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

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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 55-78 years. Arterial stiffness was strongly associated with age (mean difference (SE) per decade: men 1.37 (0.06) m/s, women 1.39 (0.10)). This association was robust to individual and combined adjustment for pulse pressure, mean arterial pressure, anti-hypertensive treatment and chronic disease. Participants took an 8 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=10 were compared. One SD higher stiffness was associated with lower walking speed (coefficient (95%CI) -0.79 (-1.11 to -0.47)) m/s) and physical component summary score (-0.74 (-1.06 to -0.42)), and poorer lung function (-1.17 (-1.49 to -0.86)) 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.

Keywords
Epidemiology, aging, physical function, functional limitation, arterial stiffness, pulse pressure

Introduction

Aortic pulse wave velocity (PWV) predicts cardiovascular disease (CVD) events and all-cause mortality.[1] Clinical CVD 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 PVW with functional outcomes remains 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 heart beats, 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 to 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 pulsality 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 aortic 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 55-78 years for the relations of PWV, measured by applanation tonometry, with objective and subjective measures of physical functioning: walking speed, lung function and the Short Form-36 physical component summary (SF-36 PCS) score, and with self-reported functional limitation. Pulse pressure, mean arterial pressure (MAP), heart rate, chronic disease and anti-hypertensive treatment are taken into account to examine the association of vascular aging measured by PWV with these functional aging outcomes.[4, 8]

Methods

Study sample

The Whitehall II study is a longitudinal study of 10,308 male and female civil servants (initially aged 35 – 55 years) based in London and set up in 1985. The response rate was 73%.[9] The cohort has been followed with clinical examinations every 5 years and with questionnaires every 2-3 years up to the end of 2009 (Phase 9). Approvals from the local Research 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 two samples: the 'observed PWV clinic sample' (N=4347) based on those who attended and the clinical 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 pulse wave velocity 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 mm Hg was calculated as: DBP + 0.33(SBP-DBP). PWV was then assessed between the carotid and femoral sites using applanation tonometry (SphygmoCor, Atcor Medical, Australia).[10] Path length was determined with a tape measure by subtracting the carotid-sternal notch distance from the femoral-sternal notch distance. In each participant, PWV

was measured twice and if the difference in velocity between the two measurements was larger than 0.5 m/s, a third measurement was taken. The average of all the measurements was used in the analysis. PWV measurements were repeated in 137 study participants within 60 days to assess the short-term reproducibility. The median intra-individual difference in PWV was 0.87 m/s (interquartile range 0.41-1.38).

Physical function

At Phase 9, walking speed was measured by a trained nurse over a clearly marked eight foot walking course using a standardized protocol.[11, 12] Participants wore either low-heeled close-fitting footwear or walked barefoot. Prior to 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 up to five measurements was used to define forced expiratory volume in 1 second (FEV). The UK version of the SF-36 questionnaire was administered by self-completion questionnaire. The physical component summary (PCS) score combines four of the eight scales: physical function, role limitations due to physical problems, pain and general health perceptions.[13, 14] The PCS score is scaled 0 to 100 with 100 indicating high functioning.

Functional limitation

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 (Online supplement, please see http://hyper.ahajournals.org). The ADL scale consists of six self-completed questions on the participant's ability to carry out everyday tasks, such as dressing, walking, washing, 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 one or more difficulty from the list of six 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 one or more difficulty at either phase.

Vascular disease, diabetes and anti-hypertensive medication

Prevalent vascular disease status (myocardial infarction and/or stroke) was determined using self-report of doctor diagnosis, hospitalization with verification from medical records where available. Prevalent diabetes was determined by self-report of doctor diagnosis and/or medication, or oral glucose tolerance test.[15]

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 maximise the number of participants in the analyses and to check for potential selection bias due to exclusion of those with missing values by comparing analyses performed with and without imputation. Additionally, pulse wave velocity 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 the analysis variables together with other variables thought to predict missingness. We used the improved strategy of multiple imputation, then deletion which re-sets the imputed values for outcome variables (e.g. walking speed) back to missing.[16]

The associations of pulse wave velocity, blood pressure measures and chronic disease with age and physical function score outcomes were estimated using linear least squares regression while 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. In order to compare the associations between pulse wave velocity and the other blood pressure predictors we standardised these measures, separately in men and women, to have a mean of zero and standard deviation of one. In addition, to allow comparison across the different physical function score outcomes we standardised these scores, separately in men and women, to have a standard deviation of 10. The estimates from these regressions in the 10 imputed datasets were averaged using Rubin's rules which take into account the uncertainty in the imputation as well as the uncertainty due to random variation, as in all multivariable analyses. [17]

Two sets of sensitivity analyses were conducted in order 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 pulse wave velocity 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).

Results

Characteristics of the Phase 9 clinic sample are shown in table 1. The proportion of missing values was non-trivial for PWV (men 17.9%, women 23.4%) and maximum FEV (men 22.8%, women 17.9%). The proportions with prevalent cardiovascular disease and diabetes were respectively about one in 30 and one in seven. Around one third of participants reported they were taking antihypertensive medication. Mean SF-36 PCS score was close to the mid-point of the scale. One or more functional limitations were reported by about 12% on the ADL questionnaire and 9% on the IADL questionnaire.

Figure 1 shows a marked age-trend in mean PWV in men and women by 5-year age group. Table 2 shows the association between PWV and age per decade, controlling separately for pulse pressure, MAP, MAP and antihypertensive medication, and chronic disease and then for all of these covariates. The association was similar in size in men and women. The age-PWV association was weakened after adjustment for pulse pressure (attenuation: men 14%, women 29%), but robust to adjustment for other covariates. Further analyses were conducted on men and women combined with adjustment for sex.

Higher PWV was associated with lower physical functioning after adjustment for age, sex and ethnic group (table 3). Pulse pressure and MAP were associated with lung function but not with walking speed or PCS score. The association of lung function with PWV was stronger than with MAP. Current use of antihypertensive medication and prevalent chronic disease were linked with lower physical functioning. The PWV-physical functioning associations were largely robust to adjustment for blood pressure measures and chronic disease (attenuation: 1-22%). Higher PWV was associated with ADL and IADL functional limitations (table 4), as was current use of antihypertensive medication and prevalent chronic disease. Pulse pressure and MAP were not associated with functional limitations in the expected direction. 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 two 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, please see http://hyper.ahajournals.org). For lung function the coefficients were similar, while for walking speed and PCS score coefficients tended to be smaller compared to 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, please see http://hyper.ahajournals.org) 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 around age 65 years. 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, mean arterial pressure, anti-hypertensive treatment and presence of 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.[18 8 4] As expected, there was a clear age trend in aortic stiffness, here assessed 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.[19-21] Importantly, the vascular aging effect captured by PWV was not attributable to increasing age-related prevalence of overt vascular disease including diabetes. 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.[22]. 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 fibre content, calcification, and increased muscle tone due to endothelial cell senescence induced by oxidative stress.[18, 23-26] 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.[27] 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 achievably low levels. More recently, Nilsson and colleagues proposed PWV measurement as a means to identify, and monitor interventions to slow early vascular aging.[4] 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.

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 m timed test, the Health ABC 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.[3] Among Welsh men at mean age 74 years, PWV and lung function were associated, using the same methods of measurement as in our study.[2] 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 rheumatoid arthritis patients free of overt arterial disease. [28]

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. [29] The strong association between PWV and hypertension [30] is likely to be bidirectional, the product of a vicious cycle of arterial changes and blood pressure disturbances.[18] While 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 mean arterial pressure in the Chinese study. [29] 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. [31]

Strengths and limitations

While 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. [32] 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, BMI and vascular risk factors shown to predict PWV in the study sample. All functioning measures of interest were included in the imputation model and imputed values subsequently set to missing in the computation of the effects reported.[16] Sensitivity analyses with the pulse pressure variable suggested 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 observed pulse pressure values were used (data not shown).

We restricted the analytic sample to participants who attended our clinic, since this was the group targeted for the PWV measurement. The main analyses were additionally carried out with imputation of PWV values for all 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 three 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 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 [2] 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.[33] 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 mean arterial pressure, 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 as 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 more precise and powerful method for evaluating aortic stiffness than measurement of pulse pressure, which was associated only with lung function. Further 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 to several ageing outcomes after taking account of chronological age, MAP, pulse pressure, heart rate and chronic disease status.

Perspectives

Arterial stiffness based on pulse wave velocity has been proposed as an indicator of vascular aging. We found associations of stiffness with walking speed, lung function, SF-36 physical component summary 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 pulse wave velocity 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.

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Conflict(s) of Interest/Disclosure(s)

None of the authors has any conflict of interest.

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Table 1. Characteristics of the 5392 participants seen at the clinical examination.

Characteristics	MEN (N=3942)		WOMEN (N=1450)	
	N	Mean (SD) or %	N	Mean (SD) or %
Age (years)	3942	65.5 (5.8)	1450	65.2 (5.8)
Non-white (%)	3933	6.0	1448	14.3
Self reported stroke (%)	3942	0.7	1450	0.4
Coronary heart disease (%)	3942	5.2	1450	2.1
Diabetes (%)	3942	14.8	1450	15.0
Pulse Wave Velocity (m/s)	3237	8.5 (2.0)	1110	8.2 (2.0)
Pulse Pressure (mmHg)	3940	54.0 (10.3)	1448	53.0 (11.7)
Mean arterial pressure (mmHg)	3940	89.2 (10.6)	1448	86.4 (11.4)
Heart rate (beats/min)	3941	66.6 (12.4)	1449	68.3 (11.0)
Anti-hypertensive treatment (%)	3938	35.6	1448	32.0
Walking speed (m/s)	3860	1.22 (0.28)	1426	1.09 (0.26)
SF-36 Physical Component Summary score	3860	49.8 (7.8)	1367	47.2 (9.8)
Maximum FEV(l)	3044	3.22 (0.71)	1190	2.18 (0.53)
Self-reported ADL (%)	3934	10.1	1446	14.5
Self-reported IADL (%)	3934	6.8	1446	12.2

SD: Standard Deviation; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living
Maximum FEV(l): Maximum forced expiratory volume in 1 s

Table 2. Association of pulse wave velocity with age in those seen at the clinical examination.

Further adjustments*	Men (N=3942)		Women (N=1450)		All (N=539	
	Coeff† (95% CI)	p-value	Coeff (95% CI)	p-value	Coeff (95% CI)	value
None	1.34 (1.23, 1.45)	<0.001	1.42 (1.23, 1.62)	<0.001	1.36 (1.26, 1.45)	
Pulse pressure	1.15 (1.04, 1.26)	<0.001	1.01 (0.81, 1.22)	<0.001	1.11 (1.02, 1.21)	
MAP	1.38 (1.27, 1.48)	<0.001	1.34 (1.16, 1.52)	<0.001	1.37 (1.27, 1.46)	
MAP, anti-hypertensive treatment	1.30 (1.20, 1.41)	<0.001	1.32 (1.13, 1.50)	<0.001	1.30 (1.21, 1.39)	
Chronic disease‡	1.29 (1.19, 1.40)	<0.001	1.36 (1.17, 1.56)	<0.001	1.31 (1.21, 1.40)	
Pulse pressure, MAP, heart rate, anti-hypertensive medication, chronic disease	1.08 (0.98, 1.18)	<0.001	0.96 (0.77, 1.14)	<0.001	1.05 (0.96, 1.14)	

MAP: Mean arterial pressure

*All coefficients are adjusted for ethnic group. The combined group of men and women is also adjusted for sex. Multiple imputation was used to fill missing values for all covariates other than age and sex

† Coefficients show the change in pulse wave velocity per 10 years of age.

‡Chronic disease defined as prevalent stroke, MI or diabetes

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.

Independent measures	Walking speed (N=5286)		SF-36 Physical Component Summary score (N=5227)		
	Coeff † (95% CI)	p-value	Coeff † (95% CI)	p-value	Coeff
Pulse wave velocity	-0.96 (-1.29, -0.64)	<0.001	-0.91 (-1.21, -0.60)	<0.001	-1
Pulse pressure	-0.08 (-0.37, 0.21)	0.58	0.25 (-0.05, 0.55)	0.11	-0
Mean arterial pressure	-0.20 (-0.47, 0.08)	0.16	0.26 (-0.02, 0.55)	0.07	-0
Anti-hypertensive treatment (yes v no)	-1.96 (-2.53, -1.39)	<0.001	-3.27 (-3.85, -2.68)	<0.001	-1
Chronic disease‡	-1.80 (-2.50, -1.10)	<0.001	-3.10 (-3.83, -2.37)	<0.001	-2
Pulse wave velocity – fully adjusted§	-0.67 (-1.06, -0.24)	<0.001	-0.70 (-1.09, -0.31)	<0.001	-0

*All models are adjusted for age, sex and ethnic group. Analytic samples were restricted to those with observed physical function outcomes.

† Regression coefficients of functioning scores scaled to SD = 10, per 1SD change in pulse wave velocity, pulse pressure, 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 4. Association of pulse wave velocity, blood pressure measures and chronic disease* with self-reported functional limitation in those seen at the clinical examination.

Independent measures	ADL (N=5380)		IADL (N=5380)	
	Odds Ratio † (95% CI)	p-value	Odds Ratio † (95% CI)	p-val
Pulse wave velocity	1.23 (1.12, 1.35)	<0.001	1.18 (1.07, 1.31)	0.002
Pulse pressure	0.93 (0.84, 1.02)	0.12	0.94 (0.84, 1.05)	0.28
Mean arterial pressure	0.95 (0.87, 1.04)	0.30	0.90 (0.81, 0.99)	0.04
Anti-hypertensive treatment (yes v no)	1.58 (1.32, 1.88)	<0.001	1.29 (1.05, 1.59)	0.01
Chronic disease ‡	1.42 (1.15, 1.74)	<0.001	1.48 (1.17, 1.87)	<0.001
Pulse wave velocity – fully adjusted §	1.20 (1.08, 1.34)	<0.001	1.21 (1.06, 1.37)	<0.003

*All models are adjusted for age, sex and ethnic group. Analytic samples were restricted to those with observed physical function outcomes.
† 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

Figure 1 Pulse wave velocity (mean and 95%CI) by sex and age group

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

Online supplement

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.

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

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

*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

Independent measures	ADL		IADL	
	Odds Ratio † (95% CI)	p-value	Odds Ratio † (95% CI)	p-value
Participants in whom pulse wave velocity was measured at the clinical examination				
No. of participants in analysis	4339		4339	
Pulse wave velocity	1.16 (1.05, 1.28)	0.004	1.15 (1.03, 1.29)	0.01
Pulse pressure	0.89 (0.80, 1.00)	0.05	0.93 (0.82, 1.06)	0.30
Mean arterial pressure	0.93 (0.83, 1.03)	0.14	0.93 (0.82, 1.05)	0.22
Anti-hypertensive treatment (yes v no)	1.57 (1.28, 1.94)	<0.001	1.30 (1.02, 1.65)	0.04
Chronic disease ‡	1.26 (0.98, 1.62)	0.08	1.38 (1.04, 1.84)	0.03
Pulse wave velocity – fully adjusted §	1.18 (1.06, 1.32)	0.004	1.17 (1.03, 1.33)	0.016
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 t