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BRIEF REPORT

Hypertension and risk of death from external causes in the Physicians' Health Study enrollment cohort

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Abstract
Objectives To address the recent hypothesis that hypertension increases the risk of death from external causes.
Methods We examined blood pressure and death from external causes among 82,037 male physicians who were screened for eligibility to enroll in the Physicians' Health Study.
Results During up to 6.6 years of mortality follow-up, there were 304 deaths from external causes. No association was found overall, although we observed an increased risk of non-passive external causes of death, particularly death due to falls, which was independent of various lifestyle, medical, and pharmacological risk factors.
Conclusions The results of our study support this novel hypothesis. Further studies are needed to explore potential causal mechanisms between elevated BP and the risk of external death.

Keywords Injuries · External causes of death · Epidemiologic studies · Hypertension · Mortality

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Introduction

The possibility that hypertension increases the risk of death from external causes was supported by a recent study that used 25 years of mortality follow-up data from the large cohort of men screened for MRFIT (Terry et al. 2007), and that study showed a 40–50% increased risk of death from external causes, particularly injuries, in men with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Chobanian et al. 2003) stage 2 hypertension, consistent with the results of three (Tamosiunas et al. 2005; Vartiainen et al. 1994; Farchi et al. 1987) but not another (Strandberg et al. 1995) of four smaller studies. These findings are also consistent with the data showing that hypertension-related cerebrovascular damage (Manolio et al. 2003; Raz et al. 2003; DeCarli et al. 1999) may lead to subtle cognitive and/or functional changes (Raz et al. 2003; Tullberg et al. 2004; Prins et al. 2005; Anstey et al. 2005; Sierra et al. 2004; Onen et al. 2004; Starr et al. 2003) that may predispose individuals to falls or other injuries (Anstey et al. 2005; Kuo and Lipsitz 2004). Nonetheless, epidemiological studies of this issue remain few, and control for potentially confounding variables, such as socioecomonic status (SES), alcohol consumption, physical activity, and use of various medications, has been limited (Terry et al. 2007). Given the potential public health significance of this issue, we sought to clarify the association between hypertension and risk of death from external causes using mortality follow-up data from the Physicians' Health Study Enrollment Cohort.

Methods

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design

testing two primary prevention hypotheses: (1) whether 325 mg of aspirin taken every other day reduces CVD mortality (Steering Committee of the Physicians' Health Study Research Group 1989) and (2) whether 50 mg of β-carotene taken on alternate days decreases the incidence of cancer (Hennekens et al. 1996). Starting in 1982, letters of invitation, informed consent forms and baseline questionnaires were mailed to 261,248 potentially eligible US male physicians on the American Medical Association mailing list. By 27 February 1984, 112,528 physicians had responded to the initial enrollment questionnaire. These analyses are confined to the 82,037 respondents aged 39–85 years who at baseline provided self-reported BP measurements and had no prior history of myocardial infarction, stroke, cancer, TIA, peptic ulcers, or liver disease.

On the baseline questionnaire, physicians reported their cardiovascular risk factors including age, height (inches), weight (pounds), history of treatment for hypertension (never, past, or current) or hypercholesterolemia (never, past, or current), serum cholesterol (mg/dL), cigarette smoking (never, past, or current), frequency of vigorous exercise (<1/week or ≥1/week), alcohol use (rarely/never, <1 per week, ≥1 per week), history of diabetes mellitus (yes/no), current use of aspirin (≥1 per week) and current use of multivitamins (≥1 per week). Body mass index (kg/m^2) was calculated using weight and height. Self-reported systolic blood pressure (SBP) and diastolic blood pressure (DBP) were collected, which have been highly correlated with measured SBP ($r = 0.72$) and DBP ($r = 0.60$) in a sample of physicians (Klag et al. 1993). Individuals were placed in one of the following JNC 7 categories irrespective of treatment status: normal <120 mmHg systolic and <80 mmHg diastolic; pre-hypertension, 120–139 mmHg systolic or 80–89 mmHg diastolic; stage 1 hypertension, 140–159 mmHg systolic or 90–99 mmHg diastolic; stage 2 hypertension, ≥160 mmHg systolic or ≥100 mmHg diastolic.

Our primary endpoint was external cause of death. Death certificates were obtained for the respondents who died before 01 February 1988, using the National Death Index. The deaths were classified by trained nosologists using the first revision of the Ninth International Classification of Diseases (ICD-9) in conjunction with the Automated Classification of Medical Entities Decision Tables to manually select underlying cause of death. Deaths from external causes (ICD-9 E800-E999) were further categorized as external causes (deaths not due to suicide or homicide), i.e., those resulting from unintentional injuries. We also categorized "non-passive" deaths by further excluding unintentional injury deaths that were not likely due to actions taken by the victim, for example, death resulting from being a passenger in a fatal motor vehicle accident, death from falling objects, death during surgery, or death from reaction to therapeutic medication. We did not include the following causes of death in analyses of "non-passive" deaths: E800-E803, E804, E805, E806, E807, E810-E825, E837, E850-E879, and E890-E899, E900-E915, E916, E917.1, E929.4, E929.5, E930-E949, E980-E999.

Means and standard deviations (or percentages, when appropriate) were tabulated for the following individual risk factors according to the cause of death: SBP, DBP, age, body mass index, current cigarette smoking, current use of aspirin, vigorous physical activity, alcohol consumption, serum cholesterol, presence of hypertension, and history of the following: diabetes, angina, TIA, renal disease, high cholesterol, and use of medicine for hypertension or high cholesterol. (Cox 1972) were used to model the associations of blood pressure (BP) with all external causes of death (injuries, suicides, and homicides) and individual causes. Hazard ratios (HRs) and 95% confidence intervals (CIs) are cited.

Hypertension risk categories were based on the classifications outlined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Chobanian et al. 2003), as was described in detail above.

The multivariate model adjusted for age, cigarette smoking (current, former, never), physical activity (4 categories), body mass index, alcohol consumption, aspirin use (yes or no), and history of the following (yes or no): diabetes, renal disease, drug treatment for hypertension, and drug treatment for high cholesterol. We also examined whether there was a non-linear effect for the categorical SBP and DBP models (separately) in the multivariable model, in which we compared models with just the linear trend term with the model with both the linear trend plus quadratic (squared) linear trend term, and the −2 log likelihood calculated. All analyses were conducted using SAS 9.1 (SAS Institute Inc, Cary, NC) software. All p values were from two-sided tests.

Results

The average duration of follow-up (from receipt of the PHS enrollment questionnaire through death or 31 January 1988) for all 82,037 men was 5.4 years (a total of 446,641 person-years), and included 304 deaths from external causes (176 injuries, 119 suicides, and 9 homicides). Of the 176 external causes of death not due to suicide or homicide, 122 were considered as not "passive," e.g., they were drivers and not merely passengers in fatal automobile accidents.

Mean baseline BP levels and the prevalence of hypertension were greater for men who died from external deaths

and subcategories of these deaths than for the cohort as a whole (Table 1). Men who died of external causes were also more likely to smoke cigarettes at baseline, have a sedentary lifestyle, have a history of diabetes, and have a history of transient ischemic attacks.

Hypertension status was not associated with the risk of death from combined external causes (Table 2). When compared with individuals who had "normal" BP levels according to JNC 7, the multivariate-adjusted HRs (95% CIs) for pre-hypertension, stage 1 hypertension, and stage 2 hypertension were 0.99 (0.68, 1.45), 1.03 (0.66, 1.62), and 1.24 (0.62, 2.49), respectively. When all external deaths not due to suicide or homicide were separated and examined, the multivariate-adjusted HRs (95% CIs) for pre-hypertension, stage 1 hypertension, and stage 2 hypertension were 0.96 (0.57, 1.61), 1.08 (0.59, 1.96), and 1.81 (0.81, 4.06), respectively. When we examined only "non-passive" deaths, the multivariate-adjusted HR and 95% CIs for pre-hypertension, stage 1 hypertension, and stage 2 hypertension were 1.36 (0.69–2.66), 1.64 (0.76–3.54), and 4.10 (1.56–10.8), respectively. The latter statistically significant finding suggests the possibility of a positive association between hypertension and risk of death from non-passive unintentional injuries. Other statistically significant inverse predictors of non-passive deaths included age and physical activity level.

Although the number of deaths was too low to examine subcategories of non-passive deaths reliably, our results suggest that the association of hypertension status with death from falls may be particularly strong. The age-adjusted HR (95% CI) of falls for men with stage 2 hypertension (vs. normal) was 11.3 (95% CI 1.28, 99.4; $p = 0.03$), although this was based on very small numbers. The multivariate-adjusted HR for falls was similar (data not shown).

Based on the above results, we decided to further examine the relationship of BP levels with "non-passive" deaths. For these 122 deaths, there was a positive association between each increasing 10 mmHg category of SBP and DBP and an increased risk of death. The multivariate-adjusted HRs (95% CIs) for men with SBP levels of 110–119 mmHg and each successive 10 mmHg category when compared with men with SBP <110 mmHg (the referent category, limited to 2 deaths) were, respectively, 0.87 (0.19–3.95), 1.01 (0.24–4.26), 1.46 (0.35–6.14), 1.57 (0.36–6.89), 2.15 (0.44–10.6), 3.90 (0.74–20.5), and 5.12

Table 1 Self-reported baseline characteristics of men in the Physicians' Health Study Enrollment Cohort (USA, 1982–1984) according to cause of death

	All external deaths[a] ($n = 304$)	All injury deaths[b] ($n = 176$)	Injury deaths excluding "passive" deaths[c] ($n = 122$)	All deaths ($n = 3,451$)	All men ($n = 82,037$)
SBP (mean mmHg)	130.4	131.8	133.2	135.1	127.6
DBP (mean mmHg)	80.2	80.9	81.6	80.9	79.3
SBP ≥140 or DBP ≥90 (%)	31.6	35.2	36.9	44.1	24.2
Age at recruitment (mean years)	58.5	59.7	58.6	65.9	55.3
Body mass index (mean)	25.3	25.4	25.6	25.0	25.0
Any history of hypertension treatment (%)	25.9	28.7	25.0	37.0	18.9
Any history of high cholesterol (%)	13.1	14.2	11.1	16.0	14.6
Any history of high cholesterol treatment	5.3	6.4	3.2	4.1	2.5
Total cholesterol (mean mg/dl)	202.5	203.9	204.4	209.2	211.4
Current smoker (%)	21.8	20.6	17.2	19.3	12.2
Vigorous physical activity <1 time/week (%)	36.5	36.4	36.9	43.6	29.4
History of diabetes (%)	4.9	5.1	2.5	11.1	3.3
History of angina (%)	3.3	2.8	2.5	7.8	3.1
History of transient ischemic attack (%)	3.6	3.5	1.7	6.2	1.5
History of renal disease (%)	1.0	1.7	0.8	3.2	0.9
Current regular use of aspirin	36.0	31.4	27.7	37.3	29.3
No consumption of alcohol (%)	18.2	17.5	17.5	22.1	17.2

[a] All external causes of death, i.e., any death that is other than from natural causes (ICD-9 E800-E999)

[b] All external causes of death excluding "suicide and homicide" (E950-E969)

[c] All external causes of death excluding deaths that are not likely due to actions taken by the victim, for example, death resulting from being a passenger in a fatal motor vehicle accident, death from falling objects, death during surgery, death from reaction to therapeutic medication (E800-E803, E804, E805, E806, E807, E810-E825, E837, E850-E879, and E890-E899, E900-E915, E916, E917.1, E929.4, E929.5, E930-E949, E980-E999)

Table 2 Hazard ratios (95% CIs) of external causes of death by Joint National Committee 7 (JNC 7) Blood Pressure Classification (USA, 1982–1988)

Cause of death	JNC 7 Blood Pressure Classification[a]			
	Normal (n = 12,432)	Pre-hypertension (n = 49,772)	Stage 1 hypertension (n = 17,446)	Stage 2 hypertension (n = 2,387)
All external causes	39[b]	169	81	15
Age adjusted	1.00	1.00 (0.71–1.42)	1.18 (0.79–1.75)	1.45 (0.78–2.69)
Multivariate[c]	1.00	0.99 (0.68–1.45)	1.03 (0.66–1.62)	1.24 (0.62–2.49)
All injuries	21	93	50	12
Age adjusted	1.00	1.00 (0.62–1.61)	1.26 (0.74–2.13)	1.93 (0.92–4.04)
Multivariate[c]	1.00	0.96 (0.57–1.61)	1.08 (0.59–1.96)	1.81 (0.81–4.06)
Injuries excluding "passive" injuries	11	66	35	10
Age adjusted	1.00	1.41 (0.74–2.68)	1.90 (0.95–3.81)	3.69 (1.51–8.99)
Multivariate[c]	1.00	1.36 (0.69–2.66)	1.64 (0.76–3.54)	4.10 (1.56–10.8)

[a] Individuals were placed in one of the following JNC 7 categories: normal <120 mmHg systolic and <80 mmHg diastolic; pre-hypertension, 120–139 mmHg systolic or 80–89 mmHg diastolic; stage 1 hypertension, 140–159 mmHg systolic or 90–99 mmHg diastolic, stage 2 hypertension, ≥160 mmHg systolic or ≥100 mmHg diastolic

[b] Number of deaths

[c] Model includes covariates corresponding to age, smoking category, vigorous physical activity, body mass index, use of aspirin, use of alcohol, use of medicine for hypertension, use of medicine for high cholesterol, history of diabetes, and history of renal disease

(0.81–32.4). The test for linear trend was statistically significant ($p = 0.001$). Analyses for DBP in increasing 5 mmHg increments up to ≥100 mmHg when compared with the referent of DBP <70 mmHg showed a similar tendency towards an increasing risk of death, although the linear trend ($p = 0.24$) was not monotonic among the middle DBP categories. The results were similar when analyses were restricted to participants without history of antihypertensive medication use (data not shown). No significant non-linear associations were observed in separate models for either SBP or DBP.

Discussion

In this cohort of initially healthy, middle-aged and older male physicians, we found an increased risk of external causes of death not due to suicide or homicide among men with high BP, particularly among those with JNC 7 stage 2 hypertension. However, our results were statistically significant only for those deaths after exclusion of deaths that were classified as being "passive." This study represents one of the larger cohort studies of BP and external causes of death to date, although a maximum follow-up of 6.6 years resulted in a smaller number of deaths than the MRFIT cohort that benefited from 25 years of follow-up. The shorter follow-up likely helped to reduce misclassification by BP and potential confounding variables because these risk factors (including prescribed antihypertensive medicine formulations) tend to change over time. Notably, the strongest association between BP and risk of external causes of death was observed in MRFIT during the first 10 years of follow-up (Terry et al. 2007).

A notable strength of this study was the ability to evaluate the potential role of confounding, including that by lifestyle factors (smoking, alcohol consumption, and physical activity level), history of taking aspirin or medications for BP, high cholesterol and diabetes, cholesterol level, and other related factors. Because all study participants were practicing physicians, adjustment for education or SES variables was not necessary. These results suggest that confounding likely does not explain the positive association suggested in our data or that shown in MRFIT and some (Tamosiunas et al. 2005; Vartiainen et al. 1994; Farchi et al. 1987), but not all (Strandberg et al. 1995) previous studies.

Hypertension may lead to cerebrovascular damage and consequent cognitive or functional decline (Manolio et al. 2003; Raz et al. 2003; DeCarli et al. 1999), which then increases the risk of death from external causes. Hypertension-related pathological changes in the brain and its vasculature include vascular remodeling, impaired cerebral autoregulation, cerebral microbleeds, white matter lesions, unrecognized lacunar infarcts, and Alzheimer-like changes, such as amyloid angiopathy and cerebral atrophy (Manolio et al. 2003; Raz et al. 2003; DeCarli et al. 1999). These changes, particularly in white matter lesions, have been associated with declines in frontal lobe integrity and executive function (Raz et al. 2003; Tullberg et al. 2004; Prins et al. 2005), attention and reaction time (Anstey et al. 2005; Sierra et al. 2004), lower extremity mobility and balance (Onen et al. 2004; Starr et al. 2003), and, perhaps

as a consequence, with potentially fatal injuries, including those from motor vehicle accidents (Anstey et al. 2005) and falls (Kuo and Lipsitz 2004).

In conclusion, our study supports the findings from most (Tamosiunas et al. 2005; Vartiainen et al. 1994; Farchi et al. 1987), but not all (Strandberg et al. 1995), studies that examined the roles of BP and hypertension status on external causes of death. We found the strongest positive association among men with JNC 7 stage 2 hypertension and their risk of "non-passive" deaths, and it was the only statistically significant association. As with MRFIT (Terry et al. 2007), we observed the strongest magnitude of effect between hypertension and death from falls. Although our conclusions for all external causes of death and its subcategories must be tempered by relatively small case counts, unlike previous studies we comprehensively adjusted for potential confounders. Further studies are needed to explore potential causal mechanisms between elevated BP and the risk of external death.

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Conflict of interest None.

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