SUPPLEMENTAL MATERIAL

Contents

Supplemental Methods

Measurement of BP and subclinical CVD

At the sixth examination cycle, BP levels were measured twice on the participant's left arm by a Heart Study physician using a mercury column sphygmomanometer and a cuff of appropriate size, after the participant has been seated in a chair for ≥5 minutes. The assessment of subclinical disease traits is described below. To determine the ankle-brachial index (ABI), BP was measured twice on both the arms and at both the ankles, using an 8-MHz Doppler pen probe and an ultrasonic Doppler flow detector (Park Medical Electronics Inc., Shaw, Aloha, Ore), as described in the detail elsewhere.[1] ABI was calculated as the average systolic BP of both ankles divided by the average systolic BP of the arms.[1] Participants also underwent transthoracic echocardiography and M-Mode images were used to determine parameters of left ventricular (LV) structure, including septal wall thickness (SWT), posterior wall thickness (PWT) and LV end-diastolic diameter (LVEDD). Left ventricular mass (in g) was calculated as 0.8(1.04([LVEDD+ PWT + SWT]^3−[LVEDD]^3)) + 0.6 as described by Devereux et al.;[2] and the sex-specific 80th percentile of LV mass was used as cut-point for echocardiographic evidence of LV hypertrophy consistent with prior publications (**Table S1**).[3] LV fractional shortening (defined as ([LVEDD - LV end-systolic diameter]/LVEDD) and visually assessed ejection fraction served as measures of LV systolic function. The excellent reproducibility of our echocardiographic measurements has been previously reported.[4] In addition, a 12-lead electrocardiogram was obtained with participants in supine position. Sex-specific Cornell voltage criteria were used to assess electrocardiographic evidence of LV hypertrophy.[3, 5] Ultrasound of the carotid arteries was performed as described previously.[6] Images of the common carotid artery and of the internal carotid artery were obtained using a 7.5-MHz transducer and a 5.0-MHz transducer, respectively.[6] These images were used to calculate near- and far-wall intima media thickness (IMT). The reproducibility of these measurements was good.[7] Stenoses of the carotid arteries were likewise assessed, with greater 25% stenoses indicating significant narrowing of the carotid artery. IMT values that met or exceeded the sex-specific 80th percentile were defined as increased carotid artery IMT (**Table**

S1).[3] Urinary albumin and creatinine were measured in a spot urine sample obtained in the morning. Urine albumin was assayed using an immunoturbidimetric test (Tinaquant Albumin assay, Roche Diagnostics), urinary creatinine was determined with a modified Jaffe method. Interassay coefficients of variation for urinary albumin and urinary creatinine assays were 7.2% and 2.3%, respectively.[8]

Subclinical disease score

We quantified the cumulative subclinical disease burden by generating a subclinical disease score as reported previously.[3] A detailed description of the score is provided in **Table S1**. In essence, this score is the sum of five dichotomized indices of subclinical atherosclerosis and target organ damage: LV hypertrophy (by ECG or echocardiography); LV systolic dysfunction (by echocardiography), abnormal ultrasound of the carotid arteries (increased IMT or carotid artery stenosis), peripheral artery disease (abnormal ABI) and glomerular endothelial dysfunction (as indicated by microalbuminuria).[3] Thus, the score ranged from 0 (none of the above abnormal) to 5 (all abnormal). In addition to this score, we evaluated the 5 individual components of the score. We also modeled subclinical disease as a binary variable (yes/no). The complete score and its components were available in a subgroup of 1915 participants.

Supplemental Tables

Table S1. Definitions of subclinical vascular disease*[3]

Characteristic	Definition of subclinical disease component	Cut points for subclinical disease presence used in the present study
LV hypertrophy by electrocardiography or echocardiography		
LV hypertrophy by Cornell criteria using electrocardiography	Sum of the R-wave in a VL and the *S* wave in lead V3 exceeding 2.8 mV in men and 2.0 mV in women.[5]	Presence of LV hypertrophy by Cornell criteria using electrocardiography or a height-adjusted LV mass using echocardiography that met or exceeded the sex-specific 80th percentile[9]
LV hypertrophy by echocardiography	LV mass was calculated as $0.8(1.04([IVS+LVEDD+PW]^3-[LVEDD]^3))+0.6g$.[2] LV mass values were then adjusted for height using the ratio of LV mass to height.	
LV systolic dysfunction by echocardiography		
LV systolic dysfunction	LV fractional shortening was calculated as (LVEDD-LVESD)/LVEDD[10]	A fractional shortening of <0.29 by M mode, or by evidence on two-dimensional echocardiography of mild or greater systolic dysfunction on visual assessment in multiple views (corresponding to ejection fraction <50%), or by both criteria.[11]
Carotid ultrasound abnormality		
Increased carotid artery IMT	A composite measure that combined the maximal common carotid artery IMT and maximal internal carotid artery IMT was obtained by averaging these two measurements after standardization (subtraction of the mean and division by the SD for the measurement)[12]	A standardized carotid IMT that met or exceeded the sex-specific 80th percentiles in the sample,[13] an extreme increase of common carotid IMT, or presence of carotid artery stenosis ≥25%
Extreme increase of common carotid artery IMT	An extreme increase of common carotid IMT ≥1 mm[14]	
Carotid artery stenosis ≥25%	Presence of a stenosis of ≥25% in the internal or common carotid artery[13]	
Peripheral arterial disease		
Ankle-brachial index ≤0.9	Defined as the ratio of the average systolic blood pressure at the ankle of each leg divided by the average systolic blood pressure in the arm with the highest blood pressure.	An ankle-brachial index at or below 0.9 in either leg[13, 15]
Glomerular endothelial dysfunction		
Microalbuminuria	An urine albumin-to-creatinine ratio ≥25 μg/mg in men, and ≥35 μg/mg in women[16]	Presence of microalbuminuria according to the definition

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IMT, intima media thickness; LV, left ventricular; SD, standard deviation. *Copyright 2007 American Diabetes Association. From Diabetes®, Vol. 56, 2007; 1718-1726. Reprinted with permission from The American Diabetes Association.

Table S2. Baseline characteristics of the subclinical disease sample by blood pressure group

Blood pressure (in mm Hg) group	<120/80 (N=640)	120/80-140/90 (N=608)	<140/90 on Rx (N=223)	≥140/90 (N=243)	≥140/90 on Rx (N=201)	p for trend
Clinical and biochemical features						
Age, years; mean ± SD	52.9 ± 8.3	57.3 ± 9.1	59.5 ± 8.3	61.3 ± 8.7	65.3 ± 8.4	<0.0001
Women n, (%)	415 (64.8)	349 (57.4)	115 (51.6)	139 (57.2)	110 (54.7)	0.0022
Systolic BP, mmHg; mean ± SD	109 ± 7	128 ± 7	125 ± 10	152 ± 13	155 ± 15	<0.0001
Diastolic BP, mmHg; mean ± SD	68 ± 6	77 ±7	75 ± 8	83 ± 9	82 ± 10	<0.0001
Hypertension treatment, (%)	0 (0.0)	0 (0.0)	223 (100.0)	0 (0.0)	201 (100.0)	<0.0001
Body Mass Index, kg/m^2; mean ± SD	25.9 ± 4.1	27.3 ± 4.5	28.6 ± 5.4	27.7 ± 4.6	28.2 ± 4.4	<0.0001
Smoking, n (%)	117 (18.3)	81 (13.3)	22 (9.9)	34 (14.1)	13 (6.5)	<0.0001
Diabetes, n (%)	11 (1.7)	23 (3.8)	27 (12.1)	19 (7.8)	29 (14.4)	<0.0001
Total cholesterol, mg/dL; mean ± SD	199 ± 36	211 ± 38	202 ± 34	214 ± 38	209 ± 39	<0.0001
HDL cholesterol, mg/dL; mean ± SD	55 ± 15	54 ± 16	49 ± 16	53 ± 16	50 ± 17	<0.0001
Measures of subclinical disease						
Subclinical disease score (unadjusted) mean SD	0.29 ± 0.53	0.47 ± 0.69	0.94 ± 0.94	0.79 ± 0.77	1.17 ± 1.01	<0.0001
Prevalence of subclinical disease (score ≥1), (%)	166 (25.9)	222 (36.5)	136 (61.0)	145 (59.7)	145 (72.1)	<0.0001
LVH, echocardiographically or electrocardiographically, (%)	69 (10.8)	103 (16.9)	82 (36.7)	65 (26.8)	80 (39.8)	<0.0001
LV systolic dysfunction, (%)	16 (2.5)	17 (2.8)	14 (6.3)	6 (2.5)	9 (4.5)	0.1403
Carotid ultrasound abnormality, (%)	5 (0.8)	14 (2.3)	14 (6.3)	22 (9.1)	21 (10.5)	<0.0001
Peripheral artery diseas (ABI ≤ 0.9), (%)	2 (0.3)	7 (1.2)	7 (3.1)	4 (1.7)	9 (4.5)	<0.0001
Microalbuminuria, (%)	37 (5.8)	32 (5.3)	31 (13.9)	28 (11.5)	37 (18.4)	<0.0001

Rx indicates blood pressure lowering medication; BP, blood pressure; SD, standard deviation; HDL, high-density lipoprotein; GFR, glomerular filtration rate

Table S3. Hazard ratio for incident CVD in different statistical models, with and without adjustment for a propensity score

	BP group	BP treatment	HR (95% CI)*	HR (95% CI)**	HR (95% CI)+	HR (95% CI)** +	HR (95% CI)***
1	**<120/80**	No	1	1	1	1	1
2	**120/80≤140/90**	No					
3	**<140/90**	Yes	1.64 (1.25, 2.15)	1.50 (1.13, 1.99)	1.58 (1.18, 2.12)	1.46 (1.09, 1.94)	1.17 (0.79, 1.75)
4	**≥140/90**	No	1	1	1	1	1
5	**≥140/90**	Yes	1.32 (0.98, 1.77)	1.28 (0.94, 1.73)	1.24 (0.92,1.68)	1.27 (0.94, 1.72)	1.05 (0.72, 1.54)

*adjusted for age and sex

** adjusted for age, sex, total/HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use and estimated glomerular filtration rate

+ adjusted for the propensity score only

**+ adjusted for age, sex, total/HDL cholesterol, intake of lipid-lowering medication, smoking, diabetes, aspirin use, estimated glomerular filtration rate and the propensity score

*** adjusted for age, sex, total/HDL cholesterol, intake of lipid-lowering medication, smoking, and diabetes, aspirin use, estimated glomerular filtration rate, duration of hypertension and duration of hypertension treatment

Supplemental Figures

Figure S1. Multivariable-adjusted Relative Risks for presence of subclinical disease (score ≥1) by blood pressure group

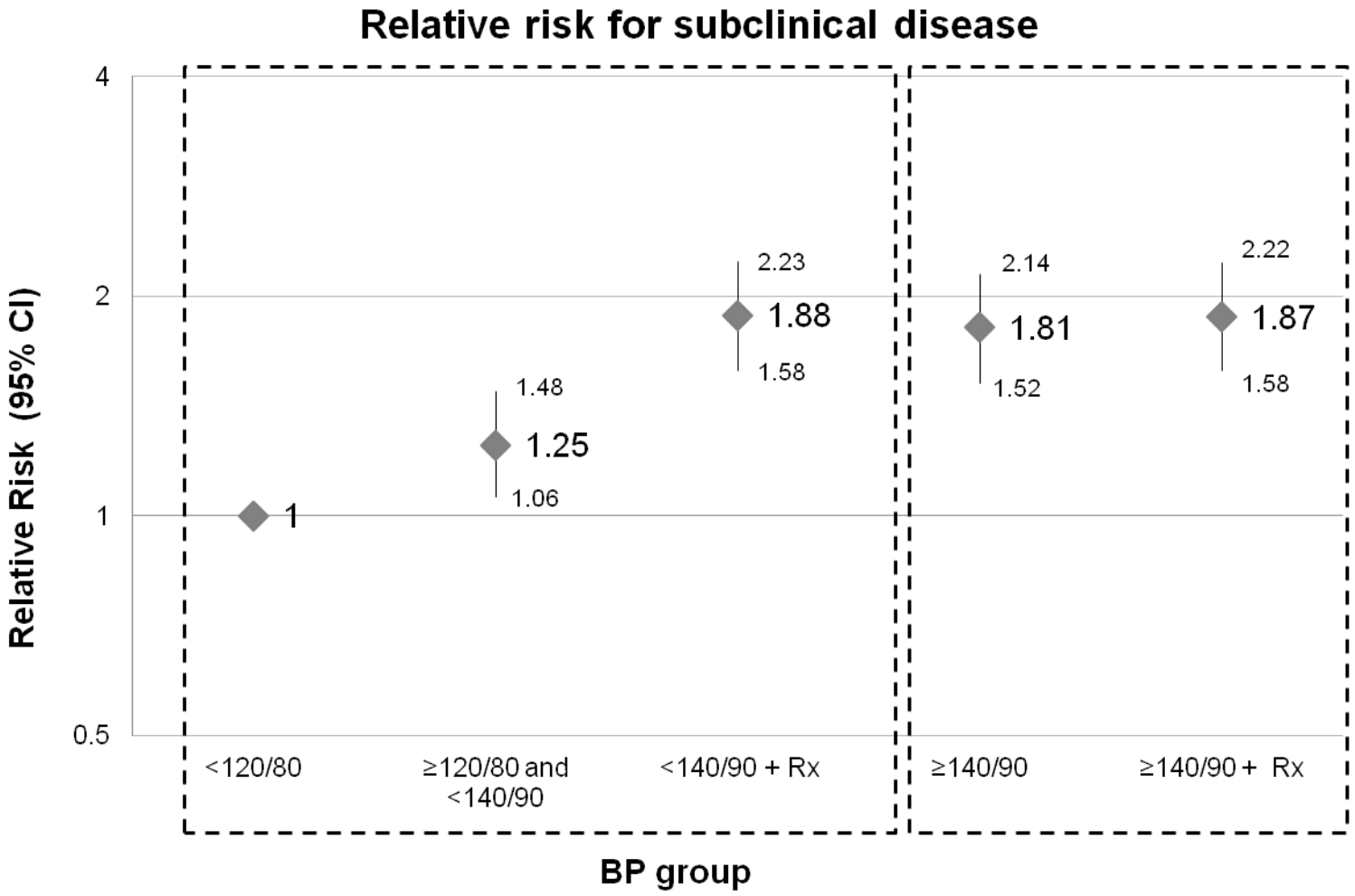
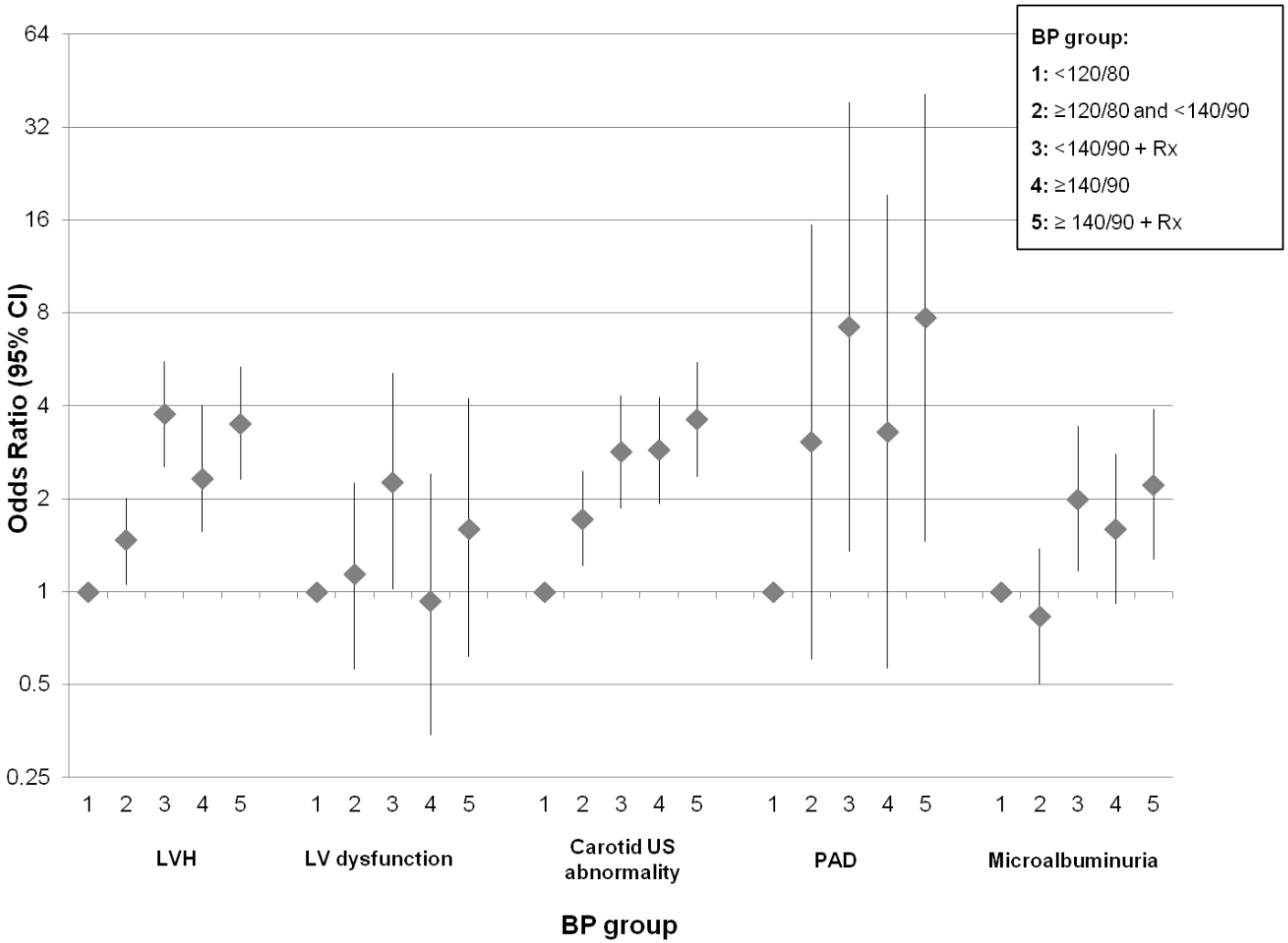


Figure S2. Odds ratio for select subclinical disease abnormalities, stratified by BP group



LVH, left ventricular hypertrophy; LV, left ventricular; US, ultrasound; PAD, peripheral artery disease

Supplemental References

1. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: The framingham study. *Arch Intern Med*. 2003;163:1939-1942.
2. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol*. 1986;57:450-458.
3. Ingelsson E, Sullivan LM, Murabito JM, Fox CS, Benjamin EJ, Polak JF, Meigs JB, Keyes MJ, O'Donnell CJ, Wang TJ, D'Agostino RB, Sr., Wolf PA, Vasan RS. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. *Diabetes*. 2007;56:1718-1726.
4. Sundstrom J, Sullivan L, Selhub J, Benjamin EJ, D'Agostino RB, Jacques PF, Rosenberg IH, Levy D, Wilson PW, Vasan RS. Relations of plasma homocysteine to left ventricular structure and function: The framingham heart study. *Eur Heart J*. 2004;25:523-530.
5. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: Validation with autopsy findings. *Circulation*. 1987;75:565-572.
6. Maas R, Xanthakis V, Polak JF, Schwedhelm E, Sullivan LM, Benndorf R, Schulze F, Vasan RS, Wolf PA, Boger RH, Seshadri S. Association of the endogenous nitric oxide synthase inhibitor adma with carotid artery intimal media thickness in the framingham heart study offspring cohort. *Stroke*. 2009;40:2715-2719.
7. Fox CS, Cupples LA, Chazaro I, Polak JF, Wolf PA, D'Agostino RB, Ordovas JM, O'Donnell CJ. Genomewide linkage analysis for internal carotid artery intimal medial thickness: Evidence for linkage to chromosome 12. *Am J Hum Genet*. 2004;74:253-261.

8. Lieb W, Pencina MJ, Wang TJ, Larson MG, Lanier KJ, Benjamin EJ, Levy D, Tofler GH, Meigs JB, Newton-Cheh C, Vasan RS. Association of parental hypertension with concentrations of select biomarkers in nonhypertensive offspring. *Hypertension*. 2008;52:381-386.

9. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med*. 2006;355:138-147.

10. Quinones MA, Pickering E, Alexander JK. Percentage of shortening of the echocardiographic left ventricular dimension. Its use in determining ejection fraction and stroke volume. *Chest*. 1978;74:59-65.

11. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, Levy D. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: The framingham heart study. *JAMA*. 2002;288:1252-1259.

12. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study collaborative research group. *N Engl J Med*. 1999;340:14-22.

13. Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN, O'Leary DH, Savage PJ, Tell GS, Tracy R. Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation*. 1995;92:720-726.

14. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: The atherosclerosis risk in communities (aric) study, 1987-1993. *Am J Epidemiol*. 1997;146:483-494.

15. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the framingham offspring study. *Am Heart J*. 2002;143:961-965.

16. Karalliedde J, Viberti G. Microalbuminuria and cardiovascular risk. *Am J Hypertens*. 2004;17:986-993.