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Prospective cohort studies of dietary vitamin B6 intake and risk of cause-specific mortality

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Abstract

Background & aims: Vitamin B6 has been postulated to play an important role in determining chronic diseases. However, few studies have evaluated associations between dietary vitamin B6 and cause-specific mortality comprehensively.

Methods: We investigated the associations between vitamin B6 from diet and risk of all-cause, and cause-specific mortality in 134,480 participants from the Shanghai Men's Health Study (2002–2014) and Shanghai Women's Health Study (1997–2014). The median follow-up periods for men and women were 10.3 and 16.2 years, respectively. We estimated hazard ratio (HR) and 95% confidence interval (CI) using Cox proportional hazards models.

Results: After adjustment for suspected confounders, the multivariable-adjusted HR for the highest versus lowest quintiles for total, CVD, stroke, and CHD mortality among men were 0.83 (95%CI=0.76, 0.90), 0.73 (95%CI=0.63, 0.85), 0.71 (95%CI=0.58, 0.88), 0.66 (95%CI=0.47, 0.91), accordingly. Women with the highest intake had significantly 17% (HR=0.83; 95% CI=0.77, 0.90), 20% (HR=0.80; 95% CI=0.70, 0.92), and 28% (HR=0.72; 95% CI=0.59, 0.86) lower risks of total, CVD, and stroke mortality compared with those of women with lowest vitamin B6 intake. No significant association was observed between dietary vitamin B6 and cancer mortality both among men and women.

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Conflict of interest statement and funding sources

The authors declare no conflicts of interest.

Conclusions: In the current study with two prospective Chinese cohorts, high dietary vitamin B6 consumption was inversely associated with risk of all-cause and CVD mortality.

Keywords

Diet; vitamin B6; all-cause mortality; cohort study; cancer mortality; CVD mortality

INTRODUCTION

Vitamin B6, also known as pyridoxine, is an indispensable coenzyme in human catabolism and anabolism processes [1]. Multiple effects of vitamin B6 make it possible to influence the pathology of chronic disease incidence and mortality [2, 3]. This water soluble vitamin can be found in a wide variety of foods presented as pyridoxine from plant sources and as pyridoxal or pyridoxamine from animal foods. Foods high in vitamin B6 included red meat, white meat, eggs, spinach, potatoes, bananas, beans, and nuts [2].

Epidemiological studies have been accumulated to investigate the associations between dietary vitamin B6 and risk of chronic diseases. In the general population, lower intake of vitamin B6 is related with an increased risk of aging-associated diseases, such as cardiovascular diseases [3–5] and specific cancers [6]. However, the associations between vitamin B6 intake from diet and risk of cause-specific mortality were rarely investigated. Cui et. al. found that high dietary intake of vitamin B6 was associated with lower risk of mortality from stroke and coronary heart disease among Japanese during a 14-year follow-up [7]. Another study conducted in Taiwan reported that higher vitamin B6 intake was related to lower risk of all-cause mortality [8]. However, no study has evaluated associations between dietary vitamin B6 and cause-specific mortality comprehensively.

The requirement for vitamin B6 for the human body is increasing with ageing [9]. It is crucially important to illustrate the association between dietary vitamin B6 and risk of mortality, especially in an elderly population. Therefore, we conducted a comprehensive evaluation of vitamin B6-mortality association in two on-going cohorts of middle aged and elderly men and women in Shanghai, China.

METHODS

Study design and participants

Shanghai Men’s Health Study (SMHS) and Shanghai Women’s Health Study (SWHS) are two ongoing prospective cohort studies performed in Shanghai, China. Details of the study designs, scientific rationale, and baseline characteristics of the participants can be found elsewhere [10, 11]. Briefly, the SMHS baseline survey was conducted between 2002 and 2006 involving 61,478 men aged 40–74 years with no history of cancer, with a response rate of 74.0% (61,478/83,033). The SWHS recruited 74,940 women with age of 40–70 years between 1997 and 2000, with a response rate of 92.3% (74,940/81,170). At baseline interview, the trained retired nurses or doctors performed a face-to-face interview at each participant’s home. A structured questionnaire was used to collect information on demographic characteristics, lifestyles (including smoking status and alcohol uses), diet,

physical activity, dietary supplements use, medical history, and family history of cancers. Information on the menopausal status and hormone replacement therapy use was also collected for women. Additionally, we obtained anthropometric measurements for each participant. Our studies were approved by the Institutional Review Boards of the Shanghai Cancer Institute and Vanderbilt University. All participants in the cohorts provided informed consent.

In the current analyses, we excluded 10 men and 3 women participants because of loss to follow-up immediately after enrollment. We also excluded participants with extreme values for total energy intake (for men: <800 or >4000 kcal/day, n=256; for women: <500 or >3500 kcal/day, n=125), participants with missing data for any of the covariates of interest (n=1466 for men, n=78 for women). After these exclusions, 134,480 participants (59,746 men and 74,734 women) were available for analyses.

Assessment of exposure

Dietary information was collected using quantitative food frequency questionnaire (FFQ) with 81 (for men) and 77 (for women) food items. Both of FFQs have been previously validated [12, 13]. In brief, we used Chinese Food Composition Tables [14] to obtain each nutrient in specific foods. Then we calculated nutrient intakes by summing the nutrients from all food items.

Ascertainment of outcome

We visited the participants per 2–3 years to obtain the information on health status. In addition, we linked outcome information with the Shanghai Vital Statistics Registry annually. For the SMHS, the response rates were 97.6% and 91.9% for the first (2004–2008) and second (2008–2011) follow-up surveys. For the SWHS, the response rates for the first (2000–2002), second (2002–2004), third (2004–2007), and fourth (2008–2011) follow-up were 99.8%, 98.7%, 96.7%, and 92.0%, respectively.

The main outcome of interest is all-cause mortality that occurred before 31 December, 2014. The cause of death was recorded according to the International Classification of Diseases, Ninth Revision (ICD-9) [15]. The major specific mortality was coded including CVD mortality (390–459) and cancer mortality (140–208). Deaths due to CVD mortality were further classified into the following groups: stroke mortality (430–438), coronary artery heart disease (CHD) mortality (410–414), and acute myocardial infarction (AMI) mortality (410).

Statistical analyses

We adjusted total energy intake for nutrients using residual method and standardized to the mean daily energy intake calculated from the sex-specific cohort [16]. The energy-adjusted vitamin B6 intake was categorized by quintiles based on its distribution among the entire study population at baseline.

We used Cox proportional hazards model to evaluate the associations between dietary vitamin B6 intake and cause-specific mortality risk using age as the time scale with

stratification on birth cohort in 5-year intervals. We checked proportional hazards assumption using the Schoenfeld residual method with no evidence of violation observed. Tests for linear trends of HRs across vitamin B6 quintiles were performed by modeling the median values in each quintile as continuous variables.

We provided two models in current analyses. The crude model was adjusted for age at baseline and energy intake (kcal/day, quartiles). The multivariable model was additionally adjusted for other potential confounders as follows: education (four categories: illiteracy or elementary school, middle school, high school, or graduate school), income (four categories: low, lower middle, upper middle, or high), occupation (three categories for men: professional or administrator, clerical or service worker, or manual laborer; four categories for women: housewife, professional or administrator, clerical or service worker, or manual laborer), smoking status (never, ever and current smokers), alcohol intake (never, <2 drinks/day, or ≥2 drinks/day), body mass index (BMI; four categories:<18.5, 18.5–23.9, 24.0–27.9, or ≥28 kg/m^2), waist-hip ratio (three categories: <0.90, 0.90–0.99, or ≥1.0 for men; <0.85, 0.85–0.94, or ≥0.95 for women), physical activity (metabolic equivalent-hours per week, quartiles), history of hypertension (yes/no), diabetes (yes/no), coronary heart disease (yes/no), stroke (yes/no), vitamin B supplements use (yes/no), menopausal status (yes/no, women only), and hormone replacement therapy (yes/no, women only).

Secondary analyses included sensitivity analyses and subgroup analyses. First, we adjusted a diet quality score calculated based on Chinese Food Pagoda to measure the adherence to 2007 Chinese Dietary Guidelines, which is an indication of diet quality [17].

Moreover, due to the high relation between vitamin C, dietary fiber and vitamin B6 (Supplementary table 1), we additionally included dietary fiber, vitamin C, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids in the multivariable model to exclude the potential confounding of these nutrients. In order to eliminate the effect of reverse causality bias, we reanalyzed the data in participants with follow-up years >=2 years. In subgroup analyses, we reanalyzed the data stratified by age at baseline, smoking status (men, only), alcohol intake (men, only), BMI, energy intake, history of main chronic diseases (diabetes, CHD, stroke), B vitamin supplements use and menopausal status (women only). P value for interaction was obtained from multivariable model by including the cross-product term between a continuous term for vitamin B6 intake and categorical terms for stratification factors.

We performed all statistical analyses in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). *P* values of less than 0.05 with two-sided were considered to indicate statistical significance.

RESULTS

Baseline characteristics

During up to 10.3 years of follow-up in SMHS (604,777 person-years), we identified 5,705 deaths (cancer: 2,411, CVD: 1,906); during up to 16.2 years of follow-up in SWHS (1,166,138 person-years), we obtained 7,555 deaths (cancer: 3,148, CVD: 2,486). Baseline

characteristics of participants (59,746 men and 74,734 women) according to the dietary vitamin B6 intake are shown in Table 1. Participants with higher intake of dietary vitamin B6, in general, tended to be younger, more likely to use vitamin B supplements and they were less likely to smoke cigarettes and consume alcohol, and they consumed more fruit, vegetables, fish, and red meat.

Vitamin B6 intake and cause-specific mortality

Table 2 presents the associations between dietary vitamin B6 intake and total and cause-specific mortality among men. In age- and energy-adjusted analyses, we observed an inverse association between dietary vitamin B6 and risk of total, cancer, CVD, stroke, CHD and AMI mortality. After multivariable adjustment, inverse associations were still statistically significant for total, CVD, stroke and CHD mortality ($P < 0.01$ for trend across categories). A reduced risk of total mortality of 17% was observed for individuals in the highest compared with the lowest quintiles of dietary vitamin B6 intake (HR=0.83, 95%CI=0.76, 0.90). The multivariable HR (95% CIs) for the highest versus lowest quintiles were 0.73 (95%CI=0.63, 0.85), 0.71 (95%CI=0.58, 0.88), 0.66 (95%CI=0.47, 0.91) for CVD, stroke and CHD mortality, accordingly. For cancer mortality, we observed an inverse association with a borderline statistically significant ($HR_{highest\ vs.\ lowest}$=0.89, 95%CI=0.78, 1.01; P_{trend}=0.087).

Table 3 presents the associations between dietary vitamin B6 intake and total and cause-specific mortality among women. Similar to men, dietary vitamin B6 was inversely associated with risk of total, CVD, and stroke mortality among women (All $P_{trend} < 0.01$). However, we did not observe a significant association between vitamin B6 intake and CHD mortality. Women with the highest intake had significantly 17% (HR=0.83; 95% CI=0.77, 0.90), 20% (HR=0.80; 95% CI=0.70, 0.92), and 28% (HR=0.72; 95% CI=0.59, 0.86) lower risks of total, CVD and stroke mortality compared with those of women with lowest vitamin B6 intake. For death due to cancer, we found a statistically significant lower risk associated with the increase of dietary vitamin B6 intake ($HR_{highest\ vs.\ lowest}$=0.88, 95%CI=0.78, 0.99; P_{trend}=0.063).

Subgroup and sensitivity analyses

In analyses stratified according to age at baseline, smoking status (men only), alcohol use (men only), BMI, history of chronic disease, menopause status (women only) and energy intake, the association of vitamin B6 with total mortality appeared to be similar across subgroups (Tables 4–5). However, we observed an effect modification by history of main chronic diseases. In men with a history of diabetes, CHD, stroke, vitamin B6 intake was not linearly associated with risk of all-cause mortality ($P_{interaction}$=0.048). For women, the P value for interaction is statistically significant for history of diabetes, CHD, stroke ($P_{interaction}$=0.002). However, the estimates were not much different between the two subgroups among women.

We conducted several sensitivity analyses (Supplementary tables 2–4). Firstly, when we included the dietary quality score in the main model, the results remain stable and robust (Supplementary table 2), which indicated that vitamin B6-mortality association is

independent with diet quality. Secondly, we observed similar patterns when additionally adjusting dietary fiber, vitamin C, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids in the multivariable model except for stroke mortality among women (Supplementary table 3). Dietary vitamin B6 was no longer associated with stroke mortality after adjusted these nutrients. In addition, when we further adjusted other B vitamins, such as folate acid, vitamin B2, vitamin B3, and vitamin B12 in our multivariable model, we found similar results compared with our main analyses (data not shown). Moreover, after excluding participants with a follow-up year less than two years, the results did not change materially (Supplementary table 4).

DISCUSSION

In these two large, prospective Chinese cohort studies, we observed a dose-dependent inverse association between vitamin B6 from diet and total, and CVD mortality, after adjusting for potential confounders. As compared with participants who had the lowest intake of vitamin B6, participants who had the highest intake had a 17% lower risk of total death both among men and women. Results were similar in several sensitivity analyses, and the inverse association remained across subgroups generally.

Our results support a strong association between dietary vitamin B6 intake and the risk of mortality, which is consistent with the previous studies. For example, a prospective study conducted in Taiwan reported that high intake of dietary vitamin B6 was associated with lower risk of all-cause mortality [8]. Another cohort study performed among 58,730 Japanese found that vitamin B6 intake from diet can reduce the risk of mortality from stroke, CHD, and heart failure both among men and women after adjusting n-3 and n-6 polyunsaturated fatty acid [7]. Besides, other studies focused on the health effect of vitamin B6 also provide evidence to support the protective role of the nutrient. Epidemiological evidence has been accumulated that low vitamin B6 intake is associated with increased risk of CVD [3, 5] and cancer [18–20]. Recently, a meta-analysis found that based on the observational studies, both vitamin B6 from diet and pyridoxal 5’-phosphate (PLP) blood levels are associated with a reduced risk of cancer from any site in terms of dose-response relationship [6], which was consistent with our research results.

Biologically, the beneficial effect of vitamin B6 seems plausible. As it is known, chronic diseases, such as diabetes, cancer, heart disease, and ageing, have been related to metabolic and epigenetic factors that play roles in pathogenesis [21]. Deficiencies of vitamin B6 may increase the chance of disruption of the pathway and/or lead to aberrations in DNA methylation, imbalance in DNA precursors, and deficiency in DNA repair, all of which are responsible for adverse health effects [22]. Therefore, it can cut off the complicated regulatory network of one-carbon metabolism and then result in chronic diseases. Secondly, vitamin B6 also affects immune function and gene transcription or expression [23]. Studies from both animal and human have revealed that vitamin B6 may play a crucial role in cell-mediated and humoral immunity [24]. Additionally, Morris et al. found that vitamin B6 intake from diet was inversely associated with C-reaction protein in the National Health and Nutrition Examination Survey [25]. It indicates that vitamin B6 may also have strong anti-inflammatory properties in human body [26].

Aging process leads to a higher requirement of vitamin B6 intake for human body [9]. Among the young, overt vitamin B6 deficiency caused by diets is rare because vitamin B6 is naturally present in common foods [2]. However, the high prevalence of vitamin B6 deficiency in older people cannot be ignored. According to the surveys conducted in large population, the prevalence varies from 11% to 65% in UK (National Diet and Nutrition survey; 11%-27% people lived dependently, 30%-65% people lived in institutions) [27] and US (National Health and Nutrition Examination Survey; 15%-23% men, 14%-49% women) [28]. In our cohorts, dietary vitamin B6 intake in 36.5% of men and 40.3% of women were lower than reference nutrient intake. Therefore, the dietary intake of vitamin B6 should increase with age, especially in population with a poor nutritional status.

Current study was based on two on-going prospective studies, which can reduce the possibility of several common biases. The population-based design and high response rate can make the conclusion less prone to be affected by selection bias and more possible to extrapolate it to overall world population. Our FFQs were validated for men and women separately, with a fine validity and reproducibility of micronutrients (r=0.33–0.58 in men and r=0.41–0.59 in women) [12, 13]. In addition, we controlled a series of potential confounders selected *in prior*.

However, several limitations of the present study must also be acknowledged. Firstly, the true effect of vitamin B6 remains very difficult to separate from that of other nutrients. People eat foods containing vitamin B6, like fruit and vegetables, along with other potential healthful nutrients, such as vitamin C and fiber. Even though we conducted sensitivity analyses by adjusting for other nutrients, such as fiber, vitamin C, saturated fatty acid, monounsaturated fatty acid, and polyunsaturated fatty acids, we cannot rule out the underlying effect of residual confounders. Additionally, information on nutrient intake and covariates was only collected at baseline, which might fail to consider the change during our follow-up and represent the true exposure level. Finally, there are potential measure error in assessment of dietary vitamin B6 intake from FFQs, leading to an attenuation of the observed association between dietary vitamin B6 and mortality. However, studies have shown that serum PLP concentration was reasonably associated with dietary vitamin B6 intake [29].

CONCLUSIONS

In summary, using data from two prospective cohort studies among Chinese, we found a significantly inverse association between dietary vitamin B6 intake and risk of all-cause and CVD mortality. Due to current evidence mainly on Asian population, further studies are needed to confirm the mortality-vitamin B6 association in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' responsibilities

Y-BX, X-OS and WZ obtained the funding and designed the study; Y-T G, H-LL, JG, L-HH JW and JF collected the data; L-GZ and Y-BX analyzed and interpreted the data; L-GZ drafted first manuscript; Y-BX had the primary responsibility for the final content of the manuscript; and all authors reviewed and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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Abbreviations used:

SMHS	Shanghai Men's Health Study
SWHS	Shanghai Women's Health Study
BMI	body mass index
FFQ	food frequency questionnaire
CVD	cardiovascular disease
CHD	coronary artery heart disease
AMI	acute myocardial infarction
HR	hazard ratios
CIs	confidence intervals

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Highlights

- Dietary vitamin B6 was inversely associated with all-cause mortality in China.
- These associations were also found for cardiovascular disease mortality.
- Dietary vitamin B6 might not be associated with cancer mortality risk.

Table 1

Characteristics of participants by sex and quintile of energy-adjusted dietary vitamin B6 intake [a]

	Men			Women		
	Quintiles of dietary vitamin B6 intake			Quintiles of dietary vitamin B6 intake		
Characteristics [b]	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Age at baseline (years), mean (SD)	55.77 (9.82)	55.39 (9.73)	54.57 (9.51)	55.05 (9.41)	52.36 (8.99)	50.87 (8.36)
Body mass index (kg/m^2), mean (SD)	23.56 (3.1)	23.62 (3.02)	24.11 (3.07)	24.26 (3.67)	23.89 (3.4)	24.13 (3.28)
Physical activity (MET-h/week), mean (SD)	59.21 (33.93)	58.55 (33.24)	62.84 (36.18)	106.36 (45.37)	104.49 (43.87)	110.8 (47.14)
Total energy (kcal/d), mean (SD)	2049.9 (481.8)	1821.89 (445.87)	1993.1 (492.57)	1781.7 (410.95)	1597.97 (363.81)	1750.45 (419.64)
Rice (g/d), mean (SD)	423.27 (44.37)	365.89 (35.03)	303.53 (55)	364.95 (41.9)	308.2 (31.1)	252.46 (44.69)
Fruit (g/d), mean (SD)	66.83 (69.95)	143.39 (89.3)	240.49 (157.5)	120.88 (98.27)	247.12 (116.69)	420.25 (197.97)
Vegetables (g/d), mean (SD)	183.55 (90.32)	318.73 (101.46)	530.16 (215.77)	162.15 (81.52)	277.27 (95.55)	449.51 (192.05)
Fish (g/d), mean (SD)	26.71 (27.72)	49.49 (35.54)	75.81 (59.84)	27.23 (28.51)	49.16 (35.05)	71.55 (56.16)
Red meat (g/d), mean (SD)	41.37 (30.19)	61.6 (30.8)	78.79 (51.05)	33.77 (24.03)	50.28 (26.13)	60.77 (42.45)
Education, N (%)						
Elementary school or less	1241 (10.38)	712 (5.96)	454 (3.8)	5371 (35.93)	2905 (19.43)	1802 (12.06)
Middle school	4710 (39.41)	3902 (32.66)	3406 (28.5)	5239 (35.05)	5590 (37.4)	5632 (37.68)
High school	4074 (34.09)	4430 (37.08)	4537 (37.97)	3039 (20.33)	4255 (28.47)	4970 (33.25)
Professional education/college or higher	1925 (16.11)	2904 (24.31)	3552 (29.73)	1298 (8.68)	2198 (14.7)	2542 (17.01)
Income [c], N (%)						
Low	2021 (16.91)	1338 (11.2)	1280 (10.71)	3118 (20.86)	2252 (15.07)	2071 (13.86)
Lower middle	5635 (47.15)	5119 (42.84)	4577 (38.3)	6101 (40.82)	5634 (37.69)	5494 (36.76)
Upper middle	3562 (29.81)	4347 (36.38)	4507 (37.72)	3874 (25.92)	4281 (28.64)	4223 (28.26)
High	732 (6.13)	1144 (9.57)	1585 (13.26)	1854 (12.4)	2781 (18.6)	3158 (21.13)
Occupation, N (%)						
House wife	-	-	-	96 (0.64)	49 (0.33)	43 (0.29)
Professional, administrator	2371 (19.84)	3257 (27.26)	3712 (31.07)	3083 (20.63)	4486 (30.01)	4982 (33.33)
Clerical or service worker	2470 (20.67)	2598 (21.74)	2815 (23.56)	3054 (20.43)	3068 (20.52)	3186 (21.32)
Manual laborer	7109 (59.49)	6093 (51)	5422 (45.38)	8714 (58.3)	7345 (49.14)	6735 (45.06)
Smoke status, N (%)						

Characteristics [b]	Men			Women		
	Quintiles of dietary vitamin B6 intake			Quintiles of dietary vitamin B6 intake		
	Q1	Q3	Q5	Q1	Q3	Q5
Never smoker	3128 (26.18)	3715 (31.09)	4005 (33.52)	14300 (95.67)	14597 (97.65)	14615 (97.79)
Pack-years<20	1260 (10.54)	1299 (10.87)	1315 (11.01)	90 (0.6)	60 (0.4)	45 (0.3)
Pack-years>=20	7562 (63.28)	6934 (58.03)	6629 (55.48)	557 (3.73)	291 (1.95)	286 (1.91)
Alcohol intake, N (%)						
Never drinker	8458 (70.78)	7999 (66.95)	7380 (61.76)	14694 (98.31)	14687 (98.25)	14574 (97.51)
<=2 drinks/day	2045 (17.11)	2459 (20.58)	2647 (22.15)	234 (1.57)	247 (1.65)	343 (2.29)
>2 drinks/day	1447 (12.11)	1490 (12.47)	1922 (16.09)	19 (0.13)	14 (0.09)	29 (0.19)
History of diabetes, N (%)	645 (5.4)	782 (6.55)	706 (5.91)	855 (5.72)	669 (4.48)	437 (2.92)
History of hypertension, N (%)	3445 (28.83)	3541 (29.64)	3541 (29.63)	3882 (25.97)	3547 (23.73)	3328 (22.27)
History of coronary heart disease, N (%)	537 (4.49)	610 (5.11)	664 (5.56)	1137 (7.61)	1089 (7.29)	1064 (7.12)
History of stroke, N (%)	508 (4.25)	446 (3.73)	391 (3.27)	228 (1.53)	162 (1.08)	124 (0.83)
Family history of cancer, N (%)	3294 (27.56)	3451 (28.88)	3516 (29.43)	3699 (24.75)	4014 (26.85)	4167 (27.88)
Supplemental B vitamins users, N (%)	924 (7.73)	1304 (10.91)	1664 (13.93)	1173 (7.85)	1605 (10.74)	1913 (12.8)
Menopause status, N (%)	-	-	-	8960 (59.95)	7198 (48.15)	6332 (42.37)
Hormone replacement therapy, N (%)	-	-	-	201 (1.34)	280 (1.87)	426 (2.85)

Abbreviation: Q, quintiles; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; SD, standard deviation.

[a] All exposures were associated with dietary vitamin B6 intake, with P<0.001 for trends across categories, except for history of diabetes in men (P=0.057), history of hypertension in men (P=0.007) and women (P=0.006).

[b] Food intake (except for energy) was energy-adjusted by residual methods.

[c] Income level, four categories: Low: less than ¥10000 per family per year for women and less than ¥500 per person per month for men; lower middle: ¥10000–19999 per family per year for women and ¥500–999 per person per month for men; Upper middle: ¥20000–29999 per family per year for women and ¥1000–1999 per person per month for men; high: greater than ¥30000 per family per year for women and more than ¥2000 per person per month for men.

Table 2

Association of energy-adjusted dietary vitamin B6 intake with cause-specific mortality in SMHS (2002–2014)

	Quintiles of dietary vitamin B6 intake						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**Per Q**
Median intake (mg/d)	1.31	1.53	1.69	1.87	2.2		
Person years	118973	119988	120600	121289	123925		
Total mortality							
No. of deaths	1423	1227	1084	1038	933		
Crude HR (95%CIs) [a]	1.00 (reference)	0.79 (0.73,0.85)	0.72 (0.67,0.78)	0.71 (0.65,0.77)	0.68 (0.62,0.74)	<0.001	0.91 (0.89,0.93)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.84 (0.78,0.91)	0.82 (0.75,0.89)	0.83 (0.76,0.90)	0.83 (0.76,0.90)	<0.001	0.96 (0.94,0.98)
Cancer mortality							
No. of deaths	596	479	471	430	435		
Crude HR (95%CIs) [a]	1.00 (reference)	0.76 (0.67,0.86)	0.77 (0.68,0.87)	0.71 (0.63,0.81)	0.75 (0.66,0.85)	<0.001	0.93 (0.91,0.96)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.81 (0.72,0.91)	0.86 (0.76,0.97)	0.82 (0.73,0.94)	0.89 (0.78,1.01)	0.087	0.97 (0.95,1.00)
CVD mortality							
No. of deaths	502	449	342	326	287		
Crude HR (95%CIs) [a]	1.00 (reference)	0.81 (0.71,0.92)	0.64 (0.56,0.74)	0.63 (0.55,0.73)	0.60 (0.52,0.70)	<0.001	0.87 (0.85,0.90)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.86 (0.76,0.98)	0.74 (0.64,0.85)	0.75 (0.65,0.87)	0.73 (0.63,0.85)	<0.001	0.92 (0.89,0.95)
Stroke mortality							
No. of deaths	268	226	167	154	140		
Crude HR (95%CIs) [a]	1.00 (reference)	0.76 (0.63,0.90)	0.58 (0.48,0.71)	0.55 (0.45,0.67)	0.54 (0.44,0.67)	<0.001	0.85 (0.81,0.89)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.82 (0.69,0.99)	0.69 (0.57,0.84)	0.70 (0.57,0.86)	0.71 (0.58,0.88)	<0.001	0.91 (0.87,0.96)
CHD mortality							
No. of deaths	110	105	71	78	58		
Crude HR (95%CIs) [a]	1.00 (reference)	0.88 (0.67,1.16)	0.62 (0.46,0.84)	0.71 (0.53,0.95)	0.57 (0.42,0.79)	<0.001	0.87 (0.81,0.94)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.93 (0.71,1.22)	0.71 (0.52,0.96)	0.81 (0.60,1.09)	0.66 (0.47,0.91)	0.006	0.90 (0.84,0.97)
AMI mortality							
No. of deaths	74	85	50	66	47		

	Quintiles of dietary vitamin B6 intake						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**Per Q**
Crude HR (95%CIs) [a]	1.00 (reference)	1.10 (0.80,1.50)	0.67 (0.47,0.97)	0.91 (0.65,1.27)	0.69 (0.48,0.99)	0.019	0.91 (0.84,0.98)
Multivariable HR (95%CIs) [b]	1.00 (reference)	1.16 (0.84,1.59)	0.76 (0.52,1.09)	1.02 (0.72,1.43)	0.78 (0.53,1.13)	0.137	0.94 (0.87,1.02)

Abbreviation: Q, quintiles; SMHS, Shanghai Men's Health Study; HR, hazards ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary artery heart disease; AMI, acute myocardial infarction.

[a]Crude HR: Adjusted for age at baseline, energy intake.

[b]Multivariable HR: Additionally adjusted for education, income, occupation, smoke, alcohol, body mass index, waist-hip ratio, physical activity, history of diabetes, hypertension, coronary heart disease and stroke, vitamin B supplements use.

Table 3

Association of energy-adjusted dietary vitamin B6 intake with cause-specific mortality in SWHS (1997–2014)

	Quintiles of dietary vitamin B6 intake						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**Per Q**
Median intake (mg/d)	1.24	1.45	1.62	1.79	2.11		
Person years	229890	232273	233661	234814	235497		
Total mortality							
No. of deaths	2169	1698	1412	1239	1037		
Crude HR (95%CIs) [a]	1.00 (reference)	0.86 (0.81,0.92)	0.81 (0.76,0.87)	0.79 (0.74,0.85)	0.74 (0.68,0.79)	<0.001	0.93 (0.91,0.94)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.90 (0.85,0.96)	0.88 (0.82,0.94)	0.88 (0.81,0.94)	0.83 (0.77,0.90)	<0.001	0.96 (0.94,0.98)
Cancer mortality							
No. of deaths	816	670	594	572	496		
Crude HR (95%CIs) [a]	1.00 (reference)	0.91 (0.82,1.01)	0.87 (0.79,0.97)	0.90 (0.81,1.01)	0.83 (0.74,0.92)	0.002	0.96 (0.94,0.99)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.93 (0.84,1.03)	0.91 (0.82,1.02)	0.95 (0.85,1.06)	0.88 (0.78,0.99)	0.063	0.98 (0.95,1.00)
CVD mortality							
No. of deaths	781	549	452	392	312		
Crude HR (95%CIs) [a]	1.00 (reference)	0.79 (0.71,0.88)	0.76 (0.68,0.85)	0.76 (0.67,0.85)	0.70 (0.61,0.80)	<0.001	0.92 (0.89,0.95)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.82 (0.73,0.91)	0.83 (0.74,0.94)	0.85 (0.75,0.96)	0.80 (0.70,0.92)	0.001	0.95 (0.92,0.98)
Stroke mortality							
No. of deaths	426	271	245	221	154		
Crude HR (95%CIs) [a]	1.00 (reference)	0.71 (0.61,0.83)	0.75 (0.64,0.88)	0.78 (0.66,0.91)	0.63 (0.52,0.76)	<0.001	0.91 (0.88,0.95)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.75 (0.64,0.87)	0.84 (0.71,0.98)	0.87 (0.74,1.03)	0.72 (0.59,0.86)	0.006	0.94 (0.91,0.98)
CHD mortality							
No. of deaths	132	98	75	65	60		
Crude HR (95%CIs) [a]	1.00 (reference)	0.83 (0.64,1.08)	0.75 (0.56,0.99)	0.75 (0.55,1.01)	0.81 (0.60,1.11)	0.07	0.94 (0.87,1.01)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.85 (0.65,1.11)	0.81 (0.61,1.08)	0.83 (0.61,1.13)	0.91 (0.66,1.24)	0.351	0.97 (0.90,1.04)
AMI mortality							
No. of deaths	89	66	50	48	41		

	Quintiles of dietary vitamin B6 intake						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**Per Q**
Crude HR (95%CIs) [a]	1.00 (reference)	0.85 (0.61,1.17)	0.75 (0.53,1.07)	0.82 (0.58,1.17)	0.81 (0.56,1.18)	0.200	0.95 (0.87,1.03)
Multivariable HR (95%CIs) [b]	1.00 (reference)	0.88 (0.64,1.22)	0.82 (0.58,1.17)	0.92 (0.64,1.31)	0.91 (0.62,1.33)	0.589	0.98 (0.90,1.06)

Abbreviation: Q, quintiles; SWHS, Shanghai Women's Health Study; HR, hazards ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary artery heart disease; AMI, acute myocardial infarction.

[a]Crude HR: Adjusted for age at baseline, energy intake.

[b]Multivariable HR: Additionally adjusted for education, income, occupation, smoke, alcohol, body mass index, waist-hip ratio, physical activity, history of diabetes, hypertension, coronary heart disease and stroke, vitamin B supplements use, menopausal status, and hormone replacement therapy.

Table 4

Subgroup analysis of association of energy-adjusted dietary vitamin B6 intake with all-cause mortality in SMHS (2002–2014)

	Quintiles of dietary vitamin B6 intake [a]						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**P for interaction**
Age at baseline							0.459
Age <60 y							
No. of deaths	270	234	245	235	233		
HR (95%CIs)	1.00 (reference)	0.89 (0.74,1.06)	0.94 (0.79,1.12)	0.88 (0.74,1.06)	0.85 (0.71,1.01)	0.091	
Age>=60 y							
No. of deaths	1153	993	839	803	700		
HR (95%CIs)	1.00 (reference)	0.83 (0.76,0.91)	0.80 (0.73,0.87)	0.82 (0.75,0.90)	0.82 (0.74,0.90)	<0.001	
Smoke status							0.798
Never smoker							
No. of deaths	371	371	334	342	333		
HR (95%CIs)	1.00 (reference)	0.88 (0.76,1.01)	0.78 (0.67,0.91)	0.79 (0.68,0.92)	0.86 (0.74,1.01)	0.046	
Ever smoker							
No. of deaths	1052	856	750	696	600		
HR (95%CIs)	1.00 (reference)	0.83 (0.76,0.91)	0.84 (0.77,0.93)	0.85 (0.77,0.94)	0.81 (0.73,0.90)	<0.001	
Alcohol use							0.731
Never use							
No. of deaths	952	808	689	637	573		
HR (95%CIs)	1.00 (reference)	0.86 (0.78,0.94)	0.83 (0.75,0.91)	0.80 (0.72,0.89)	0.84 (0.75,0.93)	<0.001	
Ever use							
No. of deaths	471	419	395	401	360		
HR (95%CIs)	1.00 (reference)	0.81 (0.71,0.93)	0.81 (0.70,0.93)	0.87 (0.76,1.00)	0.80 (0.70,0.92)	0.017	
Body mass index							0.294
BMI<24 kg/m^2							
No. of deaths	801	714	593	556	438		
HR (95%CIs)	1.00 (reference)	0.86 (0.78,0.95)	0.80 (0.72,0.89)	0.82 (0.73,0.91)	0.80 (0.71,0.90)	<0.001	
BMI>=24 kg/m^2							
No. of deaths	622	513	491	482	495		

	Quintiles of dietary vitamin B6 intake [a]						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**P for interaction**
HR (95%CIs)	1.00 (reference)	0.81 (0.72,0.92)	0.84 (0.75,0.95)	0.84 (0.74,0.95)	0.85 (0.76,0.96)	0.04	
Energy intake							0.036
<Median							
No. of deaths	731	814	733	652	450		
HR (95%CIs)	1.00 (reference)	0.77 (0.69,0.85)	0.77 (0.69,0.85)	0.77 (0.69,0.86)	0.74 (0.66,0.84)	<0.001	
>=Median							
No. of deaths	692	413	351	386	483		
HR (95%CIs)	1.00 (reference)	0.95 (0.84,1.07)	0.88 (0.77,1.00)	0.91 (0.80,1.04)	0.92 (0.81,1.03)	0.133	
History of main chronic disease							0.048
No							
No. of deaths	995	815	717	688	621		
HR (95%CIs)	1.00 (reference)	0.84 (0.76,0.92)	0.79 (0.72,0.87)	0.80 (0.73,0.89)	0.78 (0.70,0.86)	<0.001	
Yes							
No. of deaths	428	412	367	350	312		
HR (95%CIs)	1.00 (reference)	0.86 (0.75,0.98)	0.88 (0.76,1.01)	0.90 (0.78,1.04)	0.92 (0.79,1.07)	0.496	
Vitamin B supplements use							0.921
No							
No. of deaths	1284	1081	939	874	763		
HR (95%CIs)	1.00 (reference)	0.84 (0.77,0.91)	0.82 (0.75,0.89)	0.83 (0.76,0.91)	0.83 (0.75,0.91)	<0.001	
Yes							
No. of deaths	139	146	145	164	170		
HR (95%CIs)	1.00 (reference)	0.86 (0.68,1.09)	0.82 (0.65,1.04)	0.82 (0.65,1.04)	0.84 (0.67,1.07)	0.228	

Abbreviation: Q, quintiles; SMHS, Shanghai Men's Health Study; HR, hazards ratio; CI, confidence interval.

[a]HR: Adjusted for age, energy intake, education, income, occupation, smoke, alcohol, body mass index, waist-hip ratio, physical activity, history of diabetes, hypertension, coronary heart disease and stroke, vitamin B supplements use.

Table 5

Subgroup analysis of association of energy-adjusted dietary vitamin B6 intake with all-cause mortality in SWHS (1997–2014)

	Quintiles of dietary vitamin B6 intake [a]						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**P for interaction**
Age at baseline							0.542
Age <60 y							
No. of deaths	305	336	331	320	331		
HR (95%CIs)	1.00 (reference)	1.05 (0.89,1.22)	0.97 (0.83,1.14)	0.94 (0.80,1.11)	0.94 (0.80,1.10)	0.216	
Age>=60 y							
No. of deaths	1864	1362	1081	919	706		
HR (95%CIs)	1.00 (reference)	0.88 (0.82,0.94)	0.87 (0.80,0.94)	0.87 (0.81,0.95)	0.82 (0.75,0.89)	<0.001	
Body mass index							0.057
BMI<24 kg/m^2							
No. of deaths	885	774	649	520	394		
HR (95%CIs)	1.00 (reference)	0.94 (0.85,1.03)	0.94 (0.85,1.04)	0.86 (0.77,0.96)	0.80 (0.71,0.91)	<0.001	
BMI>=24 kg/m^2							
No. of deaths	1284	924	763	719	643		
HR (95%CIs)	1.00 (reference)	0.88 (0.80,0.95)	0.84 (0.77,0.92)	0.88 (0.81,0.97)	0.85 (0.77,0.94)	0.001	
Energy intake							0.015
<Median							
No. of deaths	1101	1140	921	736	434		
HR (95%CIs)	1.00 (reference)	0.89 (0.82,0.97)	0.86 (0.79,0.94)	0.85 (0.78,0.94)	0.77 (0.68,0.86)	<0.001	
>=Median							
No. of deaths	1068	558	491	503	603		
HR (95%CIs)	1.00 (reference)	0.90 (0.81,1.00)	0.90 (0.80,1.00)	0.90 (0.81,1.00)	0.89 (0.80,0.98)	0.024	
History of chronic							0.002
No							
No. of deaths	1512	1155	991	902	745		
HR (95%CIs)	1.00 (reference)	0.92 (0.85,0.99)	0.90 (0.83,0.97)	0.91 (0.84,0.99)	0.83 (0.76,0.91)	<0.001	
Yes							
No. of deaths	657	543	421	337	292		

	Quintiles of dietary vitamin B6 intake [a]						
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**	**P for interaction**
HR (95%CIs)	1.00 (reference)	0.86 (0.77,0.97)	0.85 (0.75,0.96)	0.80 (0.70,0.91)	0.85 (0.74,0.98)	0.004	
Vitamin B supplements use							0.015
No							
No. of deaths	1951	1491	1246	1066	904		
HR (95%CIs)	1.00 (reference)	0.90 (0.84,0.97)	0.90 (0.84,0.97)	0.89 (0.82,0.96)	0.86 (0.79,0.93)	<0.001	
Yes							
No. of deaths	218	207	166	173	133		
HR (95%CIs)	1.00 (reference)	0.87 (0.71,1.05)	0.72 (0.59,0.89)	0.78 (0.64,0.96)	0.65 (0.52,0.81)	<0.001	
Menopause status							0.983
No							
No. of deaths	221	229	234	222	237		
HR (95%CIs)	1.00 (reference)	0.96 (0.79,1.16)	0.91 (0.75,1.10)	0.86 (0.71,1.04)	0.88 (0.73,1.06)	0.102	
Yes							
No. of deaths	1948	1469	1178	1017	800		
HR (95%CIs)	1.00 (reference)	0.89 (0.84,0.96)	0.88 (0.82,0.95)	0.89 (0.82,0.96)	0.83 (0.76,0.90)	<0.001	

Abbreviation: Q, quintiles; SWHS, Shanghai Women's Health Study; HR, hazards ratio; CI, confidence interval.

[a]HR: Adjusted for age, energy intake, education, income, occupation, smoke, alcohol, body mass index, waist-hip ratio, physical activity, history of diabetes, hypertension, coronary heart disease and stroke, vitamin B supplements use, menopausal status, and hormone replacement therapy.