Published in final edited form as:
Prev Med. 2013 December ; 57(6): 807–812. doi:10.1016/j.ypmed.2013.09.006.

A Prospective Study of Variability in Systolic Blood Pressure and Mortality in a Rural Bangladeshi Population Cohort

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Abstract

Objective—Limited studies suggest that blood pressure variability over time is a risk factor of long-term cardiovascular outcomes. However, most of these were in populations with pre-existing CVD and studies in general population are lacking.

Methods—The study included 11,153 participants in a population-based, prospective cohort study in Araihazar, Bangladesh. Resting blood pressure was measured at baseline and every two years thereafter. Participants were followed-up for an average of 6.5 years (2002–2009).

Results—Male gender, older age, baseline SBP, and absence of betel leaf use were independently positively associated with greater SBP variability over time. There was a significant association between SBP variability and the risk of death from overall CVD, especially from major CVD events. The positive association with the risk of death from any cause and stroke in age- and sex-adjusted models was attenuated in fully-adjusted models. In addition, the hazard ratio (HR) of stroke mortality was greater for individuals with both high baseline and high SBP variability. Similar patterns of HRs were observed for all-cause and CVD mortality.

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Conflict of Interest: The authors declare there is no conflict of interest.

Conclusion—In this rural Bangladeshi population, variability in SBP contributes to the risk of death from CVD and may further potentiate the increased mortality risk associated with high SBP.

Keywords

blood pressure; cardiovascular disease; cerebrovascular disorders; heart diseases; mortality; variability

Introduction

Cardiovascular diseases (CVD) are the primary cause of death globally, accounting for approximately 30% of all deaths with over 80% of all cases occurring in low- and middle-income countries (World Health Organization (WHO), 2011). High blood pressure (BP) is the most prominent risk factor associated with CVD (Kaplan and Victor, 2009) and is the leading cause of deaths globally with the most significant contribution by low- and middle-income countries (Lawes et al, 2001; WHO, 2009). CVD mortality is projected to increase by approximately 30% by the year 2030 in low- and middle- income countries, comparing to 2008, while no significant change is projected in high-income countries (WHO, 2008). Therefore, there is a need to investigate the risk factors associated with CVD mortality with a special attention to populations from developing countries.

Variability in BP has long been considered a risk factor for CVD mortality among hypertensive people (Parati et al, 1987; Pringle et al, 2003) and there is also evidence for a positive association with left ventricular mass index, an important intermediate risk factor for CVD, in the general population (Sega et al, 2002). In recent years, several publications reported that long-term BP variability, on the scale of months through years, may also have a clinical significance (Muntner et al, 2011; Rothwell et al, 2010; Brunelli et al, 2008; Cuffe et al, 2006). However, most of these studies (except for Muntner et al, 2011) have focused on susceptible populations but not in general population.

In this study, using data from 11,153 apparently healthy individuals participating in an ongoing population-based cohort study in Araihazar, Bangladesh, we assessed the association of BP variability over time with the risk of death from any cause, overall CVD, major CVD events, stroke, and heart disease.

Materials and Methods

Study population

The study population consists of individuals participating in the ongoing population-based, prospective cohort study, Health Effects of Arsenic Longitudinal Study (HEALS), in Araihazar, Bangladesh established in 2000 to investigate the health effects of arsenic exposure from groundwater. Details of the study have been presented elsewhere (Ashan et al, 2006). A total of 11,746 apparently healthy individuals were recruited between October, 2000 and May, 2002 from a well-defined 25 km^2 area in Araihazar with a response rate of 97.5%. The key eligibility criteria were being married, being 18 years of age or older, and being a resident in the area for at least 5 years. Participants were followed up with in-home visits every two years, including a physical examination, blood pressure measurement, and

structured interview. Diabetes at baseline was assessed using questionnaire. The self-report status has been shown to be related to levels of HbA1c and urinary glucose level in our cohort (Chen et al, 2010). Both height and weight were measured three times at baseline and averaged. BMI was calculated as average weight in kilograms divided by average height in meters, squared (Pierce et al, 2010). The study procedures were approved by the Ethical Committee of the Bangladesh Medical Research Council and the Institutional Review Boards of Columbia University and the University of Chicago.

The present study included data from baseline, follow-up 1 (9/2002–5/2004), follow-up 2 (6/2004–8/2006), and follow-up 3 (1/2007/3/2009). Mean period between visits was 2.2 years. Blood pressure was measured at the baseline, first, second and third follow-ups with the same methodology as in the baseline and the participation rate was 97.5, 96.9, 93.6, and 92.2% of the cohort participants at the baseline, respectively. We limited the analysis to individuals who had their BP recorded at baseline and who completed at least one additional BP measurement during follow-up and estimated variability as the standard deviation (SD) across the study visits. Health awareness and knowledge about the etiology of hypertension is very limited in rural Bangladesh, and only 2–3 % individuals with high BP have any treatments in our cohort (Chen et al, 2006; Chen et al, 2007). We also excluded individuals with missing information regarding body mass index (BMI), betel leaf use, smoking status and education. The total number of individuals excluded was 593 (5% of total cohort). The distributions of other lifestyle and demographic variables among those excluded were very similar to the overall cohort (data not shown). The final study population included 11,153 subjects. Details of baseline characteristics of the entire cohort relative to the participants included in this analysis are presented in Appendix Table 1.

Blood pressure measurements

Briefly, blood pressure was measured by trained clinicians using an automatic sphygmomanometer (HEM 712-C; Omron Healthcare GmbH, Hamburg, Germany) (Chen et al, 2011; Chen et al, 2007; Pierce et al, 2010). This model has been validated to have 85 percent of readings falling within 5–10 mmHg of the mercury standard. Measurements were taken with participants in a seated position after 5 minutes of rest, with the cuff around the upper left arm, in accordance with recommended guidelines. Measurements were done in the right arm at all visits. Two additional measurements were taken after for respondents found to have a SBP of ≥140 mmHg and/or a DBP of ≥90 mmHg at the first measurement, and the measurement with the lowest blood pressure was recorded. Blood pressure data from individuals who were taking medicines for hypertension at the time of measurement during follow-up were censored (<2%). The number of participants who had their BP measured more than once was 1407, 1125, 1506, and 1229 in follow-ups 1,2,3, and 4 respectively. Study participants were asked to show all medicines they were taking regularly, and the interviewers recorded generic names. A total of 818 participants were hypertensive at baseline and only 110 participants were taking antihypertensive medicines at the time of baseline interview.

Follow-Up

The study outcome of interest was 1) all-cause mortality; 2) CVD mortality, defined as deaths due to disease of circulatory system (ICD-10 I00–I99); 3) major CVD mortality (ICD-10 I20–I25 and I60–I69); 4) stroke mortality (I60–I69); and 5) heart disease mortality, which included deaths due to ischemic heart disease (I20–I25) and deaths due to other forms of heart disease (I30–I52). We *a priori* combine deaths due to ischemic heart disease and other forms of heart disease in a category for heart disease (Chen et al, 2011). Deaths were identified among cohort participants from baseline to March 18, 2009 (end of third follow-up). Details of the methods for the assessment of causes of deaths are described elsewhere (Chen et al, 2011; Pierce et al, 2010; Argos et al, 2010). Briefly, we adapted a validated verbal autopsy procedure, developed by International Centre for Diarrhea Disease Research, Bangladesh (ICDDR, B) in collaboration with WHO. During the follow-up, upon receipt of a death reported by family or neighbors, a team of study physician and a trained social worker administered the verbal autopsy form to the next of kin. Medical records of the deceased were collected. Information on death certificates and biopsies was ascertained. Causes of deaths were coded by an outcome assessment committee blinded to participants' blood pressure records according to the WHO classification (WHO, 2007) and the International Classification of Diseases, 10^{th} Revision (ICD-10). ICDDR, B has used this method to ascertain causes of deaths since 1971 (Baqui et al, 1998; Sohel et al, 2009) and documented an overall 95% specificity and up to 85% sensitivity for cardiovascular deaths (Howard and Rothwell, 2009). We observed 113, 120, and 174 deaths during the first, second, and the third follow-up, respectively. The ascertainment for cause of death had a minimal loss, as previously described (Argos et al, 2010). We were unable to ascertain the relationship status of one informant. In three cases, we could not ascertain the causes of death.

Statistical Analysis

For each subject, we estimated SD of systolic BP (SBP) using all available longitudinal measurements of BP ascertained at baseline and during follow-up before death or end of the third biennial follow-up visit, whichever came earlier. We first conducted descriptive analyses to examine trends in baseline characteristics across tertiles of SD of SBP. In linear regression models, log-transformed SD of SBP was used as the dependent variable. We assessed the baseline characteristics first individually as the independent variables and then repeated the analysis including all the variables that were significantly related to the SD of SBP ($p < 0.05$) in the model.

We then used Cox proportional hazards models to estimate hazard ratios (HR) for deaths due to any cause, CVD, major CVD, heart disease, and stroke per increase in SD of SBP. The assumption of proportional hazards was examined by testing the cross product terms between covariate variables and log function of survival time, and P values for all the terms were >0.10. We used SD of SBP (log transformed) as a continuous variable first in an unadjusted model. In separate models, we adjusted potential confounders including age, sex, baseline SBP, and betel leaf use; these were risk factors of all-cause and CVD mortality that were also predictive of SD of SBP in our population, based on the results of the linear regression. Evidence from several epidemiologic studies has suggested that betel nut use,

which is common in South Asian, is related to CVD (Guh et al, 2007; Lin et al, 2008; Yen et al, 2008; Heck et al, 2012). Analyses with additional adjustments for BMI and smoking status were conducted; however the effect estimates did not change appreciably and therefore the results are not shown. We also calculated HRs comparing each of the higher tertiles of SD of SBP with the lowest tertile as the referent group to describe the shape of the associations.

In addition, we estimated the joint effect of baseline SBP and the SD of longitudinal SBP. We estimated hazard ratios for all-cause, overall CVD, major CVD, heart disease, and stroke mortality comparing joint status of baseline SBP and the SD of longitudinal SBP, with each variable dichotomized using the median in the population, using individuals with low baseline SBP and low SD of SBP as the reference group. Sensitivity analyses were conducted excluding individuals who were taking blood pressure medicine at baseline (n = 105). All analyses were conducted using R version 2.14.0.

Results

The average number of SBP measurements was 3.84 (range: 2–4). The characteristics of our study population were similar to those of the entire cohort (Appendix Table 1). The majority of study participants (88%) completed all four BP measurements, 8% exactly three and the remaining 2% completed only two. The mean SD of SBP, which did not differ by number of BP measurements available for analyses, was 10.17, 10.62, and 10.27, for participants who completed 2, 3, and 4 BP measurements, respectively. Summary of SBP per visit according to sex and age group is presented in Appendix Table 2.

Correlates of Standard Deviation of Longitudinal Systolic Blood Pressure

Participants with higher level of variation of SD in longitudinal SBP were more likely to be older, women, and to have a higher level of BMI, baseline SBP and diastolic BP (DBP) (Table 1). In addition, the proportion of participants who chew betel leaf was lower in increasing tertiles of SD of longitudinal SBP.

Table 2 shows relationships between selected cardiovascular disease risk factors and SD of SBP estimated using a linear regression. In model 1 we included age, sex, BMI, education, smoking status, baseline SBP and DBP, betel leaf use, diabetes status and well arsenic, alternatively one at the time. Each of the variables including age, sex, baseline SBP and betel leaf use was significantly related to the SD of the SBP after controlling for all the other variables (model 2). Age, sex, and baseline SBP were positively related to SD of the SBP, while betel leaf use was inversely related to it.

Association between Standard Deviation of Longitudinal SBP and Mortality

During an average of 6.5 years of follow-up, 333 participants died. Among them, 151 (45%) died from CVD (ICD-10 I00–I99), of which 66 died from stroke (I60–I69), and 127 died from heart disease, including 52 from ischemic heart disease (I20–I25) and 25 due to other forms of heart disease (I30–I52), which consisted mostly of heart failure (I50.0–I50.9, n = 24) and ventricular tachycardia (I47, n = 1).

Overall, there was a positive association between SD of SBP and all-cause mortality (Table 3). Participants in the highest tertile of SD of SBP were 1.66 (95% CI 1.30–2.13) times more likely to die. However, the association disappeared after adjusting for age and sex and other potential confounders (Models 1 and 2 in Table 3). The positive associations of the SD of SBP with all- and major- CVD mortality were significant in all three models when SD of SBP was considered as a continuous variable, although the point estimates were not always statistically significant. Participants in the highest tertile of SD of SBP were 1.27 (95% CI 0.85–1.92) and 1.70 (1.03–2.82) times more likely to die from any CVD and major CVD, respectively. There was also a positive, significant association between SD of SBP and stroke mortality in sex and age adjusted models, but the association was not significant with additional adjustments (p- trend = 0.16). In sensitivity analyses, the association did not differ appreciably after excluding 105 people taking antihypertensive medicine (not shown).

Stratified Analysis According to joint status of SD of SBP and Baseline SBP

Compared with individuals with low baseline SBP and low SD of SBP, the risk of death from any cause, all CVD, and major CVD was significantly greater among those with high baseline SBP and high SD of SBP in the age- and sex- adjusted model; on the other hand, the risk of death from any cause, all CVD, or major CVD was not statistically significant among participants with either high SD only or high SBP only. In the fully adjusted models, compared with individuals with low baseline SBP and low SD of SBP, the risk of death from overall CVD, major CVD, or stroke was significantly greater among those with high baseline SBP and high SD of SBP, but the risks of death from CVD were not statistically significant among participants with either high SD only or high SBP.

Discussion

In this rural Bangladeshi population, we found a positive association between variability in longitudinal SBP and the risk of death due to overall CVD, major CVD, and stroke. However, the association for all-cause mortality and mortality from CVD subtypes were attenuated after controlling for baseline systolic blood pressure and other variables. The main effect of longitudinal blood pressure variation on mortality from overall and major CVD was independent of usual blood pressure level. In stratified analysis however, we found that risk of all-cause, overall CVD, major CVD and stroke mortality was greater for individuals with high baseline and high SD of SBP than those with either high baseline SBP or high SD of SBP alone, suggesting that usual value and variability of SBP jointly increased mortality risk.

Several studies have reported an association between long-term BP variability and mortality among individual with pre-existing CVD (Rothwell et al, 2010; Brunelli et al, 2008). More recently, Muntner et al (2011) reported a positive association between long-term SBP variability and total mortality, independent of the usual level of systolic blood pressure in US adults. To the best of our knowledge, the present study is the first that investigated the relationship between variation in blood pressure and mortality in a rural population of a low-income country. We found that BP variability over time was significant related to the risk of overall CVD and major CVD but not all-cause mortality. There could be a few possible

reasons for the difference in the findings reported in this study and the ones reported by Muntner et al. First, although both studies considered the general population there are inherent differences in both populations in terms of socioeconomic development Bangladesh is one of the Least Developed Countries according to the United Nations' classification, and half of the study population did not have any formal education at baseline. Second, the usual SBP in the US population is much higher than that in rural Bangladeshi population. Also, the follow-up time in our study (6.5 years) was much shorter than that in Muntner et al (12–18 years). Visit-to-visit SBP variability observed over several years, as observed in the present study, may be more specifically related to CVD mortality.

We found that there was no joint effect of baseline SBP and high SD of SBP on heart disease mortality, implying that the positive associations observed for all-cause and CVD mortalities are driven by stroke mortality. Unlike the usual level of SBP which has a linear relationship between risk of both heart disease and stroke, variability of the SBP over time may be a risk factor unique to stroke. There have been a few hypotheses about the mechanisms by which visit-to-visit BP variation can cause cardiovascular events. For example, it could be an expression of some underlying cardiovascular pathology such as baroreceptor reflex dysfunction (Rothwell, 2010). Another explanation could be the use of calcium-channel blockers (reduce BP variability) or t β-blockers (increase BP variability) (Rothwell, 2010), which do not apply to our population as most study participants do not take medications.

Our study is innovative in that it is the first one considering a South-Asian population. The strength of this study lies in the use of a very large apparently healthy population cohort for which comprehensive data for all other risk factors were available. We cannot rule out the role of potential confounders such as physical activity and psychosocial stress that were not fully controlled for in the analyses. Potential confounding due to these factors could be controlled for to the extent that BMI and educational attainment were related to these factors. While it is possible that we introduced a bias due to exclusion of participants with less than 2 SBP measurements, the characteristics of the entire cohort are very similar to those of our study population (Appendix Table 1). On the other hand, the study population was very lean, with an average BMI of 19.8 kg/m^2, and our study is limited by the relatively short follow-up period. Therefore, the results may not be generalized to other populations, especially the western population.

Conclusion

In a rural Bangladeshi population, visit-to-visit SBP variability observed over an average of 6.5 years may be an important risk factor for overall and major CVD mortality, especially in individuals with a higher than usual SBP. The findings, if confirmed by future studies, may have public health implication that it is critical to reduce variation of SBP among those with a high SBP.

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Appendix

Appendix Table 1

Comparison of baseline characteristics: all cohort vs. subjects qualified for this study

Baseline Characteristics	All Cohort (n=11746)	This Study (n=11153)
Female, %	57.1	57.4
Age, years	37.1	37.0
Body mass index, kg/m^2	19.8	19.8
Education Length, years	3.5	3.5
Smoker (ever), %	35.5	35.0
Baseline SBP, mmHg	114.7	114.6
Baseline DBP, mmHg	74.0	73.9
Betel use (past/current), %	38.0	37.9
Betel number per day	5.1	5.1

Baseline Characteristics	All Cohort (n=11746)	This Study (n=11153)
Diabetes, %	2.1	2.2
Well As, µg/L	101.5	101.3
Urine As, µg/g creatinine	281.3	282.3

Appendix Table 2

Mean (SD) of SBP per visit according to sex and age group

	Visit			
	1	**2**	**3**	**4**
Male	115.4 (17.9)	116.4 (18.2)	120.5 (17.1)	113.1 (16.7)
Female	114.0 (17.5)	113.2 (17.6)	118.1 (16.5)	112.9 (16.8)
<35	112.0 (15.0)	111.4 (14.4)	115.9 (13.0)	110.1 (13.9
35–45	114.6 (17.7)	114.6 (17.6)	118.9 (16.6)	113.2 (16.9)
>45	120.1 (21.4)	121.2 (22.4)	126.0 (21.7)	118.9 (20.2)

Highlights

- Male gender, age, baseline SBP, and betel leaf use were associated with SBP variability.
- There was a positive association between SBP variability and the risk of death from CVD.
- Greater CVD and stroke mortality in those with both high SBP and high BP variability

Prev Med. Author manuscript; available in PMC 2015 February 03.

Table 1

Subject characteristics by tertile of standard deviation of systolic blood pressure. HEALS, 2002–2009.

Baseline Characteristics	Tertile of Standard Deviation of SBP			P- Trend*	Standard Error
	<7.36 (n = 3705)	7.36–11.49 (n = 3723)	>11.49 (n = 3725)		
Female, %	56	58.6	58.1	0.02	
Age, years	35.9	36.4	38.7	<0.01	0.09
BMI, kg/m^2	19.7	19.8	19.8	<0.01	0.03
Education Length, years	3.4	3.5	3.5	0.59	0.04
Smoker (ever), %	34.7	33.9	36.4	0.27	
Baseline SBP, mmHg	111.4	112.6	119.8	<0.01	0.17
Baseline DBP, mmHg	72.1	72.8	76.8	<0.01	0.11
Betel use (past/current), %	40.6	35.8	37.3	<0.01	
Diabetes, %	2.5	1.8	2.1	0.6	
Well Arsenic, µg/L	99.9	104.6	99.7	0.53	1.09

*Calculated by linear regression of standard deviation of log of SBP

Table 2

Coefficient estimates of characteristics associated with the standard deviation of log of SBP in a linear regression. HEALS, 2002–2009.

	Model 1		Model 2 *	
	Estimate (SE)	**P-value**	**Estimate (SE)**	**P-value**
Female	0.112 (0.016)	<0.01	0.094 (0.012)	<0.01
Age, 10years	0.071 (0.006)	<0.01	0.072 (0.006)	<0.01
BMI, 5 kg/m^2	−0.012 (0.009)	0.19		
Education, years	0.002 (0.002)	0.32		
Smoker (ever/never)	0.027 (0.017)	0.11		
Baseline SBP, 20 mmHg	0.133 (0.006)	<0.01	0.131 (0.006)	<0.01
Betel use (ever/never)	−0.028 (0.011)	0.01	−0.030 (0.011)	<0.01
Diabetes at baseline	−0.013 (0.038)	0.73		
Well As, 50 μg/L	0.002 (0.002)	0.35		

* includes only those variables shown to be significant in model 1 (P<0.05).

Table 3

Hazard ratios for all-cause, disease of the circulatory system, heart disease, and stroke mortality associated with standard deviation of SBP (n=11153). HEALS, 2002–2009.

	Hazard Ratio (95% CI) per standard deviation of log of SBP	Hazard Ratio (95% CI) by tertile of SD of SBP			
		1 (<7.36)	2 (7.36–11.49)	3 (>11.49)	p trend*
Follow-up person-years	73862.2	24497	24708.7	24656.5	
All-cause mortality					
n of deaths	333	100	64	169	
Model 1†	1.43 (1.18–1.74)	1 (ref)	0.63 (0.46–0.86)	1.66 (1.30–2.13)	<0.01
Model 2‡	1.04 (0.86–1.24)	1 (ref)	0.59 (0.43–0.80)	1.16 (0.90–1.49)	0.10
Model 3§	0.99 (0.82–1.19)	1 (ref)	0.57 (0.42–0.78)	1.00 (0.78–1.31)	0.64
All CVD					
n of deaths	151	35	23	93	
Model 1†	2.83 (2.08–3.86)	1 (ref)	0.64 (0.38–1.09)	2.63(1.78–3.88)	<0.01
Model 2‡	1.76 (1.31–2.36)	1 (ref)	0.58 (0.35–0.99)	1.71 (1.15–2.54)	<0.01
Model 3§	1.41 (1.04–1.92)	1 (ref)	0.56 (0.33–0.96)	1.27 (0.85–1.92)	0.09
Major CVD					
n of deaths	118	21	17	80	
Model 1†	4.68 (3.32–6.61)	1 (ref)	0.79 (0.42–1.50)	3.76 (2.32–6.08)	<0.01
Model 2‡	2.75 (1.94–3.90)	1 (ref)	0.71 (0.38–1.36)	2.39 (1.47–3.89)	<0.01
Model 3§	1.84 (1.27–2.66)	1 (ref)	0.69 (0.36–1.30)	1.70 (1.03–2.82)	<0.01
Heart disease					
n of deaths	102	38	31	33	
Model 1†	0.82 (0.61–1.09)	1 (ref)	0.81 (0.50–1.30)	0.86 (0.54–1.38)	0.53
Model 2‡	0.84 (0.63–1.12)	1 (ref	0.82 (0.51–1.32)	0.90 (0.56–1.44)	0.65
Model 3§	0.78 (0.56–1.08)	1 (ref)	0.78 (0.49–1.27)	0.89 (0.55–1.44)	0.62
Stroke					
n of deaths	66	12	10	44	
Model 1†	3.56 (2.23–5.70)	1 (ref)	0.82 (0.35–1.90)	3.63 (1.92–6.88)	<0.01

	Hazard Ratio (95% CI) per standard deviation of log of SBP	Hazard Ratio (95% CI) by tertile of SD of SBP			
		1 (<7.36)	2 (7.36–11.49)	3 (>11.49)	p trend*
Model 2‡	1.94 (1.24–3.05)	1 (ref)	0.73 (0.31–1.68)	2.15 (1.13–4.11)	<0.01
Model 3§	1.51 (0.93–2.44)	1 (ref)	0.70 (0.30–1.63)	1.43 (0.73–2.79)	0.16

*Estimated using tertiles as a categorical variable in the model

†Unadjusted

‡Adjusted for age (years) and sex

§Adjusted for age (years), sex, baseline SBP (mmHg), heart rate, and betel leaf use (ever/never)

Table 4

Hazard ratios by category of baseline SBP (high/low)* and SD of SBP (high/low)†. HEALS, 2002–2009.

	Hazard Ratio (95% CI)			
	Low baseline, low SD	**Low baseline, high SD**	**High baseline, low SD**	**High baseline, high SD**
n	3321	2519	2257	3056
Follow-up person-years	22049.8	16737.2	14870.1	20205.1
All-cause mortality				
n of deaths	67	59	68	139
Model 1‡	1 (ref)	1.16 (0.82–1.65)	1.51 (1.08–2.12)	2.26 (1.68–3.02)
Model 2§	1 (ref)	0.95 (0.67–1.35)	1.18 (0.84–1.65)	1.37 (1.01–1.84)
Model 3‖	1 (ref)	0.94 (0.66–1.33)	1.10 (0.78–1.55)	1.28 (0.95–1.73)
All CVD				
n of deaths	20	23	25	83
Model 1‡	1 (ref)	1.52 (0.83–2.76)	1.87 (1.04–3.36)	4.55 (2.79–7.42)
Model 2§	1 (ref)	1.20 (0.66–2.19)	1.40 (0.77–2.52)	2.55 (1.55–4.19)
Model 3‖	1 (ref)	1.17 (0.64–2.14)	1.32 (0.73–2.38)	2.40 (1.45–3.96)
Major CVD				
n of deaths	72	17	19	10
Model 1‡	1 (ref)	2.51 (1.17–5.39)	2.54 (1.16–5.55)	7.89 (4.07–15.29)
Model 2§	1 (ref)	1.96 (0.91–4.21)	1.87 (0.85–4.09)	4.27 (2.18–8.36)
Model 3‖	1 (ref)	1.91 (0.89–4.12)	1.81 (0.82–3.97)	4.10 (2.09–8.05)
Heart disease				
n of deaths	33	28	20	21
Model 1‡	1 (ref)	1.14 (0.69–1.88)	0.91 (0.52–1.59)	0.70 (0.40–1.21)
Model 2§	1 (ref)	1.15 (0.70–1.91)	0.94 (0.54–1.65)	0.74 (0.43–1.29)
Model 3‖	1 (ref)	1.11 (0.66–1.84)	0.97 (0.55–1.69)	0.75 (0.43–1.31)
Stroke				
n of deaths	5	9	11	41
Model 1‡	1 (ref)	2.38 (0.80–7.09)	3.30 (1.15–9.50)	9.02 (3.56–22.83)
Model 2§	1 (ref)	1.75 (0.59–5.24)	2.30 (0.80–6.64)	4.42 (1.72–11.32)
Model 3‖	1 (ref)	1.74 (0.58–5.21)	2.33 (0.80–6.75)	4.43 (1.72–11.40)

*Based on median (=113 mmHg)

†Based on median (=9.32 mmHg)

‡Unadjusted

§Adjusted for age (years) and sex

‖Adjusted for age (years), sex, heart rate, and betel leaf use (ever/never)