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THE EFFECT OF PULSE PRESSURE ON ALL-CAUSE AND CARDIOVASCULAR-SPECIFIC MORTALITY RISKS IN US ADULTS

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Objectives: To examine the effect of pulse pressure on all-cause and cardiovascular-specific mortality risks and whether this effect varies with sex and race/ethnicity among adults who participated in the third National Health and Nutrition Examination Survey and were followed to December 31, 2006.

Design: Cohort/Longitudinal.

Setting: United States.

Main Outcome Measure: All-cause and cardiovascular-specific mortality.

Methods: Hazard rates and 95% confidence intervals (CI) for all-cause and cardiovascular-specific mortality associated with the pulse pressure quartiles (Q) were estimated through Cox proportional regression before and after controlling for selected characteristics.

Results: Relative to adults with pulse pressure in the first quartile, death rate for all-cause mortality was 29% (95% CI: 1.03, 1.62) and 54% (95% CI: 1.22, 1.95) higher in adults with pulse pressures in Q3 and Q4, respectively, after adjustment for all study covariates. These associations were further observed in Whites and Mexican Americans only. For cardiovascular-specific mortality, the adjusted death rates for Q3 and Q4 were 57% (95% CI: 1.00, 2.44) and 76% (95% CI: 1.16, 2.67).

Conclusions: Our findings suggest that pulse pressure could be associated with all-cause and CVD-specific mortality risk among US adults. (*Ethn Dis*. 2015;25[2]:152–156)

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INTRODUCTION

Pulse pressure, an indicator of arterial stiffness[1,2] and marker of atherosclerosis,[1,3] has been associated with all-cause[3–6] and cardiovascular (CVD)-specific mortality in adults.[3–9] However, most of the evidence is supported by findings among men. For example, Benetos et al found increased odds of dying of at least 11% for all-cause mortality among French men aged 40 to 69 years after controlling for selected covariates including mean blood pressure.[5] These findings were further observed among French men regardless of the presence of hypertension for CVD-specific mortality but only for men with hypertension for all-cause mortality.[6] In the United States, using data from the first National Health and Nutrition Examination Survey (NHANES) and the 1992 Epidemiological Follow Up Study, Fang et al reported that the rate of CVD-specific mortality increased by 2.5 times with each 10 mm Hg increase in pulse pressure among men aged <55 years.[8] However, this study, although national, was restricted to normotensive adults and did not examine the effect of sex and race/ethnicity on this association. The latter are important given that the evidence is mostly observed among men and the high prevalence of hypertension among non-Hispanic Blacks in the United States.[10] Thus, this study investigated the effect of pulse pressure on all-cause and cardiovascular-specific mortality risks among US adults who participated in the NHANES III and were followed to December 31, 2006 to determine their mortality status and whether these associations vary with sex and race/ethnicity.

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METHODS

For this analysis, we used public-use NHANES III data (household adult, examination, and laboratory files) for US adults for whom records were linked to the 2010 National Death Index-linked Mortality Public-use File and followed through December 31, 2006 (n=20,050).[11] To link these two datasets, the National Center for Health Statistics (NCHS) used a probabilistic matching algorithm using social security number, first name, middle initial, last name or surname, month, day and year of birth, sex, father's surname, state of

birth, race, state of residence, and marital status.[12]

To specify mortality status for all-cause, we used the underlying cause of death (UCOD) according to the International Classification of Diseases (ICD), Ninth and Tenth Revisions.[13] In addition, we determined CVD-specific mortality using ICD Tenth Revision codes 100-I78 from the 113 UCOD.[13] Using information provided in the dataset, we calculated the time at risk of death in person-years by dividing the time in months of follow-up by 12 for each person from interview date to death for those who die and from interview to December 31, 2006 for those alive.[11]

Pulse pressure was specified as the difference between systolic and diastolic blood pressures and further categorized into quartiles (Q) using the population distribution (Q1: 15 to ≤39; Q2: >39 to ≤47; Q3: >47 to 59 and Q4: >59 to 175 mm Hg). Measures of systolic and diastolic blood pressures used to calculate pulse pressure represent an average of three measures for systolic (SBP) and diastolic (DBP) blood pressures obtained during NHANES full medical examination.[14]

Consistent with previous studies,[3,5,6,8,15,16] we included age (continuous), sex (male/female), race/ethnicity (non-Hispanic White, non-Hispanic Black and Mexican American), marital status (married, divorced, single and widowed), education (< high-school diploma or general equivalency diploma (GED), high-school diploma or GED, and >high-school diploma or GED), and total family 12-month income (≤$14,999, $15,000 to $24,999, and ≥$25,000). Smoking status was defined using two self-report questions (''Have you smoked 100 cigarettes in your lifetime?'' and, ''Do you smoke now?'') and categorized as current (if individuals answered yes to both questions), former (if they answered yes to the first question and no to the second); and never smokers (if they answered no to both questions). Leisure-time physical activity (LTPA) in the past month was specified as a response to ''yes'' to any of the following activities: jog or run; ride bicycle/exercise bicycle; swim; do aerobics or aerobic dancing; do other dancing, do calisthenics or exercises; do garden/yard work; lift weights; or any other exercises or sports. Body mass index was defined using federal guidelines (BMI: underweight [<18.5 kg/m^2], normal weight [18.5 kg/m^2 to <25.0 kg/m^2], overweight [25.0 kg/m^2 to <30.0 kg/m^2], obesity grade I [30.0 kg/m^2 to <35.0 kg/m^2], obesity grade II [35.0 kg/m^2 to <40.0 kg/m^2], and extreme obesity grade III [≥40.0 kg/m^2]).[17] Total cholesterol was categorized under control using ≤240 mg/dL as the cut point.[18] Hypertension was defined using objective measures of SBP (>140 mm Hg) and DBP (>90 mm Hg) as well as information on self-reported use of medications for hypertension.[19] Mean arterial pressure (MAP) was specified as one-third of SBP plus two-thirds of DBP. [20]

We excluded records of individuals who were: <18 years of age at the time of the interview (n=432); ineligible for follow-up (n=25); did not have information on PP (n=2,354) or mortality status (n=56), total cholesterol (n=900), reported a race/ethnicity as ''other'' (n=649); and did not have information on education (n=92). These exclusions yielded a final sample of 15,542, including 3,774 deaths and approximately 208,266.67 person-years (median=14.33, range: 0 to 18.2 years).

STATISTICAL ANALYSIS

Descriptive statistics for selected characteristics were presented according to pulse pressure quartiles and the overall population. In addition, death rates for all-cause and CVD-specific mortality were calculated. After examining the proportional hazards assumption,[21] Cox proportional hazards regression was used to estimate the all-cause and CVD-specific mortality rates associated with pulse pressure categories before and after controlling for age, sex, race/ethnicity, education, BMI, smoking status, LTPA, total cholesterol and hypertension. We also considered MAP during adjustment. Marital status and income did not change our estimates, and therefore, were not included in the final models. In models for CVD-specific mortality, deaths attributed to other causes were treated as censored at the time the death occurred. To examine heterogeneity of these associations, we tested interaction terms of pulse pressure with sex and race/ethnicity in the fully adjusted model.

All data management procedures were conducted with SAS for Windows Release 9.3 (SAS Institute Inc. Cary, NC) while statistical analyses were conducted with SUDAAN Release 11.0.1 (Research Triangle Institute, Research Triangle Park, NC). SUDAAN takes into account the complex sampling design used in NHANES.[22] Sample sizes presented in Table 1 were unweighted, but all other estimates (proportions, standard errors, rates, hazard rates [HRs] and their 95% CIs) were weighted.

RESULTS

Table 1 shows that more than half of US adults in the dataset had a pulse pressure in Q1 and Q2 and less than one fifth have a pulse pressure in Q4. In the study population, adults were more likely to be younger than 44 years of age, female, White, married, had more than a high school education, earned more than $25,000 annually, had a normal weight, reported never smoking and being physically active during their leisure time. In addition, <20% of the population had high total cholesterol and hypertension. This pattern was observed across pulse pressure quartiles with few exceptions: Adults with pulse pressures in Q2 and Q3 were more

Table 1. Distribution of selected characteristics[a] for US adults according to pulse pressure quartiles: The Third National Health and Nutrition Examination Survey (1988–1994)-linked Mortality Files 2006

Characteristics	Pulse Pressure[b]				Total (*N*=15,542)
	Q1: 15 to ≤39 (*n*=3,915)	Q2: >39 to ≤47 (*n*=3,795)	Q3: >47 to ≤59 (*n*=3,870)	Q4: >59 to 175 (*n*=3,962)	
Prevalence of PP, %	30.0 (1.07)	28.4 (.81)	23.1 (.58)	18.5 (.82)	
Age, years					
18–29	28.9 (.95)	29.2 (.95)	25.0 (1.40)	8.3 (1.27)	24.3 (.84)
30–44	51.5 (1.09)	39.9 (1.31)	23.5 (1.72)	5.3 (.65)	33.2 (.97)
45–64	17.6 (.95)	26.4 (1.02)	34.4 (1.52)	26.5 (.99)	25.6 (.61)
≥65	1.9 (.22)	4.4 (.37)	17.1 (1.28)	59.9 (1.64)	16.9 (.98)
Male, %	42.1 (1.02)	50.5 (1.05)	55.1 (1.08)	44.4 (1.29)	47.4 (.44)
Race/ethnicity					
Non-Hispanic White	82.9 (.88)	83.3 (1.16)	81.4 (1.14)	84.7 (1.04)	83.0 (.84)
Non-Hispanic Black	11.2 (.73)	10.6 (.88)	12.7 (.90)	11.2 (.91)	11.4 (.70)
Mexican American	5.9 (.57)	6.1 (.65)	5.9 (.52)	4.0 (.32)	5.6 (.46)
Marital Status					
Married	66.5 (1.43)	65.4 (1.40)	63.3 (1.65)	56.8 (1.42)	63.6 (.84)
Divorced	12.9 (.98)	11.9 (.94)	11.2 (.98)	8.7 (.83)	11.5 (.50)
Single	19.5 (1.05)	20.3 (1.29)	18.8 (1.39)	9.9 (1.16)	17.8 (.87)
Widow	1.1 (.24)	2.4 (.26)	6.7 (.62)	24.5 (1.03)	7.1 (.38)
Education					
<High school	17.1 (1.23)	19.8 (1.20)	26.0 (1.37)	40.0 (1.78)	24.2 (1.03)
High school/GED	34.0 (1.07)	36.0 (1.31)	35.8 (1.40)	33.4 (1.53)	34.9 (.76)
>High school	48.9 (1.65)	44.2 (1.52)	38.2 (1.57)	26.6 (1.58)	40.9 (1.32)
Income					
≤$14,999	17.1 (1.07)	16.8 (.94)	18.3 (1.26)	31.0 (1.64)	19.9 (.85)
$15,000–$24,999	16.6 (.93)	17.8 (1.19)	19.7 (1.38)	23.7 (.86)	19.0 (.71)
≥$25,000	62.0 (1.39)	59.6 (1.55)	54.9 (1.83)	37.0 (1.97)	55.0 (1.20)
Missing	4.2 (.51)	5.9 (.83)	7.1 (.71)	8.3 (.65)	6.1 (.41)
BMI					
Underweight	4.0 (.49)	1.9 (.33)	1.5 (.26)	1.6 (.24)	2.4 (.20)
Normal	48.4 (1.41)	46.2 (1.30)	37.8 (1.47)	35.1 (1.29)	42.8 (.91)
Overweight	29.6 (1.02)	32.4 (.99)	35.6 (1.25)	34.6 (1.15)	32.7 (.57)
Obesity grade I	11.2 (.69)	13.2 (.76)	15.5 (.87)	18.7 (.86)	14.2 (.39)
Obesity grade II	4.8 (.63)	3.8 (.35)	5.7 (.56)	6.6 (.77)	5.1 (.39)
Obesity grade III	2.0 (.26)	2.5 (.36)	2.9 (.50)	3.4 (.47)	2.8 (.23)
Smoking					
Current	30.7 (1.29)	32.5 (1.79)	29.1 (1.17)	19.9 (1.25)	28.8 (.86)
Former	21.2 (.77)	22.5 (1.04)	28.4 (1.28)	35.6 (1.55)	25.9 (.59)
Never	48.1 (1.14)	44.9 (1.68)	42.5 (1.05)	44.5 (1.37)	45.2 (.76)
Leisure physical activity in the past month, no, %	18.2 (1.03)	17.3 (1.16)	20.5 (1.35)	28.6 (1.63)	20.4 (.93)
Total cholesterol ≥240 mg/dL, %	12.7 (.83)	16.4 (1.15)	21.7 (.97)	30.5 (1.10)	19.1 (.65)
Hypertension, yes, %	6.4 (.63)	9.5 (.78)	21.4 (.97)	46.5 (1.06)	18.2 (.65)

[a] Data are proportion (SE) unless indicated otherwise.
[b] All *P* for Chi-square comparing pulse pressure quartiles were <.001.

likely to be males while those with a pulse pressure in Q4 were aged >45 years, less educated, earned <$15,000, more likely to report being former smokers and physically inactive, as well as had hypertension and total cholesterol levels >240 mg/dL.

Unadjusted and adjusted HRs associated with pulse pressure quartiles on all-cause and CVD-specific mortality risks are presented in Table 2. For the unadjusted analyses, pulse pressure was associated with significant increased death rates for all-cause and CVD-specific mortality. These rates seem to increase as quartiles increase. When controlling for age, sex and race/ethnicity, the death rates for both all-cause and CVD-specific mortality risks were greatly attenuated and remained significant only for adults with pulse pressures

Table 2. Unadjusted and adjusted hazard ratios (95% confidence intervals)[a] for pulse pressure quartiles on all-cause and cardiovascular disease (CVD)-specific mortality rates for US adults aged ≥18 years: The Third National Health and Nutrition Examination Survey (1988–1994)-linked Mortality Files 2006

	All-cause			
Pulse pressure quartiles	**Unadjusted**	**Model 1**	**Model 2**	**Model 3**
Q1: 15 to ≤39	1.00	1.00	1.00	1.00
Q2: >39 to ≤47	1.43 (1.14, 1.79)	1.00 (.80, 1.25)	.98 (.78, 1.23)	.97 (.77, 1.23)
Q3: >47 to ≤59	3.71 (2.93, 4.69)	1.37 (1.09, 1.72)	1.32 (1.05, 1.66)	1.29 (1.03, 1.62)
Q4: >59 to 175	13.10 (10.36, 16.58)	1.72 (1.33, 2.21)	1.63 (1.28, 2.06)	1.54 (1.22, 1.95)
		CVD-specific		
Q1: 15 to ≤39	1.00	1.00	1.00	1.00
Q2: >39 to ≤47	1.81 (1.14, 2.86)	1.15 (.74, 1.80)	1.11 (.71, 1.74)	1.09 (.69, 1.71)
Q3: >47 to ≤59	6.03 (3.85, 9.45)	1.75 (1.14, 2.68)	1.67 (1.08, 2.59)	1.57 (1.00, 2.44)
Q4: >59 to 175	23.69 (15.56, 36.07)	2.13 (1.43, 3.17)	1.99 (1.34, 2.95)	1.76 (1.16, 2.67)

[a] Association of pulse pressure quartiles categories with all-cause and CVD (Unadjusted); HRs adjusted for age (continuous), sex, race/ethnicity (Model 1); additionally adjusted for education, BMI, smoking and physical inactivity (Model 2); and finally, additional adjustment for hypertension and total cholesterol (Model 3).

in Q3 and Q4. The rates of dying from all-cause mortality associated with having a pulse pressure in Q3 and in Q4 were 1.37 (95% CI:1.09, 1.72) and 1.72 (95% CI:1.33, 2.21), respectively. The corresponding death rates for CVD-specific mortality were 1.75 (95% CI:1.14, 2.68) and 2.13 (95% CI:1.43, 3.17) respectively. These estimates remained significant after further adjustment for education, BMI, smoking and physical inactivity (Model 2) as well as with additional adjustment for total cholesterol levels and hypertension (Model 3) although the strengths of the estimates were attenuated for both all-cause and CVD-specific mortality risks. For instance, analyses from the fully-adjusted model (Model 3) show that the rates of dying from all-cause were 29% (95% CI: 1.03, 1.62) and 54% (95% CI: 1.22, 1.95) greater among adults with pulse pressures in Q3 and Q4, respectively, relative to adults with pulse pressure in Q1. The death rates for CVD-specific mortality were 1.57 (95% CI: 1.00, 2.44) and 1.76 (95% CI:1.16, 2.67) for adults with pulse pressures in Q3 and Q4, respectively. These estimates remained identical whether we included hypertension or MAP in the fully-adjusted model. Since the latter could be correlated with pulse pressure, we chose to control for hypertension in the final model.

Racial/ethnic heterogeneity was observed for the association between pulse pressure and all-cause mortality (*P* for interaction: .007) but not for CVD-specific mortality (*P* for interaction: .12; Figure 1). Non-Hispanic Whites had death rates of 1.34 (95% CI: 1.02, 1.77) and 1.58 (95%CI: 1.18, 2.10) associated with pulse pressures in Q3 and Q4 as compared with their counterparts with pulse pressure in Q1. Among Mexican Americans, a death rate of 1.50 (95% CI: 1.12, 2.01) was observed for those in the third quartile only. No association was observed among non-Hispanic Blacks. No heterogeneity was observed according to sex for neither all-cause nor CVD-specific mortality (*P* for interactions: .62 and .19).

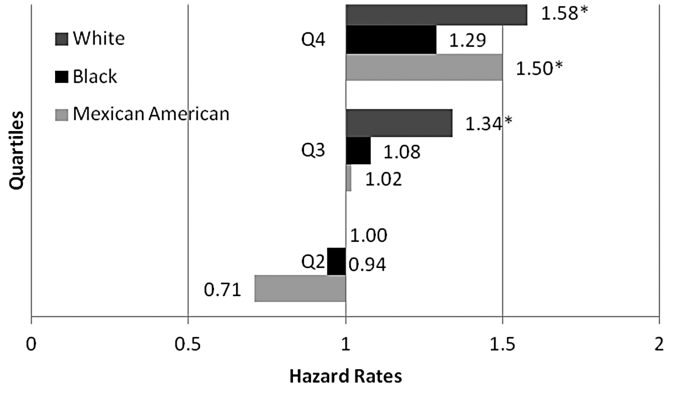

Fig 1. Hazard rates for all-cause mortality associated with pulse pressure quartiles (Q1: Reference): The third National Health and Nutrition Examination Survey (1988–1994)-linked Mortality Files 2006. *95% CIs do not include 1.00

DISCUSSION

Similar to previous studies,[3,5,6,8,9] pulse pressure was associated with increased death rates for all-cause and CVD-specific mortality risks among US adults. We found that adults with pulse pressures >47 mm Hg (Q3 and Q4) had at least a 29% increased rate of dying from all-cause and CVD-specific mortality regardless of sex. Association for pulse pressure and all-cause mortality varied with race/ethnicity with non-Hispanic White and Mexican American adults exhibiting the greatest death burden.

We found that adults with pulse pressures >47 mm Hg (Q3 and Q4) had at least a 29% increased rate of dying from all-cause and CVD-specific mortality regardless of sex.

To the best of our knowledge, this is the first study that examines the association between pulse pressure and mortality using a large and diverse nationally representative population of US adults. However, the inclusion of all deaths, regardless of the follow-up period, could be a limitation as early deaths may not be related to pulse pressure. To tease this out, we repeated the analyses excluding deaths occurring during the first two years of follow-up. The results indicated a stronger association suggesting that, if anything, the inclusion of the deaths may underestimate our results (data not shown).

Our findings that pulse pressure is associated with all-cause and CVD-specific mortality call attention to the need to consider pulse pressure as a risk factor for CVD risk and mortality overall. Interestingly, the associations for all-cause mortality were driven by non-Hispanic Whites and Mexican Americans, racial/ethnic groups with blood pressure lower than non-Hispanic Blacks.[10] The latter suggests that pulse pressure may be a biomarker and/or risk factor for mortality risk independent from hypertension. Thus, further and future studies should include and consider the effect of pulse pressure and hypertension as they may have independent effects on mortality risks. The latter may contribute to our understanding of the high all-cause and CVD-specific mortality rates observed among non-Hispanic Blacks relative to non-Hispanic Whites.

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AUTHOR CONTRIBUTIONS

Design and concept of study: Borrell, Samuel
Acquisition of data: Borrell
Data analysis and interpretation: Borrell
Manuscript draft: Borrell, Samuel
Statistical expertise: Borrell