



## The effect of alcohol on osteoporosis: A systematic review and meta-analysis

Zahra Cheraghi<sup>a</sup>, Amin Doosti-Irani<sup>b,c</sup>, Amir Almasi-Hashiani<sup>d</sup>, Vali Baigi<sup>e</sup>, Nasrin Mansournia<sup>f</sup>, Mahyar Etminan<sup>g</sup>, Mohammad Ali Mansournia<sup>h,\*</sup>

<sup>a</sup> Department of Epidemiology, Research Center of Modeling of Non-Communicable Disease, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>b</sup> Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>c</sup> Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>d</sup> Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran

<sup>e</sup> Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

<sup>f</sup> Department of Endocrinology, AJA University of Medical Sciences, Tehran, Iran

<sup>g</sup> Department of Ophthalmology and Visual Sciences, The Eye Care Center, University of British Columbia, Room 323-2550 Willow Street, Vancouver BC, V5Z 3N9, Canada

<sup>h</sup> Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, 6517838695, Iran

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### ABSTRACT

**Background:** Osteoporosis is a multifactorial disease hallmarked by the interaction of genetic, nutritional and environmental factors. We aimed to assess the effect of alcohol consumption on the osteoporosis by undertaking a systematic review and meta-analysis.

**Methods:** We searched electronic databases including MEDLINE, Scopus, and Web of Science until June 2018. We identified all pertinent observational studies that examined the risk of OSTEOPOROSIS with alcohol use including cohort, case-control and cross-sectional studies. Relative risks (RR) for cohort studies and odds ratios (ORs) for case-control studies were pooled using the random effects model. Risk of bias was assessed using the Newcastle-Ottawa scale.

**Results:** From a pool of 3479 studies identified six met the study inclusion criteria (three case control, two cohorts and one cross-sectional study). Compared with abstainers of alcohol, persons consuming 0.5–1 drinks per day had 1.38 times the risk of developing osteoporosis (adjusted RR = 1.38, 95% CI: 0.90–2.12), persons consuming 1–2 drinks per day had 1.34 times the risk of developing OSTEOPOROSIS (adjusted RR = 1.34, 95% CI: 1.11–1.62), and persons consuming two drinks or more per day had 1.63 times the risk of developing osteoporosis (adjusted RR = 1.63, 95% CI: 1.01–2.65). We found a positive association between alcohol consumption and osteoporosis in the case-control studies (adjusted OR = 2.95, 95% CI: 1.78–4.90).

**Conclusion:** Our study demonstrates a positive relationship between alcohol consumption and osteoporosis.

### 1. Introduction

Osteoporosis is a skeletal disorder characterized by a reduction of bone mineral density (BMD). Osteoporosis is a silent and asymptomatic condition and is often first diagnosed upon onset of a fracture (Saad et al., 2007). In patients with osteoporosis, bone is qualitatively normal but quantitatively diminished (Bartl and Frisch, 2004). In these patients, the level of bone mineral density is 2.5 of standard deviations or more (T-score  $\leq$  -2.5) lower than the bone mineral density of young adults (Chen et al., 2007). The prevalence of osteoporosis increases with age and is more common in older people, especially older women

(Cummings and Melton, 2002; Woolf and Pflieger, 2003; Doosti Irani et al., 2013).

Osteoporosis not only leads to bone fractures, but is also associated with hospitalizations secondary to other osteoporosis related complications (Cummings and Melton, 2002). The most common of these include fractures of the hip, spine and forearm of which hip fracture is the most serious and carries a highest burden of illness (Cummings and Melton, 2002). In the year 1990, the prevalence of pathologic fracture of the hip worldwide has been estimated as 1.3–1.7 million. It is predicted that this figure will increase to about 3 million by 2025 (Cooper et al., 2011).

\* Corresponding author.

E-mail addresses: [cheraghiz@ymail.com](mailto:cheraghiz@ymail.com) (Z. Cheraghi), [a\\_doostiirani@yahoo.com](mailto:a_doostiirani@yahoo.com) (A. Doosti-Irani), [amiralmasi2007@gmail.com](mailto:amiralmasi2007@gmail.com) (A. Almasi-Hashiani), [v-baigi@razi.tums.ac.ir](mailto:v-baigi@razi.tums.ac.ir) (V. Baigi), [nasrin\\_sept@yahoo.com](mailto:nasrin_sept@yahoo.com) (N. Mansournia), [etminanm@mail.ubc.ca](mailto:etminanm@mail.ubc.ca) (M. Etminan), [mansournia\\_ma@yahoo.com](mailto:mansournia_ma@yahoo.com) (M.A. Mansournia).

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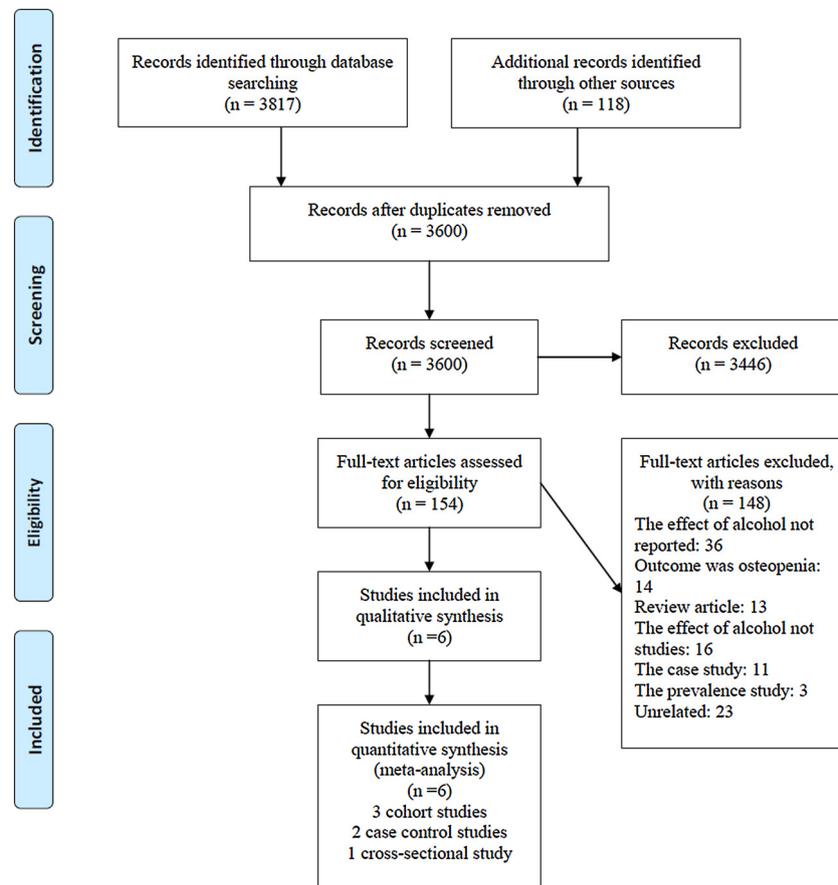


Fig. 1. Flowchart of selection of studies in the Meta-analysis.

With the rise in life expectancy around the world especially among older adults, osteoporosis is expected to become a major public health problem (Maalouf et al., 2007). Studies have shown that a major player in the pathology of osteoporosis might be the interaction between genetic and environmental factors (Rizzoli et al., 2001). These include low physical activity, smoking, alcohol consumption, weight loss, calcium malabsorption and vitamin D, a history of fracture, use of corticosteroids, hormonal factors, genetic factors and female gender (Johnell and Hertzman, 2006; Doosti-Irani et al., 2018). Given that osteoporosis is one of the most important public health issues in an ever-aging world this disease should be considered as a health care priority for older adults. Identifying potential risk factors is necessary for implementation of public health activities that aim to lower osteoporosis risk. To date several studies have assessed the association between alcohol consumption and osteoporosis and have reported varying estimates for this relationship. In some studies (Kanis et al., 2005; Hannan et al., 2000; Cummings and Melton, 2002), alcohol consumption has been shown to be a risk factor for osteoporosis while other studies have not shown this association (Berg et al., 2008). Thus, we sought to estimate a summary measure for the effect of alcohol consumption on osteoporosis by undertaking a systematic review and meta-analysis of the available literature.

## 2. Material and methods

### 2.1. Eligibility criteria

We included all observational (cohort, case-control and cross-sectional) studies that addressed the association of alcohol consumption and osteoporosis risk. The studies were included without restriction of date of publication and language. The study population consisted of

men and women irrespective of their race, age and marital status. The outcome of interest was the all types of osteoporosis (senile osteoporosis and postmenopausal osteoporosis). We did not include osteopenia outcome in our search. All included studies were required to have presented as summary measure (relative risk or odds ratio) or enough information that allowed its computation.

### 2.2. Exposure and outcome variables

The outcome of interest was osteoporosis and the exposure of interest was alcohol consumption. For studies that provided alcohol use with different units of measurement we converted alcohol consumption into drinks per day using the assumption that each standard drink is equal to 14 g or 0.6 ounces of pure alcohol. Finally, we categorized alcohol consumption into three levels: 1) 0.5–1 drinks per day, 2) > 1 to 2 drinks per day, or 3) > 2 drinks per day (Australian Government Department of Health, 2016). In cases where studies did not report categories of alcohol consumption, we summarized the results in two groups of drinkers and non-drinkers (Guo et al., 2013; Poór et al., 1995)

### 2.3. Search strategy

We used the following terms for our search using electronic databases including Scopus, MEDLINE, Web of Science, and google scholar from the first available date to June 2018: ["Osteoporosis", OR "Bone disease metabolic" OR "Bone Mineral Density" OR "BMD" OR "Alcohol Drinking" OR "Alcoholic Beverages" OR "Beer" OR "Wine"] AND ["Case-Control Studies", OR "Cohort Studies" OR "Retrospective Studies" OR "Prospective Studies" OR "Longitudinal Studies" OR "cross-sectional studies" OR "observational studies"].

We also searched the reference list of retrieved articles to ensure no

**Table 1**  
Characteristics of included studies in the Meta-analysis.

Author (Year)	Design	Country	Gender	Organ	Age	OR*	RR*	0.95% CI	Adjusted Factors
Guo et al. (2013)	Case-Control	China	Both	Femur	66.28	8.44	-	[1.7, 41.9]	Age, BMI, Hormone Therapy
Kanis et al. (2005)	Prospective Cohort	Australia, Netherlands, Canada	Both	Hip	65.00	-	1.34	[1.11, 1.61]	Smoking
Tanaka et al. (2001) §	Cross Sectional	Brazil	Male	Femur	62.5	0.70	-	[0.31, 1.60]	No adjustment.
Hernandez-Avila et al. (1991)	Prospective Cohort	USA	Female	Forearm	NR	-	1.38	[1.09, 1.74]	Age, BMI, Menopause Status, Estrogen-Replacement Therapy
Hernandez-Avila et al. (1991)	Prospective Cohort	USA	Female	Hip	NR	-	2.33	[1.18, 4.58]	Age, BMI, Menopause Status, Estrogen-Replacement Therapy
Poór et al. (1995)	Matched Case-Control	USA	Male	Hip	78.5	2.18	-	[1.4, 5.59]	Age
Seeman et al. (1983)	Matched Case-Control	Australia	Male	Spine	64.7	2.4	-	[1.04, 5.53]	Age

NR = not reported, \*OR: odds ratio, \*\*RR: relative risk.

pertinent studies were missed. Authors of selected papers were contacted to obtain data on unpublished studies. Eligible studies that might have been presented in conference proceedings were also scanned.

**2.4. Data extraction and selection of relevant studies**

Two authors (ADI and AA) were independently and simultaneously responsible for selection of studies that met our inclusion criteria. The third author (Z.Ch) was contacted in case of any disagreements between the two authors and if necessary final approval was obtained from the third author. Degree of consistency and agreement on the choice of studies was based on the kappa statistics which was computed to be 82%. From the pool of studies that met the study inclusion criteria, we extracted the following information: year of publication, the location of the study (country), mean age, gender, odds ratios (ORs) with 95% confidence intervals for cross-sectional and case-control studies and relative risks (RRs) with 95% confidence intervals for cohort studies. The Newcastle-Ottawa scale (Wells et al., 2010) was used to evaluate the potential risk of bias. Four criteria were used to assess the risk of bias in the case-control studies, including: 1) case definition, 2) selection of controls, 3) ascertainment of exposure, and 4) non-response rate. In cohort studies, 1) selection of the non-exposed cohort, 2) ascertainment of exposure, 3) assessment of outcome, and 4) adequacy of follow-up of cohorts were used for assessing the risk of bias.

The chi-squared test (Chi<sup>2</sup>) at a significance level of 10% was used to assess the statistical heterogeneity. This cut-off was selected for better detection of heterogeneity given the low power of this test to detect heterogeneity especially when the number of included studies is low (Dickersin and Berlin, 1992). In addition, the I-squared statistic was used to quantify the heterogeneity across the included studies (Higgins et al., 2003). Between-study variance for the calculation of this metric was computed using the tau-squared statistic (Higgins and Green, 2008).

The funnel plot was also used to investigate the publication bias visually (Higgins and Green, 2008), and Begg’s (Begg and Mazumdar, 1994) and Egger’s (Egger et al., 1997) tests were used to assess publication bias quantitatively.

Study effect sizes (adjusted RRs or ORs) were pooled by their inverse variances using the random effects method to generate a pooled effect size for the association between alcohol consumption and osteoporosis (DerSimonian and Laird, 1986). Results were reported with each study RR/OR and corresponding 95% confidence interval (95% CI). STATA 11 (StataCorp, College Station, TX, USA) and Review Manager 5.3 were employed for data analysis.

**3. Results**

Out of 3935 retrieved records, 335 references were excluded because of duplication, 3446 references were excluded because they did not address the study question and 148 references were excluded because they were not eligible to be included in the meta-analysis after checking the full text. 6 articles (Poór et al., 1995; Seeman et al., 1983; Kanis et al., 2005; Tanaka et al., 2001; Hernandez-Avila et al., 1991; Guo et al., 2013) were included in the meta-analysis (Fig. 1 and Table 1).

The study designs of the included studies were two cohort studies, three case-control studies and one cross-sectional. We only included case-control studies and cohort studies in the meta-analysis and provide data on the one cross-sectional study.

Four studies (57.1%) met all four Newcastle-Ottawa quality assessment scale and was considered as having a low risk of bias while the remaining studies (42.9%) were considered as having a moderate risk of bias.

Two cohort studies were also included. In one study (Kanis et al., 2005a), RR for association of alcohol consumption and osteoporosis was adjusted for body mass index, and smoking. In the second cohort

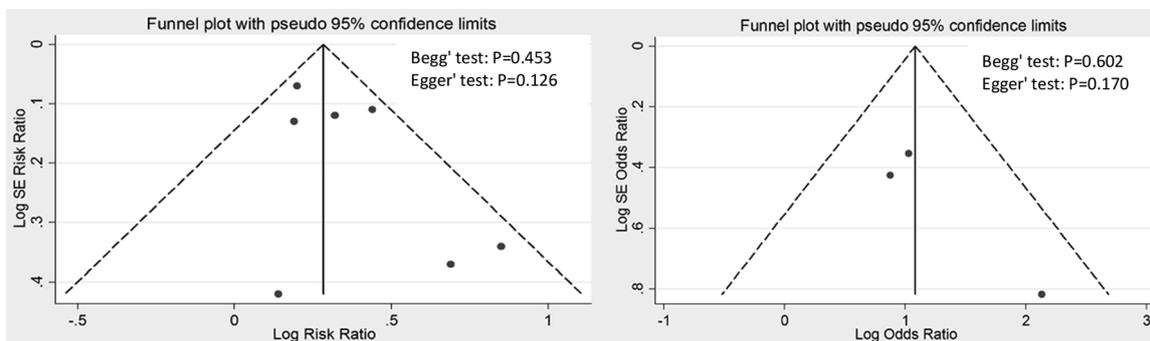


Fig. 2. Funnel plot of included studies by study design.

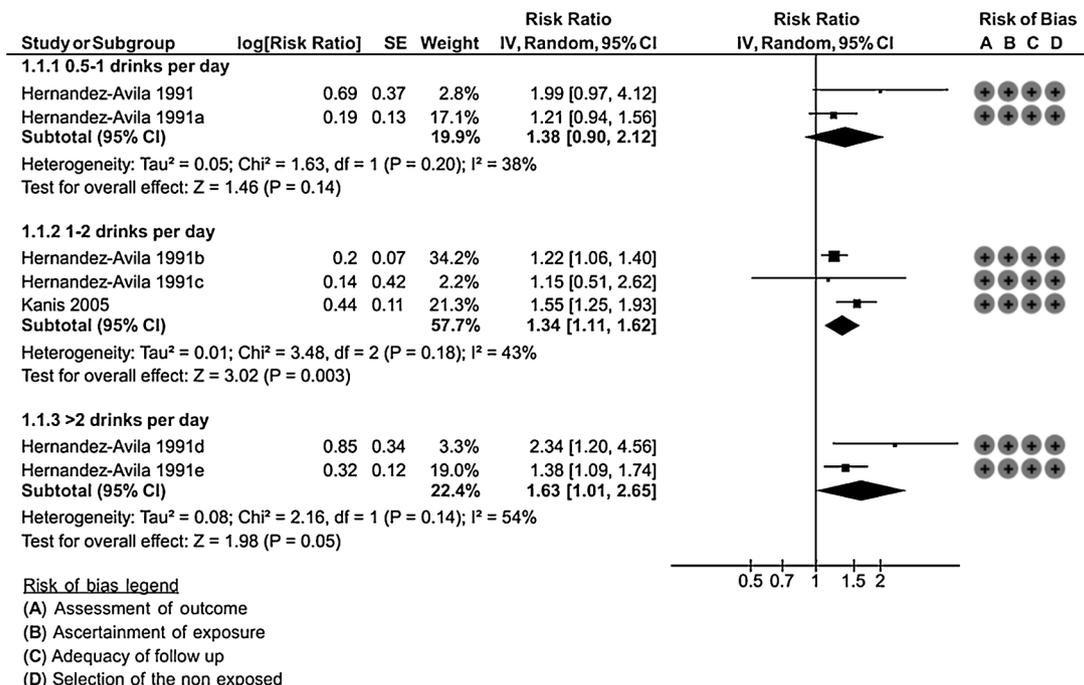


Fig. 3. Forest plot of adjusted relative risk of alcohol consumption and the risk of osteoporosis.

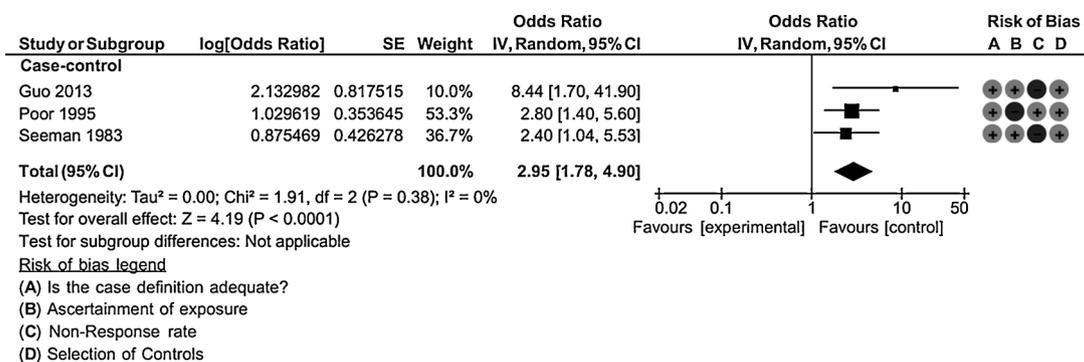


Fig. 4. Forest plot of adjusted odds ratio of alcohol consumption and the risk of osteoporosis.

study (Hernandez-Avila et al., 1991), RR was adjusted for age, Quetelet's Index (BMI), menopause status (that restricted to females), and estrogen-replacement therapy. Among the three case-control studies, one study (Guo et al., 2013) adjusted the OR for age, body mass index, and hormone therapy whereas the other two case-control studies (Seeman et al., 1983; Poór et al., 1995) were only matched on age.

We assessed the possibility of publication bias using the funnel plot as well as Begg's and Egger's tests (Fig. 2). The studies scattered nearly

symmetrically on both sides of the vertical line reflecting the absence of publication bias. The results of Begg's and Egger's tests confirmed the absence of publication bias in both case-control (Begg' test: P = 0.602, Egger' test: P = 0.170) and cohort studies (Begg' test: P = 0.453, Egger' test: P = 0.126).

Also, the results of I-squared statistic and chi-squared tests indicated absence of heterogeneity in both cohort and case-control studies (I-squared = 0% and chi-squared = 1.91, P-value = 0.38 for case-control

studies and I-squared = 0.26% and chi-squared = 8.16, P-value = 0.23 for cohort studies). Overall the heterogeneity was under 30% (Figs. 3 and 4).

### 3.1. Alcohol consumption and osteoporosis risk

The results of the random-effects meta-analysis and the pooled adjusted RR for association of alcohol consumption of 0.5–1 drinks per day and osteoporosis was 1.38 [95% CI: 0.90, 2.12] in the cohort studies (Fig. 3). Compared with abstainers, persons consuming 1–2 alcoholic drinks per day had 1.34 times the osteoporosis risk (adjusted RR = 1.34, 95% CI: 1.11–1.62), and persons consuming more than 2 alcoholic drinks per day had 1.63 times the osteoporosis risk (adjusted RR = 1.63, 95% CI: 1.01–2.65) (Fig. 3).

There was a positive association between alcohol consumption and osteoporosis in the case-control studies (adjusted OR = 2.95, 95% CI: 1.78–4.90) (Fig. 4). There was one cross-sectional study which was not included in meta-analysis (Tanaka et al., 2001). In this study the crude OR for alcohol drinkers versus nondrinkers was 0.70 (95% CI: 0.31, 1.60).

## 4. Discussion

The results of this systematic review of six observational studies suggest an increase in the risk of osteoporosis among consumers of alcohol. The degree of heterogeneity among the studies was low (under 30%). Also, there was no evidence of publication bias among the included studies. However, both heterogeneity and publication bias tests might have inadequate statistical power to be able to detect heterogeneity and publication bias due to the small number of studies included in the meta-analysis (Higgins and Green, 2008). In this meta-analysis, we only included adjusted effect sizes (RRs and ORs) as crude effect sizes reported in observational studies are considered to be biased (Greenland, 1987). However, the adjusted effect sizes might not have adjusted for all potential confounders leaving the possibility of residual confounding.

Based on the results of meta-analysis, alcohol consumption was shown to be a risk factor for osteoporosis in both study designs (case-control and cohort) though the magnitude of the pooled OR in the case-control studies was higher than the pooled RRs in cohort studies, (2.95 vs. 1.63). The discrepancy can be explained by differences in study design and confounding adjustment as well as the possibility of sparse data bias (Greenland et al., 2016; Mansournia et al., 2017; Greenland and Mansournia, 2015) away from the null represented in the unrealistically large odds ratio estimate in Guo et al case-control study. Moreover, osteoporosis is not uncommon and thus the OR is expected to exaggerate the RR (Doosti Irani et al., 2013; International Osteoporosis Foundation, 2015; Rothman et al., 2008).

Our result is consistent with the results of other studies (Sampson, 2002; Kanis et al., 2005b) which showed negative effects of alcohol on bone health mainly interfering with the balance of calcium, a vital nutrient for bone health. In addition, heavy drinking of alcohol may cause hormone deficiencies in adults irrespective of gender. Moreover, similar studies have shown increased risk of any fracture including hip and vertebral fractures among heavy drinkers (Mostofsky et al., 2016; Nevitt et al., 2005; Cawthon et al., 2006; Poór et al., 1995).

Our results revealed a positive relationship for the effect of alcohol consumption on osteoporosis. Specifically, compared with abstainers, persons consuming 1–2 alcoholic drinks per day had 1.34 times the osteoporosis risk and persons consuming two alcoholic drinks per day had 1.63 times the osteoporosis risk. The results of this study are also consistent with a previous meta-analysis (Berg et al., 2008) that showed alcohol drinkers who drank more than 0.5–1.0 drinks per day had a lower hip fracture risk (relative risk = 0.80 [95% CI: 0.71–0.91]) than nondrinkers and those who had two drinks per day had higher risk (relative risk = 1.39 [95% CI: 1.08–1.79]). This study also

demonstrated a linear association between greater alcohol consumption and bone density loss over time.

Our study has some limitations. Since the studies did not control for important confounders including nutritional status, gender, ethnicity, family history and cigarette smoking, our results are not adjusted for these variables. Similarly, due to a small number of studies included in our meta-analysis we were not able to do a subgroup analysis on important factors such as quality of reporting, gender, and age. Future studies that intend to examine the risk of alcohol use and osteoporosis should also measure bone mineral density (BMD) as this variable is an appropriate outcome for this question.

## 5. Conclusion

Our study demonstrates a positive relationship between alcohol consumption and osteoporosis. Persons who consume two alcoholic drinks or more per day experience the highest risk of developing osteoporosis.

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### Contributors

Z.Ch. conducted research, Z.Ch. and A.D. provided essential reagents or provided essential materials. Z.Ch., V.B. and A.D. performed the statistical analysis. Z.Ch., A.A., M.E. and MA.M. wrote the paper. Z.Ch., A.D., M.E. and MA.M. had primary responsibility for final content; Z.Ch. had responsibility for all parts of the manuscript).

All authors have approved the final article should be true and included in the disclosure.

### Conflict of interest

No conflict declared.

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