Alcohol intake, specific alcoholic beverages and risk of hip fractures in postmenopausal women and men age 50 and older

Running Head: Alcohol intake and hip fracture risk

Teresa T. Fung, Kenneth J. Mukamal, Eric B. Rimm, Haakon E. Meyer, Walter C. Willett, Diane Feskanich

Affiliations:
Department of Nutrition, Simmons University, 300 The Fenway, Boston, MA 02115, USA (TTF)
Department of Nutrition, 667 Huntington Ave, Harvard TH Chan School of Public Health, Boston, MA 02115, USA (TTF, EBR, WCW)
Department of Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02446, USA (KJM)
Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115 (EBR, WCW, DF)
Department of Community Medicine and Global Health, University of Oslo, Postboks 1130, Blindern 0318, Oslo, Norway (HEM)

Authors last name: Fung, Mukamal, Rimm, Meyer, Willett, Feskanich

Correspondence: Teresa Fung, Department of Nutrition, Simmons University, Boston, MA 02115, USA, 617-521-2712, fung@simmons.edu

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Abbreviations:
FFQ: Food Frequency Questionnaire
HPFS: Health Professionals Follow-up Study
NHS: Nurses' Health Study
METs: Metabolic Equivalent Hours

Abstract

Background: While a number of studies have examined the association between alcohol intake and hip fractures, few have considered specific alcoholic beverages separately.

Objectives: We prospectively assessed total alcohol and specific alcoholic beverage consumption and risk of hip fractures in U.S. men and women.

Methods: Health, lifestyle information, and hip fractures were self-reported on biennial questionnaires between 1980-2014 in 75,180 post-menopausal women from the Nurses' Health Study, and between 1986-2014 in 38,398 men 50 years of age and older from the Health Professionals Follow-up Study. Diet was assessed approximately every 4 years with a semi-quantitative food frequency questionnaire. Relative risks (RR) were computed for hip fracture using Cox proportional hazards models, adjusting for potential confounders.

Results: We ascertained 2,360 incident low trauma hip fractures in women and 709 in men. Among women, relative risks for low trauma hip fractures compared with non-drinkers were 0.89 (95% CI=0.80, 0.99) for an average daily consumption of <5.0g, 0.81 (95% CI=0.70, 0.94) for 5.0 to <10.0g, 0.83 (95% CI=0.71, 0.96) for 10.0 to <20.0 g, and 0.93 (95% CI=0.78, 1.10) for 20.0g+. Among men, risk decline linearly with higher alcohol consumption (p trend=0.002). Multivariable RR compared with non-drinkers was 0.77 (95% CI=0.59, 1.01), 0.69 (0.49, 0.96), and 0.67 (0.48, 0.95) for intake of an average of 10g/d to <20g/d, 20g/d to <30g/d, and 30.0g/d or more. In women, the alcoholic beverages most significantly associated with hip fracture risk was red wine (RR per serving=0.59, 95% CI=0.45, 0.79). In men, there was no clear association with specific alcoholic beverages.

Conclusion: In these two U.S. cohorts, low to moderate alcohol consumption when compared with no consumption, was associated with a lower risk of hip fractures, particularly with red wine consumption among women.

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Keywords: alcohol, fractures, nutrition, epidemiology, beer, wine, liquor

Introduction

The risk of hip fractures increases greatly with age. An estimated 2.9% of individuals age 50-59 have a 10-year risk greater than 20%. The proportion rises to an estimated 27.4% for individuals age 80 and older with a 10-year risk greater than 20% (1). Bone fractures in older adults is a significant cause of morbidity and mortality in the U.S with an increased risk of death (2), hospitalization (3), and reduced mobility (4).

Alcohol is shown to influence bone metabolism (5). While chronic heavy drinking displaces intake of other important nutrients and is associated with unfavorable profiles of bone mineral density, bone remodeling markers and increased risk of fractures (6), moderate consumption may have a different influence. In women, moderate alcohol consumption increases circulating estrogen levels (7) which in turn may reduce bone remodeling after menopause (8). Moderate alcohol consumption has also been shown to be inversely associated with the bone resorption marker NTX:Cr (9). A meta-analysis showed that moderate alcohol consumption is associated with higher femoral neck bone mineral density (BMD) (10). An U.S. study suggested a possibility that the favorable relationship might be apparent with wine but not liquor (11). In addition, several studies have found that low to moderate amounts of alcohol consumption is associated with lower risk of fractures in both men (12) and women (13), but there also could be a U-shaped relationship (14). In vivo and in vitro studies have indicated that flavonoids in wine can promote osteoblast proliferation and inhibit osteoclasts differentiation (15). In ovarectomized mice, long term resveratrol supplementation has shown to reduce bone loss(16). However, only a handful of studies have explored different types of alcoholic beverages where the data points toward a stronger inverse association with wine (14, 17, 18).

None of these studies measured specific types of alcoholic beverage consumption more than once beyond baseline and therefore could not take into account changes in intake. In addition, there was little data on patterns of alcohol consumption, such as regular versus episodic consumption. Only one study in men examined the association between episodic heavy drinking and did not observed any association (12).

In the U.S., the proportion of adults aged 45 to 64 who reported consuming alcohol in the past 12 months has increased from 64.3% to 71.9% between 2001-2002 and 2012-2013 (19). Although fewer individuals aged 65 and older consumed alcohol, the proportion still increased from 45.2% to 55.2% in the same time period. In addition, in 2015 over 20% of individuals age 45 to 64 consumed at least one drink of alcohol in the past month (20). In light of the common usage of alcohol in the U.S. and its potential influence on bone fractures in older adults, we conducted a prospective analysis of alcohol consumption and hip fractures in two long term U.S. cohorts of men and women, the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS). In addition, we also examined the association of specific alcoholic beverages and alcohol consumption patterns. As the majority of the hip fractures in our cohorts were from low trauma causes, we used this as our primary endpoint.

Methods

Participants

Women in this analysis were participants of the ongoing U.S. Nurses' Health Study which began in 1976 with 121,700 nurses aged 30–55 in 11 states (21). Lifestyle, heath, including menopausal status, disease information was self-reported through questionnaires every 2 years. Dietary intake was assessed with a food-frequency questionnaire (FFQ) in 1980, 1984, 1986, and every 4 years thereafter. In this analysis, we used data collected from 1980 to 2014. Men in this analysis were participants of the ongoing U.S. Health Professionals Follow-up Study (HPFS), a cohort similar to the NHS. HPFS began in 1986 with 51,529 male U.S. health professionals aged 40-75 (22). Lifestyle, health, medication, and dietary information were collected through self-administered questionnaires every two years similar to the NHS and FFQs was collected every four years (**Figure 1**). In this analysis, we used data collected from 1986 to 2014. In most 2-year questionnaire cycles a response of at least 90% was achieved.

In this analysis, we included only white men and women due to the small number of Asian and black participants (<3%) and different rates of fractures in some minority groups. For women, follow-up began in 1980 if they were already postmenopausal at that time. Otherwise, we follow-up began when they reported reaching menopause, including surgical menopause, on a subsequent questionnaire. For men, follow-up began in 1986 if they were at least 50 years old. Otherwise, we included them in the follow-up at the questionnaire cycle when they reached age 50. We excluded individuals without dietary assessment in one of the last two FFQ cycles or who had previously reported a hip fracture, diagnosis of cancer or osteoporosis at entry to follow-up. Individual with a history of cancer at entry to follow-up were excluded because they may have received medications that adversely affect bone mineral density. Those with diagnosed osteoporosis are at high risk of fractures and may also have changed their diet, therefore were excluded from the analysis as well. In total, this analysis included 75,180 women and 38,398 men **(Supplemental Figure 1)**. This study was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health, Boston MA.

Dietary assessment

In NHS, 9 FFQs were administered between 1980 and 2010 (23). In HPFS, a similar FFQ was administered 7 times between 1986 and 2010 (22). Both FFQs were validated and designed to assess intake in the past 12 months (22, 24). Correlation coefficients between FFQ and four 1-week diet records for ethanol was 0.90 in NHS and 0.86 in HPFS (25). In addition, ethanol intake assessed through the FFQ was also significantly correlated with serum HDL (r=0.33 for NHS, 0.38 for HPFS). For specific alcoholic beverages, the correlation coefficients between the FFQ and multiple weeks of diet records were 0.83 for wine, 0.77 for liquor, and 0.89 for beer in the NHS (24). In the HPFS, the deattenuated correlation coefficients corrected for within-person variation in the diet records were 0.83 for red wine, 0.78 for white wine, 0.85 for liquor, and 0.88 for beer, as calculated previously (26). Each FFQ contained approximately 135 items except for the 1980 FFQ which contained 61 items. Standard portion size was provided for each item and nine frequency choices (never or less than once per month, 1-3 per month, 1 per week, 2-4 per week, 5-6 per week, 1 per day, 2-3 per day, 4-5 per day, 6+ per day). Portion size was 12 fluid ounce (oz) (356g) for beer, and 1 drink or shot, equivalent to approximately 1.5 oz (42g) for liquor. For red and white wine, portion size was 4 oz (118g) until 2002 when it changed to 5 oz (148g) to better reflect the increase in typical serving size. Alcohol intake for each FFQ year was computed by summing ethanol content of each alcoholic beverage type. We used 12.4 g of alcohol (ethanol) for 1 serving of red wine (4 oz/serving), 12.1 g for white wine (4 oz/serving), 13.9 g for 1 serving of regular beer (12 oz/serving), 13.1 g for 1 serving of light beer (12 oz/serving) and 14.0 g for 1 serving of liquor (1 shot).

The number of alcohol consumption days in a typical week was assessed in NHS in 1988, 1996, 2000, 2004, 2012, and in HPFS in 1986, 1988, 1998, 2002, 2004, 2006, 2008, and 2012.

The highest number of drinks per day was assessed in 1988, 1996, 2000, 2004, 2012 in NHS and in 1988, 1992, 1996, 2004, 2006, 2008, and 2012 in HPFS **(Figure 1)**.

Assessment of hip fractures

Hip fractures incidence and date of diagnosis were self-reported by participants on biennial questionnaires. The circumstances of fracture occurrence were also reported in both cohorts to categorize the level of trauma. Fractures caused by high impact trauma such as motor vehicle accidents, horseback riding, skiing, and other similar events were excluded in the analysis of low trauma hip fractures as they are likely unavoidable even in individuals with high BMD. For HPFS hip fractures that occurred after 2010, all were considered to be low trauma as the number of traumatic fractures in older adults had been very low. Based on the time period that causes of fractures were reported, we estimated that about 1% of the total cases due to high trauma origin. We expect self-reporting of hip fractures to be highly accurate as all participants were health professionals. In a validation study in the NHS, medical record review confirmed each reported fractures in all 30 sampled cases (21). Hip fractures were also identified from death records in both cohorts.

Assessment of other lifestyle characteristics

BMI was calculated at each questionnaire cycle using self-reported height measurement at baseline and weight at each biennial questionnaire. Also assessed by self-report every 2 years were smoking, use of thiazide diuretics, lasix, and anti-inflammatory steroids (yes or no), use of brand-specific multivitamins (yes or no), use of calcium, vitamin D, and retinol supplements (no or daily amount), diagnosis of osteoporosis and diabetes (yes or no), and in women, postmenopausal hormone use. Leisure-time physical activity was assessed multiple times during follow-up with 10 activities and reported as hours per week and were assigned a metabolic equivalent score (27). These scores were then summed over all activities to create a value in metabolic equivalent task hours per week.

Statistical analysis

For women who had already reached menopause in 1980, we used the FFQ in that year as the first diet assessment. However, for analysis of the red and white wine separately, the earliest follow-up began in 1984 as that was the first time when these two types of wine were assessed separately. For men who were age 50 in 1986, the FFQ administered that year was the earliest used. Participants were censored on the date of hip fracture, death from hip fracture or other causes, last questionnaire response, or in 2014 (June 1 for women and January 1 for men). Follow-up time at each 2-year cycle was excluded if participants had missing data for the two most recent FFQs. Cumulative averages were computed for alcohol consumption as grams of total ethanol as well as volume of specific types of alcoholic beverages from each FFQ (28, 29) cycle to reduce within-person variation and represent long-term intake (30). For example, if a participant entered into follow-up in 1994, alcohol intake in 1998 was calculated as the mean of 1994 and 1998. Alcohol intake in 1994 was then used to predict the risk of hip fractures between 1994 and 1998, and the mean of 1994 and 1998 intake was used to predict the risk of hip fractures between 1998 to 2002.

The main endpoint for this analysis was low trauma hip fractures, but we also considered all hip fractures as an additional analysis. Association with alcohol intake was examined using Cox proportional hazard models (SAS PROC PHREG) and Anderson-Gil data structure was used with time varying exposure and covariates in this analysis. The time scale for the analysis was months since the start of the current questionnaire cycle, which is equivalent to age in months because of the way we structured the data and formulated the model for analysis. conditioned on months of age and the year of the biennial lifestyle and health questionnaire cycle separately for men and women. We tested for proportional hazard assumption by including an interaction term between age and alcohol consumption and used the likelihood ratio test between the model with the interaction term and the model without. All Cox models were adjusted by age (in months) at start of follow-up for each woman and the calendar year of each questionnaire cycle. Multivariable models were also adjusted for BMI (< 20, 20 to < 22, 22 to <23, 23 to <24, 24 to <25, 25 to <27, 27 to <29, and 29+), height (continuous), leisure-time physical activity (Metabolic equivalent hours <3, 3 to <9, 9 to <15, 15 to <21, and 21+), use of thiazides, Lasix or oral anti-inflammatory steroids (yes or no), smoking (never smokers; past smokers quitting <5 yr, quitting5-9 yr, quitting 10+yr; current smokers of <15 cigarettes/d, 25-14 cigarettes/d, 25+ cigarettes/d), postmenopausal hormone use (women only, never/past/current), history of diabetes (yes/no), caffeine intake (quintiles), multivitamin use (yes/no), sugar sweetened beverages (no consumption, <2/wk, 2 to <5/wk, 5 to <10/wk, 10+/wk), quintiles of protein intake, quintiles of total (dietary and supplemental) intakes of calcium, retinol, vitamin K, and vitamin D. These were chosen as they have shown association with hip fractures in the literature or in our cohorts. Restricted cubic splines for proportional hazard models were conducted to identify potential deviation from linearity in the association between alcohol consumption and fracture risk. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. All analysis had the same sample size and was conducted using SAS v9.4, Cary NC.

Total alcohol consumption was classified as non-drinkers (reference group), <5.0g/d, 5.0 to <10.0g/d, 10.0 to <20.0g/d, and 20.0+ g/d of ethanol for women. For men, the highest group was furthered divided into 20 to <30g/d and 30+g/day. Cumulative averages of wine intake (as grams of the alcoholic beverage, not as ethanol) were classified as the average of < 1 serving/wk, 1 serving/wk to 3 servings/wk, and > 3 servings/wk. Beer and liquor were classified into < 1 serving/wk, 1 serving/wk to 3 servings/wk, and > 3 servings/wk.

We explored potential effect modification with strata of age (<75 vs 75+), BMI (<25 vs 25+), and physical activity (above or below cohort median) by stratifying the analysis by these factors. Tests for 2-way interaction between alcohol consumption and each of these factors were conducted using the likelihood ratio test comparing regression models with and without an interaction term. In a sensitivity analysis, we excluded drinkers if they became abstainers during follow-up to avoid inclusion of individuals with declining health who reduced alcohol consumption and experienced frailty leading to increased risk of falls. As an alternative to the temporal relationship represented by cumulative analysis, the association between alcohol intake and hip fractures was also examined by using recent alcohol consumption, computed as the mean of the two most recent FFQs.

We also examined current patterns of alcohol consumption and hip fracture risks among drinkers as the typical number of days per week consuming alcohol and the highest number of drinks in a day. Number of days/wk consuming alcohol was classified into <1d/wk, 1 to 2d/wk, 3 to 4d/wk, and 5 to 7d/wk. The highest number of drinks per day was classified into <1 drink/d, 1 to 2 drinks/d, 3 to 5 drinks/d, and 6+ drink/d.

Results

In up to 34 years of follow-up, there were 2,360 incident low trauma hip fractures in women and 709 in men. Median follow-up for women was 22.6 years (inter-quartile range 16.5 to 28.8 years) and for men was 18.2 years (inter-quartile range 12.7 to 23.9 years). Women and men with higher total alcohol consumption tended to be leaner, and had lower calcium intake, but more likely to be current smokers, and consumed more caffeine **(Table 1)**. On the other hand, non-drinkers tended to have higher prevalence of diabetes.

Among women, there was an inverse association with alcohol consumption categories up to 10g/d in the model adjusted only for age, energy intake, and physical activity with low impact fractures **(Table 2)**. However, after adjusting for BMI, when compared with non-drinkers, a lower risk of low trauma hip fractures was observed for each category of consumption up to an average intake of 20g/d. Compared to non-drinkers, in the multivariable adjusted model, RR was 0.89 (95% CI=0.80, 0.99) for those who consumed less than a cumulative average of <5g/d, 0.81 (95% CI=0.70, 0.94) for those who consumed 5.0 to less than 10.0g/d, and 0.83 (95% CI=0.71, 0.96) for those who consumed 10.0 to less than 20.0g/d. When we further divided alcohol consumers who consumed <5g/d to 0.1g to 2.4g/d and 2.5g to <5.0 g/d, the RRs were essentially the same (0.87 and 0.88, respectively). Compared to non-drinkers, consumption of 20.0g/d or greater was not associated with hip fractures in women (RR=0.93, 95% CI=0.78, 1.10). Additional adjustment for fruits and vegetables did not change the risk estimates in either men or women. Restricted cubic spline regression adjusted for confounders did not detect a significant non-linear relationship between alcohol consumption and fracture risk.

Among men, a significant inverse association was observed with increasing total alcohol consumption in all models (p values for linear trend<0.05). Compared to non-drinkers, multivariable RR for intake of an average of 30.0g/d or more was 0.67 (95% CI=0.48, 0.95, p for linear trend=0.002). In addition, results from analysis that excluded former drinkers remained similar to our main analysis in both men and women **(Supplemental Table 1)**. Analyses examining recent consumption did not result in meaningful difference from cumulative consumption **(Supplemental Table 2)**.

Among specific alcoholic beverage intake, total wine intake was associated with a lower risk of low trauma hip fractures in women but not in men **(Table 3)** after adjusting for potential confounders and other types of alcoholic beverage. The RR in women for each serving of wine was 0.86 (95% CI=0.76, 0.96). The association was particular apparent for red wine, with RR=0.59 (95% CI=0.45, 0.79) for each serving. In men, a near significant inverse association was observed with liquor (RR for each serving = 0.88, 95% CI=0.77, 1.00) and beer (RR for each serving=0.82, 95% CI=0.68, 1.00) in the multivariable model. On the other hand, there was no clear linear trend association with beer or liquor in women. Results did not change when we additionally adjusted for total alcohol (ethanol) intake (data not shown). The associations also did not change appreciably when we restricted the analysis to drinkers only (data not shown).

In stratified analysis, the association between cumulative average alcohol intake and low trauma hip fractures did not appear to differ by age, BMI, or physical activity in either men or women **(Supplemental Table 3)**.

When we examined drinking patterns among drinkers, a higher number of alcohol consuming days/week was associated with a lower risk of low trauma hip fractures among women. Compared to those who consumed =<1/day/wk, multivariable relative risk in those who consumed 2 day/week was 0.94 (95% CI=0.74, 1.18), and 3-4 d/wk 0.75 (95% CI=0.60, 0.94) **(Table 4)**. Among men who consumed alcohol, when compared to those who consumed =<1/day/wk, the lower low trauma hip fracture risk for increasing number of alcohol consuming days/week extended to 5-7d/wk (RR=0.66, 95% CI=0.52, 0.85) in the multivariable model. In both men and women, additional adjustment for total alcohol intake did not materially change the results **(Table 4)**. We also examined the association between the maximum number of drinks consumed per drinking occasion and risk of low trauma hip fractures among drinkers but no association was observed in either men or women **(Supplemental Table 4)**.

Hip fractures in our cohorts were primarily of low trauma origin. When we considered all hip fractures, we obtained an additional 120 cases in women (total 2,480 cases) and 65 cases in men (total 741 cases). **(Supplemental Table 5)**. Compared with non-drinkers, RR for women with 20g/d or more of alcohol consumption was 0.91 (95% CI=0.77, 1.06, p trend=0.13), and men with consumption of 30g/d or more was 0.74 (95% CI=0.53, 1.02, p trend=0.006).

Discussion

In this analysis, moderate alcohol consumption was inversely associated with risk of hip fractures in middle-aged and older men and women. Among specific alcoholic beverages, red wine was most clearly associated with lower risk of hip fractures among women whereas total alcohol consumption most consistently contributed to a lower risk in men.

Existing studies in older women shows that low to moderate alcohol intake were either not associated with or inversely associated with hip fracture risk while high intake trended toward an increased risk (13, 31-35). In this study, we too observed a reduced risk with low to moderate intakes, equivalent to about 1.5 drinks/day, when compared with abstainers. While many studies in women were adjusted for multiple confounders and had long follow-up, none had multiple measurements of diet or lifestyle factors. We were able to update lifestyle information and observed consistent inverse associations with both cumulative and recent alcohol consumption. Therefore, data from this and previous studies provide strong indication that light to moderate alcohol consumption is associated with a lower risk of hip fractures in women. A number of studies in men had suggested a lower risk with low to moderate intake (13, 17, 31, 36) and this analysis showed an apparent inverse trend even with 30+g/d of consumption, equivalent to over 2 drinks/day. However, a Norwegian study among men over age 60 showed no association up to consumption of 27 servings a week and a suggestion of increased risk above that (35). Therefore, our data agree with others who found low to moderate alcohol intake is not associated with an increased risk but a potential for a lower risk of hip fracture in middle aged and older men.

Alcohol consumption at low to moderate levels has been associated with higher BMD (9, 11, 37). Women with moderate alcohol consumption had lower bone resorption marker N telopeptide creatinine (NTx/cr), parathyroid hormone, but also lower serum osteocalcin, suggesting lower bone turnover (9). Also, abstinence after habitual consumption increased these markers (38). Estrogen has regulatory influence in bone turnover and higher circulating estrogen levels has been observed in women with moderate alcohol consumption (5). In turn, higher estrogen levels is associated with higher BMD in both men and women (39) and post-menopausal hormone use was associated with lower risk of fractures (40).

Although few studies examined specific types of alcohol and fracture risk, they were consistent in suggesting an inverse association for a preference of wine (14, 17, 18). While this analysis also pointed toward a lower risk of hip fractures with wine consumption in women, the association appeared to be somewhat stronger for red wine. Besides the ethanol content, wine, especially red wine contains flavonoids which some are potent antioxidants (41). It has been shown that increased oxidative stress, which is related to aging, may negatively affect BMD

(42). Inflammatory markers such as tumor necrosis factor alpha-1 and those in the interleukin family have shown to increase the expression of receptor activated nuclear factor kappa-B ligand (RANKL), which in turn promotes differentiation of osteoclasts (43). In addition, low grade inflammation can also increase osteoblast apoptosis. Human data has shown a higher BMD with higher polyphenols intake(44, 45). Red wine has several times the phenolic compounds than white wine. In vitro studies have shown that many are phytoestrogen and can reduce osteoclast differentiation (15). This weak estrogenic activity might be particularly more important in post menopausal women, and data from in vivo studies is needed to determine actual effect in women. While there was no clear association with red wine in men, the risk estimate suggested a sign of potential inverse association, but it did not reach statistical significance and could be less stable due to few number of cases and fewer men consuming higher levels of red wine.

Among studies that examined beer consumption (14, 17, 18), only one showed a suggestion of a lower risk of hip fractures (14). In this analysis, we noted an inverse association with beer in men only. In one U.S. study, men had higher beer intake than women and beer was associated with higher BMD of the hip only in men (11). Besides ethanol, beer contains bioavailable silicon (46) and another study showed direct association with bone mineral density in both men and younger women (47). Infrequent intake is more difficult to recall accurately with FFQ as participants were asked to report usual intake. This in combination with an overall lower beer consumption in women may be a reason for a lack of association in women in our cohorts. However, as data on beer consumption and fractures is scarce, we cannot be certain that there is no sex difference. Overall, with the most consistent results observed in total alcohol intake, further studies are needed to determine the role of ethanol versus components in specific alcoholic beverages in the association with fracture risk.

We examined patterns of alcohol consumption and observed a suggestion of a reducing risk with more days/week of consumption in both men and women. However, in women, the reduction in risk was no longer apparent with consumption on five or more days of the week. As these results were controlled for total ethanol consumption, it would suggest mechanisms in part mediated by the differential effect of ethanol and bone turnover based on dose as suggested by a U-shaped association between ethanol and bone mineral density (14). On the other hand, we also cannot rule out residual confounding by lifestyle factors.

The long follow-up in this study allowed us to examine long term association of diet and fracture risk. This is one of the few studies with multiple assessments of diet and other lifestyle factors to update the status of confounders during follow-up. The detailed alcohol intake data which included specific types of alcoholic beverages and consumption patterns, allowed us to examine overall intake and recent intake. However, there are also a number of limitations that should be mentioned. Under-reporting of alcohol consumption could be possible due to social desirability. Interestingly, under-reporting might be more common among those with high consumption (48) and those with infrequent consumption (49, 50). This would suggest that the risk estimates observed in the lower categories might actually represent moderate intake. Nevertheless, this still indicated that moderate alcohol consumption is not associated with a higher risk of hip fracture but potentially a lower risk. In our sample, we have few individuals with habitually high intake, with only 0.5% of person-time among women and 2.4% among men with an average of 50g/d or more of alcohol consumption. Therefore, we did not have enough statistical power to exclude an increased risk with high intake. We also did not have a large number of individuals with a high number of drinks in a day, thus we were limited in detecting the association of episodic consumption and fracture risk. Moreover, it is possible that individuals with high amounts of consumption would under report their intake. As there is no valid recovery biomarker for alcohol consumption, it is challenging to accurately assess alcohol consumption. However, we do not expect widespread under reported as our validation data showed high correlation between intake recorded from diet records and FFQ. In addition, the participants were Caucasian limiting the generalizable of these results to other ethnicities.

In conclusion, this analysis showed that low to moderate alcohol consumption is associated with a lower risk of low trauma hip fractures, especially with red wine consumption among women. The lowest risks occurred when alcohol was consumed over 3-4 days per week in women and 5-7 days per week in men.

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TTF, KJM, DF designed the research, TTF conducted the analysis, wrote the paper, and has primary responsibility for final content, WCW, HEM, and EBR provided data-analysis strategies, all authors revised and approved the final manuscript. None of the authors have conflicts of interest to declare.

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Table 1: Lifestyle and dietary characteristics (mean ± SD) by categories of total alcohol intake (g/day) at entry to follow-up. (women n=75,180, men n=38,398)

	Non drinkers	< 5.0	5.0 to < 10.0	10.0 to <20.0	20.0+	P value for trend
Women						
Age at entry (years)	53.3 ± 4.2	53.1 ± 4.3	53.2 ± 4.1	53.4 ± 4.0	53.3 ± 3.9	<0.001
BMI (kg/m^2)	26.1 ± 5.2	25.4 ± 4.6	24.5 ± 3.9	24.1 ± 3.7	24.0 ± 3.7	<0.001
Height (cm)	163.4 ± 8.0	163.5 ± 8.3	163.8 ± 8.4	163.9 ± 7.7	164.1 ± 8.0	<0.001
Physical activity (METs[1])	8 ± 14	9 ± 15	10 ± 15	9.1 ± 15.3	8.2 ± 14.6	<0.001
Current smoker (%)	17.8	20.2	23.0	28.7	38.7	<0.001
Menopause hormone use (%)	30.1	32.2	34.1	31.0	30.6	<0.001
Multivitamin use (%)	39.1	40.2	40.2	39.5	39.9	0.01
Calcium supplement use (%)	28.9	30.1	30.3	28.8	28.3	<0.001
Vitamin D supplement use (%)	2.4	2.5	2.1	2.1	2.0	<0.001
History of diabetes (%)	4.9	2.3	1.5	1.4	1.5	<0.001
Thiazide use (%)	12.5	11.8	11.2	11.8	14.1	<0.001
Energy (kcal/day)	1644 ± 528	1643 ± 520	1665 ± 510	1671 ± 506	1800 ± 509	<0.001
Wine (servings/day)	0	0.1 ± 0.1	0.3 ± 0.3	0.5 ± 0.4	1.1 ± 1.2	<0.001
Beer (servings/day)	0	0.02 ± 0.04	0.1 ± 0.1	0.2 ± 0.3	0.6 ± 1.1	<0.001
Liquor (servings/day)	0	0.04 ± 0.05	0.2 ± 0.2	0.4 ± 0.4	1.2 ± 1.2	<0.001
Protein[2] (g/day)	76 ± 15	77 ± 14	76 ± 13	75 ± 13	69 ± 12	<0.001
Calcium[2] (mg/day)	918 ± 476	921 ± 457	899 ± 435	848 ± 408	770 ± 401	<0.001
Vitamin D[2] (IU/day)	353 ± 284	349 ± 273	341 ± 263	327 ± 258	298 ± 233	<0.001
Retinol[2] (mcg/day)	4785 ± 6103	4678 ± 5467	4454 ± 4973	4436 ± 4923	4177 ± 4663	<0.001
Vitamin K[2] (mcg/day)	93 ± 108	99 ± 112	100 ± 107	89 ± 110	84 ± 103	<0.001
Caffeine[1] (mg/day)	307 ± 260	340 ± 251	357 ± 242	376 ± 244	379 ± 240	<0.001
Sugar sweetened beverages (servings/day)	2.4 ± 4.6	2.0 ± 3.9	1.7 ± 3.2	1.6 ± 3.3	1.6 ± 3.8	<0.001
Men						
Age at entry (years)	57.2	56.8	56.8	57.0	57.4	<0.001
BMI (kg/m^2)	25.8 ± 3.4	25.7 ± 3.2	25.5 ± 3.0	25.5 ± 2.9	25.6 ± 2.9	0.29
Height (cm)	178.1 ± 6.5	178.0 ± 6.7	178.3 ± 6.4	178.5 ± 6.5	178.7± 6.4	<0.001
Physical activity (METs)	21 ± 26	23 ± 26	25 ± 26	25 ± 26	24 ± 27	<0.001
Current smoker (%)	5.5	6.1	6.4	7.9	13.3	<0.001
Multivitamin use (%)	42	42	44	44	44	<0.001
Calcium supplement use (%)	17.2	15.2	16.0	16.7	16.4	0.79
Vitamin D supplement use (%)	3.5	3.0	3.1	3.3	3.2	0.69
History of diabetes (%)	4.4	2.7	2.0	1.8	1.8	<0.001
Thiazide use (%)	8.2	8.3	8.3	8.2	10.9	<0.001

Energy (kcal)	1934 ± 619	1907 ± 599	1947 ± 590	1986 ± 587	2169 ± 589	<0.001
Wine (servings/day)	0	0.1 ± 0.1	0.2 ± 0.2	0.4 ± 0.4	0.8 ± 1.0	<0.001
Beer (servings/day)	0	0.05 ± 0.06	0.2 ± 0.2	0.3 ± 0.3	0.9 ± 1.2	<0.001
Liquor (servings/day)	0	0.04 ± 0.05	0.2 ± 0.2	0.4 ± 0.4	1.3 ± 1.3	<0.001
Protein[2] (g/day)	93.2 ± 17.5	94.7 ± 16.5	93.9 ± 15.7	92.3 ± 15.2	85.9 ± 14.7	<0.001
Calcium[2] (mg/day)	987 ± 476	936 ± 422	915 ± 411	894 ± 404	810 ± 369	<0.001
Vitamin D[2] (IU/day)	427 ± 323	429 ± 310	435 ± 319	421 ± 306	382 ± 288	<0.001
Retinol[2] (mcg/day)	5512 ± 6696	5280 ± 6042	5506 ± 6501	5351 ± 6250	4915 ± 5597	<0.001
Vitamin K[2] (mcg/day)	182 ± 119	188 ± 114	191 ± 118	190 ± 107	182 ± 102	<0.001
Caffeine[2] (mg/day)	191 ± 227	213 ± 218	227 ± 214	244 ± 216	282 ± 231	<0.001
Sugar sweetened beverages (servings/day)	0.4 ± 0.6	0.3 ± 0.6	0.3 ± 0.5	0.3 ± 0.4	0.2 ± 0.5	<0.001

[1]Metabolic Equivalent.

[2] energy adjusted with the residual method (reference 22), micronutrients intake included supplemental sources.

Table 2: Relative risks[1] (95% CI) for low trauma hip fractures by categories of cumulative average alcohol intake (g/day). (women n=75,180, men n=38,398)

	Non drinkers	< 5.0	5.0 to < 10.0	10.0 to <20.0	20.0 to <30[2]	30+	P trend[3]
Women							
No. of fractures	567	1006	286	287	214		
Person years	406,316	696,130	221,148	213,611	132,718		
Age & energy adjusted	1.00	0.87 (0.78, 0.96)	0.81 (0.70, 0.93)	0.86 (0.74, 0.99)	1.06 (0.90, 1.24)		0.38
Above + physical activity	1.00	0.89 (0.80, 0.99)	0.85 (0.74, 0.98)	0.91 (0.79, 1.05)	1.09 (0.93, 1.28)		0.20
Above + BMI	1.00	0.89 (0.80, 0.99)	0.80 (0.69, 0.92)	0.82 (0.71, 0.95)	0.96 (0.82, 1.13)		0.42
Multivariable[4] adjusted	1.00	0.89 (0.80, 0.99)	0.81 (0.70, 0.94)	0.83 (0.71, 0.96)	0.93 (0.78, 1.10)		0.25
Men							
No. of fractures	114	229	111	136	57	62	
Person-years	111,955	180,883	110,209	144,371	57,372	72,992	
Age & energy adjusted	1.00	1.00 (0.79, 1.26)	0.86 (0.67, 1.13)	0.79 (0.61, 1.02)	0.75 (0.54, 1.05)	0.76 (0.55, 1.04)	0.01
Above + physical activity	1.00	1.00 (0.79, 1.26)	0.87 (0.67, 1.14)	0.80 (0.62, 1.04)	0.76 (0.55, 1.05)	0.76 (0.55, 1.05)	0.02
Above + BMI	1.00	1.00 (0.79, 1.27)	0.88 (0.67, 1.15)	0.82 (0.63, 1.06)	0.77 (0.56, 1.07)	0.77 (0.56, 1.06)	0.02
Multivariable[4] adjusted	1.00	0.99 (0.78, 1.26)	0.86 (0.66, 1.14)	0.77 (0.59, 1.01)	0.69 (0.49, 0.96)	0.67 (0.48, 0.95)	0.002

[1] Computed using Cox proportional hazard model.[2]In women, the 20.0 to < 30g category was combined with 30+ category.

[3]Linear trend

[4]Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only), protein, total intake of vitamin K, retinol, vitamin D, and calcium.

Table 3: Relative risks[1] (95% CI) for low trauma hip fractures by categories of cumulative average alcoholic beverage intake. (women n=75,180, men n=38,398)

	Non-drinkers	0 specific alcohol[2]	< 1 serving /week	1 to 3 serving /week	> 3 serving /week	Per serving/day increase
TOTAL WINE						
Women						
No. of fractures	567	194	827	442	330	
Person years	406,309	131,089	528,787	335,393	268,318	
Age, energy, other alcoholic beverage adjusted	1.00	1.03 (0.87, 1.22)	0.85 (0.76, 0.95)	0.82 (0.72, 0.93)	0.74 (0.64, 0.86)	0.86 (0.77,0.96)
Multivariable adjusted [3]	1.00	0.98 (0.82, 1.17)	0.88 (0.78, 0.98)	0.87 (0.76, 0.99)	0.75 (0.64, 0.87)	0.86 (0.76,0.96)
Men						
No. of fractures	114	74	206	179	136	
Person years	111,955	75,203	163,099	182,871	144,654	
Age, energy, other alcoholic beverage adjusted	1.00	1.05 (0.77,1.44)	0.93 (0.73, 1.18)	0.92 (0.71, 1.18)	0.86 (0.66, 1.12)	0.92 (0.76,1.10)
Multivariable adjusted[3]	1.00	1.04 (0.76,1.43)	0.93 (0.73, 1.19)	0.94 (0.73, 1.22)	0.87 (0.66, 1.15)	0.91 (0.75,1.10)
WHITE WINE						
Women						
No. of fractures	586	280	873	324	210	
Person years	408,212	189,511	610,337	260,833	153,965	
Age, energy, other alcoholic beverage adjusted	1.00	1.02 (0.88, 1.18)	0.82 (0.74, 0.92)	0.84 (0.72, 0.96)	0.89 (0.75, 1.05)	0.98 (0.86,1.12)
Multivariable adjusted[3]	1.00	0.98 (0.84, 1.13)	0.84 (0.75, 0.94)	0.84 (0.73, 0.98)	0.85 (0.71, 1.01)	0.95 (0.83,1.08)
Men						
No. of fractures	114	108	300	187		
Person years	111,955	108,817	259,502	197,508		
Age, energy, other alcoholic beverage adjusted	1.00	0.98 (0.74, 1.29)	0.94 (0.75, 1.19)	0.95 (0.73, 1.24)		1.05 (0.79,1.39)
Multivariable adjusted[3]	1.00	0.97 (0.73, 1.29)	0.96 (0.76, 1.22)	0.96 (0.73, 1.26)		1.03 (0.78,1.38)
RED WINE						
Women						
No. of fractures	586	614	799	210	64	
Person years	408,212	447,801	536,609	167,657	62,578	
Age, energy, other alcoholic beverage adjusted	1.00	0.93 (0.83, 1.05)	0.80 (0.71, 0.89)	0.74 (0.62, 0.87)	0.62 (0.47, 0.80)	0.59 (0.45,0.79)

Multivariable adjusted[3]	1.00	0.91 (0.81, 1.03)	0.82 (0.73, 0.92)	0.75 (0.63, 0.89)	0.58 (0.54, 0.76)	0.59 (0.45,0.79)
Men						
No. of fractures	114	157	264	174		
Person years	111,955	166,468	222,237	177,123		
Age, energy, other alcoholic beverage adjusted	1.00	0.99 (0.76, 1.28)	0.92 (0.72, 1.16)	0.84 (0.64, 1.10)		0.77 (0.56,1.07)
Multivariable adjusted[3]	1.00	0.97 (0.74, 1.26)	0.94 (0.74, 1.21)	0.87 (0.66, 1.15)		0.79 (0.57,1.09)
BEER						
Women						
No. of fractures	567	1055	501	153	84	
Person years	406,309	756,904	334,090	114,586	58009	
Age, energy, other alcoholic beverage adjusted	1.00	0.87 (0.78, 0.97)	0.83 (0.73, 0.94)	0.97 (0.80, 1.17)	1.02 (0.81, 1.29)	1.15 (1.01,1.31)
Multivariable adjusted[3]	1.00	0.89 (0.80, 1.00)	0.87 (0.76, 0.99)	1.01 (0.83, 1.22)	0.90 (0.70, 1.14)	1.03 (0.90,1.18)
Men						
No. of fractures	114	124	244	141	86	
Person years	111,955	117,417	190,107	153,017	105,286	
Age, energy, other alcoholic beverage adjusted	1.00	0.88 (0.67,1.15)	0.96 (0.76, 1.22)	0.95 (0.72, 1.24)	0.85 (0.63, 1.16)	0.89 (0.73,1.07)
Multivariable adjusted[3]	1.00	0.88 (0.67, 1.16)	0.98 (0.77, 1.26)	0.94 (0.71, 1.24)	0.80 (0.58, 1.10)	0.82 (0.68,1.00)
LIQUOR						
Women						
No. of fractures	567	582	655	254	302	
Person years	406,309	455,957	445,022	186,158	176,451	
Age, energy, other alcoholic beverage adjusted	1.00	0.88 (0.78, 0.99)	0.84 (0.75, 0.95)	0.89 (0.77, 1.05)	1.00 (0.86, 1.16)	1.14 (1.04,1.25)
Multivariable adjusted[3]	1.00	0.90 (0.79, 1.01)	0.88 (0.78, 1.00)	0.92 (0.78, 1.08)	0.93 (0.80, 1.08)	1.04 (0.95,1.14)
Men						
No. of fractures	114	161	174	108	152	
Person years	111,955	150,818	157,787	116,481	140,741	
Age, energy, other alcoholic beverage adjusted	1.00	1.03 (0.80, 1.32)	0.95 (0.73, 1.22)	0.86 (0.64, 1.14)	0.80 (0.63, 1.05)	0.91 (0.81,1.04)
Multivariable adjusted[3]	1.00	1.03 (0.79, 1.33)	0.95 (0.73, 1.23)	0.87 (0.65, 1.17)	0.76 (0.57, 1.00)	0.88 (0.77,1.00)

[1] Computed using Cox proportional hazard model.
[2] Consumption of the alcoholic beverage in question was 0 but total alcohol consumption from other types of alcoholic beverages were greater than 0.

[3]Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, specific alcoholic beverage type, multivitamin use, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only), protein, total intake of vitamin K, retinol, vitamin D, and calcium.

Table 4: Relative risks[1] (95% CI) for low trauma hip fractures by number of days/week consuming alcohol (among drinkers) (women n=75,180, men n=38,398)

	1 day/week or less	2 day/week	3-4 days/week	5-7 days/week	P for linear trend
Women					
No. of fractures	378	96	105	315	
Person years	305,295	79,383	102,012	192,009	
Age adjusted	1.00	0.95 (0.76,1.19)	0.80 (0.64,0.99)	1.11 (0.95, 1.29)	0.18
Multivariable[2]	1.00	0.94 (0.74, 1.18)	0.75 (0.60,0.94)	0.97 (0.82, 1.14)	0.67
Above + alcohol	1.00	0.93 (0.74, 1.16)	0.73 (0.58,0.92)	0.91 (0.74, 1.11)	0.24
Men					
No. of fractures	117	51	74	176	
Person years	93,649	50,055	84,413	185,349	
Age adjusted	1.00	0.84 (0.60, 1.19)	0.82 (0.61, 1.11)	0.74 (0.58, 0.94)	0.08
Multivariable[2]	1.00	0.81 (0.57, 1.15)	0.82 (0.61, 1.11)	0.66 (0.52, 0.85)	0.007
Above + alcohol	1.00	0.81 (0.57, 1.16)	0.83 (0.60, 1.13)	0.68 (0.50, 0.91)	0.06

[1] Computed using Cox proportional hazard model.
[2]Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only), protein, total intake of vitamin K, retinol, vitamin D, and calcium.

Figure legend

Figure 1: Timeline of data collection for the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

Figure 1: Timeline of data collection for the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

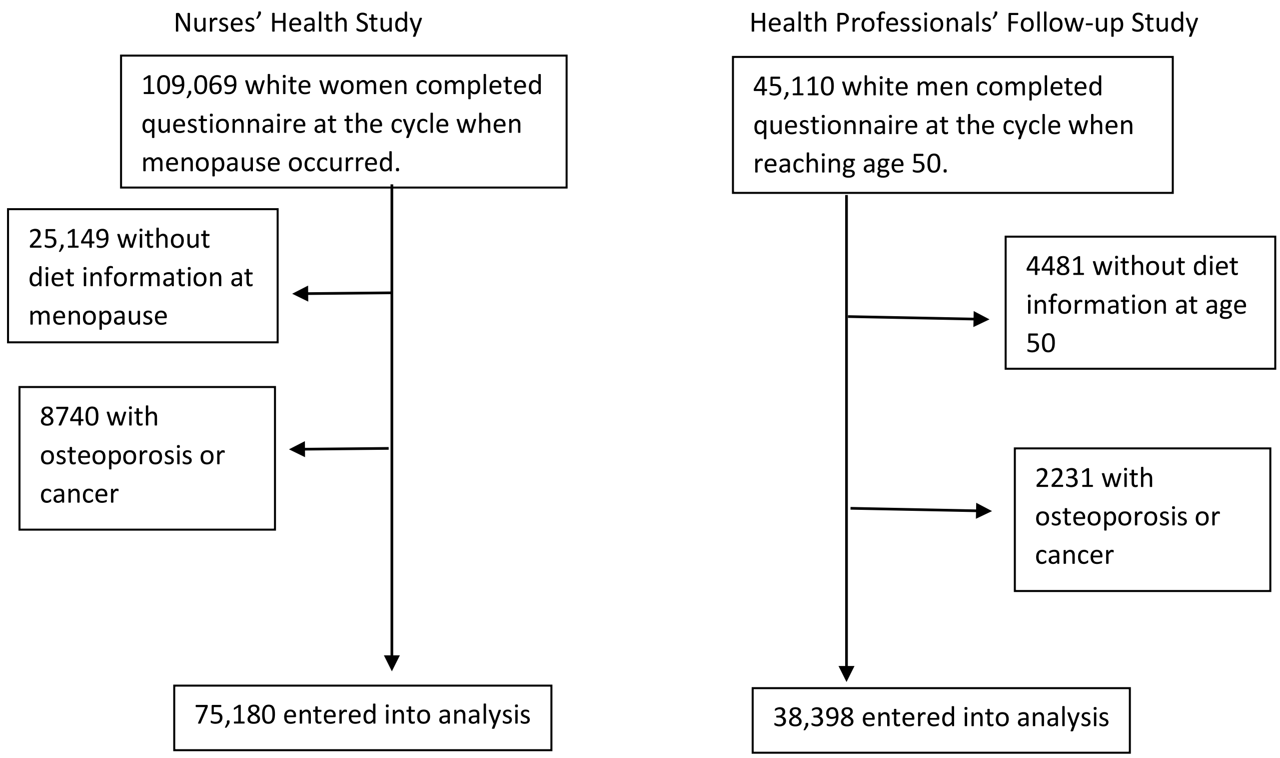
NHS

Year	80	82	84	86	88	90	92	94	96	98	00	02	04	06	08	10	12	14
Lifestyle																		
FFQ																		
#Drinking days/Wk																		
#Drinks/Day																		

HPFS

Year	86	88	90	92	94	96	98	00	02	04	06	08	10	12	14
Lifestyle															
FFQ															
#Drinking days/Wk															
#Drinks/Day															

Supplemental Figure 1: Participant flow chart



Supplemental table 1: Relative risks[1] (95% CI) for low trauma hip fractures by categories of **cumulative** alcohol intake (g/day) excluding former drinkers. (women n=75,180, men n=38,398)

	Non drinkers	< 5.0	5.0 to < 10.0	10.0 to <20.0	20.0 to <30.0[2]	30.0+	P for linear trend
Women							
No. of fractures	769	685	229	256	191		
Person years	500,759	556,687	199,656	202,507	128,154		
Age & energy adjusted	1	0.83 (0.75, 0.92)	0.79 (0.68, 0.91)	0.86 (0.75, 0.99)	1.02 (0.86, 1.19)		0.62
Multivariable3 adjusted	1	0.85 (0.76,0.94)	0.79 (0.67,0.92)	0.81 (0.70, 0.94)	0.87 (0.74,1.04)		0.12
Men							
No. of fractures	84	173	93	124	53	59	
Person years	804,28	151,751	102,420	139,239	55,471	71,668	
Age & energy adjusted	1	0.98 (0.75, 1.29)	0.81 (0.59, 1.09)	0.73 (0.55, 1.09)	0.71 (0.49, 1.01)	0.73 (0.51, 1.02)	0.02
Multivariable3 adjusted	1	1.05 (0.77, 1.43)	0.86 (0.61, 1.21)	0.77 (0.55, 1.08)	0.68 (0.46, 1.02)	0.67 (0.45, 0.99)	0.003

[1] Computed using Cox proportional hazard model.
[2]In women, the 20.0 to < 30g category was combined with 30+ category.
[3]Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, protein, vitamin K, retinol, vitamin D, calcium, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only).

Supplemental table 2: Relative risks[1] (95% CI) for low trauma hip fractures by categories of **recent** (mean of past 2 FFQ cycles) alcohol intake (g/day) (women n=75,180, men n=38,398)

	Non drinkers	< 5.0	5.0 to < 10.0	10.0 to <20.0	20.0 to <30.0[2]	30.0+	P trend
Women							
No. of fractures	1074	593	243	260	190		
Person years	613,821	518,920	193,998	211,479	131,678		
Age & energy adjusted	1	0.82 (0.74, 0.91)	0.87 (0.75, 1.00)	0.81 (0.71, 0.93)	1.00 (0.85, 1.17)		0.98
Above + physical activity	1	0.85 (0.77, 0.94)	0.91 (0.79, 1.05)	0.86 (0.75, 0.99)	1.03 (0.88, 1.20)		0.64
Above + BMI	1	0.85 (0.76, 0.94)	0.86 (0.75, 0.99)	0.78 (0.68, 0.89)	0.92 (0.79, 1.08)		0.21
Multivariable[3] adjusted	1	0.84 (0.76, 0.93)	0.85 (0.74, 0.98)	0.76 (0.66, 0.88)	0.86 (0.31, 1.01)		0.05
Men							
No. of fractures	214	158	94	126	44	72	
Person years	148,754	152,265	97, 352	147, 911	52,515	79,241	
Age & energy adjusted	1	0.84 (0.67, 1.03)	0.83 (0.65, 1.07)	0.64 (0.51, 0.81)	0.65 (0.47, 0.91)	0.73 (0.56, 0.97)	0.004
Above + physical activity	1	0.84 (0.68, 1.04)	0.84 (0.66, 1.08)	0.66 (0.52, 0.82)	0.66 (0.77, 0.93)	0.74 (0.56,0.98)	0.006
Above + BMI	1	0.85 (0.69, 1.05)	0.86 (0.67, 1.10)	0.67 (0.48, 0.94)	0.67 (0.48, 0.94)	0.75 (0.57, 0.99)	0.007
Multivariable[3] adjusted	1	0.86 (0.70, 1.07)	0.85 (0.66, 1.10)	0.66 (0.51, 0.82)	0.64 (0.45, 0.91)	0.70 (0.52, 0.94)	0.002

[1] Computed using Cox proportional hazard model.
[2] In women, the 20.0 to < 30g category was combined with 30+ category.
[3] Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, protein, vitamin K, retinol, vitamin D, calcium, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only).

Supplemental table 3: Multivariable[1] relative risks[2] (95% CI) for low trauma hip fractures by categories of cumulative alcohol intake stratified by selected fracture risk factors (women n=75,180, men n=38,398)

	0g/d	< 5.0g/d	5.0 to < 10.0 g/d	10.0 to < 20.0 g	20+ g/day	P trend	P interaction
Age							
WOMEN							
Age < 75 (fractures = 1238)	1	0.89 (0.77, 1.02)	0.79 (0.65, 0.96)	0.83 (0.69, 1.01)	0.91 (0.73, 1.13)	0.39	0.72
Age ≥ 75 (fractures = 1122)	1	0.91 (0.78, 1.06)	0.88 (0.72, 1.08)	0.86 (0.70, 1.06)	1.01 (0.79, 1.29)	0.56	
MEN							
Age < 75 (fractures = 271)	1	0.75 (0.52, 1.07)	0.64 (0.42, 0.98)	0.49 (0.32, 0.75)	0.58 (0.38, 0.88)	0.15	0.24
Age ≥ 75 (fractures = 437)	1	1.24 (0.89, 1.71)	1.08 (0.74, 1.56)	1.04 (0.73, 1.49)	0.76 (0.51, 1.13)	0.002	
BMI							
WOMEN							
BMI < 25 (fractures = 1464)	1	0.87 (0.76, 0.99)	0.87 (0.73, 1.03)	0.88 (0.74, 1.05)	0.93 (0.76, 1.14)	0.39	0.21
BMI ≥ 25 (fractures = 896)	1	0.94 (0.80, 1.10)	0.74 (0.58, 0.95)	0.76 (0.58, 1.00)	0.95 (0.70, 1.28)	0.34	
MEN							
BMI < 25 (fractures =376)	1	0.97 (0.70, 1.35)	0.69 (0.46, 1.03)	0.78 (0.53, 1.13)	0.69 (0.46, 1.04)	0.06	0.97
BMI ≥ 25 (fractures =332)	1	0.94 (0.65, 1.35)	0.96 (0.64, 1.44)	0.72 (0.48, 1.09)	0.65 (0.42, 1.01)	0.04	
Physical activity							
WOMEN							
MET < median (fractures = 1253)	1	0.95 (0.82, 1.09)	0.78 (0.64, 0.96)	0.85 (0.69, 1.05)	1.02 (0.82, 1.28)	0.68	0.81
MET ≥ median (fractures = 1107)	1	0.82 (0.70, 0.96)	0.84 (0.68, 1.02)	0.80 (0.66, 0.99)	0.83 (0.65, 1.06)	0.20	
MEN							
MET < median (fractures =459)	1	1.02 (0.75, 1.38)	1.00 (0.71, 1.42)	0.82 (0.58, 1.16)	0.73 (0.50, 1.05)	0.02	0.03
MET ≥ median (fractures =249)	1	0.96 (0.64, 1.43)	0.71 (0.44, 1.15)	0.67 (0.42, 1.06)	0.68 (0.42, 1.10)	0.16	

[1] Multiavariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, protein, vitamin K, retinol, vitamin D, calcium, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only), except for variable of stratification.
[2] Computed using Cox proportional hazard model.

Supplemental table 4: Relative risks[1] (95% CI) for low trauma hip fractures by maximum number of drinks/day on days consuming alcohol (drinkers only) (women n=75,180, men n=38,398)

	< 1 drink/d	1-2 drinks/d	3-5 drinks/d	6+ drinks/d
Women				
No. of fractures	104	596	165	28
Person years	575,66	441,746	159,902	20,702
Age adjusted	1	0.82 (0.66, 1.01)	0.89 (0.68, 1.14)	1.01 (0.66, 1.55)
Multivariable2	1	0.80 (0.64, 1.00)	0.82 (0.63, 1.06)	0.85 (0.55, 1.32)
Above + alcohol	1	0.79 (0.63, 0.98)	0.77 (0.58, 1.02)	0.81 (0.51, 1.26)
Men				
No. of fractures	45	252	93	29
Person years	36,850	219,646	111,809	23,757
Age adjusted	1	0.85 (0.61, 1.19)	0.80 (0.55, 1.17)	1.29 (0.79, 2.12)
Multivariable2	1	0.85 (0.60, 1.20)	0.77 (0.52, 1.13)	1.30 (0.78, 2.17)
Above + alcohol	1	0.88 (0.62, 1.24)	0.84 (0.55, 1.28)	1.39 (0.82, 2.35)

[1] Computed using Cox proportional hazard model.

[2]Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, protein, vitamin K, retinol, vitamin D, calcium, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only)

Supplemental table 5: Relative risks[1] (95% CI) for **total** hip fractures by categories of cumulative average alcohol intake (g/day) (women n=75,180, men n=38,398)

	Non drinkers	< 5.0	5.0 to < 10.0	10.0 to <20.0	20.0 to <30.0[2]	30.0+	P trend
Women							
No. of fractures	856	808	294	303	219		
Person years	512,475	580,866	221,140	213,591	132,707		
Age & energy adjusted	1	0.86 (0.78,0.94)	0.80 (0.70, 0.91)	0.87 (0.76, 0.99)	1.04 (0.89,1.20)		0.63
Multivariable adjusted [3]	1	0.89 (0.80,0.99)	0.80 (0.70, 0.92)	0.84 (0.73, 0.96)	0.91 (0.77,1.06)		0.13
Men							
No. of fractures	154	213	116	146	64	70	
Person years	127,903	165,032	110,220	144,410	57,385	73,039	
Age & energy adjusted	1	0.97 (0.78, 1.20)	0.83 (0.64,1.06)	0.77 (0.61, 0.97)	0.78 (0.58, 1.05)	0.79 (0.59, 1.05)	0.03
Multivariable adjusted [3]	1	1.01 (0.81, 1.27)	0.85 (0.65,1.01)	0.79 (0.61, 1.02)	0.75 (0.54, 1.03)	0.74 (0.53, 1.02)	0.006

[1] Computed using Cox proportional hazard model.
[2]In women, the 20.0 to < 30g category was combined with 30+ category.
[3]Multivariable adjusted for age, BMI, height, smoking, physical activity, energy intake, multivitamin use, protein, vitamin K, retinol, vitamin D, calcium, caffeine, sugar sweetened beverages, thiazide use, history of diabetes, post-menopausal hormone use (women only).