# Inverse association between fruit and vegetable intake and all-cause mortality: Japan Public Health Center-based prospective study

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*Conflict of interest*

The authors have no conflicts of interest to disclose.

Running title: Fruit intake and mortality in Japan: JPHC study

**Abbreviations used:** BMI: body mass index; CIs: confidence intervals; DR: dietary record; FFQ: food frequency questionnaire; HR: hazards ratio; IQR: interquartile range; JPHC: Japan Public Health Center-based; WHO: World Health Organization.

## ABSTRACT

### Background

A dose-response and nonlinear association between fruit and vegetable intake and mortality has been reported in Europe and the United States, but little is known about this association in Asia.

### Objective

This study aimed to evaluate the association of fruit and vegetable intake with all-cause, cancer, cardiovascular, and respiratory disease mortality in a Japanese cohort.

### Methods

In the Japan Public Health Center-based prospective study, we included 94,658 participants (mean age; 56.4 ± 7.8 years, male; 46.0%) without cancer and cardiovascular disease at baseline. Information on fruit and vegetable intake was collected using a validated food frequency questionnaire. The Cox proportional-hazards model was used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) of each quintile of fruit and vegetable intake, separately, in relation to all-cause and cause-specific mortality using the first quintile as a reference. Nonlinear associations were evaluated using a likelihood ratio test, comparing a linear model with a restricted cubic spline model.

### Results

During a median of 20.9 follow-up years (interquartile range: 19.6-23.8), 23,687 all-cause deaths were documented. After adjusting for age, sex, and potential confounding factors, fruit and vegetable intake was nonlinearly and significantly associated with lower all-cause mortality, with the fourth and fifth quintiles having comparable HRs (fruit: fourth quintile, HR: 0.91; 95%CI: 0.87, 0.95, fifth quintile, HR: 0.92; 95%CI: 0.88, 0.96; *P* for nonlinearity < 0.001; vegetable: fourth quintile, HR: 0.92; 95%CI: 0.88, 0.97, fifth quintile,

HR: 0.93; 95%CI: 0.89, 0.98; *P* for nonlinearity = 0.002). Fruit intake was significantly associated with lower cardiovascular mortality (HR in the fifth quintile: 0.91; 95%CI: 0.83, 0.99; *P* for nonlinearity = 0.01).

**Conclusions**

In the Japanese population, higher intake of fruits and vegetables was nonlinearly associated with decreased all-cause mortality. These findings may contribute to the establishment of dietary recommendations for enhancing life expectancy in Asia.

**Keywords:** fruit intake, life expectancy, mortality, vegetable intake.

## Introduction

Increasing evidence supports the protective role of fruit and vegetable consumption in non-communicable diseases (1-4). Fruit and vegetables are rich sources of vitamins, minerals, dietary fiber, carotenoids, polyphenols, and other nutrients that have favorable health effects (5). The World Health Organization (WHO) recommends a daily consumption of > 400 g of fruits and vegetables (6). However, a substantial number of deaths worldwide are attributable to a low intake of fruits (2 million) and vegetables (1.5 million) (4).

Many prospective cohort studies conducted in Western populations have reported an inverse association between fruit and vegetable intake and all-cause and cause-specific mortality. A recent meta-analysis revealed a nonlinear association, showing the lowest mortality observed with a daily intake of approximately five servings(1). Few prospective studies have investigated this association in Asian populations but were often limited by relatively short follow-up periods(7-10) and exposure measurements with food frequency questionnaires (FFQs) that had not been validated against gold standards such as multiple-day weighed diet records(11). Furthermore, there is a lack of clarity regarding the potential nonlinear relationship between fruit and vegetable intake and mortality in Asian populations.

The insufficient evidence in Asian populations is an impediment for evidence-informed policymaking. The WHO recommendations(6) for fruit and vegetable intake are mainly based on North American(12) and European studies(13). In adopting these recommendations, regional differences in socioeconomic status, lifestyle, dietary habits, ingredients, obesity prevalence, disease prevalence, and prognosis need to be considered. Further, an understanding of the association between fruit and vegetable intake and all-cause and cause-specific mortalities in a country with a higher life expectancy and fewer health disparities, such as Japan, may contribute to global health planning for further enhancing life

expectancy. In this large-scale, population-based, prospective cohort study across Japan with over 20 years of follow-up, we aimed to examine the association of fruit and vegetable intake with all-cause and cause-specific mortalities.

## Methods

*Study population*

The Japan Public Health Center-based (JPHC) study is a prospective, population-based cohort study launched in 1990 and included participants aged 40–69 years from 11 public health center areas across Japan(14). The aim of the JPHC study was to identify the association between lifestyle habits and the development of disease and cause-specific mortality by tracking participants for ≥ 20 years(14). Information based on a self-reported questionnaire survey was obtained at baseline and at the 5- and 10-year follow-ups. The analytic cohort included 103,801 participants with five-year survey data (14). A flowchart of the study is shown in **Figure 1**. Participants with the following conditions were excluded based: those with a history of cardiovascular disease, cerebrovascular disease, and cancer (*n*=5,845), those who were lost to follow-up because of emigration overseas or refusal (*n*=342), and participants with extreme total energy intake (upper or lower 1% of total energy intake)(*n*=2,956). The final analytic cohort included 94,658 participants (43,574 men and 51,084 women).

*Ethics*

The institutional review boards of the National Cancer Center (Tokyo, Japan) and Yokohama City University (Yokohama, Japan) approved the study protocol. All participants were informed of the study's aims, and completion of the survey questionnaire was regarded as an agreement to participate.

*Follow-up*

Since the FFQs of the 5-year survey contained more detailed survey items, the date of the 5-year survey was defined as the starting point of the study. Follow-up was performed from the point through December 31, 2009 for participants who lived in Tokyo (*n*=2,446), December 31, 2012 for participants who lived in Osaka (*n*=7,497), and December 31, 2018 for all other participants, respectively. Participants were followed-up until their death, the date of emigration overseas, or the last day of follow-up, whichever occurred first.

*Covariates*

Obtained variables included age, body mass index (BMI), smoking status, residential area, alcohol intake, amount of daily physical activity, self-reported history of hypertension and diabetes, marital status, and living status (solitary living), in addition to the daily consumption of fruits and vegetables. A self-reported questionnaire of the 5-year survey (the second survey) was used to obtain covariates since the FFQs contained more comprehensive survey items, as previously described. History of diabetes and hypertension were self-reported, and the use of antidiabetic and antihypertensive drugs was recorded.

*Primary outcomes*

The primary outcomes were all-cause, cancer, cardiovascular disease (heart disease, vascular disease, or cerebrovascular disease), and respiratory disease mortality. The causes of death were confirmed using death certificates and defined based on the International Classification of Disease, 10$^{th}$ revision(15) with the following criteria: cancer mortality (C00-C97), cardiovascular mortality (I00-I99), heart disease (I20-I52), vascular disease (I70-I79),

cerebrovascular disease (I60–I69), and respiratory disease mortality (J10-18 and J40-47).

*Diet assessment*

Daily dietary information was assessed using a semiquantitative FFQ in the 5-year survey, which included questions about dietary lifestyle over the preceding year. The FFQ contained a list of 147 food and beverage items (in nine categories) with standard amounts/units and frequencies. Participants evaluated their usual portion size with reference to the specified standard portion size defined for each food using the following three options: < 0.5, equivalent, and > 1.5 times. Details of the types of fruits, vegetables, and fruit juices included in the FFQ; the standard portion size of each food item; detailed calculation algorithms; and the questionnaire structure have been published elsewhere(16). Both the frequency and amount of intake were used to convert to an average daily intake for each participant. The amount of fruit, vegetables, coffee, meat, green tea, dairy, added sugar, protein, fat, and salt consumption were adjusted for energy intake using a residual method, separately for men and women(17).

According to a validation study among a subpopulation ($n$=565) of the JPHC study that examined the validity and reproducibility of a self-administered FFQ, Spearman's rank correlation coefficients for the validity of the FFQ and 28-day dietary records (DRs) of energy-adjusted food intake were 0.41 for men and 0.23 for women for fruit intake, and 0.22 for men and 0.32 for women for vegetable intake in the subpopulation of the JPHC Cohort I(18). Similarly, the Spearman's rank correlation coefficients were 0.55 for men and 0.29 for women for fruit intake, and 0.44 for men and 0.47 for women for vegetable intake in the subpopulation of the JPHC Cohort II(19). As for reproducibility, Spearman's rank correlation coefficients for energy-adjusted intake measured with 1-year intervals using the FFQ were 0.50 for men and women for fruit intake, and 0.62 for men and 0.53 for women for vegetable

intake in Cohort I (18); in Cohort II, the coefficients were 0.57 for men and 0.54 for women for fruit intake, and 0.56 for men and 0.59 for women for vegetable intake(19). Dietary intakes used in this study were previously validated(18), with the exception of added sugar intake.

In addition, to evaluate the absolute differences in the estimated fruit and vegetable intake from FFQs and DRs, the estimated intakes using FFQs were compared to the estimates from DRs according to quintiles of energy-adjusted intake estimated from FFQs. The intake estimated from the FFQ overestimated the absolute intake of fruit in the second to the fifth quintiles; it underestimated the absolute intake of vegetables in the first to the fourth quintiles and overestimated the absolute intake in the fifth quintile (Supplementary Table 1).

*Statistical analysis*

Categorical variables are shown as numbers and percentages, and continuous variables are described as the median and interquartile ranges (IQR). Missing values were complemented to estimate hazard ratios (HRs) using multiple imputation by chaining equations(20). Ten rounds of multiple imputations were performed, and final estimates were computed according to Rubin's rule(21). The covariates used for multiple imputation were sex, age, BMI, smoking status, residential area, alcohol intake, amount of daily physical activity, history of hypertension, history of diabetes, marital status, living status, daily energy intake, daily coffee intake, daily meat intake, daily green tea intake, daily salt consumption, daily consumption of fruits and vegetables, and mortality status. Participants were divided into quintiles of fruit or vegetables intake, separately for men and women. Adjusted HRs and 95% confidence intervals (CIs) were calculated using a Cox proportional hazard model for quintiles of fruit or vegetable intakes, using the lowest quintile as a reference. Hazard ratios were calculated for vegetable and fruit intake, separately. Adjusted variables included the following potential confounding factors: age (continuous), sex (category), BMI (≤ 18.9, 19–

22.9, 23–24.9, 25–26.9, ≥ 27), smoking status (never, past, current [< 20 cigarettes per day], current [≥ 20 cigarettes per day]), amount of physical activity (metabolic equivalents hours/week; quintile), history of hypertension (binary), history of diabetes (binary), total energy intake (quintile), marital status (binary), solitary living status (binary), coffee intake (tertile), meat intake (quintile), green tea intake (quintile), salt intake (quintile), residential area (category), and alcohol consumption (never, occasional, and current drinkers of 1–149g/week, 150–299 g/week, 300–449 g/week, and ≥450 g/week, respectively). Occasional alcohol drinkers were defined as those who responded "occasionally drink" regardless of the number of grams they consumed.

*P*-values for linear trends were calculated using regression models by assigning the median intake value in each intake category as a continuous variable. The dose-response associations between fruit and vegetable intake and all-cause mortality were evaluated using restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentiles. The dose-response analyses were performed, separately for fruit and vegetable intake. *P*-values for nonlinear trends were estimated using the likelihood ratio test to compare a linear model with a restricted cubic spline model(1). We conducted a sensitivity analysis using the following methods: (Ⅰ) using a subgroup of participants without a history of hypertension and diabetes at baseline for all-cause and cause-specific mortalities; (Ⅱ) adjusting participation in medical checkups during the previous year at the time of the second survey, in addition to other covariates; (III) adjusting added sugar intake in addition to other covariates, (IV) analyzing the association between fruit and vegetable intake and all-cause mortality using a stratified group with and without a habit of smoking at baseline, and (V) examining the association between subgroups of fruit and vegetable (total green and yellow vegetables, cruciferous vegetables, and citrus fruit) and all-cause mortality (22). In an additional sensitivity analysis, we included added sugar as a covariate. Added sugar intake was estimated by sum of mono-

and disaccharides added during the processing of foods and drinks, sugars eaten separately, and sugars added to foods and drinks at the table. The entire list of food items used for the estimation are provided in Supplemental Table 2. Detailed methods and the validity and reproducibility of the intake of sugars, not specifically for added sugar, have been reported previously(23).A two-sided *P*-value < 0.05, was considered statistically significant. All statistical analyses were performed using R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

The baseline characteristics of the participants are described in Table 1. Those who consumed more fruit and vegetables were more likely to be older, have hypertension or diabetes, and higher salt intake. In addition, they were more likely to never use tobacco, and were likely to consume less alcohol and total energy. During a median follow-up of 20.9 years (1,880,336 person-years, IQR: 19.6-23.8 years), 23,678 all-cause deaths were confirmed, of which 8,274, 5,978, and 1,871 were related to cancer, cardiovascular disease, and respiratory diseases, respectively.

Table 2 shows the adjusted HRs for all-cause and cause-specific mortality according to the amount of fruit intake. Increased intake of fruit was significantly associated with decreased all-cause mortality in a nonlinear manner in the overall cohort; for increasing quintiles of fruit intake, the corresponding HRs were 1.0 (reference), 0.95, 0.94, 0.91, and 0.92 (*P* for nonlinearity < 0.001). An inverse association was observed for cardiovascular death but not for cancer or respiratory disease mortality. The stratified analyses according to sex revealed a significant inverse association between fruit intake and all-cause mortality in both men and women. Fruit intake was inversely associated with cardiovascular mortality in

women and respiratory disease mortality in men. However, fruit intake was not significantly associated with cancer mortality in both men and women.

Daily vegetable intake was inversely and nonlinearly associated with all-cause mortality (Table 3). Maximum risk reduction for all-cause mortality was observed in the fourth quintile group; for increasing quintiles of vegetable intake, the corresponding HRs were 1.0 (reference), 0.99, 0.95, 0.92, and 0.93 (*P* for nonlinearity = 0.002). The associations were not significant for cancer, cardiovascular, or respiratory disease mortality, except for the fourth quintile for cardiovascular disease mortality (HR: 0.90; 95%CI: 0.82–0.98). In the stratified analysis by sex, vegetable intake was not significantly associated with all-cause mortality in both men and women, except for the second, third, and fourth quintiles in women. As shown in Figure 2, the non-linear associations between fruit (*P* for nonlinearity< 0.001) or vegetable intake (*P* for nonlinearity= 0.001) and all-cause mortality were confirmed.

The sensitivity analyses showed that the observed associations did not substantially change by excluding participants with either hypertension or diabetes (Supplemental Tables 3-4) or by adding medical checkup status as a covariate (Supplemental Tables 5-6). In the sensitivity analysis including added sugar as a covariate resulted in similar findings (Supplemental Tables 7-8), although the results should be interpreted with caution because the validity and reproducibility of the added sugar intake has not been confirmed in the cohort. The adjusted HRs for all-cause mortality and number of deaths per person-years among participants in relation to smoking habits are shown in Supplemental Tables 9-10. Regardless of baseline smoking status, fruit intake was inversely associated with all-cause mortality. An inverse association between vegetable intake and all-cause mortality was found for men who ever smoked, but not for men who never smoked, while in women, an inverse association was found in never smokers, but not in ever smokers. In addition, inverse

associations were observed for subgroups of fruit and vegetable (total green and yellow vegetables, cruciferous vegetables, and citrus fruit) in relation to all-cause mortality (Supplemental Table 11).

**Discussion**

In this large, population-based, Japanese cohort study with > 20 years of follow-up, fruit intake was associated with a lower risk of all-cause mortality in a nonlinear manner; the risk of all-cause mortality was lowest in the fourth quintile, and a further decrease was not found in the fifth quintile. Fruit intake was also nonlinearly associated with lower cardiovascular mortality; however, a similar association was not confirmed for cancer or respiratory disease mortality. In addition, vegetable intake was nonlinearly associated with lower all-cause mortality, with the fourth and fifth quintiles having comparable HRs. The present study is the first to examine the association between fruit and vegetable intake and all-cause mortality using a large population-based Japanese cohort.

The inverse association between fruit or vegetable intake and all-cause mortality found in this study was consistent with previous epidemiological studies conducted worldwide(1, 3) and in Asian countries(8, 11). The magnitudes of the effect estimates varied across studies, possibly due differences in participant characteristics, follow-up period, study design, and regional lifestyle characteristics. Miller et al. (3) similarly reported an inverse association between all-cause mortality and fruit and vegetable intake (HR: 0.81; 95%CI:0.72, 0.93 and HR: 0.93 ;95%CI: 0.83,1.05, respectively) in a cohort that primarily included participants from the Middle East, South America, Africa, South Asia, and Southeast Asia, which is consistent with the Japanese data presented in this analysis(3).

In contrast to all-cause and cardiovascular mortality, the present study did not show a

significant association between cancer and respiratory disease mortality and fruit or vegetable intake, which is inconsistent with previous studies(2, 8). Respiratory disease mortality was relatively lower in this cohort than deaths from other causes, including cancer and cardiovascular deaths. The number of events was relatively small to observe the inverse association between fruit and vegetable intake and respiratory disease mortality. Given that an inverse association between fruit intake and respiratory disease mortality has been found in men (HR in the fifth quintile: 0.74; 95% CI, 0.61, 0.90; P for nonlinearity = 0.01), the inverse association could be found among participants with a high burden of exposure such as smoking. Differences between previous studies may come from differences in the proportion and type of exposure (e.g., smoking or air pollution) and the proportion and type of outcome (e.g., infectious respiratory disease or lung cancer).

The inconsistent results of studies conducted mainly in the United States and Europe regarding the association between fruit and vegetable intake and cancer mortality may come from differences in fruit and vegetable intake and cancer incidence. Asians are known to consume more vegetables and less fruits than European or American populations. In addition, cancer incidence is similarly different among countries, with more cancers attributed to infectious diseases in Asian countries(24). In fact, a previous study conducted in China did not find any association between fruit and vegetable intake and cancer mortality(8). Thus, the magnitudes of effects of fruit and vegetable intake may differ by race, cancer or respiratory disease incidence, mortality, treatment, and prevention between cohorts.

The estimated effect of fruit consumption on all-cause mortality was stronger than that of vegetable consumption in the present analyses. This discrepancy might have been due to the abundance of nutrients in fruits. This greater effect of fruit intake than vegetable intake

on all-cause mortality is consistent with previous studies, including studies conducted in Asian countries(2, 3, 8).

There are plausible mechanisms for the protective effects of fruits and vegetables. They are rich in vitamins(25, 26), carotenoids(27), and polyphenols(28), all of which have antioxidant properties. Excess reactive oxygen species and free radicals that arise from normal metabolic processes are related to the development of cardiovascular disease(29) (30)and cancer (31). Collectively, these antioxidant compounds have been reported to suppress the generation of reactive oxygen species and prevent atherosclerotic lesions caused by low-density lipoproteins, a particle that carries cholesterol to the arterial wall through the blood(32). Similarly, minerals such as potassium and magnesium (abundant in fruits and vegetables) have blood-pressure-lowering effects(33) and inhibit the development of cardiovascular disease and death. In addition, dietary fiber (abundant in vegetables, fruit, beans, and legumes) lowers cholesterol(34) and blood pressure(33), is anti-inflammatory, and improves insulin resistance(35), which may explain its contribution to the reduction of mortality(36). Moreover, the nonlinear relationships in the present study may derive from the threshold effects for absorption and metabolism of bioactive components in fruits and vegetables due to enzyme activities that can be saturated(17).

The WHO (6) and the National Health Service of the United Kingdom (37) recommend five servings of fruits and vegetables per day(6, 37). The American guidelines recommend consuming > 2.5 servings of vegetables and > 2 servings of fruits per day(38). In Asia, dietary guidelines of China recommend an intake of 3.5–6 servings (300–500 g) of vegetables and 2.5–4.5 servings (200–350 g) of fruits per day(39). To date, dietary guidelines worldwide do not have uniform daily fruit and vegetable intake recommendations. These

guidelines were not developed based on studies that comprehensively assessed mortality reduction and were instead developed based on studies investigating the association between dietary lifestyle and disease development. Furthermore, in Japan, a daily intake of ≥ 350 g of vegetables and ≥ 200 g of fruit is recommended(40); these doses were calculated based on the amount of fruit and vegetables needed to obtain optimal amounts of potassium, dietary fiber, and vitamins(41), and were not based on a large Japanese epidemiological study on mortality reduction and risk of disease development. To consider the optimal intake of fruits and vegetables for long-term well-being, analyses of mortality are warranted(1). Epidemiological studies worldwide have investigated the association between fruit and vegetable intake and mortality for this purpose(1-3). However, such studies are limited in Asian countries. The present study suggests that fruit and vegetable intake is associated with a lower risk of all-cause mortality in a nonlinear fashion, with the lowest risk observed in the fourth quintile and without a further decrease. According to the previously mentioned validation study among subpopulation of the JPHC study, the FFQ could not accurately estimate the absolute intake of fruits or vegetables; however, the median intake estimated from the DR in the fourth quintile according to the FFQ was estimated to be 143 g (IQR: 100–191 g) for fruit intake and 299 g (IQR: 271–346 g) for vegetable intake in the DR (Supplementary Table 1). Therefore, fruit intake of more than approximately 140 g and vegetable intake of more than approximately 300 g might be helpful to prevent all-cause deaths in Japanese populations. These results may contribute to the development of evidence-based recommendations to extend healthy life expectancy.

The strength of this study comes from its novelty, high-quality data, a large number of participants, very long follow-up duration with a low follow-up loss, and use of a validated FFQ. No previous study has comprehensively investigated the association of all-cause and

cause-specific mortality with fruit and vegetable intake in a large population-based Japanese cohort.

The present study had several limitations. First, behavioral risk factors (including dietary lifestyle, tobacco use, and daily physical activity status) and metabolic risk factors (including hypertension, diabetes, and obesity) may vary in each participant during the follow-up period. In addition, newly developed diseases that might have affected life expectancy were not considered during the long-term follow-up. Second, various potential confounders, including lifestyle factors and socioeconomic status, were adjusted for estimating associations; however, the presence of residual and unmeasured confounding factors cannot be ignored. Third, the FFQ used in this study was obtained from a 5-year survey (the second survey). However, dietary behaviors might have changed during long-term follow-up, especially in those with hypertension, diabetes, or other comorbidities based on dietary guidance. Further, the use of self-reported FFQ may have contributed to a recall bias; for example, participants with healthier lifestyles may remember their dietary habits more accurately.

In this large-scale, population-based cohort study in Japan, a higher daily intake of fruits or vegetables (intake corresponding to the fourth and fifth quintiles) was associated with almost a 10% reduced risk of all-cause mortality in relation to the lowest intake group. These findings support the current nutritional dietary recommendations to increase the intake of fruits and vegetables to enhance life expectancy.

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study as the principal investigator; ST, NS, TY,RT,JI and MI: conducted the survey; KK and RK: conducted data analysis; YS and AG: drafted the plans for data analyses; YS: conducted data analysis and drafted the manuscript; AG supervised the analysis and preparation of the manuscript; all authors: were involved in interpretation of the results and revision of the manuscript; and all authors: read and approved the final version of the manuscript.

*Data Availability*

Data access to Japan Public Health Centre-based Prospective Study data will be made available upon reasonable request. Follow the instructions at https://epi.ncc.go.jp/en/jphc/805/8155.html.

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Table 1. Participant characteristics across quintiles of combined vegetable and fruit intake[1]

| | Vegetable and fruit intake (combined) quintile | | | | |
|---|---|---|---|---|---|
| Characteristic | Q1 | Q2 | Q3 | Q4 | Q5 |
| *n* | 18,931 | 18,932 | 18,932 | 18,931 | 18,932 |
| Males | 12,634 (66.7) | 9,873 (52.1) | 8,120 (42.9) | 6,883 (36.4) | 6,064 (32.0) |
| Age, y | 54 (48-60) | 55 (49-61) | 56 (50-62) | 57 (51-63) | 58 (52-64) |
| Body mass index, kg/m$^2$ | 23.3 (21.4-25.4) | 23.3 (21.5-25.3) | 23.4 (21.5-25.3) | 23.3 (21.5-25.3) | 23.3 (21.5-25.3) |
| (Missing) | 576 | 407 | 454 | 448 | 573 |
| Hypertension | 3,036 (16.0) | 3,244 (17.1) | 3,507 (18.5) | 3,771 (19.9) | 4,029 (21.3) |
| Diabetes | 931 (4.9) | 915 (4.8) | 945 (5.0) | 977 (5.2) | 1,063 (5.6) |
| Status: Married | 13,914 (73.5) | 14,637 (77.3) | 14,610 (77.2) | 14,765 (78.0) | 14,620 (77.2) |
| Status: Solitary living | 1,117 (5.9) | 947 (5.0) | 949 (5.0) | 898 (4.7) | 1,090 (5.8) |
| Receiving medical checkup | 14,534 (76.8) | 15,662 (82.7) | 15,968 (84.3) | 16,265 (85.9) | 16,328 (86.2) |
| Smoking category | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Never use | 8,410 (47.4) | 10,949 (60.9) | 12,337 (69.0) | 13,418 (75.3) | 13,981 (79.5) |
| Past smoker | 1,913 (10.8) | 1,806 (10.1) | 1,487 (8.3) | 1,393 (7.8) | 1,170 (6.7) |
| Current: low (< 20 cigarettes/day) | 1,945 (11.0) | 1,626 (9.0) | 1,384 (7.7) | 1,078 (6.1) | 980 (5.6) |
| Current: high (≧ 20 cigarettes/day) | 5,482 (30.9) | 3,587 (20.0) | 2,667 (14.9) | 1,927 (10.8) | 1,451 (8.3) |
| (Missing) | 1,181 | 964 | 1,057 | 1,115 | 1,350 |
| Total physical activity, metabolic equivalents hours/d | 31.9 (27.1-36.0) | 31.9 (27.1-36.0) | 31.9 (27.1-35.5) | 31.9 (27.1-35.5) | 31.9 (27.1-35.5) |
| (Missing) | 4,044 | 3,166 | 3,123 | 3,063 | 3,312 |
| Alcohol consumption, n (%) | | | | | |
| None or occasional drinkers | 7,543 (40.8) | 10,065 (54.4) | 11,739 (63.8) | 13,027 (70.8) | 14,288 (78.3) |
| 1-149g/wk | 1,043 (5.6) | 1,357 (7.3) | 1,437 (7.8) | 1,583 (8.6) | 1,423 (7.8) |
| 150-299g/wk | 1,440 (7.8) | 1,445 (7.8) | 1,383 (7.5) | 1,234 (6.7) | 981 (5.4) |
| 300-449g/wk | 1,651 (8.9) | 1,501 (8.1) | 1,259 (6.8) | 1,005 (5.5) | 686 (3.8) |

| | | | | | |
|---|---|---|---|---|---|
| ≧450g/wk | 6,826 (36.9) | 4,137 (22.4) | 2,581 (14.0) | 1,550 (8.4) | 861 (4.7) |
| (Missing) | 428 | 427 | 533 | 532 | 693 |
| Total energy, kcal/d | 2,042 (1,587-2,598) | 2,009 (1,613-2,496) | 1,929 (1,556-2,391) | 1,855 (1,512-2,274) | 1,750 (1,417-2,151) |
| Sodium intake, g/d | 9 (7-12) | 11 (9-13) | 11 (9-13) | 12 (10-14) | 13 (10-16) |
| Vegetable intake, g/d | 90 (62-120) | 148 (116-183) | 190 (151-234) | 239 (186-297) | 323 (237-429) |
| Fruit intake, g/d | 52 (27-83) | 121 (86-154) | 178 (135-219) | 246 (188-301) | 387 (286-502) |
| Coffee intake, g/d | 120 (26-300) | 114 (26-300) | 79 (26-219) | 79 (0-174) | 60 (0-120) |
| Meat intake, g/d | 54 (30-85) | 55 (35-82) | 53 (33-77) | 49 (31-70) | 41 (24-62) |
| Green tea intake, g/d | 300 (86-600) | 300 (120-600) | 326 (146-626) | 420 (180-626) | 600 (240-900) |
| Combined intake of vegetables and fruits, g/d | 159 (114-192) | 271 (247-296) | 370 (344-395) | 486 (453-523) | 702 (624-833) |
| Added sugar intake, g/d | 17 (9 -29) | 20 (13-29) | 19 (13-28) | 19 (13-27) | 19 (13-27) |

| | | | | | |
|---|---|---|---|---|---|
| Protein intake, g/d | 65 (56-73) | 68 (61-75) | 69 (62-76) | 69 (62-76) | 67 (61-75) |
| Fat intake, g/d | 49 (38-61) | 53 (44-62) | 54 (46-63) | 54 (46-62) | 52 (45-62) |
| Dietary fiber intake, g/d | 8 (6-9) | 10 (9-12) | 12 (10-13) | 14 (12-16) | 17 (15-20) |
| Dairy product ,g/d | 80 (19-213) | 115 (41-233) | 134 (53-251) | 145 (61-257) | 140 (54-258) |

[1] Values are median (interquartile range: IQR) or $n$ (%). wk : week, d: day, g: grams

Table 2. Association between fruit intake and mortality due to all cause, cancer, cardiovascular disease, and respiratory diseases[1]

| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend[2] | *P* for nonlinearity[3] |
|---|---|---|---|---|---|---|---|
| **Median fruit intake (IQR), g/d** | **41 (23-58)** | **106 (91-122)** | **167 (151-184)** | **243 (221-269)** | **400 (341-502)** | | |
| *n* | 18,932 | 18,931 | 18,932 | 18,930 | 18,933 | | |
| All-cause deaths, *n* / Person-years | 5,412/369,145 | 4,755/377,630 | 4,533/378,744 | 4,432/379,265 | 4,555/375,553 | | |
| Cancer deaths, *n* | 1,844 | 1,658 | 1,605 | 1,572 | 1,595 | | |
| Cardiovascular deaths, *n* | 1,264 | 1,144 | 1,173 | 1,134 | 1,263 | | |
| Respiratory disease deaths, *n* | 423 | 365 | 340 | 374 | 369 | | |
| **All-cause mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted model* | 1.0 (reference) | 0.87 (0.84-0.91) | 0.84 (0.80-0.87) | 0.80 (0.77-0.84) | 0.80 (0.76-0.83) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.95 (0.91-0.99) | 0.94 (0.90-0.98) | 0.91 (0.87-0.95) | 0.92 (0.88-0.96) | <0.001 | <0.001 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.87 (0.82-0.91) | 0.81 (0.77-0.85) | 0.78 (0.74-0.82) | 0.76 (0.71-0.80) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.93 (0.88-0.98) | 0.92 (0.87-0.97) | 0.91 (0.86-0.96) | 0.90 (0.85-0.95) | 0.004 | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Women | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.87 (0.82-0.93) | 0.90 (0.85-0.96) | 0.82 (0.76-0.87) | 0.85 (0.79-0.91) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.93 (0.87-0.99) | 0.97 (0.90-1.03) | 0.88 (0.83-0.95) | 0.91 (0.85-0.98) | 0.01 | 0.02 |
| **Cancer mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted model* | 1.0 (reference) | 0.90 (0.84-0.96) | 0.89 (0.83-0.95) | 0.88 (0.82-0.94) | 0.82 (0.76-0.88) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.96 (0.90-1.03) | 0.99 (0.92-1.06) | 1.00 (0.93 - 1.07) | 0.95 (0.88 - 1.03) | 0.35 | 0.15 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.87 (0.80-0.95) | 0.88 (0.80-0.96) | 0.83 (0.76-0.91) | 0.75 (0.68-0.82) | <0.001 | 0.001 |
| Fully adjusted model | 1.0 (reference) | 0.92 (0.85-1.01) | 0.98 (0.89-1.07) | 0.97 (0.88-1.06) | 0.91 (0.82-1.00) | 0.13 | 0.09 |
| Women | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.85 (0.76-0.96) | 0.98 (0.88-1.10) | 0.88 (0.79-1.00) | 0.94 (0.83-1.05) | 0.48 | 0.15 |
| Fully adjusted model | 1.0 (reference) | 0.88 (0.78-0.99) | 1.03 (0.92-1.15) | 0.93 (0.82-1.05) | 0.99 (0.88-1.12) | 0.69 | 0.51 |
| **Cardiovascular mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted | 1.0 (reference) | 0.88 (0.81-0.95) | 0.84 (0.78-0.91) | 0.75 (0.69-0.82) | 0.78 (0.72-0.85) | <0.001 | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| model* | | | | | | | |
| Fully adjusted model | 1.0 (reference) | 0.97 (0.90-1.05) | 0.97 (0.89-1.05) | 0.87 (0.79-0.94) | 0.91 (0.83-0.99) | 0.01 | 0.01 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.86 (0.77-0.96) | 0.80 (0.72-0.89) | 0.76 (0.68-0.86) | 0.76 (0.68-0.85) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.93 (0.83-1.04) | 0.92 (0.82-1.03) | 0.91 (0.81-1.02) | 0.92 (0.82-1.04) | 0.35 | 0.01 |
| Women | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.90 (0.79-1.01) | 0.82 (0.72-0.92) | 0.72 (0.64-0.82) | 0.79 (0.70-0.90) | <0.001 | 0.003 |
| Fully adjusted model | 1.0 (reference) | 0.96 (0.85-1.09) | 0.88 (0.77-1.00) | 0.79 (0.69-0.90) | 0.84 (0.74-0.96) | 0.002 | 0.05 |
| **Respiratory disease mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted model* | 1.0 (reference) | 0.80 (0.70-0.92) | 0.72 (0.62-0.83) | 0.66 (0.56-0.76) | 0.67 (0.58-0.78) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.96 (0.90-1.03) | 0.99 (0.92-1.06) | 1.00 (0.93-1.07) | 0.95 (0.88-1.03) | 0.001 | 0.002 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.86 (0.72-1.02) | 0.72 (0.60-0.87) | 0.69 (0.57-0.83) | 0.64 (0.53-0.78) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.93 (0.78-1.12) | 0.83 (0.68-1.00) | 0.79 (0.65-0.96) | 0.74 (0.61-0.90) | 0.002 | 0.01 |
| Women | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimally adjusted model** | 1.0 (reference) | 0.83 (0.65-1.07) | 0.90 (0.70-1.14) | 0.70 (0.54-0.91) | 0.79 (0.61-1.02) | 0.03 | 0.09 |
| Fully adjusted model | 1.0 (reference) | 0.90 (0.70-1.16) | 0.96 (0.75 - 1.23) | 0.77 (0.59-1.00) | 0.86 (0.67-1.12) | 0.21 | 0.27 |

[1] The Cox proportional hazard model was used to calculate the hazard ratio (HR) and corresponding 95% confidence interval (CI) after ten rounds of multiple imputations. The minimally adjusted model was adjusted for sex, age, residential area (*), age, and residential area (**). In the multivariable-adjusted model, adjusted variables were as follows: age, body mass index, residential area, smoking status, alcohol intake, amount of daily physical activities, self-reported history of hypertension and diabetes, marital status, living status, and dietary habits (total energy intake, the amount of fruit, vegetables, coffee, meat, green tea, and salt intake).

[2] *P*-values for the linear trend were calculated by assigning each median intake value in each category and then including the variable in the regression model as a continuous variable.

[3] *P*-values for nonlinearity between fruit and vegetable intake and each mortality were estimated using a likelihood ratio test, comparing a linear model with a restricted cubic spline model.

Table 3. Association between vegetable intake and mortality due to all-cause, cancer, cardiovascular disease, and respiratory disease[1]

| | Q1 | Q2 | Q3 | Q4 | Q5 | *P* for trend | *P* for nonlinearity |
|---|---|---|---|---|---|---|---|
| **Median vegetable intake, IQR, g/d** | **78 (56-94)** | **133 (121-145)** | **181 (168-194)** | **240 (223-260)** | **361 (316-440)** | | |
| *n* | 18,931 | 18,932 | 18,932 | 18,931 | 18,932 | | |
| All-cause deaths, n / Person-years | 4,989/371,323 | 4,583/376,818 | 4,454/378,102 | 4,571/378,400 | 5,090/375,693 | | |
| Cancer deaths, n | 1,709 | 1,668 | 1,619 | 1,609 | 1,666 | | |
| Cardiovascular deaths, n | 1,257 | 1,102 | 1,131 | 1,129 | 1,359 | | |
| Respiratory disease deaths, n | 396 | 352 | 345 | 374 | 404 | | |
| **All-cause mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted model* | 1.0 (reference) | 0.94 (0.91-0.98) | 0.9 (0.87-0.94) | 0.89 (0.85-0.93) | 0.93 (0.89-0.97) | <0.001 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.99 (0.95 - 1.03) | 0.95 (0.91 - 0.99) | 0.92 (0.88-0.97) | 0.93 (0.89 - 0.98) | 0.002 | 0.002 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 1.00 (0.94-1.05) | 0.95 (0.90-1.00) | 0.92 (0.87-0.97) | 0.95 (0.90-1.00) | 0.02 | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fully adjusted model | 1.0 (reference) | 1.04 (0.99-1.11) | 1.00 (0.94 - 1.06) | 0.95 (0.90 - 1.01) | 0.95 (0.89 - 1.01) | 0.007 | 0.15 |
| Women | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.89 (0.83-0.95) | 0.88 (0.82-0.94) | 0.87 (0.81-0.92) | 0.92 (0.87-0.98) | 0.12 | <0.001 |
| Fully adjusted model | 1.0 (reference) | 0.92 (0.86-0.98) | 0.91 (0.85-0.97) | 0.90 (0.84-0.97) | 0.94 (0.88-1.01) | 0.34 | 0.005 |
| **Cancer mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted model* | 1.0 (reference) | 1.01 (0.94-1.08) | 0.98 (0.91-1.05) | 0.96 (0.89-1.03) | 0.95 (0.88-1.02) | 0.07 | 0.33 |
| Fully adjusted model | 1.0 (reference) | 1.03 (0.96-1.11) | 1.01 (0.94-1.08) | 0.97 (0.90-1.05) | 0.96 (0.88-1.04) | 0.09 | 0.26 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 1.07 (0.98-1.17) | 0.99 (0.91-1.09) | 0.96 (0.88-1.05) | 0.94 (0.86-1.04) | 0.03 | 0.51 |
| Fully adjusted model | 1.0 (reference) | 1.09 (1.00-1.20) | 1.02 (0.93-1.12) | 0.97 (0.88-1.07) | 0.93 (0.84-1.04) | 0.02 | 0.27 |
| Women | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.95 (0.85-1.07) | 1.00 (0.89-1.12) | 0.95 (0.85-1.07) | 0.97 (0.86-1.09) | 0.44 | 0.83 |
| Fully adjusted model | 1.0 (reference) | 0.97 (0.86-1.09) | 1.02 (0.91-1.15) | 0.98 (0.87-1.11) | 1.00 (0.87-1.14) | 0.98 | 0.93 |
| **Cardiovascular mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally | 1.0 (reference) | 0.89 (0.82-0.97) | 0.89 (0.82-0.97) | 0.85 (0.78-0.93) | 0.95 (0.87-1.03) | 0.53 | <0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| adjusted model* | | | | | | | |
| Fully adjusted model | 1.0 (reference) | 0.94 (0.87-1.02) | 0.95 (0.88-1.04) | 0.90 (0.82-0.98) | 0.97 (0.89-1.07) | 0.75 | 0.07 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.85 (0.76-0.95) | 0.96 (0.86-1.07) | 0.84 (0.75-0.94) | 0.92 (0.82-1.03) | 0.41 | 0.01 |
| Fully adjusted model | 1.0 (reference) | 0.90 (0.80-1.01) | 1.03 (0.92 - 1.16) | 0.90 (0.80 - 1.02) | 0.97 (0.85-1.10) | 0.79 | 0.37 |
| Women | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.88 (0.78-1.00) | 0.88 (0.78-1.00) | 0.86 (0.76-0.97) | 0.99 (0.88-1.11) | 0.68 | 0.01 |
| Fully adjusted model | 1.0 (reference) | 0.91 (0.80-1.03) | 0.90 (0.79-1.02) | 0.87 (0.76 - 0.99) | 0.98 (0.86-1.13) | 0.84 | 0.02 |
| **Respiratory disease mortality, HR (95% CI)** | | | | | | | |
| Overall | | | | | | | |
| Minimally adjusted model* | 1.0 (reference) | 0.95 (0.82-1.10) | 0.92 (0.80-1.07) | 0.97 (0.83-1.12) | 0.96 (0.83-1.11) | 0.82 | 0.09 |
| Fully adjusted model | 1.0 (reference) | 1.03 (0.96-1.11) | 1.01 (0.94-1.08) | 0.97 (0.90-1.05) | 0.96 (0.88-1.04) | 0.24 | 0.62 |
| Men | | | | | | | |
| Minimally adjusted model** | 1.0 (reference) | 0.95 (0.79-1.15) | 0.90 (0.74-1.09) | 1.05 (0.87-1.27) | 0.98 (0.81-1.18) | 0.81 | 0.48 |
| Fully adjusted model | 1.0 (reference) | 1.02 (0.84-1.24) | 0.94 (0.77-1.14) | 1.06 (0.87-1.29) | 0.89 (0.72-1.10) | 0.24 | 0.94 |
| Women | | | | | | | |
| Minimally adjusted | 1.0 (reference) | 0.78 (0.61-1.00) | 0.79 (0.62-1.00) | 0.71 (0.55-0.91) | 0.85 (0.67-1.08) | 0.22 | 0.07 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| model** | | | | | | | |
| Fully adjusted model | 1.0 (reference) | 0.81 (0.63-1.04) | 0.83 (0.64-1.07) | 0.76 (0.58-0.99) | 0.90 (0.69-1.19) | 0.68 | 0.25 |

[1] The Cox proportional hazard model was used to calculate the hazard ratio (HR) and corresponding 95% confidence interval (CI) after ten rounds of multiple imputations. The minimally adjusted model was adjusted for sex, age, residential area (*), age, and residential area (**). In the multivariable-adjusted model, adjusted variables were as follows: age, body mass index, residential area, smoking status, alcohol intake, amount of daily physical activities, self-reported history of hypertension and diabetes, marital status, living status, and dietary habits (total energy intake, the amount of fruit, vegetables, coffee, meat, green tea, and salt intake).
[2] P-values for the linear trend were calculated by assigning each median intake value in each category and then including the variable in the regression model as a continuous variable.
[3] P-values for nonlinearity between fruit and vegetable intake and each mortality were estimated using a likelihood ratio test, comparing a linear model with a restricted cubic spline model.

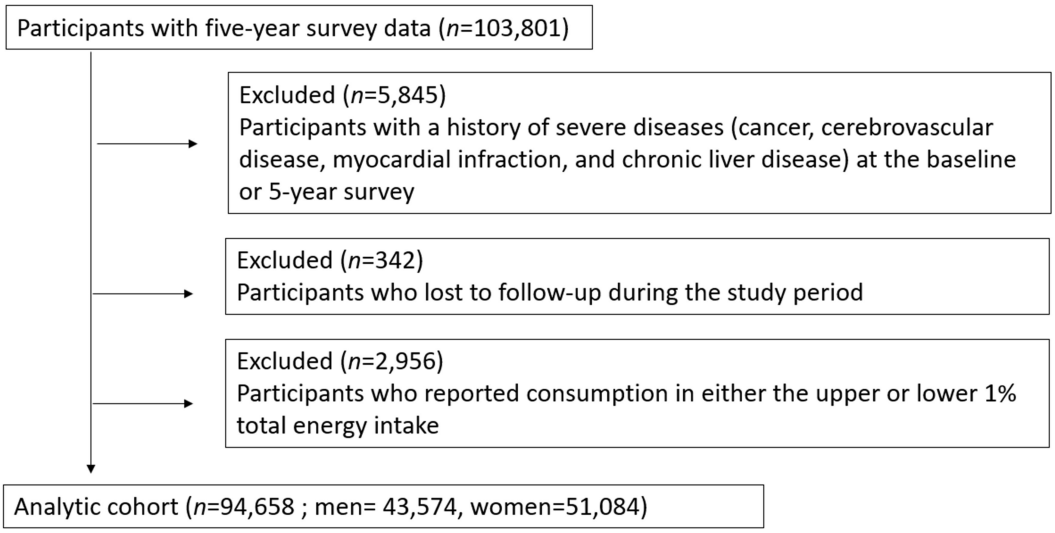


**Figure 1** Flowchart of the study

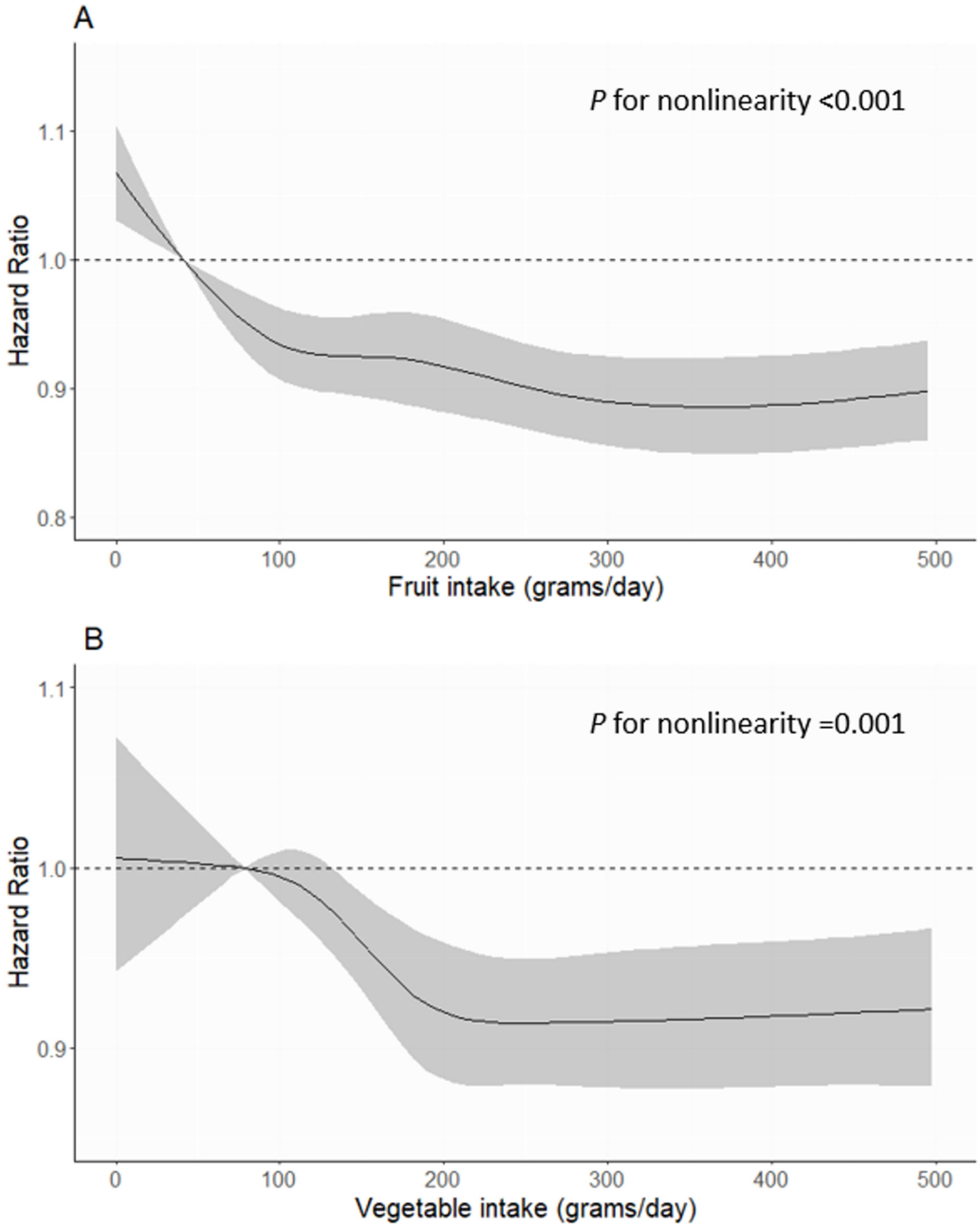


**Figure 2** Dose-response associations between fruit and vegetable consumptions and all-cause mortality. The median intake of fruit and vegetable in the lowest group were assigned to the reference for calculating the hazard risk.