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Fruit and vegetable intake and risk of hip fracture: A cohort study of Swedish men and women

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Abstract

Dietary guidelines recommend a daily intake of five servings of fruit and vegetables. Whether such intakes are associated with a lower risk of hip fracture is at present unclear. The aim of the present study was to investigate the dose-response association between habitual fruit and vegetable intake and hip fracture in a cohort study based on 40,644 men from the Cohort of Swedish Men (COSM) and 34,947 women from the Swedish Mammography Cohort (SMC) (total n=75,591), free from cardiovascular disease and cancer, who answered lifestyle questionnaires in 1997 (age 45-83 years). Intake of fruit and vegetables (servings/day) was assessed by food frequency questionnaire and incident hip fractures were retrieved from the Swedish Patient Register (1998-2010). The mean follow-up time was 14.2 years. One third of the participants reported an intake of fruit and vegetables of >5 servings/day, one third >3 to ≤5 servings/day, 28% >1 to ≤3 servings/day, and 6% reported ≤1 serving/day. During 1,037,645 person-years we observed 3,644 hip fractures (2,266, 62%, in women). The dose-response association was found to be strongly non-linear (P<0.001). Men and women with zero consumption had 88% higher rate of hip fracture compared with those consuming 5 servings/day; adjusted hazard ratio (HR), 1.88 (95% CI, 1.53-2.32). The rate was gradually lower with higher intakes; adjusted HR for 1 vs 5 servings/day, 1.35 (95% CI, 1.21-1.58). However, more than 5 servings/day did not confer additionally lower HRs (adjusted HR for 8 vs. 5 servings/day, 0.96 (95% CI, 0.90-1.03). Similar results were observed when men and women were analyzed separately. We conclude that there is a dose-response association between fruit and vegetable intake and hip fracture such that an intake below the recommended 5 servings/day confers higher rates of hip fracture. Intakes above this recommendation do not seem to further lower the risk.

Key words: Epidemiology, hip fracture, osteoporosis, nutrition, fruit and vegetables

Introduction

A daily intake of at least five servings of fruit and vegetables, recommended as a part of a healthy diet,⁽¹⁾ is associated with prolonged life⁽²⁾ and reduced risk of type 2 diabetes,⁽³⁾ cancer,⁽⁴⁻⁷⁾ and cardiovascular disease.^(7, 8) By reducing oxidative stress and inflammation processes or diet-induced metabolic acidosis,⁽⁹⁾ fruit and vegetable intake may also influence age-related bone loss⁽¹⁰⁾ and sarcopenia,⁽¹¹⁾ important determinants of fracture risk.^(12, 13) Historically, calcium and vitamin D are the nutrients mainly considered for use in prevention of fractures,⁽¹⁴⁾ but other nutrients abundant in fruit and vegetables (e.g. magnesium and potassium,^(15, 16) α -tocopherol,⁽¹⁷⁾ vitamin K⁽¹⁸⁾, and vitamin C⁽¹⁹⁾) are also associated with fracture risk. However, recommendations for separate nutrient intakes are difficult to convey to the general public⁽²⁰⁾ and dietary guidelines tend to focus on whole foods.^(1, 21) Higher fruit and vegetable intakes are associated with higher BMD in cross-sectional studies⁽²²⁻²⁴⁾ and with lower longitudinal BMD loss in men⁽²³⁾ and in premenopausal women.⁽²⁵⁾ In Chinese populations, case control studies have demonstrated associations between fruit and vegetable intake and forearm fracture among postmenopausal women⁽²⁶⁾ and hip fractures among elderly men and women,⁽²⁷⁾ and in a cohort study, the risk of hip fracture was lower with high intake of vegetables among men only.⁽²⁸⁾ Adherence to a Mediterranean diet rich in fruit and vegetables was associated with lower risk of hip fracture in one recent cohort study,⁽²⁹⁾ and with higher risk of hip fracture in another,⁽³⁰⁾ whereas adherence to other a priori defined food patterns have shown inconclusive results regarding bone health.⁽³¹⁻³⁵⁾ Studies using a posteriori defined food patterns identifying patterns characterized by high intake of fruit and vegetables, often in combination with high intake of grains and low intake of meat, showed associations with higher BMD,^(36, 37) lower level of bone resorption,⁽³⁶⁾ and lower risk of fracture,^(32, 38, 39) although one small study found an increased risk of fracture.⁽⁴⁰⁾ However, it is not clear which of the foods in these dietary patterns mediate the association. Thus, the role

of fruit and vegetable intake on hip fracture risk is unclear and studies with fracture as outcome are scarce, especially in Western populations.

In the current study, we aim to specifically investigate potential non-linear relations between fruit and vegetable intake and risk of incident hip fracture in a large population-based cohort study of Swedish men and women. We use the recommended five servings per day as a reference to see whether these are valid also for maintenance of bone health, as measured by hip fracture.

Methods

The study population included 75,591 participants from the population-based Cohort of Swedish Men (COSM) and Swedish Mammography Cohort (SMC), who were free from cancer and cardiovascular disease at baseline in 1997. In 1997, all men who were born between 1918 and 1952 and resided in Västmanland and Örebro counties (in central Sweden) were invited to participate in the COSM. Of the 100,303 eligible men, 48,850 (49%) accepted and completed a self-administered questionnaire. This questionnaire included information on diet, alcohol consumption, education, marital status, body weight and height, physical activity, smoking habits and other lifestyle factors. In 1987-1990, all women born between 1914 and 1948 and living in Västmanland and Uppsala counties (in central Sweden) were invited to participate in the SMC. Of the 90,303 women invited, 66,651 (74%) participated and completed a first self-administered questionnaire with questions regarding diet, alcohol consumption, education, cohabiting status, body weight and height. In the late fall of 1997, women who were still alive and residing in the study area received a second questionnaire that was expanded to also include information regarding smoking status, physical activity, and other lifestyle factors. Of the 56,030 distributed questionnaires, 39,227 (70%) women

responded. The 48,850 COSM men and 39,227 SMC women formed the basis for the current study. For the present analysis, we excluded participants for whom we lacked information on personal identification number (n=540), those who died before 1 January 1998 (start of follow up; n=97), persons with cancer (n=4,390) or cardiovascular disease (n=6,994) at baseline; missing data on all items regarding fruit and vegetable intake or an unlikely high value (>20 servings/day) of fruit and vegetable consumption (n=176); and those with implausible value for total energy intake (≥ 3 SDs below (n=204) or above (n=85) the log-transformed mean energy intake. Exclusion of outliers for energy intake, in addition to adjustment for total energy intake in the statistical analyses compensates for overall under- or over-reporting of dietary intake.⁽⁴¹⁾ After these exclusions, a total of 75,591 participants (40,644 men and 34,947 women) were included in the analyses.

The study was approved by the Regional Research Ethics Board at Karolinska Institutet and all participants gave their informed consent.

Exposure

The usual dietary intake over the previous year was assessed by a valid and reproducible 96-item food-frequency questionnaire (FFQ) in 1997.⁽⁴²⁻⁴⁴⁾ Participants were asked to indicate how often, on average, in the previous year they had consumed each food. There were eight possible frequency categories in increasing order from zero times/month to ≥ 3 times/day. FFQ responses were converted to average daily intake based on age and sex specific portion sizes. Our main exposure, the combined daily intake of fruit and vegetables (servings/day), was calculated by adding the intakes of 14 FFQ responses regarding vegetables (carrot, beetroot, broccoli, cabbage, cauliflower, lettuce, onion, garlic, peas, pea soup, pepper, spinach, tomato, and other vegetables), 5 regarding fruit (apple, banana, berry, orange/citrus, and other fruit) and 1 regarding orange juice.⁽²⁾ These categories represent the most commonly ingested

vegetables and fruits in Sweden at that time and could be in any form (raw, cooked, dried or in a prepared dish). Based on a validation study where four 7-day weighted dietary records were filled in at regular intervals during one year, portion sizes of the different fruit and vegetable categories have been estimated. The mean size of one serving of fruit and vegetables is 101 g (one serving of fruit 121 g, one serving of vegetables 82 g). The Spearman correlation coefficients between the averages of these four 7-day dietary records ranged between 0.4 and 0.7 for individual fruit and vegetable items (A Wolk, unpublished data, 1992). Missing values for an individual item were interpreted as no intake of that particular food.⁽⁴⁵⁾ The small fraction of missing data reported on single items, which were regarded as zero consumption, is unlikely to represent a bias for the observed findings.⁽⁴⁵⁾ In accordance with national dietary guidelines,⁽²¹⁾ only one glass of juice (fresh or from concentrate) was included in the daily intake, independent of the amount ingested. Intake of fruit and vegetables was assessed as separate exposures in sensitivity analyses.

Outcome

Information on the outcome, first incident hip fracture (International Classification of Diseases (ICD)-10 codes S720, S721, or S722) occurring between 1 January 1998 and 31 December 2010, was retrieved from the National Patient Register by individual linkage using the personal identification number. This register is valid for identification of hip fractures⁽⁴⁶⁻⁴⁸⁾ and covers all in-patient care in Sweden since 1987. Incident hip fractures were distinguished from readmissions of previous hip fractures by a valid method.⁽⁴⁹⁾

Covariates

Information on prevalent diseases, height and weight, use of supplements or medications, smoking and physical activity habits, educational level and marital status was obtained from

questionnaires. Those who were married or cohabitating were categorized as not living alone and those who were unmarried, divorced or widows/widowers were categorized as living alone. Educational level (categorized as primary school, high school, university) was used as a marker of socio-economic status.

Statistical analyses

We assessed fruit and vegetable intake as a continuous variable and categorized as ≤ 1 , >1 to ≤ 3 , >3 to ≤ 5 , >5 to ≤ 7 , and > 7 servings/day. These a priori determined categories were chosen to both reflect extreme intakes and to be reasonably large. For the continuous analysis we used 5 servings of fruit and vegetables/day as reference, and for the categorical analysis, >3 to ≤ 5 servings/day was used as reference, reflecting national dietary guidelines.⁽²¹⁾

Characteristics of the study population except age and sex were directly standardized to the age distribution of the entire study population. Cox's proportional hazards regression models were used for assessing the association between exposure and outcome (hip fracture). Time at risk was calculated from 1 January 1998 until date of hip fracture, date of death or end of follow-up (31 December 2010), whichever occurred first. The proportional hazards assumption was verified by testing for a nonzero slope when Schoenfeld's residuals were regressed against survival time; no evidence of departure from the assumption was found.

Attained age was used as primary time-scale in the Cox models. The multivariable models included as covariates the following baseline variables: sex, body mass index (BMI; kg/m²) and height (both continuous), diabetes prevalence, combination of smoking status and pack-years of smoking (never, former [<20 ; 20-39; ≥ 40 pack-years], current [<20 ; 20-39; ≥ 40 pack-years]), physical activity defined as time spent walking or cycling each day (hardly ever, <20 , 20-40, 40-60, or >60 minutes/day), alcohol consumption (usually consume alcohol, stopped drinking, lifetime abstainers), educational level (primary school, high school, university),

living alone (yes, no), total energy intake (continuous), energy adjusted dietary intake of calcium, vitamin D and retinol (continuous), and use of supplements containing calcium (yes, no) or vitamin D (yes, no).

The continuous exposure was flexibly modeled using right-restricted cubic splines with 3 knots placed at the 25th, 75th, and 90th percentiles of the distribution (3, 6, and 9 servings/day) and using 5 servings/day as reference point.⁽⁵⁰⁾ The shape of the dose-response relation was fairly insensitive to the number and the location of the knots.⁽⁵¹⁾ Linearity of the dose-response was evaluated by testing the null hypothesis that the coefficients of the unrestricted spline transformations are jointly equal to zero.⁽⁵⁰⁾ The spline method was also used in sensitivity analysis for evaluation of fruit and vegetable consumption as separate, but mutually adjusted, exposures using 3 servings per day as reference.

To avoid loss of efficiency and to limit the introduction of bias by restricting the analysis to individuals with complete data alone, missing data on covariates were imputed using a multiple imputation technique⁽⁵²⁾ (Stata's *mi* package). We used 20 imputations to reduce sampling error. The proportion of missing data was 8.8% (n=6,668) for physical activity, 5.6% (n=4,239) for height, 1.7% (n=1,281) for smoking, and all other variables were missing in 0.6% or less. Complete case analysis including the 63,293 men and women without missing data was performed as sensitivity analysis.

The potential interaction of fruit and vegetable consumption with sex was tested using the Wald test and sensitivity analyses were performed stratified by sex. Among women, we could also adjust for ever hormone replacement therapy use (yes, no).

We examined the potential explanatory role of several variables in sensitivity analyses, including energy-adjusted dietary intake of protein, non-recommended food intake⁽⁵³⁾ and previous fracture (occurring before baseline), dietary intake of α -tocopherol, and nutrients associated with dietary acidic and base load (energy adjusted intakes of phosphorous,

potassium and magnesium). The dietary acid load was further examined by calculation of net endogenous non-carbonic acid production (NEAP).⁽⁵⁴⁾ Potential interactions of fruit and vegetable intake with BMI, potassium, magnesium, and calcium were tested using the Wald test. To investigate the influence of potential misclassification bias caused by possible over-reporting of fruit and vegetable intake among overweight and obese individuals, we performed a sensitivity analysis among subjects with BMI < 25 kg/m².

P < 0.05 was considered as statistically significant and all tests were two-tailed. All analyses were performed using Stata version 13.1 (Stata Corp., College Stn, TX, USA).

Results

Age-adjusted characteristics of our study population are presented in Table 1. One third of the participants reported an intake of fruit and vegetables of >5 servings/day, one third >3 to ≤5 servings/day, 28% >1 to ≤3 servings/day, and 6% reported ≤1 serving/day. Men and women reporting ≤1 serving of fruit and vegetables/day had lower attained educational level, were less likely to be never smokers and physically active. On the other hand, total energy intake was lower and the dietary intakes of calcium, vitamin D and retinol were higher in this group.

During a mean follow-up time of 14.2 years and at total of 1,037,645 person-years we observed 3,644 hip fractures (2,266, 62%, in women). The mean (SD) age of hip fracture was 80.0 (8.6) years in men and 85.4 (6.9) years in women. We observed an inverse association between fruit and vegetable intake and hip fracture; ≤1 serving/day conferred almost 50% increased rate of fracture compared with 3-5 servings/day (Table 2). The corresponding age-adjusted rate difference during follow-up was 191 cases/100,000 person-years at risk (Table 2). Modelling fruit and vegetable intake as a continuous exposure, we found strong evidence of departure from a simple linear-response association (P < 0.001; Figure 1). Compared with

the recommended 5 servings/day, lower intakes were associated with higher rates of hip fracture; the adjusted hazard ratio (HR) for zero intake was 1.88 (95% CI, 1.53-2.32) and 1.35 (1.21-1.58) for 1 serving/day. Intakes above 5 servings/day did not confer additional benefit; the adjusted HR for 8 servings/day (vs. 5 servings/day) was 0.96 (95% CI, 0.90-1.03).

P-value for interaction between sex and fruit and vegetable intake was 0.23. The adjusted HR for hip fracture comparing ≤ 1 serving/day with 3-5 servings/day was 1.54 (95% CI, 1.27-1.87) for men and 1.38 (1.16-1.65) for women (Table 3). Additional adjustment for hormone replacement therapy use among women resulted in a HR of 1.37 (1.15-1.64).

Intakes of fruits and vegetables were analyzed separately, although mutually adjusted, with similar results as those for fruit and vegetables combined (Figure 2). Compared with 3 servings/day, the HR for zero intake of fruit was 1.39 (95% CI, 1.20-1.62) and HR for zero intake of vegetables was 1.48 (1.24-1.78).

Further sensitivity analyses including α -tocopherol intake, previous fracture, protein intake, non-recommended food intake, or nutrients associated with dietary acidic or base load, (*i.e.* phosphorous, potassium, and magnesium) or the net endogenous non-carbonic acid production (NEAP) as additional covariates in the adjusted model did not substantially change the estimates. For instance, the HR for ≤ 1 serving per day compared with 3-5 servings was 1.47 (95% CI, 1.29-1.68) when including α -tocopherol as additional covariate and 1.45 (95% CI, 1.27-1.65) when including NEAP as additional covariate. There was no evidence of interaction between fruit and vegetable intake and potassium, magnesium, calcium, or BMI ($P=0.784, 0.875, 0.488, \text{ and } 0.465$, respectively). Results remained essentially similar when restricting the analysis to normal-weight subjects ($\text{BMI} < 25 \text{ kg/m}^2$; 50% of the study population); the multivariable adjusted HR was 1.51 (95% CI, 1.10-1.89) for ≤ 1 serving of fruit and vegetables per day and 1.24 (95% CI, 1.08-1.41) for >1 to ≤ 3 servings/day, compared with >3 to ≤ 5 servings/day.

The results from complete case analysis were also similar to those using the imputed dataset: Comparing with the middle category of 3-5 servings per day, the estimates were 1.44 (95% CI, 1.23-1.70) for ≤ 1 serving, 1.18 (1.07-1.30) for 1-3 servings, 0.93 (0.83-1.03) for 5-7 servings and 0.99 (0.87-1.12) for > 7 servings per day.

Discussion

The present cohort study is the first to prospectively investigate the dose-response relation between intake of fruit and vegetables *per se* and incident hip fracture. We find that a low habitual intake of fruit and vegetables is associated with an increased risk of hip fracture whereas intakes above the recommended five servings per day do not seem to confer an additionally lowered risk. The association was independent of lifestyle factors including smoking and physical activity, related both with dietary habits and fracture risk, and was seen in both men and women.

Previously, the Mediterranean diet score and the alternate Healthy Eating index, both rich in fruit and vegetables, and the fruit/nut and vegetable components of these scores have been associated with lower^(29, 32) and higher⁽³⁰⁾ risk of hip fracture. However, these diet scores are also defined by other food items making it difficult to discern which food group mediates the observed associations. Higher intakes of fruit and vegetables are associated with higher bone mineral density or content in cross-sectional studies⁽²²⁻²⁴⁾ and with lower longitudinal BMD loss in men⁽²³⁾ and in premenopausal women.⁽²⁵⁾ In case-control studies, higher intakes of vegetables were associated with lower risk of forearm fracture⁽²⁶⁾ and higher risk of fruit, vegetables and fruit and vegetables combined were associated with lower risk of hip fracture.⁽²⁷⁾ In a recent cohort study based on a Chinese population, a high vegetable intake, but not fruit intake, was associated with lower risk of hip fracture among men only.⁽²⁸⁾ The

decreased risk seemed to be linear over quartiles of vegetable intake. In our study, fruit and vegetable intakes above the recommended five servings/day were not associated with further lowered risk of hip fracture. These discrepant results may be due to different exposure windows where the mean intake of vegetables was approximately 110 grams/day in Chinese population⁽²⁸⁾ and 190 grams/day in our Swedish population. We cannot exclude cultural differences in choice of fruits and vegetables or methods of cooking and preparation. Furthermore, the Chinese population was somewhat younger with a mean age of hip fracture of 74 years. The mean age of hip fracture in our study (around 82 years) corresponds to the mean age of hip fracture in the population. At these high ages, lifestyle and environmental factors and not genetic factors are the dominant underlying causes of hip fracture.⁽⁵⁵⁾ Thus, our results may not be applicable to fracture events occurring at lower ages. Whether the dose-response association between fruit and vegetable consumption and hip fracture risk is similar in other populations also remains to be determined. We have previously observed a similar dose-response relation with mortality,⁽²⁾ which was also the conclusion of a meta-analysis,⁽⁷⁾ whereas a recent study set in England found that even higher intakes seemed additionally beneficial to lower mortality rates.⁽⁵⁶⁾ Homeostatic regulation of micronutrient concentrations contributes to the difficulty of improving nutritional status in a well-nourished and healthy person;⁽⁵⁷⁾ a potential explanation to the observations where intakes above the recommended levels do not lead to additional beneficial effects on the risk of disease.

In the present study, approximately 1/3 of the subjects consumed more than the five servings of fruit and vegetables per day. This may seem high but similar results were presented in the Swedish national dietary survey in 1997-98 where the 75th percentile of fruit and vegetable intake for men and women aged 45 years and above was 508 grams/day.⁽⁵⁸⁾ The five servings/day in our study corresponds to approximately 500 grams of fruit and vegetables per day, which is in line with many national dietary guidelines in Sweden and many other

countries.^(1, 21) The national dietary guidelines in Sweden and in many other countries do not specify the type of fruit or vegetable recommended, although in general terms intake of cruciferous vegetables and pulses are encouraged.⁽²¹⁾ Half of the daily intake should consist of vegetables and fruit juice can only contribute to one serving independent of amount consumed, due to its high content of sugar and lower fiber content.^(1, 21)

Being rich in antioxidants, a high fruit and vegetable intake might counteract the age-related increase in oxidative stress or chronic low grade inflammation that influences both bone health^(10, 59) and muscle strength,⁽¹¹⁾ important determinants of hip fracture risk.^(12, 13) The antioxidants α -tocopherol⁽¹⁷⁾ and vitamin C⁽⁶⁰⁾ have been associated with hip fracture risk. Other nutrients abundant in fruit and vegetables, including magnesium,⁽⁶¹⁾ phytoestrogens,^(62, 63) flavonoids,⁽⁶⁴⁾ lycopenes,⁽⁶⁵⁾ and vitamin K⁽¹⁸⁾ may potentially contribute to the association with hip fracture seen in the present study. Potential mechanisms of action include both direct effects on bone or indirect effects via lower oxidative stress and inflammation where osteoblastogenesis is up-regulated and osteoclastogenesis is down-regulated, thus contributing to increased bone mass and strength and lowered risk of fracture.^(61, 62, 66) A high fruit and vegetable intake is also associated with a more diverse gut microbiota that can influence absorption of calcium and other minerals and have anti-inflammatory effects.⁽⁶⁷⁾ The acid-base balance hypothesis⁽⁶⁸⁾ where an acidic diet is thought to increase calcium resorption from bone has recently been disputed as a major mechanism of osteoporosis,^(66, 69-72) although the acid-base balance may still serve as an indicator of the amount of fruit and vegetables consumed. A higher alkaline dietary load, indicating a higher intake of fruit and vegetables, has recently been associated with greater muscle mass.⁽⁷³⁾ Our findings could not be explained by additional adjustment for phosphorous, potassium, and magnesium (nutrients associated with dietary acidic or base load) or the net endogenous non-carbonic acid production. Intervention studies indicate, although limited in size and length of follow-up, that it is

possible to increase the intake of fruit and vegetables^(74, 75) although the effect on bone health by previous studies are inconclusive⁽⁷⁵⁾ but other studies are ongoing.⁽⁷⁶⁾ Calcium is available to some extent in cruciferous vegetables and randomized intervention studies have shown that supplementation with vitamin D and calcium reduces the risk of hip fracture among institutionalized individuals.⁽⁷⁷⁾ Placebo controlled randomized studies providing other nutrients available in fruit and vegetables as supplements have not been conclusive regarding effects on bone health or fracture risk.⁽⁶²⁾ Reasons for this could be that adding supplements to a non-deficient population may not be efficacious and because the combination of nutrients in fruit and vegetables and their potential interaction may have greater benefit than the individual nutrient alone.⁽²⁰⁾

Strengths and limitations

The main strengths of the present study include its longitudinal design and population-based setting, the large sample size, the large number and valid ascertainment of hip fractures in official registers with virtually no loss to follow-up, and the detailed information on diet collected with a valid and reproducible FFQ. The main limitation of our study was the self-reported nature of the fruit and vegetable consumption with potential misclassification of the exposure but the prospective nature of the study suggests that misclassification errors are likely to be unrelated with the outcome. Biomarkers of fruit and vegetable intake were unfortunately not available allowing verification of our results. The FFQ-based total antioxidant capacity (to which the major contributors are fruit and vegetable intake) has however been reported to be a valid estimate of total antioxidant capacity in plasma in a subgroup of women in our study.⁽⁴⁴⁾ Furthermore, the currently available biomarkers fail to capture enough of the variation in long-term fruit and vegetable intake and can therefore not replace methods based on reported food intake.⁽⁴¹⁾ Although we were able to adjust for potential confounders such as education, physical activity and smoking, a high intake of fruit

and vegetables may be a marker of a healthier lifestyle not completely captured by the covariates we have included in the multivariable analysis or by the restriction to men and women free of cancer and cardiovascular disease at baseline.

Conclusions

The findings from this cohort study indicate that a habitual fruit and vegetable consumption of less than the recommended five servings/day is associated with progressively higher risk of hip fracture in a dose-response fashion. A higher consumption does not seem to add benefits with regards to hip fracture risk.

Disclosures

The authors state that they have no conflicts of interest.

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Drafting the manuscript: LB. Approving final version of manuscript: LB, AB, NO, AW, and KM. LB takes responsibility for the integrity of the data analyses.

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Figure Legends

Figure 1. Adjusted hazard ratios of hip fracture as a function of fruit and vegetable consumption. Dashed lines represent 95% confidence intervals. The reference value is 5 servings/day. The histogram shows the distribution of fruit and vegetable consumption in the cohort. The Cox's regression models were adjusted for age, sex, body mass index and height, diabetes prevalence, smoking status and pack-years of smoking, physical activity, alcohol consumption, educational level, living alone, total energy intake, energy adjusted dietary intake of calcium, vitamin D and retinol, and use of supplements containing calcium or vitamin D.

Figure 2. Adjusted hazard ratios of hip fracture as a function of fruit (panel A) and vegetable (panel B) consumption. Dashed lines represent 95% confidence intervals. The reference value is 3 servings/day. The histograms show the distribution of the consumption in the cohort. The Cox's regression models were adjusted for age, sex, body mass index and height, diabetes prevalence, smoking status and pack-years of smoking, physical activity, alcohol consumption, educational level, living alone, total energy intake, energy adjusted dietary intake of calcium, vitamin D and retinol, and use of supplements containing calcium or vitamin D, and mutually adjusted for fruit and vegetable intake.

Table 1. Age-adjusted characteristics of 75,591 Swedish men and women, by daily intake of fruit and vegetables

	Fruit and vegetable intake, servings/day				
	≤1	>1 - ≤3	>3 - ≤5	>5 - ≤7	>7
Total number	4205	21300	25084	14861	10141
Men, n (%)	2992 (7.4)	14060 (34.6)	13556 (33.4)	6538 (16.1)	3498 (8.6)
Women, n (%)	1213 (3.5)	7240 (20.7)	11528 (33.0)	8323 (23.8)	6643 (19.0)
Age, years, mean (SD)	63.1 (10.0)	60.8 (9.7)	59.9 (9.3)	59.9 (9.1)	59.7 (8.9)
BMI, kg/m ²	25.8	25.6	25.2	25.2	25.1
Height, m	1.73	1.73	1.72	1.71	1.70
Fruit intake, g/day	32	98	181	269	386
Vegetable intake, g/day	41	108	176	246	370
Fruit and vegetables, g/day	71	206	356	513	754
Daily dietary intakes ^a					
Energy intake, kcal/day	1889	2159	2235	2308	2446
Calcium, mg/day	1506	1358	1262	1200	1142
Magnesium, mg/day	394	394	394	396	402
Potassium, mg/day	3277	3390	3518	3673	3923
Vitamin D, µg/day	6.12	5.93	5.66	5.45	5.18
Retinol, µg/day	1117	1158	1102	1046	958
NEAP, mEq/day	52.6	47.6	43.2	39.7	35.3
Calcium supplement use, %	7.8	12.2	17.2	22.0	26.5

Vitamin D supplement use, %	8.8	13.4	17.7	21.4	24.8
Diabetes, %	5.3	5.2	4.7	4.9	5.6
Physical activity (walking/cycling), %					
Hardly Ever	20.9	15.5	11.3	9.4	8.3
<20 minutes/day	23.9	24.8	21.5	19.6	16.2
20-40 minutes/day	25.6	29.1	32.2	33.4	32.7
40-60 minutes/day	12.1	24.6	17.3	18.4	20.3
>60 minutes/day	17.5	16.0	17.7	19.1	22.5
Never	34.5	41.1	47.9	50.6	52.0
Smoking status, %					
Former, <20 pack-years	13.8	18.4	20.3	21.6	21.2
Former, 20-39 pack-years	7.0	7.7	6.7	5.6	5.3
Former, \geq 40 pack-years	6.0	4.8	3.5	3.3	3.3
Current, < 20 pack-years	12.8	11.3	10.2	9.7	10.4
Current, 20-39 pack-years	14.3	10.9	8.3	6.8	5.5
Current \geq 40 pack-years	11.6	5.8	3.2	2.4	2.2
Alcohol consumption, %					
Current	80.2	85.9	86.6	87.7	86.9
Ex	7.5	4.3	3.4	3.4	3.8
Never	12.3	9.7	9.7	8.9	9.2
Education, %					
Primary school	85.2	79.2	71.8	67.1	63.4
High school	7.9	9.6	11.5	11.5	11.8
University	6.9	11.2	16.8	21.3	24.8
Cohabiting status: Living alone, %	32.5	23.4	20.0	18.8	20.5

Ever hormone replacement therapy use (women only), %	8.4	13.7	19.8	25.5	30.0
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^a Energy-adjusted nutrient intakes are presented.

NEAP: Net-endogenous non-carbonic acid production

All variables except age and sex were directly standardized to the age distribution of the entire study population

Table 2. Hazard ratios of hip fracture according to daily fruit and vegetable consumption

Fruit and vegetable intake, servings/day	N hip fractures	Hip fracture rate ^a per 100,000 person-years	Model 1 ^b		Model 2 ^c	
			HR	95% CI	HR	95% CI
≤1	339	556.0	1.49	1.32-1.68	1.47	1.29-1.67
>1 - ≤3	1142	418.3	1.16	1.06-1.26	1.17	1.07-1.27
>3 - ≤5	1068	365.3	1.0 (reference)		1.0 (reference)	
>5 - ≤7	649	377.9	0.98	0.89-1.08	0.97	0.88-1.07
>7	446	403.2	1.03	0.92-1.15	0.99	0.88-1.11
Continuous per serving/day	3644	351.2	0.97	0.95-0.98	0.96	0.95-0.98

HR: Hazard ratio, CI: Confidence interval

^aAge-adjusted rates per 100,000 person-years at risk

^bModel 1, adjusted for age and sex

^cModel 2, Adjusted for adjusted for age, sex, body mass index and height, diabetes prevalence, smoking status and pack-years of smoking, physical activity, alcohol consumption, educational level, living alone, total energy intake, energy adjusted dietary intake of calcium, vitamin D and retinol, and use of supplements containing calcium or vitamin D.

Table 3. Adjusted hazard ratios of hip fracture according to daily fruit and vegetable consumption, by sex

Fruit and vegetable intake, servings/day	Men (N hip fractures=6,298)		Women (N hip fractures=17,646)			
	HR ^a	95% CI	HR ^a	95% CI	HR ^b	95% CI
≤1	1.54	1.27-1.87	1.38	1.16-1.65	1.37	1.15-1.64
>1 - ≤3	1.22	1.06-1.39	1.13	1.01-1.26	1.13	1.01-1.26
>3 - ≤5	1.0 (reference)		1.0 (reference)		1.0 (reference)	
>5 - ≤7	0.95	0.80-1.14	0.97	0.86-1.09	0.97	0.86-1.10
>7	1.10	0.90-1.36	0.94	0.82-1.08	0.94	0.82-1.08

HR: Hazard ratio, CI: Confidence interval

N=40,644 men and 34,947 women

^aAdjusted for adjusted for age, body mass index and height, diabetes prevalence, smoking status and pack-years of smoking, physical activity, alcohol consumption, educational level, living alone, total energy intake, energy adjusted dietary intake of calcium, vitamin D and retinol, and use of supplements containing calcium or vitamin D.

^bAs model ^a and additionally adjusted for hormone replacement therapy.

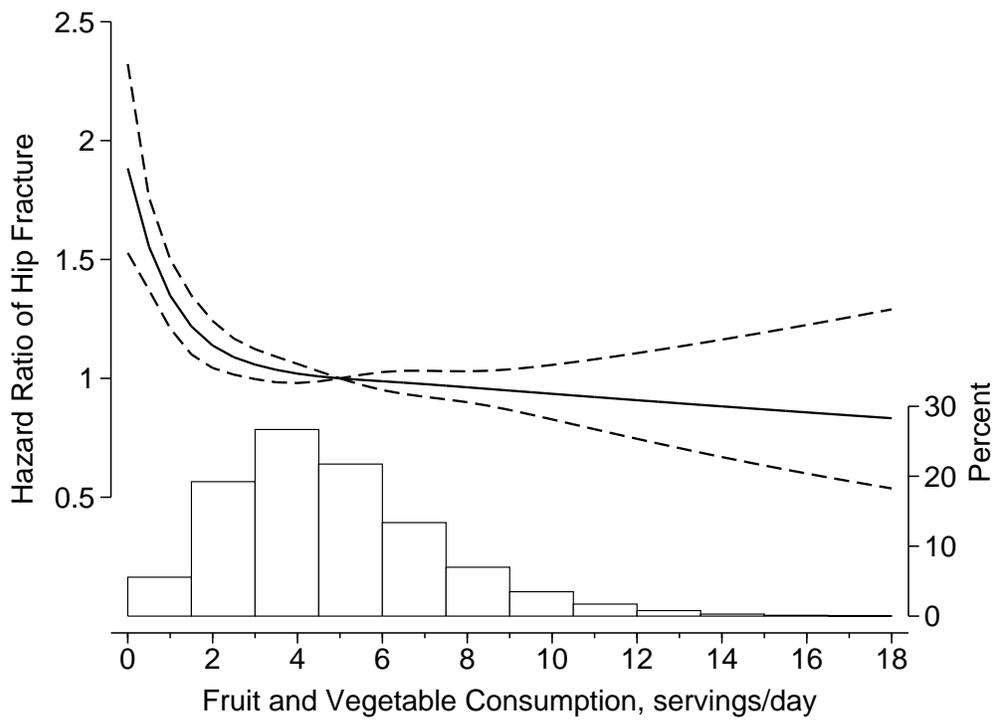


Figure 1.

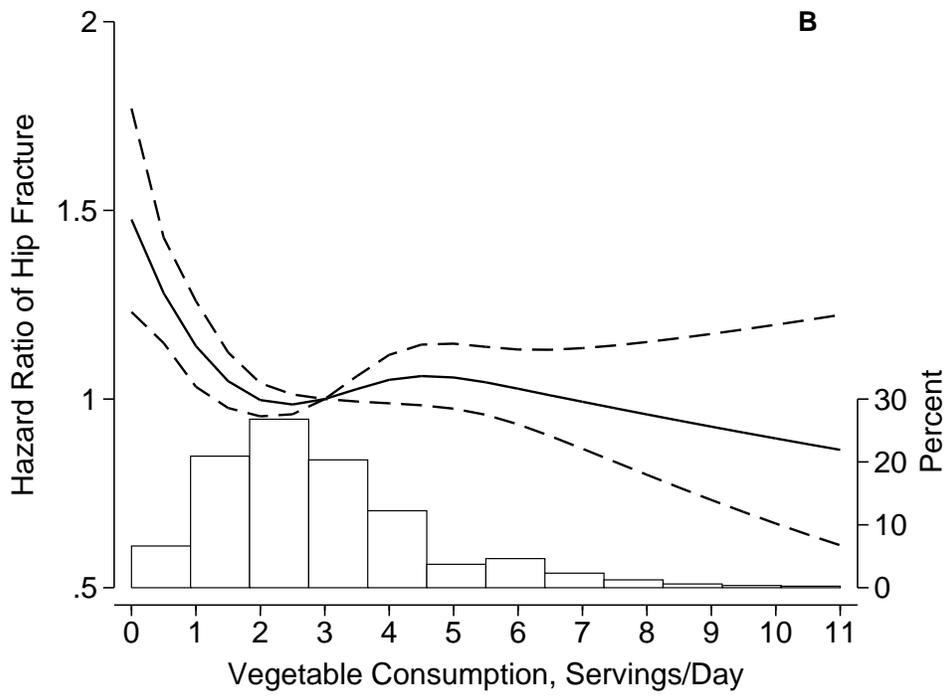
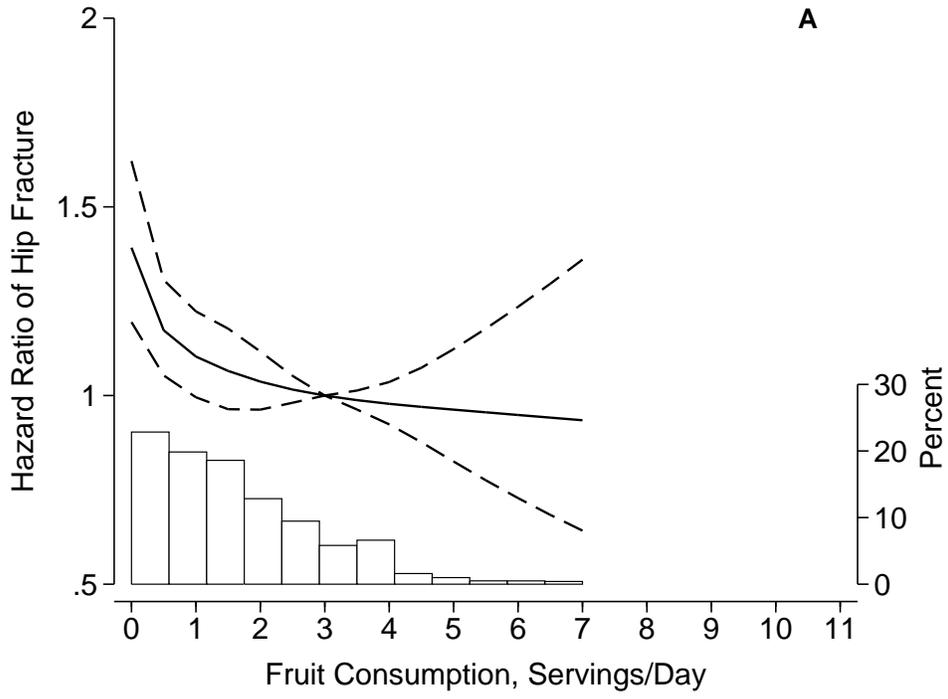


Figure 2.