

Alcohol consumption, bone density, and hip fracture among older adults: the cardiovascular health study

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Abstract

Introduction Previous studies have found inconsistent relationships of alcohol consumption with risk of hip fracture, and the importance of bone mineral density and risk of falls in mediating such a relationship has not been determined.

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Methods As part of the Cardiovascular Health Study, a population-based cohort study of adults aged 65 years and older from four U.S. communities, 5,865 participants reported their use of beer, wine, and liquor yearly. We identified cases of hip fracture unrelated to malignancy or motor vehicle accidents using hospitalization discharge diagnoses. A subgroup of 1,567 participants in two communities underwent dual-energy x-ray absorptiometry scans to assess bone mineral density.

Results A total of 412 cases of hip fracture occurred during an average of 12 years of follow-up. There was a significant U-shaped relationship between alcohol intake and risk of hip fracture (p quadratic 0.02). Compared with long-term abstainers, the adjusted hazard ratios for hip fracture were 0.78 (95% confidence interval [CI], 0.61–1.00) among consumers of up to 14 drinks per week and 1.18 (95% CI, 0.77–1.81) among consumers of 14 or more drinks per week. Alcohol intake was associated with bone mineral density of the total hip and femoral neck in a stepwise manner, with approximately 5% (95% CI, 1%–9%) higher bone density among consumers of 14 or more drinks per week than among abstainers. These relationships were all similar among men and women.

Conclusions Among older adults, moderate alcohol consumption has a U-shaped relationship with risk of hip fracture, but a graded positive relationship with bone mineral density at the hip.

Keywords Alcohol · Bone mineral density · Epidemiology · Hip fracture · Nutrition

Introduction

Hip fractures are common causes of morbidity and mortality in older adults, [1], with a lifetime cost for all

hip fractures sustained yearly in the United States of \$20 billion [2]. Two of the most important proximal factors leading to hip fracture are low bone density (osteopenia or osteoporosis) and falls. Alcohol consumption may influence each of these factors.

Although alcohol use has been associated with an increased risk for falls, leading to injury or death in a variety of populations [3], this relation among older adults has been surprisingly inconsistent in previous studies [4–6]. In a previous analysis of older adults participating in the Cardiovascular Health Study (CHS) [7], we found that an intake of fewer than 14 drinks per week was not associated with the risk of falls when compared with abstinence, but heavier alcohol use was associated with increased risk. Moderate alcohol use has also been associated with increased bone mineral density (BMD) in many studies [8–12], which may be attributable to higher endogenous estrogen levels among moderate drinkers [13, 14].

The associations of alcohol use with bone density and falls might be expected to have opposing effects on risk of hip fracture – a lower risk related to bone density but a higher risk related to falls. Studies of moderate alcohol consumption and hip fractures underscore this inconsistency, as they variously show more fractures [15–21], fewer fractures [22–25], or no association [26–29]. However, these studies have generally been limited by small numbers of cases and limited and often retrospective assessment of alcohol consumption or other covariates, and few have had any data on bone density measurements. Limited evidence also suggests that beverage type may be of some importance, but this has not been widely addressed [30].

To assess the effects of alcohol consumption on BMD and the risk of hip fracture among older adults, we studied participants enrolled in CHS, a longitudinal study of community-dwelling older adults.

Materials and methods

Study population and design

The CHS is a prospective study of 5888 men and women aged 65 years or older who were randomly selected from Medicare-eligibility lists in four communities in the United States. Participants were not institutionalized or wheelchair-dependent, did not require a proxy for consent, were not under treatment for cancer at the time of enrollment, and were expected to remain in their respective regions for at least 3 years. In 1989 and 1990, 5201 participants were recruited and examined (the original cohort); in 1992 and 1993, an additional 687 black participants were recruited and examined. The institutional review board at each participating center approved the study, and each partici-

pant gave informed consent. For all analyses, we excluded 23 participants with missing information on baseline alcohol use, leaving 5865 participants potentially eligible for analysis.

The CHS study design and objectives have been published previously [31]. The baseline examination included standardized medical history questionnaires, physical examination, performance-based measurements, and laboratory examination. Follow-up contact occurred every 6 months, alternating between telephone calls and clinic visits.

Assessment of alcohol consumption

At the baseline visit and annually until 1999, participants reported their usual frequency of consumption of beer, wine, and liquor, and the usual number of 12-ounce cans or bottles of beer, 6-ounce glasses of wine, and shots of liquor that they drank on each occasion. For administrative reasons, alcohol consumption was not determined at the 1990–1991 CHS visit and was assessed in 1995–1996 with a validated food frequency questionnaire [32]. At baseline, participants reported whether they changed their pattern of consumption during the past 5 years and whether they ever regularly consumed five or more drinks daily. Participants who reported abstinence at baseline but responded yes to either of these questions were classified as former drinkers. In a validation study of reported alcohol use among CHS participants [33], we found a correlation of reported alcohol intake and high-density lipoprotein cholesterol (HDL-C) of 0.24 ($p < 0.001$), the magnitude expected from previous reports [32, 34].

We categorized participants into categories according to ethanol consumption as follows: long-term abstainers, former drinkers, <1 drink weekly, 1–6 drinks weekly, 7–13 drinks weekly, and 14+ drinks weekly. For regression analyses, long-term abstainers served as the reference category.

Measurement of BMD

In 1994–1995, 1591 participants at the Sacramento and Pittsburgh clinic sites underwent routine dual-energy x-ray absorptiometry scans; complete data were subsequently available for 1567. Scans were offered to participants in the order in which they came to the study centers for their annual visits – until funding was exhausted. BMD was measured with QDR-2000 bone densitometers [dual-energy x-ray absorptiometry (DEXA); Hologic, Bedford, Mass.] according to a written protocol. Scans were performed locally, with independent external quality assurance, and read blindly at the University of California, San Francisco using Hologic software, as described [35]. We used BMD

(in gm/cm^2) of the total hip and femoral neck as our primary measures of bone density.

Determination of hip fracture

Details of the CHS protocol for identification of hip fracture have been published [36]. The CHS investigators conducted active and passive surveillance to capture all hospitalizations for each participant. Participants reported hospitalizations and other acute events at annual clinic visits and interim telephone interviews, and discharge summaries and diagnoses were obtained for all hospitalizations. These records were supplemented with information from the Centers for Medicare and Medicaid Services (CMS) health care-utilization database for hospitalizations.

We defined hip fracture by a hospital discharge International Classification of Diseases, Ninth Revision (ICD-9), code of 820.xx without a concomitant code for motor vehicle accident (E810–E819) or pathologic fracture (733.1x).

Other covariates

At baseline, participants were asked whether they had frequent falls in the past year; no specific prompt regarding the definition of “frequent falls” was given. At the subsequent yearly clinic visits, participants reported whether they had a fall in the past year. Participants also self-reported whether they had arthritis and whether they had difficulty arising from a bed or chair.

We defined hypertension, orthostatic hypotension, and diabetes with standard criteria, as previously described [7]. Field center staff directly measured weight, standing height, and waist circumference. Gait speed was assessed at each visit with a 15-foot walk at the usual pace. Leisure-time physical activity was assessed as a weighted sum of kilocalories expended in specific physical activities [37]. Clinical cardiovascular disease included confirmed coronary heart disease, congestive heart failure, cerebrovascular disease, and peripheral vascular disease [38, 39]. Psychoactive medication use included antidepressants, benzodiazepines, and antipsychotic agents. Depressive symptoms were assessed at baseline with the CES-D scale [40]. Cognitive function testing included the 30-point Mini-Mental State Examination (MMSE) [41] at baseline. Participants reported their general health yearly in five categories (which we grouped as fair-poor, good, and very good-excellent).

ApoE genotype testing was performed as described [42]. Of the 5888 CHS participants for the analyses, 5612 provided consent for genetic testing and 380 did not have necessary DNA stored or were not successfully genotyped, yielding 5232 participants with information on apoE genotype. ApoE4 genotype has been shown to modify

several effects of alcohol consumption in this cohort [33, 43–45] and has been independently associated with BMD and risk for hip fracture in other studies [46, 47].

Statistical analysis

For analyses of hip fracture during follow-up, participants accrued person-time from study entry until their first hospitalization with a hip fracture (the endpoint of interest), death, or June 2002. We tested Kaplan-Meier estimates of survival free of hip fracture with the log-rank test.

In the initial Cox proportional hazards regression analyses, we initially adjusted for age, race, sex, height, and current weight. In multivariable analyses, we further adjusted for smoking status (current/former and pack-years), self-reported difficulty getting out of a chair or bed, arthritis, diabetes, hypertension, clinical cardiovascular disease, previous cancer, current weight, height, weight in early teens (in three categories), visual problems, MMSE score, use of estrogens, thiazide-type diuretics, and thyroid agents, and leisure-time physical activity. Because self-reported health, gait speed, self-reported falls, and orthostatic hypotension are plausible mediators of effects of alcohol, we assessed them in the sensitivity analyses. No violations of the proportional hazards assumption for alcohol were detected using time-varying covariates [48]. Results using a stepwise selection procedure (with entry and stay criteria of 0.15) were similar to those from the full multivariable model and are not shown.

For participants in California and Pennsylvania who underwent bone densitometry, we first assessed the cross-sectional relationship of alcohol use to BMD of the hip and femoral neck (in gm/cm^2) with generalized linear models; both variables were approximately normally distributed. We next assessed the adjusted association of alcohol intake and risk of subsequent hip fracture in the subgroup of participants free of hip fracture at the time of densitometry. Scanned participants had a low incidence of subsequent fracture [36], thereby requiring the grouping of consumers of 7–13 and 14 or more drinks per week for precision; hazard ratios were similar among scanned participants in the two intake groups. Finally, we introduced BMD into these models and compared the regression coefficients (the log of the hazard ratio) associated with alcohol to determine the degree to which the relationship of alcohol intake and BMD mediated the underlying relation of alcohol use and hip fracture. As an exploratory approach, we also examined the projected change in hip fracture rates expected from the observed change in BMD using a meta-analytic estimate of the BMD-hip fracture association.

We assigned indicator variables or set values to the sex-specific mean for participants with missing information for covariates; results excluding these participants were un-

changed. We performed likelihood ratio tests of nested models (for proportional hazards regression) or *F*-tests (for generalized linear models) and tested quadratic trends after centering a linear trend variable.

We performed analyses using two methods to assess alcohol consumption – simple updating and cumulative averaging [49]. In updated analyses, we prospectively assessed the risk of hip fracture in yearly increments, based upon alcohol consumption derived from the preceding questionnaire. In these analyses, we grouped participants who stopped drinking during follow-up with former drinkers at baseline. In cumulatively averaged analyses, we assessed the risk of hip fracture based upon mean consumption from all previous questionnaires. Where missing data on alcohol intake occurred, previous data were carried forward. We also treated plausible intermediates (gait speed, self-reported general health, self-reported falls) as time-varying covariates and assessed the relation of alcohol use, BMD, and subsequent hip fracture with the cumulative average of all reports of alcohol up to the time of scanning.

In beverage-specific analyses, we simultaneously controlled for the standard covariates that we incorporated into other models and the intake of each of the other beverage types [50]. We created a single category of seven or more

servings of each individual beverage per week because the number of participants in categories of 7–13 and 14 or more drinks per week was small.

We conducted prespecified stratified analyses according to median age, sex, and ApoE4 genotype. We tested for interaction by comparing nested models with and without all interaction terms (i.e., each level of intake multiplied by the binary stratifiers). All analyses were conducted using SAS FOR WINDOWS ver. 9.1 (SAS Institute, Cary, N.C.).

Results

Baseline characteristics

The characteristics of CHS participants according to baseline alcohol use are shown in Table 1. Alcohol intake was generally positively associated with male sex and current smoking. Approximately 41% of participants were long-term abstainers.

Average alcohol consumption and risk of hip fracture

A total of 412 cases of hip fracture occurred during follow-up. Median follow-up time was 12.0 years among partic-

Table 1 Selected baseline characteristics of 5865 Cardiovascular Health Study (CHS) participants according to baseline alcohol consumption

Baseline characteristics ^a	Weekly number of drinks					
	None (<i>n</i> =2406)	Former (<i>n</i> =537)	<1 (<i>n</i> =1124)	1–6 (<i>n</i> =999)	7–13 (<i>n</i> =349)	14+ (<i>n</i> =450)
Drinks per week	0	0	0.2±0.2	2.0±1.2	7.8±0.9	20.8±10.3
Age (years)	73.3±5.8	72.8±5.7	72.6±5.5	72.2±5.4	73.0±5.6	72.2±5.0
Female	70%	40%	62%	46%	43%	38%
Black	20%	25%	12%	11%	7%	8%
Body mass index (kg/m ²)	27.2±5.2	26.8±5.1	26.6±4.6	26.3±4.1	25.4±3.6	25.7±3.7
Current smoker	9%	14%	12%	14%	11%	20%
History of:						
Hypertension	62%	64%	56%	52%	48%	63%
Diabetes	20%	27%	12%	11%	8%	11%
Cardiovascular disease	26%	34%	25%	24%	21%	21%
Cancer	13%	13%	15%	16%	19%	17%
Arthritis	57%	53%	51%	46%	47%	45%
Frequent falls	5%	5%	3%	1%	2%	1%
Difficulty arising from bed or chair	3%	6%	4%	3%	1%	2%
Use of:						
Psychoactive medication	15%	15%	11%	9%	9%	9%
Thiazide diuretics	23%	19%	18%	17%	13%	17%
Thyroid agents	9%	5%	9%	10%	9%	6%
Estrogen (women)	7%	11%	15%	17%	21%	21%
Physical activity (kcal)	1531±1911	1523±1934	1746±2078	1999±2156	1968±1937	1964±2263
Mini-Mental Status Exam (MMSE) score (0–30)	27.1±3.0	26.8±3.4	27.8±2.3	27.9±2.3	28.0±2.1	28.2±2.0

^a Means and standard deviations are shown for continuous variables, and proportions (in percentages) are shown for categorical variables

ipants who did not sustain a hip fracture and 7.1 years among those who did. Figure 1 shows Kaplan-Meier estimates of survival free of hip fracture among CHS participants according to baseline alcohol consumption. The risk of hip fracture tended to be highest among abstainers and the heaviest drinkers.

Table 2 shows age-, sex-, race-, height-, and weight-adjusted and multivariable-adjusted analyses of the risk of hip fracture according to alcohol consumption. Risk across the three intermediate drinking categories tended to be similar and 20–25% lower than both abstainers and heavy drinkers, although only the hazard ratios for consumers of <1 drink per week were statistically significant. A test for quadratic trend was significant in basic ($p=0.003$) and multivariable-adjusted models ($p=0.02$). The magnitude of lower risk in the intermediate drinking categories was modestly attenuated after multivariable adjustment and in analyses that incorporated the cumulative average of alcohol intake. Former drinkers were not at higher risk than long-term abstainers. When the three intermediate drinking categories were combined, the multivariable-adjusted hazard ratio compared with long-term abstainers was 0.78 [95% confidence interval (CI): 0.61–1.00; $p=0.04$]; risk in the three intermediate groups also appeared to be statistically different from the risk among heavy drinkers ($p=0.06$).

Results among men and women were highly consistent (p interaction: 0.39). Compared with long-term abstaining women, the hazard ratios among women who consumed <14 and 14 or more drinks per week were 0.77 (95% CI: 0.58–1.03) and 1.15 (95% CI: 0.66–2.01); the corresponding hazard ratios among men were 0.80 (95% CI: 0.50–1.29) and 1.19 (95% CI: 0.60–2.34). There were also no consistent or significant differences in the association of alcohol intake with risk of hip fracture among participants stratified by median age ($p=0.46$). ApoE4

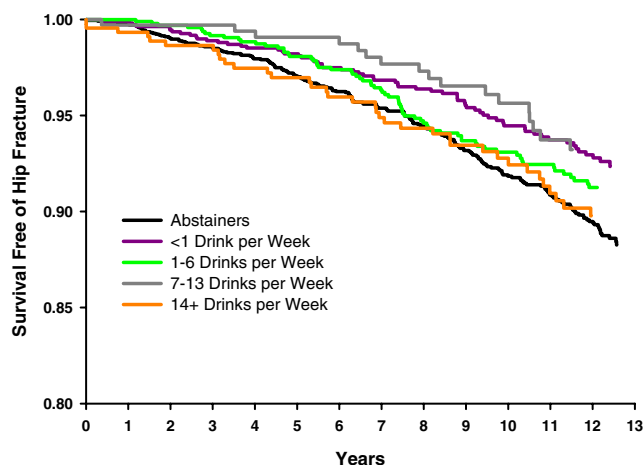


Fig. 1 Kaplan-Meier estimates of survival free of hip fracture among Cardiovascular Health Study (CHS) participants according to baseline alcohol consumption

status was not independently associated with risk of hip fracture (hazard ratio: 1.14; 95% CI: 0.90–1.44). Although there was an interaction of borderline statistical significance ($p=0.05$) between genotype and alcohol intake on risk of hip fracture, this was primarily related to a markedly lower risk of hip fracture among apoE4-positive consumers of <1 drink per week (hazard ratio: 0.38; 95% CI: 0.15–0.96); no other level of consumption significantly interacted with ApoE genotype. We could not assess interaction with race because only 24 African-American participants sustained a hip fracture. Additional adjustment of our main analyses for waist circumference, depressive symptom score, psychoactive medication use, or orthostatic hypotension did not substantially alter our findings.

Beverage type and risk of hip fracture

We explored the association of individual beverage types with risk of hip fracture using updated analyses (Table 3). The hazard ratios for beer tended to be lowest and to parallel those for alcohol overall. Wine intake did not appear to be associated with risk, while liquor intake tended to be associated with higher risk, although individual hazard ratios were not statistically significant.

Average alcohol consumption and BMD

Baseline characteristics of those participants who underwent BMD testing have been published previously [36]. Table 4 shows average BMD at the total hip and femoral neck among the 1567 participants who underwent densitometry based upon their average use of alcohol from baseline to the visit at which the scanning occurred. There was a strong, graded, positive relationship between greater alcohol consumption and greater BMD at both sites, with approximately 5% higher BMD (95% CI: 1–9%) across the range of alcohol intake. BMD was similar among abstainers and consumers of <1 drink per week, a finding which was confirmed in analyses using baseline alcohol consumption. Analyses of individual beverage types (not shown) did not reveal clear differences among beverages; trends between intake and BMD were generally positive in all three cases.

Although ApoE4-positive status itself was modestly associated with lower total hip BMD (-0.014 gm/cm²; 95% CI: -0.029 to 0.001 ; $p=0.08$), we did not find statistical evidence that alcohol consumption interacted with ApoE genotype ($p=0.48$) or sex ($p=0.47$). Interactions of alcohol with age ($p=0.01$) and race ($p=0.01$) were both related to an intake of 14 or more drinks per week. Specifically, among younger and white participants, BMD levels among consumers of 14 or more drinks were higher than any other level of intake. In contrast, among the 29

Table 2 Hazard ratios and 95% confidence intervals^a for risk of hip fracture according to alcohol consumption

	Number of drinks Per week						<i>p</i> value ^b
	None	Former	<1	1–6	7–13	14+	
Simple updating							
Cases	165	102	55	41	22	27	
Basic Model ^c	1.00	0.79 (0.61–1.04)	0.71 (0.53–0.96)	0.72 (0.51–1.01)	0.72 (0.46–1.13)	1.14 (0.76–1.72)	0.06
MV Model ^d	1.00	0.81 (0.62–1.05)	0.76 (0.56–1.03)	0.80 (0.56–1.14)	0.81 (0.51–1.28)	1.18 (0.77–1.81)	0.21
MV with mediators ^e	1.00	0.82 (0.62–1.07)	0.79 (0.58–1.08)	0.87 (0.61–1.24)	0.87 (0.55–1.36)	1.30 (0.85–1.99)	0.25
Cumulative average							
Basic Model ^c	1.00	0.91 (0.54–1.52)	0.75 (0.59–0.95)	0.76 (0.56–1.02)	0.76 (0.50–1.15)	1.19 (0.74–1.90)	0.10
MV Model ^d	1.00	0.84 (0.50–1.43)	0.77 (0.61–0.98)	0.83 (0.61–1.12)	0.82 (0.53–1.26)	1.20 (0.74–1.95)	0.24

^a Values are presented as hazard ratios followed by the 95% confidence intervals (in parenthesis)

^b *p* values derive from likelihood ratio tests of nested models with 5 df

^c The basic model adjusted for age, sex, race, current weight, and height

^d The multivariable (MV) model adjusted for covariates in the basic model and smoking status (current/former and pack-years), difficulty arising from a chair or bed, arthritis, diabetes, hypertension, clinical cardiovascular disease, previous cancer, weight in early teens, leisure-time physical activity, visual problems, MMSE score, and use of estrogens, thiazide-type diuretics, and thyroid agents

^e Plausible mediators included a 15-foot walk time, falls, and self-reported health, all updated yearly

adults above the median age and the 11 black adults who were in the highest drinking category, BMD was similar to abstainers. Alcohol intake was positively related to BMD in white and black and older and younger participants at levels up to 13 drinks per week.

A total of 84 hip fractures occurred following scanning among screened participants. Compared with abstainers, the multivariable-adjusted hazard ratios for hip fracture were 0.75 (95% CI: 0.41–1.35) among consumers of <1 drink per week, 0.96 (95% CI: 0.48–1.91) among consumers of one to six drinks per week, and 0.56 (95% CI: 0.25–1.24; regression coefficient: -0.580) among consumers of seven or more drinks per week. When total hip BMD was added to the multivariable model, the adjusted hazard ratio among consumers of seven or more drinks per week was 0.69 (95% CI: 0.31–1.53; regression coefficient: -0.373), corresponding to a 36% attenuation in the regression coefficients. Thus, approximately 36% of the apparent

effect of the consumption of seven or more drinks per week may be attributable to its effects on BMD.

We also explored an alternate approach to assess the mediating effect of BMD (Fig. 2). Among all participants who underwent densitometry measurements, the mean total hip bone density was 0.829, with a standard deviation (SD) of 0.181. The age-adjusted risk of hip fracture for a 1-SD decrease in total hip BMD in CHS was 3.17 (95% CI: 2.36–4.26), which is comparable to a meta-analytic estimate of 2.6 [51]. Using the meta-analytic estimate for the association of BMD and risk of hip fracture, we estimated the relative risks of hip fracture according to alcohol intake that would be expected solely from the observed differences in BMD. We then compared these to the observed risks to estimate the “non-BMD” effects of alcohol intake. For an intake of 1–13 drinks per week, the hypothesized and observed risks were comparable, suggesting that higher BMD is largely responsible for the lower risk of

Table 3 Adjusted hazard ratios and 95% confidence intervals^a for risk of hip fracture according to updated consumption of individual alcoholic beverages

	Number of drinks per week			
	0	<1	1–6	7+
Beer				
Hazard ratio	1.00	0.66 (0.44–0.99)	0.68 (0.36–1.28)	0.80 (0.37–1.72)
Wine				
Hazard ratio	1.00	1.00 (0.75–1.32)	0.75 (0.48–1.17)	0.89 (0.53–1.50)
Liquor				
Hazard ratio	1.00	0.81 (0.53–1.22)	1.16 (0.74–1.81)	1.30 (0.86–1.96)

^a Values are presented as adjusted hazard ratios followed by the 95% confidence intervals (in parenthesis). Hazard ratios are adjusted for age, sex, race, current weight, height, smoking status (current/former and pack-years), difficulty arising from a chair or bed, arthritis, diabetes, hypertension, clinical cardiovascular disease, previous cancer, weight in early teens, leisure-time physical activity, visual problems, MMSE score, and use of estrogens, thiazide-type diuretics, and thyroid agents

Table 4 Adjusted mean bone mineral densities and 95% confidence intervals^a of the total hip and femoral neck according to average alcohol consumption between study entry and DEXA scanning

	Drinks Per Week						<i>p</i> value ^b
	None (<i>n</i> =345)	Former (<i>n</i> =81)	<1 (<i>n</i> =554)	1–6 (<i>n</i> =334)	7–13 (<i>n</i> =149)	14+ (<i>n</i> =104)	
Total hip							
Basic Model ^c	0.817 (0.803–0.831)	0.841 (0.813–0.870)	0.821 (0.810–0.831)	0.828 (0.814–0.842)	0.849 (0.828–0.870)	0.870 (0.845–0.895)	0.003
MV Model ^d	0.819 (0.805–0.833)	0.843 (0.815–0.871)	0.819 (0.808–0.830)	0.830 (0.816–0.843)	0.850 (0.830–0.871)	0.867 (0.841–0.892)	0.005
Femoral neck							
Basic Model ^c	0.689 (0.677–0.702)	0.716 (0.690–0.741)	0.692 (0.683–0.702)	0.702 (0.690–0.715)	0.724 (0.705–0.742)	0.738 (0.716–0.761)	<0.001
MV Model ^d	0.692 (0.679–0.704)	0.715 (0.690–0.740)	0.691 (0.682–0.701)	0.703 (0.691–0.715)	0.725 (0.707–0.744)	0.736 (0.713–0.759)	<0.001

^a Values are presented as adjusted mean bone mineral densities (in gm/cm²) followed by the 95% confidence intervals (in parenthesis)

^b *p* values derive from *F*-tests with 5 *df*

^c The basic model adjusted for age, sex, race, current weight, and height.

^d The multivariable model adjusted for covariates in the basic model and smoking status (current/former and pack-years), difficulty arising from a chair or bed, arthritis, diabetes, hypertension, clinical cardiovascular disease, previous cancer, weight in early teens, leisure-time physical activity, visual problems, MMSE score, and use of estrogens, thiazide-type diuretics, and thyroid agents

hip fracture in these groups. The observed risk among consumers of 14 or more drinks per week appeared to reflect both their lower risk related to high BMD and a approximately 50% higher risk related to unmeasured non-BMD effects.

Discussion

In this prospective cohort study, alcohol intake had a significant U-shaped relationship with risk of hip fracture, with an approximately 20% lower risk among consumers of up to 13 drinks per week than abstainers, even after multivariable adjustment. At the same time, there was a graded positive relationship between alcohol intake and BMD of the hip.

The occurrence of hip fracture is the final, morbid event for two separate clinical processes – bone loss leading to osteopenia and osteoporosis, and gait instability and imbalance leading to falls. Findings from CHS provide an abundance of evidence for the intricate interplay of alcohol with these two processes. In several previous, typically short studies, alcohol intake was not associated with falls in the elderly [4–6]. Indeed, the cross-sectional relationship of alcohol intake and frequent falls is inverse, even in CHS [7]. However, when examined prospectively, alcohol intake of 14 or more drinks per week is linked to a 25% higher risk of self-reported falls in CHS [7]. At the same time, alcohol intake may be associated with greater bone density at the hip, which, given the strong relationship of BMD with several types of fracture [1], would be expected to

reduce risk of hip fracture. The competing balance between the effects of alcohol on these dual processes appears to explain the U-shaped relationship seen here and the great diversity of findings in previous studies of alcohol and hip fracture.

Our findings on BMD are consistent with those reported by several other studies that have associated moderate drinking with higher BMD. Sex steroid hormone levels

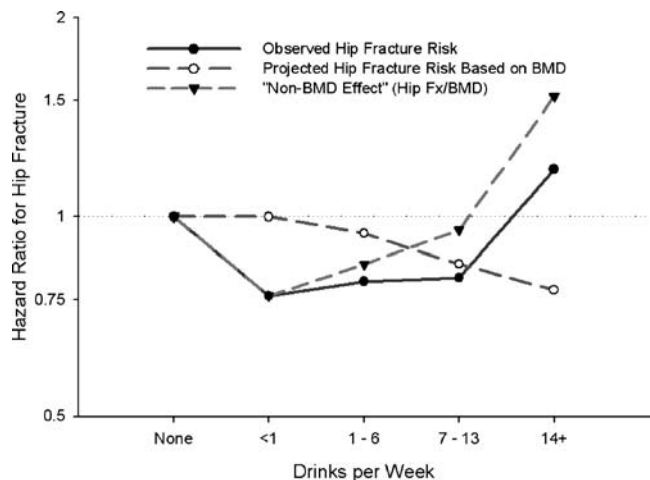


Fig. 2 Multivariable-adjusted hazard ratios for risk of hip fracture among CHS participants according to alcohol consumption (solid line with filled circles), imputed hazard ratios for risk of hip fracture after accounting for alcohol-BMD relationship (dashed line with open circles), and the estimated residual effect of alcohol after accounting for BMD (dashed line with filled triangles). The risk associated with changes in BMD was imputed by estimating that observed differences in total hip BMD (Table 4) corresponded to a 2.6-fold increase in risk for each decrease in BMD of 0.181 (1-SD) in gm / cm²

may play a key role in this regard. Several observational studies have found higher levels of sex steroids among moderate drinkers [13, 14, 52]. Hines et al. also found that a common polymorphism in the alcohol dehydrogenase 1C gene modifies the relationship of alcohol intake with levels of dehydroepiandrosterone sulfate (DHEA-S) and sex-hormone binding globulin [53]. Most definitively, a 24-week randomized trial of alcohol consumption among 51 premenopausal women demonstrated that alcohol produces dose-dependent increases in both estrone sulfate and DHEA-S [54]; a smaller trial found similar increases in DHEA-S among both men and women [55]. The relationship of alcohol intake with higher levels of sex steroid hormones is also supported by the strong epidemiological relationship of moderate drinking with higher risk of breast cancer [56].

The fact that heavier drinking did not lower risk of hip fracture, despite being most strongly associated with higher BMD, presumably reflects effects of alcohol outside of bone mineralization, such as on cerebellar or peripheral nerve function [57, 58]. We estimate that these effects would lead to an approximately 50% increase in the risk of hip fracture among heavier drinkers were they not balanced by higher BMD, a magnitude of risk quite similar to that estimated from a meta-analysis of three studies that included adjustment for BMD (relative risk: 1.68) [29]. Another possibility is that the higher BMD among heavy alcohol drinkers does not reflect a proportionate increase in bone strength, akin to the apparently discrepant effects of fluoride on BMD and hip fracture risk [59, 60].

CHS has both strengths and limitations. Because of its rich, longitudinal data collection, we had the ability to conduct a comprehensive analysis of the relationship between alcohol consumption and hip fracture, the most devastating fracture associated with osteoporosis. We had extensive information on alcohol intake and type of alcohol consumed annually over a 12-year period. Our analytical strategies incorporated these repeated assessments using both simple updating and a cumulative average approach. We studied both men and women and adjusted for important covariates often unavailable in other studies, such as physical activity, teenage weight, and detailed medication use. Finally, although BMD was measured in only about one-quarter of the subjects, we estimated the degree to which the alcohol-fracture associations could be explained by BMD.

On other hand, specific limitations of our study warrant discussion. Although CHS is a population-based cohort study, our results are most appropriately generalized to healthy, community-dwelling older adults. CHS did not perform adjudicated reviews of diagnoses of hip fracture and hence relied upon discharge diagnoses of hip fracture, although active and passive surveillance of

hospitalizations was performed, and most evidence suggests that such misclassification is not likely to be extensive [61, 62]. For the same reason, we were unable to evaluate vertebral and other fractures that do not routinely require hospitalization.

It is also difficult to determine the exact nature of the dose-response relationship with precision, especially at high levels of intake and for individual beverage types. In many cases, relative risks for individual categories of consumption were not statistically significant even when more powerful trend tests were. We were also limited by the small number of subsequent fractures among participants who underwent BMD screening, conceivably related to clinical decisions prompted by the results of screening (which were conveyed to participants) [36], although even our limited results suggested that BMD had a substantial mediating role.

We had limited information on lifelong drinking patterns and did not have sufficient variation to judge how changes in alcohol use affect risk of hip fracture. We also had no data on the timing of last alcohol use prior to the occurrence of hip fracture. Although alcohol intake is acutely associated with non-fatal injury [63, 64], its relationship with hip fracture per se still requires clarification. Finally, we did not have extensive information on gait instability, balance, and the frequency and severity of falls among CHS participants, limiting our ability to define the pathways by which heavier drinking increases hip fracture risk relative to moderate drinking.

In summary, alcohol consumption had a U-shaped relationship with risk of hip fracture among older adults, while also being positively associated with BMD at the hip. Our results underscore the complex relationship of alcohol use and fracture risk in the elderly, owing to its multifaceted effects on both bone and other organ systems, and are consistent with guidelines [65] that limit alcohol use among older adults to one drink per day.

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