Associations of Dietary Intakes of Vitamins B1 and B3 with Risk of Mortality from Cardiovascular Disease among Japanese Men and Women: the Japan Collaborative Cohort Study

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Running title: Vitamins B1 and B3 intakes and cardiovascular mortality.
Abstract:

Purpose: We aimed to examine the association of dietary vitamin B1 and B3 intakes with risk of mortality from cardiovascular disease (CVD) among Japanese men and women aged 40 to 79 years using the Japan Collaborative Cohort study (JACC), a nationwide, community-based prospective study.

Methods: The Cox proportional hazard model estimated the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals of CVD mortality across increasing energy-adjusted quintiles of dietary vitamins B1 and B3 intakes among 58,302 JACC study’s participants (22,989 men and 35,313 women) who completed a food frequency questionnaire.

Results: During 960,225 person-years of follow-up, we documented a total of 3,371 CVD deaths. After adjustment for age, sex, and other CVD risk factors, HRs of mortality from ischemic heart disease, myocardial infarction, and heart failure in the highest versus lowest vitamin B1 intake quintiles were 0.57 (0.40-0.80; \( P \) for trend <0.01), 0.56 (0.37-0.82; \( P \) for trend <0.01), and 0.65 (0.45-0.96; \( P \) for trend =0.13). The multivariable HR of myocardial infarction mortality in the highest versus lowest vitamin B3 intake quintiles was 0.66 (0.48-0.90; \( P \) for trend = 0.02). A tendency towards a reduced risk of hemorrhagic stroke mortality was observed with a higher dietary intake of vitamin B3; HR: 0.74 (0.55-1.01) but not vitamin B1.

Conclusions: Higher dietary intakes of vitamins B1 and B3 were inversely associated with mortality from ischemic heart disease and a higher dietary intake of vitamin B1 was inversely associated with a reduced risk of mortality from heart failure among Japanese men and women.

Keywords: Dietary Vitamin B1; dietary vitamin B3; cardiovascular disease; cohort study.
Introduction

Vitamin B complex exerts its function in energy metabolism, immune function, and DNA synthesis, methylation, and repair \(^{(1)}\). Vitamin B deficiency has been associated with cardiovascular disorders, particularly in ageing population \(^{(1)}\).

Among the B complex group, vitamin B1 and vitamin B3 come mainly from cereals, beef and pork, seeds and nuts, and yeast \(^{(2)}\). Vitamin B1 deficiency results in beriberi, a neurological and cardiovascular disorder \(^{(3)}\), while deficient vitamin B3 can cause pellagra-induced dilated cardiomyopathy \(^{(4)}\). The potential positive impacts of vitamin B1 and B3 on cardiovascular health were suggested in several animal studies and supplemental clinical trials. In a Langendorff perfused rat hearts, vitamin B1 excreted protective effects against myocardial ischemic injury via maintaining mitochondrial size and adenosine triphosphate (ATP) levels \(^{(5)}\). A randomized controlled trial (RCT) on chronic heart failure patients who used diuretics reported that 300 mg/day of vitamin B1 supplementation for 28 days increased the left ventricular ejection fraction by 3.9% \(^{(6)}\). On the other hand, 1500 to 2000 mg/day vitamin B3 supplementation was shown to decrease low-density lipoprotein cholesterol (LDL-C) level, triglyceride, and lipoprotein(a) levels, while increasing high-density lipoprotein cholesterol (HDL-C) \(^{(7, 8)}\). A meta-analysis of clinical trials suggested that vitamin B3 supplements significantly reduced major coronary events, stroke, and other cardiovascular events \(^{(9)}\).

Despite the abundant evidence on cardiovascular beneficial effects of vitamins B1 and B3 from animal studies \(^{(3, 10, 11)}\) and supplemental clinical trials \(^{(12, 13)}\); however, no human observational studies so far have investigated the associations of dietary vitamins B1 and B3 intakes with risk of CVD. Previous studies indicated that food sources rich in vitamins B1 and B3 such as fish/seafood and vegetables were associated with a reduced risk of mortality from CVD \(^{(14, 15)}\). Yet, the evidence on dietary vitamin B complex/CVD association was mainly directed to vitamin B2, B6, B12, and folate, while the effects of dietary vitamins B1 and B3 intakes were not studied. Another issue is that most of the clinical trials on cardiovascular risk used high dosages of vitamin B1 (200 to 300 mg/day) and B3 supplement (1500 to 2000 mg/day), while the recommended dietary allowances (RDAs) of vitamin B1 for Japanese men and women aged 50-69 years were 1.3 and 1.1 mg/day, respectively and
RDAs of vitamin B3 were 14 and 11 mg/day, respectively \(^{(16)}\). Among Japanese men aged 30-49 years, the estimated average requirement (EAR) and RDA were 1.2 and 1.4 mg/day, respectively for vitamin B1, and those for vitamin B3 were 13 and 15 mg/day, respectively. Among Japanese women aged 30-49 years, the corresponding EAR were 0.9 and 1.1 mg/day, and RDA were 10 and 12 mg/day. The EAR and RDA of vitamins B1 and B3 in Japanese men and women aged over 70 years were even less than any other age groups \(^{(16)}\). Not all individuals prefer or can afford vitamin supplements for their health; thus, improving the dietary vitamins intakes is more achievable and acceptable by the general population. Therefore, after established effects of supplementary intakes of vitamin B1 and B3 have been determined, studying the cardiovascular impacts of dietary intakes of vitamin B1 and B3 is now warranted. Owing to the research gap in the field of epidemiology and similar food sources of vitamins B1 and B3, their associations with CVD mortality were hypothesized in the present study. Therefore, we aimed to investigate the associations of dietary vitamins B1 and B3 intakes with risk of CVD mortality, which was considered as a proxy of CVD incidence risk, among Japanese men and women using the Japan Collaborative Cohort (JACC) study, a nationwide, community-based prospective cohort study.

**Methods**

Study population and baseline data

Under the sponsorship of the Ministry of Education, Sports, and Science, the JACC study had the baseline survey (1988-1990) of 110,585 Japanese men (n=46,395) and women (n=64,190) aged 40 to 79 years from 45 areas all over Japan. A detailed cohort profile of the JACC study was published previously \(^{(17)}\). Data on the baseline lifestyle and participants’ characteristics, including demographic data, medical history of chronic diseases, diabetes mellitus, and hypertension, smoking, alcohol consumption, exercise, diet, and other items were compiled via a self-administered questionnaire (Supplementary Methods). The questionnaire included a validated 40-food item/food frequency questionnaire (FFQ) which was distributed in 32 areas; therefore, we started with 86,401 subjects from those 32 areas. After the exclusion of non-respondents to FFQ (n=24,614), we further excluded those who reported a medical history of CVD or cancer (n=3,142) and those who had implausible
energy intakes defined as outliers of mean ± three standard deviations (n=343). Finally, a total of 58,302 individuals were eligible for the present study (22,989 men and 35,313 women) (Supplemental Figure 1). Written informed consent was acquired from community leaders or the individuals. The protocol of JACC study was approved the Medical Ethical Committees of Nagoya University School of Medicine.

Dietary intake assessment

The participants were required to choose one from five frequency responses to describe the usual consumption frequency of 40 food and beverage items over the past 12 months without specification of the portion size. The five responses were rarely, 1 to 2 times/month, 1 to 2 times/week, 3 to 4 times/week, and almost every day. These frequencies were transformed into weekly consumption scores of 0, 0.38, 1.5, 3.5, and 7.0 per week respectively (17, 18). A validation study among 85 individuals using four 3-d weighed dietary records over a 1-year period as a reference standard determined the portion size for each food and validated the FFQ intakes. The amount of nutrients in each food was calculated by multiplying the weekly consumption scores by the estimated portion size. The values of vitamins B1 and B3 and other nutrients from each food category were calculated according to the Standardized Tables of Food Composition, 5th revised version (19) which listed the nutrients content in 100 gm of different foods. Thus, the total vitamin B1 and B3 intakes were calculated by summing their intakes from all over the foods in the FFQ. The details of computation of nutrient intakes from FFQ (18) and the accuracy of food composition tables in Japan (20,21) were published previously. The Spearman rank correlation coefficients for vitamins B1 and B3 intakes between the FFQ and the four 3-d dietary records were 0.36 and 0.32 respectively after energy adjustment (22). The energy-adjusted mean ± standard deviation intakes in mg/day from weighed dietary record and FFQ were 1.08 ± 0.20 and 0.71 ± 0.20 for vitamin B1, but the respective values for vitamin B3 were not reported (18).

Mortality surveillance

The investigators annually or biannually confirmed the dates and causes of death in each area (17). The International Classification of Diseases, 10th revision (ICD10) codes were
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applied to determine the underlying causes of death. In this study, our primary outcome was the total CVD mortality (ICD I01-I99). Cause-specific outcomes included mortalities from total stroke (ICD I60-I69), hemorrhagic stroke (ICD I60-I61), ischemic stroke (ICD I63.0-I63.9), ischemic heart disease (ICD I20-I25), myocardial infarction (ICD I20), and heart failure (ICD I50). This death certificate ascertainment was applied to all deaths within our cohort except for deaths that occurred outside of the original resident areas, which were treated as censored cases.

Statistical analysis

Energy-adjusted dietary intakes of vitamins B1 and B3 were categorized into five categorical groups (quintiles). The significance of differences in means or proportions of participants’ characteristics and known risk factors of CVD in each quintile were tested by the analysis of covariance and $\chi^2$ test.

Person-years of follow-up were calculated from the baseline in 1988 to 1990 to their first endpoint in this follow-up as follows: death, moving out, or the end of follow-up, whichever came first. The follow-up for mortality from CVD was conducted until 31 December, 2009 in general; however, in 4 areas the follow-up was stopped until 31 December, 1999, in another 4 areas until 31 December, 2003, and in 2 areas until 31 December, 2008 (17). The Cox proportional hazard model was applied to calculate crude and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for risk of mortality from CVD during the follow-up period (1988-2009) across quintiles of dietary vitamins B1 and B3 intakes. We confirmed no violation of the Cox proportional hazard assumption because there were no significant interactions between the categorical rank variables of dietary vitamins B1 and B3 intakes and a function of survival time for all the tested outcomes. Multiplicative interactions of vitamins B1 and B3 with sex were tested to decide on presenting the data sex-specifically or for combined men and women. The hypothesized confounders included age, sex, medical history of hypertension and diabetes, smoking status, ethanol intake, hours of sports, hours of walking, quintiles of body mass index (BMI), years of education, perceived mental stress, daily utilization of multivitamin supplementation, energy-adjusted quintiles of sodium and saturated fatty acids intakes, and quintiles of total energy intake. Details of these factors are
given in Supplementary Methods.

We assigned the median values to each quintile of vitamins B1 and B3 and tested their significance to calculate the trends across quintiles of vitamins B1 and B3 intakes. We further conducted a sensitivity analysis by excluding those who died within first 3 years of follow-up to avoid potential as-yet-undiagnosed diseases at baseline. All probability values for statistical test were two-tailed, and $P < 0.05$ was regarded as statistically significant. We applied the SAS statistical package (Version 9.4; SAS Institute Inc., Cary, NC) for statistical analysis.

Results

As shown in Table 1, participants in the highest quintile of both vitamins B1 and B3 intake were older, less educated, under less mental stress, had more walking time, had higher BMI, and were less likely to be current smoker and to have a history of hypertension or diabetes. They also used multivitamin supplementation less frequently, consumed less alcohol, but consumed more sodium, saturated fatty acid, and total energy when compared to those in the lowest quintile. In this study, sources of vitamin B1 were 31% from pork, 17% from vegetables, 10% from fish, and 7% from potatoes, while sources of vitamin B3 were 43% from fish, 13% from vegetables, 8% from pork, 7% from coffee, and 6% from green tea (data not shown in tables).

Since no interaction with sex was observed for the association of vitamins B1 and B3 with CVD and specific endpoints, we combined the results of men and women in the main analyses. During 960,225 person-years of follow-up for 58,302 participants, we documented a total of 3,371 deaths due to CVD, among whom there were 1504 deaths due to stroke (549 of which were due to hemorrhagic stroke and 816 of which were due to ischemic stroke), 699 deaths were due to ischemic heart disease (including 524 deaths due to myocardial infarction), and 564 deaths were due to heart failure.

As shown in Table 2, the dietary intake of vitamin B1 was not associated with mortality from total stroke or its subtypes. On the other hand, a higher dietary vitamin B1 intake was associated with the reduced risk of ischemic heart disease, myocardial infarction, and total CVD; HRs (95% CIs) were 0.57 (0.40-0.80; $P$ for trend <0.01), 0.56 (0.37-0.82; $P$ for trend
<0.01) and 0.85 (0.73-0.99, \( P \) for trend =0.03) respectively in the highest versus lowest intake quintile. Moreover, the multivariable-adjusted HR (95% CI) of heart failure mortality in the highest versus lowest intake quintiles was 0.65 (0.45-0.96; \( P \) for trend = 0.13).

For vitamin B3, as shown in Table 3, there was no association with the mortality from stroke or heart failure. Statistically significant inverse trends in risks of mortality from total CVD, hemorrhagic stroke, ischemic heart disease, and myocardial infarction were observed in the age- and sex- adjusted model. However, after the multivariate adjustment, these associations were weakened; the multivariable-adjusted HRs (95% CIs) in the highest versus lowest quintiles of dietary vitamin B3 were 0.90 (0.80-1.03; \( P \) for trend = 0.13) for total CVD mortality, 0.74 (0.55-1.01; \( P \) for trend = 0.16) for hemorrhagic stroke, 0.79 (0.60-1.04; \( P \) for trend = 0.05) for ischemic heart disease, and 0.66 (0.48-0.90; \( P \) for trend = 0.02) for myocardial infarction.

There were 456 participants who died within the first 3 years of follow-up, and excluding those subjects yielded no substantial changes in the associations of vitamin B1 and B3 with mortality from ischemic heart disease and myocardial infarction (Supplementary Table 1).

**Discussion**

In this large community-based prospective cohort study of Japanese men and women, higher dietary intakes of vitamins B1 and B3 were associated with reduced risks of mortality from total CVD, ischemic heart disease, and myocardial infarction. Neither dietary vitamin B1 nor vitamin B3 intake was associated with the mortality risk of stroke, except for a tendency towards a reduced risk of hemorrhagic stroke with a higher dietary vitamin B3 intake. Moreover, a higher dietary intake of vitamin B1 was associated with a reduced risk of heart failure.

As far to our knowledge, the present study is the first to investigate associations of dietary vitamins B1 and B3 intakes with risk of CVD mortality despite the abundant evidence from animal studies and clinical trials on vitamins B1 and B3 supplements. Vitamin B1 and B3 in animal studies and human clinical trials showed protective effects against myocardial ischemia.
One study on dogs showed that administration of vitamin B1 decreased the metabolic needs of the heart, which was manifested as reduced myocardial oxygen consumption, mean peripheral pressure, and left ventricular pressure up to 45%, 25%, and 10% respectively (11). A clinical trial on 10 healthy adults and 10 type 2 diabetes patients reported improvements in the brachial artery vasoactivity and the endothelium-dependent vasodilatation in both groups after a week of daily intravenous administration of 100 mg of vitamin B1 (23). Another randomized, cross-over, and investigator-blinded trial on 20 adult healthy volunteers indicated the flow mediated dilatation of the brachial artery was reduced by 50% of its baseline diameter after smoking one cigarette, and the reduction in the flow mediated vasodilatation with smoking one cigarette was only 25% when 1050 mg/day oral benfotiamine was administered for three days before the experiment (24).

On the other hand, vitamin B3 is a candidate to lower the risk of CVD as it is known to decrease LDL-C level, triglyceride, and lipoprotein(a) levels, while increasing HDL-C (7). Among 8,341 American men aged 30 to 64 years from Coronary Drug Project with previous myocardial infarction, 3000 mg/day vitamin B3 versus placebo for a follow-up of 15 years reduced 14% of the mortality from total CVD and 26% of the mortality from ischemic attack after a mean follow-up of fifteen years (12). Additionally, a meta-analysis of 23 RCTs including 39,195 participants reported a pooled risk ratio (CIs) of mortality from fatal or non-fatal myocardial infarction (odds ratio (OR): 0.93; 95%CI: 0.87-1.00) for vitamin B3 (median dose: 2g/day; median duration: 11.5 months) versus control (13). Another meta-analysis of 11 RCTs including 6,616 participants showed vitamin B3 (250 to 3000 mg/day) significantly decreased major coronary events (OR: 0.75; 95%CI: 0.65-0.96), stroke (OR: 0.74; 95%CI: 0.59-0.92) and any cardiovascular events (OR: 0.73; 95%CI: 0.63-0.85) (9). In a recent meta-analysis of 17 clinical trials including 35,760 participants, vitamin B3 therapy (100 to 4000 mg/day) was shown to be associated with reduction of acute coronary syndrome (relative risk: 0.74; 95%CI: 0.58-0.96) and stroke (relative risk: 0.74; 95%CI: 0.59-0.94) (25). A meta-analysis including 9,959 subjects reported similar results for total CVD events (OR: 0.66; 95%CI: 0.49-0.89) and major coronary events (OR: 0.75; 95%CI: 0.59-0.96), but not for stroke (OR: 0.88; 95%CI: 0.50-1.54) (26). Another meta-analysis of 13 trials of vitamin B3 treatment demonstrated a significant reduced risk of nonfatal myocardial
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infarction (risk ratio: 0.85; 95%CI: 0.73-1.00), a weak association with CVD mortality (risk ratio: 0.91; 95%CI: 0.81-1.02), and no association with stroke (risk ratio: 0.89; 95%CI: 0.72-1.10)\(^{(27)}\).

The mechanisms by which vitamin B1 and B3 might be protective against CVD mortality, especially those from ischemic heart disease could be summarized here. Vitamin B1 deficiency was highly prevalent in patients with type 2 diabetes\(^{(28)}\), which is considered as one of the risk factors for ischemic heart disease. In addition, vitamin B1 inhibits human infragenicular accelerated proliferation of arterial smooth muscle cells and mitigates atherosclerosis and endothelial dysfunction\(^{(29)}\). Another potential mechanism might be the protective effects of vitamin B1 against ischemic injury via reducing the metabolic needs of heart\(^{(5)}\). For vitamin B3, the reduced CVD risk may be involved in the favorable effects of vitamin B3 on lipid metabolism\(^{(7,8)}\). Vitamin B3 also has anti-inflammatory properties demonstrated by lowering C-reactive protein lipoprotein-associated phospholipase A2 and, inhibiting pro-atherogenic chemokines, and enhancing serum levels of adiponectin\(^{(26)}\). Moreover, an antihypertensive effect of vitamin B3 was also suggested\(^{(30)}\).

We observed that a higher dietary vitamin B1 intake was associated with reduced risk of mortality from heart failure. Vitamin B1 deficiency was commonly considered to be correlated with a failing heart. In a meta-analysis of 9 observational studies, the prevalence of vitamin B1 deficiency was higher with an odds ratio (CIs) of 2.5 (1.7-3.9) in heart failure group than in control\(^{(31)}\). Also known as wet beriberi or cardiac beriberi, vitamin B1 deficiency was characterized by peripheral neuropathy and muscle weakness resulting in heart failure\(^{(3)}\). The vitamin B1 deficiency-related heart failure was attributed to the vitamin B1 role in energy metabolism\(^{(3)}\). Some studies reported that vitamin B1 supplementation had beneficial effects on cardiac function\(^{(6)}\), but the evidence is still inconclusive\(^{(3)}\).

The dietary intake of vitamin B3 in our study tended to associate with a lower risk of mortality from hemorrhagic stroke. In a case control study including 69 stroke cases and 69 controls, vitamin B3 was found to be inversely correlated with risk of stroke (OR: 0.17; 95%CI: 0.04-0.82)\(^{(32)}\). However, some meta-analyses concluded that vitamin B3 had similar protective effects on both coronary heart disease and stroke outcomes\(^{(9,25)}\); while others failed to find protective effects against stroke\(^{(26,27)}\). The available studies and meta-analyses
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did not comment on the effect of vitamin B3 on stroke subtypes. Vitamin B3 was shown to reduce the blood pressure, an important risk factor for hemorrhagic stroke\(^{(30)}\). On the other hand, vitamin B3 may promote vascular plasticity after an acute attack of stroke. In an animal experiment, Niaspan treatment of stroke in rats with diabetes promoted vascular remodeling and improved functional outcome\(^{(33)}\). Therefore, an impact of vitamin B3 on risk of hemorrhagic stroke mortality could be plausible.

To the best of our knowledge, this is the first study to investigate the association of dietary intakes of vitamins B1 and B3 with the risk of mortality from CVD among Japanese population. The JACC study is a large, nationwide, community-based, prospective Japanese cohort study. The large sample size allowed us to investigate the associations of quintile categories of dietary vitamins B1 and B3 intakes with the risks of type-specific cardiovascular mortality as well as total CVD in Japanese population. Other strengths of this study included the prospective study design, the utilization of a validated FFQ, the consistent endpoint determination, and the exclusion of participants with CVD and cancer before the starting point of follow-up.

Limitations of this study mainly originate from the dietary assessment. The one-time measurement of dietary intakes cannot completely represent the consumption of nutrients during a long-term follow-up. The exclusion of 18,428 non-respondents to FFQ might result in a selection bias. Compared with 24,614 non-respondents to FFQ, the 61,787 respondents were more likely to be young and more educated (Supplementary Table 2). Several research of the JACC study reported the underestimation of nutrients intakes, which could be attributed to the limited number of food items in the used FFQ. Second, we had no data about the exact amounts or types of vitamin supplementation. To our knowledge, in the past century, vitamin supplementation was not common among Japanese population, thus we believe that it would not affect the result substantially. In this study, approximately 88% of participants did not use any vitamin supplementation and only 3% used it on daily basis. The exclusion of daily supplementation uses did not change the result. Third, in Japan, the accuracy of heart failure death certificate diagnosis is a questionable issue. It is generally believed that heart failure death was overestimated before 1994, because most deaths of unknown origin such as cardiac arrest or arrhythmic death were more likely diagnosed as unspecific heart failure\(^{(34)}\).
Therefore, approximately 27% to 50% heart failure deaths were accounted for this misclassification\textsuperscript{(34)}. Lastly, we did not have data on biomarkers of atherosclerosis and endothelial dysfunction, lipid metabolism, and systematic inflammation such as C-reactive protein, lipoprotein-associated phospholipase A2, pro-atherogenic chemokines, or serum levels of adiponectin, and cannot determine all confounding effects from some other nutrients, lifestyles and socioeconomic factors.

**Conclusions**

In this prospective cohort study, higher dietary intakes of vitamins B1 and B3 were inversely associated with a reduced risk of mortality from CVD among Japanese men and women. Dietary intakes of these vitamins from their food sources are available, accessible, affordable, safe, and more acceptable by the general population than supplementary intakes. Therefore, dietary intakes of food rich in these vitamins could be encouraged for decreasing the risk of CVD mortality. However, our findings are warrant further studies in different populations.

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Conflict of Interest: The authors have no conflict of interest to declare.

Authors' contributions: Chengyao T. designed the study, analyzed the data, and wrote the manuscript. Ehab S. E. and Hiroyasu I. conducted the technique review and reviewed and edited the manuscript. Kokoro S. and Akiko T. made critical revisions of the manuscript. Chengyao T. and Hiroyasu I. had primary responsibility for final content. All authors read and approved the final manuscript.
References


Table 1. Participants’ characteristics and dietary variables according to quintiles of dietary vitamins B1 and B3 intakes at baseline in a cohort of 22,989 men and 35,313 women with a total of 3,371 cases

<table>
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<th>Quintile</th>
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<th>3</th>
<th>4</th>
<th>5 (high)</th>
<th>P for difference</th>
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<td>11661</td>
<td>11660</td>
<td>11661</td>
<td>11660</td>
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</table>

**Vitamin B1**

- Vitamin B1 intake, mg/d
  - Quintile 1 (Low): 0.8
  - Quintile 2: 0.9
  - Quintile 3: 1.0
  - Quintile 4: 1.0
  - Quintile 5 (high): 1.2
  - P for difference: <0.001

- Female, %
  - Quintile 1 (Low): 21.1
  - Quintile 2: 57.2
  - Quintile 3: 69.9
  - Quintile 4: 76.3
  - Quintile 5 (high): 78.3
  - P for difference: <0.001

- Age, y
  - Quintile 1 (Low): 54.8
  - Quintile 2: 56.3
  - Quintile 3: 56.3
  - Quintile 4: 56.6
  - Quintile 5 (high): 56.8
  - P for difference: <0.001

- Body mass index, kg/m2
  - Quintile 1 (Low): 22.7
  - Quintile 2: 22.8
  - Quintile 3: 22.8
  - Quintile 4: 23.0
  - Quintile 5 (high): 22.9
  - P for difference: <0.001

- Ethanol intake, g/d
  - Quintile 1 (Low): 42.8
  - Quintile 2: 21.5
  - Quintile 3: 17.3
  - Quintile 4: 14.1
  - Quintile 5 (high): 12.8
  - P for difference: <0.001

- Current smoker, %
  - Quintile 1 (Low): 52.4
  - Quintile 2: 26.8
  - Quintile 3: 18.1
  - Quintile 4: 14.1
  - Quintile 5 (high): 12.7
  - P for difference: <0.001

- History of hypertension, %
  - Quintile 1 (Low): 20.8
  - Quintile 2: 20.7
  - Quintile 3: 20.2
  - Quintile 4: 19.8
  - Quintile 5 (high): 18.4
  - P for difference: <0.001

- History of diabetes, %
  - Quintile 1 (Low): 5.6
  - Quintile 2: 4.9
  - Quintile 3: 4.5
  - Quintile 4: 4.2
  - Quintile 5 (high): 3.5
  - P for difference: <0.001

- Sports ≥5 h/week, %
  - Quintile 1 (Low): 5.6
  - Quintile 2: 5.3
  - Quintile 3: 5.1
  - Quintile 4: 5.2
  - Quintile 5 (high): 5.7
  - P for difference: 0.14

- Walking ≥5 h/week, %
  - Quintile 1 (Low): 47.7
  - Quintile 2: 48.4
  - Quintile 3: 49.2
  - Quintile 4: 52.1
  - Quintile 5 (high): 56.4
  - P for difference: <0.001

- > 18 y education, %
  - Quintile 1 (Low): 16.7
  - Quintile 2: 13.9
  - Quintile 3: 13.6
  - Quintile 4: 12.9
  - Quintile 5 (high): 11.8
  - P for difference: <0.001

- High mental stress, %
  - Quintile 1 (Low): 26.2
  - Quintile 2: 23.3
  - Quintile 3: 21
  - Quintile 4: 20.9
  - Quintile 5 (high): 20.2
  - P for difference: <0.001

- Multivitamin supplementation, %
  - Quintile 1 (Low): 3.9
  - Quintile 2: 3.4
  - Quintile 3: 3.0
  - Quintile 4: 3.2
  - Quintile 5 (high): 3.0
  - P for difference: <0.001

- Sodium intake, mg/d
  - Quintile 1 (Low): 1498.4
  - Quintile 2: 1779.6
  - Quintile 3: 2005.3
  - Quintile 4: 2221.4
  - Quintile 5 (high): 2515.4
  - P for difference: <0.001

- Saturated fatty acid intake, mg/d
  - Quintile 1 (Low): 8.0
  - Quintile 2: 9.2
  - Quintile 3: 9.8
  - Quintile 4: 10.4
  - Quintile 5 (high): 11.9
  - P for difference: <0.001

- Total energy intake, kcal/d
  - Quintile 1 (Low): 1665.6
  - Quintile 2: 1446.3
  - Quintile 3: 1457.5
  - Quintile 4: 1512.2
  - Quintile 5 (high): 1680.2
  - P for difference: <0.001

- Vitamin B3 intake, mg/d
  - Quintile 1 (Low): 15.2
  - Quintile 2: 17.3
  - Quintile 3: 18.1
  - Quintile 4: 18.9
  - Quintile 5 (high): 20.4
  - P for difference: <0.001

**Vitamin B3**

- Vitamin B3 intake, mg/d
  - Quintile 1 (Low): 14.4
  - Quintile 2: 16.7
  - Quintile 3: 17.9
  - Quintile 4: 19.2
  - Quintile 5 (high): 21.5
  - P for difference: <0.001

- Female, %
  - Quintile 1 (Low): 30.1
  - Quintile 2: 59.6
  - Quintile 3: 67.4
  - Quintile 4: 71.3
  - Quintile 5 (high): 74.4
  - P for difference: <0.001

- Age, y
  - Quintile 1 (Low): 55.7
  - Quintile 2: 56.2
  - Quintile 3: 56.1
  - Quintile 4: 56.2
  - Quintile 5 (high): 56.7
  - P for difference: <0.001
<table>
<thead>
<tr>
<th></th>
<th>22.7</th>
<th>22.8</th>
<th>22.8</th>
<th>22.9</th>
<th>23.0</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol intake, g/d</td>
<td>42.3</td>
<td>23.8</td>
<td>19.7</td>
<td>16.9</td>
<td>13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>42.9</td>
<td>24.5</td>
<td>20.7</td>
<td>18.8</td>
<td>17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>22.0</td>
<td>20.8</td>
<td>19.6</td>
<td>19.5</td>
<td>18.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>5.8</td>
<td>4.6</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sports ≥5 h/week, %</td>
<td>5.8</td>
<td>4.7</td>
<td>5.2</td>
<td>5.5</td>
<td>5.7</td>
<td>0.88</td>
</tr>
<tr>
<td>Walking ≥5 h/week, %</td>
<td>47.5</td>
<td>47.7</td>
<td>50.5</td>
<td>52.0</td>
<td>56.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt; 18 y education, %</td>
<td>17.5</td>
<td>14.2</td>
<td>13.1</td>
<td>12.6</td>
<td>11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High mental stress, %</td>
<td>24.8</td>
<td>23.1</td>
<td>22.2</td>
<td>21.0</td>
<td>20.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivitamin supplementation, %</td>
<td>4.2</td>
<td>3.6</td>
<td>2.9</td>
<td>3.0</td>
<td>3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium intake, mg/d</td>
<td>1678.5</td>
<td>1894.9</td>
<td>2016.8</td>
<td>2113.8</td>
<td>2316.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Saturated fatty acid intake, mg/d</td>
<td>8.8</td>
<td>9.6</td>
<td>9.8</td>
<td>10.1</td>
<td>10.9</td>
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</tr>
<tr>
<td>Total energy intake, kcal/d</td>
<td>1639.1</td>
<td>1461.6</td>
<td>1478.0</td>
<td>1536.6</td>
<td>1646.6</td>
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</tr>
<tr>
<td>Vitamin B1 intake, mg/d</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2. Hazard ratio (HRs) and 95% confidence intervals (CIs) of cardiovascular disease (CVD) according to quintiles of vitamin B1 intake

<table>
<thead>
<tr>
<th></th>
<th>Q1 (low)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (high)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>11660</td>
<td>11661</td>
<td>11660</td>
<td>11661</td>
<td>11660</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
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<td>185652</td>
<td>192066</td>
<td>197635</td>
<td>202313</td>
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</table>

**CVD**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of case</td>
<td>675</td>
<td>701</td>
<td>651</td>
<td>674</td>
<td>670</td>
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<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.92(0.83-1.03)</td>
<td>0.86(0.77-0.96)</td>
<td>0.83(0.75-0.93)</td>
<td>0.80(0.71-0.89)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.92(0.83-1.03)</td>
<td>0.86(0.77-0.96)</td>
<td>0.84(0.75-0.93)</td>
<td>0.80(0.71-0.89)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.01(0.90-1.14)</td>
<td>0.93(0.82-1.05)</td>
<td>0.90(0.79-1.02)</td>
<td>0.86(0.75-0.98)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.00</td>
<td>0.98(0.87-1.11)</td>
<td>0.88(0.76-1.00)</td>
<td>0.85(0.74-0.98)</td>
<td>0.85(0.73-0.99)</td>
</tr>
</tbody>
</table>

**Stroke**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of case</td>
<td>284</td>
<td>300</td>
<td>313</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.94(0.80-1.11)</td>
<td>0.91(0.77-1.08)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.94(0.79-1.11)</td>
<td>0.92(0.77-1.09)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.11(0.92-1.33)</td>
<td>1.08(0.89-1.31)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.00</td>
<td>1.06(0.87-1.28)</td>
<td>1.00(0.81-1.23)</td>
</tr>
</tbody>
</table>

Hemorrhagic stroke

| No. of case | 119 | 105 | 101 | 104 | 120 |
| Model 1 | 1.00 | 0.79(0.60-1.04) | 0.74(0.56-0.97) | 0.71(0.54-0.95) | 0.79(0.60-1.04) | 0.09 |
| Model 2 | 1.00 | 0.79(0.60-1.04) | 0.74(0.56-0.98) | 0.73(0.55-0.96) | 0.80(0.61-1.05) | 0.15 |
| Model 3 | 1.00 | 0.94(0.70-1.27) | 0.89(0.65-1.23) | 0.88(0.64-1.22) | 0.97(0.70-1.33) | 0.93 |
| Model 4 | 1.00 | 0.91(0.66-1.24) | 0.85(0.61-1.19) | 0.84(0.59-1.21) | 1.02(0.70-1.50) | 0.74 |

Ischemic stroke

| No. of case | 141 | 169 | 161 | 175 | 170 |
| Model 1 | 1.00 | 1.05(0.84-1.32) | 1.03(0.82-1.30) | 1.04(0.83-1.31) | 0.99(0.79-1.25) | 0.89 |
| Model 2 | 1.00 | 1.04(0.83-1.31) | 1.03(0.81-1.30) | 1.03(0.82-1.30) | 0.98(0.77-1.23) | 0.83 |
| Model 3 | 1.00 | 1.22(0.95-1.57) | 1.18(0.90-1.54) | 1.18(0.90-1.54) | 1.12(0.85-1.48) | 0.62 |
| Model 4 | 1.00 | 1.13(0.87-1.47) | 1.06(0.80-1.41) | 1.08(0.80-1.45) | 1.06(0.77-1.47) | 0.99 |

Ischemic heart disease

<p>| No. of case | 174 | 163 | 134 | 122 | 106 |
| Model 1 | 1.00 | 0.90(0.72-1.11) | 0.75(0.60-0.95) | 0.65(0.51-0.83) | 0.55(0.43-0.71) | &lt;0.001 |</p>
<table>
<thead>
<tr>
<th>Model</th>
<th>No. of case</th>
<th>Hazard Ratio (95% CI)</th>
<th>0.50 (95% CI)</th>
<th>0.40 (95% CI)</th>
<th>0.30 (95% CI)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2</td>
<td>133</td>
<td>1.00</td>
<td>0.90(0.70-1.15)</td>
<td>0.77(0.58-1.00)</td>
<td>0.65(0.49-0.87)</td>
<td>0.55(0.41-0.74)</td>
</tr>
<tr>
<td>Model 3</td>
<td>122</td>
<td>1.00</td>
<td>0.89(0.69-1.15)</td>
<td>0.76(0.58-1.00)</td>
<td>0.65(0.49-0.86)</td>
<td>0.54(0.4-0.73))</td>
</tr>
<tr>
<td>Model 4</td>
<td>101</td>
<td>1.00</td>
<td>0.90(0.68-1.19)</td>
<td>0.74(0.55-1.01)</td>
<td>0.63(0.46-0.87)</td>
<td>0.53(0.38-0.74)</td>
</tr>
<tr>
<td>Model 5</td>
<td>90</td>
<td>1.00</td>
<td>0.88(0.66-1.17)</td>
<td>0.73(0.53-1.00)</td>
<td>0.63(0.44-0.90)</td>
<td>0.56(0.37-0.82)</td>
</tr>
<tr>
<td>Model 6</td>
<td>78</td>
<td>1.00</td>
<td>0.90(0.70-1.15)</td>
<td>0.77(0.58-1.00)</td>
<td>0.65(0.49-0.87)</td>
<td>0.55(0.41-0.74)</td>
</tr>
</tbody>
</table>

**Myocardial Infarction**

<table>
<thead>
<tr>
<th>Model</th>
<th>No. of case</th>
<th>Hazard Ratio (95% CI)</th>
<th>0.50 (95% CI)</th>
<th>0.40 (95% CI)</th>
<th>0.30 (95% CI)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>103</td>
<td>1.00</td>
<td>0.91(0.69-1.19)</td>
<td>0.80(0.60-1.06)</td>
<td>0.80(0.60-1.05)</td>
<td>0.78(0.59-1.03)</td>
</tr>
<tr>
<td>Model 2</td>
<td>118</td>
<td>1.00</td>
<td>0.90(0.69-1.18)</td>
<td>0.80(0.60-1.06)</td>
<td>0.81(0.61-1.07)</td>
<td>0.79(0.60-1.04)</td>
</tr>
<tr>
<td>Model 3</td>
<td>107</td>
<td>1.00</td>
<td>0.91(0.67-1.23)</td>
<td>0.77(0.56-1.06)</td>
<td>0.78(0.57-1.07)</td>
<td>0.75(0.55-1.04)</td>
</tr>
<tr>
<td>Model 4</td>
<td>119</td>
<td>1.00</td>
<td>0.87(0.64-1.18)</td>
<td>0.69(0.49-0.97)</td>
<td>0.67(0.47-0.96)</td>
<td>0.65(0.45-0.96)</td>
</tr>
</tbody>
</table>

**Heart failure**

Model 1: crude Cox proportional hazard model with adjustment for age and sex.

Model 2: model with adjustment for age, sex and socioeconomic status (educational status).
Model 3: model with adjustment for age, sex, socioeconomic status (educational status) and health behaviors (hours of walking, hours of sports, ethanol intake and smoking status).

Model 4: full mode with adjustment for age, sex, history of hypertension and diabetes, smoking status, body mass index, hours of walking, hours of sports, educational status, perceived mental stress, ethanol intake, multivitamin supplementation, quintiles of energy-adjusted sodium and saturated fatty acid intakes and total energy intakes.
Table 3. Hazard ratio (HRs) and 95% confidence intervals (CIs) of cardiovascular disease (CVD) according to quintiles of vitamin B3 intake

<table>
<thead>
<tr>
<th></th>
<th>Q1 (low)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (high)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>11660</td>
<td>11661</td>
<td>11660</td>
<td>11661</td>
<td>11660</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>180265</td>
<td>187575</td>
<td>194533</td>
<td>197250</td>
<td>200601</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of case</td>
<td>715</td>
<td>658</td>
<td>663</td>
<td>649</td>
<td>686</td>
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</tr>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.89(0.80-0.99)</td>
<td>0.88(0.79-0.98)</td>
<td>0.85(0.76-0.94)</td>
<td>0.86(0.77-0.95)</td>
<td>0.004</td>
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<tr>
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<td>1.00</td>
<td>0.89(0.80-0.99)</td>
<td>0.88(0.79-0.98)</td>
<td>0.84(0.75-0.94)</td>
<td>0.85(0.77-0.95)</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>0.93(0.83-1.05)</td>
<td>0.92(0.82-1.03)</td>
<td>0.87(0.78-0.99)</td>
<td>0.88(0.78-1.00)</td>
<td>0.03</td>
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<tr>
<td>Model 4</td>
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<td>0.91(0.81-1.03)</td>
<td>0.88(0.78-0.99)</td>
<td>0.90(0.80-1.03)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke</td>
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<tr>
<td>No. of case</td>
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<td>300</td>
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<td>0.82(0.69-0.97)</td>
<td>0.93(0.79-1.09)</td>
<td>0.92(0.78-1.08)</td>
<td>0.85(0.72-1.00)</td>
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### Hemorrhagic stroke

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<tr>
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<th>No. of case</th>
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<th>94</th>
<th>104</th>
<th>101</th>
<th>112</th>
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<tbody>
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<td>1.00</td>
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<td>0.68(0.52-0.88)</td>
<td>0.64(0.49-0.83)</td>
<td>0.68(0.52-0.88)</td>
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<td>0.67(0.52-0.88)</td>
<td>0.64(0.49-0.83)</td>
<td>0.67(0.52-0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>0.69(0.52-0.91)</td>
<td>0.74(0.55-0.98)</td>
<td>0.69(0.52-0.93)</td>
<td>0.73(0.55-0.98)</td>
<td>0.13</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.00</td>
<td>0.67(0.50-0.89)</td>
<td>0.71(0.53-0.95)</td>
<td>0.68(0.50-0.92)</td>
<td>0.74(0.55-1.01)</td>
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### Ischemic stroke

<table>
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<tr>
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<td>0.87(0.69-1.10)</td>
<td>1.13(0.91-1.41)</td>
<td>1.12(0.90-1.40)</td>
<td>0.96(0.77-1.21)</td>
<td>0.67</td>
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<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.86(0.68-1.09)</td>
<td>1.11(0.89-1.38)</td>
<td>1.11(0.89-1.38)</td>
<td>0.95(0.76-1.20)</td>
<td>0.98</td>
</tr>
<tr>
<td>Model 3</td>
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<td>0.95(0.75-1.22)</td>
<td>1.23(0.97-1.56)</td>
<td>1.21(0.95-1.55)</td>
<td>1.05(0.81-1.35)</td>
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<tr>
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<td>0.92(0.72-1.18)</td>
<td>1.17(0.92-1.50)</td>
<td>1.17(0.91-1.50)</td>
<td>1.01(0.77-1.32)</td>
<td>0.96</td>
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### Ischemic heart disease

<table>
<thead>
<tr>
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<th>136</th>
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<tbody>
<tr>
<td>Model</td>
<td>Hazard Ratio</td>
<td>95% Confidence Interval</td>
<td>Age- and Sex-Adjusted Hazard Ratio</td>
<td>95% Confidence Interval</td>
<td>Significance</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>----------------------------------</td>
<td>-------------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.89(0.71-1.11)</td>
<td>0.81(0.64-1.02)</td>
<td>0.68(0.53-0.86)</td>
<td>0.71(0.56-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.88(0.71-1.10)</td>
<td>0.80(0.64-1.01)</td>
<td>0.67(0.53-0.86)</td>
<td>0.71(0.56-0.90)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.00</td>
<td>0.88(0.70-1.12)</td>
<td>0.80(0.62-1.02)</td>
<td>0.66(0.51-0.86)</td>
<td>0.69(0.53-0.90)</td>
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</tr>
<tr>
<td>Model 4</td>
<td>1.00</td>
<td>0.90(0.71-1.15)</td>
<td>0.84(0.65-1.08)</td>
<td>0.72(0.55-0.95)</td>
<td>0.79(0.60-1.04)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Myocardial Infarction**

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Age- and Sex-Adjusted Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>0.93(0.72-1.20)</td>
<td>0.75(0.57-0.98)</td>
<td>0.67(0.51-0.89)</td>
<td>0.68(0.51-0.89)</td>
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<tr>
<td>Model 2</td>
<td>1.00</td>
<td>0.93(0.72-1.19)</td>
<td>0.74(0.57-0.97)</td>
<td>0.67(0.51-0.88)</td>
<td>0.68(0.51-0.89)</td>
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<tr>
<td>Model 3</td>
<td>1.00</td>
<td>0.92(0.70-1.2)</td>
<td>0.72(0.54-0.96)</td>
<td>0.64(0.47-0.87)</td>
<td>0.64(0.48-0.87)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.00</td>
<td>0.91(0.70-1.20)</td>
<td>0.72(0.54-0.97)</td>
<td>0.65(0.48-0.88)</td>
<td>0.66(0.48-0.90)</td>
</tr>
</tbody>
</table>

**Heart failure**

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Age- and Sex-Adjusted Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.00</td>
<td>1.03(0.79-1.35)</td>
<td>0.96(0.73-1.27)</td>
<td>0.81(0.61-1.07)</td>
<td>1.01(0.77-1.31)</td>
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<tr>
<td>Model 2</td>
<td>1.00</td>
<td>1.02(0.78-1.34)</td>
<td>0.95(0.73-1.25)</td>
<td>0.80(0.60-1.06)</td>
<td>1.00(0.76-1.31)</td>
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<tr>
<td>Model 3</td>
<td>1.00</td>
<td>1.04(0.78-1.39)</td>
<td>0.95(0.71-1.28)</td>
<td>0.79(0.58-1.07)</td>
<td>0.97(0.72-1.31)</td>
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<tr>
<td>Model 4</td>
<td>1.00</td>
<td>1.03(0.77-1.38)</td>
<td>0.95(0.70-1.28)</td>
<td>0.79(0.57-1.08)</td>
<td>0.97(0.71-1.33)</td>
</tr>
</tbody>
</table>

Model 1: crude Cox proportional hazard model with adjustment for age and sex.
Model 2: model with adjustment for age, sex and socioeconomic status (educational status).

Model 3: model with adjustment for age, sex, socioeconomic status (educational status) and health behaviors (hours of walking, hours of sports, ethanol intake and smoking status).

Model 4: full model with adjustment for age, sex, history of hypertension and diabetes, smoking status, body mass index, hours of walking, hours of sports, educational status, perceived mental stress, ethanol intake, multivitamin supplementation, quintiles of energy-adjusted sodium and saturated fatty acid intakes and total energy intakes.