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Premenstrual syndrome and alcohol: a systematic review and meta-analysis.

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Abstract

Objective: Premenstrual syndrome (PMS) is a very common disorder worldwide which carries an important economic burden. We conducted a systematic review and a meta-analysis to assess the role of alcohol in the occurrence of PMS.

Data Sources: We searched MEDLINE, EMBASE, the 5 regional bibliographic databases of the World Health Organization (WHO), the ISI-Proceedings databases and the Open Access Thesis and Dissertations (OATD) from inception to May 2017. We also reviewed the references of every article retrieved and established personal contact with researchers to trace further publications or reports. We did not include any language limitations.

Methods of Study Selection: Studies were included if: 1) they presented original data from cohort, case-control or cross-sectional studies, 2) PMS was clearly defined as the outcome of interest, 3) one of the exposure factors was alcohol consumption, 4) they provided estimates of odds ratios, relative risks, or any other effect measure and their confidence intervals, or enough data to calculate them.

Tabulation, Integration, and Results: We identified 38 studies of which 20 were eligible. Intake of alcohol was associated with a moderate increase in the risk of PMS (RR=1.36, 95%CI: 1.11-1.67). Heavy drinking yielded a larger increase in the risk than any drinking (RR=1.70, 95%CI: 1.35-2.14).

Conclusion: Our results suggest that alcohol intake presents a moderate association with PMS risk. Future studies should avoid cross-sectional designs and focus on determining whether there is a threshold of alcohol intake under which the harmful effect on PMS is non-existent.

Strengths and limitations of this study

- This is the first meta-analysis carried out on the relation between alcohol consumption and risk of premenstrual syndrome (PMS), a highly prevalent condition worldwide.
- Exhaustive search of studies was carried out in several bibliographic databases, and unpublished studies were included.
- Intensive sensitivity analyses were performed to assess potential for publication bias and confounding.
- In our subgroup analyses, we were unable to identify any factors that accounted for study heterogeneity.
- In some studies included in this meta-analysis, the assessment of alcohol intake was probably concomitant to the assessment of PMS. A reverse causation process, in which PMS-affected women use alcohol to mitigate the effect of the syndrome, is then plausible.

Introduction

Premenstrual syndrome (PMS) consists of a series of recurrent physical and emotional symptoms, including mood swings, tender breasts, food craving, fatigue, irritability and depression, during the luteal phase of the menstrual cycle.[1,2] The severity of the syndrome varies from woman to woman and is related to the type and intensity of the symptoms.[1,3] While in the United States, the prevalence of the syndrome varies between 20 and 40% for cases of moderate severity and between 3 and 8% for severe cases [2], a recent prevalence meta-analysis shows that the worldwide prevalence sways between 10% and 98%.[4]

The economic burden of the syndrome is far from being negligible. For a week every month women affected by this syndrome suffer distress and impairment in interpersonal or workplace functioning. This can lead to at least two days per month of absenteeism at work and an increase in medical appointments.[2,5] In the US, the cost of the syndrome

reaches $5000 per case per year.[2] Each affected woman experiences a total of 3000 days with disabling symptoms during her reproductive life.[2] The large majority of cases are not diagnosed, either because affected women do not seek medical help or because physicians have difficulties in establishing a firm diagnosis.[6] Furthermore, premenstrual syndrome was recently found to be a risk factor for hypertension increasing its incidence by 40%.[7]

The World Health Organization (WHO) warned recently against the increasing alcohol consumption among women related to economic development and changing gender roles, and emphasized the fact that women may be more vulnerable to alcohol-related harm than men.[8] Several studies have identified an increased burden of PMS among women who consume alcohol.[9-11] However, it is not clear whether this increase in the risk of PMS is due to alcohol consumption or whether alcohol is consumed in an attempt to mitigate the symptoms of the syndrome.[12] Other studies found that the relation between alcohol and PMS was weak or even non-existent.[12-14] Furthermore, assessing the role of alcohol in prospective studies is not straightforward. Indeed, it is not feasible to relate alcohol intake to the first occurrence of PMS in the life of a woman, as the first bout of the disease appears at an early age, probably before any alcohol is consumed. Prospective studies aim at determining the role of regular alcohol intake in the occurrence of the *next* episode of the disease, not the *first* one.

We are not aware of the existence of any meta-analysis on the topic. We therefore conducted a systematic review of the literature and a meta-analysis to assess the role of alcohol in the occurrence of PMS.

Sources

To identify all potentially eligible studies, we searched MEDLINE, EMBASE, the 5

regional bibliographic databases of the WHO (AIM, LILACS, IMEMR, IMSEAR, WPRIM), the Conference Proceedings Citation Index, the Open Access Thesis and Dissertations (OATD), from inception to May 2017.

For Medline, we used the following algorithm both in Medical Subject Heading and in free text words: ("premenstrual syndrome"[MeSH Terms] OR "premenstrual syndrome"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields]). Similar strategies were used for the other databases.

We also reviewed the references of every article retrieved. Furthermore, we established personal contact with researchers to trace further publications or reports. We did not include any language limitations. All searches were carried out independently by two researchers and results were merged.

The review protocol of this meta-analysis was registered in Prospero.[15]

Study selection

Studies were included if: 1) they presented original data from cohort, case-control or cross-sectional studies, 2) PMS was clearly defined as the outcome of interest, 3) one of the exposure factors was alcohol consumption, 4) they provided estimates of odds ratios (OR), relative risks (RR), or prevalence odds ratios and their confidence intervals, or enough data to calculate them.

If data on the same population were duplicated in more than one publication, the most recent study was included in the analysis.

We developed a standard data-recording form in which we recorded authors, year of publication, study location, study design, sample size, outcome, outcome measurement details, effect estimator (OR, RR, other), effect estimate, 95% Confidence Intervals, and adjustment, restriction or matching factors used.

When further clarification was necessary, we attempted to contact the authors.[14,16,17]

Quality Assessment

Study quality was assessed using a five-point binary scale specifically developed for this study. The scale is based on the Newcastle-Ottawa scale with modifications in view of standard guidelines and our own judgment.[18] The Newcastle-Ottawa scale is a scoring system that assesses every aspect of an observational epidemiologic study from a methodological point of view. For this meta-analysis, we tried to use those elements that were common to all epidemiological designs and thus shortened the scale considerably. We used the following criteria labelled as "1" or "0": 1) Measurement of alcohol intake: through standard or validated questionnaire which includes quantity and/or frequency: 1, else (simple question, no data on frequency or quantity) or not explained: 0; 2) PMS diagnosis: through standard or validated questionnaire: 1, else or not explained: 0; 3) Confounding assessment: results adjusted at least for age and smoking, either in the design phase or in the analysis: 1, else: 0; 4) Participation: participation exceeded 80% of the people initially approached: 1, else or data not provided: 0; 5) Target population: target population clearly defined: 1, based on convenience sampling of subjects such as patients of a single consultation or volunteers or not explained: 0

Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as "0". We carried out a pooled analysis on those studies that fulfilled at least 3 criteria and compared with those that fulfilled fewer than 3. Furthermore, we did not grade cross-sectional studies differently from the case-controls studies in spite of their evident high potential for bias. Our aim was to evaluate design and analysis features that are common to both types of studies. The influence of

the design on the pooled estimate was assessed separately from the quality.

Abstracts' review, data extraction and quality scoring were performed independently by two reviewers (J.S and M.F.) and the results were merged by consensus. The complete protocol and results for quality scoring are available from the corresponding author.

Data synthesis and analysis

We weighted the study-specific log odds ratios or other ratio measures for case control and cross-sectional studies by the inverse of their variance to compute a pooled estimate. In our search we could not find any cohort studies. For each study, we used the estimate of the effect measure that was adjusted for the largest number of confounders. We present both fixed-effects and random-effects pooled estimates but use the latter when heterogeneity was present. Odds ratios were assumed to be unbiased estimates of the relative risk.[19]

We calculated odds ratios for any intake of alcohol and for high intake, following the classification given by each individual study. The estimates of studies which failed to provide data for different levels of alcohol intake but, instead, assessed alcohol consumption on a yes/no basis, were included in the "any intake" group.

When results were not available as odds ratios estimates but rather as correlation coefficients between alcohol intake and PMS score[20,21] or differences in means of intake between cases of PMS and controls[22,23], they were transformed into odds ratios estimates corresponding to an increase of 1 unit of exposure, i.e. 1 average drink.[24] As drinking patterns vary widely between countries, we calculated the content in ethanol of an average drink using data on consumption of beer, wine and spirits, specific to each country and used different sources to define low, moderate and heavy drinking.[8,12] We

considered a consumption of less than 10g/day of ethanol as low intake, a consumption between 10g/day and the content in ethanol of 1 average drink/day as moderate intake, and a consumption equal or higher than the content in ethanol of 1 average drink/day as heavy intake. To compute an estimate for the category "any drinking", we pooled the odds ratios obtained in the 3 categories (low, moderate and heavy intake).

We used a version adapted to small samples of the DerSimonian and Laird Q test to check for heterogeneity.[25] To quantify this heterogeneity we calculated the proportion of the total variance due to between-study variance (Ri statistic).[25] We later explored the origin of heterogeneity by restricting the analysis to subgroups of studies defined by study characteristics such as study design, adjustment, origin and quality score. All secondary analyses were planned a priori.

We assessed publication bias, first visually, using funnel plots and then, more formally, using the test proposed by Egger et al.[26] We also used the trim-and-fill method to correct for potential publication bias. All analyses were performed with the software HEpiMA® version 2.1.3 [27] and STATA version 12 .

Results

Table 1 and figures 2 and 3 present the studies of our meta-analysis. We identified 20 studies of 7 different countries that met our inclusion criteria.[9-14,16,20-23,28-36]

The large majority of the articles retrieved initially were excluded because they did not provide any effect measure. More specifically, we discarded 18 studies (figure 1) that could have been eligible for the following reasons: 4 did not assess PMS cases,[17,37-39] 2 lacked any control group,[40,41] 5 did not present data on alcohol consumption[42-45] and one

of them did not present a confidence interval,[46] the full text of one could not be traced[47], one was a duplicate publication,[48] 4 presented insufficient data to calculate effect measures estimates, [49-52] and one assessed PMS as a risk factor for alcoholism.[53]

For further information we contacted the authors of articles for which the details of the data were not sufficient for effect measures to be computed. We obtained collaboration from 3 authors.[14,16,17] The study by Kiesner et al. was finally excluded as its outcome was "change in PMS score" rather than occurrence of PMS.[17]

Tables 2 and 3 show that, globally, heterogeneity was substantial overall, and similarly high after stratification by design, quality features, including adjustment for confounders. No individual study seemed to represent an influential point that increased heterogeneity dramatically. We focused on the random effects analyses and presented the fixed effects results for comparison purposes only.

Intake of alcohol was associated with a moderate increase of the risk of PMS (OR=1.36, 95%CI: 1.11-1.67), while heavy drinking yielded a larger increase in the risk than any drinking (OR=1.70, 95%CI: 1.35-2.14). Heavy drinking was associated with a higher risk than any drinking in all subgroup estimates. The pooled estimate of case-control studies was higher than that of cross-sectional studies both for any drinking and heavy drinking. When we restricted our analysis to those studies that presented odds ratio estimates, i.e. when we excluded studies that computed correlation coefficients and means, the pooled estimates were higher: pooled OR= 1.53; 95%CI 1.19-1.98 for any drinking and 1.90; 95%CI 1.45-2.49 for heavy drinking.

The pooled estimate of studies with high quality scores was slightly higher than that from low quality studies.

Except for the criteria "complete adjustment of confounding" in the any drinking group, when we considered the quality criteria individually instead of just as a global quality

score, as recommended by the MOOSE guidelines,[54] the studies that fulfilled the criteria yielded lower pooled estimates than studies which did not. However, the estimates remained statistically significant.

Two-thirds of the studies included in this meta-analysis were carried out in US populations. The estimates from American studies and from studies carried out in other countries were similar in the any drinking group but were slightly lower for American studies then for non-American studies in the heavy drinking group.

Publication Bias

The funnel plot (figure 4) for the any drinking group did not suggest asymmetry, a result confirmed by a p-value of the Egger's test of 0.74. However, the trim-and-fill procedure indicated 4 potentially missing studies though the corrected pooled odds ratio, OR=1.35 (95%CI 1.31-1.39), was almost identical to the odds ratio we obtained. Again, the funnel plot for heavy drinking did not suggest any publication bias (p-value Egger's test = 0.41) and the trim-and-fill method indicated one potentially missing study though the corrected pooled estimate was even higher than the one we obtained before correction (pooled OR= 1.87; 95%CI: 1.78-1.96).

Sensitivity Analysis

To further evaluate the possibility that our results could be due to publication bias, we assumed that cross-sectional studies represent the design for which publication is least likely if the results were null. We recalculated our pooled estimates under the following extreme assumptions: (1) published cross-sectional studies are only half of the studies of alcohol drinking and PMS ever conducted, (2) all unpublished studies found an OR

of 1, (3) the unpublished studies found the same prevalence of PMS as the average of the published studies. Under these extreme assumptions, the random effects pooled estimates still showed a significant increase in risk: OR=1.18 (95%CI 1.03-1.35) for any alcohol drinking and OR= 1.34 (95% CI 1.11–1.61) for heavy drinking.

Discussion

The results of our systematic review and meta-analysis suggest that alcohol drinking is associated with a moderate increase in the risk of PMS. This increase is more pronounced for heavy drinking, which favours a causal explanation of the relation between alcohol intake and PMS.

These findings are important given that the worldwide prevalence of alcohol drinking among women is not negligible. Worldwide, the proportion of current female drinkers is 28.9%, while that of heavy female drinkers is 5.7%. In Europe and America these figures are much higher and reach 59.9% for current drinking and 12.6% for heavy drinking in Europe.[8] Based on the figures above and on our results we estimate that approximately 10% of the PMS cases may be associated to alcohol intake worldwide and 18% in Europe.[55] Furthermore, heavy drinking may be associated with 4% of the PMS cases in the world and over 8% in Europe. If this association is of causal nature, eliminating heavy drinking in women would then prevent one in every twelve cases of PMS in Europe.

Alcohol use may plausibly increase the risk of PMS by altering levels of sex steroid hormones and gonadotropin during the menstrual cycle. PMS was previously found to be linked to fluctuations of these sex hormones during the cycle.[12,56] Furthermore, alcohol intake may increase the risk of PMS through its effect on serotonin and gamma-

amino butyric acid (GABA) activity. On the one hand, women who present alterations in the serotonin and GABA systems may be more sensitive to alcohol. On the other hand it is known that the activity of both serotonin and GABA is altered among subjects with PMS.[12] In fact, selective serotonin reuptake inhibitors (SSRIs) as well as the GABA-ergic anxiolytic alprazolam may represent effective treatments in PMS cases.[56,57]

The relatively large number of studies conducted and the consistency of the results across study designs and settings provide substantial epidemiological evidence that alcohol drinking may be associated with an increase in the risk of PMS. However, non-causal explanations of the relation should be carefully evaluated.

First, publication bias is a highly unlikely explanation for our results, as the association between alcohol drinking and PMS remained strong even after extremely conservative assumptions regarding the number, size, and findings of studies potentially conducted and not included in our meta-analysis. Also, the findings of the asymmetry tests of the funnel plot as well as those of the trim-and-fill method did not alter our results.

Second, residual confounding (confounding from unknown variables that is not eliminated by adjustment) may have introduced bias as in any meta-analysis of observational studies. It is remarkable that only one-third of the studies included in this meta-analysis considered tobacco smoking in their adjustment in spite of the potential for confounding of this factor.[12] In our meta-analysis, restricting our analysis to studies that adjusted for potential confounders, including tobacco smoking, did not introduce any substantial modification in the estimate corresponding to any intake of alcohol. The estimate corresponding to heavy intake decreased substantially after restriction to studies with complete adjustment but still shows a 38% increase in the risk. Furthermore, other confounders that were not measured in the studies of this meta-

analysis could explain our results. Recently, some genetic polymorphisms, such as those of the ESR1 gene and those associated to the serotonin 1A receptor have been implicated in the occurrence of PMS.[58,59] Such genetic factors could theoretically play a role of confounders and explain the results of this meta-analysis concerning alcohol drinking. However, this hypothesis is highly unlikely to be true. First, to act as a confounder, a genetic factor must be related to PMS on the one hand and to alcohol drinking on the other hand. No such factor has been described so far. Second, even if this hypothetical factor could double the risk of PMS among subjects exposed to it (OR confounder–disease = 2) and, simultaneously, this factor happened to be twice as prevalent among alcohol drinkers than among non-drinkers (OR confounder–exposure = 2), the adjusted OR of the relation between any alcohol drinking and PMS would still be 1.21 and that of the relation between heavy drinking and PMS would still be 1.51 (assuming one-third of people are exposed to this unknown factor).[60] The existence of an unknown factor so strongly related to alcohol intake and to PMS is highly improbable.

Third, measurement error and misclassification of alcohol intake is likely to occur since women may understate their intake of alcohol as many societies hold more negative attitudes towards women's alcohol drinking than men's drinking.[8] However, this misclassification is probably non differential regarding PMS, i.e. women with PMS do not underestimate their drinking habits in a different fashion from women who do not suffer PMS. In this case, the bias introduced is then towards the null value. The true OR is then even higher than the one we report in our meta-analysis. Similarly, misclassification of the outcome is also possible (i.e. women with PMS who are diagnosed as non-cases, and conversely non-diseased women who are erroneously

diagnosed as PMS cases). As previously, this possible misclassification is unlikely to occur differently in women who consume alcohol and in those women who do not. The bias introduced, if any, is towards the null value.

Fourth, given that a substantial proportion of the studies included in this meta-analysis used a cross-sectional design, a reverse causation process, in which PMS-affected women use alcohol to mitigate the effect of this syndrome, could explain the results observed. Although this hypothesis should be rejected due to the fact that the pooled estimates for both categories of drinking are higher for case-control studies than for cross-sectional studies, it should be noted that, in several case-control studies included in this meta-analysis, the assessment of alcohol intake was probably concomitant to the assessment of PMS. This hypothesis remains then plausible.

Furthermore, in our subgroup analyses, we were unable to identify any factors that accounted for study heterogeneity. This situation is extremely frequent and for meta-analysis experts, heterogeneity should be viewed more as the rule rather than the exception.[61] As recommended by experts when heterogeneity is present, in order to deal with this issue, we focused our interpretation on the random effects estimates that are, in general, more conservative.[62]

Our meta-analysis shows that alcohol intake is moderately associated with PMS risk. The consistency of the results and the existence of a plausible biologic mechanism strengthen our conclusions. Future studies should minimize measurement error in the exposure by using validated questionnaires. These studies should avoid cross-sectional designs and focus on determining whether there is a threshold of alcohol intake under which the harmful effect on PMS is non-existent.

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María del Mar Fernández performed the computerized systematic search, literature revision, risk of bias assessment, meta-analysis and redaction of the manuscript, figures and tables.

Jurgita Saulyte assessed the risk of bias and revised the manuscript.

Hazel Inskip provided unpublished data and participated in the redaction of the manuscript

Bahi Takkouche did the complementary searches, assessment of the publication bias and revision of the final manuscript, figures and tables. He acts as a guarantor of the study

All authors approved the final version of the article.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1. Odds Ratios and 95% confidence intervals of premenstrual syndrome and alcohol drinking

Source	Design	Country	Population	Any Drinking	Light drinking	Moderate drinking	Heavy drinking	Study size	Adjustment variables
Wilsnack 1984[16]	Cross-Sectional	USA	National sample ≥ 21 years	1.11 (0.89-1.40)	0.86 (0.59-1.25)	1.15 (0.80-1.65)	1.57 (0.99-2.49)	2552	Not specified
Stout 1986[28]	Case-Control	USA	Patients 20-48 years	3.32 (1.85-5.97)	---	---	3.32 (1.85-5.97)	223/923	Not specified
Griffin 1987[20]	Cross-Sectional	USA	Volunteers 21-36 years	1.15 (1.11-1.20)	1.11 (1.06-1.16)	1.29 (1.15-1.44)	1.43 (1.21-1.67)	30	Not specified
Rossignol 1991[29]	Cross-Sectional	USA	Students18-22 years	2.11 (1.99-2.22)	----	2.35 (1.64-3.37)	2.10 (1.99-2.22)	853	Not specified
Caan 1993[30]	Case-Control	USA	Volunteers	2.00 (0.96-4.17)	1.34 (0.82-2.19)	1.40 (0.63-2.13)	9.73 (2.68-35.29)	102/102	Age, ethnicity
Chuong 1995[31]	Case-Control	USA	Patients	3.74 (2.27-6.18)	3.29 (1.95-5.56)	5.39 (1.12-25.87)	9.41 (1.14-77.57)	190/182	Not specified
Deuster 1999[9]	Cross-Sectional	USA	General population 18-44 years	2.5 (1.1-5.9)	---	---	2.5 (1.1-5.9)	874	Age, ethnicity, age at menarche, length of menses, body mass index, education, smoking, stress score, diet, physical activity
Hourani 2004[32]	Case-Control	USA	Navy workers 18-49 years	1.62 (1.08-2.42)	---	---	1.62 (1.08-2.42)	3861/2165	Demographic variables and lifestyle
Strine 2005[10]	Cross-sectional	USA	National sample 18-55 years	1.4 (1.1-1.7)			1.4 (1.1-1.7)	11648	Age, ethnicity, education, marital status, employment status
Bryant 2006[22]	Case-Control	UK	Volunteers 18-47 years	0.87 (0.65-1.15)	0.90 (0.66-1.23)	0.77 (0.35-1.67)	0.69 (0.23-2.05)	31/27	Age, body mass index
Gold 2007[13]	Cross-Sectional	USA	Population from a cohort 42-52 years	0.64 (0.44-0.92)	1.06 (0.09-11.93)	0.63 (0.40-0.91)	---	2758	Not specified

Table 1. Odds Ratios and 95% confidence intervals of premenstrual syndrome and alcohol drinking (cont.)

Source	Design	Country	Population	Any Drinking	Light drinking	Moderate drinking	Heavy drinking	Study size	Variables of adjustment, matching or restriction
Reed 2008[23]	Case-Control	USA	Volunteers	0.74 (0.50-1.10)	0.80 (0.51-1.24)	0.57 (0.18-1.73	0.45 (0.09-2.16)	14/15	Not specified
Bertone-Johnson 2009[12]	Case-Control	USA	Population from the Nurses' Health Study	1.13 (1.03-1.27)	1.05 (0.91-1.20	1.28 (1.10-1.50)	1.09 (0.92-1.28)	762/1968	Age, diagnosis year, parity, contraception, smoking, pregnancies, body mass index, tubal ligation, antidepressants, childhood trauma, diet
Nillni 2010[21]	Cross-Sectional	USA	Volunteers	1.12 (0.81-1.55)	1.09 (0.76-1.56)	1.24 (0.50-3.04)	1.35 (0.38-4.80)	46	Not specified
Sadler 2010[14]	Cross-Sectional	UK	General population 20-34 years	0.83 (0.65-1.08)	0.83 (0.53-1.29)	0.80 (0.51-1.25)	0.87 (0.56-1.35)	974	Age, education, body mass index, smoking, stress, hormonal contraception
Skrzypulec-Plinta 2010[11]	Cross-Sectional	Poland	General population 18-45 years	2.43 (0.86-6.89)	---	---	---	1540	Not specified
Forrester-Knauss 2011[33]	Cross-Sectional	Switzerland	National sample >50 years	0.59 (0.27-1.27)	0.78 (0.58-1.04)	0.34 (0.13-0.88)	---	3518	Not specified
Pinar 2011[34]	Cross-Sectional	Turkey	Students18-28 years	0.80 (0.43-1.48)	---	---	---	316	Not specified
Hong 2012[35]	Cross-Sectional	Korea	Population from a catchment area 18-49 years	3.32 (1.76-6.27)	---	---	3.32 (1.76-6.27)	2499	Age
Cheng 2013[36]	Cross-Sectional	Taiwan	Students	2.85 (1.18-6.84)	---	---	2.85 (1.18-6.84)	1699	Age, education, cycle regularity, smoking, exercise, diet

Table 2. Pooled Odds Ratios (RR) and 95% confidence intervals (CI) of premenstrual syndrome and any intake of alcohol

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test p value
All studies	20	1.42 (1.38-1.46)	1.36 (1.11-1.67)	0.97	0.0001
Case-control studies	7	1.19 (1.08-1.31)	1.53 (1.06-2.20)	0.92	0.0001
Cross-sectional studies	13	1.44 (1.40-1.49)	1.29 (0.99-1.67)	0.98	0.0001
Direct calculations	16	1.79 (1.71-1.86)	1.53 (1.19-1.98)	0.96	0.0001
Quality score ≥ 3	10	1.15 (1.11-1.20)	1.23 (1.06-1.44)	0.87	0.0004
Quality score < 3	10	1.92 (1.84-2.02)	1.34 (0.95-1.89)	0.98	0.0001
Full adjustment	6	1.14 (1.03-1.26)	1.39 (1.02-1.91)	0.84	0.003
Incomplete adjustment	14	1.45 (1.40-1.49)	1.33 (1.04-1.70)	0.98	0.0001
Validated exposure	12	1.13 (1.09-1.17)	1.06 (0.94-1.20)	0.84	0.0001
Non validated exposure	8	2.06 (1.96-2.16)	1.91 (1.40-2.62)	0.96	0.0001
Validated diagnosis	14	1.42 (1.38-1.47)	1.28 (1.00-1.64)	0.98	0.0001
Non validated diagnosis	6	1.34 (1.18-1.51)	1.57 (1.05-2.36)	0.90	0.0001
High response rate	6	1.15 (1.11-1.20)	1.21 (1.03-1.41)	0.88	0.007
Low response rate	14	1.87 (1.79-1.96)	1.38 (1.03-1.86)	0.97	0.0001
Defined target population	11	1.19 (1.09-1.29)	1.28 (1.02-1.61)	0.80	0.0001
Undefined target population	9	1.45 (1.41-1.50)	1.42 (1.04-1.93)	0.99	0.0001
US studies	14	1.43 (1.38-1.47)	1.38 (1.10-1.73)	0.98	0.0001
Rest of the world	6	1.04 (0.85-1.28)	1.37 (0.77-2.45)	0.86	0.0001

* Proportion of total variance due to between-study variance

Table 3. Pooled Odds Ratios (RR) and 95% confidence intervals (CI) of premenstrual syndrome and high intake of alcohol

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test p value
All studies	16	1.85 (1.77-1.94)	1.70 (1.35-2.14)	0.93	0.0001
Case-control studies	7	1.25 (1.04-1.44)	1.82 (1.04-3.18)	0.90	0.0001
Cross-sectional studies	9	1.95 (1.85-2.04)	1.68 (1.32-2.13)	0.93	0.0001
Direct calculations	12	1.91 (1.82-2.01)	1.90 (1.45-2.49)	0.95	0.0001
Quality score ≥ 3	8	1.32 (1.20-1.46)	1.51 (1.19-1.92)	0.77	0.0001
Quality score < 3	8	2.04 (1.94-2.15)	1.93 (1.34-2.77)	0.95	0.0001
Full adjustment	5	1.17 (1.02-1.34)	1.38 (0.98-1.96)	0.79	0.02
Incomplete adjustment	11	1.97 (1.87-2.07)	1.86 (1.45-2.40)	0.92	0.0001
Validated exposure	10	1.28 (1.16-1.41)	1.35 (1.06-1.72)	0.71	0.004
Non validated exposure	6	2.06 (1.95-2.17)	2.25 (1.66-3.06)	0.95	0.0004
Validated diagnosis	11	1.88 (1.79-1.98)	1.63 (1.20-2.21)	0.96	0.0001
Non validated diagnosis	5	1.56 (1.33-1.82)	1.81 (1.30-2.53)	0.71	0.045
High response rate	5	1.32 (1.19-1.47)	1.59 (1.18-2.14)	0.83	0.001
Low response rate	11	2.01 (1.91-2.12)	1.73 (1.28-2.33)	0.94	0.0001
Defined target population	7	1.33 (1.19-1.48)	1.64 (1.26-2.13)	0.76	0.001
Undefined target population	9	1.99 (1.89-2.10)	1.69 (1.21-2.37)	0.95	0.0001
US studies	13	1.86 (1.78-1.95)	1.68 (1.31-2.14)	0.94	0.0001
Rest of the world	3	1.50 (1.07-2.09)	1.95 (0.74-5.10)	0.88	0.001

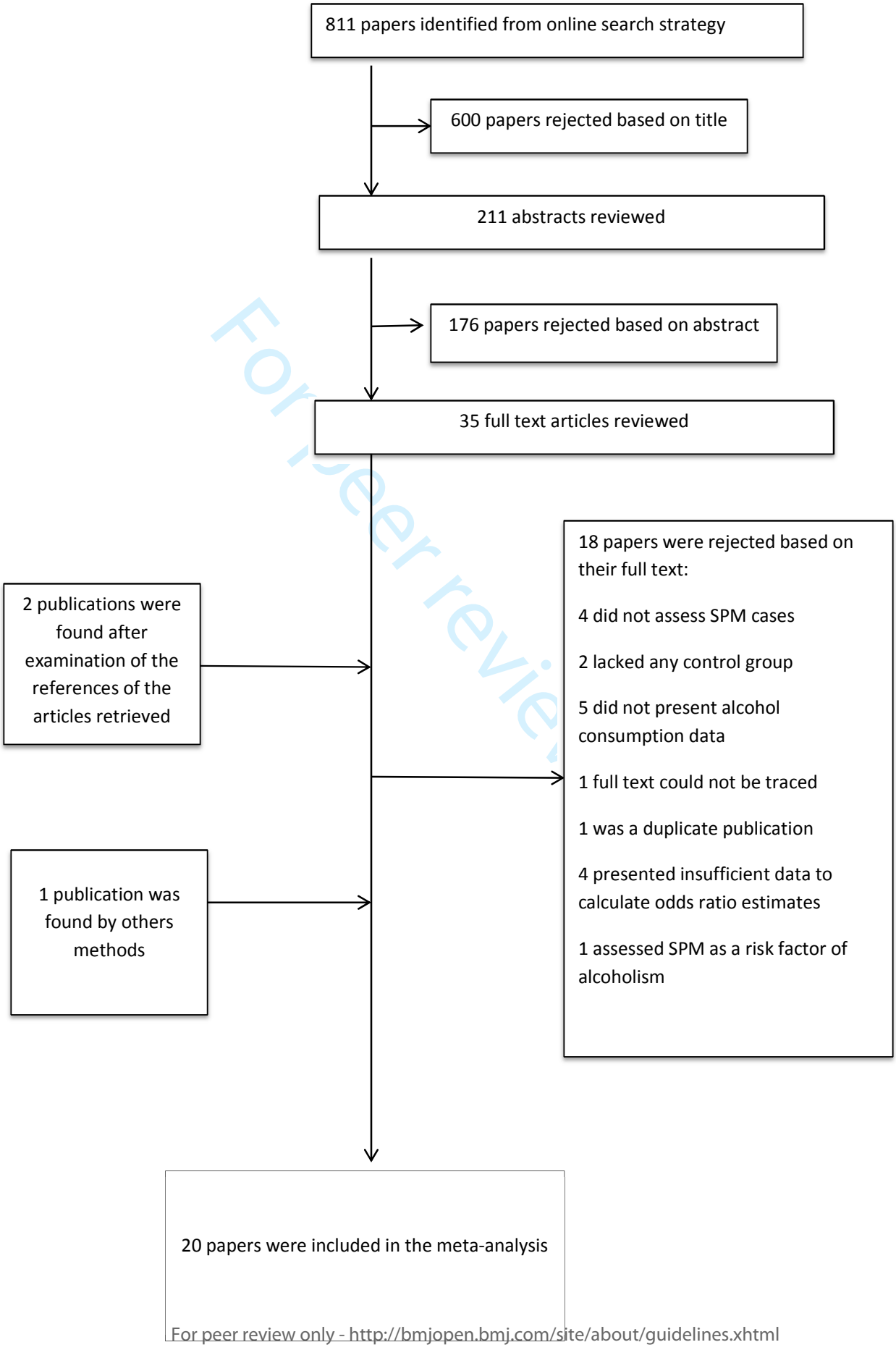
* Proportion of total variance due to between-study variance

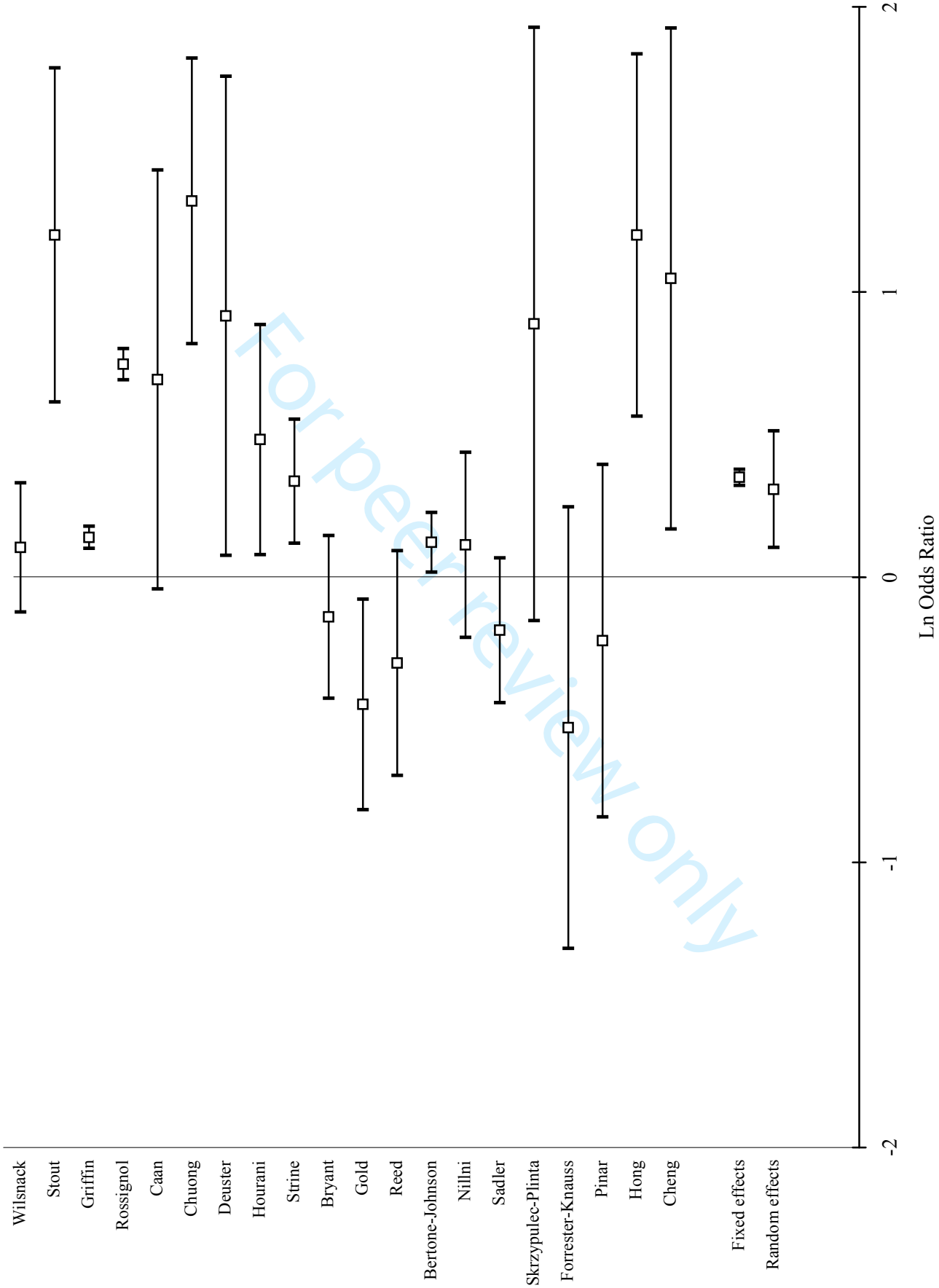
Figure 1. Flow diagram for study selection

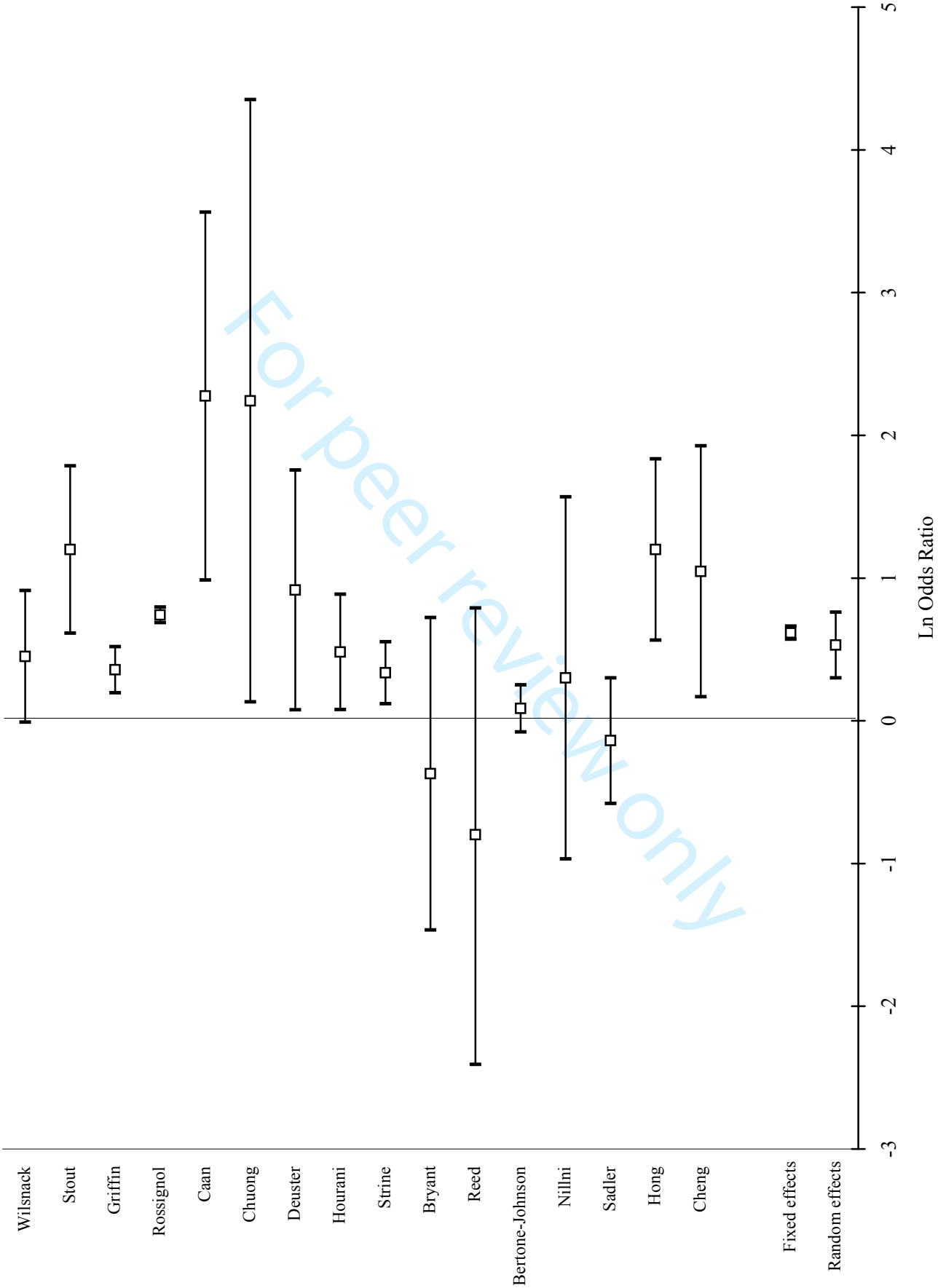
Figure 2. Study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: any drinking

Figure 3. Study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: heavy drinking

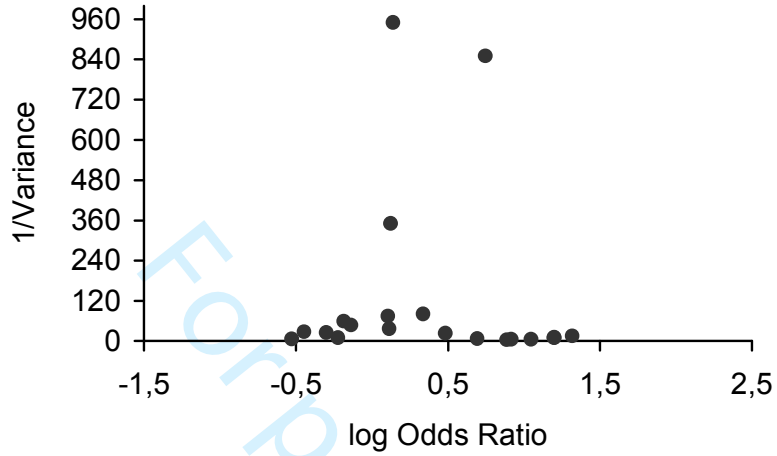
Figure 4: Funnel plot of Odds Ratios versus standard error of Odds Ratios of alcohol drinking and premenstrual syndrome



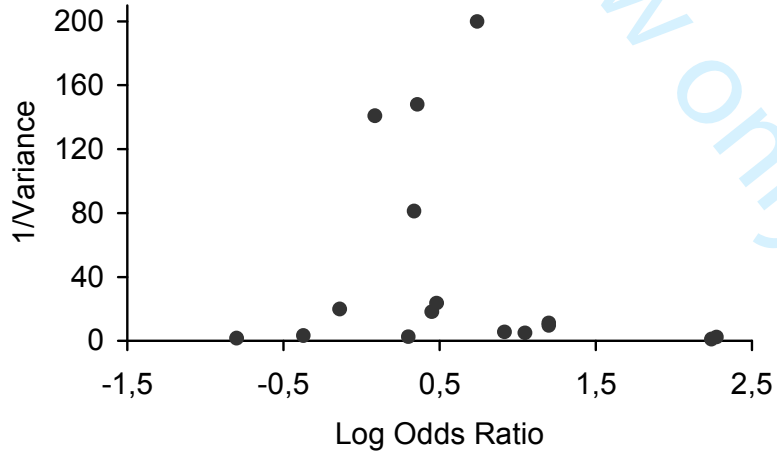




Any drinking



Heavy drinking



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 + figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2 and 3 (quality score + detailed score available from corresponding author)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 and 3 + pages 9, and 10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10 + Table 2 and 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2 and 3 + pages 9 and 10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Page 2 of 2

BMJ Open

Premenstrual syndrome and alcohol: a systematic review and meta-analysis.

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Premenstrual syndrome and alcohol: a systematic review and meta-analysis.

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Abstract

Objective: Premenstrual syndrome (PMS) is a very common disorder worldwide which carries an important economic burden. We conducted a systematic review and a meta-analysis to assess the role of alcohol in the occurrence of PMS.

Methods: We searched MEDLINE, EMBASE, the 5 regional bibliographic databases of the World Health Organization (WHO), the ISI-Proceedings databases and the Open Access Thesis and Dissertations (OATD) from inception to May 2017. We also reviewed the references of every article retrieved and established personal contact with researchers to trace further publications or reports. We did not include any language limitations. Studies were included if: 1) they presented original data from cohort, case-control or cross-sectional studies, 2) PMS was clearly defined as the outcome of interest, 3) one of the exposure factors was alcohol consumption, 4) they provided estimates of odds ratios, relative risks, or any other effect measure and their confidence intervals, or enough data to calculate them.

Results: We identified 39 studies of which 19 were eligible. Intake of alcohol was associated with a moderate increase in the risk of PMS (OR=1.45, 95%CI: 1.17-1.79). Heavy drinking yielded a larger increase in the risk than any drinking (OR=1.79, 95%CI: 1.39-2.32).

Discussion: Our results suggest that alcohol intake presents a moderate association with PMS risk. Future studies should avoid cross-sectional designs and focus on determining whether there is a threshold of alcohol intake under which the harmful effect on PMS is non-existent.

Strengths and limitations of this study

- This is the first meta-analysis carried out on the relation between alcohol consumption and risk of premenstrual syndrome (PMS), a highly prevalent condition worldwide.
- Exhaustive search of studies was carried out in several bibliographic databases, and unpublished studies were included.
- Intensive sensitivity analyses were performed to assess potential for publication bias and confounding.
- In our subgroup analyses, we were unable to identify any factors that accounted for study heterogeneity.
- In some studies included in this meta-analysis, the assessment of alcohol intake was probably concomitant to the assessment of PMS. A reverse causation process, in which PMS-affected women use alcohol to mitigate the effect of the syndrome, is then plausible.

Introduction

Premenstrual syndrome (PMS) consists of a series of recurrent physical and emotional symptoms, including mood swings, tender breasts, food craving, fatigue, irritability and depression, during the luteal phase of the menstrual cycle.[1,2] The severity of the syndrome varies from woman to woman and is related to the type and intensity of the symptoms.[1,3] While in the United States, the prevalence of the syndrome varies between 20 and 40% for cases of moderate severity and between 3 and 8% for severe cases [2], a recent prevalence meta-analysis shows that the worldwide prevalence sways between 10% and 98%.[4]

The economic burden of the syndrome is far from being negligible. For a week every month women affected by this syndrome suffer distress and impairment in interpersonal or workplace functioning. This can lead to at least two days per month of absenteeism at work and an increase in medical appointments.[2,5] In the US, the cost of the syndrome

reaches $5000 per case per year.[2] Each affected woman experiences a total of 3000 days with disabling symptoms during her reproductive life.[2] The large majority of cases are not diagnosed, either because affected women do not seek medical help or because physicians have difficulties in establishing a firm diagnosis.[6] Furthermore, premenstrual syndrome was recently found to be a risk factor for hypertension increasing its incidence by 40%.[7]

The World Health Organization (WHO) warned recently against the increasing alcohol consumption among women related to economic development and changing gender roles, and emphasized the fact that women may be more vulnerable to alcohol-related harm than men.[8] Several studies have identified an increased burden of PMS among women who consume alcohol.[9-11] However, it is not clear whether this increase in the risk of PMS is due to alcohol consumption or whether alcohol is consumed in an attempt to mitigate the symptoms of the syndrome.[12] Other studies found that the relation between alcohol and PMS was weak or even non-existent.[12-14] Furthermore, assessing the role of alcohol in prospective studies is not straightforward. Indeed, it is not feasible to relate alcohol intake to the first occurrence of PMS in the life of a woman, as the first bout of the disease appears at an early age, probably before any alcohol is consumed. Prospective studies aim at determining the role of regular alcohol intake in the occurrence of the *next* episode of the disease, not the *first* one.

We are not aware of the existence of any meta-analysis on the topic. We therefore conducted a systematic review of the literature and a meta-analysis to assess the role of alcohol in the occurrence of PMS.

Sources

To identify all potentially eligible studies, we searched MEDLINE, EMBASE, the 5

regional bibliographic databases of the WHO (AIM, LILACS, IMEMR, IMSEAR, WPRIM), the Conference Proceedings Citation Index, the Open Access Thesis and Dissertations (OATD), from inception to May 2017.

For Medline, we used the following algorithm both in Medical Subject Heading and in free text words: ("premenstrual syndrome"[MeSH Terms] OR "premenstrual syndrome"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields]). An example of this search is given in Supplement 1. Similar strategies were used for the other databases.

We also reviewed the references of every article retrieved. Furthermore, we established personal contact with researchers to trace further publications or reports. We did not include any language limitations. All searches were carried out independently by two researchers and results were merged.

The review protocol of this meta-analysis was registered in Prospero.[15]

Study selection

Studies were included if: 1) they presented original data from cohort, case-control or cross-sectional studies, 2) PMS or its more severe form, Premenstrual Dysphoric Disorder (PMDD), were clearly defined as the outcome of interest, 3) one of the exposure factors was alcohol consumption, 4) they provided estimates of odds ratios (OR), rate ratios (RR), or prevalence odds ratios and their confidence intervals, or enough data to calculate them.

If data on the same population were duplicated in more than one publication, the most recent study was included in the analysis.

We developed a standard data-recording form in which we recorded authors, year of publication, study location, study design, sample size, outcome, outcome measurement

details, effect estimator (OR, RR, other), effect estimate, 95% Confidence Intervals, and adjustment, restriction or matching factors used.

When further clarification was necessary, we attempted to contact the authors.[14,16,17]

Quality Assessment

Study quality was assessed using a five-point binary scale specifically developed for this study. The scale is based on the Newcastle-Ottawa scale with modifications in view of standard guidelines and our own judgment.[18] The Newcastle-Ottawa scale is a scoring system that assesses every aspect of an observational epidemiologic study from a methodological point of view. For this meta-analysis, we tried to use those elements that were common to all epidemiological designs and thus shortened the scale considerably. We used the following criteria labelled as "1" or "0": 1) Measurement of alcohol intake: through standard or validated questionnaire which includes quantity and/or frequency: 1, else (simple question, no data on frequency or quantity) or not explained: 0; 2) PMS diagnosis: through standard or validated questionnaire: 1, else or not explained: 0; 3) Confounding assessment: results adjusted at least for age and smoking, either in the design phase or in the analysis: 1, else: 0; 4) Participation: participation exceeded 80% of the people initially approached: 1, else or data not provided: 0; 5) Target population: target population clearly defined: 1, based on convenience sampling of subjects such as patients of a single consultation or volunteers or not explained: 0

Throughout this assessment, when the information on a specific item was not provided by the authors, we graded this item as "0". We carried out a pooled analysis on those studies that fulfilled at least 3 criteria and compared with those that fulfilled fewer than 3. Furthermore, we did not grade cross-sectional studies differently from the case-

controls studies in spite of their evident high potential for bias. Our aim was to evaluate design and analysis features that are common to both types of studies. The influence of the design on the pooled estimate was assessed separately from the quality.

Abstracts' review, data extraction and quality scoring were performed independently by two reviewers (J.S and M.F.) and the results were merged by consensus. The complete results for quality scoring are available in Supplement 2.

Data synthesis and analysis

We weighted the study-specific log odds ratios or other ratio measures for case control and cross-sectional studies by the inverse of their variance to compute a pooled estimate. In our search we could not find any cohort studies. For each study, we used the estimate of the effect measure that was adjusted for the largest number of confounders. We present both fixed-effects and random-effects pooled estimates but use the latter when heterogeneity was present. Odds ratios were assumed to be unbiased estimates of the incidence rate ratio.[19]

We calculated odds ratios for any intake of alcohol and for high intake, following the classification given by each individual study. The estimates of studies which failed to provide data for different levels of alcohol intake but, instead, assessed alcohol consumption on a yes/no basis, were included in the "any intake" group.

As no interpretable odds ratio can be computed from them, we excluded those studies the results of which were presented as correlation coefficients between alcohol intake and PMS score [20,21]. When results were presented as standardized differences in means of alcohol intake between cases of PMS and controls[22,23], they were transformed into odds ratios estimates of exposure on a dichotomous scale (drinkers versus non

drinkers).[24] As drinking patterns vary widely between countries, we calculated the content in ethanol of an average drink using data on consumption of beer, wine and spirits, specific to each country and used different sources to define low, moderate and heavy drinking.[8,12] We considered a consumption of less than 10g/day of ethanol as low intake, a consumption between 10g/day and the content in ethanol of 1 average drink/day as moderate intake, and a consumption equal or higher than the content in ethanol of 1 average drink/day as heavy intake. To compute an estimate for the category "any drinking", we pooled the odds ratios obtained in the 3 categories (low, moderate and heavy intake).

We used the DerSimonian and Laird Q test to check for heterogeneity. To quantify this heterogeneity we calculated the proportion of the total variance due to between-study variance (Ri statistic).[25] Large values (>0.75) indicate large amount of heterogeneity, values between 0.4 and 0.75 suggest a moderate amount while small values (<0.4) indicate low heterogeneity. We later explored the origin of heterogeneity by restricting the analysis to subgroups of studies defined by study characteristics such as study design, adjustment, origin and quality score. All secondary analyses were planned a priori.

We assessed publication bias, first visually, using funnel plots and then, more formally, using the test proposed by Egger et al.[26] We also used the trim-and-fill method to correct for potential publication bias. All analyses were performed with the software HEpiMA® version 2.1.3 [27] and STATA version 12. The transformation of standardized mean differences into odds ratios was performed with the software Comprehensive Meta-Analysis (Englewood, New Jersey, USA).

Results

We identified 19 studies of 8 different countries that met our inclusion criteria.[9-14,16,22,23,28-37]

The large majority of the articles retrieved initially were excluded because they did not provide any effect measure. More specifically, we discarded 20 studies (figure 1) for the following reasons: 4 did not assess PMS cases,[17,38-40] 2 lacked any control group,[41,42] 5 did not present data on alcohol consumption[43-46] and one of them did not present a confidence interval,[47] the full text of one could not be traced[48], one was a duplicate publication,[49] 6 presented insufficient data to calculate effect measures estimates, [20,21,50-53] and one assessed PMS as a risk factor for alcoholism.[54]

For further information we contacted the authors of articles for which the details of the data were not sufficient for effect measures to be computed. We obtained collaboration from 3 authors.[14,16,17] The study by Kiesner et al. was finally excluded as its outcome was "change in PMS score" rather than occurrence of PMS.[17] Table 1 and figures 2 and 3 present the studies that were finally included in our meta-analysis.

Tables 2 and 3 show that, globally, heterogeneity was substantial overall, and similarly high after stratification by design, quality features, including adjustment for confounders. No individual study seemed to represent an influential point that increased heterogeneity dramatically. We focused on the random effects analyses and presented the fixed effects results for comparison purposes only.

Intake of alcohol was associated with a moderate increase of the risk of PMS (OR=1.45, 95%CI: 1.17-1.79), while heavy drinking yielded a larger increase in the risk than any drinking (OR=1.79, 95%CI: 1.39-2.32). Heavy drinking was associated with a higher risk than any drinking in all subgroup estimates. The pooled estimate of case-control

studies was higher than that of cross-sectional studies both for any drinking and heavy drinking. When we restricted our analysis to those studies that presented odds ratio estimates, i.e. when we excluded studies that computed standardized mean differences, the pooled estimates were higher: pooled OR= 1.51; 95%CI 1.22-1.88 for any drinking and 1.90; 95%CI 1.45-2.49 for heavy drinking.

The pooled estimate of studies with high quality scores was lower than that from low quality studies.

Except for the criteria "validated diagnosis" and the criteria "high response rate" in the any drinking group for which the estimates were similar, when we considered the quality criteria individually instead of just as a global quality score, as recommended by the MOOSE guidelines,[55] the studies that fulfilled the criteria yielded lower pooled estimates than studies which did not.

About two-thirds of the studies included in this meta-analysis were carried out in US populations. The estimates from American studies were higher than those from other countries, both in the any drinking group and the heavy drinking group.

Publication Bias

The funnel plot (figure 4) for the any drinking group did not suggest asymmetry, a result confirmed by a p-value of the Egger's test of 0.85. However, the trim-and-fill procedure indicated 2 potentially missing studies though the corrected random effects pooled odds ratio, OR=1.31 (95%CI 1.08-1.61), was very close to the odds ratio we obtained. Again, the funnel plot for heavy drinking did not suggest any publication bias (p-value Egger's test = 0.61) and the trim-and-fill method indicated 2 potentially missing studies and a corrected pooled estimate that was very similar to that obtained

before correction (random effects pooled OR= 1.68; 95%CI: 1.30-2.16).

Sensitivity Analysis

To further evaluate the possibility that our results could be due to publication bias, we assumed that cross-sectional studies represent the design for which publication is least likely if the results were null. We recalculated our pooled estimates under the following extreme assumptions: (1) published cross-sectional studies are only half of the studies of alcohol drinking and PMS ever conducted, (2) all unpublished studies found an OR of 1, (3) the unpublished studies found the same prevalence of PMS as the average of the published studies. Under these extreme assumptions, the random effects pooled estimates still showed a significant increase in risk: OR=1.21 (95%CI 1.06-1.39) for any alcohol drinking and OR= 1.39 (95% CI 1.15–1.69) for heavy drinking.

Discussion

The results of our systematic review and meta-analysis suggest that alcohol drinking is associated with a moderate increase in the risk of PMS. This increase is more pronounced for heavy drinking, which favours a causal explanation of the relation between alcohol intake and PMS.

These findings are important given that the worldwide prevalence of alcohol drinking among women is not negligible. Worldwide, the proportion of current female drinkers is 28.9%, while that of heavy female drinkers is 5.7%. In Europe and America these figures are much higher and reach 59.9% for current drinking and 12.6% for heavy drinking in Europe.[8] Based on the figures above and on our results we estimate that 11% of the PMS cases may be associated to alcohol intake worldwide and 21% in Europe.[56]

Furthermore, heavy drinking may be associated with 4% of the PMS cases in the world and over 9% in Europe. If this association is of causal nature, eliminating heavy drinking in women would then prevent one in every twelve cases of PMS in Europe.

Alcohol use may plausibly increase the risk of PMS by altering levels of sex steroid hormones and gonadotropin during the menstrual cycle. PMS was previously found to be linked to fluctuations of these sex hormones during the cycle.[12,57] Furthermore, alcohol intake may increase the risk of PMS through its effect on serotonin and gamma-amino butyric acid (GABA) activity. On the one hand, women who present alterations in the serotonin and GABA systems may be more sensitive to alcohol. On the other hand it is known that the activity of both serotonin and GABA is altered among subjects with PMS.[12] In fact, selective serotonin reuptake inhibitors (SSRIs) as well as the GABA-ergic anxiolytic alprazolam may represent effective treatments in PMS cases.[57,58]

The relatively large number of studies conducted and the consistency of the results across study designs and settings provide substantial epidemiological evidence that alcohol drinking may be associated with an increase in the risk of PMS. However, non-causal explanations of the relation should be carefully evaluated.

First, publication bias is a highly unlikely explanation for our results, as the association between alcohol drinking and PMS remained strong even after extremely conservative assumptions regarding the number, size, and findings of studies potentially conducted and not included in our meta-analysis. Also, the findings of the asymmetry tests of the funnel plot as well as those of the trim-and-fill method did not alter our results.

Second, residual confounding (confounding from unknown variables that is not eliminated by adjustment) may have introduced bias as in any meta-analysis of

observational studies. It is remarkable that only one-third of the studies included in this meta-analysis considered tobacco smoking in their adjustment in spite of the potential for confounding of this factor.[12] In our meta-analysis, restricting our analysis to studies that adjusted for potential confounders, including tobacco smoking, did not introduce any substantial modification in the estimate corresponding to any intake of alcohol. The estimate corresponding to heavy intake decreased substantially after restriction to studies with complete adjustment but still shows a 38% increase in the risk. Furthermore, other confounders that were not measured in the studies of this meta-analysis could explain our results. Recently, some genetic polymorphisms, such as those of the ESR1 gene and those associated to the serotonin 1A receptor have been implicated in the occurrence of PMS.[59,60] Such genetic factors could theoretically play a role of confounders and explain the results of this meta-analysis concerning alcohol drinking. However, this hypothesis is highly unlikely to be true. First, to act as a confounder, a genetic factor must be related to PMS on the one hand and to alcohol drinking on the other hand. No such factor has been described so far. Second, even if this hypothetical factor could double the risk of PMS among subjects exposed to it (OR confounder–disease = 2) and, simultaneously, this factor happened to be twice as prevalent among alcohol drinkers than among non-drinkers (OR confounder–exposure = 2), the adjusted OR of the relation between any alcohol drinking and PMS would still be 1.21 and that of the relation between heavy drinking and PMS would still be 1.51 (assuming one-third of people are exposed to this unknown factor).[61] The existence of an unknown factor so strongly related to alcohol intake and to PMS is highly improbable.

Third, measurement error and misclassification of alcohol intake is likely to occur since

women may understate their intake of alcohol as many societies hold more negative attitudes towards women's alcohol drinking than men's drinking.[8] However, this misclassification is probably non differential regarding PMS, i.e. women with PMS do not underestimate their drinking habits in a different fashion from women who do not suffer PMS. In this case, the bias introduced is then towards the null value. The true OR is then even higher than the one we report in our meta-analysis. Similarly, misclassification of the outcome is also possible (i.e. women with PMS who are diagnosed as non-cases, and conversely non-diseased women who are erroneously diagnosed as PMS cases). As previously, this possible misclassification is unlikely to occur differently in women who consume alcohol and in those women who do not. The bias introduced, if any, is towards the null value.

Fourth, given that a substantial proportion of the studies included in this meta-analysis used a cross-sectional design, a reverse causation process, in which PMS-affected women use alcohol to mitigate the effect of this syndrome, could introduce what is known as protopathic bias and thus, explain the results observed. Although in theory this hypothesis should be rejected due to the fact that the pooled estimates for both categories of drinking are higher for case-control studies than for cross-sectional studies, it should be noted that, in several case-control studies included in this meta-analysis, the assessment of alcohol intake was probably concomitant to the assessment of PMS. This hypothesis remains then plausible.

Furthermore, in our subgroup analyses, we were unable to identify any factors that accounted for study heterogeneity. This situation is extremely frequent and for meta-analysis experts, heterogeneity should be viewed more as the rule rather than the exception.[62] As recommended by experts when heterogeneity is present, in order to deal

with this issue, we focused our interpretation on the random effects estimates that are, in general, more conservative.[63]

Our meta-analysis shows that alcohol intake is moderately associated with PMS risk. The consistency of the results and the existence of a plausible biologic mechanism strengthen our conclusions. Future studies should minimize measurement error in the exposure by using validated questionnaires. These studies should avoid cross-sectional designs and focus on determining whether there is a threshold of alcohol intake under which the harmful effect on PMS is non-existent.

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All authors approved the final version of the article.

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The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Contributorship statement

María del Mar Fernández performed the computerized systematic search, literature revision, risk of bias assessment, meta-analysis and redaction of the manuscript, figures and tables.

Jurgita Saulyte assessed the risk of bias and revised the manuscript.

Hazel Inskip provided unpublished data and participated in the redaction of the manuscript

Bahi Takkouche did the complementary searches, assessment of the publication bias and revision of the final manuscript, figures and tables. He acts as a guarantor of the study.

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Table 1. Odds Ratios and 95% confidence intervals of premenstrual syndrome and alcohol drinking

Source	Design	Country	Population	Any Drinking	Light drinking	Moderate drinking	Heavy drinking	Study size *or* #cases / #controls	Adjustment variables
Wilsnack 1984[16]	Cross-Sectional	USA	National sample ≥ 21 years	1.11 (0.89-1.40)	0.86 (0.59-1.25)	1.15 (0.80-1.65)	1.57 (0.99-2.49)	2552	Not specified
Stout 1986[28]	Case-Control	USA	Patients 20-48 years	3.32 (1.85-5.97)	---	---	3.32 (1.85-5.97)	223/923	Not specified
Rossignol 1991[29]	Cross-Sectional	USA	Students18-22 years	2.11 (1.99-2.22)	----	2.35 (1.64-3.37)	2.10 (1.99-2.22)	853	Not specified
Caan 1993[30]	Case-Control	USA	Volunteers	2.00 (0.96-4.17)	1.34 (0.82-2.19)	1.40 (0.63-2.13)	9.73 (2.68-35.29)	102/102	Age, ethnicity
Chuong 1995[31]	Case-Control	USA	Patients	3.74 (2.27-6.18)	3.29 (1.95-5.56)	5.39 (1.12-25.87)	9.41 (1.14-77.57)	190/182	Not specified
Deuster 1999[9]	Cross-Sectional	USA	General population 18-44 years	2.5 (1.1-5.9)	---	---	2.5 (1.1-5.9)	874	Age, ethnicity, age at menarche, length of menses, body mass index, education, smoking, stress score, diet, physical activity
Hourani 2004[32]	Case-Control	USA	Navy workers 18-49 years	1.62 (1.08-2.42)	---	---	1.62 (1.08-2.42)	3861/2165	Demographic variables and lifestyle
Strine 2005[10]	Cross-sectional	USA	National sample 18-55 years	1.4 (1.1-1.7)	---	---	1.4 (1.1-1.7)	11648	Age, ethnicity, education, marital status, employment status
Bryant 2006[22]	Case-Control	UK	Volunteers 18-47 years	0.73 (0.28-1.85)	---	---	---	31/27	Age, body mass index
Gold 2007[13]	Cross-Sectional	USA	Population from a cohort 42-52 years	0.98 (0.89-1.07)	0.82 (0.66-1.01)	1.02 (0.91-1.13)	---	3012	Not specified

Table 1. Odds Ratios and 95% confidence intervals of premenstrual syndrome and alcohol drinking (cont.)

Source	Design	Country	Population	Any Drinking	Light drinking	Moderate drinking	Heavy drinking	Study size *or* #cases / #controls	Variables of adjustment, matching or restriction
Reed 2008[23]	Case-Control	USA	Volunteers	0.51 (0.13-1.93)	---	---	---	14/15	Not specified
Bertone-Johnson 2009[12]	Case-Control	USA	Population from the Nurses' Health Study	1.13 (1.03-1.27)	1.05 (0.91-1.20	1.28 (1.10-1.50)	1.09 (0.92-1.28)	1057/1968	Age, diagnosis year, parity, contraception, smoking, pregnancies, body mass index, tubal ligation, antidepressants, childhood trauma, diet
Sadler 2010[14]	Cross-Sectional	UK	General population 20-34 years	0.83 (0.65-1.08)	0.83 (0.53-1.29)	0.80 (0.51-1.25)	0.87 (0.56-1.35)	974	Age, education, body mass index, smoking, stress, contraception
Skrzypulec-Plinta 2010[11]	Cross-Sectional	Poland	General population 18-45 years	2.43 (0.86-6.89)	---	---	---	1540	Not specified
Forrester-Knauss 2011[33]	Cross-Sectional	Switzerland	National sample >50 years	0.59 (0.27-1.27)	0.78 (0.58-1.04)	0.34 (0.13-0.88)	---	3518	Not specified
Pinar 2011[34]	Cross-Sectional	Turkey	Students18-28 years	0.80 (0.43-1.48)	---	---	---	316	Not specified
Hong 2012[35]	Cross-Sectional	Korea	Population from a catchment area 18-49 years	3.32 (1.76-6.27)	---	---	3.32 (1.76-6.27)	2499	Age
Cheng 2013[36]	Cross-Sectional	Taiwan	Students	2.85 (1.18-6.84)	---	---	2.85 (1.18-6.84)	1699	Age, education, cycle regularity, smoking, exercise, diet
Ju 2015[37]	Cohort	Australia	General population 18-23 years	1.10 (1.05-1.14)	---	---	1.17 (1.07-1.28)	7102	Age, drug use, education, marital status, income, residence, BMI, smoking, gynecologic variables, depression

Table 2. Pooled Odds Ratios (OR) and 95% confidence intervals (CI) of premenstrual syndrome and any intake of alcohol

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test p value
All studies	19	1.31 (1.28-1.35)	1.45 (1.17-1.79)	0.98	0.0001
Case-control studies	7	1.27 (1.14-1.41)	1.66 (1.04-2.64)	0.93	0.0001
Cross-sectional studies	11	1.67 (1.60-1.74)	1.40 (1.00-1.94)	0.98	0.0001
Direct calculations	17	1.31 (1.28-1.35)	1.51 (1.22-1.88)	0.98	0.0001
Quality score ≥ 3	10	1.11 (1.07-1.14)	1.22 (1.05-1.42)	0.90	0.0003
Quality score < 3	9	1.73 (1.66-1.80)	1.50 (1.03-2.20)	0.98	0.0001
Full adjustment	7	1.10 (1.07-1.14)	1.18 (1.01-1.38)	0.90	0.005
Incomplete adjustment	12	1.70 (1.63-1.77)	1.47 (1.07-2.03)	0.98	0.0001
Validated exposure	11	1.09 (1.05-1.12)	1.09 (0.99-1.20)	0.77	0.006
Non validated exposure	8	2.06 (1.96-2.16)	1.91 (1.40-2.62)	0.96	0.0001
Validated diagnosis	12	1.85 (1.77-1.94)	1.38 (0.99-1.92)	0.97	0.0001
Non validated diagnosis	7	1.10 (1.07-1.14)	1.38 (1.16-1.65)	0.95	0.0001
High response rate	5	1.16 (1.05-1.28)	1.36 (0.99-1.88)	0.86	0.003
Low response rate	14	1.32 (1.29-1.36)	1.46 (1.13-1.89)	0.98	0.0001
Defined target population	12	1.10 (1.07-1.13)	1.20 (1.07-1.36)	0.86	0.0001
Undefined target population	7	2.05 (1.95-2.15)	1.65 (1.02-2.67)	0.99	0.0001
US studies	12	1.63 (1.57-1.70)	1.56 (1.17-2.08)	0.98	0.0001
Rest of the world	7	1.10 (1.06-1.14)	1.24 (0.89-1.72)	0.98	0.0001

* Proportion of total variance due to between-study variance

Table 3. Pooled Odds Ratios (OR) and 95% confidence intervals (CI) of premenstrual syndrome and high intake of alcohol

	Number of studies	OR (95% CI) Fixed effects	OR (95% CI) Random effects	Ri*	Q test p value
All studies	13	1.71 (1.63-1.78)	1.79 (1.39-2.32)	0.96	0.0001
Case-control studies	5	1.27 (1.10-1.47)	2.48 (1.30-4.76)	0.93	0.0001
Cross-sectional studies	7	2.02 (1.91-2.12)	1.76 (1.32-2.36)	0.95	0.0001
Direct calculations	12	1.91 (1.82-2.01)	1.90 (1.45-2.49)	0.95	0.0001
Quality score ≥ 3	8	1.20 (1.11-1.29)	1.41 (1.14-1.74)	0.81	0.001
Quality score < 3	5	2.05 (1.95-2.16)	2.33 (1.60-3.41)	0.96	0.0001
Full adjustment	6	1.17 (1.08-1.26)	1.23 (1.03-1.48)	0.72	0.03
Incomplete adjustment	7	2.05 (1.95-2.16)	2.25 (1.66-3.05)	0.95	0.0001
Validated exposure	7	1.18 (1.09-1.27)	1.32 (1.06-1.64)	0.81	0.003
Non validated exposure	6	2.06 (1.95-2.17)	2.25 (1.66-3.06)	0.95	0.0004
Validated diagnosis	7	1.95 (1.85-2.06)	1.98 (1.31-3.00)	0.98	0.0001
Non validated diagnosis	6	1.26 (1.16-1.36)	1.58 (1.22-2.05)	0.86	0.001
High response rate	4	1.23 (1.06-1.42)	1.84 (1.07-3.17)	0.91	0.001
Low response rate	9	1.76 (1.68-1.84)	1.80 (1.32-2.47)	0.97	0.0001
Defined target population	8	1.23 (1.15-1.32)	1.45 (1.21-1.75)	0.78	0.001
Undefined target population	5	2.09 (1.98-2.21)	2.49 (1.36-4.58)	0.99	0.0001
US studies	9	1.92 (1.83-2.02)	1.91 (1.41-2.59)	0.96	0.0001
Rest of the world	4	1.19 (1.09-1.30)	1.58 (0.95-2.63)	0.96	0.001

* Proportion of total variance due to between-study variance

Figure 1. Flow diagram for study selection

Figure 2. Forest plot of study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: any drinking

Figure 3. Forest plot of study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: heavy drinking

Figure 4: Funnel plot of log Odds Ratios versus standard error of log Odds Ratios of alcohol drinking and premenstrual syndrome

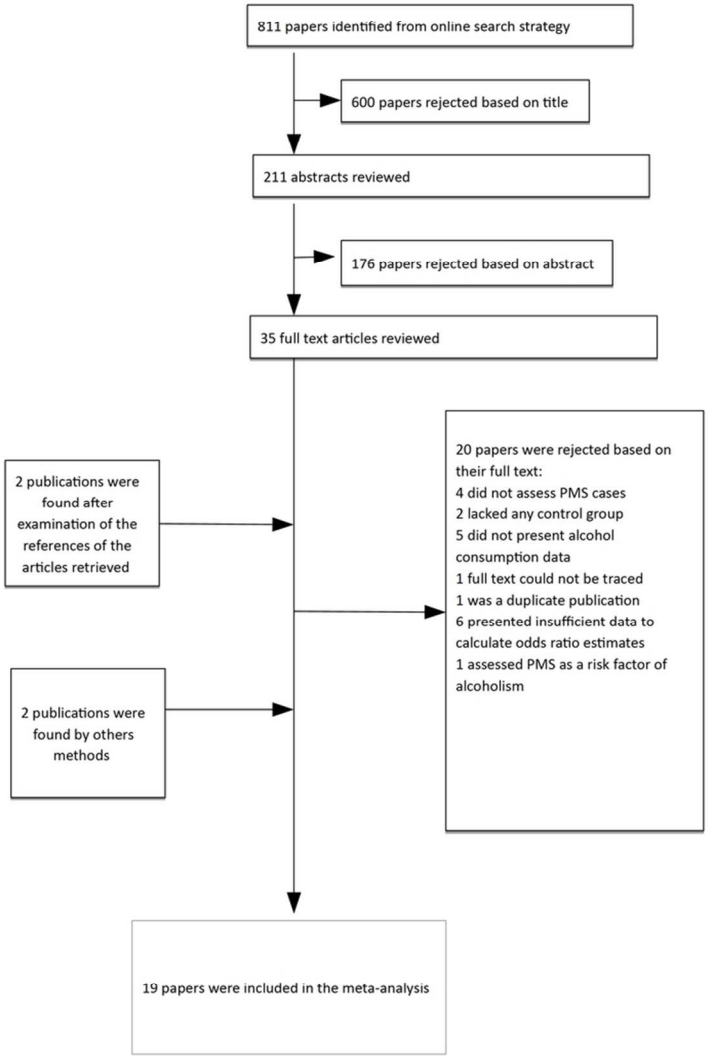

Figure 1. Flow diagram for study selection

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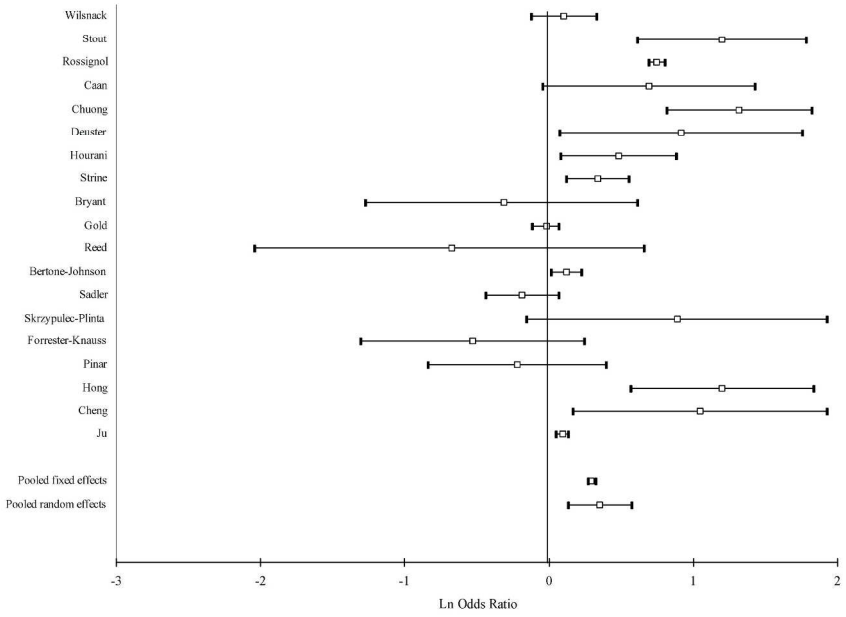

Figure 2. Forest plot of study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: any drinking

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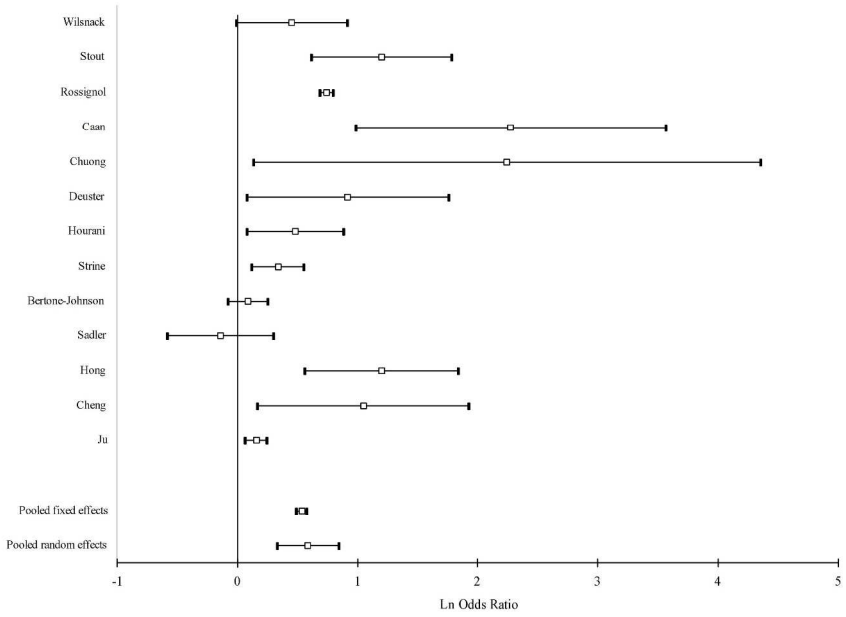

Figure 3. Forest plot of study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: heavy drinking

328x254mm (300 x 300 DPI)

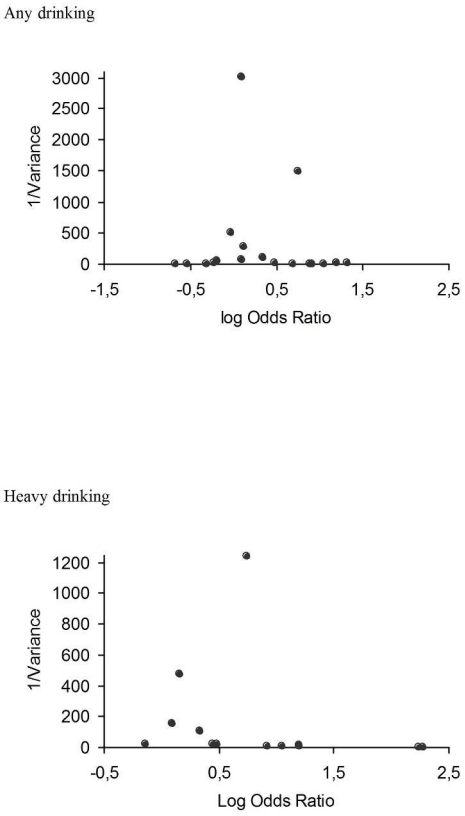

Figure 4: Funnel plot of log Odds Ratios versus standard error of log Odds Ratios of alcohol drinking and premenstrual syndrome

254x359mm (300 x 300 DPI)

Supplement 1. Medline search

("premenstrual syndrome"[MeSH Terms] OR "premenstrual syndrome"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields])

1: Acikgoz A, Dayi A, Binbay T. Prevalence of premenstrual syndrome and its relationship to depressive symptoms in first-year university students. Saudi Med J. 2017 Nov;38(11):1125-1131. doi: 10.15537/smj.2017.11.20526. PubMed PMID: 29114701.

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Supplement 2: quality assessment

Source	Exposure assessment	PMS diagnosis	Confounding	Participation	Target population	Total
Wilsnack 1984[16]	1	0	0	1	1	3
Stout 1986[28]	0	0	0	0	0	0
Rossignol 1991[29]	0	1	0	0	0	1
Caan 1993[30]	1	1	0	0	0	2
Chuong 1995[31]	0	0	0	0	0	0
Deuster 1999[9]	1	1	1	0	1	4
Hourani 2004[32]	1	0	1	0	1	3
Strine 2005[10]	0	0	0	0	1	1
Bryant 2006[22]	1	1	0	0	0	2
Gold 2007[13]	1	0	0	0	1	2
Reed 2008[23]	1	1	0	0	0	2
Bertone-Johnson 2009[12]	1	1	1	1	1	5
Sadler 2010[14]	1	1	1	0	0	3
Skrzypulec-Plinta 2010[11]	1	1	1	0	1	4
Forrester-Knauss 2011[33]	0	1	0	0	1	2
Pinar 2011[34]	0	1	0	1	1	3
Hong 2012[35]	0	1	0	1	1	3
Cheng 2013[36]	0	1	1	1	1	4
Ju 2015[37]	1	0	1	0	1	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 + figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2 and 3 (quality score + detailed score available from corresponding author)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 and 3 + pages 9, and 10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10 + Table 2 and 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2 and 3 + pages 9 and 10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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