BMJ Open

Racial/ethnic heterogeneity in associations of blood pressure and incident cardiovascular disease by functional status in a prospective cohort: the Multi-Ethnic Study of Atherosclerosis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017746
Article Type:	Research
Date Submitted by the Author:	24-May-2017
Complete List of Authors:	Kaiser, Paulina; Oregon State University, College of Public Health & Human Sciences Peralta, Carmen; University of California San Francisco Department of Medicine Kronmal, Richard; University of Washington Department of Statistics, Collaborative Health Studies Coordinating Center Shlipak, Michael; University of California San Francisco School of Medicine Psaty, Bruce; University of Washington, Cardiovascular Health Research Unit; Kaiser Permanente Washington Health Research Institute Odden , MC ; Oregon State University, School of Biological and Population Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Public health
Keywords:	blood pressure, epidemiology of cardiovascular disease, physical function

Title: Racial/ethnic heterogeneity in associations of blood pressure and incident cardiovascular disease by functional status in a prospective cohort: the Multi-Ethnic Study of Atherosclerosis

Authors:

Paulina Kaiser*, School of Biological and Population Health Sciences, Oregon State University; Corvallis, OR, USA

Carmen A. Peralta, Department of Medicine, Department of Epidemiology and Biostatistics, University of California, San Francisco; San Francisco, CA, USA

Richard Kronmal, Department of Biostatistics, University of Washington; Seattle, WA, USA

Michael G. Shlipak, General Internal Medicine Section, Veterans Affairs Medical Center, and the Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco; San Francisco, CA, USA

Bruce M. Psaty, Cardiovascular Health Research Unit, University of Washington and Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA

Michelle C. Odden, School of Biological and Population Health Sciences, Oregon State University; Corvallis, OR, USA

***Corresponding author:**

Paulina Kaiser
155 Milam Hall
Oregon State University
Corvallis, OR 97331
Paulina.kaiser@oregonstate.edu
541-737-5522

Abstract

Objectives: Research has demonstrated that the association between high blood pressure and outcomes is attenuated among older adults with functional limitations, compared to healthier elders. However, it is not known whether these patterns vary by racial/ethnic group. We evaluated race/ethnicity-specific patterns of effect modification in the association between blood pressure and incident cardiovascular disease by functional status.

Setting: We used data from the Multi-Ethnic Study of Atherosclerosis (2002-2004, with an average of 8.8 years of follow up for incident cardiovascular disease). Functional status was assessed by self-reported physical limitations.

Participants: The study included 6,117 participants (aged 46 to 87; 40% white, 27% black, 22% Hispanic, and 12% Chinese) who did not have cardiovascular disease at the second study exam (when self-reported physical limitations were assessed).

Outcome measures: Incident cardiovascular disease was defined as an incident myocardial infarction, coronary revascularization, resuscitated cardiac arrest, angina, stroke (fatal or non-fatal), or CVD death.

Results: We observed weaker associations between systolic blood pressure and cardiovascular disease among white adults with low functional status (e.g. IRR per 10-mmHg higher systolic blood pressure among those without and with physical limitations, 1.29 [95% CI: 1.19, 1.40] vs. 1.09 [0.99, 1.20], p-value for interaction, <0.01). We found a similar pattern among black, but not Hispanic or Chinese, adults. The attenuated associations were consistent across both multiplicative and additive scales.

Conclusion: Attenuated associations between high blood pressure and incident cardiovascular disease were not consistent across racial/ethnic groups, though small sample sizes remain a limitation. Identifying the characteristics that distinguish those in whom high SBP is associated with varying risk of morbidity or mortality may inform our understanding of the consequences of hypertension among older adults.

Keywords: blood pressure, epidemiology of cardiovascular disease, physical function

Strengths and limitations of this study:

- The Multi-Ethnic Study of Atherosclerosis is the largest cohort of middle aged and older adults in the US from four racial/ethnic groups (white, black, Hispanic, and Chinese).
- We used self-reported physical limitations as the primary measure of functional status, and chronological age as a comparative measure.

- Small sample size among some racial/ethnic groups limited the precision of our estimates.
- Additional research is needed to investigate patterns of SBP and CVD risk among diverse minority populations, and understand the underlying biological mechanisms.

High blood pressure is a major cause of morbidity and mortality among American adults, and is responsible for an estimated $49 billion in direct and indirect costs per year.[1] However, the risks of cardiovascular events associated with high blood pressure are not consistent for all adults. Previous research has shown that among older adults with functional limitations, measured by slow gait speed[2,3] or by limitations in activities of daily living,[4,5] the association between high blood pressure and morbidity and mortality is attenuated compared to healthier elders. However, it is not yet clear which factors can best discriminate between those at high risk and low risk of blood pressure-related cardiovascular events.

Additionally, it is plausible that the patterns of blood pressure, frailty, and morbidity and mortality vary by racial/ethnic group. Race/ethnicity, as a proxy for biological characteristics as well as life-long contextual influences, cultural norms, and cumulative stressors,[6] is associated with blood pressure levels and with rates of cardiovascular disease (CVD). For example, a 10-mmHg higher systolic blood pressure level is associated with a larger increase in stroke risk for blacks than for whites.[7] Our objective was to explore racial/ethnic heterogeneity in the interaction of blood pressure and functional status on CVD outcomes.

Methods

Study population

We used data from the Multi-Ethnic Study of Atherosclerosis (MESA) to explore race/ethnicity-specific patterns of effect modification in the association between blood pressure and incident CVD by functional status.

MESA includes 6,814 adults aged 45-84 who self-identified as white, black, Hispanic, or Chinese from six areas across the U.S. (New York, New York; Baltimore, Maryland; Forsyth

County, North Carolina; Chicago, Illinois; St Paul, Minnesota; and Los Angeles, California). White participants were recruited at all sites; black participants were recruited at all sites except for Minnesota. Hispanic participants came from New York, Minnesota, and California, and Chinese participants came from Chicago and California. Participants were excluded if they had a history of heart attack, angina, stroke or transient ischemic attack, heart failure, resuscitated cardiac arrest, or procedures related to cardiovascular disease. Participants were followed from 2000-2002 until 2010-2012, with a total of five study exams. Retention was 92.4% from the first exam to the second exam, and 75.7% from the fourth exam to the final exam.[8] The study was approved by the institutional review board at each participating site, and participants provided informed consent.[9]

Exposure: systolic blood pressure

Blood pressure was measured at each exam, following a standardized protocol. After five minutes of seated rest, systolic (SBP) and diastolic (DBP) blood pressures were measured three times, at two-minute intervals, using an automated oscillometric sphygmomanometer.[10] The average of the second and third measurements were used for analysis. We used SBP measured at the second exam (2002-2004) as the primary exposure of interest, because physical limitations were not assessed at the baseline exam.

Effect modifier: functional status

The primary measure of functional status for this analysis was self-reported physical limitations. Physical limitations were assessed at Exam 2, in 2002-2004, and measured with two questions based off the same prompt: "During the past 4 weeks, have you had any of the

following problems with your work or other regular daily activities as a result of your physical health?" Participants were considered to have physical limitations if they answered 'yes' to either "You accomplished less than you would have liked to" or "You were limited in the kind of work you do or other regular daily activities."

As a comparative measure, we used chronological age (measured in calendar years) as a crude proxy for functional status. Chronological age has been shown to be inferior to measures of biological age in predicting mortality,[11] but is often used in clinical risk calculators and policy guidelines. As a secondary analysis, we used summary scores from a modified version of the 12-Item Short Form Health Survey (SF-12) (version 2)[12] to measure overall physical health and well-being. The SF-12 survey is a shortened version of the SF-36 scale and has been validated in a variety of settings.[13,14] The Physical Component Summary score (SF12-P) is a weighted average of questions about general health, limitations in moderate activities or climbing stairs, physical limitations, emotional limitations, pain interfering with work, feeling downhearted and blue, and health interfering with social activities. SF12-P scores range from 0-100 and are standardized so that a score of 50 reflects the average of the general U.S. population.[15] The SF12-P scale was used as a secondary analysis because it includes the physical limitation questions described above, in addition to other covariates that were less related to the underlying construct of functional status.

Outcome: incident cardiovascular disease

The outcome of interest was incident CVD, measured through the end of 2012. MESA participants were contacted every 9 to 12 months and asked about interim cardiovascular events. Medical records, death certificates, and next-of-kin interviews (for out-of-hospital cardiovascular

deaths) were used by a team of two study cardiologists, cardiovascular epidemiologists, or neurologists to determine the date of incident CVD.[16] CVD was defined as an incident myocardial infarction, coronary revascularization, resuscitated cardiac arrest, angina, stroke (fatal or non-fatal), or CVD death.[17]

Covariates

All covariates were measured at the second exam (2002-2004). Demographic confounders included age, sex, and income. Income was dichotomized for this analysis at earning $75,000 per year. Additional covariates included smoking (never, former, or current smoker), body mass index (BMI), total cholesterol, diabetes status, and medication use. Diabetes status was categorized as normal, impaired fasting glucose or untreated diabetes, and treated diabetes based on the 2003 American Diabetes Association fasting criteria algorithm. Medications (antihypertensives and statins) were assessed by visual inspection of medication containers by study personnel or by self-report.

Statistical methods

We first stratified the study population by race/ethnicity, and summarized blood pressure, functional status, and other covariates within each racial/ethnic group. Then we used Poisson models to estimate the incident rate ratios (IRR) for incident CVD per 10 mmHg higher SBP, by including time to the first event as an offset. All models were adjusted for age, sex, and income. A likelihood ratio test provided evidence for a 3-way interaction (on a multiplicative scale) between race/ethnicity, functional status, and SBP, so we present models stratified on

race/ethnicity. Within the race/ethnicity-stratified models, we also tested a two-way interaction term between SBP and functional status.

We explored the impact of adjusting for additional covariates (smoking, diabetes, antihypertensive medication, statins, total cholesterol, DBP, and BMI) among white and black subgroups only, due to limited sample size. Due to conceptual concern over distinguishing confounders from mediators in the joint effects of SBP and functional status on CVD, we present the minimally-adjusted models as our primary results.

We also explored the relationship between SBP and CVD by functional status on an additive scale, because departures from multiplicativity may result from different baseline levels of risk in the subgroups of interest. We used Poisson models to estimate incident rates of CVD by quintile of SBP stratified by race/ethnicity and functional status, and graphed the estimated rates to visualize the patterns. We then used multivariable regression spline models to identify the best-fit form of the association between SBP and CVD.

As a comparison, we ran a similar set of analyses using DBP instead of SBP as the primary exposure.

Results

Our analysis included 6,117 participants who attended Exam 2 but did not have prevalent CVD at Exam 2. The analytic sample ranged in age from 46 to 87. Participants were followed for up to 10 years (until time of CVD incidence, death, or loss to follow-up; average of 8.8 years), during which time there were 557 incident cases of CVD detected.

White participants were older than members of other racial/ethnic groups, and had higher average education and income levels (Table 1). Black participants had the highest mean SBP

and were most likely to be on anti-hypertensive medications. Black participants were most likely to report physical limitations, while white participants were most likely to be diagnosed with CVD during follow-up.

We observed a generally weaker association between SBP and CVD among low-functioning subgroups (those with physical limitations or over age 65) compared to high-functioning subgroups (Table 2). This pattern was most apparent among white participants, though there was a similar pattern among black participants that did not reach statistical significance for the interaction of SBP and physical limitations. Among Hispanic and Chinese participants, the association between SBP and CVD appeared not to be modified by measures of functional status. Among all racial/ethnic groups, higher SBP was associated with higher incidence of CVD.

The estimated CVD incidence rates by quintile of SBP revealed more nuances about the race/ethnicity-specific associations between SBP, functional status, and CVD. In Figure 1, the slope across SBP quintiles represents the average incidence rate difference (IRD) per quintile. Though age was modeled continuously, we estimated incidence rates at the 1st and 3rd quintiles (age 54 and 70, respectively) to illustrate differences.

Among all racial/ethnic groups, the incidence of CVD was higher among low-functioning subgroups than high-functioning subgroups. Spline models confirmed that a linear fit was appropriate for the association between SBP and CVD in all subgroups. Among white participants, the association between SBP and CVD appeared weaker among those with physical limitations compared to those without physical limitations. However, the average IRD across quintiles of SBP was slightly larger among older whites compared with younger whites. Among black participants, the association of SBP and CVD was weaker both among participants with

physical limitations and among older participants, compared to those without physical limitations and younger participants respectively. Among Hispanic participants, those with low functional status had higher incidence rates and larger IRDs for SBP than those with high functional status. Large confidence intervals limit generalizations among Chinese participants.

Adjustment for additional covariates resulted in generally attenuated but consistent results (Figure 2). Among both white and black participants, the adjusted association of SBP with CVD risk was statistically significant among those with high functional status, but approached unity in those with low functional status. Patterns with DBP were also broadly consistent to those with SBP, but with smaller magnitude of differences (results not shown); likelihood ratio tests of three-way interactions provided evidence of racial/ethnic differences in the linear, multiplicative association between DBP and CVD (p=0.04 for physical limitations and p=0.01 for age) but within-racial/ethnic group tests for interaction by functional status were non-significant (e.g. for whites, IRR for interaction between DBP and physical limitations = 0.93, p=0.55; for blacks, IRR = 0.80, p=0.18). Using SF12-P scores to measure functional status produced similar patterns to those in Figure 1 but with smaller differences between low-functioning and high-functioning groups (Appendix Figure 1).

Discussion

We observed attenuated associations between SBP and incident CVD among those with low functional status (measured by self-reported physical limitations and by chronological age) among white and black adults, but not among Hispanic or Chinese adults. This pattern appeared to be consistent across both multiplicative and additive scales using self-reported physical limitations, but not age. Our findings are consistent with previous research that has found

attenuated or inverted associations between blood pressure and health outcomes among low-functioning subgroups (defined by age, walking speed, or limitations in activities of daily living).[2-5]

Blood pressure treatment guidelines and randomized controlled trials have frequently used age to define treatment targets or populations of interest.[18-21] Chronological age is an imprecise measure of functional status, though it is easily and routinely collected. Others have recognized the limitations of relying on chronological age to predict health-related outcomes.[11] Among white participants, using self-reported physical limitations as a measure of functional status provided consistent evidence of attenuated associations between SBP and incident CVD across multiplicative and additive scales, while chronological age did not. Where feasible, physical limitations and other specific measures of functional status may be more useful than chronological age in estimating risk.

We observed no apparent patterning of SBP and CVD by functional status among Hispanics or Chinese participants. For Chinese participants, the small sample size is likely a key limitation for distinguishing patterns by functional status. For Hispanic participants, associations between SBP and CVD were similar by functional status on a multiplicative scale, and on an additive scale appeared to be stronger (larger average IRDs across quintiles) for low-functioning groups than high-functioning groups. Previous research in a Hispanic population found that the association between SBP and all-cause mortality was attenuated among slow walkers compared to fast walkers;[2] however, these participants were older (mean age 70.5 years) and less healthy overall (mean SBP 139 mmHg, 22.8% on diabetes medication) than MESA's Hispanic participants (mean age 62.7 years, mean SBP 125 mmHg, 16.3% on diabetes medication).

Future research should continue to investigate patterns of SBP and CVD risk among diverse minority populations.

Additionally, more research is needed to inform how observed differences in CVD risk associated with SBP should influence treatment of high blood pressure. The biologic mechanism mediating an attenuated association between high blood pressure and outcomes among low functioning older adults remains uncertain, although there are several plausible explanations. Poor physical functioning may be associated with compromised hemodynamic regulation, vascular stiffening, and insufficient cerebral, myocardial, or renal perfusion. Others have noted the challenges in accurate measurement of blood pressure in older adults, due to orthostatic hypotension, pseudohypertension, and postprandial hypertension.[22] Another possibility is that treatment of high blood pressure, which often requires multiple medications, could result in polypharmacy or other adverse events such as falls and fractures,[23] and these adverse events could initiate a cascade of events that could result in hospitalization, morbidity, and even death. Our analysis shows that future studies that evaluate treatment benefits should examine the role of race/ethnicity as well as functional status.

The presence of racial/ethnic variation in associations between SBP, incident CVD, and functional status do not imply biologically predetermined differences in risks; rather, our findings should caution against generalizing results from predominantly white study populations to other racial/ethnic populations. The observed differences that we found are likely the result of broad social and environmental influences throughout the life course that are strongly patterned by racial/ethnic identity in the U.S. However, these findings are also novel and, if replicated, much more research is needed to understand the causal pathways resulting in racial/ethnic heterogeneity in associations between SBP, functional status, and CVD.

In summary, we found that the risks associated with high blood pressure appear to be attenuated among some adults with poor functional status. In a diverse cohort of middle aged and older adults, we observed distinct racial/ethnic patterning in the influence of functional status on associations between SBP and incident CVD. Additionally, using self-reported physical limitations as a measure of functional status provided consistent results across multiplicative and additive scales, in contrast to using chronological age to measure functional status. Identifying the characteristics that best distinguish those in whom high blood pressure does not substantially increase risk of morbidity or mortality may inform our understanding of the consequences of hypertension among older adults.

Acknowledgments

Table 1. Characteristics of analytic sample at MESA Exam 2 by race/ethnicity

	White	Black	Hispanic	Chinese	p-value
N=	2421	1659	1320	717	
Age (yrs)	64.1	63.5	62.7	63.3	<0.01
Female	51.6%	54.9%	52.3%	51.3%	0.17
Income					
<$16,000	10.0%	19.9%	38.6%	44.5%	
$16,000 - $39,999	21.2%	32.0%	35.3%	22.4%	
$40,000 - $74,999	30.9%	30.1%	18.6%	15.4%	
$75,000+	37.8%	18.0%	7.5%	17.7%	<0.01
BMI (kg/m$^{2)}$	27.7	30.1	29.6	24.1	<0.01
Current smoker	10.9%	16.0%	10.2%	5.6%	<0.01
DBP (mmHg)	68.9	73.5	70.1	69.3	<0.01
Total cholesterol (mg/dL)	192.8	188.4	194.1	189.9	<0.01
Taking statins	23.5%	18.8%	16.6%	17.2%	<0.01
Diabetes					
Impaired fasting glucose	17.9%	20.1%	21.7%	20.6%	
Treated diabetes	5.9%	16.6%	16.6%	11.2%	<0.01
Taking anti-hypertension medication	37.8%	54.0%	37.3%	32.1%	<0.01
SBP, mean	121.0	130.2	125.0	120.7	<0.01
SBP quintiles					
Quintile 1 (60-107 mmHg)	24.3%	12.2%	20.7%	27.8%	
Quintile 2 (107.5-116.5 mmHg)	23.3%	16.8%	20.2%	19.4%	
Quintile 3 (117-127 mmHg)	19.2%	19.8%	18.7%	18.0%	
Quintile 4 (127.5-141 mmHg)	19.0%	23.7%	20.0%	18.6%	
Quintile 5 (141.5-230 mmHg)	14.2%	27.6%	20.5%	16.3%	<0.01
Self-reported physical limitations	26.4%	31.7%	27.2%	20.8%	<0.01
Accomplish less than like	23.1%	27.8%	24.6%	19.1%	
Limited in daily work	17.2%	20.7%	21.8%	16.5%	
SF12-P score	49.9	47.8	47.9	48.9	<0.01
Incident CVD	10.2%	8.9%	9.2%	5.7%	<0.01
Mean time to CVD or end of follow-up (yrs)	8.9	8.6	8.7	9.0	<0.01

Table 2. Estimated associations (IRR[1] per 10-mmHg higher SBP) between SBP and incident CVD by measures of functional status and racial/ethnic group.

		No physical limitations	With physical limitations	Age <65	Age >= 65
Overall	N=	4446	1671	3218	2899
	IRR	1.21	1.10	1.30	1.11
	95% CI	1.16-1.27	1.03, 1.17	1.22, 1.39	1.06, 1.17
	P-value for interaction	0.04		<0.01	
White	N=	1783	638	1229	1192
	IRR	1.29	1.09	1.33	1.17
	95% CI	1.19, 1.40	0.99, 1.20	1.18, 1.49	1.01, 1.07
	P-value for interaction	<0.01		<0.01	
Black	N=	1134	525	864	795
	IRR	1.25	1.10	1.36	1.10
	95% CI	1.14, 1.37	0.96, 1.25	1.22, 1.52	1.00, 1.21
	P-value for interaction	0.14		<0.01	
Hispanic	N=	961	359	740	580
	IRR	1.11	1.10	1.13	1.08
	95% CI	1.00, 1.23	0.95, 1.27	0.97, 1.31	0.98, 1.19
	P-value for interaction	0.89		0.66	
Chinese	N=	568	149	385	332
	IRR	1.21	1.23	--[3]	1.10
	95% CI	1.01, 1.44	0.95, 1.58	--[3]	0.94, 1.29
	P-value for interaction	0.93		--	
Three-way interaction across racial/ethnic groups[2]		<0.01		<0.01	

[1] *From Poisson models with offset for person-time contributed; all models adjusted for age, gender, and income*
[2] *Based on a likelihood ratio test of nested models*
[3] *Omitted due to small number of events (<10)*

Contributorship statement

Dr. Kaiser developed the initial research question, conducted all analyses and drafted the manuscript. Dr. Odden provided oversight, including review of analyses and editing the manuscript. Drs. Peralta, Kronmal, Shlipak, and Psaty reviewed results and provided guidance on interpretation, and provided comments on multiple drafts of the manuscript.

Competing interests

The authors have no competing interests.

Funding

This research was supported by grants K01AG039387 and R01AG46206 from the National Institute on Aging; contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute; and grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from NCATS.

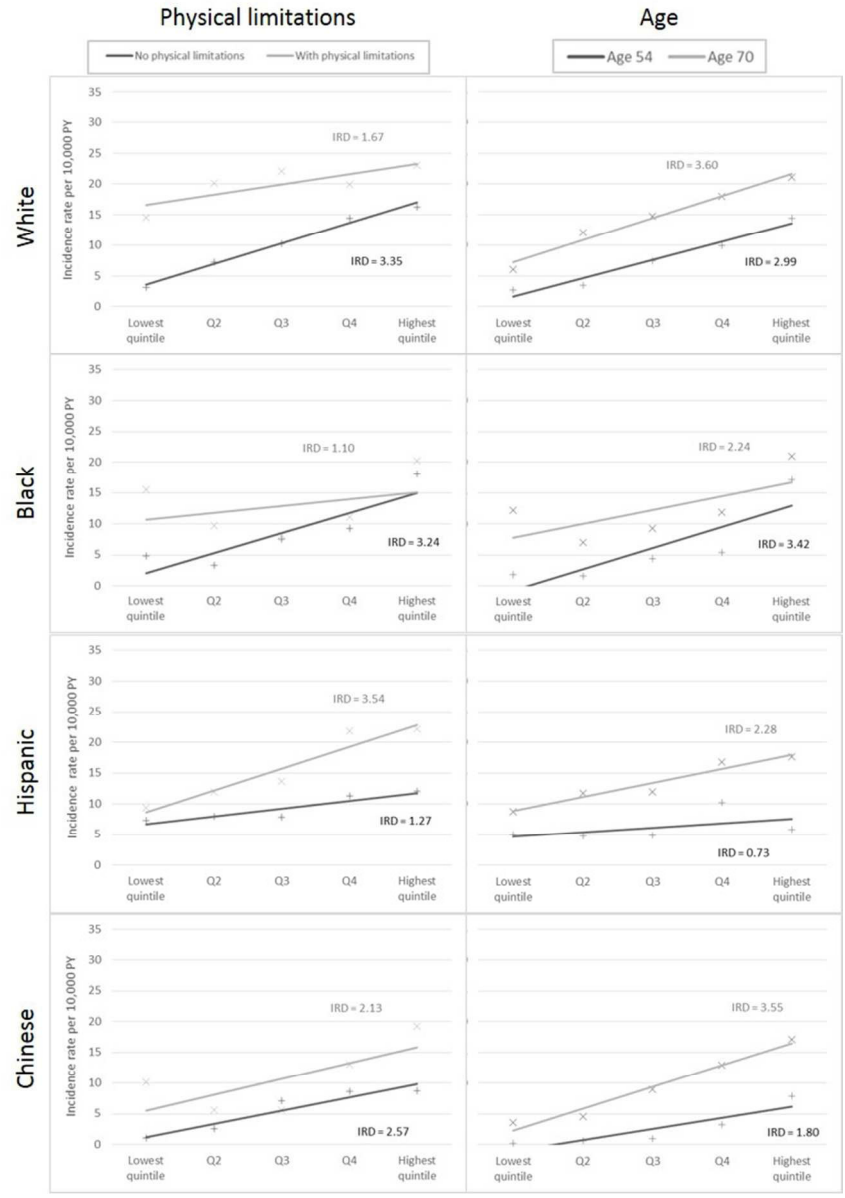
Data sharing statement

No additional unpublished data are available. More information about MESA, including all participating MESA investigators and institutions, can be found at http://www.mesa-nhlbi.org.

References

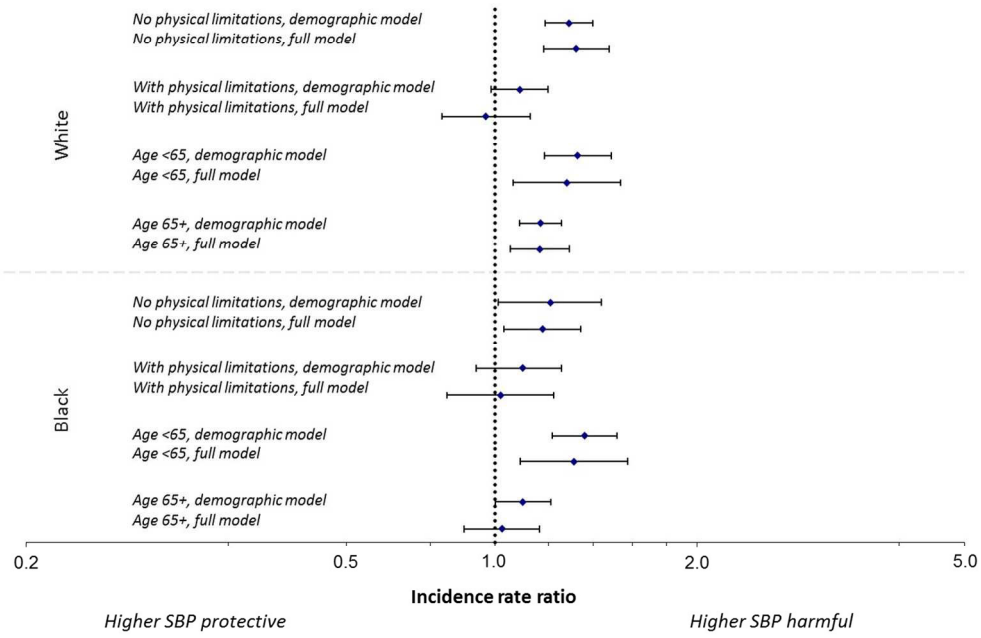
1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2016 Update A Report From the American Heart Association. *Circulation.* 2015:CIR. 0000000000000350.
2. Odden MC, Covinsky KE, Neuhaus JM, Mayeda ER, Peralta CA, Haan MN. The association of blood pressure and mortality differs by self-reported walking speed in older Latinos. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2012;67(9):977-983.
3. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Archives of internal medicine.* 2012;172(15):1162-1168.
4. Peralta CA, Katz R, Newman AB, Psaty BM, Odden MC. Systolic and Diastolic Blood Pressure, Incident Cardiovascular Events, and Death in Elderly Persons The Role of Functional Limitation in the Cardiovascular Health Study. *Hypertension.* 2014;64(3):472-480.
5. Windham BG, Griswold ME, Lirette S, et al. Effects of Age and Functional Status on the Relationship of Systolic Blood Pressure With Mortality in Mid and Late Life: The ARIC Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2015:glv162.
6. Geronimus AT, Hicken M, Keene D, Bound J. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *American journal of public health.* 2006;96(5):826-833.
7. Howard G, Lackland DT, Kleindorfer DO, et al. Racial differences in the impact of elevated systolic blood pressure on stroke risk. *JAMA internal medicine.* 2013;173(1):46-51.
8. Christine PJ, Auchincloss AH, Bertoni AG, et al. Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the multi-ethnic study of atherosclerosis (MESA). *JAMA internal medicine.* 2015;175(8):1311-1320.
9. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *American journal of epidemiology.* 2002;156(9):871-881.
10. Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. *Circulation.* 1993;88(5):2460-2470.
11. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2013;68(6):667-674.
12. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care.* 1996;34(3):220-233.
13. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *Journal of Public Health.* 1997;19(2):179-186.
14. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *Journal of clinical epidemiology.* 1998;51(11):1171-1178.
15. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. *How to score version 2 of the SF-12 health survey (with a supplement documenting version 1).* QualityMetric Incorporated; 2002.
16. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Archives of internal medicine.* 2008;168(12):1333-1339.
17. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study the multi-ethnic study of atherosclerosis. *Circulation.* 2009;120(6):502-509.

18. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama.* 2014;311(5):507-520.
19. Group SR. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;2015(373):2103-2116.
20. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine.* 2008;358(18):1887-1898.
21. Trialists'Collaboration BPLT, Turnbull F, Neal B, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Bmj.* 2008;336(7653):1121-1123.
22. Morley JE. Systolic hypertension should not e treated in persons aged 80 and older until blood pressure is greater than 160 mmHg. *Journal of the American Geriatrics Society.* 2013;61(7):1197-1198.
23. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine.* 2014;174(4):588-595.



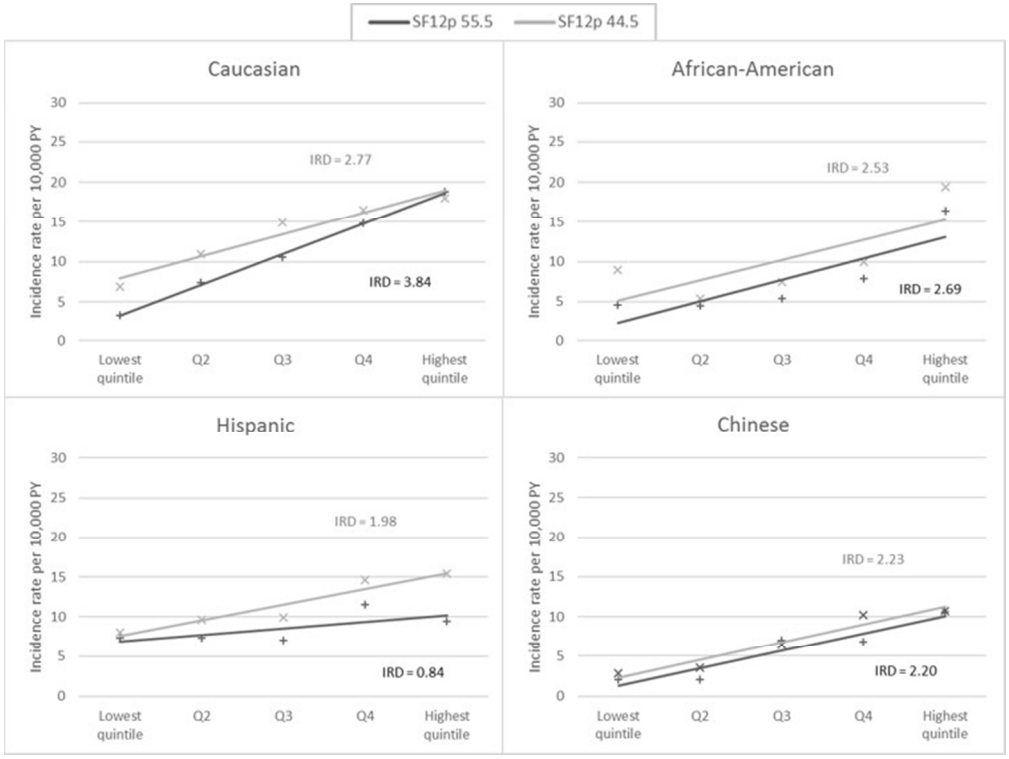
Estimated incidence rates of CVD by quintile of SBP, by measures of functional status and race/ethnicity.

128x183mm (150 x 150 DPI)



Forest plot of adjusted IRR for incident CVD per 10 mmHg higher SBP among white and black participants.

372x262mm (96 x 96 DPI)



Estimated incidence rates of CVD by quintile of SBP, by SF-12 physical summary score and race/ethnicity.

127x96mm (150 x 150 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pg 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pg 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pg 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Pg 4
Methods			
Study design	4	Present key elements of study design early in the paper	Pg 4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pg 4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pg 4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pg 5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pg 5-6*
Bias	9	Describe any efforts to address potential sources of bias	Pg 7-8
Study size	10	Explain how the study size was arrived at	Pg 4, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pg 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pg 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Pg 8
		(*c*) Explain how missing data were addressed	Pg 8
		(*d*) If applicable, explain how loss to follow-up was addressed	Pg 8
		(*e*) Describe any sensitivity analyses	Pg 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pg 4, 8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pg 8-9, 14
		(b) Indicate number of participants with missing data for each variable of interest	Pg 8
		(c) Summarise follow-up time (eg, average and total amount)	Pg 8
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pg 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Pg 15

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Pg 7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Fig 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pg 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pg 10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pg 11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pg 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pg 11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pg 16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Racial/ethnic heterogeneity in associations of blood pressure and incident cardiovascular disease by functional status in a prospective cohort: the Multi-Ethnic Study of Atherosclerosis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017746.R1
Article Type:	Research
Date Submitted by the Author:	21-Dec-2017
Complete List of Authors:	Kaiser, Paulina; Oregon State University, College of Public Health & Human Sciences Peralta, Carmen; University of California San Francisco Department of Medicine Kronmal, Richard; University of Washington Department of Statistics, Collaborative Health Studies Coordinating Center Shlipak, Michael; University of California San Francisco School of Medicine Psaty, Bruce; University of Washington, Cardiovascular Health Research Unit; Kaiser Permanente Washington Health Research Institute Odden , MC ; Oregon State University, School of Biological and Population Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Public health
Keywords:	blood pressure, epidemiology of cardiovascular disease, physical function

Title: Racial/ethnic heterogeneity in associations of blood pressure and incident cardiovascular disease by functional status in a prospective cohort: the Multi-Ethnic Study of Atherosclerosis

Authors:

Paulina Kaiser*, School of Biological and Population Health Sciences, Oregon State University; Corvallis, OR, USA

Carmen A. Peralta, Department of Medicine, Department of Epidemiology and Biostatistics, University of California, San Francisco; San Francisco, CA, USA

Richard Kronmal, Department of Biostatistics, University of Washington; Seattle, WA, USA

Michael G. Shlipak, General Internal Medicine Section, Veterans Affairs Medical Center, and the Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco; San Francisco, CA, USA

Bruce M. Psaty, Cardiovascular Health Research Unit, University of Washington and Kaiser Permanente Washington Health Research Institute, Seattle, WA, USA

Michelle C. Odden, School of Biological and Population Health Sciences, Oregon State University; Corvallis, OR, USA

***Corresponding author:**

Paulina Kaiser
155 Milam Hall
Oregon State University
Corvallis, OR 97331
Paulina.kaiser@oregonstate.edu
541-737-5522

Abstract

Objectives: Research has demonstrated that the association between high blood pressure and outcomes is attenuated among older adults with functional limitations, compared to healthier elders. However, it is not known whether these patterns vary by racial/ethnic group. We evaluated race/ethnicity-specific patterns of effect modification in the association between blood pressure and incident cardiovascular disease by functional status.

Setting: We used data from the Multi-Ethnic Study of Atherosclerosis (2002-2004, with an average of 8.8 years of follow up for incident cardiovascular disease). We assessed effect modification of systolic blood pressure and cardiovascular outcomes by self-reported physical limitations and by age.

Participants: The study included 6,117 participants (aged 46 to 87; 40% white, 27% black, 22% Hispanic, and 12% Chinese) who did not have cardiovascular disease at the second study exam (when self-reported physical limitations were assessed).

Outcome measures: Incident cardiovascular disease was defined as an incident myocardial infarction, coronary revascularization, resuscitated cardiac arrest, angina, stroke (fatal or non-fatal), or death from cardiovascular disease.

Results: We observed weaker associations between systolic blood pressure and cardiovascular disease among white adults with physical limitations (IRR per 10-mmHg higher systolic blood pressure: 1.09 [95% CI: 0.99, 1.20]) than those without physical limitations (IRR 1.29 [1.19, 1.40]; p-value for interaction, <0.01). We found a similar pattern among black adults. Poor precision among the estimates for Hispanic or Chinese participants limited the findings in these groups. The attenuated associations were consistent across both multiplicative and additive scales, though physical limitations showed clearer patterns than age on an additive scale.

Conclusion: Attenuated associations between high blood pressure and incident cardiovascular disease were observed for blacks and whites with poor function, though small sample sizes remain a limitation for identifying differences among Hispanic or Chinese participants. Identifying the characteristics that distinguish those in whom higher systolic blood pressure is associated with less risk of morbidity or mortality may inform our understanding of the consequences of hypertension among older adults.

Keywords: blood pressure, epidemiology of cardiovascular disease, physical function

Strengths and limitations of this study:

- The Multi-Ethnic Study of Atherosclerosis is the largest cohort of middle aged and older adults in the US from four racial/ethnic groups (white, black, Hispanic, and Chinese).

- We evaluated self-reported physical limitations (based on 2 questions) and chronological age as potential effect modifiers of systolic blood pressure and cardiovascular outcomes.
- Small sample size among some racial/ethnic groups limited the precision of our estimates.
- Additional research is needed to investigate heterogeneity in associations between systolic blood pressure and cardiovascular disease among racial/ethnic minority populations, and to understand the underlying biological mechanisms.

High blood pressure (systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg or taking antihypertensive medicine) is a major cause of morbidity and mortality among American adults, and is responsible for an estimated $48.6 billion in direct and indirect costs per year.[1] However, the health risks associated with high blood pressure are not uniform in all adults; some subgroups have been identified in which elevated blood pressure is not associated with increased morbidity or mortality. For example, among older adults with poor functional status, measured by slow gait speed[2,3] or by functional limitations, the association between high blood pressure and mortality is attenuated compared with elders with better functional status.[4] Interestingly, in this latter study, the effect modification of blood pressure and mortality by functional status was less apparent in middle-aged participants. [4] There are limited data on functional status as an effect modifier of blood pressure and cardiovascular outcomes; existing studies have been limited to older adults.[5,6] Thus, it is not yet clear how age and functional limitations pattern risks of CVD associated with elevated SBP.

Additionally, it is plausible that the patterns of blood pressure, functional status, and morbidity vary by racial/ethnic group. Previous research has demonstrated patterns of attenuation in populations of Latinos[2] and populations of white Americans and African Americans.[4,5] Race/ethnicity, as a proxy for biological characteristics as well as life-long contextual influences, cultural norms, and cumulative stressors,[7] is associated with blood pressure levels and with rates of cardiovascular disease (CVD). For example, a 10-mmHg higher systolic blood pressure level is associated with a larger increase in stroke risk for blacks than for whites.[8] Our objective was to explore racial/ethnic heterogeneity in the interaction of blood pressure and functional status on incident CVD.

Methods

Study population

We used data from the Multi-Ethnic Study of Atherosclerosis (MESA) to explore race/ethnicity-specific patterns of effect modification in the association between blood pressure and incident CVD by physical limitations and by age.

MESA includes 6,814 adults aged 45-84 who self-identified as white, black, Hispanic, or Chinese from six areas across the U.S. (New York, New York; Baltimore, Maryland; Forsyth County, North Carolina; Chicago, Illinois; St Paul, Minnesota; and Los Angeles, California). White participants were recruited at all sites; black participants were recruited at all sites except for Minnesota. Hispanic participants came from New York, Minnesota, and California, and Chinese participants came from Chicago and California. Participants were excluded if they had a history of heart attack, angina, stroke or transient ischemic attack, heart failure, resuscitated cardiac arrest, or procedures related to cardiovascular disease. Participants were followed from 2000-2002 until 2010-2012, with a total of five study exams. Retention was 92.4% from the first exam to the second exam, and 75.7% from the fourth exam to the final exam.[9] The study was approved by the institutional review board at each participating site, and participants provided informed consent.[10]

Exposure: systolic blood pressure

Blood pressure was measured at each exam, following a standardized protocol. After five minutes of seated rest, SBP and DBP were measured three times, at two-minute intervals, using an automated oscillometric sphygmomanometer.[11] The average of the second and third measurements were used for analysis. We used SBP measured at the second exam (2002-2004)

as the primary exposure of interest, because physical limitations were not assessed at the baseline exam.

Effect modifiers:

We used two effect modifiers for this analysis: self-reported physical limitations and age. Physical limitations were assessed at Exam 2, in 2002-2004, and measured with two questions based off the same prompt: "During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?" Participants were considered to have physical limitations if they answered 'yes' to either "You accomplished less than you would have liked to" or "You were limited in the kind of work you do or other regular daily activities."

As a secondary analysis, we used summary scores from a modified version of the 12-Item Short Form Health Survey (SF-12) (version 2)[12] to measure overall physical health and well-being. The SF-12 survey is a shortened version of the SF-36 scale and has been validated in a variety of settings.[13,14] The Physical Component Summary score (SF12-P) is a weighted average of questions about general health, limitations in moderate activities or climbing stairs, physical limitations, emotional limitations, pain interfering with work, feeling downhearted and blue, and health interfering with social activities. SF12-P scores range from 0-100 (higher scores represent better function) and are standardized so that a score of 50 reflects the average of the general U.S. population.[15] The SF12-P scale was used as a secondary analysis because it includes the physical limitation questions described above, in addition to other covariates that were less related to the underlying construct of functional status.

Outcome: incident cardiovascular disease

The outcome of interest was incident CVD, measured through the end of 2012. MESA participants were contacted by phone every 9 to 12 months and asked about interim cardiovascular events. Medical records, death certificates, and next-of-kin interviews (for out-of-hospital cardiovascular deaths) were used by a team of two study cardiologists, cardiovascular epidemiologists, or neurologists to determine the date of incident CVD.[16] CVD was defined as an incident myocardial infarction, coronary revascularization, resuscitated cardiac arrest, angina, stroke (fatal or non-fatal), or CVD death.[17]

Covariates

All covariates were measured at the second exam (2002-2004). Demographic confounders included age, sex, and income. Income was dichotomized for this analysis at earning $75,000 per year. Additional covariates included smoking (never, former, or current smoker), body mass index (BMI), total cholesterol, diabetes status, and medication use. Diabetes status was categorized as normal, impaired fasting glucose or untreated diabetes, and treated diabetes based on the 2003 American Diabetes Association fasting criteria algorithm. Medications (antihypertensives and statins) were assessed by visual inspection of medication containers by study personnel or by self-report.

Statistical methods

Participants with missing data on SBP or physical limitations at exam 2, or on incident CVD status, were excluded, as were participants who had developed CVD by exam 2. We first stratified the study population by race/ethnicity, and summarized blood pressure, functional

status, and other covariates within each racial/ethnic group. Then we used Poisson models to estimate the incident rate ratios (IRR) for incident CVD per 10 mmHg higher SBP, using an offset for the person-time contributed until incident CVD, death, or lost to follow-up. A likelihood ratio test provided evidence for a three-way interaction (on a multiplicative scale) between race/ethnicity, age, and SBP (p=0.07), so we present models stratified on race/ethnicity.

All models were adjusted for age (as a linear term), sex, and income. We ran separate sets of models for each modifier of interest: self-reported physical limitations, age, and SF12-P score. We checked for a three-way interaction between SBP, physical limitations, and age (<65 vs. >=65) in race-specific models, but did not find any evidence that the association between SBP and physical limitations on incident CVD varied by age category.

To assess modification on a multiplicative scale, we ran Poisson models stratified by functional status (e.g. e.g. with physical limitations; without physical limitations; age <65; age ≥65) and by race/ethnicity to estimate the association between SBP (as a continuous measure) and CVD. We tested for interaction by running models with an interaction term between SBP and the measure of functional status. We explored the impact of adjusting for additional covariates (smoking, diabetes, antihypertensive medication, statins, total cholesterol, DBP, and BMI) among white and black subgroups only, due to limited sample size. Due to conceptual concern over distinguishing confounders from mediators in the joint effects of SBP and functional status on CVD, we present the minimally-adjusted models as our primary results.

We also explored the relationship between SBP and CVD by functional status on an additive scale, because departures from multiplicativity may result from different baseline levels of risk in the subgroups of interest. We ran Poisson models with SBP categorized into quintiles, in order to estimate the incidence rate of CVD at each quintile. Models of physical limitation

were stratified (with limitations vs. without limitations) and adjusted for age. In the models for age, incidence rates were estimated at the first and third quartile (age 54 and 70, respectively). We used multivariable regression spline models to evaluate the best shape (linear or non-linear) of the trend in incidence rate across quintiles. We calculated slopes across quintiles to represent the average incidence rate difference (IRD) per quintile.

All analyses were done in Stata 13.1.

Results

Our analysis excluded 584 participants who did not have a blood pressure measurement at Exam 2, 14 participants who did not have physical function measures at Exam 2, five participants with missing information on incident CVD, and three participants who had prevalent CVD at Exam 2. Excluded participants were older (mean age 67.9 vs. 63.5), more likely to be male (61.2% vs. 47.4%), less well educated (22.7% vs. 36.7% with bachelor's or higher), had lower incomes (2.0% vs. 22.6% with income >$75,000), and were more likely to report physical limitations (50.5% vs. 27.3%). SBP, DBP, and racial/ethnic distribution were similar among excluded and included participants. Among the analytic sample of 6,117 participants, age at baseline ranged from 46 to 87. Participants were followed for an average of 8.8 years (until time of CVD incidence, death, loss to follow-up, or December 31, 2012), during which time there were 557 incident cases of CVD detected.

White participants were older, more educated, and had higher income levels than members of other racial/ethnic groups (Table 1). Black participants had the highest mean SBP and were most likely to be on anti-hypertensive medications. Black participants were most

likely to report physical limitations, while white participants were most likely to be diagnosed with CVD during follow-up.

We observed a generally weaker association between SBP and CVD among low-functioning subgroups (those with physical limitations or over age 65) compared to high-functioning subgroups (Table 2). This pattern was most apparent among white participants, though there was a similar pattern among black participants that did not reach statistical significance for the interaction of SBP and physical limitations. Among Hispanic and Chinese participants, the association between SBP and CVD appeared not to be modified by measures of functional status. Among all racial/ethnic groups, higher SBP was associated with higher incidence of CVD. There was no evidence for an interaction between SBP, age, and physical limitation among white (p=0.71) or black (p=0.22) participants. Sample sizes were insufficient to estimate the three-way interaction among Hispanic or Chinese participants.

The estimated CVD incidence rates by quintile of SBP revealed more nuances about the race/ethnicity-specific associations between SBP, functional status, and CVD (Figure 1). Among all racial/ethnic groups, the incidence of CVD was higher among low-functioning subgroups (with physical limitations or older age) than high-functioning subgroups (without physical limitations or younger age). Multivariable spline regression models reported that a linear fit was appropriate for the association between SBP and CVD in all subgroups.

Among white participants, the estimated increase in CVD per quintile higher SBP was *smaller* for those with physical limitations than for those without physical limitations (IRD 1.67 vs. 3.35 per 1,000 person-years). However, the average IRD across quintiles of SBP was slightly *larger* among older whites (estimated at age 70) compared with younger whites (estimated at age 54). Among black participants, the association of SBP and CVD was weaker both among

participants with physical limitations and among older participants, compared to those without physical limitations and younger participants. In contrast, among Hispanic participants, those with physical limitations and those of older age had larger IRDs (a larger increase in CVD incidence per quintile higher SBP) than those with no physical limitations and at younger ages, respectively. Large confidence intervals limit generalizations among Chinese participants. Chinese participants were less likely to reported physical limitations and less likely to develop CVD than other racial/ethnic groups, further hindering statistical power.

Adjustment for additional covariates resulted in generally attenuated but consistent results among white and black participants (Figure 2). The adjusted association of SBP with CVD risk was statistically significant among those with high functional status, but approached unity in those with physical limitations or age >= 65.

Using SF12-P scores to measure functional status produced similar patterns to those in Figure 1 but with smaller differences between low-functioning (estimated at SF12-P = 44.5) and high-functioning (SF12-P = 55.5) groups (Appendix Figure 1).

Discussion

Overall, we observed attenuated associations between SBP and incident CVD among those with low functional status (measured by self-reported physical limitations and by chronological age) among white and black adults. This pattern was generally consistent across both multiplicative and additive scales using self-reported physical limitations, but not age (as older white participants had a slightly larger increase in risk per quintile higher SBP than younger white participants). Our findings are consistent with previous research that has found attenuated or inverted associations between blood pressure and health outcomes among low-

functioning subgroups (defined by age, walking speed, or limitations in activities of daily living).[3,4,18,19]

Blood pressure treatment guidelines and randomized controlled trials have frequently used age to define treatment targets or populations of interest.[20-23] Chronological age is an imprecise measure of functional status, though it is easily and routinely collected. Others have recognized the limitations of relying on chronological age to predict health-related outcomes.[24] Among white participants, using self-reported physical limitations as a measure of functional status provided consistent evidence of attenuated associations between SBP and incident CVD among adults with physical limitations across multiplicative and additive scales, while there was not an attenuated association between SBP and incident CVD among older adults on an additive scale. Among blacks, both older age and physical limitations revealed attenuated associations between SBP and CVD on both multiplicative and additive scales (though not statistically significant for physical limitations on a multiplicative scale). Additionally, across all race/ethnic groups, those with physical limitations had higher incidence of CVD at all levels of SBP than those without physical limitations, after adjusting for age. Where feasible, self-reported physical limitations or other specific measures of functional status may be a useful addition to methods of assessing risk in clinical settings.

We observed no apparent patterning of SBP and CVD by functional status among Hispanics or Chinese participants. For Chinese participants, the small sample size is likely a key limitation for distinguishing patterns by functional status. Additionally, Chinese participants were least likely to report physical limitations and had the lowest incidence of CVD. For Hispanic participants, associations between SBP and CVD were similar by functional status on a multiplicative scale, and on an additive scale appeared to be stronger (larger average IRDs across

quintiles of SBP) for those with physical limitations and those at higher ages than those without physical limitations and at lower ages, respectively. Hispanic participants were also the youngest of the racial/ethnic groups in MESA. Previous research in a Hispanic population found that the association between SBP and all-cause mortality was attenuated among slow walkers compared to fast walkers;[18] however, these participants were older (mean age 70.5 years) and less healthy overall (mean SBP 139 mmHg, 22.8% on diabetes medication) than MESA's Hispanic participants (mean age 62.7 years, mean SBP 125 mmHg, 16.3% on diabetes medication). Future research should continue to investigate patterns of SBP and CVD risk among diverse minority populations.

Some limitations are important to consider. Self-reported physical limitations, assessed by two questions, is a crude measure of functional status; more objective measures may demonstrate even better discrimination in CVD risk. Additionally, previous research has shown that the health risks of high SBP among those with functional impairments may be stronger among older adults than among middle-aged adults.[4] We did not find any evidence that the association between SBP and physical limitations varied by age (<65 vs. >=65), though we may have been underpowered to detect heterogeneity statistically.

Additionally, more research is needed to inform how observed differences in CVD risk associated with SBP should influence treatment of high blood pressure. The biologic mechanism mediating an attenuated association between high blood pressure and outcomes among low functioning older adults remains uncertain, although there are several plausible explanations. Poor physical functioning may be associated with compromised hemodynamic regulation, vascular stiffening, and insufficient cerebral, myocardial, or renal perfusion, resulting in poorer health outcomes independent of SBP. Others have noted the challenges in accurate measurement

of blood pressure in older adults, due to orthostatic hypotension, pseudohypertension, and postprandial hypertension,[25] suggesting that attenuated association with outcomes may reflect measurement error. Another possibility is that treatment of high blood pressure, which often requires multiple medications, could result in polypharmacy or other adverse events such as falls and fractures,[26] and these adverse events could initiate a cascade of events that could result in hospitalization, morbidity, and even death. Thus, observed low blood pressures may be correlated poorer outcomes. Our analysis shows that future studies that evaluate benefits of treating high blood pressure should explore patterns by race/ethnicity as well as functional status.

The presence of racial/ethnic variation in associations between SBP, incident CVD, and functional status do not imply biologically predetermined differences in risks; rather, our findings should caution against generalizing results from predominantly white study populations to other racial/ethnic populations. The observed differences that we found are likely the result of broad social and environmental influences throughout the life course that are strongly patterned by racial/ethnic identity in the U.S. However, these findings are also novel and, if replicated, much more research is needed to understand the causal pathways resulting in racial/ethnic heterogeneity in associations between SBP, functional status, and CVD.

In summary, we found that the risk of incident CVD associated with high blood pressure appears to be attenuated among white and black adults with physical limitations and at older ages in a diverse cohort of middle aged and older adults. Patterns among Hispanic and Chinese adults were less clear, which likely reflects limited sample sizes. Understanding how functional status (or factors underlying functional impairments) influence CVD risk across racial/ethnic groups could be useful for identifying at-risk persons and informing public health strategies to improve health and reduce CVD risk.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Figure Legends

Figure 1. Estimated incidence rates of CVD by quintile of SBP, by measures of functional status and race/ethnicity.

Figure 2. Forest plot of adjusted IRR for incident CVD per 10 mmHg higher SBP among white and black participants.

Table 1. Characteristics of analytic sample at MESA Exam 2 by race/ethnicity

	White	Black	Hispanic	Chinese	p-value
N=	2421	1659	1320	717	
Age (yrs)	64.1	63.5	62.7	63.3	<0.001
Female	51.6%	54.9%	52.3%	51.3%	0.17
Income					
<$16,000	10.0%	19.9%	38.6%	44.5%	
$16,000 - $39,999	21.2%	32.0%	35.3%	22.4%	
$40,000 - $74,999	30.9%	30.1%	18.6%	15.4%	
$75,000+	37.8%	18.0%	7.5%	17.7%	<0.001
Education					
High school or less	21.1%	29.9%	63.7%	39.1%	
Some college or Associate's	27.8%	35.2%	26.0%	20.3%	
Bachelor's or more	51.1%	34.9%	10.3%	40.6%	<0.001
BMI (kg/m$^{2)}$	27.7	30.1	29.6	24.1	<0.001
Current smoker	10.9%	16.0%	10.2%	5.6%	<0.001
Total cholesterol (mg/dL)	192.8	188.4	194.1	189.9	<0.001
Taking statins	23.5%	18.8%	16.6%	17.2%	<0.001
Diabetes					
Impaired fasting glucose	17.9%	20.1%	21.7%	20.6%	
Treated diabetes	5.9%	16.6%	16.6%	11.2%	<0.001
DBP (mmHg)	68.9	73.5	70.1	69.3	<0.001
Taking anti-hypertension medication	37.8%	54.0%	37.3%	32.1%	<0.001
SBP, mean	121.0	130.2	125.0	120.7	<0.001
SBP quintiles					
Quintile 1 (60-107 mmHg)	24.3%	12.2%	20.7%	27.8%	
Quintile 2 (107.5-116.5 mmHg)	23.3%	16.8%	20.2%	19.4%	
Quintile 3 (117-127 mmHg)	19.2%	19.8%	18.7%	18.0%	
Quintile 4 (127.5-141 mmHg)	19.0%	23.7%	20.0%	18.6%	
Quintile 5 (141.5-230 mmHg)	14.2%	27.6%	20.5%	16.3%	<0.001
Self-reported physical limitations	26.4%	31.7%	27.2%	20.8%	<0.001
Accomplished less than liked	23.1%	27.8%	24.6%	19.1%	
Limited in work or daily activities	17.2%	20.7%	21.8%	16.5%	
SF12-P score	49.9	47.8	47.9	48.9	<0.001
Incident CVD	10.2%	8.9%	9.2%	5.7%	<0.01
Mean time to CVD or end of follow-up (yrs)	8.9	8.6	8.7	9.0	<0.001

Table 2. Estimated associations (IRR[1] per 10-mmHg higher SBP) between SBP and incident CVD by measures of functional status and racial/ethnic group.

		No physical limitations	With physical limitations	Age <65	Age >= 65
Overall	N=	4446	1671	3218	2899
	IRR	1.21	1.10	1.30	1.11
	95% CI	1.16, 1.27	1.03, 1.17	1.22, 1.39	1.06, 1.17
	P-value for interaction	0.04		<0.01	
White	N=	1783	638	1229	1192
	IRR	1.29	1.09	1.33	1.17
	95% CI	1.19, 1.40	0.99, 1.20	1.18, 1.49	1.01, 1.07
	P-value for interaction	<0.01		<0.01	
Black	N=	1134	525	864	795
	IRR	1.25	1.10	1.36	1.10
	95% CI	1.14, 1.37	0.96, 1.25	1.22, 1.52	1.00, 1.21
	P-value for interaction	0.14		<0.01	
Hispanic	N=	961	359	740	580
	IRR	1.11	1.10	1.13	1.08
	95% CI	1.00, 1.23	0.95, 1.27	0.97, 1.31	0.98, 1.19
	P-value for interaction	0.89		0.66	
Chinese	N=	568	149	385	332
	IRR	1.21	1.23	--[2]	1.10
	95% CI	1.01, 1.44	0.95, 1.58	--[2]	0.94, 1.29
	P-value for interaction	0.93		--	

[1] *From Poisson models with offset for person-time contributed until incident CVD, death, or loss to follow-up. Models for physical limitations were adjusted for age (continuous), gender, and income (dichotomized at $75,000. Models by age category were adjusted for gender and income (dichotomized at $75,000).*

[2] *Omitted due to small number of events (<10)*

Contributorship statement

Dr. Kaiser developed the initial research question, conducted all analyses and drafted the manuscript. Dr. Odden provided oversight, including review of analyses and editing the manuscript. Drs. Peralta, Kronmal, Shlipak, and Psaty reviewed results and provided guidance on interpretation, and provided comments on multiple drafts of the manuscript.

Competing interests

The authors have no competing interests.

Funding

This research was supported by grants K01AG039387 and R01AG46206 from the National Institute on Aging; contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute; and grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from NCATS.

Data sharing statement

No additional unpublished data are available. More information about MESA, including all participating MESA investigators and institutions, can be found at http://www.mesa-nhlbi.org.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2016 Update A Report From the American Heart Association. *Circulation.* 2015:CIR. 0000000000000350.
2. Odden MC, Covinsky KE, Neuhaus JM, Mayeda ER, Peralta CA, Haan MN. The association of blood pressure and mortality differs by self-reported walking speed in older Latinos. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences.* 2012;67(9):977-983.
3. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Archives of internal medicine.* 2012;172(15):1162-1168.
4. Windham BG, Griswold ME, Lirette S, et al. Effects of Age and Functional Status on the Relationship of Systolic Blood Pressure With Mortality in Mid and Late Life: The ARIC Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2015:glv162.
5. Peralta CA, Katz R, Newman AB, Psaty BM, Odden MC. Systolic and Diastolic Blood Pressure, Incident Cardiovascular Events, and Death in Elderly PersonsNovelty and Significance. *Hypertension.* 2014;64(3):472-480.
6. Sabayan B, van Vliet P, de Ruijter W, Gussekloo J, de Craen AJ, Westendorp RG. High blood pressure, physical and cognitive function, and risk of stroke in the oldest old. *Stroke.* 2013;44(1):15-20.
7. Geronimus AT, Hicken M, Keene D, Bound J. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *American journal of public health.* 2006;96(5):826-833.
8. Howard G, Lackland DT, Kleindorfer DO, et al. Racial differences in the impact of elevated systolic blood pressure on stroke risk. *JAMA internal medicine.* 2013;173(1):46-51.
9. Christine PJ, Auchincloss AH, Bertoni AG, et al. Longitudinal associations between neighborhood physical and social environments and incident type 2 diabetes mellitus: the multi-ethnic study of atherosclerosis (MESA). *JAMA internal medicine.* 2015;175(8):1311-1320.
10. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *American journal of epidemiology.* 2002;156(9):871-881.
11. Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. *Circulation.* 1993;88(5):2460-2470.
12. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care.* 1996;34(3):220-233.
13. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *Journal of Public Health.* 1997;19(2):179-186.
14. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *Journal of clinical epidemiology.* 1998;51(11):1171-1178.
15. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. *How to score version 2 of the SF-12 health survey (with a supplement documenting version 1).* QualityMetric Incorporated; 2002.
16. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Archives of internal medicine.* 2008;168(12):1333-1339.
17. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study the multi-ethnic study of atherosclerosis. *Circulation.* 2009;120(6):502-509.

18. Odden MC, Covinsky KE, Neuhaus JM, Mayeda ER, Peralta CA, Haan MN. The association of blood pressure and mortality differs by self-reported walking speed in older Latinos. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2012;67(9):977-983.
19. Peralta CA, Katz R, Newman AB, Psaty BM, Odden MC. Systolic and Diastolic Blood Pressure, Incident Cardiovascular Events, and Death in Elderly Persons The Role of Functional Limitation in the Cardiovascular Health Study. *Hypertension.* 2014;64(3):472-480.
20. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama.* 2014;311(5):507-520.
21. Group SR. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med.* 2015;2015(373):2103-2116.
22. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine.* 2008;358(18):1887-1898.
23. Trialists'Collaboration BPLT, Turnbull F, Neal B, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Bmj.* 2008;336(7653):1121-1123.
24. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2013;68(6):667-674.
25. Morley JE. Systolic hypertension should not e treated in persons aged 80 and older until blood pressure is greater than 160 mmHg. *Journal of the American Geriatrics Society.* 2013;61(7):1197-1198.
26. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine.* 2014;174(4):588-595.

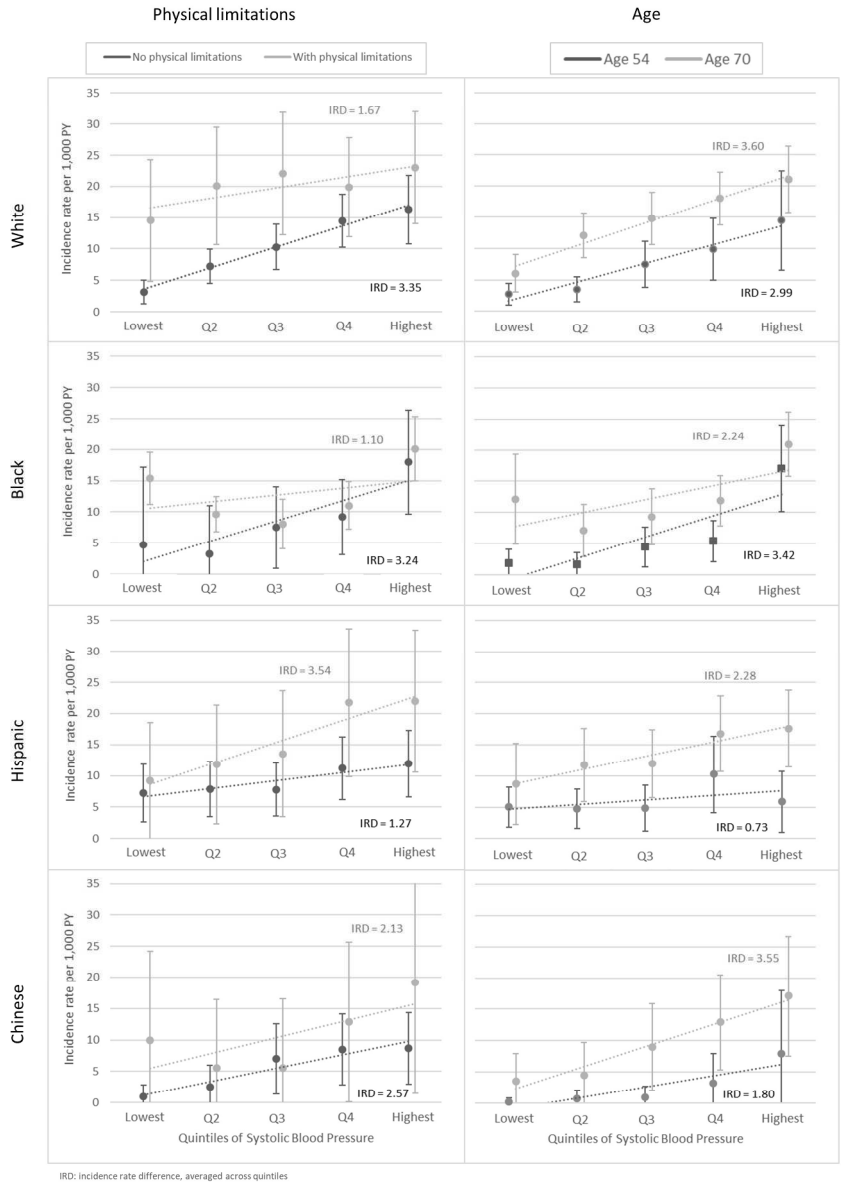


Figure 1. Estimated incidence rates of CVD by quintile of SBP, by measures of functional status and race/ethnicity.

190x254mm (300 x 300 DPI)

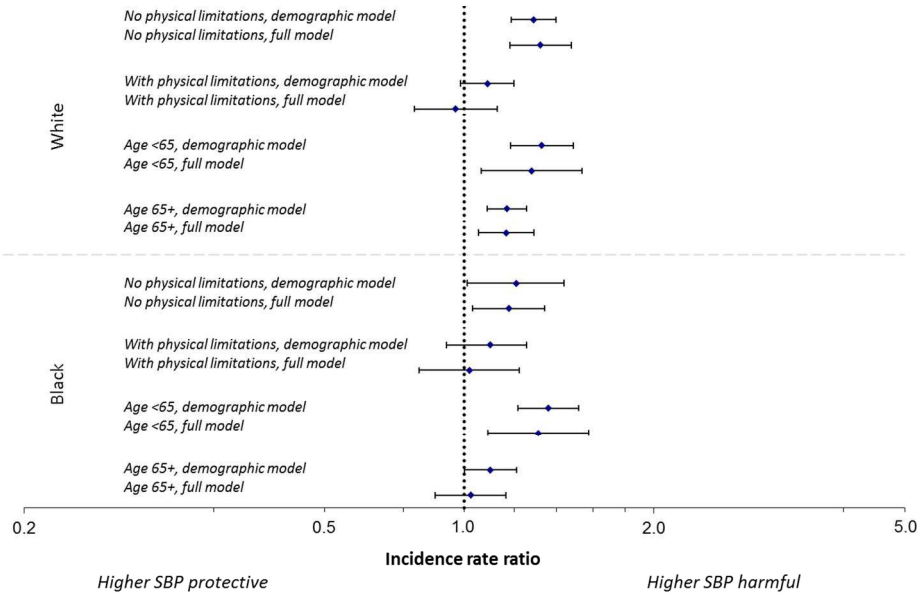
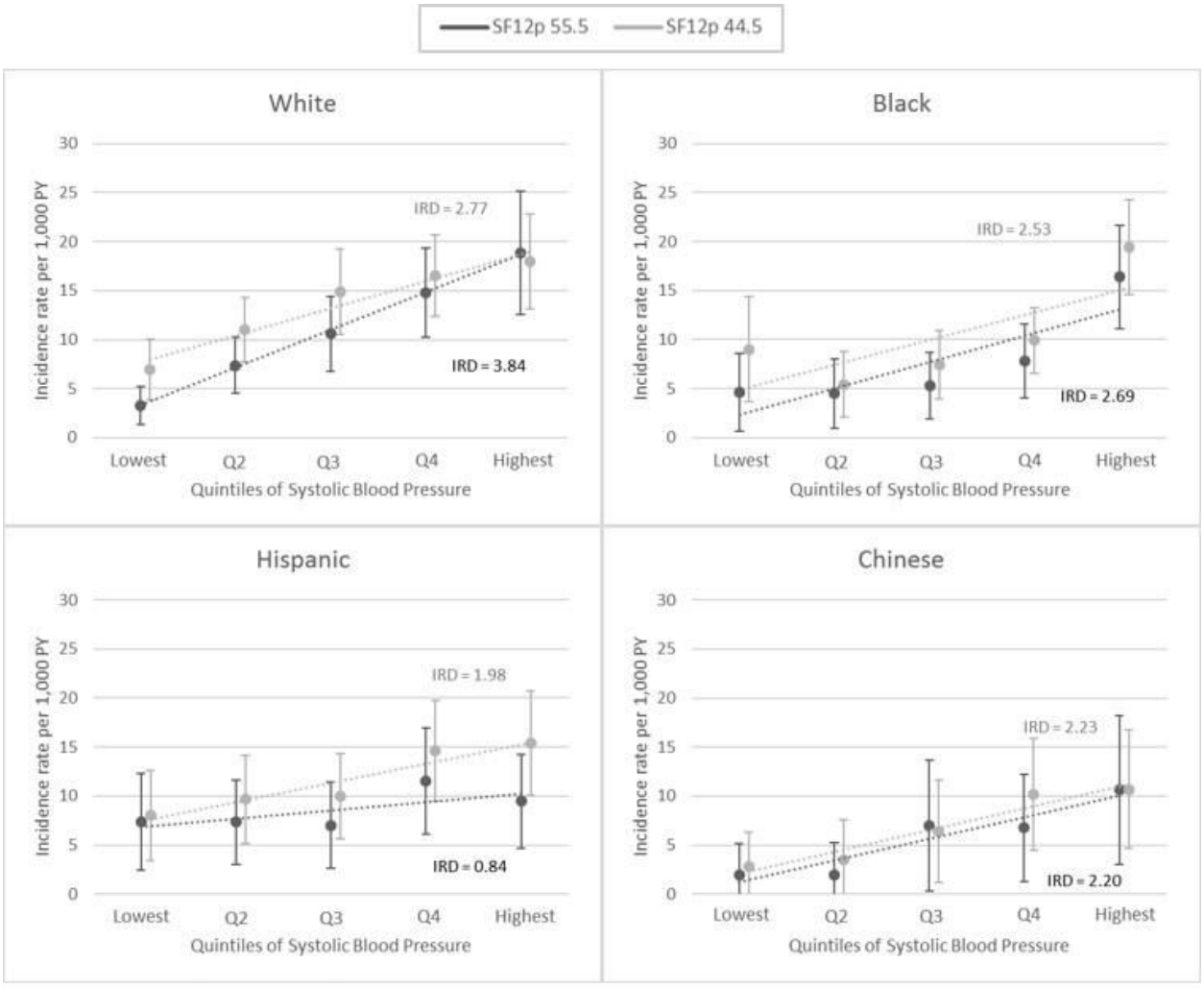


Figure 2. Forest plot of adjusted IRR for incident CVD per 10 mmHg higher SBP among white and black participants.

254x190mm (300 x 300 DPI)

Appendix Figure 1. Estimated incidence rates of CVD by quintile of SBP, by SF-12 physical summary score and race/ethnicity.



IRD: incidence rate difference, averaged across quintiles

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pg 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pg 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pg 4
Objectives	3	State specific objectives, including any prespecified hypotheses	Pg 4
Methods			
Study design	4	Present key elements of study design early in the paper	Pg 4-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pg 4-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pg 4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pg 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pg 5-7*
Bias	9	Describe any efforts to address potential sources of bias	Pg 8-9
Study size	10	Explain how the study size was arrived at	Pg 5, 7, 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pg 7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pg 7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Pg 8-9
		(*c*) Explain how missing data were addressed	Pg 7
		(*d*) If applicable, explain how loss to follow-up was addressed	Pg 7
		(*e*) Describe any sensitivity analyses	Pg 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pg 4, 9
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pg 9, 16
		(b) Indicate number of participants with missing data for each variable of interest	Pg 9
		(c) Summarise follow-up time (eg, average and total amount)	Pg 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pg 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	Pg 17

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Pg 7, 17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Fig 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pg 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pg 11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pg 12-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pg 11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pg 12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pg 18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.