Blood pressure categories and long-term risk of cardiovascular disease by age groups in Japanese men and women

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Abstract

A blood pressure (BP) category defined with both systolic (SBP) and diastolic blood pressure (DBP) is commonly used. However, BP category-specific cardiovascular disease (CVD) risk has not been thoroughly investigated in aged populations. The aim of this study is to assess long-term CVD risk and its impact according to BP categories by age groups.

Pooling individual data from 10 cohorts, we studied 67,309 Japanese men and women (40 to 89 years) free of CVD at baseline according to three age groups: “middle-aged” (40-64 years), “elderly” (65-74 years), and “very elderly” (75-89 years). BP was classified according to the 2009 Japanese Society of Hypertension guidelines. Cox models were used to estimate multivariable adjusted hazard ratios for CVD death.

We observed 1,944 CVD deaths over a mean follow-up of 10.2 years. In all age groups, the overall relationship of BP categories with CVD risk was positive and graded with greater strength seen with younger age. We observed a trend of increase in risk from SBP/DBP ≥130/85 mmHg in the very elderly, and a significant increase from SBP/DBP ≥120/80 mmHg in the other age groups. The population attributable fractions (PAFs) of CVD death beyond the SBP/DBP <120/80 mmHg category ranged from 23.4% in the very elderly to 60.3% in the middle-aged.

We found an overall graded increase in CVD risk according to BP category in the very elderly. The corresponding PAF suggest that keeping BP levels low is an important strategy for

primary CVD prevention even in an elderly population.

Key Words: blood pressure category, cardiovascular death, cohort, elderly, population attributable fraction

INTRODUCTION

Epidemiological studies have shown that the effect of both systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the risk for cardiovascular disease (CVD) is continuous and consistent [1, 2]. Because both SBP and DBP are independent predictors of CVD risk [3-7], current guidelines on adult blood pressure (BP) management have agreed on the following: (1) BP category is defined by taking both SBP and DBP into account, and (2) the most favorable BP category is SBP <120 mmHg and DBP <80 mmHg, irrespective of age [8-11].

Although such BP categorization is widely used, only limited evidence is available that assesses long-term cardiovascular disease (CVD) risk according to BP categories, particularly among an elderly population. Given the worldwide trend of an aging [12], assessing long-term risk of elevated BP and its impact on aged population is increasingly important from both clinical and public health standpoints. The Framingham Heart Study reported graded increases in major CVD risk across higher BP categories among 1932 participants aged 80 years or older [13]. However, their follow-up period was relatively short (mean, 2.7 years) [13]. Therefore, long-term CVD risk was not fully demonstrated in that study. Other Western studies seeking BP-category specific risk on CVD events were based on subjects aged 75 years or younger [5, 14-16]. Epidemiological studies on long-term CVD risk among an elderly population are also limited [17, 18], hence needed[19], in Asia.

The objectives of this study are to (1) estimate long-term CVD mortality risk according to BP categories defined by both SBP and DBP; (2) examine whether the relationship of BP category and CVD risk differs by age groups; and (3) compare the impact of increased BP on long-term CVD risk among different age groups by population attributable fractions (PAFs). We particularly focused on an elderly population.

METHODS

Design

This study is a part of a pooling project in which individual participants' data from 13 observational cohorts across Japan were combined. The project was designed to examine the relationship between disease mortality and various exposure factors including laboratory and lifestyle/behavioral factors. The project is called Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN). The inclusion criteria for a cohort were as follows: collection of health examination measures, follow-up of almost 10 years, and a number of participants greater than 1,000. Both nationwide and regional cohort studies were included. Other details were reported elsewhere [20].

Study population

Ten of 13 cohorts provided data on cause of death (n=90,528). Of those, we used the following exclusion criteria for the present study: age younger than 40 years or older than 89 years at baseline (n=10,528); history of cardiovascular disease at baseline (n=5,031); missing values for SBP, DBP, or both (n=147); and missing adjusting covariates (n=7,513). Thus, 67,309 individuals from 10 cohort studies were pooled (Tanno-Sobetsu, Ohsaki, Ohasama, Oyabe, YKK workers, the Radiation Effects Research Foundation (RFRF) cohort, Hsayama, JACC study, NIPPON DATA80, and NIPPON DATA90; see supplemental TableS1 for demographics of each cohort).

Death ascertainment

In accordance with the Family Registration Law in Japan, all death certificates are forwarded to the Ministry of Health, Labour, and Welfare via the public health center in the area of residency. Registration of death is required by Law and believed to be complete. The underlying cause of death is coded according to *the International Classification of Disease* (ICD) for the National Vital Statistics based on the criteria proposed by World Health Organization [21].

Cause of death was sought in great detail using the available sources in each cohort study. In most studies, death certificates were reviewed and/or the National Vital Statistics were used

after obtaining permission. Other sources used in some studies included autopsy, medical records, health examination, and questionnaires. Cause of death was coded based on either ICD-9 or ICD-10. Classification codes used in the study were as follows: death from CVD (390-459 by ICD9; I00-I99 by ICD10), total stroke (410-414 or 430-438; I20-I25 or I60-I69), ischemic stroke (433 or 434 or 437.8; I63 or I69.3), intracerebral hemorrhage (431-432; I61 or I69.1), coronary heart disease (CHD) (410-414; I20-I25), and heart failure (428; I50).

BP measurement

The detailed information for BP measurement method in each cohort was provided in supplemental table S2. BP measurements were obtained using a mercury sphygmomanometer from a participant in a seated position in all but two cohort studies. In one cohort (Ohasama), an automated device was used[22]. In the other study (JACC), BP values were based on self-recorded values after BP was measured at a health check-up[23]. In most cohorts, BP was measured once with a participant in seated position after a rest.

BP categories

Participants were categorized according to the modified classification of 2009 Japanese Society of Hypertension guidelines (JSH2009) [10]. The cut-off values for the BP classification were same as the 2007 Guidelines by the European Society of Hypertension and of the

European Society of Cardiology (ESH-ESC 2007) [8]. Optimal BP was defined as SBP <120 mm Hg and DBP <80 mm Hg; the corresponding SBP and DBP values were 120–129 mm Hg and 80–84 mm Hg for normal/non-optimal BP, 130–139 mm Hg or 85–89 mm Hg (whichever was greater) for high-normal BP, 140–159 mm Hg or 90–99 mm Hg for Grade I hypertension, 160–179 mm Hg or 100–109 mm Hg for Grade II hypertension, and ≥180 mm Hg or ≥110 mm Hg for Grade III hypertension.

Statistical Analysis

We estimated multivariable adjusted hazard ratios (HRs) of death from total CVD and its subtypes for each BP category by Cox proportional hazards models in reference to the optimal BP category. We constructed two models to adjust for potential confounders. First, we adjusted for age (years), sex and cohort (model 1). Second, we further adjusted for serum total cholesterol (mmol/L), body mass index (BMI, kg/m^2), smoking status (current, past, never)[24], and alcohol intake (current, past, never) (model 2).

To examine whether the relationship of BP category and risk of CVD death differed by age, we divided participants into three groups based on their age at baseline: “middle-aged” represented those 40 to 64 years, “elderly” represented those 65 to 74 years, and “very elderly” represented those 75 to 89 years. Hazard ratio (HR) and the corresponding PAF of CVD

deaths were estimated for each BP category in each age group. In order to assess heterogeneity, we assumed monotonic association of CVD risk with BP-categories, and created pertinent variables. In assessing heterogeneity among cohorts, we created a forest plot. PAF was calculated as pd×(RR-1)/RR, where pd represents the proportion of exposed deaths in a specific BP category, and RR is the corresponding multivariable adjusted HR in reference to optimal BP category[25]. Additionally, we calculated gender-specific mortality risks and PAFs for CVD, total stroke, ischemic stroke, intracerebral hemorrhage, CHD, and heart failure according to the BP categories. In testing statistical evidence of interaction by sex and BP category on the effect of CVD risk, we first visually confirmed the overall positive relationship between BP category and CVD risk in both sexes. Then, we created an ordinal variable for BP category and its interaction term with sex, and inserted them in the models.

We performed the following sensitivity analyses: (a) excluding those who died from any cause within the first 3 years with an attempt to eliminate potential reverse causality by low BP [26, 27], (b) restricting the subjects to non-users of anti-hypertensive medication at baseline, and (c) adding diabetes mellitus (DM) status (yes, no) into the models among those participants with diabetes-defining variables available (n=36,393). We defined DM as either fasting glucose of ≥126mg/dL (7.0 mmol/L), or casual glucose of ≥200mg/dL (11.1 mmol/L), or hemoglobin A1c of ≥6.5%, or history of DM, or taking medication for DM.

All statistical analyses were performed using SAS version 9.13 (SAS Institute Inc, Cary, NC). All of the *P* values for statistical tests were two-tailed, and *P* values less than 0.05 were regarded as statistically significant. The study protocol was approved by the internal review board at each study center.

RESULTS

The participants' characteristics at baseline according to BP category are shown in Table 1. The proportions of each BP category among all the participants (n=67,309) were 21.9% (optimal BP), 20.2% (normal/non-optimal BP), 21.3% (high-normal BP), 24.9% (Grade I hypertension), 9.0% (Grade II hypertension), and 2.7% (Grade III hypertension) at baseline. Compared with participants in higher BP categories, those in the optimal BP category tended to be younger and have a lower BMI and lower total cholesterol level at baseline. The number (%) of those categorized as the middle-aged, elderly, and very elderly were 49,935 (74.2%), 13,707 (20.4%), and 3,667 (5.4%), respectively.

During a mean follow up of 10.2 years, we observed 1,944 CVD deaths; 917 for total stroke, 479 for ischemic stroke, 220 for intracerebral hemorrhage, 388 for CHD, and 343 for heart failure in all age-groups combined. In the Cox regression models, CVD risk increased almost

continuously as BP category advanced. In disease-specific analyses, risk of total stroke and CHD increased similarly as BP category advanced (see supplemental TableS2). PAF estimates indicated that elimination of normal/non-optimal BP to Grade III hypertension could have prevented almost half of CVD deaths. Results were similar in both sexes with no statistical evidence of interaction (*P* for interaction by sex 0.95) (see supplemental TableS3, TableS4 for sex-specific results).

Crude death rates, adjusted hazard ratios, and PAFs according to BP category for each age group were shown in Table 2. The overall relationship between BP categories and CVD risk was positive and graded in all age groups with greater strength of association seen with younger group (*P* for heterogeneity<0.001). For both the middle-aged and elderly groups, CVD risk in reference to optimal BP category increased significantly from the normal/non-optimal BP category and continued beyond this category. For the very elderly group, in contrast, both optimal and normal/non-optimal BP categories appeared to be at the lowest CVD risk. The PAFs of CVD death beyond optimal BP category tended to be greater in younger groups, accounting for 60%, 49%, and 23% of all CVD deaths in the middle-aged, elderly, and very elderly groups, respectively. There is no statistical evidence that these trends differ by sex in any of the age groups (*P*s for interaction by sex were 0.23, 0.11, and 0.50 for the middle-aged, elderly, and very elderly, respectively). (For sex-specific results by

age-group, see supplemental TableS5, TableS6).

The forest plot by cohort indicated apparently stronger effect of BP in the YKK-workers cohort than other cohorts (Supplement Figure S1). However, the exclusion of this cohort did not change the results substantially (data not shown). We did not observe clear difference by methods of BP-measurement in the forest plot.

In the first sensitivity analyses excluding deaths within the first 3 years, the observed association of BP category with CVD death became stronger in the very elderly group compared to that of the main result such that CVD risk significantly increased from the high-normal BP category and up (Table 3). Results in other age groups were similar to those in the main analysis. In the second sensitivity analysis, restricted to non-users of anti-hypertensive medication at baseline (29,097 participants, 823 CVD deaths), we observed similar results to the main analysis in all age groups (see supplemental TableS7). In the third sensitivity analysis including DM status in the model, the relationship of BP categories with CVD risk was attenuated in both the elderly and very elderly groups, whereas the relationship was slightly strengthened in the middle-aged group (see supplemental TableS8).

DISCUSSION

This pooled analysis of 10 well-qualified, prospective cohort studies in Japan enabled us to investigate detailed relationship of BP categories to long-term CVD mortality risk in a broad age range. We found an overall positive relationship in all age groups studied. In the middle-aged and elderly groups, the risk was lowest at the optimal BP category. Importantly, the relationship appeared to increase from the high-normal BP category in a graded fashion even in the very elderly. The relationship became stronger in this age group when excluding the first 3 years of death. Another important finding of our study is that an impact of elevated BP, estimated by PAF, remained substantial in older groups, suggesting that maintaining optimal BP could have eliminated as many as one quarter of CVD deaths in the very elderly and half of those in the elderly.

In many guidelines, categorization of BP is similar with respect to use of both SBP and DBP to define a category, and the same cut-off values being used irrespective of age [8-11]. However, only a few studies have examined BP category-specific CVD risk in an elderly population. To our knowledge, this is the first observational study that has demonstrated a long-term CVD risk and its impact according to BP categories in a group of very elderly Asian men and women aged 75 or older. From North America/European regions, the Framingham Heart Study (FHS) showed that major CVD risk increased in a graded fashion with advancing BP categories among those aged 80 years or older [13]. Most other studies from the regions

examined populations aged 75 years or younger [5, 14-16]. The FHS observed 336 CVD events among 1932 elderly over a mean of 2.7 years [13]. Compared with the FHS, we observed more than five times as many CVD events among twice as many elderly participants over a mean of 10.2 years. Furthermore, the number of BP categories we divided into was six as compared to four in FHS using a modified version of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guidelines [9]. This allows us to show finer BP-category specific CVD risks such as those for normal/non-optimal BP, or high-normal BP categories. Nevertheless, our results were broadly consistent with those in the FHS. There are a few large-scale meta-analyses, with individual participants data pooled, that studied association between blood pressure and CVD risk: the Prospective Studies Collaboration (PSC)[2] and The Asia Pacific Cohort Studies Collaboration (APCSC)[28]. Having the consistent results with these studies, our study has a significant difference from them with respect to BP measurements. The PSC and APCSC used either continuous DBP or SBP alone, whereas we used BP categories that accounted for both SBP and DBP. Several studies from Japan have reported both BP category-specific risk and/or PAF on CVD events [29-33]. Because of the small sample sizes, however, none of them sought detailed estimates for the very elderly population aged 75 or older as we did in the present study. A recent large prospective study from China showed both BP category-specific risk and PAF on CVD events [18]. However, this study provided only limited information with regard to

BP-category specific risk and impact among the very elderly population because they grouped those aged 65 years or older together and used fewer BP categories that are similar to those in FHS.

When excluding the first 3 years of death in the very elderly, we observed a stronger overall relationship between BP category and CVD risk with a significant increase in risk seen from the high-normal BP category and up. This observation may suggest the presence of reverse causality in which a poor health condition could have caused a lower BP [34, 35]. Exclusion of the first few years of deaths from analysis was proposed as one way to deal with such reverse causality, particularly when analyzing an elderly population [26, 27, 35]. Therefore, the lack of difference in CVD risk between the lowest two BP categories in the very elderly group may be attributed to reverse causality. Another possible explanation is due to an attenuated strength of association of BP with CVD risk in this age group compared to younger age groups [3, 28].

We observed significant difference in strength of association between BP and CVD risk (i.e. difference in relative risk for CVD) by age-group. Such heterogeneity in the effect of blood pressure by age has been observed consistently in many large observational studies.[18, 28, 32, 36] However, the recent meta-analysis of clinical trials by Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) concluded that there was no evidence for the statistical

heterogeneity in the effect of blood pressure lowering therapy on the CVD risk between younger and older subjects.[37] We speculate this contrast could be due to difference in observational study and clinical trial, and/or due to underpower of the BPLTTC study as the authors of the study pointed out by themselves.[37]

Regarding sex difference, we observed that absolute risk for CVD was generally higher in men than in women in all age-groups, while the relative risk of BP categories (expressed in hazard ratio) for CVD was similar between men and women (Supplemental tables S4 through S7). These findings were consistent with previous large observational studies.[18, 38]

The PAF estimates calculated in our study imply greater impact of BP on CVD risk than that of smoking [24, 39, 40] or elevated cholesterol [41] among a Japanese population. Combined with the observed lower CVD risks associated with lower BP categories, the results endorse maintaining low BP throughout one's life as an important strategy for CVD prevention both at an individual level as well as at population level. It should be emphasized, however, that our results do not necessarily endorse pharmaceutical treatment for hypertension because the study design was observational among a general population, not interventional on a group of patients. In fact, recent studies indicated that use of antihypertensive medication is unlikely to lower the risk to the same level as those who remain in low BP categories without such treatment [42]. Furthermore, evidence on pharmaceutical treatment for hypertension in the very

elderly is still limited, as stated in the recent consensus document by the American College of Cardiology Foundation and the American Heart Association [43].

Several limitations need to be considered when interpreting our results. First, we did not take into account for use or non-use of anti-hypertensive medication in the main analyses due to a substantial amount of missing information. However, the sensitivity analysis restricted to non-users of such medication at baseline showed similar results to the main analyses in all three age groups. Thus, it is less likely that this limitation would change our inference materially. Second, we based on a single occasion of blood pressure measurements, and did not account for regression dilution bias [2]. Therefore, the results of the study are likely to underestimate of true association. Third, our estimates in the main analyses were not adjusted for DM. However, we found qualitatively similar results in the sensitivity analyses that adjusted for DM. Therefore, the influence of such a limitation on our conclusion would likely be small. Strength of the study includes a prospective design with long follow-up period (over 10 years). Other strength is that the results are likely to be generalizable to wide age range of adult men and women given the nature of our samples obtained from across the nation.

In summary, we observed a graded positive trend in CVD mortality risk from the high-normal BP category and up (SBP/DBP>130/85 mmHg) among the very elderly, and a significant increase in risk from normal/non-optimal BP category and up (SBP/DBP>120/80 mmHg)

among the middle-aged and elderly groups. The strength of association between BP categories and CVD risk was attenuated but remained positive and graded in the very elderly. PAFs revealed that keeping BP level low could avoid one quarter of CVD deaths in the very elderly and one half of those in the elderly. These findings suggest that maintaining low BP is an important strategy for primary CVD prevention in an elderly population even such as those aged 75 to 89 years.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary tables available at *Hypertension Research*'s website

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Table 1. Baseline characteristics of participants according to blood pressure category

	Blood pressure category*						
Variable	Optimal (N=14764)	Normal/non-optimal (N=13607)	High-normal (N=14325)	Grade I hypertension (N=16729)	Grade II hypertension (N=6079)	Grade III hypertension (N=1805)	Total (N=67309)
Women, %	66.1%	60.0%	56.8%	55.4%	53.6%	51.2%	58.7%
Age, mean (SD), years	53.7 (9.7)	55.5 (10.0)	58.0 (10.0)	59.9 (10.0)	61.5 (10.0)	62.1 (10.4)	57.4 (10.3)
Body mass index, mean (SD), kg/m^2	22.2 (2.8)	23.0 (2.9)	23.3 (3.0)	23.7 (3.2)	24.0 (3.4)	24.1 (3.6)	23.2 (3.1)
Total cholesterol, mean (SD), mmol/L†	5.05 (0.91)	5.11 (0.93)	5.21 (0.94)	5.23 (0.97)	5.24 (0.99)	5.27 (1.05)	5.16 (0.95)

Smoking							
Never, %	69.5%	66.2%	64.4%	63.1%	61.1%	58.0%	65.1%
Past, %	6.7%	9.0%	10.5%	11.6%	12.4%	12.9%	9.9%
Current, %	23.8%	24.8%	25.2%	25.3%	26.5%	29.1%	25.1%
Drinking							
Never, %	61.5%	57.7%	55.6%	54.8%	53.7%	51.5%	56.8%
Past, %	2.7%	2.5%	2.8%	2.8%	3.0%	3.2%	2.8%
Current, %	35.8%	39.8%	41.6%	42.4%	43.3%	45.3%	40.4%

* Blood pressure categories were defined as follows; "Optimal" as systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg; the corresponding systolic and diastolic blood pressure values were 120–129 mm Hg and 80–84 mm Hg for "Normal/non-optimal," 130–139 mm Hg or 85–89 mm Hg (whichever was greater) for "high-normal," 140–159 mm Hg or 90–99 mm Hg for "Grade I hypertension," 160–179 mm Hg or 100–109 mm Hg for "Grade II hypertension," and ≥180 mm Hg or ≥110 mm Hg for "Grade III hypertension." †The conversion factor for total cholesterol level from mmol/L to mg/dL is 38.67.

Table 2. Cardiovascular death according to blood pressure categories by age group

	Optimal	Normal/non-optimal	High-normal	Grade I hypertension	Grade II hypertension	Grade III hypertension	Total
Very elderly (75-89y)							
Number at risk	350	483	726	1251	616	241	3667
Person-year	2627	3786	5563	9655	4855	1810	28296
CVD death	38	45	105	206	137	60	591
Crude rate*	14.46	11.89	18.88	21.34	28.22	33.15	20.89
HR† (95% CI)	1	0.83 (0.54-1.28)	1.27 (0.87-1.84)	1.38 (0.97-1.97)	1.46 (1.01-2.12)	1.73 (1.14-2.64)	
PAF‡	-	-1.6%	3.7%	9.7%	7.3%	4.3%	23.4%

Elderly (65-74y)							
Number at risk	1880	2227	3105	4290	1735	470	13707
Person-year	16086	19202	26249	38491	15973	4391	120392
CVD death	45	96	104	267	146	66	724
Crude rate*	2.80	5.00	3.96	6.94	9.14	15.03	6.01
HR† (95% CI)	1	1.76 (1.23-2.51)	1.40 (0.99-1.99)	2.20 (1.59-3.03)	2.64 (1.87-3.73)	3.96 (2.67-5.85)	
PAF‡	-	5.7%	4.1%	20.1%	12.5%	6.8%	49.3%
Middle-aged (40-64y)							
Number at risk	12534	10897	10494	11188	3728	1094	49935
Person-year	132300	117254	109424	122301	40846	12756	534880
CVD death	51	87	102	194	124	71	629
Crude rate*	0.39	0.74	0.93	1.59	3.04	5.57	1.18

HR† (95% CI)	1	1.77 (1.25-2.51)	1.94 (1.38-2.73)	2.99 (2.17-4.11)	5.23 (3.71-7.35)	8.50 (5.81-12.43)	
PAF‡	-	6.0%	7.9%	20.5%	15.9%	10.0%	60.3%

* Crude rate was expressed as per 1000 person-year. †Hazard ratio was adjusted for age, sex, cohort, body mass index (kg/m^2), total cholesterol (mmol/L), smoking, and drinking (model 2). ‡PAF estimate was based on the hazard ratio obtained by model 2.

HR indicates hazard ratio; 95%CI, 95% confidence intervals; PAF, population attributable fraction; CVD, cardiovascular disease.

Table 3. Risk of cardiovascular death in the subgroup with those died in the first 3 years excluded

	Optimal	Normal/non-optimal	High-normal	Grade I hypertension	Grade II hypertension	Grade III hypertension	Total
Very elderly (75-89y)							
No. at risk	296	429	648	1087	518	190	3168
Person-year	2518	3655	5372	9298	4620	1712	27175
CVD death	20	34	81	150	94	40	419
Crude rate*	7.94	9.3	15.08	16.13	20.35	23.37	15.42
HR†	1	1.17 (0.67-2.04)	1.87 (1.14-3.05)	1.91 (1.19-3.07)	1.83 (1.12-3.01)	2.14 (1.23-3.72)	-
Elderly (65-74y)							
No. at risk	1829	2141	2980	4136	1655	437	13178

Person-year	15970	18998	25923	38126	15789	4315	119120
CVD death	39	78	77	223	117	51	585
Crude rate*	2.44	4.11	2.97	5.85	7.41	11.82	4.91
HR†	1	1.62 (1.10-2.38)	1.19 (0.81-1.76)	2.01 (1.42-2.85)	2.26 (1.55-3.29)	3.28 (2.13-5.04)	-
Middle-aged (40-64y)							
No. at risk	12440	10811	10400	11057	3657	1066	49431
Person-year	132096	117053	109187	121997	40667	12700	533700
CVD death	40	69	87	155	102	60	513
Crude rate*	0.3	0.59	0.8	1.27	2.51	4.72	0.96
HR†	1	1.75 (1.19-2.60)	2.08 (1.43-3.05)	2.91 (2.03-4.16)	5.21 (3.55-7.64)	8.39 (5.50-12.8)	-

*Crude rate was expressed as per 1000 person-year. †Hazard ratio (95% confidence interval) adjusted for age (years), sex, cohort, body mass index (kg/m^2), total cholesterol (mmol/L), smoking (current, never, past), and drinking (current, never, past)

CVD indicates cardiovascular disease; HR, hazard ratio.