of the study sample. The first is the Observed Pulse Wave Velocity (PWV) Clinic Sample, based on 4347 participants in whom pulse wave velocity was measured at the clinical examination. Imputation was not used in this complete cases analysis. The second is the Imputed PWV Clinic and Home Sample based on all 6225 participants who were examined in the clinic (n=5392) or at home (n=833). See Methods *Study Sample* and *Statistical Analysis* for details of the sample definitions, imputation and analytical methods.
1. **Functional limitation questionnaire**

The Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales were worded as follows.

“Here are a few everyday activities. Please tell us if you have any difficulties (Yes/No) with these because of a physical, mental, emotional or memory problem. Exclude any difficulties you expect to last less than three months.”

**ADL**

(a) Dressing, including putting on shoes and socks

(b) Walking across a room

(c) Bathing of showering

(d) Eating, such as cutting up your food

(e) Getting in or out of bed

(f) Using the toilet, including getting up or down

**IADL**

(a) Preparing a hot meal

(b) Shopping for groceries

(c) Making telephone calls

(d) Taking medication

(e) Doing work around the house or garden
(f) Managing money, such as paying bills and keeping track of expenses
Table S1. Association of pulse wave velocity, blood pressure measures and chronic disease* with standardized physical function scores

<table>
<thead>
<tr>
<th>Independent measures</th>
<th>Walking speed</th>
<th>Physical Component Score (SF-36)</th>
<th>Lung function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff† (95% CI) p-value</td>
<td>Coeff† (95% CI) p-value</td>
<td>Coeff† (95% CI) p-value</td>
</tr>
<tr>
<td>Among 4347 participants in whom pulse wave velocity was measured at the clinical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants in analysis</td>
<td>4264</td>
<td>4220</td>
<td>3463</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>-0.79 (-1.11, -0.48) &lt;0.001</td>
<td>-0.73 (-1.06, -0.41) &lt;0.001</td>
<td>-1.18 (-1.50, -0.87) &lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>-0.01 (-0.33, 0.31) 0.95</td>
<td>0.35 (0.03, 0.68) 0.03</td>
<td>-0.76 (-1.09, -0.42) &lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.16 (-0.46, 0.14) 0.29</td>
<td>0.27 (-0.03, 0.58) 0.08</td>
<td>-0.41 (-0.73, -0.09) 0.01</td>
</tr>
<tr>
<td>Anti-hypertensive treatment (yes v no)</td>
<td>-1.96 (-2.60, -1.33) &lt;0.001</td>
<td>-2.67 (-3.31, -2.03) &lt;0.001</td>
<td>-1.53 (-2.17, -0.89) &lt;0.001</td>
</tr>
<tr>
<td>Chronic disease ‡</td>
<td>-1.55 (-2.34, -0.76) &lt;0.001</td>
<td>-2.34 (-3.14, -1.53) &lt;0.001</td>
<td>-2.03 (-2.84, -1.22) &lt;0.001</td>
</tr>
<tr>
<td>Pulse wave velocity – fully adjusted §</td>
<td>-0.65 (-1.01, -0.29) &lt;0.001</td>
<td>-0.59 (-0.94, -0.23) 0.001</td>
<td>-0.78 (-1.14, -0.43) &lt;0.001</td>
</tr>
<tr>
<td>Among 6225 participants who were screened in the clinic or at home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants in analysis</td>
<td>6052</td>
<td>5999</td>
<td>4845</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>-1.01 (-1.33, -0.69) &lt;0.001</td>
<td>-1.10 (-1.47, -0.73) &lt;0.001</td>
<td>-1.25 (-1.56, -0.93) &lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>-0.06 (-0.32, 0.21) 0.68</td>
<td>0.25 (-0.03, 0.54) 0.08</td>
<td>-0.74 (-1.02, -0.46) &lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.14 (-0.39, 0.12) 0.30</td>
<td>0.28 (0.00, 0.55) 0.05</td>
<td>-0.42 (-0.69, -0.14) 0.003</td>
</tr>
<tr>
<td>Anti-hypertensive treatment (yes v no)</td>
<td>-1.96 (-2.50, -1.42) &lt;0.001</td>
<td>-3.61 (-4.18, -3.04) &lt;0.001</td>
<td>-1.66 (-2.20, -1.11) &lt;0.001</td>
</tr>
<tr>
<td>Chronic disease ‡</td>
<td>-2.13 (-2.78, -1.48) &lt;0.001</td>
<td>-3.57 (-4.27, -2.87) &lt;0.001</td>
<td>-2.15 (-2.82, -1.48) &lt;0.001</td>
</tr>
<tr>
<td>Pulse wave velocity – fully adjusted §</td>
<td>-0.76 (-1.20, -0.32) &lt;0.001</td>
<td>-0.72 (-1.17, -0.28) 0.002</td>
<td>-0.82 (-1.19, -0.45) &lt;0.001</td>
</tr>
</tbody>
</table>
*All models are adjusted for age, sex and ethnic group

† Regression coefficients of functioning scores scaled to SD = 10, per 1SD change in pulse wave velocity, pulse pressure and mean arterial pressure.

‡ Chronic disease defined as prevalent stroke, MI or diabetes

§ Fully adjusted model is adjusted for age, sex, ethnic group, pulse pressure, mean arterial pressure, heart rate, anti-hypertensive treatment and chronic disease
Table S2. Association of pulse wave velocity, blood pressure measures and chronic disease* with self-reported functional limitation

<table>
<thead>
<tr>
<th>Independent measures</th>
<th>ADL</th>
<th>IADL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio † (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Participants in whom pulse wave velocity was measured at the clinical examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants in analysis</td>
<td>4339</td>
<td>4339</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>1.16 (1.05, 1.28)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.89 (0.80, 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.93 (0.83, 1.03)</td>
<td>0.14</td>
</tr>
<tr>
<td>Anti-hypertensive treatment (yes v no)</td>
<td>1.57 (1.28, 1.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic disease ‡</td>
<td>1.26 (0.98, 1.62)</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulse wave velocity – fully adjusted §</td>
<td>1.18 (1.06, 1.32)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Participants who were screened in the clinic or at home

| No. of participants in analysis | 6198 | 6198 |
| Pulse wave velocity | 1.23 (1.13, 1.34) | <0.001 | 1.22 (1.07, 1.39) | 0.004 |
| Pulse pressure      | 0.93 (0.87, 1.01) | 0.08  | 0.93 (0.86, 1.02) | 0.14 |
| Mean arterial pressure | 0.96 (0.89, 1.03) | 0.27  | 0.89 (0.82, 0.98) | 0.01 |
| Anti-hypertensive treatment (yes v no) | 1.53 (1.31, 1.78) | <0.001 | 1.22 (1.02, 1.46) | 0.03 |
| Chronic disease ‡ | 1.40 (1.17, 1.67) | <0.001 | 1.43 (1.17, 1.75) | <0.001 |
| Pulse wave velocity – fully adjusted § | 1.19 (1.08, 1.31) | <0.001 | 1.20 (1.06, 1.37) | 0.004 |
*All models are adjusted for age, sex and ethnic group

† Odds ratios of having one or more ADL or IADL disability per 1SD change in pulse wave velocity, pulse pressure and mean arterial pressure.

‡ Chronic disease defined as prevalent stroke, MI or diabetes

§ Fully adjusted model is adjusted for age, sex, ethnic group, pulse pressure, mean arterial pressure, heart rate, anti-hypertensive treatment and chronic disease