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Original Article

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The dose–response relationship of pre-menopausal alcohol consumption with age at menopause: a population study of 280 497 women in Norway

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Abstract

Background: Previous research suggests that alcohol consumption is associated with high age at menopause. Yet, knowledge about the dose–response relationship is inconsistent. Thus, we studied the pattern of the association of pre-menopausal alcohol consumption with age at natural menopause.

Methods: We performed a retrospective population-based study using self-reported data from 280 497 women aged 50–69 years attending the Norwegian breast cancer screening programme (BreastScreen Norway) during 2006–15. Associations of weekly alcohol consumption between the age of 20 and 49 years with age at menopause were estimated as hazard ratios (HRs) using Cox proportional hazard models with restricted cubic splines to allow for non-linear associations. We adjusted for year and place of birth, number of childbirths, educational level, body mass index and smoking habits.

Results: Mean age at natural menopause was 51.20 years (interquartile range: 49–54 years). The adjusted HR of reaching menopause was highest for women with no alcohol consumption (reference) and the HR decreased by alcohol consumption up to 50 grams per week (adjusted HR 0.87; 95% CI: 0.86–0.88). Above 50 grams, there was no further decrease in the HR of reaching menopause (P for non-linearity of <0.001).

Conclusions: Women who did not consume alcohol were youngest at menopause. The lack of a dose–response association among alcohol consumers implies virtually no relation of alcohol consumption with age at menopause. Our findings may suggest that characteristics of the women who did not consume alcohol, not accounted for in the data analyses, explain their younger age at menopause.

Keywords: Alcohol drinking, life course perspective, menopause, population study, risk factors.

Key Messages

- The dose–response relationship between alcohol consumption and age at menopause followed a non-linear pattern.
- Women who did not consume alcohol had the youngest age at menopause.
- Age at menopause increased with increasing alcohol consumption of up to 50 grams per week, but above 50 grams, there was no further increase.
- The relatively small difference in age at menopause between non-consumers and consumers of alcohol, and the lack of a dose–response association among the alcohol consumers, implies virtually no relation of alcohol consumption with age at menopause.
- Unmeasured characteristics of the non-consumers of alcohol may explain their younger age at menopause.

Introduction

Menopause is the permanent cessation of menstruation and a normal part of female ageing. Age at natural menopause varies considerably between women, from 40 to 60 years of age.[1] Early menopause is associated with osteoporosis, cardiovascular disease, and early death,[2,3] whereas late menopause is associated with increased risk of hormone-related cancers, such as certain breast and endometrial cancers.[4,5] Thus, identification of factors that determine age at menopause may improve our understanding of the biological mechanisms leading to important diseases in women.

Age at menopause is influenced by genetics[6] and displays geographical variation.[1] Previous research has also shown

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that lifestyle factors play a role.[1] It is well known that women who smoke cigarettes reach menopause 1–2 years earlier than non-smokers.[1] The effect of alcohol consumption on age at menopause remains unsettled. However, alcohol consumption has been assumed to decrease the rate of ovarian follicle atresia[7] and menopause occurs when only a few follicles remain in the ovaries.[8]

Several studies have reported no or minor effects of alcohol consumption on the age at natural menopause.[9–16] Conversely, a meta-analysis including 20 unique studies and a total of 105 207 women reported that low and moderate alcohol consumers reached menopause later than non-consumers.[17] The largest study included in this meta-analysis was based on data from 50 678 women in the Breakthrough Generations Study in the UK.[18] This study reported that age at menopause increased with increasing alcohol consumption (categorized into four groups, P for trend = 0.001). In contrast, a recent prospective study of 107 817 women in the Nurses' Health Study II found no dose–response relationship of alcohol consumption with the risk of early menopause.[19] However, the women with a moderate alcohol consumption had a lower risk of early menopause compared with non-consumers.

Previous knowledge about the dose–response relationship of alcohol consumption with age at menopause is inconsistent. Such inconsistency could possibly be explained by different data analytic approaches or lack of statistical power in previous studies. Valid knowledge about the dose–response pattern may confirm or reject a possible causal relationship. To date, no studies have allowed for non-linear association of alcohol consumption with age at menopause in their analytic approach. Therefore, we studied the pattern of the association of pre-menopausal alcohol consumption (in grams per week) with age at natural menopause among 280 497 women in Norway.

Materials and methods

Study design, recruitment and data collection

We performed a retrospective population-based study of women who had participated in the Norwegian breast cancer screening programme (BreastScreen Norway). This programme is administered by the Cancer Registry of Norway and mammographic screening is offered biennially to all women between the ages of 50 and 69 years with residency in Norway. During our study period, 2006–15, 84% of the invited women participated in the screening programme at least once.[20] Non-attendance has been shown to be associated with low educational attainment and immigrant background.[21]

All women who participated in the breast cancer screening programme during the years 2006–15 were asked to answer two self-administered questionnaires.[22,23] The first questionnaire included questions about socio-demographic factors, reproductive factors, height, weight and health behaviours before the age of 50 years. The second questionnaire included questions about current health behaviours along with questions about menstruation, surgery on the uterus or the ovaries, and use of menopausal hormone therapy.

Study sample

Of the 394 206 women who answered both questionnaires (71.2% of the total sample), we excluded 91 987 (23.3%) women due to missing information about alcohol consumption (Figure 1). We also excluded women who had never had menstrual periods (n = 157) and women who had missing or implausible values of age at menopause (<15 or >71 years) (n = 35 572). Finally, we excluded women who had undergone surgery with removal of the uterus and/or both ovaries but did not report age at such surgery (n = 2599). Thus, 280 497 women were included in our study sample and they were born during the years 1936–66.

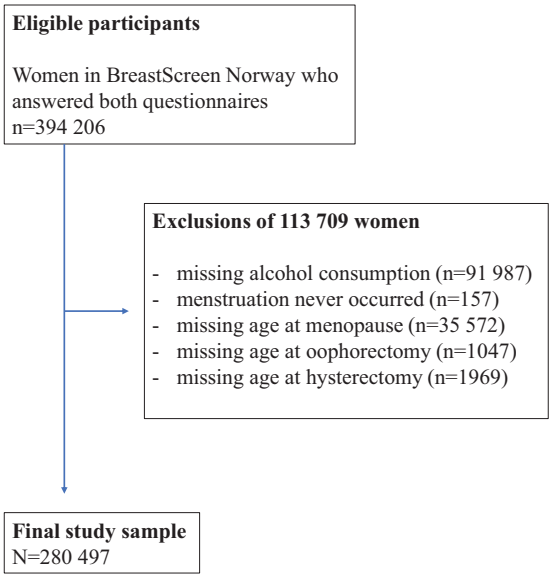

Figure 1. Flow chart of the study sample

Main study factors

Our outcome variable was age at natural menopause (in years). Age at menopause was based on the questions: 'Are you still having menstrual periods?' (yes/yes, but irregularly/no) and 'If you no longer have menstrual periods, how old were you at your last menstrual period?'.

Our main exposure variable was alcohol (in grams) consumed per week. Information about previous alcohol consumption was based on the following questions: 'Did you drink alcohol?' (yes/no) and 'If yes, indicate the average number of glasses of beer, wine and liquor you consumed per month'. The women answered separately for each of the following age intervals; 20–29, 30–39 and 40–49 years old. We converted glasses into grams of alcohol by assuming that one glass of beer (500 mL) contains 20 grams of alcohol, one glass of wine (125 mL) 12 grams and one glass of liquor (50 mL) 14 grams.[24] Thereafter, we calculated mean alcohol consumption in grams per week between the ages of 20 and 49 years. Alcohol consumption was included as a continuous variable in the main analyses. In additional analyses, we included alcohol consumption as a categorical variable: no alcohol consumption (reference), 1–25, 26–50, 51–75, 76–100, 101–125 and >125 grams per week.

Other study factors

We performed a literature search and used directed acyclic graphs to identify possible confounding factors of the association of alcohol consumption with age at menopause.[25] We identified year of birth (birth cohort), place of birth, number of childbirths, educational level, body mass index (BMI, kg/m^2) and smoking habits as possible confounders since these factors have been associated with alcohol consumption[26–29] and age at menopause.[1,30,31] Year of birth and BMI were included as

continuous variables in the data analyses, whereas we treated place of birth (Norway, Europe, outside Europe), number of childbirths (0, 1, 2, ≥3), educational level (<high school, high school, <4 years of university, ≥4 years of university) and smoking habits (never smoker, former smoker, smoker) as categorical variables.

Statistical methods

Since not all women in our study had reached menopause, we applied time-to-event analyses to estimate the mean age at natural menopause with 95% CIs. The follow-up time was from birth (age 0 years) until age at menopause or censoring. Women who had regular (17.9%) or irregular menstrual cycles (8.3%) were censored at their attained age at data collection. Women who had undergone surgical removal of the uterus (6.2%), both ovaries (0.6%) or both surgeries (2.9%) prior to natural menopause were censored at their attained age at surgery.

The association of grams of alcohol consumed per week (as a continuous variable) with age at menopause was estimated as crude and adjusted hazard ratios (HRs) by applying Cox proportional hazard models with a restricted cubic spline function with knots at the 5th, 35th, 65th and 95th percentiles of the alcohol distribution. Tests for non-linearity were conducted by testing the coefficients of the spline transformations equal to zero. We used 0 grams of alcohol per week as the reference (no alcohol consumption). HR of <1.00 indicates later menopause compared with the reference. The proportional hazards assumption for applying Cox proportional hazard models was evaluated by the Schoenfeld residuals and by inspection of the log–log plots.

We estimated crude HRs (Model 1). Thereafter, we made adjustment for year of birth to account for any unmeasured temporal changes that may have influenced alcohol consumption and/or age at menopause (Model 2). In the final model, we also included place of birth, number of childbirths, educational level, current BMI and smoking habits (Model 3). We performed separate analyses according to smoking habits (never smoker, former smoker, smoker).

Since women who use systemic menopausal hormone therapy (HT) or hormonal intrauterine devices (IUDs) may experience irregular or absent vaginal bleedings,[32] such use could lead to inaccurate reporting of age at menopause. Therefore, we performed supplemental analyses among the women who had never used systemic menopausal HT or hormonal IUDs. We also performed supplemental analyses after excluding the non-consumers of alcohol (reference 25 grams). To check for consistency of our findings, we performed additional analyses by including alcohol consumption as a categorical variable (no alcohol consumption, 1–25, 26–50, 51–75, 76–100, 101–125, >125 grams of alcohol per week) by applying Cox proportional hazard models without the restricted cubic spline function. All data analyses were performed by using the statistical software package Stata/IC version 16.0 (StataCorp, College Station, TX, USA).

Results

At the time of data collection, the women's mean age was 56.3 years (SD 5.7 years, range 48–71 years) and 64.1% had undergone natural menopause (Table 1). The mean alcohol consumption between the ages of 20 and 49 years was 21.2 grams (SD 23.2 grams) per week. Further descriptions of the study sample are presented in Table 1 and Supplementary Table S1 (available as Supplementary data at *IJE* online). The women who were excluded from the study sample due to lack of information about alcohol consumption (23.3%) were older, had lower education, were more often smokers and were younger at menopause compared with the women who were included (Supplementary Table S2, available as Supplementary data at *IJE* online).

Table 1. Characteristics of the study sample: 280 497 women in BreastScreen Norway (2006–15)

Characteristic	Value[a]
Natural menopause, *n* (%)	
Yes	179 694 (64.1%)
No	100 803 (35.9%)
Surgery on uterus or ovaries before menopause, *n* (%)	
Hysterectomy	17 405 (6.5%)
Bilateral oophorectomy	1576 (0.6%)
Hysterectomy and bilateral oophorectomy	8300 (3.1%)
Age at data collection, years, mean (SD)	56.3 (5.7)
Ever used systemic menopausal hormone therapy, *n* (%)	88 616 (31.6%)
Ever used hormonal intrauterine device, *n* (%)	60 036 (21.4%)
Ever used oral contraceptives, *n* (%)	153 092 (54.6%)
Place of birth, *n* (%)	
Norway	259 938 (93.5%)
Other countries in Europe	11 574 (4.2%)
Countries outside Europe	6441 (2.3%)
Missing information	2544
Number of childbirths, *n* (%)	
0	24 713 (9.7%)
1	28 453 (11.2%)
2	107 784 (42.3%)
≥3	93 603 (36.8%)
Missing information	25 944
Educational level, *n* (%)	
<High school	59 643 (21.6%)
High school	114 702 (41.5%)
<4 years of college/university	62 395 (22.6%)
≥4 years of college/university	39 546 (14.3%)
Missing information	4211
Body mass index at data collection, kg/m^2, mean (SD)	25.8 (4.6)
Missing information	20 361
Smoking habits at data collection, *n* (%)	
Never smoker	117 479 (42.9%)
Former smoker	88 816 (32.4%)
Smoker	67 747 (24.7%)
Missing information	6455

[a] Values are number (%) or mean (SD), as shown.

The mean age at natural menopause was 51.20 years (95% CI: 51.18–51.22 years) and the median age was 52 years (interquartile range: 49–54 years). The crude HR of reaching menopause was highest for women with no alcohol consumption and the HR estimates decreased by increasing alcohol consumption up to 50 grams per week (HR 0.87; 95% CI: 0.86–0.88). Above 50 grams of alcohol per week, the HR estimates tended to increase, but the confidence intervals were wide (Figure 2 and Table 2). Similarly, in the two adjusted models, the HR of reaching menopause was highest for women with no alcohol consumption and decreased by alcohol consumption up to 50 grams per week (Figure 2 and Table 2). After adjustment for birth year, the estimated HR of menopause at 50 grams of alcohol per week was 0.93 (95% CI: 0.92–0.94) (Model 2). The HR at 50 grams decreased to 0.87 (95% CI: 0.86–0.88) after additional adjustment for place of birth, number of childbirths,

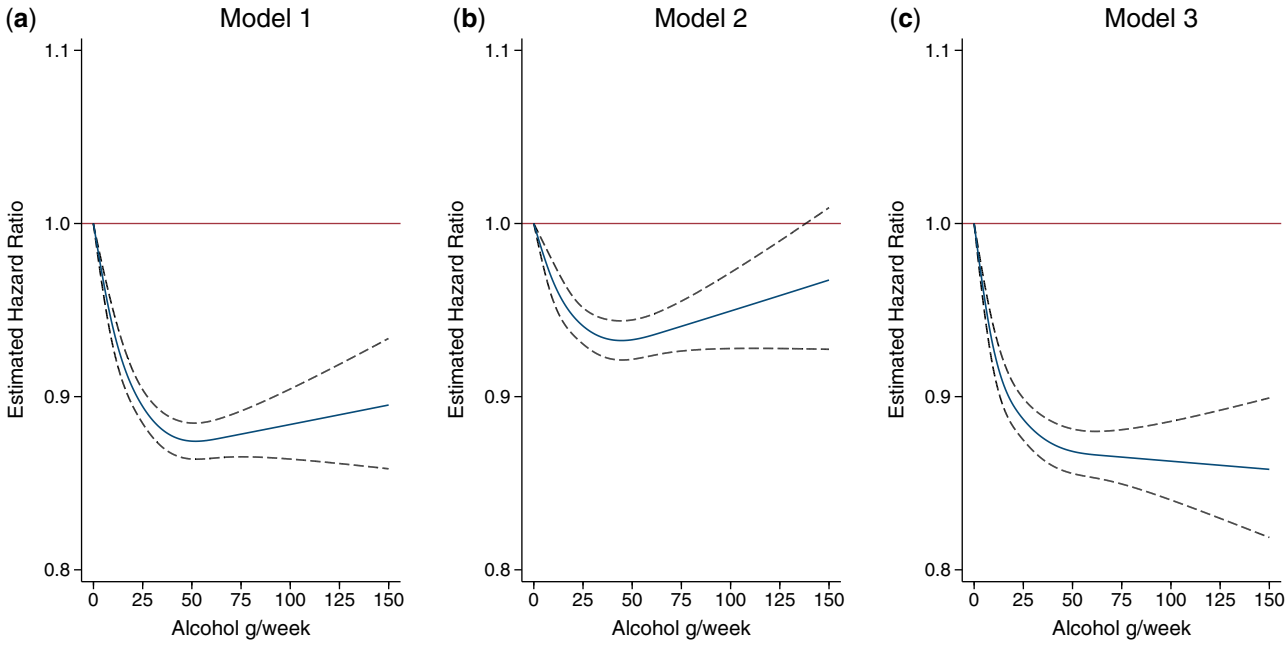

Figure 2. The hazard ratios (solid line) of reaching natural menopause with 95% CIs (dashed lines) according to alcohol consumption (grams/week) among 280 497 women in BreastScreen Norway 2006–15. (a) Crude hazard ratios. (b) Hazard ratios adjusted for year of birth. (c) Hazard ratios adjusted for year of birth, place of birth, number of childbirths, educational level, current body mass index and smoking habits ($n = 228\,860$). The associations of alcohol consumption with age at menopause were estimated as crude and adjusted hazard ratios by applying the Cox proportional hazard model with a restricted cubic spline function with knots at the 5th, 35th, 65th and 95th percentiles of the alcohol distribution. The reference is no alcohol consumption (0 grams). In Model 3, the study sample was restricted to women with information on all variables. A hazard ratio of <1.00 indicates later menopause compared with the reference

Table 2. Hazard ratios of reaching menopause according to pre-menopausal alcohol consumption (included as a continuous variable) among 280 497 women in BreastScreen Norway, born during the years 1936–66

	Model 1		Model 2		Model 3	
Alcohol, grams/week	Crude HR	95% CI	Adjusted HR[a]	95% CI	Adjusted HR[b]	95% CI
0 g	Reference		Reference		Reference	
25 g	0.89	0.88–0.90	0.94	0.93–0.95	0.89	0.87–0.90
50 g	0.87	0.86–0.88	0.93	0.92–0.94	0.87	0.86–0.88
75 g	0.88	0.87–0.89	0.94	0.93–0.96	0.87	0.85–0.88
100 g	0.88	0.86–0.90	0.95	0.93–0.97	0.86	0.84–0.89
125 g	0.89	0.86–0.92	0.96	0.93–0.99	0.86	0.83–0.89
150 g	0.90	0.86–0.93	0.97	0.93–1.01	0.86	0.82–0.90
P for non-linearity		<0.001		<0.001		<0.001

The associations were estimated as crude and adjusted HRs by applying a Cox proportional hazard model with a restricted cubic spline function with knots at the 5th, 35th, 65th and 95th percentiles of the alcohol distribution (grams per week). Alcohol consumption values represent specific points along the distribution. The reference is no alcohol consumption (0 grams). HR <1.00 indicates later menopause compared with the reference.

[a] Model adjusted for year of birth.

[b] Model adjusted for year of birth, place of birth, number of childbirths, educational level, current body mass index and smoking habits. The study sample was restricted to women with information on all variables ($n = 228\,860$).

HR, hazard ratio.

educational level, BMI and smoking habits (Model 3). In all models, consumption above 50 grams of alcohol per week did not further decrease the HRs of menopause (Figure 2 and Table 2). Thus, the association of alcohol consumption with age at menopause displayed a non-linear dose–response pattern (*P* for non-linearity of <0.001). Also in the separate analyses according to smoking habits, we found a non-linear association of alcohol consumption with age at menopause (Table 3). We found similar results after excluding women (31.9%) who had used systemic menopausal HT or hormonal IUDs (Supplementary Table S3, available as Supplementary data at *IJE* online). In the analyses restricted to alcohol consumers (81.8%), the HR estimates suggest no or minimal association of alcohol consumption with age at menopause (Supplementary Table S4, available as Supplementary data at *IJE* online).

We performed additional analyses by using alcohol consumption as a categorical variable (Table 4). The dose–response patterns and the strength of the associations were very similar to the results of the spline models (Table 2). The mean age at natural menopause was 50.80 years among non-consumers (reference), 51.20 years for women who consumed 1–25 grams of alcohol per week (adjusted HR 0.92, 95% CI: 0.91–0.93)

Table 3. Hazard ratios of reaching menopause according to pre-menopausal alcohol consumption (included as a continuous variable) by strata of smoking habits

	Never smokers (*n*=95 995)		Former smokers (*n*=75 453)		Smokers (*n*=55 412)	
Alcohol, grams/week	**Adjusted HR**	**95% CI**	**Adjusted HR**	**95% CI**	**Adjusted HR**	**95% CI**
0	Reference		Reference		Reference	
25	0.89	0.88–0.91	0.90	0.87–0.92	0.88	0.86–0.91
50	0.88	0.86–0.90	0.87	0.85–0.90	0.85	0.83–0.88
75	0.86	0.83–0.89	0.87	0.84–0.90	0.86	0.83–0.89
100	0.85	0.80–0.89	0.87	0.83–0.91	0.87	0.83–0.91
125	0.83	0.77–0.89	0.87	0.82–0.92	0.88	0.83–0.93
150	0.82	0.75–0.90	0.87	0.80–0.93	0.89	0.82–0.96
P for non-linearity		<0.001		<0.001		<0.001

The associations were estimated as crude and adjusted HRs by applying a Cox proportional hazard model with a restricted cubic spline function with knots at the 5th, 35th, 65th and 95th percentiles of the alcohol distribution (grams per week). Alcohol consumption values represent specific points along the distribution. The reference is no alcohol consumption (0 grams). HR <1.00 indicates later menopause compared with the reference.
Models adjusted for year of birth, place of birth, number of childbirths, educational level and current body mass index. The study sample was restricted to women with information on all variables.
HR, hazard ratio.

Table 4. Mean age at menopause and hazard ratios of reaching menopause according to pre-menopausal alcohol consumption among 280 497 women in BreastScreen Norway, born during the years 1936–66

				Model 1		Model 2		Model 3	
Alcohol, grams/week	**No. of women**	**Mean age (years)**	**95% CI**	**Crude HR**	**95% CI**	**Adjusted HR[a]**	**95% CI**	**Adjusted HR[b]**	**95% CI**
0	51 065	50.80	50.76–50.85	Reference		Reference		Reference	
1–25	140 609	51.20	51.17–51.23	0.92	0.91–0.93	0.95	0.94–0.97	0.92	0.91–0.93
26–50	61 731	51.46	51.41–51.51	0.87	0.86–0.89	0.93	0.91–0.94	0.88	0.86–0.89
51–75	18 064	51.47	51.38–51.56	0.86	0.85–0.88	0.93	0.91–0.95	0.87	0.85–0.89
76–100	5746	51.57	51.39–51.74	0.87	0.84–0.90	0.93	0.90–0.97	0.86	0.83–0.90
101–125	1916	51.30	51.06–51.54	0.87	0.82–0.93	0.94	0.89–1.00	0.86	0.81–0.92
>125	1366	51.17	50.83–51.50	0.92	0.86–0.99	0.99	0.92–1.06	0.86	0.80–0.93

The associations were estimated as crude and adjusted HR using the Cox proportional hazard model. HR <1.00 indicates later menopause compared with the reference group (no alcohol consumption).
[a] Model adjusted for year of birth.
[b] Model adjusted for year of birth, place of birth, number of childbirths, educational level, current body mass index and smoking habits. The study sample was restricted to women with information on all variables ($N = 228\,860$).
HR, hazard ratio.

and 51.47 years for women who consumed 51–75 grams per week (adjusted HR 0.87, 95% CI: 0.85–0.89) (Table 4).

Discussion

In this population study of 280 497 women in Norway, women with no alcohol consumption during their pre-menopausal years were younger at natural menopause than women who consumed alcohol. Age at menopause increased with increasing alcohol consumption up to 50 grams per week, but above 50 grams, there was no further increase. Our findings do not support a linear dose–response relationship of alcohol consumption with age at menopause.

Strengths and limitations

Our study is the largest study yet about the association of pre-menopausal alcohol consumption and age at natural menopause. As far as we know, no previous studies have investigated the dose–response relationship of alcohol consumption with age at menopause by including alcohol consumption as a continuous variable in the data analytic approach and allowing for non-linear association.

Our results may be biased since some women in the source population did not participate in the breast cancer screening programme and immigrant women, women with low income and unmarried women were under-represented.[21] In addition, women without information about alcohol consumption were excluded from our study sample. These women were older, had lower education, were more often smokers and were younger at menopause compared with women with complete information (Supplementary Table S2, available as Supplementary data at *IJE* online). It is possible that the data were not missing completely at random, since the oldest women and women with low education were less likely to consume alcohol, whereas smokers were more likely to consume alcohol (Supplementary Table S1, available as Supplementary data at *IJE* online). Also, we cannot rule out that the non-responders were more prone to being non-drinkers, or heavy drinkers unwilling to report their consumption, than the women included. Non-response could therefore be related to drinking behaviours and the exclusion of women without information about alcohol consumption could have biased the direction and the magnitude of the estimated association.

Although age at menopause may have been erroneously reported in our study, we have little reason to believe that errors in the reporting of age at menopause were related to the level of alcohol consumption. Thus, imprecise reporting of

age at menopause or alcohol consumption may have resulted in an underestimation of the associations. In our study, alcohol consumption was based on self-reports at the time of data collection. Alcohol consumption among women has become more socially acceptable in the Nordic countries during the last decades. Therefore, alcohol consumption at a younger age may have been overreported.[33] The previous studies suggest that self-reported alcohol consumption is lower than the actual consumption.[34] Our participants reported their typical mean monthly alcohol consumption. However, the reporting of both the quantity and the frequency of alcohol consumption appears to have better validity.[35]

In our study, age at menopause was reported when the women were between 50 and 69 years old. A Swedish study found that self-reported age at menopause was fairly accurate almost 20 years after the occurrence of menopause.[36] Other studies have reported a decrease in the validity and reliability in reported age at menopause with time.[37,38] Age at natural menopause is defined as the age at last menstrual period and should be confirmed by 1 year without menstrual periods.[39] In our study, 2.8% reported their last menstrual period within the year prior to data collection, and menstrual periods could possibly reoccur. It is unlikely, however, that exclusion of this small proportion would have influenced our estimates. The use of systematic menopausal HT and hormonal IUDs may also have caused imprecise reporting of age at menopause.[32] We excluded these users in supplementary analyses and found a similar pattern as in the main analyses.

We first made adjustment for the woman's year of birth since alcohol consumption and age at menopause have changed over time.[29,30] We made additional adjustment for place of birth, number of childbirths, educational level, current BMI and smoking habits.[1,26–31] Given the importance of smoking on age at menopause and the well-established relationship between alcohol consumption and smoking, we also performed separate analyses according to smoking habits. The association was similar in all strata, but the CIs were wide and overlapping (Table 3). A confounder is associated with and precedes both the exposure and the outcome.[25] Thus, we did not make adjustment for variables with uncertain relation to alcohol consumption or age at menopause, such as hormonal contraceptive use and breastfeeding.[40,41] Unfortunately, we lacked information about BMI at young age, diet and health status. We used BMI at the time of data collection as a proximate measure of BMI at young age.[25] Life-long abstainers of alcohol may have poorer health than alcohol consumers[42] and women with chronic disease may be at increased risk of early menopause.[43] Adjustment for chronic disease would probably attenuate our estimated association of alcohol consumption with age at menopause. Thus, residual confounding may remain.

Comparison with other studies

Comparison with other studies is challenging since few studies have included alcohol consumption as a continuous variable. In studies in which alcohol consumption is categorized, the categories differ between studies, probably as a result differences in reporting. In accordance with previous studies,[18,19,44,45] we found that women with no alcohol consumption were younger at menopause compared with women who consumed alcohol. In the Breakthrough Generations Study,[18] the mean alcohol consumption between the ages of 25 and 49 years was grouped into four categories (0, 0.1–6.9, 7–13.9, >14 UK units per week) and the HR of reaching menopause decreased by increasing alcohol consumption. The study of 107 817 women in the USA grouped alcohol into six categories (non-drinker, 0.1–4.9, 5.0–9.9, 10.0–14.9, 15.0–29.9, ≥30.0 grams per day) and found that non-consumers had higher risk of early menopause than women with a moderate alcohol consumption (10–14.9 grams per day), but no trend was reported.[19] A study of 7719 women in Canada grouped alcohol consumption into three categories (never, drinks less than weekly, drinks at least weekly)[44] and found that non-consumers reached menopause earlier than alcohol consumers. Finally, a study of 12 676 women in Central and Eastern Europe grouped alcohol consumption into four categories (never, low, moderate, every day).[45] Also in that study, non-consumers reached menopause earlier than alcohol consumers, but a dose–response relationship of alcohol consumption with age at menopause was not found. This finding is in line with our results.

Interpretations

Menopause occurs when the number of ovarian follicles reaches a critical level.[8] It has been proposed that alcohol consumption decreases the rate of follicle atresia and thereby delays menopause.[7,46] Such a hypothesis has been supported by higher ovarian follicle counts in alcohol consumers compared with non-consuming women.[7] Another study found no relation of alcohol consumption with ovarian follicle count.[47] In contrast, a cross-sectional study of 1654 women aged 23–34 years found that frequent 'binge-drinkers' (at least two binges per week) had 26% lower levels of anti-Müllerian hormone compared with drinkers who never binged, indicating that alcohol may increase the rate of ovarian follicle atresia.[46] Alcohol consumption has been associated with increased oestrogen levels but the mechanisms are not well understood.[48]

If alcohol truly influences the ovarian follicle reserve, it would be expected that the association of alcohol consumption with age at menopause displays a linear dose–response pattern. We found, however, no evidence of a dose–response relation of alcohol consumption with age at menopause above 50 grams of alcohol per week. Notably, there was larger difference in the HR of reaching menopause between non-consumers and consumers of 1–25 grams per week than between consumers of 1–25 and >125 grams per week. Also the results of the analyses restricted to alcohol consumers do not support a dose–response pattern (Supplementary Table S4, available as Supplementary data at *IJE* online). Thus, our findings may suggest that certain characteristics of women who do not consume alcohol, not accounted for in our data analyses, may explain their younger age at menopause.

Underlying differences in health traits or health status between non-consumers and consumers of alcohol may explain our findings. Previous research has reported reduced risk of several diseases, such as coronary heart disease, certain cancers and all-cause death, among people with moderate drinking behaviours.[26,48,49] However, studies based on modern epidemiologic methods, such as Mendelian randomization and inverse probability weighting, have challenged previously reported health benefits of moderate drinking behaviours.[50,51] The estimated positive effects of a moderate alcohol consumption in previous studies may therefore be explained by self-selection and lack of comparability between the exposed and non-exposed.[26,52,53] We propose that

underlying unmeasured health-related characteristics explain the younger age at menopause among the life-long abstainers.

Both high alcohol consumption and late menopause are associated with increased risk of certain breast and endometrial cancers after the menopause.[5,54] The relatively small difference in age at menopause between non-consumers and consumers of alcohol, and the modest association among women who consumed alcohol (Supplementary Table S4, available as Supplementary data at *IJE* online), imply virtually no relation of alcohol consumption with age at menopause. Thus, our results also suggest that the increased risk of breast and endometrial cancer in women with a high alcohol consumption[24,54] is not likely to be explained by a delayed menopause in these women.

In conclusion, age at natural menopause increased with increasing alcohol consumption up to 50 grams per week in this study of 280 497 women in Norway. Above 50 grams of alcohol per week, there was no further increase. Our findings suggest virtually no relation of alcohol consumption with age at menopause.

Ethics approval

This study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (reference no. 226831 REK South-East D) and by the Data Protection Official at Akershus University Hospital (reference no. 21/02604).

Data availability

The data set analysed in the current study is not publicly available. It was obtained from the Cancer Registry of Norway under a specific ethical approval by the Regional Committee for Medical and Health Research Ethics in the South-Eastern Health Region of Norway. Researchers with appropriate approvals can apply for Norwegian health registry data from https://helsedata.no/.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

E.K.B. and A.E. had the original idea for this study. J.R.L., E.K.B., A.E. and S.H. contributed to the study design, the planning of the data analytic approaches and the interpretation of the results. S.H. was responsible for the data collection. J.R.L. performed the data analyses and wrote the first version of the manuscript. All authors commented on previous versions of the manuscript and read and approved the final manuscript. E.K.B. is the guarantor of the study.

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Conflict of interest

None declared.

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