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Association of alcohol consumption with the onset of natural menopause: a systematic review and meta-analysis

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BACKGROUND: Early onset of menopause is associated with long-term health risks, including cardiovascular disease and premature death. Although alcohol intake has been suggested to affect the age at which natural menopause occurs, results from observational studies are not consistent.

OBJECTIVE AND RATIONALE: In the view of the differing risks to the health of early menopause and the increasing trends in alcohol consumption in women, in this systematic review, we aimed to quantify the association between all levels of alcohol consumption and menopause onset.

SEARCH METHODS: Six electronic databases (Medline, Embase, Cochrane, PubMed, Google Scholar and Web of Science) were systematically searched until 4 November 2015 to identify relevant studies assessing the association between alcohol consumption and onset of menopause. Two independent reviewers screened the titles and abstracts of all initially identified studies according to the selection criteria. Studies were sought if they (i) were observational cross-sectional, prospective and interventional studies, (ii) had reported on natural onset of menopause, (iii) had reported on alcohol consumption, (iv) had assessed the association between alcohol consumption and menopause onset, (v) were conducted in humans and (vi) were not conducted in patients with cancer. Data were extracted by two independent

reviewers using a predesigned data-collection form. The primary exposure variable was the presence of active alcohol drinking at baseline compared with a reference group of non-drinkers. Pooled relative risks (RRs) were calculated.

OUTCOMES: Of the 1193 references (all in English language) reviewed for eligibility, 22 articles based on 20 unique studies were included in the final analysis. A total of 41 339 and 63 868 non-overlapping women were included in the meta-analysis of cross-sectional and observational cohort studies, respectively. In cross-sectional studies, the pooled RR for earlier onset of menopause was 0.86 (95% confidence interval (CI): 0.78–0.96) between drinkers versus non-drinkers. Analysis of the levels of alcohol consumed showed that low and moderate alcohol consumption (more than one drink per week (RR = 0.60; 95% CI: 0.49–0.75) and three or fewer drinks per week (RR = 0.75; 95% CI: 0.60–0.94)) were associated with later menopause onset, compared to non-drinkers. In prospective studies, RR for earlier menopause onset was 0.95 (95% CI: 0.91–0.98) when comparing women who reported drinking alcohol versus women who did not. Analysis of the dose of alcohol consumed showed that low-to-moderate alcohol intake (0–8 g/day (RR = 0.95; 95% CI: 0.93–0.98), and 16 g/day (RR = 0.89, 95%CI: 0.86–0.92)) was associated with later menopause onset, compared to non-drinking.

WIDER IMPLICATIONS: The findings of this review indicate that alcohol consumption, particularly low and moderate alcohol intake, might be associated with later onset of menopause although the magnitude of the association is low. Further studies are needed to corroborate these findings, clarify the level of alcohol intake at which menopause is delayed and identify the potential mechanisms behind this association.

Key words: alcohol / low and moderate drinking / menopause / age of menopause / menopause onset / late menopause / early menopause.

Introduction

Menopause is an inevitable component of aging and encompasses the permanent cessation of menses following the loss of ovarian follicular activity. Menopause can occur naturally (spontaneously)—on average around age 51years—or be induced through a medical intervention, such as the removal of both ovaries (surgical menopause), as well as ovarian failure resulting from chemotherapy or radiotherapy (Harlow *et al.*, 2012).

The age at natural menopause holds intrinsic clinical and public health interest because the age at which the final menstrual period occurs may be a marker of aging and health (Gold, 2011). Early age at natural menopause is associated with long-term health risks, including shorter overall survival and increased risk of mortality, cardiovascular disease, osteoporosis and a reduced risk of breast, endometrial and ovarian cancer (Jacobsen *et al.*, 1999; Atsma *et al.*, 2006; Shuster *et al.*, 2010). Also, women who undergo natural menopause before age 45 years have an earlier decline in cognitive function and an increased risk for mood disorders (Gold, 2011). Furthermore, onset of menopause is also a determinant of fertility problems due to the current tendency in western countries to postpone childbearing (Treloar *et al.*, 1967). Five to ten percent of women experience natural menopause before the age of 45 years and one-third of women's lives is spent postmenopause (Cramer and Xu, 1996). To date, although genetic, neuroendocrine and environmental factors have been suggested to play a role, it is unclear why ovaries stop their function at menopause (Gold, 2011). Identifying modifiable risk factors that may influence age at natural menopause may have far-reaching implications for reproductive and other health issues.

Alcohol intake has been suggested to affect the age of natural menopause; however, the pathways are not fully understood. Initially, it was suggested that alcohol consumption may be associated with earlier age at menopause, based on observed adverse effects on animal reproduction (Gavaler, 1985). Alcohol intake was correlated with higher levels of follicle-stimulating hormone (FSH) in women of childbearing age and with oxidative stress in rats, which have been associated with ovarian damage (Faut *et al.*, 2009; Li *et al.*, 2013; Rachdaoui and Sarkar, 2013). However, recent data show that alcohol can induce a rise in circulating estrogen levels, which has been associated with delayed onset of menopause (Gavaler and Rosenblum, 1987; Ginsburg *et al.*, 1996; Muti *et al.*, 1998; Gill, 2000). Furthermore, alcohol consumption is not associated with menstrual cycle disturbances or with a decrease in the number of recruited antral follicles, important indicators of ovarian age, whereas abstainers from alcohol have shown higher odds of irregular and short cycles (Kinney *et al.*, 2007; Schliep *et al.*, 2015). The data from observational studies regarding a connection of alcohol consumption to onset of menopause are also inconsistent; a few studies showing alcohol consumption to be associated with earlier onset of menopause (Sammel *et al.*, 2009), some showing no effect (Bernis and Reher, 2007; Nagata *et al.*, 2012) and several studies indicating delayed onset of menopause (Torgerson *et al.*, 1997; Cooper *et al.*, 2001; Morris *et al.*, 2012). Therefore, there is a need for a comprehensive assessment of the association between alcohol consumption and onset of menopause. This is of particular importance since several studies have recently reported a rise in alcohol consumption among premenopausal women (Fleming, 1996; Crome and Kumar, 2007; Johansson *et al.*, 2012). Additionally, similar to age of menopause, there is a paradoxical association between alcohol consumption and other health outcomes in women. Low-to-moderate alcohol consumption (as well as late menopause onset) is associated with reduced risk of cardiovascular diseases and Type 2 diabetes (Atsma *et al.*, 2006; Ronksley *et al.*, 2011). Paradoxically, epidemiological studies show a dose–response relationship between alcohol consumption (as well as age of menopause) and increased risk of breast cancer (Hamajima *et al.*, 2002; Collaborative Group on Hormonal Factors in Breast Cancer, 2012).

We conducted a systematic review and meta-analysis of all available evidence to quantify the association of alcohol consumption with onset of menopause.

Methods

Data sources and search strategy

This review was conducted in accordance with the PRISMA and MOOSE guidelines. Studies were sought using Medline, Embase, Cochrane, PubMed, Google Scholar and Web of Science from inception until 4, November 2015 (date last searched) with the help of an experienced information specialist (W.M.B.). The computer-based searches combined terms related to the exposure (e.g. alcohol, drinking behavior) and outcomes (e.g. a combination of terms for menopause, with terms for timing, e.g. late, premature), without any language restriction. Details on the search strategy are provided in Supplementary Data. Furthermore, in order to identify additional studies, we checked the reference lists of relevant studies and contacted experts in the field.

Study selection and eligibility criteria

Two independent reviewers screened the titles and abstracts of all initially identified studies according to the selection criteria. Studies were included if they (i) were observational cross-sectional, prospective and interventional studies, (ii) had reported on natural menopause onset, (iii) had reported on drinking behavior, (iv) had examined the association between drinking behavior (as primary exposure) and menopause onset, (v) were conducted in humans and (vi) were not conducted in patients with cancer. No exclusion was performed with regard to other disease status of women included in the studies. Full texts were retrieved from studies that satisfied all selection criteria.

Data extraction and quality assessment

A predesigned data extraction form was used to extract the relevant information. The form included questions on study design, baseline population, location; age at baseline, duration of follow-up, reported degree of adjustment, type of outcome and reported risk estimates. In the case of multiple publications, the most up-to-date or comprehensive information was included. The primary exposure variable was the presence of active alcohol drinking at baseline compared with a reference group of non-drinkers. Whenever available, we extracted information on the amount of alcohol consumed, using grams of alcohol per day and/or drinks per week as the common unit of measurement. We calculated 7 kcal of alcohol as 1 g; for Japan 1 standard drink equals 19.75 g and 25 ml, and in the UK, 1 unit equals 8 g and 10 ml of alcohol (Boyle *et al.*, 2013). Study quality was assessed by two independent reviewers based on the nine-star Newcastle–Ottawa Scale (NOS) using three predefined domains, namely selection of participants (population representativeness), comparability (adjustment for confounders) and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability and three points for outcome. Studies that received a score of nine stars were judged to be at low risk of bias, studies that scored seven or eight stars were considered at medium risk and those that scored six or less were considered at high risk of bias.

Data synthesis and analysis

The relative risk (RR) was used as the common measure of association across studies. An RR <1 implies that alcohol consumption was associated with later onset of menopause and an RR >1 implies that alcohol consumption was associated with earlier onset of menopause. The inverse-variance weighted method was used to combine RRs to produce a pooled RR using random-effects models to allow for between-study heterogeneity. Additionally, we reported the results using fixed-effect models. Fixed-effects models were also used to pool RRs of the same study (e.g. the estimate for drinkers versus non-drinkers was pooled using fixed-effects models when risk estimates were reported for different categories of alcohol intake). Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic and was distinguished as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $< 75\%$) or high ($I^2 \geq 75\%$) (Higgins *et al.*, 2003). Publication bias was evaluated through a funnel plot and Egger's test (Egger *et al.*, 1997). Since smoking and socioeconomic status may be important confounders in the association between alcohol intake and menopause onset, when possible we performed a sensitivity analysis excluding studies that did not adjust for either of these factors. Also, we restricted all the main analyses to studies that reported estimates adjusted for baseline body mass index (BMI) and age. Study-level characteristics including geographical location, number of total participants, risk of bias and duration of follow-up for prospective studies were pre-specified as characteristics for the assessment of heterogeneity and were evaluated using stratified analyses and random-effects meta-regression (Thompson and Sharp, 1999). All tests were two-tailed and *P*-values ≤0.05 were considered significant. STATA release 12 (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

Results

Identification of relevant studies

The search strategy identified 678 unique citations (all in English language). Furthermore, we screened another set of 515 citations that were found in the reference lists of the relevant articles (a total of 1193 articles). Following initial screening based on titles and abstracts, 31 articles were retrieved and evaluated further. Of these articles, 9 were excluded for reasons shown in Fig. 1. The remaining 22 articles, based on 20 unique studies, met the inclusion criteria (Tables 1 and 2). The baseline age of participants of the included studies ranged from 27 to 98 years. Studies included women from the USA, UK, Spain, Japan, Korea, Poland, Russia, Czech Republic, Norway and Germany. Three studies (all cross-sectional) examined early menopause as outcome, while the rest of the studies examined menopause onset. Two studies defined early menopause as menopause onset <45 years, whereas one study defined it as menopause onset <49 years (Chang *et al.*, 2007; Mikkelsen *et al.*, 2007; Pokoradi *et al.*, 2011). Five studies (Neslihan Carda *et al.*, 1998; Celentano *et al.*, 2003; Kinney *et al.*, 2006; Dorjgochoo *et al.*, 2008; Pakarinen *et al.*, 2010) could not be pooled owing to different exposure or outcome assessments, and, therefore, 10 and 7 studies (based on 6 unique studies) were included in the meta-analysis of cross-sectional and prospective studies, respectively (Fig. 1). Consequently, 41 339 and 63 868 women were included in the meta-analysis of cross-sectional and prospective studies, respectively, with a total of 26 008 women experiencing menopause during the follow-up. In prospective studies, the follow-up ranged from 2 to 11 years (Table 2).

Alcohol consumption and menopause onset in cross-sectional studies

Seven cross-sectional studies reported on alcohol consumption compared to a reference group of non-drinkers in relation to menopause

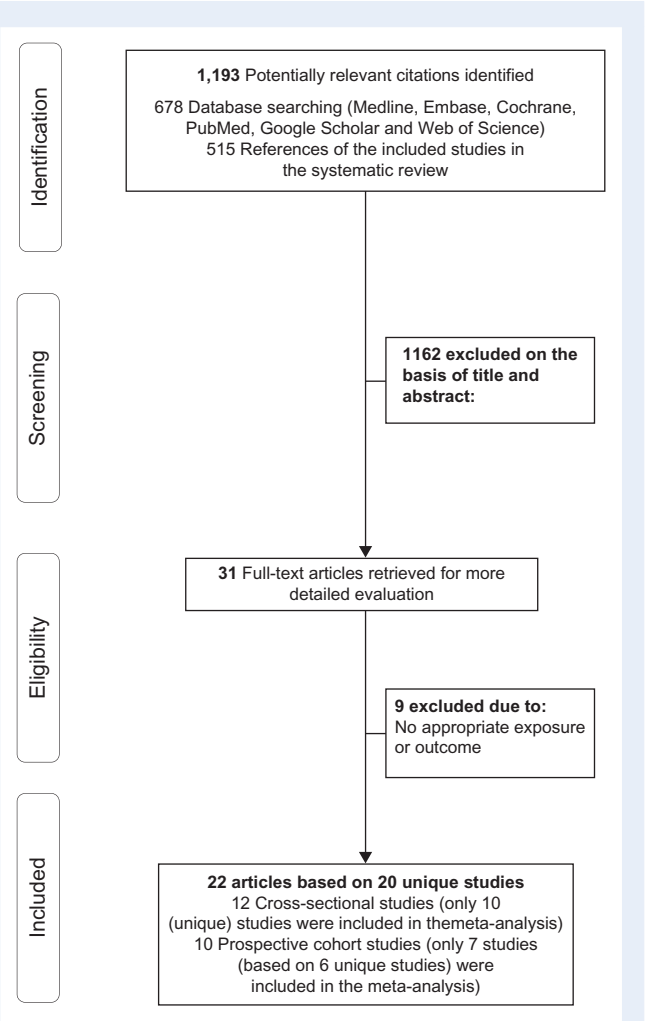

Figure 1 Flow diagram of study selection for a systematic review and meta-analysis of an association of alcohol consumption with the time of onset of natural menopause.

onset. The pooled RR for experiencing menopause between drinkers versus non-drinkers was 0.86 (95% CI: 0.78–0.96) (Fig. 2). When analyses were restricted to studies that reported adjusted estimates for smoking and/or socioeconomic status, pooled RR was 0.85 (95% CI: 0.72–1.0) (Supplementary Figure S1). Also, the results did not materially change when the analysis was restricted to studies that reported adjusted estimates for baseline BMI or age (Supplementary Figures S2 and S3). Pooled RR for early onset of menopause for drinkers versus non-drinkers was 0.90 (95%CI: 0.79–1.02) (Supplementary Figure S4). Analysis of the levels of alcohol consumed showed that consuming more than one drink per week (RR = 0.60; 95% CI: 0.49–0.75) and three or fewer drinks per week (RR = 0.75; 95% CI: 0.60–0.94) were associated with later menopause onset compared to non-drinking (Supplementary Figure S5 and S6). Two cross-sectional studies investigating the association between alcohol and age of menopause were not included to the meta-analysis; one study found a marginally significant association ($P = 0.05$) but no estimates were reported, and the other study reported no significant difference in onset of menopause between drinkers and non-drinkers ($\beta = 0.19$, 95% CI: −0.26 to 0.65, $P = 0.40$) (Neslihan Carda *et al.*, 1998; Pakarinen *et al.*, 2010).

Alcohol consumption and menopause onset in prospective studies

Six unique prospective studies reported on menopause onset in relation to alcohol consumption at baseline compared to a reference group of non-drinkers. Pooled RR for subsequent development of menopause was 0.94 (95% CI: 0.91–0.97) when comparing women who reported consumption of alcohol to those who did not (Fig. 3). When the analyses were restricted to studies that reported adjusted estimates for smoking and/or socioeconomic status ($n = 5$), the pooled RR was 0.94 (95% CI: 0.91–0.97) (Supplementary Figure S7) when comparing women who reported alcohol consumption to women who did not. The results did not differ when we restricted the analysis to studies that reported adjusted estimates for baseline BMI or age (Supplementary Figures S2, S3). Analysis of the dose of alcohol consumed showed that 0–8 g/day (RR = 0.95; 95% CI: 0.93–0.98), >8 g/day (RR = 0.91; 95% CI: 0.89–0.93) or >16 g/day (RR = 0.89, 95%CI: 0.86–0.92) were associated with later onset of menopause compared to non-drinking (Supplementary Figures S8–S10). Three prospective studies could not be included in the meta-analysis: two studies did not find any significant association by comparing ever versus never drinkers, whereas one study showed that drinkers had 1.3 years later menopause onset compared to non-drinkers (Celentano *et al.*, 2003; Kinney *et al.*, 2006; Dorjgochoo *et al.*, 2008).

Assessments of study quality, heterogeneity and publication bias

Three cross-sectional studies and eight prospective studies were judged to be at medium risk of bias, whereas the other studies were evaluated to be at high risk of bias (Tables I and 2). There was evidence of moderate between-study heterogeneity for the meta-analysis of cross-sectional studies of drinkers versus non-drinkers and onset of menopause ($I^2 = 73.4\%$, $P = 0.001$ for the Cochrane χ^2 statistic), whereas no evidence of between-study heterogeneity was found for other analyses (Figs. 2 and 3; Supplementary Figures S1–S10). This level of heterogeneity was explained to a large extent by differences in the study quality and the total number of participants (Supplementary Table S1). Visual examination of Begg's funnel plots for the analysis of cross-sectional and prospective studies on the association between alcohol drinking (yes versus no) and menopause onset (Supplementary Figure S11) was moderately symmetrical, therefore providing little evidence for publication bias. This was further supported by the results of Egger's test, which were non-significant (cross-sectional studies, $P = 0.38$; prospective studies, $P = 0.06$; Supplementary Figure S11).

Discussion

To our knowledge, this is the first meta-analysis on the association between alcohol consumption and the time of menopause onset, including more than 100 000 women. Compared to abstainers,

Table I General characteristics of the cross-sectional studies in a systematic review and meta-analysis of the association of alcohol consumption with the time of onset of natural menopause in women.

Lead author, publication date	Name of the study or source of participants	Location	Age range (years)	Total participants	Covariates adjusted	Outcomes	Quality	Alcohol scale
Bernis, 2007 (Bernis and Reher, 2007)	Decisions At Menopause Study (DAMES) and Ecology of Reproductive Aging Project	Spain	45–55	1142	Environmental context, age, children ever born, education, BMI, regular alcohol consumption, smoking, age at menarche and menarche status	Premenopausal: 585 participants Perimenopausal: 136 participants Postmenopausal: 421 participants	7	Regular consumption: • Yes–no
Kaczmarek, 2007 (Kaczmarek, 2007)	Middle-aged Women's Health and Well-being Survey (WOMID)	Poland	35–65	7183	Educational level, age at menarche, usual menstrual cycle length, use of contraceptives, number of live births, smoking status and self-reported health status	Premenopausal: 3153 participants Perimenopausal: 307 participants Postmenopausal: 2623 participants	6	Alcohol consumption: • Yes–no
Stepaniak, 2013 (Stepaniak *et al.*, 2013)	The Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) Study	Russia, Poland, Czech Republic	45–69	12 676	Age, population, education, marital status, smoking, BMI, physical activity, alcohol consumption, supplementation with vitamins and minerals, hormonal contraceptives, HRT	Premenopausal: 3582 participants Postmenopausal: 9094 participants	6	Frequency of alcohol consumption: (1) Never (2) Low (3) Moderate (4) Everyday
Nagata, 1998 (Nagata *et al.*, 1998)	NA	Japan	45–55	4186	Age and total energy	Premenopausal: 2259 participants Postmenopausal: 1445 participants	5	Alcohol consumption past year (tertiles): (1) Low (2) Middle (3) High
Mikkelsen, 2007 (Mikkelsen *et al.*, 2007)	Oslo Health Study	Norway	40–61	2123	Educational level, smoking, alcohol and coffee consumption	Early menopause: 9.6% of all the participants	6	Alcohol consumption: (1) None in last year (2) <1 per week (3) At least once per week
Torgerson, 1994 (Torgerson *et al.*, 1994)	NA	UK	45–49	1485	Not adjusted	Premenopausal: 1227 participants Postmenopausal: 258 participants	6	Alcohol use: (1) Never (2) Occasionally (3) Once/month (4) 2/3 times/month (5) 2/3 times/week (6) 4/5 times/week
Cooper, 2001 (Cooper *et al.*, 2001)	The Third National Health and Nutrition Examination Survey (NHANES III)	USA	35–49	2205	Age, smoking status, unilateral oophorectomy, hysterectomy	Premenopausal: 1555 participants Perimenopausal: 66 participants Postmenopausal: 75 participants	7	Drink per week: (1) None (2) <3 (3) ≥3

Pokoradi, 2011 (Pokoradi *et al.*, 2011)	Royal College of General Practitioners' Oral Contraception Study	UK	NA	5113	Social class, pack-years of smoking, oral contraceptive use up to age at menopause	Menopause age <49 years: 1691 participants Menopause age ≥49 years: 1959 participants	6	Unit drunk/week: (1) 0 (2) <1 (3) 1–4 (4) >4
Chang, 2007 (Chang *et al.*, 2007)	Korean Multi-center Cancer Cohort (KMCC)	Korea	27–60	1919	Age, education, duration from menopause to enrollment	Normal menopause controls: 1318 participants Natural EM cases: 261 participants Natural POF cases: 84 participants	6	Alcohol consumption: • Never–ever
Brett, 2003 (Brett and Cooper, 2003)	National Health Interview Survey (NHIS)	USA	45–54	3307	Age, age squared, smoking, race/ethnicity, education, BMI, exercise	Premenopausal: 2029 participants Perimenopausal: 584 participants Postmenopausal: 694 participants	6	(1) None in last year (2) Drinks less than weekly (3) Drinks at least weekly
Carda, 1998 (Neslihan Carda *et al.*, 1998)	NA	Turkey	41–70	1500	Not adjusted	1500 postmenopausal women	4	Alcohol consumption: • Yes–no
Pakarinen, 2010 (Pakarinen *et al.*, 2010)	National FINRISK Study	Finland	25–64	3944	Age, year, socioeconomic and lifestyle factors, age at first birth	For study at 1997: 1090 postmenopausal women For study at 2007: 1083 postmenopausal women	7	Alcohol consumption: Any use during last week? • Yes–no

BMI, body mass index; EM: early menopause; POF: premature ovarian failure; HRT: hormone replacement therapy.

Table II General characteristics of prospective studies in a systematic review and meta-analysis of the association of alcohol consumption with the time of onset of natural menopause in women.

Lead author, publication date	Name of the study or source of participants	Location	Year of baseline survey	Baseline age range (years)	Total participants	Covariates adjusted	Outcome	Follow-up time	Quality Assessment	Alcohol assessment
Torgerson, 1997 (Torgerson *et al.*, 1997)	NA	UK	1991–1992	45–49	1227	Age, age of mothers' menopause, tobacco consumption, number of children, social class, meat consumption	150 postmenopausal women	2 years	6	Alcohol consumption: 0, never to 6, daily
Nagata, 2012 (Nagata *et al.*, 2012)	Takayama study	Japan	1992	35–56	3115	Age, BMI, smoking status, parity, years of education, age at menarche, lifelong irregular menstruation cycle	1790 postmenopausal women	10 years	7	Alcohol consumption ml/day: (1) Q1 (2) Q2 (3) Q3 (4) Q4
Morris, 2012 (Morris *et al.*, 2012)	Breakthrough Generations Study	UK	2003	40–98	50 678	Age at last follow-up, parity, smoking status, BMI at 40 years of age	21 511 postmenopausal women	8 years	7	Average alcohol consumption between age 25–49 years: (1) 0 unit/week (2) 0.1–6.9 units/week (3) 7–13.9 units/week (4) ≥14 units/week
Gold, 2013 Santoro 2007 (Santoro *et al.*, 2007; Gold *et al.*, 2013)	The Study of Women's Health Across the Nation (SWAN)	USA	1996	42–52	3302	Race, financial strain, baseline smoking, time varying smoking, maternal type/age at FMP, marital status, diabetes, self-reported health, educational level, oral contraceptive, exogenous hormone therapy, employment, height, parity, physical activity, passive smoking, total calories, baseline weight, change in weight	1483 postmenopausal women	11 years	8	No. of servings/week: (1) None (2) Infrequent (<2) (3) Moderate (2–7) (4) Heavy (>7)
Nagel, 2005 (Nagel *et al.*, 2005)	EPIC- Heidelberg	Germany	1994–1998	35–65	5110	Age, total energy intake, educational level, BMI, leisure time physical activity, alcohol intake, smoking, number full term pregnancies, age at menarche, time till regular menses occurred after menarche, age at first full term pregnancy, ever HRT use	1009 postmenopausal women	9 years	7	Alcohol intake: (1) ≤5 ethanol g/day (2) >5–18 ethanol g/day (3) >18 ethanol g/day
Sammel, 2009 (Sammel *et al.*, 2009)	The Penn Ovarian Aging Studies	USA	NA	35–47	436	Not adjusted	65 postmenopausal women	9 years	8	Alcohol use: Yes–no

Kinney, 2006 (Kinney *et al.*, 2006)	NA	USA	1993	44 and older	494	Outcome of the index pregnancy, caffeine, smoking history	159 postmenopausal women	5 years	7	Alcohol consumption days/week drank: (1) None (2) One to two (3) Three to four (4) Five to seven (5) One to seven
Dorjgochoo, 2008 (Dorjgochoo *et al.*, 2008)	The Shanghai Women's Health Study (SWHS)	China	1997	40–70	74 942	Age, education, occupation, age at menarche, number of live births, past use of oral contraceptives, weight gain between age 20 and 50 years, cigarette smoking, adolescence-adult leisure time physical activity pattern, energy intake	Natural menopause: 33 054 Surgical menopause or HRT use: 4202	4 years	8	Regular alcohol consumption: • Yes–no
Celentano, 2003 (Celentano *et al.*, 2003)	EPIC-ITALY	Italy	NA	NA	32 134	Age, center and educational level	Natural menopause: 12 801 Surgical menopause: 1119	NA	8	Alcohol consumption: • Current • Past • Never

BMI, body mass index; FMP: Final menstrual period.

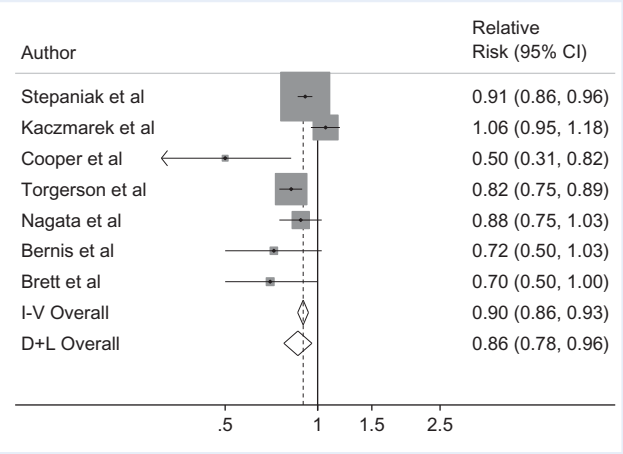

Figure 2 Pooled relative risks for menopause onset when comparing women who reported drinking alcohol versus women who did not in cross-sectional studies.
I–V: Fixed-effects model; D+L; random-effects model; Assessment of heterogeneity, $\chi^2 = 22.6$, $I^2 = 73.4\%$; $P = 0.001$.

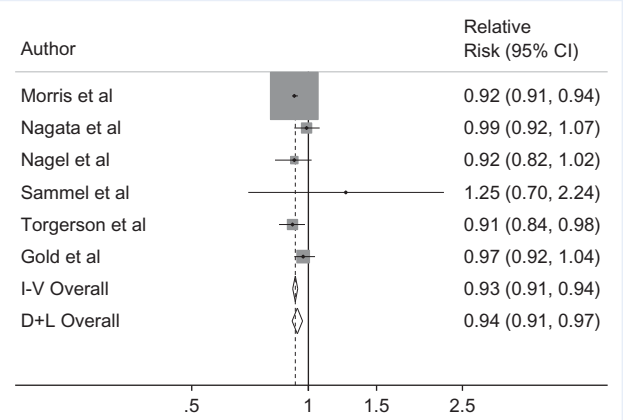

Figure 3 Pooled relative risks for menopause onset when comparing women who reported drinking alcohol to women who did not in prospective studies.
I–V: Fixed-effects model; D+L; random-effects model; Assessment of heterogeneity, $\chi^2 = 7.1$, $I^2 = 29.1\%$; $P = 0.21$.

women who consumed alcohol had a later onset of menopause, indicating that alcohol consumption may be associated with later menopause onset. Whether alcohol intake could be beneficial for delaying menopausal age remains unclear; as the magnitude of the associations were low, the included studies were prone to the influence of residual confounding, low and moderate alcohol intake could act as proxies for moderate lifestyle and the exact mechanisms of action are still unclear.

The postmenopausal period is a challenging transition time for women's health, and the menopausal period is considered as a crucial period for healthy and successful aging (Jaspers *et al.*, 2015). Later menopause onset has been associated with reduced all-cause mortality and risk of cardiovascular disease and an increased risk of cancer, including breast and ovarian cancers (Gold, 2011). Therefore, identifying the factors that may affect menopause onset may be of importance. Studies show that menopause onset varies by race and ethnicity. The median age at menopause among white women from developed countries ranges between 50 and 52 years (Gold, 2011). Compared to white women, Japanese women enter menopause later, Native Hawaiians and Latinas experience menopause earlier and black women have a similar age of onset of menopause (Henderson *et al.*, 2008). Twin studies have reported a genetic contribution to age at menopause with a heritability estimated up to 63% (Snieder *et al.*, 1998). Heritability is further supported by studies reporting maternal age at menopause to be positively associated with age at menopause (Torgerson *et al.*, 1994). Socioeconomic factors, such as education level and social class, are also associated with age at natural menopause (Luoto, Kaprio, and Uutela, 1994; Gold, 2011). Furthermore, several studies indicate that women living in the developed countries experience natural menopausal several years later than those in developing countries (Gold, 2011). In addition to demographic factors, a number of potentially modifiable factors that may affect estrogen metabolism, including smoking and diet, have been suggested to affect menopause onset (Kato *et al.*, 1998; Dorjgochoo *et al.*, 2008; Sun *et al.*, 2012).

Our findings also show that alcohol consumption may be associated with later onset of menopause. Philips *et al.* (2007) showed that while there was no association between total alcohol consumption and onset of perimenopause, there was an inverse association between red wine consumption and risk of perimenopause. Alcoholic beverages are not at all equivalent in their ability to influence health. In general, studies have shown that women are more susceptible to the benefit of wine when they consume low-to-moderate amounts compared to other alcoholic beverages, such as beer (Klatsky *et al.*, 1997; Di Castelnuovo *et al.*, 2002). Also, evidence suggests that women drink wine more frequently than the other beverages (Hupkens *et al.*, 1993). None of the studies included in our review assessed the association between different alcoholic beverages and menopause onset. Therefore, it remains unclear if the observed inverse association between alcohol and menopause onset is due to the effect of wine, any other specific type of alcoholic beverages or the effect of any other additional factor.

Our results show that low-to-moderate alcohol consumption is associated with later menopause onset. The results do not provide evidence of a different effect with increased alcohol consumption. However, our findings are based on only a few studies and the range of alcohol consumption examined is limited (up to 16 g/day). The current guidelines for daily alcohol consumption for women are consistent worldwide suggesting an average intake of 10 g/day (Furtwaengler and de Visser, 2013). In our study, the intake of alcohol within this range, and higher, is associated with later menopause onset. Results from several meta-analyses have shown that up to 30 g of alcohol consumed per day may be protective for health, including for cardiovascular disease and Type 2 diabetes, and that alcohol consumption of >60 g/day may have a negative impact (Koppes *et al.*, 2005; Ronksley *et al.*, 2011). By contrast, combined analysis of data from 53 studies worldwide suggests a dose–response relationship between alcohol consumption and increased risk of breast cancer (Hamajima *et al.*, 2002). In addition, it has been estimated that for each 10 g/day increase in alcohol, there is an

increased risk of around 5–10% for breast cancer (Schutze *et al.*, 2011). The included studies in this review were heterogeneous in the way they examined alcohol intake (i.e. some studies used alcohol intake in grams as a continuous variable, some used tertiles or quartiles and some the frequency of alcohol intake), and most did not report the range of alcohol intake in their population. Lack of information on the range of alcohol intake prevented us from investigating different amounts of alcohol intake, including heavy drinking, in relation to menopause onset. Larger prospective studies are needed to investigate the relationship between consumption of different levels of alcohol and time of onset of menopause and, if an association is present, to identify whether the association is linked to alcohol intake or to alternative factors. Larger prospective studies of this type would allow researchers to evaluate the amounts of alcohol intake that can delay menopause.

Furthermore, alcohol consumption and its impact on health are more complex than mere volume consumption measured at one point in time. Among studies included in this meta-analysis, only one used more than one alcohol measurement in its main analysis, showing an inverse association with menopause onset (Gold *et al.*, 2013). Furthermore, alcohol consumption patterns and the way alcohol is consumed have different effects on various health outcomes (Rehm *et al.*, 2003). For example, binge drinking has been associated with more adverse health outcomes (Rehm *et al.*, 2003). No study assessed the association between alcohol drinking patterns and menopause onset. Therefore, further studies investigating patterns of alcohol consumption are needed.

The underlying mechanisms linking alcohol consumption to the time of onset of menopause are unknown. Low-to-moderate alcohol intake could act as proxies for moderate lifestyle habits, including diet and physical activity, which could be responsible for the effects observed. Furthermore, alcohol consumption can cause endocrine changes that play important roles in female reproductive function and of hormones that are well documented to vary with menopause. Major hormonal changes related to menopause include the sharp decrease of endogenous estradiol and the resulting increase in circulating FSH concentrations (Burger *et al.*, 2007). Alcohol consumption is associated with changes in FSH, but the results on the direction of the association are contradictory (Mendelson *et al.*, 1987; Sarkola *et al.*, 1999; Rachdaoui and Sarkar, 2013; Schliep *et al.*, 2015). Studies are consistent, however, in showing pro-estrogenic effects of low and moderate alcohol intake on estrogen levels (Mendelson *et al.*, 1987; Reichman *et al.*, 1993; Sarkola *et al.*, 1999; Vatsalya *et al.*, 2012; Schliep *et al.*, 2015). In addition, studies show that alcohol consumption correlates with luteinizing hormone and prolactin concentrations, important hormones that regulate ovarian function (Mendelson *et al.*, 1987; Sarkola *et al.*, 1999; Burger *et al.*, 2007; Rachdaoui and Sarkar, 2013; Schliep *et al.*, 2015). Moreover, studies examining the association between alcohol intake and menstrual cycle function in women are consistent in showing no adverse effect of low and moderate alcohol consumption (Wilsnack *et al.*, 1984; Hahn *et al.*, 2013; Lyngso *et al.*, 2014; Schliep *et al.*, 2015). In contrast, a few studies have shown that abstainers had higher odds of irregular and short cycles compared with women with low weekly alcohol consumption (Wilsnack *et al.*, 1984; Lyngso *et al.*, 2014). None of the studies included in this systematic review adjusted for sex hormone levels in their analyses. Therefore, it remains unclear whether the association we found between alcohol consumption and onset of menopause is independent from changes in hormone levels.

The results of our meta-analysis should be interpreted in the context of the limitation of available data. All systematic reviews are prone to reporting bias, owing to the possibility that studies with more extreme results are more likely to be published. Despite all efforts made to undertake a comprehensive search of the published and unpublished literature, we cannot exclude the possibility of publication bias stemming from under-reporting of negative findings. Nonetheless, as demonstrated by Egger's test estimates, there was little evidence of publication bias in the current analyses. Also, the individual studies ascertained the age of menopause onset based mainly on self-report data. Studies have shown that the reported age of menopause may be inaccurate (Paganini-Hill and Ross, 1982; Hahn *et al.*, 1997), though other studies have concluded that menopause is an important event in a women's life and that she will remember it clearly (Bean *et al.*, 1979; Colditz *et al.*, 1987). However, even if the reporting is inaccurate, any recall problem should reduce the strength of the association. Furthermore, alcohol was assessed by questionnaire, which is subject to some measurement error. However, in the prospective studies, because the outcome was assessed prospectively, the subjective measure of alcohol intake would likely lead to non-differential misclassification with respect to the outcome, and therefore would likely bias our estimates toward the null. Additionally, it is well known that respondents tend to under-report their alcohol intake, resulting in a potential underestimation of the reported effect. That is, associations that appear to exist at a given consumption level in our analysis would, in fact, exist at some higher level. There is a risk of reverse causation since women who already have symptoms related to menopause may report the alcohol consumption differently and/or may alter their intake. Furthermore, the quality of individual studies varied with some studies having limited adjustment for potential confounding factors and some prospective studies having limited follow-up. Although we restricted the main analysis to include data only from studies that adjusted for smoking, socioeconomic status or BMI, the adjustments were not uniform and the studies missed adjustment for additional factors including race and ethnicity, physical activity, coffee intake, overall quality of diet, sleep patterns, hormone replacement therapy (HRT) and contraceptive use. Specific concerns include confounding due to ethnicity and HRT. Ethnicity is an important determinant of age at natural menopause (Gold, 2011). Also, there are variations across ethnicities in drinking, alcohol use disorders and alcohol problems (Chartier and Caetano, 2010). Owing to a limited number of studies, we could not investigate the impact of ethnicity *per se* in our results. However, our stratified analysis by geographic location (Europe versus non-Europe, Supplementary Table S1) showed that the association between alcohol consumption and menopause onset was stronger in studies conducted in Europe. All studies located in Europe had little variation in ethnicity and included mainly Caucasian women. By contrast, the studies that were not based in Europe included women of different ethnicities, including Asian, African American, white and Hispanic women, and most of these studies did not adjust for ethnicity in their analysis. Future studies should examine whether our findings apply to Caucasian women only or to other ethnicities as well. HRT or oral contraceptive use may vary depending on the age of menopause (a factor particularly important for cross-sectional studies) and may

affect onset of menopause (Kaczmarek, 2007). For instance, women who experience menopause at a younger age may be more likely to start HRT than women who reach menopause in their 50s. Therefore, hormone therapy use may confound the relationship between alcohol intake and menopause onset. Indeed, few studies excluded women reporting the use of HRT (one cross-sectional study), adjusted for hormone therapy and/or oral contraceptive use (three cross-sectional studies and three prospective studies) or treated HRT and oral contraceptive use as competing risks in their analysis (one prospective study) (Nagel *et al.*, 2005; Kaczmarek, 2007; Dorjgochoo *et al.*, 2008; Pokoradi *et al.*, 2011; Morris *et al.*, 2012; Nagata *et al.*, 2012; Gold *et al.*, 2013; Stepaniak *et al.*, 2013). Therefore, it precluded our ability to perform subgroup analysis by HRT and oral contraceptive use or other study level characteristics. However, for most of the analysis, we did not find evidence of heterogeneity. Future studies are needed to investigate whether the effect observed in this study is related to unmeasured residual confounding.

Nonetheless, the findings of this study may have clinical and public health implications. In the realm of clinical practice, our results may form a foundation for proposing counseling for premenopausal women to incorporate a moderate amount of alcohol into their diets to delay menopause onset. However, to apply such a clinical strategy, larger prospective studies and clinical trials are needed to assess the type of alcohol beverages, the amount, compliance, risks and benefits. With respect to public health messages, this evidence suggests that more actions are needed to communicate to the public that moderate alcohol consumption may have overall health benefits. However, to apply such a strategy, we need rigorous studies and oversights of impacts.

In conclusion, the findings from this systematic review indicate that alcohol consumption might be associated with later menopause onset. However, alcohol intake is also associated with an increased risk of cancer, which should be taken into account. Future studies are needed to establish whether alcohol intake can be beneficial for delaying menopausal age and to understand the interaction with potential dosage and the underlying mechanisms.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/

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Authors' role

P.E.T. and T.M. designed and performed the literature review, designed the search strategy, screened title/abstract, obtained full text, determined eligibility of articles, participated in data extraction, data synthesis/analysis, data interpretation, coordination and writing the manuscript. T.M. and O.H.F. conceived the study. P.E.T. and T.M. designed and performed the literature review, designed the search strategy, screened title/abstract, obtained full text, determined eligibility of articles, participated in data extraction, data synthesis/analysis, data interpretation, coordination and writing the manuscript. P.E.T. and T.M. screened title/abstract. W.M.B. helped in designing the search strategy. J.C.K.J., N.M.P.D. and O.H.F. participated in data interpretation and drafting of the final manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

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Conflict of interest

Metagenics Inc. had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation and review of the manuscript. The funder/sponsor did not have the ability to veto publication of study results and did not play any role in the decision to submit the manuscript.

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