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Timing of Alcohol Use and the Incidence of Premenstrual Syndrome and Probable Premenstrual Dysphoric Disorder

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Abstract

Background: Relatively little is known about factors that influence the initial development of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), although these conditions are common in reproductive age women and are associated with substantial impairment. Previous studies have observed higher alcohol use in prevalent PMS/PMDD patients compared with controls, but it is unknown if drinking predisposes women to developing these disorders or is instead influenced by symptom experience.
Methods: To address this, we conducted a case-control study nested within the prospective Nurses' Health Study II (NHS2). Participants were a subset of women aged 27–44 and free from PMS at baseline (1991), including 1057 women who developed PMS over 10 years of follow-up, 762 of whom also met criteria consistent with PMDD, and 1968 control women. Alcohol use at various time periods, before and after onset of menstrual symptoms, was assessed by questionnaire.
Results: Overall, alcohol use was not strongly associated with the incidence of PMS and probable PMDD. Relative risks (RR) for women with the highest cumulative alcohol use vs. never drinkers were 1.19 (95% confidence interval [CI] 0.84-1.67) for PMS and 1.28 (95% CI 0.86-1.91) for PMDD, although results did suggest a positive relationship in leaner women (p trend $= 0.002$). Women who first used alcohol before age 18 had an RR of PMS of 1.26 (95% CI 0.91-1.75) compared with never drinkers; the comparable RR for PMDD was 1.35 (95% CI 0.93-1.98).
Conclusions: These findings suggest alcohol use is not strongly associated with the development of PMS and PMDD, although early age at first use and long-term use may minimally increase risk.

Introduction

Premenstrual syndrome (PMS), a disorder characterized by the occurrence of physical and emotional symptoms in the luteal phase of the menstrual cycle,[1,2] is associated with substantial morbidity and reduced quality of life in approximately 8%–20% of reproductive age women.[3–5] Premenstrual dysphoric disorder (PMDD), a more severe condition in which affective symptoms predominate, is less common but associated with levels of impairment comparable to major depressive disorder (MDD).[6,7]

Relatively little is known about factors that influence the initial development of PMS and PMDD. To date, most epidemiologic studies of PMS and PMDD have included as cases women who have already been diagnosed with these disorders. It has, therefore, been difficult to determine if factors that differ in prevalent cases compared with symptom-free controls are etiologically related to the development of PMS/PMDD or are instead themselves influenced by menstrual symptom experience. In particular, several previous studies have found that alcohol use is more common in women currently experiencing PMS or PMDD than in controls.[4,8–12] It is unknown, however, if alcohol use predisposes women to developing PMS/PMDD or if women experiencing these disorders are more likely to consume alcohol, perhaps as a means to treat their symptoms.

To address this question, we have assessed the relationship between alcohol use at various ages and time periods, before

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and after the onset of menstrual symptoms, and the incidence of PMS and PMDD in a case-control study nested within a large prospective study.

Materials and Methods

The Nurses' Health Study II (NHS2) is a prospective cohort study established in 1989 when 116,678 U.S. female registered nurses responded to an initial questionnaire mailing. Aged 25–42 at the time of enrollment, participants provided information on their medical history and health-related behaviors, such as use of oral contraceptives (OC), menstrual and pregnancy history, and smoking status. Since 1989, participants have completed questionnaires every 2 years to update information on various risk factors, such as smoking status and body weight, and to identify new diagnoses of disease. The protocol for this study was approved by the Institutional Review Board at Brigham and Women's Hospital and Harvard School of Public Health.

NHS2 Premenstrual Syndrome Substudy

The development of the NHS2 Premenstrual Syndrome Substudy has been described in detail previously.[13,14] Briefly, information on PMS was first collected on the baseline NHS2 questionnaire in 1989, when participants were asked if they had ever received a physician diagnosis of the disorder. On subsequent questionnaires in 1993, 1995, 1997, and 2001, participants were asked if they had received a new diagnosis of PMS during the previous 2–4-year period and, if so, when the diagnosis was made.

In January 2002, we conducted a substudy among NHS2 participants to identify PMS cases and controls. First, we identified all cohort members who had not reported a diagnosis by 1991 and who, therefore, could possibly report a new diagnosis of PMS during our follow-up period (i.e., 1991–2001). To make sure that cases and controls provided information about eligibility, alcohol use, and other factors during similar time periods, we assigned each woman a reference year. For women who reported a new diagnosis of PMS on an NHS2 study questionnaire during the follow-up period, their reference year was equal to their year of diagnosis. Because control women did not develop PMS and thus did not have a year of diagnosis, we assigned each control a randomly chosen reference year between 1993 and 2001.

We used each woman's reference year to determine her eligibility for the substudy, to assess menstrual symptom experience, and to measure alcohol intake. To reduce the likelihood of including women with menstrual-type symptoms attributed to causes other than PMS, we excluded women who had reported a diagnosis of cancer, endometriosis, usually irregular menstrual cycles, infertility, hysterectomy, or menopause before their reference year. From among all remaining eligible women, we selected 6000 to participate in the PMS Substudy, including 3430 women who reported a new diagnosis of PMS between 1993 and 2001 and 2570 who did not report PMS during this period. For case selection, we gave preference to women with the most recent reference years; noncases were then frequency-matched to cases by reference year.

We mailed all 6000 participants a 2-page questionnaire based on the Calendar of Premenstrual Experiences designed by Mortola et al.[1] Women were asked to report whether, in the specific 2-year period before their reference year, they had experienced any of 26 different symptoms "most months of the year for at least several days each month before [their] menstrual period begins." We also asked about the age when symptoms first occurred, the timing of symptom onset and cessation during an average menstrual cycle, symptom severity, and the interference of symptoms with life activities and interpersonal relationships. Completed questionnaires were received from 2966 (86.5%) women self-reporting and 2504 (97.4%) women not reporting PMS.

We used information provided on the supplemental questionnaire to identify from among those self-reporting PMS the women who met our case definition, based on criteria established by Mortola et al.[1] We defined cases as women who reported a new diagnosis of PMS during the follow-up period (1991–2001) and who also reported (1) the occurrence of at least one physical and one affective menstrual symptom, (2) overall menstrual symptom severity classified as moderate or severe or effect of symptoms on life activities and social relationships classified as moderate or severe, (3) symptoms beginning within 14 days of the onset of menses, (4) symptoms ending within 4 days after the onset of menses, and (5) symptoms absent in the week after menses ends. Overall, 1057 (35.6%) of the 2966 women self-reporting PMS met these criteria and were included as validated PMS cases in our analysis.

From among validated PMS cases, we further identified women who met criteria consistent with those for PMDD, based on those established by the *Diagnostic and Statistical Manual for Mental Disorders*, 4th ed.[15] Probable PMDD cases were defined as women who (1) met all criteria for PMS, as defined above, (2) experienced at least 1 of the following affective symptoms: irritability, mood swings, depression, or anxiety, and (3) reported 5 of more of the following symptoms/symptom groups: irritability or anger, mood swings, depression, anxiety, hypersensitivity, desire for aloneness, insomnia, difficulty concentrating, fatigue, food cravings, or physical symptoms. A total of 762 (72.1%) of our validated PMS cases also met criteria consistent with a diagnosis of PMDD.

We then identified a comparison group from among participants who both did not report a diagnosis of PMS before or during the follow-up period (through 2001) and experienced either no menstrual symptoms or only mild symptoms that had no substantial effect on life activities and relationships. A total of 1968 of the 2504 noncases (78.6%) met these criteria and were included in subsequent analyses as validated controls. Women who did not meet criteria for either cases or controls were excluded from analysis.

The validity of our approach to identifying PMS cases and controls was assessed previously.[14] Briefly, participants included 135 members of the NHS2 PMS Substudy who first reported PMS by questionnaire in 2001 and 371 who never reported PMS (1989–2001). We found that the menstrual symptom occurrence, timing, and severity in women meeting criteria based on those established by Mortola et al.[1] as assessed by our retrospective questionnaire were essentially identical to those who also reported clinician-supervised prospective symptom charting as part of their diagnosis.

Assessment of alcohol use and other factors

Alcohol use was first assessed on biennial NHS2 questionnaires in 1989, when participants were asked to report

their usual number of drinks of alcohol at ages 15–17, 18–22, and 23–30 years. Total number of drinks was defined as the total number of bottle/cans of beer, 4-oz glasses of wine, and shots of liquor combined. There were nine response options, ranging from "none or less than one drink per month" to "40 or more drinks per week." In addition, women were asked about their alcohol use in the previous year. Questions assessed the usual frequency of consumption of each type of alcoholic beverage (i.e., beer, wine, and liquor), the usual number of days per week alcohol was consumed, and the largest number of alcoholic drinks consumed in a single day during a usual month.

In 1991, 1995, and 1999, participants completed a 131-item semiquantitative food frequency questionnaire (SFFQ) as part of their NHS2 questionnaire. Women were asked to record, on average, how often they consumed a single serving of regular beer (1 can), light beer, red wine (4 oz glass), white wine, and liquor (1 drink or shot). Response options ranged from less than once per month to 6 or more times per day.

We collected information on other factors potentially associated with PMS and alcohol intake throughout the study period. Information on age, body weight, number of full-term pregnancies (i.e., pregnancies lasting longer than 6 months), age at first birth, tubal ligation, and OC use was updated biennially. In 1989, participants were asked to report the number of cigarettes smoked per day at different ages as well as current smoking status, and smoking information was then updated every 2 years. Data on smoking frequency and duration were multiplied and summed across time periods to calculate pack-years. Age at menarche, menstrual cycle characteristics, weight at age 18, and height were each assessed once in 1989. Physical activity level was measured in 1991 and 1997 and used to calculate metabolic equivalent task hours (MET-hours) per week.[16] Childhood and adolescent trauma related to punitive parenting was assessed in 2001 with a supplemental questionnaire and was used to create a childhood trauma score, ranging from 5 (no report of trauma) to 25 (report of severe trauma).[17] Macronutrient and micronutrient intake was measured by SFFQ in 1991, 1995, and 1999, and nutrients were adjusted for total energy intake by the residual method.[18] Finally, our supplemental menstrual symptom questionnaire inquired as to whether women had been diagnosed with depression and had taken antidepressants and the timing of each.

Statistical analysis

Using information provided on the baseline NHS2 questionnaire in 1989 and subsequent SFFQs in 1991, 1995, and 1999, we identified the age at which alcohol use was first reported (<18, 18–22, 23–30, >30 years), and among all cases and those controls who experienced any menstrual symptoms, whether first alcohol use preceded the age when participants reported first experiencing symptoms.

To calculate each woman's total alcohol intake in grams per day during each time period, we multiplied the intake frequency of each beverage type by its alcohol content, defined as follows: one 360 mL can of beer, 12.8 g; each 120-mL glass of wine, 11.0 g; one standard drink of liquor, 14.0 g.[19,20] We then divided women into categories based on alcohol use at ages 15–17, 18–22, and 23–30 years, in 1989, at the beginning of follow-up in 1991, and during the 2–4-year period prior to their individual reference year. Because a large number of women ceased consuming alcohol at baseline or during follow-up and alcohol cessation may be related to menstrual symptom experience, we classified "never drinkers" and "former drinkers" separately for each time period from 1989 onward. Finally, we estimated total number of drinking-years by multiplying each woman's reported alcohol intake during each time period by the length of that period and then summing across all periods; after separating out never drinkers, the remaining women were divided into quintiles.

We compared baseline characteristics of PMS cases, probable PMDD cases, and controls with *t* tests and Pearson's chi-square tests. We used odds ratios (OR) to estimate the relative risk (RR) of PMS for women across categories of alcohol use and calculated 95% confidence intervals (CI). Analyses were then repeated to estimate risk of probable PMDD. All statistical analyses were conducted with SAS (SAS Institute, Inc., Cary, NC). In multivariable analyses, we included factors in logistic regression models that were confounders of the alcohol-PMS relationship, as well as factors associated with alcohol or PMS or both in previous studies. These included age, diagnosis year, pack-years of cigarette smoking, number of full-term pregnancies, body mass index (BMI, calculated as weight in kg divided by the square of height in meters), tubal ligation, duration of OC use, antidepressant use, history of childhood trauma, and intake of calcium, vitamin D, vitamin B_6, and potassium from foods and supplements (see Table 2, footnote[b] for variable categories). Several additional variables were not included in the final analysis because they were unrelated to the development of PMS/PMDD or alcohol intake, including age at first birth, physical activity, BMI at age 18, and dietary intake of magnesium, manganese, vitamin E, linolenic acid, total carotenoids, and caffeine. The Mantel extension test for trend was used to evaluate linear trend across categories by modeling the median value of each category as a continuous variable in the multivariable regression models.

We assessed whether the relationship between alcohol use and risk of PMS was modified by other factors, including BMI (normal weight vs. overweight/obese: <25.0 vs. $\geq 25.0\,kg/m^2$) and age at PMS diagnosis (below median vs. above median: <40 vs. ≥ 40 years). Interactions were considered statistically significant if the Wald 2-sided *p* value for the multiplicative interaction term in the multivariable model was <0.05. Finally, we repeated our analyses in subgroups limited to women with no history of depression prior to their reference year, never smokers, and women who were not using OCs at the start of follow-up (1991).

Results

Characteristics of PMS and probable PMDD cases and controls at baseline are presented in Table 1. PMS and PMDD cases were slightly younger than controls and had a significantly higher mean BMI at baseline ($p < 0.001$ for all). Current and former smoking was also significantly more common in PMS and PMDD cases compared with controls, as was ever use of OC ($p < 0.0001$ for all). Approximately 16% of both PMS and PMDD cases reported having had a diagnosis of depression at baseline compared with 7.5% of controls ($p < 0.0001$ for both). Use of antidepressant medications was also more common in both PMS and PMDD cases than in controls ($p < 0.0001$).

Table 1. Age-Standardized Characteristics of Premenstrual Syndrome (PMS) Cases, Probable Premenstrual Dysphoric Disorder (PMDD) Cases, and Controls at Baseline, NHS2[a] PMS Substudy, 1991–2001

	Controls (n = 1968)	*PMS cases (n = 1057)*		*Probable PMDD cases (n = 762)*[c]	
Characteristic[b]	*Mean (SE)*	*Mean (SE)*	p *value*[d]	*Mean (SE)*	p *value*[d]
Age	35.0 (3.9)	34.4 (4.3)	0.0002	34.2 (4.2)	<0.0001
Body mass index (1991)	23.7 (0.1)	24.6 (0.2)	<0.0001	24.4 (0.2)	0.001
Body mass index at age 18	21.1 (0.07)	21.4 (0.1)	0.03	21.2 (0.1)	0.42
Age at menarche	12.5 (0.03)	12.4 (0.04)	0.08	12.4 (0.05)	0.42
Number of full-term pregnancies	1.7 (0.03)	1.7 (0.04)	0.52	1.7 (0.04)	0.86
Age at first birth (in parous women)	26.1 (0.1)	25.9 (0.1)	0.22	25.9 (0.2)	0.45
MET-hours of physical activity per week	23.3 (1.3)	22.9 (1.8)	0.88	21.9 (2.0)	0.54
	%	%	p *value*[e]	%	p *value*[e]
Current smoking	6.5	12.3	<0.0001	13.2	<0.0001
Former smoking	18.2	26.5	<0.0001	27.1	<0.0001
Ever used oral contraceptives	77.7	85.7	<0.0001	85.3	<0.0001
>4 years of oral contraceptive use	36.6	42.0	0.004	41.6	0.02
Previous diagnosis of depression	7.5	16.7	<0.0001	16.3	<0.0001
Previously used antidepressant medication	4.7	12.1	<0.0001	11.7	<0.0001

[a]NHS2, Nurses' Health Study II; PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder; MET, metabolic equivalent.
[b]All characteristics except age standardized to the age distribution of cases and controls in 1991. Standard deviation presented for age instead of standard error.
[c]Probable PMDD cases are a subset of PMS cases.
[d]Calculated using the *t* statistic; comparisons are between PMS cases and controls and between PMDD cases and controls.
[e]Calculated using the chi-square statistics; comparisons are between PMS cases and controls and between PMDD cases and controls.

We estimated age-adjusted and multivariable relative risks of PMS and probable PMDD by level of alcohol intake during adolescence and young adulthood (Table 2). Overall, age-adjusted RR suggested that alcohol use was positively associated with the incidence of PMS. For example, women whose first use of alcohol was before age 18 had a significant 92% higher risk of developing PMS than women never consuming alcohol (RR = 1.92, 95% CI 1.45-2.54). After adjustment for other factors, however, results were substantially attenuated; control for pack-years of cigarette smoking explained most of the difference between age-adjusted and multivariable results. In multivariable analyses, results suggested that women who started drinking before age 18 had a modestly higher risk of developing PMS than those whose first alcohol use was at older ages (p for trend among drinkers = 0.02), but risk was not significantly different from that of nondrinkers.

Sixty-seven percent of PMS cases reported first using alcohol before the age at which their menstrual symptoms began. Among all cases and those controls reporting any menstrual symptoms, women who reported first using alcohol before the age at which their menstrual symptoms started had an RR of 1.18 compared with never drinkers (95% CI 0.86-1.62), whereas those reporting first alcohol use after the age of symptom onset had an RR of 0.88 (95% CI 0.62-1.23). The amount of alcohol consumed during each time period in adolescence and early adulthood was not linearly related to risk of PMS. Results further adjusted for smoking status at each specific age and total drinking-years were identical.

For most analyses, results for probable PMDD were slightly stronger than those for PMS (Table 2). For example, women whose first use of alcohol was before age 18 had an RR of 1.35 (95% CI 0.93-1.98) compared with never drinkers. However, as with PMS, we did not observe a linear relationship with quantity of alcohol use at any specific age and incidence of probable PMDD.

We also did not observe evidence of a linear relationship between alcohol intake in 1989, at baseline in 1991, and during follow-up and risk of incident PMS or probable PMDD (Table 3). At each time period, risk tended to be higher in former drinkers than in never drinkers and current drinkers. For example, women who were former drinkers in 1989 (i.e., had consumed alcohol during a previous time period but did not consume alcohol in 1989) had a 32% higher risk of PMS (95% CI 0.97-1.78) compared with women who had not consumed alcohol before 1989 (i.e., never drinkers). Results were slightly stronger for PMDD, suggesting a 60% higher risk of PMDD (95% CI 1.13-2.27) in former drinkers compared with never drinkers. Among current drinkers, results suggested that risk of PMS was inversely related to level of alcohol intake; at reference year, this trend was statistically significant (for PMS, $p = 0.006$; for PMDD, $p = 0.02$). Additional analyses evaluating beer, wine, and liquor intake separately did not suggest that risk differed by alcohol type (results not shown).

To determine if long-term alcohol intake was differently related to risk than drinking during any single time period, we calculated total drinking-years for each woman, which took into consideration both duration of alcohol use and quantity at each age. Compared with never drinkers, women in the highest quintile of drinking-years, a level equivalent to one or more glasses of wine per day for ≥13 years, did not have a significantly higher risk of PMS. For probable PMDD, risk was significantly 50% higher in women in quintiles 3 and 4 compared with never drinkers but not in quintile 5 (p for trend = 0.52). Results pertaining to drinking pattern also did not suggest that women who used alcohol regularly in 1989 had an increased risk of developing PMS/PMDD.

Table 2. Alcohol Intake during Adolescence and Young Adulthood and Risk of PMS and Probable PMDD, NHS2[a] PMS Substudy, 1991–2001

		PMS			Probable PMDD		
Alcohol intake	*Controls*	*Cases*	*Age Adjusted RR*	*MV[b] adjusted RR (95% CI)*	*Cases*	*Age Adjusted RR*	*MV[b] adjusted RR (95% CI)*
Age at first alcohol use, years							
Never	243	92	1.00	1.00	56	1.00	1.00
<18	465	349	1.92	1.26 (0.91-1.75)	252	2.24	1.35 (0.93-1.98)
18–22	1002	506	1.38	1.06 (0.79-1.42)	380	1.72	1.29 (0.91-1.82)
23–30	185	81	1.21	0.95 (0.64-1.41)	57	1.42	1.09 (0.69-1.73)
>30	73	29	1.14	0.74 (0.43-1.29)	17	1.12	0.71 (0.37-1.38)
				$p = 0.02$[c]			$p = 0.05$[c]
Timing of first alcohol use[d]							
Never	172	86	1.00	1.00	52	1.00	1.00
Before symptoms started	852	662	1.56	1.18 (0.86-1.62)	484	1.89	1.36 (0.94-1.96)
After symptoms started	432	257	1.22	0.88 (0.62-1.23)	190	1.50	1.05 (0.71-1.55)
Alcohol intake (gs/day)							
Ages 15–17							
0	1489	702	1.00	1.00	505	1.00	1.00
>0–<5	268	182	1.38	1.19 (0.94-1.51)	129	1.33	1.08 (0.83-1.41)
5–<10	124	102	1.62	1.41 (1.03-1.93)	78	1.67	1.37 (0.97-1.93)
≥10	73	65	1.72	1.09 (0.73-1.62)	45	1.58	0.88 (0.56-1.38)
				$p = 0.22$			$p = 0.1$
Ages 18–22							
0	503	207	1.00	1.00	133	1.00	1.00
>0–<5	637	297	1.14	1.02 (0.81-1.30)	228	1.36	1.21 (0.93-1.59)
5–<10	373	254	1.64	1.42 (1.10-1.84)	187	1.87	1.55 (1.15-2.07)
10–<15	384	246	1.49	1.15 (0.88-1.51)	172	1.60	1.17 (0.86-1.59)
≥15	61	47	1.75	1.15 (0.72-1.85)	38	2.14	1.33 (0.79-2.23)
				$p = 0.32$			$p = 0.45$
Ages 23–30							
0	497	235	1.00	1.00	163	1.00	1.00
>0–<5	814	404	1.08	0.95 (0.76-1.19)	299	1.16	1.00 (0.79-1.28)
5–<10	373	226	1.33	1.09 (0.84-1.41)	169	1.44	1.13 (0.85-1.51)
10–<15	237	159	1.48	1.05 (0.78-1.42)	109	1.47	0.95 (0.68-1.34)
≥15	35	21	1.36	0.86 (0.46-1.62)	17	1.62	1.01 (0.51-2.02)
				$p = 0.85$			$p = 0.95$

[a]NHS2, Nurses' Health Study II; PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder; MET, metabolic equivalent; MV, multivariable; RR, relative risk; CI, confidence interval.

[b]Multivariable relative risks are adjusted for the following factors assessed at reference year: age (<30, 30–34, 35–39, ≥40 years), diagnosis year (1993, 1994–1995, 1996–1997, 1998–1999, 2000–2001), parity (0, 1–2, 3–4, or ≥5 pregnancies lasting ≥6 months), oral contraceptive use and duration (never, 1–23, 24–71, 72–119, ≥120 months), pack-years of cigarettes smoking (quintiles), body mass index (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥30.0 kg/m^2), history of tubal ligation (no, yes), antidepressant use (never, ever), history of childhood trauma (4 categories), and dietary intake of alcohol, vitamin B_6, potassium, calcium, and vitamin D (each in quintiles). Numbers of cases and controls may not sum to totals due to missing data.

[c]Tests for trend for analyses of age at first use include drinkers only (never drinkers excluded).

[d]Analysis includes all cases and only those controls reporting any menstrual symptoms ($n = 1456$).

In our analyses of potential effect modification, results stratified by BMI at reference year suggested the possibility of an increased risk of PMS and probable PMDD associated with alcohol use in leaner women (Table 4). For example, in women with BMI <25.0 kg/m^2, we observed a positive linear relationship between total drinking-years and risk of PMS. Compared with never drinkers, multivariable RR for quintiles 1–5 were 1.01, 1.10, 1.52, 1.63, and 1.74 (95% CI for quintile 5 vs. 1 = 1.11-2.72), respectively (p for trend = 0.002). In heavier women, risk was not associated with total drinking-years; compared with never drinkers, RR for quintiles 1–5 in this group were 1.03, 0.95, 0.89, 1.06, and 0.66 (95% CI for quintile 5 vs. 1 = 0.37-1.16, p for trend = 0.10), respectively (p for interaction = 0.01). We also observed significantly higher risks of PMS in leaner women who first used alcohol before age 18 and before menstrual symptoms started but not in heavier women (results not shown). The relationship between age at first alcohol use and PMS was slightly higher in those with younger reference ages than older ages, but interactions were not statistically significant (results not shown).

Results from subanalyses limited to women not using OCs at baseline, never smokers, and women who had not received a diagnosis of depression before PMS diagnosis were very similar to the main analysis (results not shown).

Discussion

Overall, results from our study do not suggest that use of alcohol is strongly associated with the initial development of PMS and symptom experience consistent with PMDD. We

Table 3. Alcohol Intake before Baseline and during Follow-Up and Risk of PMS[a] and Probable PMDD, NHS2 PMS Substudy, 1991–2001

		PMS			Probable PMDD		
Alcohol intake	*Controls*	*Cases*	*Age-adjusted RR*	*MV-adjusted RR[b] (95% CI)*	*Cases*	*Age-adjusted RR*	*MV-adjusted RR[b] (95% CI)*
In 1989[c]							
Never drinker	288	107	1.00	1.00	65	1.00	1.00
Former drinker	422	268	1.72	1.32 (0.97-1.78)	205	2.17	1.60 (1.13-2.27)
Current drinker, g/day							
>0–<5	849	445	1.41	1.11 (0.84-1.47)	321	1.68	1.28 (0.92-1.78)
5–<10	203	126	1.68	1.30 (0.91-1.86)	88	1.94	1.41 (0.93-2.14)
10–<15	123	69	1.54	1.09 (0.71-1.67)	52	1.91	1.30 (0.80-2.10)
≥15	67	31	1.24	0.80 (0.46-1.37)	23	1.54	0.90 (0.49-1.66)
				$p = 0.43$			$p = 0.26$
In 1991							
Never drinker	272	99	1.00	1.00	60	1.00	1.00
Former drinker	548	336	2.09	1.26 (0.94-1.70)	253	2.09	1.56 (1.10-2.21)
Current drinker, g/day							
>0–<5	764	427	1.81	1.17 (0.87-1.57)	304	1.81	1.31 (0.93-1.85)
5–<10	216	120	1.85	1.17 (0.81-1.68)	88	1.85	1.38 (0.90-2.10)
10–<15	92	45	1.69	0.97 (0.60-1.59)	33	1.69	1.09 (0.63-1.91)
≥15	76	30	1.52	0.73 (0.43-1.26)	24	1.52	0.94 (0.52-1.71)
				$p = 0.25$			$p = 0.13$
In reference year							
Never drinker	264	98	1.00	1.00	60	1.00	1.00
Former drinker	563	330	1.93	1.22 (0.90-1.65)	246	1.93	1.47 (1.03-2.08)
Current drinker, g/day							
>0–<5	714	424	1.89	1.18 (0.88-1.59)	306	1.89	1.32 (0.93-1.86)
5–<10	235	128	1.73	1.17 (0.81-1.67)	91	1.73	1.32 (0.87-2.00)
10–<15	100	47	1.60	0.90 (0.56-1.45)	35	1.60	1.00 (0.58-1.73)
≥15	88	28	1.16	0.60 (0.35-1.03)	22	1.16	0.74 (0.40-1.35)
				$p = 0.006$			$p = 0.02$
Total drinking-years[d]							
Never drinker	264	98	1.00	1.00	60	1.00	1.00
Ever drinker							
Quintile 1	334	151	1.21	1.05 (0.75-1.45)	114	1.49	1.28 (0.87-1.87)
Quintile 2	343	166	1.32	1.04 (0.75-1.44)	118	1.53	1.19 (0.81-1.74)
Quintile 3	342	212	1.67	1.26 (0.91-1.74)	161	2.07	1.52 (1.04-2.22)
Quintile 4	339	213	1.71	1.32 (0.95-1.84)	151	1.99	1.51 (1.02-2.21)
Quintile 5	343	215	1.73	1.17 (0.83-1.64)	156	2.05	1.28 (0.86-1.91)
				$p = 0.27$			$p = 0.52$
Drinking pattern							
Average number of days/week alcohol was consumed (1989)							
0	1050	542	1.00	1.00	393	1.00	1.00
1	490	267	1.03	0.91 (0.74-1.11)	194	1.03	0.88 (0.70-1.10)
2	174	116	1.27	1.16 (0.87-1.55)	82	1.23	1.09 (0.79-1.51)
3	102	60	1.14	1.02 (0.70-1.48)	42	1.10	0.93 (0.61-1.43)
≥4	151	68	0.91	0.77 (0.54-1.08)	47	0.87	0.69 (0.47-1.03)
				$p = 0.43$			$p = 0.19$
Largest number of drinks in single day (1989)							
0	545	288	1.00	1.00	211	1.00	1.00
1–2	861	409	0.90	0.87 (0.71-1.07)	288	0.87	0.83 (0.66-1.05)
3–5	462	280	1.13	1.01 (0.80-1.28)	205	1.13	0.98 (0.75-1.27)
≥6	99	79	1.41	1.05 (0.71-1.53)	57	1.35	0.95 (0.62-1.45)
				$p = 0.57$			$p = 0.91$

[a]NHS2, Nurses' Health Study II; PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder; MET, metabolic equivalent; MV, multivariable; RR, relative risk; CI, confidence interval.

[b]Multivariable relative risks are adjusted for age, diagnosis year, parity, oral contraceptive use and duration, pack-years of cigarette smoking, body mass index, history of tubal ligation, antidepressant use, history of childhood trauma, and dietary intake of alcohol, vitamin B_6, potassium, calcium, and vitamin D. See footnote[b] to Table 2 for variable categories. For analyses of alcohol use in 1989 and 1991, covariates were assessed in 1991; analyses for reference year and total drinking-years include covariate levels assessed at reference age. Numbers of cases and controls may not sum to totals because of missing data.

[c]For each year, Former drinker includes all participants who reported alcohol intake at an earlier time period but reported no intake in the current time period. Never drinker includes all participants who had not reported any alcohol intake on any assessment up to and including the current time period. Tests for trend for analyses of g/day include drinkers only (never and former drinkers excluded).

[d]Total drinking-years = sum of g/day at each age * years at that age. The reference group is women reporting no alcohol use up to and including their reference year. Drinker are divided into quintiles based on the distribution in controls (>0–<17.0, 17.0–<40.8, 40.8–<83.2, 83.2–<146.0, ≥146.0).

Table 4. Multivariable Relative Risks and 95% Confidence Intervals of PMS and Probable PMDD by Total Drinking-Years of Alcohol Stratified by Body Mass Index at Time of Diagnosis, NHS2[a] PMS Substudy, 1991–2001

	PMS				*Probable PMDD*			
	BMI $< 25.0\,kg/m^2$		*BMI* $\geq 25.0\,kg/m^2$		*BMI* $< 25.0\,kg/m^2$		*BMI* $\geq 25.0\,kg/m^2$	
	Cases/ controls	*MV-adjusted RR*[b]	*Cases/ controls*	*MV-adjusted RR (95% CI)*	*Cases*[c]	*MV-adjusted RR*	*Cases*[c]	*MV-adjusted RR (95% CI)*
Never drinker	50/161	1.00	45/98	1.00	98	1.00	26	1.00
Ever drinker								
Quintile 1	75/217	1.01 (0.64-1.58)	70/107	1.03 (0.61-1.76)	107	1.26 (0.75-2.10)	52	1.26 (0.68-2.34)
Quintile 2	92/218	1.10 (0.71-1.71)	68/118	0.95 (0.56-1.61)	118	1.33 (0.80-2.21)	44	0.92 (0.49-1.72)
Quintile 3	130/227	1.52 (0.99-2.33)	74/109	0.89 (0.52-1.54)	109	1.94 (1.19-3.18)	53	0.98 (0.52-1.85)
Quintile 4	134/229	1.63 (1.06-2.52)	76/99	1.06 (0.61-1.84)	99	1.88 (1.13-3.11)	54	1.22 (0.64-2.33)
Quintile 5	141/213	1.74 (1.11-2.72)	68/114	0.66 (0.37-1.16)	114	2.00 (1.18-3.38)	46	0.61 (0.31-1.20)
p trend		0.002		0.10		0.009		0.06
p interaction		0.01				0.02		

[a]NHS2, Nurses' Health Study II; PMS, premenstrual syndrome; PMDD, premenstrual dysphoric disorder; MET, metabolic equivalent; MV, multivariable; RR, relative risk; CI, confidence interval; BMI, body mass index.

[b]Multivariable relative risks are adjusted for age, diagnosis year, parity, oral contraceptive use and duration, pack-years of cigarette smoking, body mass index, history of tubal ligation, antidepressant use, history of childhood trauma, and dietary intake of alcohol, vitamin B_6, potassium, calcium, and vitamin D. See footnote[b] to Table 2 for variable categories. Numbers of cases and controls may not sum to totals because of missing data.

[c]Control numbers in each category are the same as for the analysis of PMS.

observed some evidence that first use of alcohol during adolescence and long-term alcohol use may minimally increase risk, especially in lean women. However, we did not find that older reproductive age women who consumed alcohol regularly were more likely to develop PMS or probable PMDD over 10 years of follow-up.

Reduction in alcohol intake is often suggested as a means to reduce PMS symptom occurrence and severity, although this recommendation is largely based on anecdotal evidence.[21] Several[4,9,10,12,22] but not all studies[8,23] have suggested that alcohol use is more common in women experiencing PMS or menstrual problems. Deuster et al.[4] observed a 2.5-fold higher PMS prevalence in women reporting consuming 1 or more alcoholic beverages per day (POR = 2.5, 95% CI 1.1-5.9) compared with those consuming alcohol less frequently. Intake of more than 1 alcoholic drink per day was also more common in women with menstrual problems in the National Health Interview Survey.[9] However, these previous studies, which assessed the prevalence of alcohol use among women who already had PMS or PMDD, are limited in their ability to determine if alcohol use is etiologically related to these disorders or whether women consume alcohol as a means of managing their menstrual symptoms.

Results from our study emphasize the importance of taking cigarette smoking into consideration when evaluating how alcohol may relate to PMS/PMDD. Previous studies in our population[24] and others[3,4,8,9,25] have reported that women who smoke are significantly more likely than nonsmokers to experience PMS. Alcohol intake and cigarette smoking were strongly correlated in our study population. For example, in controls, mean alcohol intake at baseline in current smokers was 7.1 g/day (SD = 9.6) compared with 2.4 g/day (SD = 5.0) in never smokers ($p < 0.0001$). In our analysis, RRs unadjusted for cigarette smoking did suggest a significant positive relation with alcohol intake. However, control for pack-years of cigarette smoking, a measure that takes both smoking intensity and duration into consideration, substantially attenuated results, and the modest positive relationships that remained after adjustment may be attributable to residual confounding. Given these findings, it is possible that the positive relationships between alcohol and PMS/PMDD observed in previous studies are to some extent attributable to residual confounding by cigarette smoking or by another factor.

Previous studies have suggested that the occurrence of PMS and PMDD may be related to sex steroid hormones or gonadotropin fluctuations during the menstrual cycle.[26] Alcohol use may, therefore, plausibly increase the risk of PMS by altering levels of these hormones, although results from laboratory-based studies of these relationships have been inconsistent. Several studies have suggested that estradiol levels increase with alcohol intake during one or more phases of the menstrual cycle,[27–29] although other have not observed a clear linear relationship.[30–34] Verkasalo et al.[32] observed significant inverse relationships between daily alcohol intake and sex hormone-binding globulin (SHBG) and follicle-stimulating hormone (FSH) levels but no clear linear relationship with progesterone, estradiol, and luteinizing hormone (LH) levels. Luteal phase progesterone levels were higher in women consuming 1 or more drinks per week than in nondrinkers in one study,[34] whereas others have found that luteal phase levels of the progesterone metabolite allopregnanolone are reduced after alcohol intake.[35] There is evidence that alcohol use may possibly be protective against PMS by increasing 25-hydroxyvitamin D and lowering parathyroid hormone (PTH) levels,[36,37] which have been related to PMS/PMDD incidence in several studies.[13,38]

Alcohol use also may be related to PMS and PMDD through its effect on serotonin and gamma-amino butyric acid (GABA) activity. Several studies have suggested that the activity of serotonin and GABA may be altered in women with these disorders[26,39] and that whole blood and platelet serotonin and plasma GABA levels in the mid–late luteal phase of the menstrual cycle may be different in women with

PMS/PMDD compared with control women.[26,39,40] Furthermore, selective serotonin reuptake inhibitors (SSRIs) are effective in treating PMS/PMDD in some patients,[21] as is the GABA-ergic anxiolytic alprozolam.[26] Laboratory-based studies suggest that frequent alcohol use may alter both serotonin and GABA receptor activity.[41] It is possible that women with underlying abnormalities of the serotonergic and GABA-ergic systems may be more sensitive to the effects of alcohol on these receptors and, consequently, more likely to develop PMS/PMDD.

Our study has several limitations. Because of the constraints of large prospective cohort studies, we were unable to use daily symptom diaries to confirm incident diagnoses of PMS or PMDD among participants, as is the standard in clinical practice. However, in a recent study in our population,[24] we found that prospective reporting of new PMS diagnoses combined with a short retrospective symptoms questionnaire to confirm symptom occurrence, timing, and severity can accurately identify women with PMS. Although this method may not be as accurate as those used in clinical practice and intervention studies, it appears to be sensitive enough to identify risk factors for incident PMS.[13,24] Also, because alcohol use during adolescence and young adulthood was reported by participants in 1989 when participants were 25–44 years old, the recall of age at first alcohol use and frequency of use at young ages may have been somewhat inaccurate. However, all information on alcohol intake used in our analysis was collected prior to the timing of PMS diagnosis, therefore limiting the likelihood of bias. In addition, because of the age of our participants at baseline (e.g., $\geq$27 years in 1991), we were not able to assess factors associated with PMS developing at younger ages. Consequently, our findings may be generalizable only to women who develop PMS in middle-to-older reproductive years. Although the generalizability of our findings may also be limited by the fact that our participants are all registered nurses, such participants are probably more likely than most women to report menstrual symptom experience and alcohol use reliably.

Conclusions

We did not observe a strong relationship between alcohol use and the initial development of PMS and probable PMDD, although first use during adolescence and long-term use may minimally increase risk. Previous observations of greater alcohol use in prevalent PMS and PMDD cases compared with controls may largely reflect self-treatment of menstrual symptoms with alcohol, as opposed to an etiological relationship. Additional studies are needed to further evaluate this hypothesis.

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Disclosure Statement

The authors have no conflicts of interest to report.

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