Interarm differences in systolic blood pressure and mortality among US army veterans

Interarm Differences in Systolic Blood Pressure and Mortality Among US Army Veterans: Aetiological Associations and Risk Prediction in the Vietnam Experience Study

James White, Ph.D [1], Laust H. Mortensen, Ph.D [2], Mika Kivimäki, Ph.D [3],

Catharine R. Gale, Ph.D [4], G. David Batty, Ph.D [3]

[1]School of Medicine, Cardiff University; [2]Section of Social Medicine, University of Copenhagen; [3]Department of Epidemiology and Public Health, University College London; [4]Medical Research Council Lifecourse Epidemiology Unit, University of Southampton.

Address for Correspondence:

James White, Ph.D

Cardiff University, School of Medicine, 4th Floor Neuadd Meirionnydd, Heath Park, CF14 4YS. U.K.

Telephone: +44 (0) 29 20 687243

Fax: +44 (0) 29 20 687236

Email: whitej11@cf.ac.uk

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Abstract

Background: Differences between the arms in systolic blood pressure [SBP] of ≥10 mm Hg have been associated with an increased risk of mortality in patients with hypertensive and chronic renal disease. For the first time, we examined these relationships in a non-clinical population.

Design: Cohort study.

Methods: Participants were 4419 men [mean age, 38.37] from the Vietnam Experience Study. Bilateral SBP and diastolic BP [DBP], serum lipids, fasting glucose, erythrocyte sedimentation rate [ESR], metabolic syndrome, and ankle brachial index were assessed in 1986.

Results: Ten percent of men had an interarm difference of ≥10 and 2.4% of ≥15 mmHg. A 15-year follow-up period gave rise to 246 deaths [64 from cardiovascular disease [(CVD)]. Interarm differences of ≥10 mm Hg were associated with an elevated risk of all-cause [hazard ratio (HR) = 1.49, 95% confidence interval (CI), 1.04 – 2.14] and CVD mortality [HR = 1.93, 95% CI, 1.01 – 3.69]. After adjusting for SBP, DBP, lipids, fasting glucose and ESR, associations between interarm differences of ≥10 mm Hg and all-cause (HR=1.35, 95% CI = 0.94 – 1.95) and CVD mortality (HR = 1.62, 95% CI, 0.84 - 3.14) were significantly attenuated.

Conclusions: In this non-clinical cohort study, interarm differences in SBP were not associated with mortality after accounting for traditional CVD risk factors. Interarm differences might not be valuable as an additional risk factor for mortality in populations with a low risk of CVD.

Key words: Epidemiology; Risk Factors; Hypertension.

Introduction

A marked difference in SBP between the arms have been linked to subclavian stenosis,[1, 2] atherosclerotic plaque,[3] and are most commonly observed in patients with hypertension,[4] diabetes,[5] and chronic renal disease,[1] suggesting interarm differences are a marker of peripheral vascular disease.[6] The presence of an interarm difference has been linked to the delayed diagnosis[7] and poor control of hypertension,[8] and as such are recommended in screening guidelines on the assessment of hypertension.[9,10] Despite these associations, few cohorts record information on SBP in both arms and as a result associations with mortality are unclear. A small number of studies have shown differences of ≥ 10mm Hg between the arms in SBP are associated with an increased risk for all-cause [4, 6] and CVD mortality in high risk patients (e.g. hypertension, [4, 11] chronic renal disease [1]). However, owing to a paucity of data, the extent to which these results are apparent in non-clinical groups is unclear.

Accordingly, the aim of the present study was to examine whether interarm differences in SBP are associated with all-cause and cardiovascular disease mortality over a 15-year follow-up period in a cohort of middle aged men. In addition to examining the link, if any, between interarm differences in blood pressure and mortality, we also test whether incorporating information on interarm differences into an established risk score for CVD (the Framingham risk algorithm) [12] will improve its

predictive capacity for all-cause and CVD mortality.

Methods

Study design and participants

Participants were drawn from the Vietnam Experience Study. The Vietnam Experience Study is a prospective cohort of United States army veterans that was established in 1983 to compare the health of men who participated in the Vietnam war against those who did not. [13] Briefly, on 31st December 1983, 18 313 men were drawn randomly from 5 million records of men who served in Vietnam and elsewhere. Of those men who were traced, 15 288 (85.6% response) participated in a telephone survey in 1985. A random sample was taken of telephone survey respondents in 1986 and 4462 (69.3% of those invited) attended a 3-day medical examination. Ethical approval for the study protocol was given by the US Office for Technology Assessment, the Department of Health and Human Sciences Advisory Committee, the Agent Orange Working Group Science Panel, and a review panel from the US Centers for Disease Control.

Assessment of Interarm differences in Blood Pressure

Blood pressure was assessed after participants were seated for at least 2 minutes, with a standard mercury sphygmomanometer. Research nurses were instructed to ensure each arm was supported during measurements, free of clothing, and only to take

measurements when men appeared relaxed and comfortable. Measurements were made twice in both arms in an alternating sequence: right arm, left arm, right arm, left arm. Standard or large cuffs were used as appropriate. [14] Interarm differences in SBP were similar for the first (M = 1.00 mmHg; 95% CI = 0.76, 1.21) and second pair of assessments (M = 1.05 mmHg; 95% CI = 0.80, 1.29). Readings were averaged to obtain a mean SBP for each arm, which was then used to calculate an interarm difference (mean of right arm minus mean of left arm).

Assessment of Risk Factors for Cardiovascular Disease Mortality

Blood samples were taken in the morning after participants had fasted from 19:00 the previous day. Levels of triglycerides, cholesterol fractions and urinary creatinine were ascertained using a Kodak Ektachem 700 AutoAnalyzer (Eastman Kodak, Rochester, New York). Serum glucose level was determined with an adaptation of the glucose oxidase-peroxidase-chromogen-coupled system for glucose determination in biological fluids. Erythrocyte sedimentation rate (ESR) was measured using the Westergen method. Height and weight were measured from which body mass index (BMI) was calculated.

We defined the metabolic syndrome using a modified version of the Adult Treatment Panel III criteria (using BMI $\geq$30 kg/m^2 instead of waist circumference,

regarded by the WHO as an acceptable substitute).[15, 16] Diabetes status was defined as having a fasting plasma glucose ≥7.0 mmol/L and/or use of medication for diabetes.[17]

Hypertension was defined using the JNC 7 cut-points for systolic/diastolic blood pressure ≥140/≥90 mmHg, or use of antihypertensive medication. [9] Men underwent a separate examination of the peripheral arterial system to calculate the ankle brachial index (ABI) using the Doppler technique. ABI for each leg was calculated by dividing the ankle systolic pressure by the higher of the right and left brachial systolic pressures obtained during this examination, and we used the lower of the left and right leg indices in the analysis, as an indicator of worse disease. Low ABI was defined as ABI ≤0.9. [18]

Scores for the risk of coronary heart disease (CHD) at 10 years were calculated using the Framingham equation with information on age, sex, total cholesterol levels, high-density lipoprotein (HDL) cholesterol levels, SBP, and smoking habits. [12]

Ascertainment of All cause and Cardiovascular Disease Mortality

Information on deaths was collected for 15 years after the 1986 medical examination. Mortality was ascertained using databases supplied by the US army: the Veterans Administration (Beneficiary Identification and Records Locator Subsystem), the Social Security Administration, the Internal Revenue Service, and the National Center for Health Statistics (National Death Index). Events were defined as deaths from all-causes and those resulting from major cardiovascular disease (ICD-9: 390–434,436–448, ICD-

10: I00–I78). A previous analysis found the standardized (for age, race and calendar year) mortality ratios of VES participants were comparable to those of an equivalent US male population. [19]

Statistical Analysis

We compared participants' characteristics using ANOVA, Chi-square (χ^2) and the Kruskall-Wallis test according to interarm differences in SBP of 0 – 4.9, 5 – 9.9, 10 - 14.9 and ≥15 mmHg. We examined the proportional hazards assumption graphically for each interarm difference in SBP with all-cause and CVD mortality and found no evidence for violation. We therefore used Weibull regression analysis to examine the association between interarm differences and mortality (for all causes and cardiovascular disease). This model is a parametric form of the Cox proportional hazards model and accounts for the differing lengths of follow-up among participants. This model also allows researchers to calculate the risk for mortality during a fixed period of time (t) as r(t) $1 - \exp(-\exp[(\log(t) - X\beta)/\sigma])$, where X is the vector of risk factors, β is the vector of coefficients, and σ is the estimated scale parameter. This model has been used previously in the Framingham Heart Study and to describe the effect of adding new risk factors for CVD to the Framingham risk score. [20]

Interarm SBP difference was fitted as a continuous term (per 10 mmHg) and in separate models, using categories of <5 vs. ≥5 mmHg, <10 vs. ≥10 mmHg, and <15 vs. ≥ 15 mmHg. Hazard ratios and accompanying 95% CIs were sequentially adjusted for a

series of potential confounding factors previously associated with peripheral vascular disease [6] and CVD mortality. [21, 22] Adjustments were made for: obesity, smoking status, units of alcohol per week, and ethnic group (model 2); model 2 plus mean SBP and DBP (from the 4 measurements of SBP and DBP), metabolic syndrome, triglyceride, HDL-cholesterol, glucose, ESR and creatinine (model 3); model 3 plus ABI (≤0.9 vs >0.9; model 4); and model 4 plus the Framingham Risk Score (model 5). We modelled an interaction between interarm differences at each cut-point and hypertension status to examine whether associations were different in hypertensive men, as significant associations have been found in hypertensive patients before. [4, 11]

We also calculated the hazards for mortality using a Weibull model that included the Framingham Risk Score and interarm differences in SBP (at ≥5, ≥10, and ≥15 mmHg) and compared it to a model that only included the Framingham Risk Score. We examined discrimination across the 2 models by using Harell's c-index adjusted for optimism using 100 bootstrap repetitions [23]; an overall (likelihood ratio chi-square test) and penalized assessment of model fit (Akaike's Information Criterion [24], and the Bayes Information Criterion) [25]. We chose these measures of discrimination rather than the net reclassification improvement index [26], as there was a low number of deaths in men with high Framingham risk scores.

We then estimated the effect on the hazard ratio of adjusting for a particular covariate using the following formula: ([Hazard Ratio $_{\text{adjusted for age and ethnicity}}$ − 1] −

[Hazard Ratio $_{\text{adjusted for age and ethnicity plus covariate}}$ − 1]/[Hazard Ratio $_{\text{adjusted for age and ethnicity}}$ − 1]) X 100. All analyses were performed with Stata, version 11.0 using 2-sided tests with a significance level of $P<0.05$.

Results

Of the 4462 men eligible for inclusion, 4419 (99.03%) featured in the analytical sample. The 43 men who attended the medical examination but were excluded due to having missing values for some variables had a lower mean DBP (87.01 vs. 84.09 mmHg; P = 0.04) and ESR (41.63 vs. 36.90 mm/h; P = 0.03) but were similar in other respects. Supplementary material online, *eTable 1*, shows that relative to study members not selected for the medical examination, men included in the analytical sample were more likely be obese (12.7 % vs. 11.5%), but generally differences in characteristics between men included and excluded were small.

Table 1 shows the characteristics of the 4419 participants. A total of 1667 (37.7%) men had a mean interarm difference in SBP of ≥5, 435 (9.8%) of ≥10, 107 (2.4%) of ≥15 and 24 (0.5%) of ≥20 mmHg. The mean interarm difference in SBP was 1.03 mm Hg (95% CI = 0.83, 1.22), and was higher in the right arm. Interarm differences in SBP were positively associated with mean SBP (0 – 4.9 mm Hg: M = 122.7 vs. ≥15 mm Hg: M = 128.25; P < 0.001) and DBP (0 – 4.9 mm Hg: M = 83.79 vs. ≥15 mm Hg: M = 85.71; P = 0.01) and differences of 10 and 15mmHg were more common in men with hypertension (P <0.001), an ABI ≤0.9 (P = 0.01), and those who

were obese (P = 0.04). There was, however, no evidence that interarm differences were associated with glucose levels, being defined as having diabetes, or metabolic syndrome (Table 1).

A mean of 14.9 years of follow-up (range 0.03 - 15.00) gave rise to 246 (5.60%) deaths in total of which 64 (26.01%) were due to cardiovascular disease. Table 2 shows that in the unadjusted regression models, the hazard ratios for all cause mortality among men with an interarm difference in SBP of ≥5, ≥10 and ≥ 15mm Hg were 1.30 (95% CI, 1.01 to 1.67), 1.49 (95% CI, 1.04 to 2.14) and 1.37 (95% CI, 0.68 to 2.77) respectively, with stronger associations apparent for cardiovascular disease mortality: for ≥5 mmHg: HR=1.66, 95% CI, 1.02 to 2.71; ≥10 mmHg: HR=1.93, 95% CI: 1.01 to 3.69; ≥15mmHg HR= 2.00, 95% CI, 0.63 to 6.39. When interarm difference was fitted as a continuous term (per 10 mmHg), there was positive association with both all-cause (HR =1.13, 95% CI, 1.01 to 1.27) and cardiovascular disease mortality (HR =1.14, 95% CI, 0.92 to 1.40) in the fully adjusted analysis (see supplementary *eTable 2* online).

Following adjustment for established risk factors for CVD, including the Framingham risk score the adjusted hazard ratios (model 5) for interarm differences of ≥10 mm Hg were significantly attenuated, with hazard ratios of 1.35 (95% CI =0.94 to 1.95) for all-cause and 1.62 (95% CI, 0.84 to 3.14) for cardiovascular disease mortality. Supplementary material online, *eTable 3,* shows separate adjustments for factors associated with lifestyle (smoking status, units of alcohol per week, obesity status) at

the baseline assessment explained little of the attenuating effect on these associations. In general, adjustment for hypertension status (all cause mortality: 6 – 25%), metabolic syndrome (all cause mortality: 6 – 22%), and the Framingham risk score (all cause mortality: 16 – 33%) were associated with the largest percentage reduction in associations between interarm differences and mortality.

Harrell's C-indices indicated a moderate level of discrimination but estimates were not significantly different across the Framingham risk scores and Framingham plus interarm difference models. There was also little change in the penalized measures of model fit between the Framingham risk scores and Framingham plus interarm difference models (see supplementary material online, *eTable 4*). Interactions between interarm differences at 5, 10, and 15 mm Hg and hypertension status were also non-significant at each cut-point for all-cause and CVD mortality ($P>0.05$; data not tabulated).

Discussion

In a cohort of nearly 4500 men, an interarm difference in systolic blood pressure of 10 mmHg or more was associated with an increased risk for cardiovascular disease and all cause mortality. This association was, however, significantly attenuated after adjustment for established cardiovascular disease risk factors. In regard to explanatory factors, smoking status, units of alcohol per week and obesity, played little or no part in

the associations between interarm differences and mortality. Ankle brachial index, a measure of peripheral artery disease, had a small but modest effect on the interarm difference-mortality association. Adjustment for hypertension, metabolic syndrome, and in particular Framingham risk scores at the baseline assessment had the strongest attenuating effects on the interarm difference – mortality association. Consistent with this finding, we found interarm differences did not improve upon the Framingham risk score in the prediction of mortality.

We identified one recent meta analysis [6] and two cohort studies [4, 27] not included in the meta-analysis that examined the association between interarm differences in SBP and all-cause and cardiovascular disease mortality in patients with hypertension[4] and renal disease. [27] A positive association was reported in the meta analysis between all-cause mortality and an interarm difference of 10 mmHg or more in SBP (pooled HR for 2 cohorts = 1.90 (95% CI, 0.8 to 4.7); [8, 11] and two cohorts not included in this meta analysis reported results of a similar magnitude. [4, 27] One cohort of hypertensive patients reported larger hazards for CVD than all-cause mortality after five (HR = 2.8, 95% CI, 0.9 to 9.2) [11] and ten years of follow-up (HR = 4.2, 95% CI, 1.7 to 10.8), [2, 3, 4, 7, 12] with a similar pattern reported in a cross-sectional analysis of patients undergoing haemodialysis.[27] In contrast to these findings, we did not find an association between interarm differences in SBP and mortality. This inconsistency may in part be attributed to our deliberate selection of a low-risk cohort characterized by a comparatively low

prevalence of hypertension, metabolic syndrome and other CVD risk factors. This resulted in a lower event rate and smaller interarm differences than have been reported in previous studies with hypertensive patients. [4, 11] In support of this assertion, we found a lower proportion of men with interarm differences at 10 mmHg or more (13.1 vs. 24.0%) and 15 mmHg or more (3.9 vs. 9.0%)[4] and a lower proportion of deaths in the present cohort (all-cause mortality: 5.4 vs. 25.7%). [4]

Despite these differences in sample characteristics, one study with hypertensive patients reported large hazard ratios for the interarm difference - mortality association even after adjusting for the Framingham risk score (difference of 10 mm Hg in SBP: HR = 2.2; 95% CI = 1.4 to 3.6).[4] This suggests a mechanism by which interarm differences increase the risk for mortality which does not involve factors included in the Framingham risk score; and that this factor was not present in our cohort. Interarm differences have been conceptualised, and are associated with a measure of peripheral artery disease, the ankle brachial index. [1, 2] However, we found a low ABI indicative of peripheral artery disease did not explain associations between interarm differences and mortality. It is therefore possible that the cut-point we used on the ABI lacks predictive validity, or interarm differences are indicative of another comorbidity in hypertensive patients not adequately captured by traditional CVD risk factors.

The strengths of this study are its size, being larger than previous studies on interarm difference, and tracking of participants over a 15-year period. This allowed us

to evaluate the prognostic value of interarm differences over a period in middle age where screening for hypertension typically starts. The non-clinical recruitment meant we could examine associations in a low-risk population for the first time and the comprehensive measurement of CVD risk factors allowed us to address concerns that interarm differences might not add anything over routine CVD risk factor assessment.

This study is not, however, without limitations. First, the sequential method of recording blood pressure we used may have produced larger interarm differences than simultaneous readings. [28, 29] Although, little difference has been found between these methods in estimates of the association of interarm differences with ABI, or all-cause mortality.[6] Second, we did not have data on women, and all investigations to date have been in cohorts in middle to old age, [1,4, 8, 11, 27] thus further testing is needed to confirm associations in these groups. It is also worth noting that despite not adding to the prediction of mortality, assessment of blood pressure in both arms may have clinical value by increasing the sensitivity of diagnosis and management of hypertension through the use of measurements from the arm with the highest reading. Additional studies, ideally a controlled clinical trial, are needed to assess whether incorporating bi-lateral brachial assessments into screening for hypertension in primary care, would improve the identification and management of individuals at risk for a CHD event. In conclusion, we found that interarm differences were associated with survival over a 15 year period in men with a low risk of CVD, but that these associations were explained,

in part, by traditional CVD risk factors. As these risk factors are already part of routine CVD risk screening, interarm differences may not offer anything over established risk prediction algorithms, such as the Framingham risk score, in the prediction of mortality in populations with a low risk of CVD.

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Conflict of interest None declared.

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Table 1. Characteristics of participants according to interarm differences in systolic blood pressure in the Vietnam Experience Study (1986).

	Interarm difference in systolic blood pr		
	0 – 4.9 (n=2752)	5 – 9.9 (n=1 232)	10 – 14.9 (n=328
Continuous variables			
Age (Years), Mean (SD)	38.36 (2.51)	38.27 (2.49)	38.23 (2.57)
Systolic Blood Pressure (mm Hg), Mean (SD)	122.27 (11.57)	123.76 (12.23)	124.27 (12.92)
Diastolic Blood Pressure (mm Hg), Mean (SD)	83.79 (9.20)	84.40 (9.36)	84.98 (10.26)
Glucose (mmol/l), Mean (SD)	5.22 (0.93)	5.21 (0.84)	5.34 (1.47)
Triglycerides (mg/dL), Median (IQR)	1.01 (0.70, 1.51)	1.01 (0.69, 1.46)	1.08 (0.76, 1.57)
HDL Cholesterol (mg/dL), Mean (SD)	1.16 (0.33)	1.15 (0.30)	1.13 (0.29)
Erythrocyte sedimentation rate (mm/h), Mean	36.78 (17.15)	36.71 (17.28)	37.38 (17.13)
Creatinine (mg/dL), Mean (SD)	1.11 (0.18)	1.11 (0.18)	1.10 (0.18)
Alcohol intake (units per week), Median (IQR)	2.00 (0.00, 9.00)	2.00 (0.00, 8.00)	2.00 (0.00, 9.00)
Categorical variables			
Ethnic group, % (Number)			
White	81.9 (2 253)	83.1 (1 024)	78.4 (257)
Black	11.8 (325)	11.5 (142)	12.8 (42)
Other [a]	6.3 (174)	5.4 (66)	8.8 (29)
Hypertension status, % (Number) [b]	27.9 (768)	28.6 (352)	36.0 (118)
Ankle brachial index ≤0.9, % (Number)	3.3 (92)	3.7 (46)	4.3 (14)
Diabetes status, % (Number) [c]	2.1 (57)	1.7 (21)	2.4 (8)
Metabolic syndrome, % (Number) [d]	15.8 (435)	14.5 (179)	18.3 (60)
Obesity, % (Number) [e]	12.1 (334)	12.6 (155)	17.1 (56)
Current smoker, % (Number)	44.1 (1 214)	41.7 (514)	44.8 (147)

[a] Other group = Hispanics, Asians, Pacific Islanders, American Indians, and Alaskan Natives; [b] Normotensive: systolic blood pressure <140mmHg and diastolic blood pressure <90mmHg; Hypertensive: systolic blood pressure >140 mmHg or diastolic blood pressure ≥90 mm Hg or on hypertension medication (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criterion) or any hypertension medication; [c] Fasting blood glucose ≥ 7.0 mmol/l or on medication for diabetes; [d] Modified version of the Adult Treatment Panel III diagnostic criteria using BMI≥30 instead of waist circumference. [e] BMI≥30 kg/m^2. Abbreviations: BMI: body mass index; HDL: high-density lipoprotein; IQR: interquartile range; SD: standard deviation.

Table 2. Unadjusted and adjusted hazard ratios (95 % confidence interval) for all-cause and cardiovascular disease mortality at the cut-points of ≥5, ≥10 or ≥ 15mm Hg in systolic blood pressure (n = 4419)

Model [a]	Interarm difference	All deaths (n=246)			Cardiovascular deaths (n=64)		
		HR	95 % CI	P value	HR	95 % CI	P value
		ref [b]			ref [b]		
1	≥5	1.30	1.01, 1.67	0.04	1.66	1.02, 2.71	0.04
	≥10	1.49	1.04, 2.14	0.03	1.93	1.01, 3.69	0.04
	≥15	1.37	0.68, 2.77	0.38	2.00	0.63, 6.39	0.24
2	≥5	1.30	1.01, 1.67	0.04	1.67	1.02, 2.71	0.04
	≥10	1.43	1.00, 2.06	0.05	1.84	0.96, 3.53	0.07
	≥15	1.53	0.75, 3.09	0.24	2.13	0.67, 6.82	0.20
3	≥5	1.28	0.99, 1.65	0.04	1.61	0.98, 2.64	0.06
	≥10	1.37	0.95, 1.98	0.09	1.69	0.87, 3.25	0.12
	≥15	1.38	0.67, 2.82	0.37	1.86	0.57, 6.04	0.30
4	≥5	1.28	0.99, 1.65	0.06	1.61	0.98, 2.64	0.06
	≥10	1.35	0.94, 1.95	0.11	1.67	0.87, 3.23	0.12
	≥15	1.28	0.62, 2.62	0.50	1.85	0.57, 6.04	0.30
5	≥5	1.28	0.99, 1.65	0.06	1.56	0.95, 2.56	0.08
	≥10	1.35	0.94, 1.95	0.11	1.62	0.84, 3.14	0.15
	≥15	1.28	0.62, 2.63	0.50	1.62	0.49, 5.34	0.43

HR = hazard ratio; CI = confidence interval. [a] Model 1 = Unadjusted; Model 2 = model 1 + BMI ≥30 kg/m^2, smoking status, alcohol intake (units per week), ethnic group; Model 3 = model 2+, systolic blood pressure, diastolic blood pressure, metabolic syndrome, triglycerides, HDL cholesterol, glucose, erythrocyte sedimentation rate; Model 4 = model 3 + ankle brachial index ≤0.9; Model 5 = model 4 + Framingham Risk Score. [b] Reference category = interarm difference in systolic blood pressure <5; <10; <15 depending on the analysis.

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Table 1. Comparison of participants included in the analysis from the medical study (n=4419) to those who only participated in the telephone survey (n = 13 791)

	Included in analytical sample (n=4419)	Telephone survey sample (n= 13 791)	*P* value
Continuous variables			
Age (Years), Mean (SD)	37.92 (2.50)	37.95 (2.47)	0.51
Alcohol intake (units per week), Median (IQR)	2.00 (0.00, 9.00)	2.00 (0.00, 9.00)	0.61
Categorical variables			
Ethnic group, % (Number)			
White	82.0 (3,623)	82.9 (8,928)	
Black	11.7 (517)	10.8 (1,161)	
Other [a]	6.3 (279)	6.3 (677)	0.26
Obesity, % (Number) [e]	12.7 (563)	11.5 (1,241)	0.04
Current smoker, % (Number)	43.3 (1,913)	44.7 (4,811)	0.11

Table 2. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for mortality per 10 mm Hg difference in systolic blood pressure among participants

Model [a]	All deaths (n=246)			Cardiovascular deaths (n=64)		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
1	1.16	1.03, 1.30	0.01	1.66	1.02, 2.71	0.04
2	1.15	1.03, 1.30	0.02	1.20	0.96, 1.50	0.10
3	1.14	1.02, 1.28	0.03	1.16	0.94, 1.43	0.17
4	1.13	1.01, 1.27	0.04	1.16	0.93, 1.43	0.19
5	1.13	1.01, 1.27	0.04	1.14	0.92, 1.40	0.24

[a] Model 1 = Unadjusted; Model 2 = model 1 + BMI ≥30 kg/m^2, smoking status, alcohol intake (units per week), ethnic group; Model 3 = model 2+, systolic blood pressure, diastolic blood pressure, metabolic syndrome, triglycerides, HDL cholesterol, glucose, erythrocyte sedimentation rate; Model 4 = model 3 + ankle brachial index ≤0.9; Model 5 = model 4 + Framingham Risk Score. [b] Reference category = interarm difference in systolic blood pressure <5; <10; <15 depending on the analysis.

Table 3. Unadjusted and adjusted hazard ratios (95 % confidence interval) for all-cause and cardiovascular disease mortality at the cut-points of ≥5, ≥10 or ≥ 15mm Hg in systolic blood pressure (n = 4419) adjusted for CVD risk factors

Model	Interarm difference	All deaths (n=246)			Cardiovascular deaths (n=64)		
		HR	95 % CI	% change [a]	HR	95 % CI	% change [a]
		ref [b]			ref [b]		
Basic model	≥5	1.30	1.01, 1.67		1.66	1.02, 2.71	
(age and ethnicity adjusted)	≥10	1.47	1.02, 2.11		1.87	0.98, 3.59	
	≥15	1.40	0.69, 2.83		1.92	0.60, 6.14	
Basic model plus	≥5	1.30	1.01, 1.68	0	1.67	1.03, 2.74	-1.51
lifestyle	≥10	1.43	0.99, 2.06	9.30	1.82	0.95, 3.52	5.75
	≥15	1.49	0.74, 3.02	-22.5	2.03	0.64, 6.52	-11.96
Basic model plus	≥5	1.28	0.99, 1.65	6.67	1.62	1.00, 2.66	7.58
hypertension status	≥10	1.40	0.98, 2.02	16.28	1.76	0.92, 3.39	12.64
	≥15	1.30	0.64, 2.60	25.00	1.74	0.54, 5.99	19.57
Basic model plus	≥5	1.28	0.99, 1.65	6.67	1.66	1.02, 2.71	0
metabolic syndrome	≥10	1.35	0.93, 1.94	27.90	1.79	0.94, 3.45	9.20
	≥15	1.37	0.68, 2.77	7.5	1.80	0.94, 3.45	13.04
Basic model plus	≥5	1.29	1.00, 1.66	3.4	1.65	1.01, 2.70	3.03
ABI ≤0.9	≥10	1.44	1.01, 2.08	6.97	1.86	0.97, 3.56	1.15
	≥15	1.32	0.65, 2.67	20.00	1.85	0.58, 5.93	7.60
Basic model plus	≥5	1.25	0.98, 1.61	16.67	1.56	0.96, 2.56	15.15
Framingham risk score	≥10	1.38	0.96, 1.98	20.90	1.64	0.86, 3.16	35.94
	≥15	1.27	0.63, 2.57	32.50	1.61	0.50, 5.12	33.70

HR = hazard ratio; CI = confidence interval. [a] ([Hazard Ratio $_{\text{adjusted for age and ethnicity}}$ − 1] − [Hazard Ratio $_{\text{adjusted for age and ethnicity plus covariate}}$ − 1]/[Hazard Ratio $_{\text{adjusted for age and ethnicity}}$ − 1]) X 100.[b] Reference category = interarm difference in systolic blood pressure <5; <10; <15 depending on the analysis.

Table 4. Model Fit and Calibration Estimates for mortality according to interarm differences in systolic blood pressure with and without the addition of Framingham Risk Score (n = 4419)

		All deaths (n=246)			
		Model Fit		Models Penalized for Model Complexity	
Model	**C Index, 95% CI [a]**	**Likelihood Ratio Test**		**Akaike's Information Criterion [b]**	**Bayes Information Criterion [c]**
		χ^2	**P-value**		
FRS	0.60 (0.56, 0.63)	34.89	<0.001	2232.53	2251.71
FRS plus IAD 5	0.60 (0.56, 0.63)	38.10	<0.001	2231.24	2256.81
FRS plus IAD 10	0.60 (0.56, 0.64)	37.85	<0.001	2231.58	2257.16
FRS plus IAD 15	0.60 (0.56, 0.64)	35.19	<0.001	2234.23	2259.81
FRS plus IAD Per 10 mmHg	0.60 (0.56, 0.64)	39.08	<0.001	2230.35	2255.93
		Cardiovascular deaths (n=64)			
FRS	0.70 (0.64, 0.77)	40.40	<0.001	694.90	714.08
FRS plus IAD 5	0.71 (0.64, 0.77)	43.76	<0.001	693.56	719.13
FRS plus IAD 10	0.71 (0.64, 0.78)	42.60	<0.001	694.70	720.28
FRS plus IAD 15	0.70 (0.64, 0.77)	40.98	<0.001	696.32	721.89
FRS plus IAD Per 10 mmHg	0.71 (0.64, 0.77)	41.91	<0.001	695.40	720.97

[a] Harrell's C Index, an adaptation of the C statistic (a generalization of the area under the receiver operating characteristic curve) in logistic models with higher values indicating better discrimination; c-statistics are corrected for over optimisim using from 100 bootstrap repetitions. [b] Akaike's Information Criterion is a likelihood-based measure in which the -2 times the log-likelihood is penalized for the number of predictors in the model. Lower values indicate better prediction. [c] Bayes Information Criterion is similar to Akaike's Information Criterion but imposes a more severe penalty for the number of predictors. Lower values indicate better prediction.

Figure 1. Distribution of interarm differences (mean of right arm minus mean of left arm) in systolic blood pressure