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The association between alcohol consumption and risk of hip fracture differs by age and gender in Cohort of Norway.

A NOREPOS study*.

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Conflict of interest:

Anne Johanne Søgaard, Anette Hylene Ranhoff, Haakon E Meyer, Tone K Omsland, Wenche Nystad, Grethe S Tell and Kristin Holvik declare that they have no conflict of interest.

MINI ABSTRACT

The association between alcohol consumption and hip fracture differed by gender: Men aged 30-59 years drinking frequently or 14+ gl/week had higher risk than moderate drinkers. No significant association was seen in older men. Women not drinking alcohol had higher risk than those drinking moderately both regarding frequency and amount.

ABSTRACT

Purpose: We aimed to examine alcohol consumption and risk of hip fracture according to age and gender in the population-based Cohort of Norway (1994-2003).

Methods: Socio-demographics, lifestyle and health were self-reported and weight and height were measured in 70,568 men and 71,357 women ≥ 30 years. Information on subsequent hip fractures was retrieved from hospitals' electronic patient registries during 1994-2013.

Frequency of alcohol consumption was categorized: never/seldom, moderate ($\leq 2-3$ times/week) or frequent (≥ 4 times/week), and amount as number of glasses per week: 0, 1-6, 7-13, 14-27 and 28+. Type of alcohol (wine versus beer/hard liquor) was also examined. Cox's proportional hazards regression was used to estimate hazard ratios (HR) stratified on gender and baseline age <60 and ≥ 60 years.

Results: During median 15 years follow up, 1,558 men and 2,511 women suffered a hip fracture. Using moderate drinkers as reference, men <60 years drinking frequently had multivariable adjusted HR=1.73 (CI 1.02-2.96) for hip fracture and more than 2.5-times higher risk if they consumed 14+ glasses compared to 1-6 glasses per week. In other groups of age and gender, no statistically significant increased risk was found in those consuming the highest levels of alcohol. Compared to women with moderate or frequent alcohol use, never/seldom-drinking women had the highest fracture risk. In women, use of wine was associated with lower fracture risk than other types of alcohol.

Conclusions: Risk of hip fracture was highest in men <60 years with the highest frequency and amount of alcohol consumption and in non-drinking women.

Keywords: Alcohol consumption, hip fracture, age, gender, frequency, amount

INTRODUCTION

Norway has among the highest incidence rates of hip fracture ever reported [1-3]. Hip fractures cause much pain and loss of function and almost 25% of the patients die within one year after the fracture [4,5]. These fractures represent a considerable burden to the health care system, and even though the age-specific incidence is slightly decreasing [3,6,7], the actual number of fractures are forecasted to increase considerably due to an ageing population [8]. Also, the incidence rate of hip fracture has been predicted to increase in the not so far future, due to higher fracture rates now observed in the younger age-groups [9]. Thus, identifying modifiable risk factors is of great importance for fracture prevention.

Alcoholism is a well-established risk factor for hip fractures because of increased risk of falling, poor nutritional status, poor functional status, more co-morbidities, disturbances in the bone remodelling system, impaired bone quality and adverse endocrine changes [10-14]. There is less evidence of the effects of moderate alcohol consumption on bone health in the general population. Light to moderate alcohol consumption has been associated with higher bone mineral density (BMD) and reduced age-related bone loss [14]. However, much remains to be determined in understanding the complex influence of alcohol on bone health. There is, for example, limited knowledge regarding potential differences in associations by age and gender [14].

Two systematic reviews combined with meta-analyses reported a J-shaped association between alcohol consumption and hip fracture [13, 15], with increased risk among both heavy drinkers and teetotalers. The paper from 2008 [15] did not report results separately for age and gender subgroups, whereas the later paper found a lower hip fracture risk in moderate compared to non-drinking men, but not women [13]. No age-stratified analyses were presented in either publication. A few of the studies included in these two papers, reported age and/or gender stratified analyses, with inconsistent results [16-19].

Because alcohol consumption in Norway is relatively low [20], we wanted to explore whether there was a J-formed association between alcohol consumption (frequency and amount) and risk of hip fracture in the large population-based Cohort of Norway (CONOR) with available data on important confounding factors. Frequency and amount of alcohol consumption may exhibit different patterns with fracture risk, since they may reflect potentially different behaviours [21]. Our aims were to examine the associations between frequency, amount and

type of alcohol consumption and later hip fracture risk, and to study whether such associations varied by age and gender.

METHODS

Cohort of Norway (<https://www.fhi.no/en/studies/conor/>) contains baseline data from 10 regional population-based health studies carried out in the general population between 1994 and 2003. All inhabitants in predefined age-groups in the sub-studies of CONOR, were invited by mail to attend a simple physical examination and fill in questionnaires [22]. Participants in one of the studies, the Oslo Immigrant Health Study, have been excluded from the analyses due to their relatively young age, diverse cultural background and high percentage of teetotalism. In the Tromsø Study, some individuals participated twice (1994 and 2001), and only data from the first examination in Tromsø for each individual are included. Thus, there are 8 studies in our study-population. Each individual participated only once collecting all baseline information. All studies included a common core of questionnaire data (socioeconomic factors, lifestyle, health, diseases and drug use) and standardized anthropometric measurements [22]. In the age range 30 years and older at baseline, a total of 261,860 individuals were invited and 60% participated. Of these, 141,925 individuals (70,568 men and 71,357 women) had available data on measured height and weight, consumption of alcohol, self-perceived health, smoking and physical activity.

Exposure variables

Frequency of alcohol consumption

Frequency of alcohol consumption was reported by questionnaire. In the first three CONOR-studies taking place 1994-1999, contributing about 2/3 of those attending CONOR [22], participants were asked how many times per month they consumed alcohol, and whether or not they were teetotaler. In the subsequent five studies (2000-2003) the participants responded to a question on frequency of alcohol consumption during the previous year with eight response categories ranging from “Have never consumed alcohol” to “4-7 times a week or more”. Combining information from all the studies, we constructed a variable with three frequency categories of alcohol consumption: “Never/seldom” = Never, not during the last year, a few times last year; “Moderate” = Once a month to 2-3 times a week; and “Frequent” = 4-7 times or more per week. The questions and the constructed study variable is described in more detail in Supplementary table S1. Because the “Never/seldom group” may include former drinkers who had quit for health reasons [15], we decided to use the moderate drinking

group as the reference category. In the five subsequent studies we were able to separate never drinkers from those not drinking during the last year. Thus, in additional analyses, we divided the “Never/seldom” group in three and analysed a variable with five categories “Never”, “Not last year”, “A few times last year”, “Moderate” and “Frequent” (48,624 participants, 1,487 hip fractures).

Amount of alcohol consumption

In the first three studies, participants answered how many glasses of beer, wine and/or hard liquor they usually consumed in 2 weeks’ time. In the following five studies participants who had consumed alcohol during the last year were asked: “When you consumed alcohol, how many glasses or drinks did you usually consume?” Later the total amount consumed was calculated by multiplying frequency with the reported number of glasses/ drinks usually consumed [23]. Based on information from all the studies, we calculated the total amount of alcohol consumed in one week (number of glasses of alcohol) and grouped the number of glasses in 5 categories according to Høidrup et al. [18]: 0, 1-6, 7-13, 14-27 and 28+. Because few women reported drinking 28+ glasses, the two highest consumption categories in women were combined into 14+ glasses per week. These analyses were based on 126,057 participants, 3,639 hip fractures. The questions and the constructed study variable are described in more detail in Supplementary table S2.

Type of alcohol

Based on the question about number of glasses of beer, wine and hard liquor in the first three studies and an additional question in the later studies: “When you drink, do you usually consume: Beer, Wine, Hard liquor”, we dichotomized type of alcohol as wine versus beer/hard liquor (91,340 participants, 1,481 fractures). This dichotomisation was chosen based on previous studies reporting a beneficial effect on bone health of wine but not of beer/hard liquor [18, 24].

Covariates

Available variables previously shown to be confounders in the association between alcohol consumption and hip fracture were considered for inclusion. These include *age* (years), body mass index (*BMI*) defined as weight (kg) divided by height in meter squared (m^2), *height* (cm), *self-perceived health* (four levels, dichotomized into poor/not very good vs. good/very good), *smoking* (dichotomized into current daily vs. never/previously), *physical*

activity (two questions about number of hours with light or vigorous physical activity per week summarized (range 1-8) and used as continuous variable), and *place of study* - i.e. the location where the regional health studies had been conducted (8 categories). Because of missing data on some of the covariates, we did a secondary analysis adding the following variables: *length of education* (years), *marital status* (dichotomized into married/partner vs. never married/ divorced/ separated/ widowed), *place of residence* (dichotomized according to degree of urbanization, with city defined as municipalities with 20,000 inhabitants or more), and *use of postmenopausal hormone therapy* in women, dichotomized into ever use (current or previous use) vs. never-use. In addition, the following self-reported medical conditions were used as covariates in the secondary analysis: Do you have or have you had: *Myocardial infarction, angina pectoris, stroke, type 2 diabetes, osteoporosis (Yes/no)*. These five diseases were summarized into a score (range 0-5) and dichotomized into no chronic disease vs. one or more chronic diseases.

Age, gender, place of residence, marital status, date of death, date of emigration and country of birth were obtained from the National Registry. Of all incident hip fractures registered during follow-up, only 0.8% were sustained by participants born in Non-Western countries. Thus, country of birth was not included as a covariate in the analyses.

Outcome: Incident hip fractures

All hip fractures treated in Norwegian hospitals with a diagnosis code for cervical, trochanteric or sub-trochanteric hip fracture (ICD 9: 820 with all subgroups; ICD 10: S72.0-S72.2) from 1 January 1994 through 31 December 2013 were retrieved. Data were obtained from all Norwegian Hospitals (until 2008) [2] and from the Norwegian Patient Registry (2008 through 2013) and constitute the database NORHip [3, 25]. Incident hip fractures were identified by a comprehensive algorithm taking into account surgical procedure codes, additional diagnosis codes and time between hospitalizations. Dates of admission and discharge were available for all hospitalizations. Based on this information, admissions for primary hip fractures were identified. Information on hip fracture definitions, classification, quality assurance and validation is available online: www.norepos.no/documentation.

Statistical analyses

Data were analysed in IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY) and Stata Statistical Software (Release 13. College Station, TX). Time from baseline participation to the first hip fracture or censoring (emigration, death or end of follow up 31 December

2013) was computed. Baseline data are described according to frequency of alcohol consumption and tested for homogeneity (Pearson's 2-sided chi-squared test for categorical variables and F-test (ANOVA) for continuous variables). Because of the large difference in age observed between the three alcohol consumption groups (Table 1), all subsequent analyses were performed stratified on age; 30-59 years and 60 years and older.

The age cut-off was set to be able to study the effect of alcohol on hip fracture in a sufficiently large population that had not yet reached the peak age of hip fracture.

Crude incidence rates according to frequency of alcohol consumption were calculated by dividing the number of hip fractures by the total follow-up time in each alcohol consumption frequency category, and expressed as hip fractures per 10,000 person-years. Cox proportional hazards regression was performed in men and women separately, with moderate drinkers as reference category. Each individual's first hip fracture after baseline was used. In the main analysis we adjusted for age, height, BMI, physical activity, smoking, self-perceived health and place of study. Baseline characteristics of these individuals are contrasted to the same characteristics of all CONOR-participants ≥ 30 years in Supplementary table S3.

In the secondary analyses adjustments were done for all variables mentioned above. For appropriate appraisal of the influence of covariates we also performed the main analysis restricted to the participants who had information on all covariates.

Further, a corresponding Cox analysis was conducted in a subsample using the alcohol frequency variable with five categories in order to distinguish those who had never consumed alcohol from those who had not used alcohol during the last year.

To investigate whether the results could be influenced by higher mortality in those with very high or very low frequency of alcohol consumption, we performed competing risk analyses using the 'stcrreg' command in Stata, considering the two competing events: hip fracture and deaths from any cause (excluding deaths occurring after hip fracture).

Log minus log curves suggested proportional hazards for alcohol consumption. A *P*-value below 0.05 (2-sided test) was considered statistically significant.

Interaction terms were entered to test whether the three alcohol frequency groups interacted multiplicatively with potential confounding factors: age, gender, marital status, smoking,

physical activity, self-perceived health, use of hormone therapy (HT) or the variable “one or more chronic disease” on hip fracture risk.

We performed similar Cox analyses as above for the total amount of alcohol consumed per week.

In testing for trends within frequency and amount of alcohol consumption we also added a second order term to test for diversion from linearity.

Finally, we used crosstabs and Cox regression to explore the possible impact of the different types of alcohol on fracture in sub-groups of age and gender.

Both the analyses of amount of alcohol consumed and type of alcohol were adjusted for the same variables as presented above for the primary analyses of frequency.

Ethical considerations

Cohort of Norway and linkages between the data sources were approved by the Regional Committee for Medical and Health Research Ethics (region South-East) and the Norwegian Data Protection Authority. All participants in the CONOR-study gave their written informed consent. The CONOR steering committee approved the project. The study has been conducted in full accordance with the Declaration of Helsinki of the World Medical Association.

RESULTS

Among subjects aged 30 years and older at participation in CONOR, 1,886 men (2.7%) and 2,945 women (4.1%) suffered a hip fracture from baseline through 2013 (median 15.0 years). Mean age at fracture was 77 years in men and 79 years in women. Baseline characteristics of participants according to frequency of alcohol consumption are shown in Table 1. All variables were significantly associated with alcohol consumption ($P \leq 0.001$). Frequent drinkers were older, had the highest percentage living in a city and the highest percentage of single women. Never/seldom drinkers had the highest BMI, the shortest education, the lowest level of physical activity and the lowest percentage of smokers. In this group we also found the highest percentage with poor/not very good health, the highest percentage with one or more diseases and the lowest percentage of women with ever use of HT.

Risk of hip fracture according to frequency of alcohol consumption

In men 30-59 years we found a 73% increased risk of hip fracture in those drinking frequently compared to moderately drinking men after adjustments ($P = 0.038$ in test for diversion from linearity (second order term)). In men ≥ 60 years, a weak inverse association was observed (test for linear trend across the alcohol consumption groups $P = 0.028$) (Table 2).

Among women, significantly higher hip fracture risk was seen in never/seldom drinkers compared to those drinking moderately in both age strata: 29% in those 30-59 years, and 12% in those ≥ 60 years (Table 3). Tests for linear trend across alcohol frequency groups was statistically significant in both age strata ($P = 0.012$ for 30-59 years and $P < 0.005$ for ≥ 60 years).

In the secondary analyses, additional adjustments for marital status, length of education, chronic diseases, living in urban vs rural areas and use of hormone therapy in women, did not change the results materially (data not shown).

Finally, we compared moderate drinkers to those who had never consumed alcohol and to those who did not drink last year, based on data from the last five studies. Compared to moderate drinkers and after adjustment for covariates, men 30-59 years who had never consumed alcohol had a HR=1.63 (CI 0.38-6.95) for hip fracture, whereas men reporting that they did not drink last year had a HR=4.04 (CI 1.77-9.24). The corresponding hazard ratios in women 30-59 years were 3.32 (CI 1.50-7.34) and 1.07 (CI 0.33-3.51), respectively. No corresponding findings appeared in those ≥ 60 years.

No interactions were found in the association between alcohol consumption and hip fracture for marital status, BMI, smoking, physical activity, use of hormone therapy or self-perceived health, while there was a statistically significant interaction for age (two strata) ($P_{\text{genders combined}} = 0.014$), gender ($P_{\text{ages combined}} = 0.016$), and for chronic diseases in women ($P_{\text{ages combined}} = 0.004$). Nine percent of women reported one or more diseases. Stratified analyses showed that the never/seldom-drinking women with *no reported chronic diseases* had HR=1.17 (CI 1.06-1.30) for hip fracture compared to those drinking moderately. The corresponding HR for *all* women ≥ 30 years was 1.16 (CI 1.06-1.26). None of the frequent drinking categories in women were statistically significant in either strata.

Results from the competing risk analyses did not change the results appreciably.

Risk of hip fracture according to amount of alcohol consumption

Men and women 30-59 years old consumed on average 3.4 and 1.8 glasses of alcohol per week (gl/ week), respectively, whereas the corresponding consumption in those ≥ 60 were 2.8 and 1.2 gl/ week. Single men and women consumed on average significantly more glasses of alcohol per week than married individuals ($p < 0.001$). The only exception was single women ≥ 60 years who consumed *less* alcohol than their married counterparts ($p < 0.001$).

Figures 1a-d shows HRs with 95% CI for hip fracture according to weekly amount of alcohol (number of glasses) in gender- and age groups, with 1-6 gl/week as reference category. Men 30-59 years consuming 14 glasses or more per week had a statistically significant increased risk of hip fracture (14-27 glasses: HR=1.76, 95% CI 1.11-2.79; 28+ glasses: HR=3.24, 95% CI 1.02-10.28) (Fig. 1a). The risk in teetotalers were HR= 1.21 (95% CI 0.93-1.58). Test for diversion from linearity (second order term) gave $P = 0.001$. A tendency towards a similar pattern was observed in women 30-59 years, but neither the risk in teetotaler nor the risk in those drinking 14+ glasses per week reached statistical significance (HR=1.20, 95% CI 0.97-1.49 and HR=2.65, 95% CI 0.98-7.18, respectively). However, test for diversion from linearity gave $P = 0.030$ (Fig. 1b). No significant association was seen in men ≥ 60 years (Fig. 1c). In the oldest women (≥ 60 years) there was a negative linear trend ($P = 0.001$), and the relative risk of hip fracture was highest in the group with no alcohol consumption (HR=1.18, CI 1.06-1.31) (Fig. 1d).

Risk of hip fracture according to type of alcoholic drinks usually consumed

Among those drinking alcohol, 26% of men reported usually drinking wine, the corresponding percentage in women was 64% ($p < 0.001$). Among frequent drinkers, 36% of men and 76% of women reported to drink wine ($p < 0.001$). Although statistically significant, the difference between the two age-groups was moderate; 45% of the youngest and 38% of the oldest preferred wine. In multivariable analyses, the HR for hip fracture among wine-drinking women was 0.82 (95% CI 0.70-0.94) compared to those drinking beer/liquor, but there was no such difference in men. Adjustments for frequency and amount of alcohol consumption did not materially change these results.

DISCUSSION

In this large population-based cohort covering several regions of Norway, an estimated 73% increased risk of hip fracture was observed in frequent drinking men aged 30-59 compared to moderate drinkers. No association was found in older men. In women, the risk of hip fracture in never/seldom drinkers was significantly higher than in those drinking moderately, both below and above age 60 years. The amount of weekly alcohol consumption showed similar associations as the frequency of consumption, with the youngest men drinking at least 14 glasses per week having increased risk compared to those drinking 1-6 glasses per week. The oldest women not drinking alcohol had higher risk than those drinking 1-6 glasses per week. Among women, but not men, the risk of hip fracture was lower in wine drinkers compared to beer/liquor drinkers.

Several previous studies did not present or did not find different associations between alcohol consumption and hip fracture by age and gender [15, 17-19]. In our study, men below 60 years who reported drinking alcohol four times per week or more, or consuming 14 glasses or more per week, had increased risk of hip fracture, in line with findings in the Framingham Study [16]. Neither our study nor the Framingham study found a corresponding association in older men. One possible explanation could be that light to moderate alcohol consumption may affect bone beneficially in older individuals by slowing the rate of bone remodelling, while this effect is less certain in younger individuals [14]. Another possible explanation for the lack of an association in older men is selection bias, since a higher proportion of older heavy drinkers could have died before they reached the high-risk age for hip fracture, or they might have refrained from participating in the CONOR-studies because of poor health or comorbidities. Although we performed additional competing risk analyses, which did not alter the main results, and adjusted for self-reported diseases in secondary analyses, we cannot rule out the possibility of selection bias. We have previously found that the CONOR participants are quite representative for the general population of Norway [26]. There are, however, fewer participants below 40 and above 80 years in CONOR, whereas the variables gender, level of education, smoking and consumption of alcohol are comparable to the general population. A third explanation could be that the actual consumption in younger men in the highest consumption category was higher than in older men. Post hoc analyses revealed that the average number of glasses consumed per week by *frequently* drinking men 30-59 years was significantly higher than in the same category of men ≥ 60 years (14.7 vs 12.5 glasses).

A somewhat different risk pattern according to frequency of alcohol consumption was seen in women. Compared to those drinking moderately, never/seldom drinking women had significantly higher risk (Table 3). Also regarding *amount* of alcohol, women 60 years and older who reported 0 glasses per week, had higher risk than those drinking 1-6 glasses per week. This agrees with the findings in a case-control study among post-menopausal women from Sweden [27], observing a weak inverse association between alcohol consumption and hip fracture. Other studies have reported a J-shaped association also in women, with abstainers at higher risk than moderate drinkers, although not always statistically significant [13, 18, 19]. Our analysis of *amount* of alcohol consumed also suggested a higher HR among women 30-59 years consuming 14 glasses or more per week, but the association was not statistically significant (Fig. 1 panel c). There could be several reasons for our findings among women. *First*, there may be reverse causation in that poor health status may influence alcohol consumption. Never/seldom drinking women had the lowest level of physical activity, the highest percentage with poor/not very good self-reported health and the highest percentage with one or more diseases. On the other hand, there was a statistically significant increased fracture risk also in never/seldom drinking women *without* self-reported diseases, and the main results remained stable after adjustments for all these variables. However, some of these women may suffer from diseases not included in the questionnaires.

Second, our observed lower fracture risk in moderately drinking women could also be explained by the suggested positive effects of light to moderate alcohol consumption on bone health [14, 15], and a possible preventive effect of a combination of alcohol and hormone (oestrogen) therapy in postmenopausal women [14]. The percentage of women in our study who used or had used such hormone therapy was twice as high in frequent compared to never/seldom drinkers (Table 1). Among women aged 59 to 60 years in the Oslo Health Study 2000–2001, one of the CONOR sub-studies, 46% stated that they were current users of hormone therapy and 16% that they were former users [28]. Use of oestrogen therapy is positively associated with BMD [14, 15, 17, 28, 29] and decreased fracture risk [30, 31]. Moderate alcohol intake is associated with increased serum oestrogen in postmenopausal women [32]. There is evidence that moderate alcohol consumption may modulate the effects of oestrogen through different mechanisms [14]. This is supported by a study which reported a gradually increasing protective effect of hormone therapy with increasing alcohol intake. Compared to non-users of hormone therapy, those using such therapy and drinking 7 drinks or more per week had RR = 0.36 (95 percent CI: 0.14, 0.90) for hip fracture, whereas no such

effect was seen among non-drinkers of alcohol [33]. However, it is not yet clear whether changes in oestrogen levels associated with regular alcohol consumption are sufficient to impact bone metabolism [14].

Third, in accordance with our results, preference for wine over beer or hard liquor seems to be associated with lower risk of hip fracture [18, 24]. In our data, 64% of all women, and 76% of frequently drinking women, reported to usually consume wine when drinking alcohol. In the Nurses' Health Study [34] risk of hip fracture in participants 34-59 years increased with increasing total alcohol consumption, but this association was not present in those drinking wine (65 hip fractures in total). However, our results may also depend on residual confounding. Results from a Danish study revealed that wine buyers made more purchases of healthy food in general than those who bought beer [35].

Although we found no statistically significant interaction between type of alcohol consumed and use of HT, post-hoc analyses showed that wine-drinking women ≥ 60 who *used/ had used hormone therapy* had somewhat lower risk of hip fracture than wine drinking women who had *never used* HT. Future studies should scrutinize whether wine consumption is more beneficial among users of hormone therapy compared to non-users.

Women consumed about half the amount of alcohol per week compared to men. While one in four men usually preferred wine, more than 2/3 of the women did the same. This gender difference was also observed among frequent drinkers. In women wine-drinking seemed to have a beneficial effect compared to beer/hard liquor, also after adjustment for frequency and amount. Both these factors, amount and type of alcohol, may contribute to explain the different risk-patterns found between men and women in our study.

We also observed a different association between alcohol and hip fracture according to age. In individuals 60 years and older, frequently drinking men and women did not have higher risk than those drinking moderately. This age group consumed on average lower amounts of alcohol per week compared to those 30-59 years old (men ≥ 60 years consumed 4/5 of the number of gl/week compared to those 30-59 years, whereas the corresponding ratio in women was 2/3). Also type of alcohol consumed tends to differ between younger and older adults [23]. However, in our study the differences in preferences were moderate and could not

explain the observed age differences in the association between alcohol consumption and fracture risk.

Except for women ≥ 60 years, single individuals consumed on average more glasses of alcohol per week than married ones. Married adults are better off than their unmarried counterparts in a variety of domains [36], including decreased alcohol use and abuse [37, 38]. In Norway, unmarried individuals are reported to drink more than married ones [39], which was also found in our study. We have previously observed that single men 50-79 years had higher risk of hip fracture than their married counterparts, after adjustments for age [40].

Strengths and limitations

Strengths

This study is one of the largest of its kind, and we have been able to adjust for important potential confounding factors such as body mass index and socioeconomic status. Due to ample statistical power, the current study has enabled us to reveal important differences according to gender, age and marital status. We also believe that enquiring about both frequency and amount of alcohol consumption, separately for beer, wine, and liquor, as was done in CONOR, will yield the most realistic levels of intake [21, 41]. Frequency and amount may represent different behaviours. A US study revealed that infrequent drinkers consumed more drinks per day than those drinking more often [21]. In our study we found similar pattern of fracture risk for frequency and amount of alcohol consumption, but the use of alcohol in our study was roughly measured. (Supplementary tables S1 and S2).

Most studies have included both abstainers and those not drinking last year in the same category of non-drinkers, which could introduce bias because this category is likely to include both lifetime abstainers and former drinkers who have stopped for health reasons [15]. To explore this problem, we were able to perform separate analyses in life-time teetotallers and those not drinking during the previous year in a sub-group of CONOR. The 30-59 year-old men *not drinking last year* had a fourfold increased risk of hip fracture compared to those drinking moderately, whereas no increased risk was seen in the men 30-59 years old who had *never* consumed alcohol. No corresponding results were seen in women. Although the numbers of fractures were small in these subgroups, confounding by indication could, to some extent, explain the suggested upturn in risk in never/seldom drinking younger men.

In Norway, practically all hip fracture patients undergo surgery, and hospital-based register-data on hip fracture is virtually complete. In two of the CONOR-studies extensive validations were carried out comparing register data with patient records and X-ray archives at the hospitals with very good agreement (Cohen's kappa 0.95) (www.norepos.no/documentation).

Limitations:

Based on clinical findings that younger men are overrepresented among hip fracture patients with excess alcohol intake at the time of admission [12, 42], we wanted to scrutinize the frequently drinking younger men in particular. However, we do not have information about higher frequency of alcohol consumption than 4-7 times a week, which was the highest category asked in the questionnaire. Thus, we were unable to explore in detail the risk among those drinking the most.

We are aware that alcohol consumption is often underreported [43], and women seem to conceal and underreport their use of alcohol more than men [41, 42]. Although this bias could be present, particularly in those drinking the most, we do not believe that a possible underreporting by women could explain the apparent different patterns of alcohol consumption observed in men and women in our study.

Studies that only measure alcohol consumption at baseline are vulnerable to misclassification if exposure to alcohol change before the outcomes are ascertained [15]. Our data on use of alcohol was collected during 1994-2003 and the follow-up lasted through Dec 31. 2013. The total alcohol consumption in Norway increased considerably during this period, largely due to increased wine consumption [44], but we have unfortunately no follow-up information in CONOR-participants. Another limitation is the different questions used in the different CONOR studies. Combining the answers to new constructed study variables as shown in tables S1 and S2, makes the measures less precise and is an additional source of misclassification. Yet another limitation is that the way alcohol consumption was measured, may increase the risk of measurement errors and misclassification. The questions inquired about *glasses* of alcohol consumed, while the volume of a glass was not defined. A glass of beer, wine and hard liquor is assumed to contain a similar amount of pure alcohol. We do not know to what extent these limitations may have influenced our results, but the possible biases would probably attenuate the association between alcohol consumption and hip fracture.

Conclusion

The association between alcohol consumption and hip fracture varied according to age and gender. Men aged 30-59 years drinking frequently or consuming 14 glasses or more of alcohol per week, had increased risk of hip fracture compared to those drinking moderately. A different pattern was seen in women where the risk of hip fracture in those drinking never/seldom was significantly higher than in women drinking moderately both regarding frequency and amount of alcohol consumption. In women ≥ 60 years an inverse association was suggested between alcohol consumption and hip fracture. In women, use of wine was associated with lower fracture risk than other types of alcohol. However, much remains to be determined in understanding the complex associations between alcohol consumption and bone health.

Figure legends

Figure 1a – 1d. Hazard ratios (HR) with 95% confidence intervals (CI) for hip fracture in categories of number of glasses of alcohol per week. 1-6 gl/week as reference category (HR=1). Cohort of Norway. Panel a) Men aged 30-59 years; panel b) Women aged 30-59 years; panel c) Men aged ≥ 60 years; panel d) Women aged ≥ 60 years.

Acknowledgements

The authors wish to acknowledge the services of CONOR and the contributing research centers delivering data to CONOR. The authors are deeply grateful to Tomislav Dimoski (Norwegian Institute of Public Health (NIPH), the Statistics Norway, the Norwegian Patient Register and the staff at the Department of Pharmacoepidemiology (Norwegian Institute of Public Health - NIPH) contributing to the collection and encryption of the hip fracture data. Professor Aage Tverdal (NIPH) has generously managed the original project. Sincere thanks also to senior scientist Ståle Østhus (NIPH) for valuable guiding into the practical methods of calculating amount of alcohol consumption. We also want to acknowledge the other members of NOREPOS Research Group: Professor Nina Emaus, Consultant and Associate professor Guri Grimnes, Professor Berit Schei, Professor Siri Forsmo, Consultant Ellen Apalset and Post doc Cecilie Dahl.

Disclaimer: Data from the Norwegian Patient Register has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Directorate of Health is intended nor should be inferred.

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Table 1. Baseline characteristics according to frequency of alcohol consumption in men and women 30 years and older (n=141,925). Cohort of Norway¹

Frequency of alcohol consumption ²	Men			Women			
	Never/ seldom	Moderate (1/month – 2-3/week)	Total	Never/ seldom	Mod erate (1/m onth – 2- 3/we ek)	Frequent (4-7/week or more)	Total
Number of participants³	17,761	50,136	70,568	30,336	39,9 91	1,030	71,357
Age (years) (sd)	56.9 (15.0)	50.0 (13.1)	52.1 (14.0)	54.4 (15.2)	46.6 (11. 4)	55.4 (13.2)	50.1 (13.7)
Height (cm) (sd)	175.7 (7.1)	178.0 (6.7)	177.4 (6.9)	162.8 (6.7)	165. 4 (6.1)	165.3 (6.4)	164.3 (6.5)
Body mass index (kg/m ²) (sd)	26.6 (3.8)	26.4 (3.4)	26.5 (3.5)	26.6 (4.9)	25.1 (4.1)	24.2 (3.6)	25.7 (4.5)
Education (years) (sd) ⁴	10.9 (3.1)	12.1 (3.4)	11.9 (3.4)	10.7 (2.9)	12.4 (3.4)	14.5 (3.7)	11.7 (3.3)
Physical activity (range 1 (no) to 8 (max)) (sd)	4.7 (1.8)	5.1 (1.7)	5.0 (1.8)	4.4 (1.6)	5.0 (1.6)	5.4 (1.6)	4.8 (1.7)
Daily smoking (%)	24.7	31.7	29.9	25.5	36.3	35.9	31.7
Poor/not very good self-perceived health (%)	33.4	19.6	23.3	37.0	21.4	21.9	28.0
One or more chronic diseases (%) ^{4,5}	19.6	9.7	12.4	14.5	5.2	10.6	9.2
Single (%) ^{4,6}	30.5	33.7	32.8	38.8	37.0	44.3	37.9
Living in a city (≥20,000 inhab)	44.0	55.9	53.9	42.5	57.1	84.0	51.3

(%) ⁴							
Ever use of post-menopausal hormone therapy (%) ⁴	-	-	-	16.0	17.3	33.6	17.1

¹ All tests for differences across groups of alcohol consumption frequency had p-values <0.001 (Pearson 2-sided chi-squared test for categorical variables,

F-test (ANOVA) for continuous variables)

² Never/seldom=Teetotal, not last year, a few times last year; Moderate= Once a month to 2-3 times per week; Frequent=4-7 times per week or more

³ Means and standard deviations (sd) for continuous variables, proportions (%) for categorical variables. The numbers are based on participants with available data on hip fracture, age, height, body mass index, place of study, physical activity, smoking and self-perceived health.

⁴ Number of participants with available data on other variables: Marital status: 70,090 men, 71,289 women; Education: 69,470 men, 70,217 women;

Urban/rural living (living in a city): 70,482 men, 71,357 women; One or more disease: 70,290 men, 70,846 women; Post-menopausal hormone therapy: 54,239 women.

⁵ One or more of the diseases: Myocardial infarction, angina pectoris, stroke, diabetes, osteoporosis

⁶ Single= unmarried, divorced, separated, widowed

Table 2.

Number of hip fractures per 10,000 person years and hazard ratio (HR) with 95% confidence interval (CI) of hip fracture in men 30 years and older (n=70,568) in two age-strata according to frequency of alcohol consumption. Cohort of Norway

	No of hip fractures	Person years	Crude incidence of hip fracture ¹	HR (95% CI) ²	HR (95% CI) ³
Frequency of alcohol consumption					
Men <60 years					
Never/seldom (n=9,618)	76	147,817	5.1	1.13 (0.87-1.46)	1.12 (0.86-1.45)
Moderate (1/month – 2-3/week) (n=37,549)	237	580,228	4.1	1.0	1.0
Frequent (4- 7/week or more) (n=1,171)	15	16,305	9.2	1.87 (1.11-3.16)	1.73 (1.02-2.96)
Total (n=48,338)	328	744,350	4.4		
Men 60+ years ⁴					
Never/seldom (n=8,143)	653	87,563	74.6	1.09 (0.98-1.21)	1.09 (0.98-1.21)
Moderate (1/month – 2-3/week) (n=12,587)	817	147,398	55.4	1.0	1.0
Frequent (4- 7/week or	88	16,570	53.1	0.88 (0.71-1.10)	0.86 (0.69-1.07)

more) (n=1,500)					
Total (n=22,230)	1,558	251,531	61.9		

¹ Crude incidence of hip fractures per 10,000 person-years

² Adjusted for age

³ Adjusted for age, height, body mass index, smoking, physical activity, self-perceived health, place of study

⁴ Test for trend $P= 0.028$ (adjusted as model ³)

Table 3.

Number of hip fractures per 10,000 person years and hazard ratio (HR) with 95% confidence interval (CI) of hip fracture in women 30 years and older (n=71,357) in two age-strata according to frequency of alcohol consumption. Cohort of Norway

	No of hip fractures	Person years	Incidence of hip fracture ¹	HR (95% CI) ²	HR (95% CI) ³
Frequency of alcohol consumption					
Women <60 years ⁴					
Never/seldom (n=18,788)	198	292,928	6.8	1.23 (1.01-1.49)	1.29 (1.06-1.56)
Moderate (1/month – 2-3/week) (n=34,157)	231	525,010	4.4	1.0	1.0
Frequent (4-7/week or more) (n=642)	5	8,704	5.7	0.92 (0.38-2.22)	0.90 (0.37-2.21)
Total (n=53,587)	434	826,643	5.3		
Women 60+ years ⁵					
Never/seldom (n=11,548)	1,801	137,624	130.9	1.05 (0.96-1.15)	1.12 (1.02-1.23)
Moderate (1/month – 2-3/week) (n=5,834)	666	73,008	91.2	1.0	1.0
Frequent (4-7/week or more)	44	4,439	99.1	0.90 (0.66-1.22)	0.82 (0.60-1.12)

more) (n=388)					
Total (n=17,770)	2,511	215,071	116.8		

¹ Crude incidence of hip fractures per 10,000 person-years

² Adjusted for age

³ Adjusted for age, height, body mass index, smoking, physical activity, self-perceived health, place of study

⁴ Test for trend $P= 0.012$ (adjusted as model ³)

⁵ Test for trend $P= 0.005$ (adjusted as model ³)

| a)

c)

b)

d)