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Dietary B vitamin intake and risk of hip fracture: the Singapore Chinese Health Study

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Abstract

Summary—This prospective cohort study that comprehensively examined effects of different B vitamins in an Asian population showed an inverse relationship between dietary intake of pyridoxine and hip fracture risk in elderly women. These findings suggest that maintaining sufficient pyridoxine intake may be beneficial in preserving bone health in postmenopausal women.

Introduction—B vitamins have recently been investigated for their possible roles in maintaining bone health. Incidence of osteoporotic hip fracture has been rising in Asia, but epidemiological data on dietary B vitamins and risk of osteoporotic fractures are sparse. We aimed to examine the association between dietary intakes of B vitamins (thiamin, riboflavin, niacin, pyridoxine, folate, and cobalamin) and hip fracture risk among elderly Chinese in Singapore.

Methods—The current study was conducted in the Singapore Chinese Health Study, which is a population-based cohort prospective study that enrolled a total of 63,257 men and women aged

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Conflicts of interest None.

45–74 years between 1993 and 1998. Dietary intakes of B vitamins were derived from a validated food frequency questionnaire and the Singapore Food Composition Database.

Results—After a mean follow-up period of 13.8 years, 1,630 hip fracture incident cases were identified. A statistically significant inverse relationship between dietary pyridoxine intake and hip fracture risk was observed among women (p for trend=0.002) but not among men. Compared to women in the lowest quartile intake (0.37–0.61 mg/1,000 kcal/day), women in the highest quartile intake (0.78–1.76 mg/1,000 kcal/day) had a 22 % reduction in hip fracture risk (hazard ratio 0.78, 95 % confidence interval 0.66–0.93). Dietary intakes of the other B vitamins of interest were not related to hip fracture risk.

Conclusions—Our findings suggest that maintaining adequate intake of pyridoxine may prevent osteoporotic fractures among elderly women.

Keywords

B vitamins; Chinese; Hip fracture; Osteoporosis; Pyridoxine

Introduction

Hip fracture due to osteoporosis is a serious health threat among populations aged 50 years or older [1]. The consequence of hip fracture is devastating, which includes loss of independence and functions, and imposes a great economic burden to individuals as well as to the society. With the global problem of aging in both developed and developing regions, total hip fracture incident cases are projected between 4.5 and 6.3 million by year 2050 [1]. Malnutrition and low intake of nutrients have been found to be more prevalent and severe among hip fracture patients as compared to the general elderly populations, where nutrient deficiency may accelerate bone loss, microarchitectural deterioration, and increase risk for subsequent fractures [2]. Hence, a population-based strategy by improving dietary intake of specific nutrients among elderly may be effective in preventing osteoporotic hip fracture.

B vitamins have been recently investigated for their possible roles in maintaining bone health and fracture prevention. Most of the observational studies focused on the B vitamins that are cofactors involved in the one-carbon metabolism [3]. However, each of the B vitamins has other physiologic roles as well. Cobalamin (vitamin B12) was first revealed to be related to osteoporosis and fractures in patients with pernicious anemia [4, 5], although cobalamin may directly impact osteoblastic [6] and osteoclastic [7] activities in vitro. Folate (vitamin B9) can indirectly affect bone remodeling because of its involvement in intracellular DNA methylation [8]. Resorption activity was found to be declined in folate-deficient osteoclasts [7]. Evidence from embryotic chicks showed that pyridoxine (vitamin B6) is a cofactor of lysyl oxidase [9], which is an essential enzyme to collagen cross-linking formation. Other animal studies also suggested that pyridoxine may play a role in bone formation [10]. In contrast, results from epidemiologic studies on the relationship between B vitamins and osteoporosis or osteoporotic fractures were inconsistent, and almost all of these studies have been conducted in the Western populations [11–14]. Furthermore, evidence on the other B vitamins (thiamin, riboflavin, and niacin) is sparse. For example, a study among othopedic patients reported that thiamin (vitamin B1) was deficient among femoral neck

fracture patients but not among those with total hip replacement [15]; riboflavin (vitamin B2) and its photoderivatives were shown to enhance bone formation in vitro [16]; and high level of niacin (vitamin B3) was reported to have adverse effects on bone strength and growth in chicks [17]. Thus far, there is no single epidemiologic study assessed the association between all of these B vitamins and fracture risk using prospective data from a population-based cohort.

There is a rapid increase in incidence of hip fracture in Asia, and up to 50 % of total cases by year 2050 are projected to happen in this part of the world [1]. Asian populations are known to have distinct dietary and lifestyle factors from their Western counterparts [18]. Yet, prospective evidence on the association between B vitamins and hip fracture risk is lacking among Asian populations. Hence, in the present study, we hypothesized that dietary intakes of B vitamins (thiamin, riboflavin, niacin, pyridoxine, folate, and cobalamin) would reduce hip fracture risk among elderly Chinese men and women.

Methods

Study population

This study was conducted in the Singapore Chinese Health Study, a population-based prospective cohort that was established to investigate diet, lifestyle factors, and risks of chronic diseases [18]. The study enrolled a total of 63,257 participants (27,959 men and 35,298 women) aged 45–74 years who were residing in the government housing estates between April 1993 and December 1998. During the enrolment period, 86 % of residents in Singapore were living in these housing estates. The study participants were restricted to two major dialect groups in Singapore: Hokkien and Cantonese, who originated from Fujian and Guangdong Provinces in Southern China, respectively. This study was approved by the Institutional Review Board at the National University of Singapore.

Baseline exposure assessment

Baseline assessment was conducted through a face-to-face structured interview during the initial enrolment. Information was recorded by a trained interviewer using a structured questionnaire including demographics, medical history, tobacco smoking, alcohol consumption, physical activity, and detailed menstrual and reproductive history (women only). Dietary intake was recorded using the 165-item food frequency questionnaire which incorporated common and distinct food items in Singapore for food frequency and portion sizes. Intakes of food items and selected nutrients were computed for each participant by linking dietary intakes to the Singapore Food Composition Database, which provides specific levels of the nutritional components per 100 g of edible food for each food item in the questionnaire. Detail of the validation study was previously reported [18].

Case ascertainment

Hip fracture cases were identified via linkage with the hospital discharge database of the MediClaim System, which has captured inpatient discharge information from all public and private hospitals in Singapore since 1990. All cases identified via linkage were verified by records of the appropriate surgical procedures or manual review of medical records.

Mortality was recorded through linkage with the Singapore Registry of Births and Deaths. As of 31 December 2010, after excluding four cases of traumatic fractures from road traffic accidents, and one case of hip fracture due to cancer metastasis to the femur, 1,733 hip fracture cases were identified through record linkage in this cohort. We further excluded 103 prevalent cases, which occurred before subjects' recruitment to the cohort. Thus, 1,630 fracture cases and 61,524 subjects without fractures were included in the statistical analysis of this study.

Statistical analysis

We used chi-square test (for categorical variables) or Student's *t* test (for continuous variables) to examine the difference in distributions of baseline characteristics between cases and non-cases. For each study subject, person-years were counted from the date of baseline interview to the date of hip fracture diagnosis, death, migration, or the end of follow-up up to 31 December 2010, whichever occurred first. As of 31 December 2010, only 47 subjects of the original cohort participants were known to be lost to follow-up due to migration out of Singapore or for other reasons. Cox proportional hazards model was applied to assess the association between baseline dietary intake of B vitamins and hip fracture risk by comparing higher quartile intake levels of the nutrient relative to the lowest quartile intake level [19]. Quartiles of intake for each energy-adjusted nutrient were based on the combined distribution of men and women in the whole cohort. The strength of the association between B vitamins and hip fracture risk was measured by hazard ratios (HRs) and its corresponding 95 % confidence intervals. To examine linear trend, ordinal values of the quartile intake of each vitamin B was entered as a continuous variable in the Cox proportional hazards model. We did not identify any violation of the proportional hazard assumption nor multicollinearity among the covariates that were entered in the models.

We first assessed the association in a basic model which was adjusted for parameters that included age (continuous), body mass index (BMI), year of recruitment (1993–1995 and 1996–1998), dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, secondary school or higher), and total energy intake. Adjustment for year of recruitment minimized systematic errors regarding subject enrolment in the study during a different time period. There was a suggestive difference in diet found between two dialect groups [18], thus dialect group was also adjusted in our models. Adjustment for total energy intake in addition to the energy-adjusted vitamin B (exposure of interest) is based on the multivariate nutrient density model [20]. The covariates selected for the full model, taking into account the previously published risk factors for hip fracture [21, 22], were evaluated for confounding if a covariate was related to both exposure and outcome or if inclusion of the covariate in the model affected the effect size by at least 10 %. Established risk factors for hip fracture in this cohort included smoking status, BMI, calcium intake, soy isoflavone intake, and history of diabetes [21, 22]. Hence, our final model included the following covariates: age (continuous), year at recruitment (1993–1995 and 1996–1998), dialect group (Hokkien, Cantonese), level of education (no formal education, primary school, secondary school or higher), BMI (<20, 20–24, 24–28, ≥28 kg/m^2), smoking status (never, ex-smokers, current smokers), moderate physical activity (none, 2–3 h weekly, 4+ h weekly), calcium (quartiles, in milligrams/1,000 kcal/day), soy isoflavones (quartiles, in milligrams/1,000

kcal/day), total energy intake (in kilocalories per day), menopausal status (women only; yes, no), ever use of hormone replacement therapy (HRT) at recruitment (women only; yes, no), and baseline self-reported physician-diagnosed history of diabetes mellitus and stroke. Further adjusted covariates for potential confounding, one at a time or simultaneously, to evaluate if there was at least 10 % change of effect size as compared to the full model were also considered: vitamin D from diet (in international units/1,000 kcal/day), protein intake (in grams/1,000 kcal/day), potassium (in milligrams/1,000 kcal/day), zinc (in milligrams/1,000 kcal/day), caffeine (in milligrams/1,000 kcal/day), magnesium (in milligrams/1,000 kcal/day), and at least weekly use of vitamins (yes, no).

We also performed sensitivity analysis for the association of B vitamins with hip fracture risk, excluding those who had reported extreme energy intakes (≤600 and ≥3,000 kcal) from the whole cohort or excluding women who ever used HRT. Finally, as female gender, leanness (BMI <20 kg/m^2), and diabetes mellitus have been identified as independent risk factors of hip fracture in this cohort [21, 22] and also in systematic reviews of other studies [23–25], we investigated possible interaction effects of these factors in the association of pyridoxine with hip fracture risk.

All statistical analysis was conducted using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). All reported p values are two-sided; $p<0.05$ was considered statistically significant.

Results

Baseline characteristics of the study subjects of fracture cases and non-cases are described in Table 1. Fracture cases constituted 1.6 % among men, as compared to 3.3 % among women; women accounted for 72.4 % of all hip fractures. Among the 1,630 incident hip fracture cases, the mean time interval between cohort enrollment and hip fracture diagnosis was 9.9 [standard deviation (SD) 4.5] years. The mean age at fracture was 74.4 (SD 7.5) years. Women were doubled in the incidence rates of hip fractures (234 per 100,000 person-years) than men (123 per 100,000 person-years) within the cohort after adjustment for age using the age distribution of the entire cohort. Compared to non-cases, both men and women with hip fracture were older at recruitment, less educated, more likely to smoke, had lower daily energy intake, and more likely to have self-report history of physician-diagnosed diabetes mellitus or stroke at recruitment. Vitamin supplementation was not common in this population, in which about 5 % of men and 8 % of women taking vitamin supplements. To directly compare dietary intakes of vitamins and minerals between cases and non-cases for both genders, these nutrients were presented after adjustment for total energy intake. Calcium intake was similar between cases and non-cases in either gender. Among women, cases had higher intake of vitamin D and soy isoflavones. For men, hip fracture cases had lower BMI and there was a higher proportion of daily drinkers at recruitment compared to non-cases. For women, more cases were postmenopausal at recruitment relative to non-cases; use of hormonal therapy was uncommon and was only present in 4 % of women in the cohort (Table 1).

Average daily intakes of protein and B vitamins were compared between this cohort and those in the US RDA [26]. It appears that our study population had lower intakes of most

B vitamins except cobalamin, the most deficient nutrient being folate for both genders (Table 2). The top five food sources that contributed to each vitamin B in this cohort at the time of recruitment are described in Table 3. Grain products and animal meat were the common food sources for B vitamins in this cohort. Vegetable was the major food source for riboflavin and folate. There were weak to moderate correlations (range from 0.08–0.52) between intakes of individual B vitamins (data not shown). This result was expected as the sources of food for these B vitamins did not overlap considerably in this cohort.

Tables 4 and 5 show analyses for the association between dietary intake of B vitamins and risk of hip fracture in men and women separately. The results after further adjustment for other risk factors of hip fracture remained very similar as compared to the basic model. Among men (Table 4), no significant association was found between dietary intakes of all of the B vitamins and hip fracture risk in both models. Among women (Table 5), we observed a dose-dependent inverse relationship between dietary intake of pyridoxine and hip fracture risk (p for trend=0.002). Compared to the lowest quartile intake of pyridoxine (0.37–0.61 mg/1,000 kcal/day), increasing dietary intake of pyridoxine across the higher quartiles reduced hip fracture risk by 18 to 22 % (all p values ≤0.02). The risk estimates in the third and fourth quartiles were comparable. The difference in risk estimates across quartile intakes was statistically significant between men and women (p for interaction=0.008). There was a weak positive association between dietary intake of thiamin and risk of hip fracture in women. However, further adjustment for other risk factors for hip fracture attenuated the association that became statistically non-significant. Riboflavin, niacin, folate, and cobalamin had null association with hip fracture risk in women. Further adjustment for vitamin D from diet (in international units/1,000 kcal/day), protein intake (in grams/1,000 kcal/day), zinc (in milligrams/1,000 kcal/day), caffeine (in milligrams/1,000 kcal/day), magnesium (in milligrams/1,000 kcal/day), and at least weekly use of vitamins (yes, no) did not change the effect estimate materially (data not shown). Adjustment for potassium (in milligrams/1,000 kcal/day) slightly attenuated the association between pyridoxine and hip fracture risk (p for trend=0.063). However, the change in the risk estimates was less than 10 %. Compared to women in the lowest quartile of pyridoxine intake, HRs (95 % CI) for quartiles 2, 3, and 4 were 0.84 (0.72–0.99), 0.82 (0.69–0.98), and 0.84 (0.68–1.03), respectively. The loss of statistical significance was attributable to widening of confidence intervals due to certain degree of collinearity between dietary potassium and pyridoxine (correlation coefficient=0.59). On the other hand, the moderate association between dietary potassium and hip fracture risk disappeared after adjustment for pyridoxine (p for trend=0.26). We further examined the association between dietary B vitamins and hip fracture risk with the residual method to adjust for total energy intake [20] and the same covariates mentioned above, and the results remained unchanged (data not shown).

The sensitivity analysis for the B vitamin–hip fracture risk association after exclusion of participants with extreme energy intakes (≤600 and ≥3,000 kcal) also yielded similar results (data not shown). Results based on women who did not use any HRT were similar to those based on the entire dataset (data not shown). For women who were postmenopausal at recruitment, we had also computed years past menopause. When we replaced age at recruitment with years past menopause in the model, the results remained essentially

unchanged for the pyridoxine–hip fracture risk in women. The hazard ratios (95 %CI) across quartile 2 to quartile 4 for pyridoxine and risk of hip fracture among women with years past menopause instead of age as the covariate were 0.77 (0.66–0.90), 0.72 (0.62–0.85), and 0.73 (0.61–0.86), respectively (p for trend <0.0001).

We further examined whether BMI and diabetes mellitus modified the protective effect of pyridoxine on hip fracture incidence in women (Table 6). When women were stratified by BMI <20 or ≥20 kg/m^2, increasing pyridoxine intake was similarly associated with reduced risk of hip fracture for both groups of women with different BMI, although the test for trend was not statistically significant in women with BMI <20 kg/m^2. The overall pyridoxine-hip fracture risk associations were comparable for both BMI strata (p for interaction=0.74).

We also conducted stratified analysis for women by history of diabetes (Table 6). The reduction in hip fracture risk with increasing pyridoxine intake was primarily seen among women with no history of diabetes (p for trend=0.0009). On the other hand, there was no association between dietary pyridoxine and hip fracture risk in women with history of diabetes (p for trend=0.70). Diabetes significantly modified the protective effect of dietary pyridoxine intake on hip fracture risk (p for interaction=0.04).

Finally, we also assessed other nutrients that may be associated with risk of hip fracture in the current study, and did not find protective effects from dietary intakes of protein, vitamin D, potassium, zinc, or magnesium (data not shown).

Discussion

To the best of our knowledge, this is the first prospective cohort study that most comprehensively explored the associations between different B vitamins and risk of hip fracture among elderly in an Asian population. Our study showed an inverse relationship between dietary intake of pyridoxine and hip fracture risk among elderly Chinese women. Other B vitamins, namely, thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), folate (vitamin B9), and cobalamin (vitamin B12), did not show any protective or risk effect on the incidence of hip fracture.

In the present study, we used nutrient density (energy-adjusted) for B vitamins to assess the B vitamin–hip fracture association, as we believe this is a more valid comparison between an Asian population and a Western population [18]. When we compared daily average B vitamin intakes to those in several prospective studies from other Western populations regarding B vitamins and bone health, our study population had apparently lower intakes in B vitamins [12, 27]. Our previous study has also shown a lower intake of dietary calcium in our study population as compared to the Whites and Blacks in the USA [18], probably due to low dairy intake and rare supplementation. Dietary intake of vitamin D also was lower in our study population, probably also due to low consumption of milk and dairy products as well as low use of dietary vitamin D supplement, as compared with Western populations. However, sun exposure is known to be a major determinant of vitamin D status. Given that Singapore is located close to the equator, dietary intake of vitamin D may not sufficiently reflect the in vivo level of vitamin D in this study population. According to the US RDA

[26], our study population consumed a diet with much lower B vitamins with the exception of cobalamin. In addition, B vitamin-fortified food or vitamin supplementation is uncommon in Singapore. These factors may explain why vitamin intake is lower in our cohort when compared to Western populations.

Our finding on the association between intake of pyridoxine and reduced hip fracture risk is consistent with two recent population-based cohort studies, the Rotterdam Study [12] and the Framingham Osteoporosis Study [13]. Yazdanpanah et al. [12] examined dietary intake of riboflavin, pyridoxine, folate, and cobalamin and found an inverse relationship between pyridoxine and fragility and non-vertebral fracture risk among elderly Caucasians in Rotterdam. Similar to our findings, the Rotterdam Study did not find a statistically significant association between any of other three B vitamins and hip fracture risk. In the Framingham Osteoporosis Study, plasma B vitamins (pyridoxine, folate, and cobalamin) and homocysteine were quantified in elderly community-dwelling residents of Framingham. Using clinical cut points to define normal, low, or deficient vitamin status, those with deficient levels of pyridoxine had the greatest annual mean bone loss change and 73 % increased hip fracture risk as compared to those with normal levels. However, these risk estimates became attenuated and were not statistically significant after further adjusting for bone mineral density or homocysteine. This may suggest that the protective effect of pyridoxine on hip fracture could have been mediated via bone mineral density or the level of homocysteine [13]. A Japanese cross-sectional study also supported our finding. Compared to age-matched post-mortem controls, the authors found that women with intracapsular hip fracture had significantly lower plasma pyridoxal, higher plasma homocysteine levels, and reduced collagen cross-linking in high-density bone [28].

There are several potential mechanisms that pyridoxine may protect against hip fracture. One possible mechanism is that pyridoxine acts as a regulator of collagen cross-linking in bone via the expression of lysyl oxidase [9]. Pyridoxine was shown to be an essential nutrient in collagen cross-linking in chick bones [9]. In addition, deficiency of pyridoxine decreased the activity of glucose-6-phosphate dehydrogenase in bone formation and callus in rats [10], suggesting that pyridoxine was important in fracture healing. In accordance, evidence from epidemiologic studies reported that patients with lower levels of pyridoxine had altered structural and biomechanical properties of femoral heads [29], reduced enzymatic cross-links, and increased pentosidine in cortical and cancellous bone [30]. Findings from the Rotterdam Study [12] and the Framingham Study [13] also showed that pyridoxine was associated with higher femoral neck bone mineral density. Furthermore, several animal studies suggested that pyridoxine could affect the central nervous system in rats or mice, which, in turn, affects the locomotor system [31], since pyridoxine is also an important coenzyme of the neurotransmitters γ-aminobutyric acid [31]. Thus, deficiency of pyridoxine may also increase risk of falling and therefore risk of hip fracture. These experimental and observational evidences support our hypothesis that pyridoxine can affect fracture risk via its direct effects on bone.

Hyperhomocysteinemia has been shown to be a possible risk factor for osteoporotic fractures in recent epidemiologic studies [32]. Since riboflavin, pyridoxine, folate, and cobalamin are involved in the one-carbon metabolism, which includes homocysteine

degradation, it is biologically plausible that deficiency of any of these B vitamins may affect bone structure and mineralization. However, a previous study on a subpopulation (n=486) from this cohort showed that plasma folate exerted the strongest effect on homocysteine, followed by cobalamin, whereas pyridoxine exerted the weakest relationship [33]. If homocysteine mediates the association between B vitamins and hip fracture risk, it is biologically plausible that folate would have the strongest protective effect on hip fracture development. Contrary to this, we did not observe an association between folate intake and hip fracture risk in either gender. Furthermore, several observational studies were unable to link elevated homocysteine with decreased bone mineral density [13, 34]. A recent clinical study also showed that the lowering of homocysteine by B vitamin supplementation, which contained pyridoxine, folate, and cobalamin, did not affect bone turnover biomarkers [35]. In line with these findings, the Rotterdam Study suggested that pyridoxine reduced hip fracture risk independent of homocysteine level [12]. Hence, we conclude that the inverse association between pyridoxine and hip fracture risk may not be mediated via the effect of pyridoxine on homocysteine level. Unfortunately, we only had 12 cases of hip fracture in the subpopulation with plasma homocysteine measurement. Therefore, we cannot further assess the interrelation among the one-carbon metabolic B vitamins, plasma homocysteine level, and risk of hip fracture in the current study.

In this study, our novel finding that the protective effect of pyridoxine against hip fracture risk was limited to women supports the hypothesis for a gender-specific difference in bone degradation leading to fracture development. In the present study, we found that women, in general, have a twofold increase in risk of hip fracture compared to men, consistent with previous findings [36]. Gender-specific difference for fracture risk has been attributed to differences in bone geometry and sex hormone deficiency [37]. The rapid decrease of estrogen during the first decade after menopause has been postulated to lead to an accelerated phase of bone loss, followed by a slow and continuous phase during the later period [37]. Following the evidence from several epidemiologic studies that reported a protective effect of pyridoxine on breast cancer in women [38, 39], experimental studies on cancer cells have suggested that pyridoxine may act as a regulator of steroid hormone, including estrogen, through its modulation of the hormone receptors [40, 41]. Since estrogen plays a substantial role in bone turnover [42] and pyridoxine may potentially modulate estrogen, this may explain why the protective effect of pyridoxine on hip fracture risk was observed only in postmenopausal women.

Our previous study has shown a strong etiologic association between diabetes mellitus and increased hip fracture risk in the same cohort, where subjects with diabetes had about a twofold increased risk of developing hip fracture compared to those without diabetes [22]. The present analysis suggests that pyridoxine appeared to have no protective effect in women with diabetes. Diabetes mellitus is known to influence hip fracture risk via alteration of bone turnover markers, mechanical deterioration, and decrease in bone strength [43, 44]. We postulate that the protective mechanisms mediated by pyridoxine may not compensate for the aforementioned factors detrimental to bone health in patients with diabetes. Hence, the efficacy of pyridoxine in the prevention of hip fracture may be lost in women with diabetes. This hypothesis needs to be validated in further studies.

The strengths of this study are its population-based design and the reduced likelihood of recall bias in exposure data, since they were obtained prior to hip fracture. Another strength is that case ascertainment through linkage with the nationwide hospital database can be considered complete, as Singapore is a small city-state with a system for easy access to specialized medical care, and practically all hip fracture cases would seek medical attention immediately and be hospitalized. The information from the database also allows us to differentiate prevalent cases from incident cases using the dates of recruitment into the study and admission into hospital after the fracture. Food is not commonly enriched with micro-nutrients in Singapore [45]. Hence, folate fortification would not complicate our computation of folate intake in this study population. A major limitation of this study is that dietary intake of B vitamins was recorded using a food-frequency questionnaire and diet assessment only at study recruitment. Dietary changes over time after baseline interview may lead to non-differential misclassification of intake, which would result in an underestimation of the true effect size of dietary pyridoxine and other B vitamins examined on hip fracture risk. Bone mineral density (BMD) was not available at baseline measure, which could be viewed as a limitation. However, if low BMD is a physiological marker leading toward hip fracture, it would not confound the association between pyridoxine intake and risk of hip fracture. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <−2.5 SD). A recent report on a consensus statement on the diagnostic criteria for severe osteoporosis in real-life clinical setting stated that a large number of fractures occur in subjects with T-score above −2.5 [46]. This concurs with a recent WHO report that “the majority of osteoporotic fractures will occur in individuals with a negative test” for BMD [47]. As both the components of the macro- and microarchitecture of bone influence bone strength, bone mineral density represents only one of the contributors to osteoporotic fractures. Even if bone mineral density is within the acceptable range, disruption of bone microarchitecture or alteration in the amount and variety of proteins in bone can still increase the risk of fractures [46]. Another limitation of this study is lack of blood homocysteine concentration, which prohibited us on the assessment of the homocysteine in combination with B vitamins on risk of hip fracture.

In conclusion, this study reveals that dietary intake of pyridoxine is associated with reduced risk of osteoporotic hip fracture in women. The findings of the present study suggest that a balanced diet with sufficient pyridoxine intake may be beneficial in maintaining bone health. Future clinical trials are warranted to demonstrate the effectiveness of vitamin B6 supplementation on reduction of hip fracture risk in postmenopausal women.

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Table 1

Baseline characteristics of cases versus non-cases of incident hip fracture, The Singapore Chinese Health Study, 1993–2010

Characteristics	Men		Women	
	Fracture cases (*n* = 450)	Non-cases (*n*=27,463)	Fracture cases (*n* = 1,180)	Non-cases (*n*=34,061)
Age at recruitment (years) (SD)	63.5 (7.0)	56.6 (7.9)	64.2 (6.7)	56.0 (7.9)
Body mass index (SD)	22.4 (2.9)	23.0 (3.2)	23.2 (3.2)	23.2 (3.3)
Level of education (%)				
No formal education	17.1	10.8	57.5	39.8
Primary	62.9	51.0	34.3	39.1
Secondary or higher	20.0	38.2	8.2	21.1
Smoking status (%)				
Never smoker	34.2	42.1	85.7	91.4
Former smoker	28.7	21.7	4.2	2.5
Current smoker	37.1	36.2	10.1	6.1
Alcohol consumption (%)				
Daily drinkers	9.1	6.4	0.8	1.2
Daily energy intake (kcal) (SD)	1,638.2 (614.5)	1,751.5 (608.6)	1,314 (454.2)	1,402.2 (472.4)
At least weekly use of vitamin supplements (%)	4.7	4.8	6.4	7.6
Vitamin D (IU) (SD)	62 (37)	62 (35)	68 (47)	70 (43)
Calcium (mg/1,000 kcal/day) (SD)	244 (94)	240 (98)	288 (145)	293 (137)
Soy isoflavones (mg/1,000 kcal/day) (SD)	11 (9)	11 (8)	11 (10)	12.7 (9.7)
Physical activity (%)				
None	72.0	75.3	79.5	80.0
0.5–3 h per week	13.3	15.5	12.6	12.7
≥4 h per week	14.7	9.2	7.9	7.3
Postmenopausal (%)			96.7	72.6
Hormone replacement therapy (%)			0.9	3.8
Diabetes mellitus (%)	12.9	8.6	20.8	8.8
Stroke (%)	4.9	1.8	3.2	1.2

All differences between cases and non-cases of hip fractures were statistically significant at two-sided $p<0.0003$, except calcium, at least weekly use of vitamins for both genders; vitamin D, soy isoflavonoids for men; and BMI, alcohol consumption, physical activity for women ($p>0.05$)

Table 2

Comparison of average daily intake of protein and B vitamins in the Singapore Chinese Health Study (SCHS, *n*=63,154) versus the US RDA [26] for men and women (>51 years)

Nutrient	SCHS		US RDA	
	Men	Women	Men	Women
Protein intake (g/day)	65	54	56	46
Thiamin (B1) (mg/day)	1.0	0.8	1.2	1.1
Riboflavin (B2) (mg/day)	1.0	0.9	1.3	1.1
Niacin (B3) (mg/day)	12.3	9.8	16.0	14.0
Pyridoxine (B6) (mg/day)	1.2	1.0	1.7	1.5
Folate (B9) (μg/day)	169	145	400	400
Cobalamin (B12) (μg/day)	2.6	2.2	2.4	2.4

Table 3

Top five food sources contributing to each B vitamin (in percent), the Singapore Chinese Health Study (*n*=63,154), 1993–2010

Food sources	Thiamin (B1)	Riboflavin (B2)	Niacin (B3)	Pyridoxine (B6)	Folate (B9)	Cobalamin (B12)
1	Fresh meat (16.3)	Vegetable (11.5)	Rice (12.0)	Fish (15.3)	Vegetable (33.7)	Fish (36.0)
2	Bread (13.1)	Bread (10.7)	Fish (10.6)	Rice (14.6)	Citrus fruit (9.4)	Fresh meat (7.5)
3	Noodle (11.0)	Milk (9.4)	Bread (8.8)	Vegetable (12.6)	Bread (8.3)	Noodle (7.5)
4	Rice (8.5)	Fish (7.6)	Fresh meat (8.6)	Bananas (7.5)	Noodle (5.3)	Milk (7.0)
5	Fish (6.0)	Noodle (7.4)	Poultry (8.0)	Fresh meat (7.2)	Rice (4.5)	Rice (2.8)

Table 4

Dietary intake of B vitamins in relation to hip fracture risk among men (n=27,913), the Singapore Chinese Health Study, 1993–2010

Characteristics		Basic model		Full model	
	Cases	HR[a]	95 % CI	HR[b]	95 % CI
Thiamin (B1) (mg/1,000 kcal /day)					
Q1 (0.24–0.49)	137	1.0		1.0	
Q2 (0.49–0.57)	106	0.94	0.73–1.22	0.95	0.73–1.23
Q3 (0.57–0.65)	112	1.14	0.89–1.47	1.14	0.88–1.48
Q4 (0.65–1.07)	95	0.97	0.75–1.26	0.96	0.72–1.26
p for trend		0.78		0.89	
Riboflavin (B2) (mg/1,000 kcal /day)					
Q1 (0.24–0.50)	127	1.0		1.0	
Q2 (0.50–0.59)	122	1.10	0.86–1.41	1.10	0.85–1.43
Q3 (0.59–0.69)	98	0.91	0.70–1.18	0.90	0.66–1.21
Q4 (0.69–1.25)	103	1.08	0.83–1.40	1.02	0.71–1.46
p for trend		0.96		0.76	
Niacin (B3) (mg/1,000 kcal /day)					
Q1 (3.36–6.19)	110	1.0		1.0	
Q2 (6.19–6.94)	120	1.18	0.91–1.53	1.19	0.92–1.54
Q3 (6.94–7.72)	126	1.30	1.01–1.68	1.30	1.00–1.68
Q4 (7.72–10.98)	94	1.04	0.79–1.37	1.00	0.75–1.31
p for trend		0.54		0.75	
Pyridoxine (B6) (mg/1,000 kcal /day)					
Q1 (0.36–0.61)	118	1.0		1.0	
Q2 (0.61–0.69)	117	1.20	0.93–1.55	1.23	0.95–1.59
Q3 (0.69–0.78)	97	1.10	0.84–1.44	1.11	0.85–1.47
Q4 (0.78–1.70)	118	1.27	0.98–1.64	1.29	0.99–1.68
p for trend		0.13		0.11	
Folate (B9) (μg/1,000 kcal /day)					
Q1 (37.14–79.00)	138	1.0		1.0	
Q2 (79.00–96.12)	103	0.88	0.68–1.14	0.90	0.69–1.17
Q3 (96.12–117.21)	117	1.10	0.86–1.42	1.13	0.87–1.47
Q4 (117.21–228.94)	92	1.00	0.77–1.31	1.02	0.76–1.37
p for trend		0.60		0.53	
Cobalamin (B12) (μg/1,000 kcal /day)					
Q1 (0.04–1.11)	117	1.0		1.0	
Q2 (1.11–1.45)	122	1.13	0.88–1.46	1.14	0.88–1.47
Q3 (1.45–1.83)	111	1.13	0.87–1.47	1.13	0.87–1.48
Q4(1.83–3.57)	100	1.10	0.84–1.44	1.08	0.82–1.44
p for trend		0.48		0.58	

CI confidence interval

[a] HRs were adjusted for age at recruitment (in years), year of recruitment (1993–1995, 1995–1998), dialect group (Hokkien, Cantonese), body mass index (<20, 20–24, 24–28, ≥28 kg/m^2), level of education in categories (no formal education, primary school, secondary school or higher), and total energy intake (in kilocalorie)

[b] HR, further adjusted for smoking status (never, ex-smokers, current smokers), moderate physical activity (none, 2–3 h weekly, 4+ h weekly), calcium (quartiles, in milligrams/1,000 kcal/day), soy isoflavones (quartiles, in milligrams/1,000 kcal/day), and baseline self-reported physician-diagnosed history of diabetes mellitus and stroke

Table 5

Dietary intake of B vitamins in relation to hip fracture risk among women (n=35,241), the Singapore Chinese Health Study, 1993–2010

Characteristics		Basic model		Full model	
	Cases	HR[a]	95 % CI	HR[b]	95 % CI
Thiamin (B1) (mg/1,000 kcal/day)					
Q1 (0.23–0.49)	278	1.0		1.0	
Q2 (0.49–0.57)	276	1.01	0.85–1.19	1.01	0.85–1.20
Q3 (0.57–0.65)	291	1.05	0.89–1.24	1.04	0.88–1.24
Q4 (0.65–1.34)	335	1.18	1.01–1.39	1.13	0.95–1.33
p for trend		0.03		0.14	
Riboflavin (B2) (mg/1,000 kcal/day)					
Q1 (0.25–0.50)	298	1.0		1.0	
Q2 (0.50–0.59)	304	1.13	0.96–1.33	1.11	0.94–1.32
Q3 (0.59–0.69)	253	1.02	0.86–1.21	0.97	0.80–1.18
Q4 (0.69–3.89)	325	1.04	0.89–1.23	0.92	0.73–1.15
p for trend		0.91		0.29	
Niacin (B3) (mg/1,000 kcal/day)					
Q1 (3.57–6.19)	360	1.0		1.0	
Q2 (6.19–6.94)	297	0.96	0.82–1.11	0.94	0.80–1.09
Q3 (6.94–7.71)	261	0.97	0.83–1.14	0.95	0.81–1.11
Q4 (7.71–10.90)	262	1.05	0.89–1.23	1.00	0.85–1.17
p for trend		0.62		0.93	
Pyridoxine (B6) (mg/1,000 kcal/day)					
Q1 (0.37–0.61)	417	1.0		1.0	
Q2 (0.61–0.69)	285	0.82	0.70–0.95	0.82	0.71–0.96
Q3 (0.69–0.78)	249	0.79	0.68–0.93	0.79	0.67–0.93
Q4 (0.78–1.76)	229	0.77	0.66–0.91	0.78	0.66–0.93
p for trend		0.001		0.002	
Folate (B9) (μg/1,000 kcal/day)					
Q1 (26.75–78.93)	334	1.0		1.0	
Q2 (78.93–96.10)	314	1.04	0.89–1.22	1.05	0.90–1.23
Q3 (96.10–117.21)	265	0.96	0.81–1.13	0.98	0.82–1.16
Q4 (117.21–331.46)	267	1.00	0.85–1.18	1.03	0.86–1.23
Cobalamin (B12) (μg/1,000 kcal/day)					
p for trend		0.77		0.97	
Q1 (0.01–1.11)	324	1.0		1.0	
Q2 (1.11–1.45)	282	1.02	0.87–1.20	1.01	0.86–1.19
Q3 (1.45–1.83)	281	0.99	0.84–1.16	0.96	0.81–1.13
Q4(1.83–6.28)	293	0.97	0.83–1.14	0.90	0.76–1.07
p for trend		0.65		0.20	

CI confidence interval

[a] HRs were adjusted for age at recruitment (in years), year of recruitment (1993–1995, 1995–1998), dialect group (Hokkien, Cantonese), body mass index (<20, 20–24, 24–28, ≥28 kg/m^2), level of education in categories (no formal education, primary school, secondary school or higher), and total energy intake (in kilocalorie)

[b] HR, further adjusted for smoking status (never, ex-smokers, current smokers), moderate physical activity (none, 2–3 h weekly, 4+ h weekly), calcium (quartiles, in milligrams/1,000 kcal/day), soy isoflavones (quartiles, in milligrams/1,000 kcal/day), menopausal status (women only; yes, no), use of hormone replacement therapy at recruitment (women only; yes, no), and baseline self-reported physician-diagnosed history of diabetes mellitus and stroke

Table 6

Dietary intake of pyridoxine in relation to hip fracture risk among women stratified by body mass index (BMI) and diabetes status, the Singapore Chinese Health Study, 1993–2010

	Women with BMI <20 kg/m^2			Women with BMI ≥20 kg/m^2		
	Cases	**HR**[a]	**95 % CI**	**Cases**	**HR**[a]	**95 % CI**
Pyridoxine (B6) (mg/1,000 kcal/day)						
Q1 (0.37–0.61)	65	1.0		352	1.00	
Q2 (0.61–0.69)	27	0.58	0.37–0.92	258	0.86	0.73–1.01
Q3 (0.69–0.78)	40	0.82	0.54–1.24	209	0.77	0.65–0.92
Q4 (0.78–1.76)	32	0.77	0.49–1.22	197	0.78	0.65–0.93
p for trend	0.37			0.002		
	Women without diabetes			**Women with diabetes**		
	Cases	**HR**[b]	**95 % CI**	**Cases**	**HR**[b]	**95 % CI**
Pyridoxine (B6) (mg/1,000 kcal /day)						
Q1 (0.37–0.61)	348	1.00		69	1.0	
Q2 (0.61–0.69)	225	0.79	0.66–0.93	60	1.00	0.70–1.42
Q3 (0.69–0.78)	183	0.73	0.61–0.88	66	1.03	0.73–1.46
Q4 (0.78–1.76)	178	0.75	0.62–0.91	51	0.91	0.62–1.33
p for trend	0.0009			0.705		

CI confidence interval

[a]Hazard ratios (HRs) were adjusted for age at recruitment (in years), year of recruitment (1993–1995, 1995–1998), dialect group (Hokkien, Cantonese), level of education in categories (no formal education, primary school, secondary school or higher), total energy intake (in kilocalories per day), smoking status (never, ex-smokers, current smokers), moderate physical activity (none, 2–3 h weekly, 4+ h weekly), dietary calcium intake (quartiles, in milligrams/1,000 kcal/day), dietary soy isoflavones intake (quartiles, in milligrams/1,000 kcal/day), menopausal status (yes, no), use of hormone replacement therapy at recruitment (yes, no), and history of diabetes mellitus and stroke

[b]HRs were adjusted for the all variables listed above plus body mass index (<20, 20–24, 24–28, ≥28 kg/m^2) except history diabetes mellitus