Association of fractures with caffeine and alcohol in postmenopausal women: the Iowa Women's Health Study

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Abstract

Objective: To assess whether alcoholic and caffeinated beverages are associated with risk of fractures in women.
Setting: Population-based sample surveyed by post.
Subjects: A total of 34 703 postmenopausal Iowan women aged 55–69 years were surveyed.
Design: A cohort of women reported alcoholic and caffeinated beverage intake and were followed for 6.5 years for fracture occurrence. Relative risks (RR) and 95% confidence intervals (CI) were computed using Cox proportional hazards regression. Covariates included age, tobacco use, physical activity, body mass index (BMI), waist to hip ratio (WHR), oestrogen use and calcium intake.
Results: At least one fracture was reported by 4378 women (389 upper arm, 288 forearm, 1128 wrist, 275 hip, 416 vertebral and 2920 other fractures). The adjusted RR for highest versus lowest caffeine intake quintiles was 1.09 (95% CI 0.99–1.21) for combined fracture sites. Wrist fractures were associated positively (RR for extreme quintiles 1.37, 95% CI 1.11–1.69) and upper arm fractures were negatively associated (RR 0.67, 95% CI 0.48–0.94) with caffeine intake. The age-adjusted RR of total fractures for highest versus lowest frequency of beer usage was 1.55 (95% CI 1.25–1.92) and for liquor was 1.25 (95% CI 1.03–1.54). No other association was found between any specific fracture site and alcohol intake.
Conclusions: We found a modest increase in fracture risk associated with highest caffeine intake, varying by site. Alcohol intake was low, but it also showed a weak positive association with fracture risk.

Keywords
Fractures
Postmenopausal women
Caffeine
Alcohol

Osteoporosis, which is associated with an increased risk of fracture, is highly prevalent in elderly women. Estimated annual health care costs in the USA related to osteoporosis are at least $10 billion dollars per year[1]. Prevention of bone loss provides a cost-effective solution to this disease. An association of caffeinated and alcoholic beverages with fracture incidence could have important public health implications due to their widespread use in American society[2,3].

Some animal studies have shown that caffeine administration has teratogenic effects on ossification[4,5], while others found neither bony histomorphometric changes[6], nor calcium loss from bone[7]. Adult rats administered caffeine showed a negative calcium balance[8] possibly due to increased urinary and faecal calcium excretion[8,9]. In some[10–15], but not all[16,17], human metabolic studies, caffeine administration increased urine and faecal calcium excretion, regardless of sex, age or menopausal status. In one of the best studies, a double-blind, placebo-controlled, randomized cross-over trial, 400 mg day^{-1} of caffeine had no effect on the calcium economy of premenopausal women[16]. Some studies found a negative association between caffeine intake and bone mass[18–22] while others found no association[23–28] regardless of site. Yet another found an increase in bone loss associated with caffeine intake only at low calcium intakes[17]. Several epidemiological studies[29–32] have reported an increased risk of hip fractures associated with a caffeine consumption of greater than at least 190 mg day^{-1} although others found no association[33–38]. Two studies found a non-significant increase in forearm fractures and proximal humeral fractures associated with increased caffeine intake[30,39], however, another found a non-significant decrease[34].

Alcohol appears to have a multifactorial role in the genesis of fractures. Animal studies suggest alcohol suppresses bone formation[40–43]. Human studies have also shown abnormal bone histology[44,45], reduced rates of bone formation and reduced active mineralizing surfaces[46–48] in alcoholics. Several investigations reported low bone mass in alcohol users[46,47,49–53] but the evidence is inconsistent[18–20,25,26,48,54–59]. A few have even found

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alcohol use associated with an increase in bone mineral density[27,60–62]. In addition to a possible direct toxic effect on bone[42,47], alcohol consumption increases the likelihood of trauma resulting in fractures[46,63].

This study examined the association of caffeine and alcohol use with incidence of fracture in a large cohort of postmenopausal women followed for 6.5 years. In addition, we examined possible interactions of calcium intake with caffeine and alcohol and controlled for major known risk factors.

Methods

The Iowa Women's Health Study is a prospective cohort study designed to examine risk factors for cancer and other diseases in postmenopausal women initially aged 55–69 years. Potential participants were randomly selected from the 1985 Iowa Department of Transportation driver's licence list, which contained approximately 94% of all age-eligible women living in Iowa. A mailed questionnaire was sent in January 1986 to 99 826 random women; 1796 participants were ineligible due to wrong age or gender leaving 98 030 eligible. Of these, 41 836 (42.7%) returned questionnaires. Compared to responders, non-responders, as evaluated by their driver's licence and 1980 census information, were about 3 months younger, had 0.4 mg m^{-2} greater BMI, and lived in counties that were more rural and had slightly lower mean income[64].

The posted survey included a semiquantitative food frequency questionnaire developed by Willett *et al.*[65]. It included questions on dietary supplement use, caffeinated beverage use and alcohol use in addition to usual dietary habits over the past year. For each beverage a commonly used portion size was defined (one glass, bottle or can of cola or beer, one cup of coffee or tea, 4 oz of red or white wine or one drink or shot of liquor). Participants then chose one of nine categories ranging from never or less then once per month to six or more per day to indicate the frequency of average consumption of the beverage over the past year. Frequencies were determined individually for coffee, non-herbal tea, cola, low calorie cola, beer, red wine, white wine and liquor. Preparation methods were not ascertained for coffee and tea. Intake in milligrams per day for caffeine or grams per day for alcohol was computed by multiplying the frequency of consumption of each beverage by the caffeine or ethanol content of the specific beverage. Values used for caffeine were 134 mg per cup of coffee, 64 mg per cup of tea and 46 mg per glass, bottle or can of cola. Values used for ethanol were 13.2 g per glass, bottle or can of beer, 10.8 g per 4 oz of red or white wine and 15.1 g per drink or shot of liquor. The average daily caffeine or alcohol consumption was determined by summing the contribution from each beverage. For major nutrients Willett *et al.*[66] and Giovannucci *et al.*[67] have documented the reproducibility of this instrument and its correlation with food records. In addition, Munger showed high reproducibility of reported caffeine (Pearson's $r=0.95$) and alcohol (Pearson's $r=0.99$) intakes using this instrument in our cohort of Iowa women[68].

The questionnaire enquired about the frequency of moderate (e.g. walking, gardening) and vigorous (e.g. jogging, racquet sports) activity. These were combined into low, medium and high activity levels. BMI (measured in kg m^{-2}) was calculated from current self-reported height and weight. Respondents took body measurements with the aid of a friend and an enclosed tape measure. We calculated the WHR by dividing the reported waist measurement by the reported hip measurement. The body size measurements obtained by these methods were accurate and reliable[69]. In addition, the questionnaire included demographic information, smoking history and health history encompassing medication usage and past illnesses.

Follow-up postal surveys identified interim health changes in October 1987 (91% response), August 1989 (90% response) and July 1992 (83% response). The following question assessed the occurrence of fractures since baseline: 'Have you suffered a fracture (broken bone) since 1 February 1986 which required treatment by a doctor? If yes, which of the following fractures? Upper arm, forearm, wrist, ribs, hip, vertebra (part of the spine), other.' We considered an incident fracture as that which occurred after the baseline questionnaire. Women with multiple types of fractures were considered incident cases for each type. However, in analyses of total fractures, time to first fracture was used.

For this analysis, women were excluded if they were not postmenopausal ($n=569$), had previous cancer ($n=3808$), only partially completed the food frequency questionnaire (>30 blank answers) ($n=2571$) or showed extreme energy intake (<600 or >5000 kcal day^{-1}) ($n=432$). A total of 34 703 women remaining formed the cohort for analysis. Although participants were not excluded based on race or ethnicity, 99.2% of respondents were of caucasian ethnicity, thus precluding race-specific analysis.

Our hypothesis was that women who consumed a greater amount of caffeine or alcohol were at higher risk of bone fracture. Caffeine consumption was grouped into quintiles. Alcohol use was categorized as 0 g day^{-1}, >0 and <4 g day^{-1}, or ≥4 g day^{-1}. Person years of follow-up were calculated from the time of the 1986 baseline questionnaire to report of the first fracture, death or until the date of the last completed questionnaire. Deaths were found by linkage to Iowa death certificates and the National Death Index.

Means, medians and ranges were used to describe continuous variables and frequencies were determined for categorical variables. The prevalence of other osteoporosis or fracture risk factors were examined within categories of alcohol or caffeine intake. Cox

Table 1 Distributions of selected variables by alcohol and caffeine use

	Alcohol (g day^{-1})			Caffeine (mg day^{-1})		
	0	>0 to <4	⩾4	Quintile 1	Quintile 3	Quintile 5
Current smoker (%)	10.9	13.2	27.4	7.2	13.4	29.6
Current oestrogen use (%)	9.7	12.4	13.2	11.8	12.4	8.8
High physical activity (%)	23.7	26.1	26.9	27.6	25.8	20.8
Calcium >895.5 mg day^{-1} (%)*	58.7	62.0	61.2	61.7	59.9	58.5
BMI >27.43 kg m^{-2} (%)†	46.0	37.6	27.5	42.6	39.6	36.9
WHR >0.8526 (%)†	44.3	36.0	33.6	43.4	40.4	36.2

* Calcium >895.5 mg day^{-1} represents the three upper quintiles of calcium intake.
† BMI >27.43 kg m^{-2} and WHR >0.8526 represent the two upper quintiles of measurements.

proportional hazards regression was used to calculate age-adjusted and multivariate-adjusted relative risks with 95% confidence intervals. We included as covariates age (continuous), tobacco use (never, current, former), physical activity (high, medium, low), BMI (quintiles), WHR (quintiles) and oestrogen use (never, current, former). We also adjusted for calcium (dietary and supplemental) and total energy intake (each as quintiles). Modelling proceeded in a stepwise fashion adding each variable sequentially, observing for statistical significance and confounding with each addition. Interactions of caffeine with calcium and of alcohol with calcium were tested using cross-product terms in the model. The Mantel test for linear trend in relative risks across levels of independent variables was computed. Statistical significance was chosen as the 0.05 level.

Results

Participants had a mean age of 61.6 years and were, on average, postmenopausal for 13.9 years. Median caffeine consumption was 201 mg day^{-1} with a range from 0 to 1347 mg day^{-1}; 71.2% reported drinking coffee at least one time per month, 57.9% drank tea this often and 21.7% drank carbonated cola beverages at least once per month. Alcohol intake was relatively low in this cohort: median alcohol use was 0 g day^{-1} with a range from 0 to 118 g day^{-1}. Reported consumption of specific beverages at least one time per month was 18.1% for beer, 26% for liquor and 18.7% for wine.

Table 1 shows that alcohol intake was associated positively with smoking and oestrogen use and negatively with BMI and WHR. Caffeine was associated positively with smoking but negatively with oestrogen use, physical activity, BMI and WHR.

Four thousand three hundred and seventy-eight women reported at least one fracture during 187 035 person years of observation, giving an incidence rate of 23 per 1000 person years. Of these, 389 reported upper arm fractures, 288 forearm fractures, 1128 wrist fractures, 275 hip fractures, 416 vertebral fractures and 2920 were reported as rib or other fractures.

We examined the relation of other risk factors with fractures (Table 2). Although associations by fracture site are not shown, age-adjusted current oestrogen use was found to have an inverse association for all different fracture sites (RR ranged from 0.37 to 0.67) except vertebral (RR 1.09), in addition to being inverse for total fractures (fractures at all sites combined). Adjusted

Table 2 Relative risks (95% CI) of total fracture by other risk factors

	Age adjusted	Multivariate adjusted*
Oestrogen use		
Never	Reference	Reference
Former	1.11 (1.04–1.19)	1.09 (1.02–1.17)
Current	0.74 (0.67–0.83)	0.73 (0.65–0.82)
Smoking		
Never	Reference	Reference
Former	1.05 (0.98–1.14)	1.04 (0.96–1.13)
Current	1.12 (1.03–1.22)	1.03 (0.97–1.17)
BMI (kg m^{-2})		
< 22.89	Reference	Reference
22.90–25.03	0.87 (0.79–0.96)	0.89 (0.81–0.98)
25.04–27.41	0.91 (0.83–0.99)	0.90 (0.82–0.99)
27.43–30.62	0.86 (0.78–0.94)	0.86 (0.78–0.95)
>30.63	0.90 (0.82–0.99)	0.89 (0.80–0.99)
Test for trend	$P=0.03$	$P=0.03$
WHR		
<0.7643	Reference	Reference
0.7644–0.8090	0.98 (0.99–1.08)	1.01 (0.92–1.11)
0.8091–0.8525	0.97 (0.88–1.07)	1.02 (0.92–1.12)
0.8526–0.9063	1.00 (0.91–1.10)	1.04 (0.94–1.15)
>0.9064	1.01 (0.92–1.10)	1.06 (0.96–1.19)
Test for trend	$P=0.79$	$P=0.23$
Physical activity		
Low	Reference	Reference
Medium	1.00 (0.93–1.07)	1.00 (0.93–1.08)
High	0.98 (0.91–1.05)	0.97 (0.90–1.05)
Test for trend	$P=0.50$	$P=0.18$
Calcium (mg day^{-1})		
<628	Reference	Reference
628–895	1.03 (0.94–1.14)	1.02 (0.92–1.13)
896–1187	1.04 (0.94–1.14)	1.03 (0.93–1.14)
1188–1545	1.02 (0.93–1.12)	1.02 (0.91–1.13)
>1545	1.11 (1.01–1.22)	1.11 (1.01–1.24)
Test for trend	$P=0.08$	$P=0.08$

* Adjusted for age (continuous), caffeine (<65, 65–145, 146–343, 344–504, >504 mg day^{-1}), alcohol (0, >0 to <4, ⩾4 g day^{-1}), calories (600–1301, 1302–1590, 1591–1865, 1866–2238, >2238 kcal day^{-1}) and the other variables in the table.

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Table 3 Relative risks (95% CI) of fracture by quintiles of caffeine usage

	Caffeine (mg day^{-1})					Test for trend
	0–65.1	65.2–145.0	145.1–343.4	343.5–503.7	⩾503.8	
Total fractures						
n	826	889	900	849	914	
Age adjusted	Reference	1.07 (0.97–1.17)	1.09 (0.99–1.19)	1.03 (0.94–1.14)	1.15 (1.05–1.27)	$P=0.02$
Multivariate*	Reference	1.05 (0.95–1.15)	1.06 (0.97–1.17)	1.01 (0.91–1.11)	1.09 (0.99–1.21)	$P=0.22$
Wrist fractures						
n	174	239	252	238	225	
Age adjusted	Reference	1.37 (1.12–1.66)	1.44 (1.19–1.66)	1.38 (1.14–1.68)	1.35 (1.11–1.65)	$P=0.006$
Multivariate*	Reference	1.35 (1.11–1.65)	1.42 (1.16–1.73)	1.38 (1.13–1.70)	1.37 (1.11–1.69)	$P=0.005$
Forearm fractures						
n	62	54	55	55	62	
Age adjusted	Reference	0.86 (0.60–1.24)	0.88 (0.61–1.26)	0.89 (0.62–1.28)	1.03 (0.72–1.47)	$P=0.82$
Multivariate*	Reference	0.83 (0.57–1.21)	0.88 (0.60–1.28)	0.86 (0.59–1.26)	1.04 (0.72–1.52)	$P=0.78$
Upper arm fractures						
n	101	77	85	60	66	
Age adjusted	Reference	0.75 (0.56–1.01)	0.83 (0.62–1.11)	0.59 (0.43–0.82)	0.68 (0.50–0.92)	$P=0.005$
Multivariate*	Reference	0.76 (0.56–1.03)	0.83 (0.62–1.13)	0.61 (0.44–0.85)	0.67 (0.48–0.94)	$P=0.009$
Hip fractures						
n	57	59	55	51	53	
Age adjusted	Reference	1.03 (0.72–1.49)	0.98 (0.67–1.42)	0.93 (0.64–1.36)	1.05 (0.72–1.52)	$P=0.97$
Multivariate*	Reference	1.03 (0.71–1.48)	0.93 (0.63–1.35)	0.88 (0.60–1.30)	0.92 (0.62–1.36)	$P=0.49$
Vertebral fractures						
n	90	87	84	77	78	
Age adjusted	Reference	0.96 (0.72–1.29)	0.94 (0.70–1.26)	0.88 (0.65–1.19)	0.94 (0.70–1.28)	$P=0.55$
Multivariate*	Reference	0.94 (0.69–1.28)	0.96 (0.70–1.30)	0.89 (0.65–1.22)	0.88 (0.64–1.22)	$P=0.42$

* Adjusted for age (continuous), alcohol (0, >0 to <4, ⩾4 g day^{-1}), calcium (<628, 628–895, 896–1187, 1188–1545, >1545 mg day^{-1}), oestrogen (current, former, never user), smoking (current, former, never user), activity (high, medium, low levels), BMI (<22.89, 22.90–25.03, 25.04–27.41, 27.43–30.62, >30.63 kg m^{-2}), calories (600–1301, 1302–1590, 1591–1865, 1866–2238 kcal day^{-1}), WHR (<0.7643, 0.7644–0.8090, 0.8091–0.8525, 0.8526–0.9063, >0.9064).

for age, prior oestrogen use was associated with a slightly increased risk of total fractures (RR 1.11, 95% CI 1.04–1.19). Current smokers experienced a slight increase in risk of total fractures (RR 1.12, 95% CI 1.03–1.22), mainly due to a significantly increased risk of vertebral fractures (RR 1.79, 95% CI 1.37–2.26) and hip fractures (RR 1.47, 95% CI 1.06–2.03). Former smokers also experienced a slightly increased fracture risk. Fracture incidence was associated negatively with BMI. This negative association (comparing the highest versus lowest quintiles) was greatest for hip fractures (RR 0.50, 95% CI 0.35–0.72) and vertebral fractures (RR 0.62, 95% CI 0.45–0.85), and attenuated in upper extremity fractures (upper arm: RR 0.91, 95% CI 0.67–1.22; wrist: RR 0.79, 95% CI 0.65–0.95; forearm: RR 1.01, 95% CI 0.70–1.46). A greater WHR was not associated (comparing the highest versus lowest quintiles) with increased risk of total fractures (RR 1.01, 95% CI 0.92–1.10), but it was for vertebral fractures (RR 1.42, 95% CI 1.02–1.97). However, increasing WHR was associated inversely with wrist fracture (RR 0.68, 95% CI 0.57–0.82). Other fractures sites revealed no WHR association. There was no association seen between the physical activity index and fractures. Finally, increased calcium intake was associated with a slightly greater risk of fracture (trend $P=0.08$, Table 2).

Table 3 shows a weak positive association between total fractures and the quintiles of caffeine usage. The age-adjusted relative risk for the highest vs lowest quintile of caffeine was 1.15 (95% CI 1.05–1.27). Adjustment for age, calcium intake, oestrogen use, smoking, alcohol intake,

Table 4 Age-adjusted relative risks (95% CI) of fractures by type of caffeinated beverage

	Frequency					Test for trend
	< 1/month	1–4/month	2–7/week	2–5/day	⩾6/day	
Coffee (cups)						
Total fractures	Reference	0.99 (0.89–1.11)	1.00 (0.91–1.09)	1.02 (0.94–1.09)	1.11 (0.97–1.26)	$P=0.12$
Tea (cups)						
Total fractures	Reference	0.99 (0.92–1.07)	0.95 (0.88–1.03)	1.07 (0.96–1.20)	0.72 (0.44–1.19)	$P=0.26$
Cola (glasses)						
Total fractures	Reference	0.99 (0.92–1.06)	1.06 (0.95–1.18)	1.11 (0.93–1.33)	1.25 (0.96–1.60)	$P=0.04$

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physical activity level, BMI, WHR and energy intake attenuated the association (RR = 1.09, trend $P = 0.22$). The caffeine association differed according to fracture site. There was a statistically significant positive association (trend $P < 0.01$) of caffeine intake and wrist fractures, although relative risks did not increase monotonically. In contrast, there was an inverse association (trend $P < 0.01$) between caffeine intake and incidence of upper arm fractures, and no association between caffeine use and hip, vertebral or forearm fractures. For no fracture site was there any statistically significant interaction between calcium intake and caffeine consumption (data not shown).

Fractures were analysed in relation to dietary source of caffeine (Table 4). The highest category of coffee drinkers ($\geq$6 cups day^{-1}) were at non-significantly greater risk of fracture at any site overall (RR 1.11, 95% CI 0.97–1.26) compared to those who drank coffee less than once per month (trend $P = 0.12$). Cola intake also showed a positive association (trend $P = 0.04$) with risk of total fractures, with a relative risk of 1.25 (95% CI 0.96–1.60) for $\geq$6 glasses day^{-1}. There was no association noted for tea consumption (trend $P = 0.26$). No other fracture site revealed an association by source of caffeine (data not shown).

There was a weak positive association between alcohol intake and total fracture risk (Table 5). The age-adjusted relative risk for those consuming at least 4 g of alcohol day^{-1} compared to those with no intake was 1.09 (95% CI 1.02–1.18). There was no association for any specific fracture site (Table 5) nor any statistically significant interaction between calcium and alcohol intake on fracture risk (data not shown). In a supplemental analysis (not shown), we divided alcohol intake for drinkers into quintiles (upper quintile consumed 13–118 g day^{-1} of alcohol), and there was no statistically significant relation between recategorized alcohol and total or site-specific fracture incidence.

Analysis by different sources of alcohol revealed an increased risk for total fracture for those in the highest category of intake of beer (age-adjusted RR 1.55, 95% CI 1.25–1.92) and liquor (RR 1.25, 95% CI 1.03–1.54), but not for wine (Table 6). There was no association found between any other site by alcohol source (data not shown).

Discussion

This study found positive but modest age-adjusted associations of caffeine intake and alcohol consumption with overall risk of fracture. Neither association with fracture risk remained statistically significant after adjustment for several possible confounding variables. However, the associations varied somewhat by fracture site and type of caffeinated or alcoholic beverage.

Table 5 Relative risks (95% CI) of fractures by grams of alcohol use

	Alcohol (g day^{-1})			Test for trend
	0	> 0 to < 4	⩾ 4	
Total fractures				
n	2300	1104	974	
Age adjusted	Reference	1.11 (1.03–1.19)	1.09 (1.02–1.18)	$P = 0.02$
Multivariate*	Reference	1.10 (1.02–1.18)	1.06 (0.98–1.15)	$P = 0.17$
Wrist fractures				
n	591	287	250	
Age adjusted	Reference	1.12 (0.97–1.29)	1.10 (0.94–1.27)	$P = 0.23$
Multivariate*	Reference	1.07 (0.92–1.24)	1.04 (0.88–1.22)	$P = 0.65$
Forearm fractures				
n	150	74	64	
Age adjusted	Reference	1.13 (0.86–1.50)	1.10 (0.82–1.47)	$P = 0.54$
Multivariate*	Reference	1.11 (0.83–1.48)	1.07 (0.77–1.47)	$P = 0.15$
Upper arm fractures				
n	224	83	82	
Age adjusted	Reference	0.85 (0.66–1.10)	0.95 (0.73–1.22)	$P = 0.67$
Multivariate*	Reference	0.90 (0.69–1.16)	1.03 (0.78–1.36)	$P = 0.83$
Hip fractures				
n	160	62	53	
Age adjusted	Reference	0.91 (0.68–1.22)	0.90 (0.66–1.23)	$P = 0.50$
Multivariate*	Reference	0.92 (0.68–1.24)	0.79 (0.57–1.10)	$P = 0.17$
Vertebral fractures				
n	229	100	87	
Age adjusted	Reference	1.02 (0.81–1.29)	1.01 (0.79–1.30)	$P = 0.92$
Multivariate*	Reference	1.01 (0.79–1.28)	0.83 (0.64–1.09)	$P = 0.18$

* Adjusted for age (continuous), caffeine (<65, 65–145, 146–343, 344–504, >504 mg day^{-1}), calcium (<628, 628–895, 896–1187, 1188–1545, >1545 mg day^{-1}), oestrogen (current, former, never user), smoking (current, former, never user), activity (high, medium, low levels), BMI (<22.89, 22.90–25.03, 25.04–27.41, 27.43–30.62, >30.63 kg m^{-2}), calories (600–1301, 1302–1590, 1591–1865, 1866–2238 kcal day^{-1}), WHR (<0.7643, 0.7644–0.8090, 0.8091–0.8525, 0.8526–0.9063, >0.9064).

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Table 6 Age-adjusted relative risks (95% CI) of fractures by type of alcoholic beverage

	Frequency				Test for trend
	< 1/month	1–4/month	2–7/week	⩾2/day	
Beer (glasses)					
Total fractures	Reference	1.09 (1.00–1.20)	1.03 (0.90–1.18)	1.55 (1.25–1.92)	$P=0.0002$
Liquor (glasses)					
Total fractures	Reference	1.09 (1.00–1.18)	1.07 (0.96–1.19)	1.25 (1.03–1.54)	$P=0.04$
Wine (glasses)					
Total fractures	Reference	1.06 (0.99–1.14)	1.07 (0.92–1.25)	0.99 (0.82–1.20)	$P=0.96$

We found a 35% greater risk of wrist fracture in the highest quintile of caffeine use. We found a non-significant decrease in the risk of forearm fractures at modest intakes of caffeine. Kreiger *et al.*[34] found a non-significant decrease in risk (RR 0.9) of wrist fracture in women who drank >3 cups of coffee day^{-1}. Kelsey *et al.* found a non-significant increase (RR 1.1) in distal forearm fractures in those with high lifetime caffeine intake[39]. Hunter *et al.* also found a non-significant increase (RR 1.08) in forearm fractures[30]. For our analysis we distinguished between wrist and forearm fractures, although we made no separation among the types of forearm fractures (i.e. midshaft vs distal) or between carpal vs distal forearm fractures. In addition, fracture sites were self-reported without radiological confirmation.

We found a significant moderate inverse association between upper arm fractures and caffeine intake. Kelsey *et al.*, however, found a non-significant 10% increase in proximal humeral fractures with high caffeine intake[39]. Although our study included a large number of fractures (389 upper arm fractures vs 79 proximal humeral fractures in Kelsey's study), we did not ascertain the exact site of fracture.

There was no statistically significant association found between hip fractures and caffeine use. Most other studies have found a modest to strong positive association between the two. Holbrook *et al.* found a non-significant relative risk of 1.1 of hip fracture per 352 mg caffeine consumption[33]. In the Framingham study, Kiel *et al.* found an 82% increase in hip fractures with heavy caffeine use (>2.5 cups of coffee day^{-1})[29]; while Hunter *et al.*[30] found a statistically significant relative risk of 2.10 for hip fracture in those women consuming more than 817 mg of caffeine day^{-1}. However, none of these studies controlled for all of the major variables associated with osteoporosis, and all had lower numbers of fractures than our study.

We found no association between vertebral fractures and caffeine. A cross-sectional study of premenopausal women by Picard *et al.* found no relationship between previous coffee consumption and lumbar bone mineral density[26].

Total fracture incidence increased slightly with increased alcohol use, an association attenuated upon multivariate analysis. In examining the different sources of alcohol (beer, liquor, wine), only those drinking six or more glasses of beer or liquor per day showed a significantly increased risk of overall fractures. Findings from other studies have conflicted. Kelsey *et al.* found no increased risk of upper extremity fracture with alcohol use[39]. The Nurses' Health Study found an increased risk for upper extremity and hip fracture[30]. Felson *et al.* also found an increased risk of hip fracture which appeared to be attenuated in those over 65 years[70]. Others found no increased risk of hip fracture[31,33,34,71]. There is some evidence that moderate intake of alcohol may be beneficial in conserving bone mass after menopause[27,60,61,72,73]. It is unclear whether alcohol may exert an effect by direct toxic effects on bone[42], increase in falls or a combination of the two. Our cohort had a low intake of alcohol, which affected the precision of effect estimates for alcohol drinking.

The present study has several strengths and limitations. The study began in 1986, prior to widespread screening for osteoporosis and use of newer osteoporosis drugs like bisphosphonates, both of which otherwise could have been confounding variables. Because of the prospective design, the potential for recall bias was greatly reduced. The follow-up response rates were good. The baseline response was low, possibly affecting study generalizability, but respondents and non-respondents were similar in several respects[65]. Semiquantitative food frequency questionnaires have been shown to have good reliability, particularly in relation to caffeine and alcohol[67,69,74,75], although alcohol intake is widely believed to be underreported. Intake was measured only once prior to fracture occurrence; a single assessment may not reflect lifetime intake. In addition, caffeine content of coffee or tea varies according to type and brewing methods, and individuals may report varying amounts based on different ideas of what constitutes one cup. Date of fracture occurrence and site of fracture were obtained by self-report, which is undoubtedly subject to error. Reassuringly, the observed hip fracture rate approximated that from the National Hospital Discharge Survey[76]. In addition, the observed wrist fracture rate was similar to that reported by Cleghorn[77]. Colditz *et al.* reported a 100% correlation

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between self-reported fracture and medical record review ($n = 30$)[78]; however, this was a study of nurses and may not be generalizable to the rest of the population. Bush *et al.* reported a 91% agreement between self-reported fracture and medical record review, although self-reported fractures tended to be overreported[79]. Nevitt *et al.* found high accuracy in self-reported fractures, also with a tendency to overreport; they also found the site identification to be quite accurate[80]. Munger *et al.* reported high validity of hip fracture self-reports in our cohort[81]. Our study did not assess the cause of the fractures nor did it have data on bone mineral density. No distinction could be made between fractures due to minimal vs high impact trauma. Thus, we may have included non-osteoporotic-related fractures.

Several major correlates related to altered bone mass were included in the multivariate analysis. Consistent with other studies, current postmenopausal oestrogen use[19,82,83] and BMI[18,37,53,82] were associated with lower risk of fractures. WHR was not associated with an increased risk of total fractures, whereas the only other study examining this variable found a non-significant decrease in distal forearm fractures and a significant increase in proximal humeral fractures with greater WHR[39]. Both current and former smokers appear to be at increased risk of fracture, a finding from some[19,23,82] but not all studies[25,26,30,37,53,83,84]. Physical activity and total fractures were not associated, in agreement with some[39,86], but not all[31,35,37], studies. Many studies have found no association between calcium and bone mass and/or fracture[18,19,25,31,53,55,58,71,85,86] while others have shown increased bone mass and/or decreased fractures with increased calcium intake[20,26,27,62,87,88]. We found that high intakes of calcium were associated with slightly greater risk of fractures overall, but the relative risk was only 1.11 and borderline statistically significant even with our large sample size. It is not apparent why our results on calcium appear to be different from most other studies. We speculate that some women who subsequently developed fractures had been identified as high risk on the basis of family history or other factors and had only recently increased calcium intake.

In summary, this study found a weak positive association between caffeine intake and total fractures, especially for the highest quintile of caffeine consumers (equivalent to >6 cups of coffee day^{-1}). Older women wishing to prevent osteoporosis may benefit from reducing caffeine usage, although a clinical trial would be required to prove this. We also found a weak positive association of fracture with alcohol usage, particularly increased beer or liquor usage; however, the study was limited by low average alcohol usage.

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