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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.

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- Exhaustive search of studies was carried out in several bibliographic databases, and unpublished studies were included.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 cases², 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

1
2 reaches \$5000 per case per year.² Each affected woman experiences a total of 3000 days
3 with disabling symptoms during her reproductive life.² The large majority of cases are
4 not diagnosed, either because affected women do not seek medical help or because
5 physicians have difficulties in establishing a firm diagnosis.⁶ Furthermore, premenstrual
6 syndrome was recently found to be a risk factor for hypertension increasing its
7 incidence by 40%.⁷

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

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

25 **Sources**

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

1
2 regional bibliographic databases of the WHO (AIM, LILACS, IMEMR, IMSEAR,
3 WPRIM), the Conference Proceedings Citation Index, the Open Access Thesis and
4 Dissertations (OATD), from inception to May 2017.
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6

7
8 For Medline, we used the following algorithm both in Medical Subject Heading and in
9 free text words: ("premenstrual syndrome"[MeSH Terms] OR "premenstrual
10 syndrome"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR
11 "alcohol"[All Fields]). Similar strategies were used for the other databases.
12
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15 We also reviewed the references of every article retrieved. Furthermore, we established
16 personal contact with researchers to trace further publications or reports. We did not
17 include any language limitations. All searches were carried out independently by two
18 researchers and results were merged.
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20

21
22 The review protocol of this meta-analysis was registered in Prospero.¹⁵
23
24

25 26 27 28 29 30 31 **Study selection**

32
33 Studies were included if: 1) they presented original data from cohort, case-control or
34 cross-sectional studies, 2) PMS was clearly defined as the outcome of interest, 3) one of
35 the exposure factors was alcohol consumption, 4) they provided estimates of odds ratios
36 (OR), relative risks (RR), or prevalence odds ratios and their confidence intervals, or
37 enough data to calculate them.
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41 If data on the same population were duplicated in more than one publication, the most
42 recent study was included in the analysis.
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45
46 We developed a standard data-recording form in which we recorded authors, year of
47 publication, study location, study design, sample size, outcome, outcome measurement
48 details, effect estimator (OR, RR, other), effect estimate, 95% Confidence Intervals, and
49 adjustment, restriction or matching factors used.
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3 When further clarification was necessary, we attempted to contact the authors.^{14,16,17}
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6 7 *Quality Assessment*

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9 Study quality was assessed using a five-point binary scale specifically developed for
10 this study. The scale is based on the Newcastle-Ottawa scale with modifications in view
11 of standard guidelines and our own judgment.¹⁸ The Newcastle-Ottawa scale is a
12 scoring system that assesses every aspect of an observational epidemiologic study from
13 a methodological point of view. For this meta-analysis, we tried to use those elements
14 that were common to all epidemiological designs and thus shortened the scale
15 considerably. We used the following criteria labelled as “1” or “0”: 1) Measurement of
16 alcohol intake: through standard or validated questionnaire which includes quantity
17 and/or frequency: 1, else (simple question, no data on frequency or quantity) or not
18 explained: 0; 2) PMS diagnosis: through standard or validated questionnaire: 1, else or
19 not explained: 0; 3) Confounding assessment: results adjusted at least for age and
20 smoking, either in the design phase or in the analysis: 1, else: 0; 4) Participation:
21 participation exceeded 80% of the people initially approached: 1, else or data not
22 provided: 0; 5) Target population: target population clearly defined: 1, based on
23 convenience sampling of subjects such as patients of a single consultation or volunteers
24 or not explained: 0
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44 Throughout this assessment, when the information on a specific item was not provided
45 by the authors, we graded this item as “0”. We carried out a pooled analysis on those
46 studies that fulfilled at least 3 criteria and compared with those that fulfilled fewer than
47 3. Furthermore, we did not grade cross-sectional studies differently from the case-
48 controls studies in spite of their evident high potential for bias. Our aim was to evaluate
49 design and analysis features that are common to both types of studies. The influence of
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2
3 the design on the pooled estimate was assessed separately from the quality.

4 Abstracts' review, data extraction and quality scoring were performed independently by
5 two reviewers (J.S and M.F.) and the results were merged by consensus. The complete
6
7 protocol and results for quality scoring are available from the corresponding author.
8
9

10 11 12 13 *Data synthesis and analysis*

14
15 We weighted the study-specific log odds ratios or other ratio measures for case control
16 and cross-sectional studies by the inverse of their variance to compute a pooled
17 estimate. In our search we could not find any cohort studies. For each study, we used
18 the estimate of the effect measure that was adjusted for the largest number of
19 confounders. We present both fixed-effects and random-effects pooled estimates but use
20 the latter when heterogeneity was present. Odds ratios were assumed to be unbiased
21 estimates of the relative risk.¹⁹

22
23 We calculated odds ratios for any intake of alcohol and for high intake, following the
24 classification given by each individual study. The estimates of studies which failed to
25 provide data for different levels of alcohol intake but, instead, assessed alcohol
26 consumption on a yes/no basis, were included in the "any intake" group.
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30 When results were not available as odds ratios estimates but rather as correlation
31 coefficients between alcohol intake and PMS score^{20,21} or differences in means of intake
32 between cases of PMS and controls^{22,23}, they were transformed into odds ratios
33 estimates corresponding to an increase of 1 unit of exposure, i.e. 1 average drink.²⁴ As
34 drinking patterns vary widely between countries, we calculated the content in ethanol of
35 an average drink using data on consumption of beer, wine and spirits, specific to each
36 country and used different sources to define low, moderate and heavy drinking.^{8,12} We
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3 considered a consumption of less than 10g/day of ethanol as low intake, a consumption
4 between 10g/day and the content in ethanol of 1 average drink/day as moderate intake,
5 and a consumption equal or higher than the content in ethanol of 1 average drink/day as
6 heavy intake. To compute an estimate for the category “any drinking”, we pooled the
7 odds ratios obtained in the 3 categories (low, moderate and heavy intake).
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15 We used a version adapted to small samples of the DerSimonian and Laird Q test to
16 check for heterogeneity.²⁵ To quantify this heterogeneity we calculated the proportion of
17 the total variance due to between-study variance (I² statistic).²⁵ We later explored the
18 origin of heterogeneity by restricting the analysis to subgroups of studies defined by
19 study characteristics such as study design, adjustment, origin and quality score. All
20 secondary analyses were planned a priori.
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31 We assessed publication bias, first visually, using funnel plots and then, more formally,
32 using the test proposed by Egger et al.²⁶ We also used the trim-and-fill method to
33 correct for potential publication bias. All analyses were performed with the software
34 HEpiMA® version 2.1.3²⁷ and STATA version 12 .
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43 **Results**

44 Table 1 and figures 2 and 3 present the studies of our meta-analysis. We identified 20
45 studies of 7 different countries that met our inclusion criteria.^{9-14,16,20-23,28-36}
46
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48 The large majority of the articles retrieved initially were excluded because they did not
49 provide any effect measure. More specifically, we discarded 18 studies (figure 1) that
50 could have been eligible for the following reasons: 4 did not assess PMS cases,^{17,37-39} 2
51 lacked any control group,^{40,41} 5 did not present data on alcohol consumption⁴²⁻⁴⁵ and one
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2 of them did not present a confidence interval,⁴⁶ the full text of one could not be traced⁴⁷,
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4 one was a duplicate publication,⁴⁸ 4 presented insufficient data to calculate effect
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7 measures estimates,⁴⁹⁻⁵² and one assessed PMS as a risk factor for alcoholism.⁵³
8

9 For further information we contacted the authors of articles for which the details of the
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11 data were not sufficient for effect measures to be computed. We obtained collaboration
12
13 from 3 authors.^{14,16,17} The study by Kiesner et al. was finally excluded as its outcome
14
15 was “change in PMS score” rather than occurrence of PMS.¹⁷
16

17
18 Tables 2 and 3 show that, globally, heterogeneity was substantial overall, and similarly
19
20 high after stratification by design, quality features, including adjustment for
21
22 confounders. No individual study seemed to represent an influential point that increased
23
24 heterogeneity dramatically. We focused on the random effects analyses and presented
25
26 the fixed effects results for comparison purposes only.
27

28
29 Intake of alcohol was associated with a moderate increase of the risk of PMS (OR=1.36,
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31 95%CI: 1.11-1.67), while heavy drinking yielded a larger increase in the risk than any
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33 drinking (OR=1.70, 95%CI: 1.35-2.14). Heavy drinking was associated with a higher
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35 risk than any drinking in all subgroup estimates. The pooled estimate of case-control
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37 studies was higher than that of cross-sectional studies both for any drinking and heavy
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39 drinking. When we restricted our analysis to those studies that presented odds ratio
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41 estimates, i.e. when we excluded studies that computed correlation coefficients and
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43 means, the pooled estimates were higher: pooled OR= 1.53; 95%CI 1.19-1.98 for any
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45 drinking and 1.90; 95%CI 1.45-2.49 for heavy drinking.
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49 The pooled estimate of studies with high quality scores was slightly higher than that
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51 from low quality studies.

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53 Except for the criteria “complete adjustment of confounding” in the any drinking group,
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55 when we considered the quality criteria individually instead of just as a global quality
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3 score, as recommended by the MOOSE guidelines,⁵⁴ the studies that fulfilled the criteria
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5 yielded lower pooled estimates than studies which did not. However, the estimates
6
7 remained statistically significant.

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9 Two-thirds of the studies included in this meta-analysis were carried out in US
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11 populations. The estimates from American studies and from studies carried out in other
12
13 countries were similar in the any drinking group but were slightly lower for American
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15 studies than for non-American studies in the heavy drinking group.
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18 19 20 *Publication Bias*

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22 The funnel plot (figure 4) for the any drinking group did not suggest asymmetry, a
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24 result confirmed by a p-value of the Egger's test of 0.74. However, the trim-and-fill
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26 procedure indicated 4 potentially missing studies though the corrected pooled odds
27
28 ratio, OR=1.35 (95%CI 1.31-1.39), was almost identical to the odds ratio we obtained.
29
30 Again, the funnel plot for heavy drinking did not suggest any publication bias (p-value
31
32 Egger's test = 0.41) and the trim-and-fill method indicated one potentially missing study
33
34 though the corrected pooled estimate was even higher than the one we obtained before
35
36 correction (pooled OR= 1.87; 95%CI: 1.78-1.96).
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42 43 *Sensitivity Analysis*

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45 To further evaluate the possibility that our results could be due to publication bias, we
46
47 assumed that cross-sectional studies represent the design for which publication is least
48
49 likely if the results were null. We recalculated our pooled estimates under the following
50
51 extreme assumptions: (1) published cross-sectional studies are only half of the studies
52
53 of alcohol drinking and PMS ever conducted, (2) all unpublished studies found an OR
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3 of 1, (3) the unpublished studies found the same prevalence of PMS as the average of
4
5 the published studies. Under these extreme assumptions, the random effects pooled
6
7 estimates still showed a significant increase in risk: OR=1.18 (95%CI 1.03-1.35) for any
8
9 alcohol drinking and OR= 1.34 (95% CI 1.11–1.61) for heavy drinking.
10

11 12 13 **Discussion**

14
15 The results of our systematic review and meta-analysis suggest that alcohol drinking is
16
17 associated with a moderate increase in the risk of PMS. This increase is more
18
19 pronounced for heavy drinking, which favours a causal explanation of the relation
20
21 between alcohol intake and PMS.
22

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24
25 These findings are important given that the worldwide prevalence of alcohol drinking
26
27 among women is not negligible. Worldwide, the proportion of current female drinkers is
28
29 28.9%, while that of heavy female drinkers is 5.7%. In Europe and America these
30
31 figures are much higher and reach 59.9% for current drinking and 12.6% for heavy
32
33 drinking in Europe.⁸ Based on the figures above and on our results we estimate that
34
35 approximately 10% of the PMS cases may be associated to alcohol intake worldwide
36
37 and 18% in Europe.⁵⁵ Furthermore, heavy drinking may be associated with 4% of the
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39 PMS cases in the world and over 8% in Europe. If this association is of causal nature,
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41 eliminating heavy drinking in women would then prevent one in every twelve cases of
42
43 PMS in Europe.
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46
47 Alcohol use may plausibly increase the risk of PMS by altering levels of sex steroid
48
49 hormones and gonadotropin during the menstrual cycle. PMS was previously found to
50
51 be linked to fluctuations of these sex hormones during the cycle.^{12,56} Furthermore,
52
53 alcohol intake may increase the risk of PMS through its effect on serotonin and gamma-
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1
2 amino butyric acid (GABA) activity. On the one hand, women who present alterations
3 in the serotonin and GABA systems may be more sensitive to alcohol. On the other
4
5 hand it is known that the activity of both serotonin and GABA is altered among subjects
6
7 with PMS.¹² In fact, selective serotonin reuptake inhibitors (SSRIs) as well as the
8
9 GABA-ergic anxiolytic alprazolam may represent effective treatments in PMS cases.^{56,57}
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13
14 The relatively large number of studies conducted and the consistency of the results
15
16 across study designs and settings provide substantial epidemiological evidence that
17
18 alcohol drinking may be associated with an increase in the risk of PMS. However, non-
19
20 causal explanations of the relation should be carefully evaluated.
21

22
23
24 First, publication bias is a highly unlikely explanation for our results, as the association
25
26 between alcohol drinking and PMS remained strong even after extremely conservative
27
28 assumptions regarding the number, size, and findings of studies potentially conducted
29
30 and not included in our meta-analysis. Also, the findings of the asymmetry tests of the
31
32 funnel plot as well as those of the trim-and-fill method did not alter our results.
33

34
35
36 Second, residual confounding (confounding from unknown variables that is not
37
38 eliminated by adjustment) may have introduced bias as in any meta-analysis of
39
40 observational studies. It is remarkable that only one-third of the studies included in this
41
42 meta-analysis considered tobacco smoking in their adjustment in spite of the potential
43
44 for confounding of this factor.¹² In our meta-analysis, restricting our analysis to studies
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46 that adjusted for potential confounders, including tobacco smoking, did not introduce
47
48 any substantial modification in the estimate corresponding to any intake of alcohol. The
49
50 estimate corresponding to heavy intake decreased substantially after restriction to
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52 studies with complete adjustment but still shows a 38% increase in the risk.
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54 Furthermore, other confounders that were not measured in the studies of this meta-
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2
3 analysis could explain our results. Recently, some genetic polymorphisms, such as those
4
5 of the ESR1 gene and those associated to the serotonin 1A receptor have been
6
7 implicated in the occurrence of PMS.^{58,59} Such genetic factors could theoretically play a
8
9 role of confounders and explain the results of this meta-analysis concerning alcohol
10
11 drinking. However, this hypothesis is highly unlikely to be true. First, to act as a
12
13 confounder, a genetic factor must be related to PMS on the one hand and to alcohol
14
15 drinking on the other hand. No such factor has been described so far. Second, even if
16
17 this hypothetical factor could double the risk of PMS among subjects exposed to it (OR
18
19 confounder–disease = 2) and, simultaneously, this factor happened to be twice as
20
21 prevalent among alcohol drinkers than among non-drinkers (OR confounder–exposure =
22
23 2), the adjusted OR of the relation between any alcohol drinking and PMS would still be
24
25 1.21 and that of the relation between heavy drinking and PMS would still be 1.51
26
27 (assuming one-third of people are exposed to this unknown factor).⁶⁰ The existence of
28
29 an unknown factor so strongly related to alcohol intake and to PMS is highly
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31 improbable.
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36 Third, measurement error and misclassification of alcohol intake is likely to occur since
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38 women may understate their intake of alcohol as many societies hold more negative
39
40 attitudes towards women's alcohol drinking than men's drinking.⁸ However, this
41
42 misclassification is probably non differential regarding PMS, i.e. women with PMS do
43
44 not underestimate their drinking habits in a different fashion from women who do not
45
46 suffer PMS. In this case, the bias introduced is then towards the null value. The true OR
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48 is then even higher than the one we report in our meta-analysis. Similarly,
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50 misclassification of the outcome is also possible (i.e. women with PMS who are
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52 diagnosed as non-cases, and conversely non-diseased women who are erroneously
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1
2
3 diagnosed as PMS cases). As previously, this possible misclassification is unlikely to
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5 occur differently in women who consume alcohol and in those women who do not. The
6
7 bias introduced, if any, is towards the null value.
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10 Fourth, given that a substantial proportion of the studies included in this meta-analysis
11
12 used a cross-sectional design, a reverse causation process, in which PMS-affected
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14 women use alcohol to mitigate the effect of this syndrome, could explain the results
15
16 observed. Although this hypothesis should be rejected due to the fact that the pooled
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18 estimates for both categories of drinking are higher for case-control studies than for
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20 cross-sectional studies, it should be noted that, in several case-control studies included
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22 in this meta-analysis, the assessment of alcohol intake was probably concomitant to the
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24 assessment of PMS. This hypothesis remains then plausible.
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28 Furthermore, in our subgroup analyses, we were unable to identify any factors that
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30 accounted for study heterogeneity. This situation is extremely frequent and for meta-
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32 analysis experts, heterogeneity should be viewed more as the rule rather than the
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34 exception.⁶¹ As recommended by experts when heterogeneity is present, in order to deal
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36 with this issue, we focused our interpretation on the random effects estimates that are, in
37
38 general, more conservative.⁶²
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42 Our meta-analysis shows that alcohol intake is moderately associated with PMS risk.
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44 The consistency of the results and the existence of a plausible biologic mechanism
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46 strengthen our conclusions. Future studies should minimize measurement error in the
47
48 exposure by using validated questionnaires. These studies should avoid cross-sectional
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50 designs and focus on determining whether there is a threshold of alcohol intake under
51
52 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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References

1. O'Brien PM, Bäckström T, Brown C, Dennerstein L, Epperson CN, et al. Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: The IPMSD Montreal Consensus. *Arch Womens Ment Health*. 2011;14(1):13-21.
2. Rapkin AJ, Winer SA. Premenstrual syndrome and premenstrual dysphoric disorder: Quality of life and burden of illness. *Expert Rev Pharmacoecon Outcomes Res*. 2009;9(2):157-170.
3. Sternfeld B, Swindle R, Chawla A, Long S, Kennedy S. Severity of premenstrual symptoms in a health maintenance organization population. *Obstet Gynecol*. 2002;99(6):1014-1024.
4. Direkvand-Moghadam A, Sayehmiri K, Delpisheh A, Kaikhavandi S. Epidemiology of premenstrual syndrome (PMS)-A systematic review and meta-analysis study. *J Clin Diagn Res*. 2014;8(2):106-109
5. Borenstein JE, Dean BB, Endicott J, Wong J, Brown C, Dickerson V et al. Health and economic impact of the premenstrual syndrome. *J Reprod Med*. 2003;48(7):515-524.
6. Futterman LA, Rapkin AJ. Diagnosis of premenstrual disorders. *J Reprod Med*. 2006;51(4 Suppl):349-358.
7. Bertone-Johnson ER, Whitcomb BW, Rich-Edwards JW, Hankinson SE, Manson JE. Premenstrual syndrome and subsequent risk of hypertension in a prospective study. *Am J Epidemiol*. 2015;182(12):1000-1009.

1
2
3 8. World Health Organization. Global status report on alcohol and health 2014.

4 Available at:

5 http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf. Accessed

6
7
8
9 March 18th, 2017.

10
11
12 9. Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors
13 associated with premenstrual syndrome. *Arch Fam Med*. 1999;8(2):122-128.

14
15
16
17 10. Strine TW, Chapman DP, Ahluwalia IB. Menstrual-related problems and
18 psychological distress among women in the United States. *J Womens Health (Larchmt)*.
19
20 2005;14(4):316-323.

21
22
23
24
25 11. Skrzypulec-Plinta V, Droszol A, Nowosielski K, Plinta R. The complexity of
26 premenstrual dysphoric disorder--risk factors in the population of polish women.
27
28
29 *Reprod Biol Endocrinol*. 2010;8:141-7827-8-141.

30
31
32
33 12. Bertone-Johnson ER, Hankinson SE, Johnson SR, Manson JE. Timing of alcohol
34 use and the incidence of premenstrual syndrome and probable premenstrual dysphoric
35 disorder. *J Womens Health (Larchmt)*. 2009;18(12):1945-1953.

36
37
38
39
40 13. Gold EB, Bair Y, Block G, Greendale GA, Harlow SD, Johnson S et al. Diet and
41 lifestyle factors associated with premenstrual symptoms in a racially diverse community
42 sample: Study of Women's Health Across the Nation (SWAN). *J Womens Health*
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
(Larchmt). 2007;16(5):641-656.

14. Sadler C, Smith H, Hammond J, Bayly R, Borland S, Panay N et al. Lifestyle
factors, hormonal contraception, and premenstrual symptoms: The United Kingdom

- 1
2
3 Southampton Women's Survey. *J Womens Health (Larchmt)*. 2010;19(3):391-396.
4
5
6 15. Chien PF, Khan KS, Siassakos D. Registration of systematic reviews: PROSPERO.
7
8 *BJOG*. 2012;119(8):903-905.
9
10
11 16. Wilsnack SC, Klassen AD, Wilsnack RW. Drinking and reproductive dysfunction
12
13 among women in a 1981 national survey. *Alcohol Clin Exp Res*. 1984;8(5):451-458.
14
15
16 17. Kiesner J. Affective response to the menstrual cycle as a predictor of self-reported
17
18 affective response to alcohol and alcohol use. *Arch Womens Ment Health*.
19
20 2012;15(6):423-432.
21
22
23
24 18. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. (2012) The
25
26 Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in
27
28 meta-analyses. Ottawa Health Research Institute Web site. Available at:
29
30 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 18,
31
32 2017.
33
34
35
36 19. Rothman KJ, Greenland S, Lash TL. Measure of effect and measures of association.
37
38 In: *Modern Epidemiology* (3rd ed). Philadelphia: Lippincott, Williams and Wilkins;
39
40 2008. p.61.
41
42
43
44 20. Griffin ML, Mello NK, Mendelson JH, Lex BW. Alcohol use across the menstrual
45
46 cycle among marijuana users. *Alcohol*. 1987;4(6):457-462.
47
48
49 21. Nillni YI, Rohan KJ, Bernstein A, Zvolensky MJ. Premenstrual distress predicts
50
51 panic-relevant responding to a CO2 challenge among young adult females. *J Anxiety*
52
53 *Disord*. 2010;24(4):416-422.
54
55
56
57

- 1
2
3 22. Bryant M, Truesdale KP, Dye L. Modest changes in dietary intake across the
4 menstrual cycle: Implications for food intake research. *Br J Nutr*. 2006;96(5):888-894.
5
6
7
8 23. Reed SC, Levin FR, Evans SM. Changes in mood, cognitive performance and
9 appetite in the late luteal and follicular phases of the menstrual cycle in women with and
10 without PMDD (premenstrual dysphoric disorder). *Horm Behav*. 2008;54(1):185-193.
11
12
13
14
15 24. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Converting among effect
16 sizes. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-*
17 *Analysis*. Chichester, UK: John Wiley & Sons; 2009. p 45-49
18
19
20
21
22
23 25. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of
24 heterogeneity in epidemiologic meta-analysis. *Am J Epidemiol*. 1999;150(2):206-215.
25
26
27
28 26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected
29 by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
30
31
32
33
34 27. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, Spiegelman D. HEpiMA:
35 Software for the identification of heterogeneity in meta-analysis. *Comput Methods*
36 *Programs Biomed*. 2001;64(2):101-107.
37
38
39
40
41 28. Stout AL, Steege JF, Blazer DG, George LK. Comparison of lifetime psychiatric
42 diagnoses in premenstrual syndrome clinic and community samples. *J Nerv Ment Dis*.
43 1986;174(9):517-522.
44
45
46
47
48
49 29. Rossignol AM, Bonnländer H. Prevalence and severity of the premenstrual
50 syndrome. Effects of foods and beverages that are sweet or high in sugar content. *J*
51 *Reprod Med*. 1991;36(2):131-136.
52
53
54
55
56
57

60

- 1
2
3 30. Caan B, Duncan D, Hiatt R, Lewis J, Chapman J, Armstrong MA. Association
4 between alcoholic and caffeinated beverages and premenstrual syndrome. *J Reprod*
5 *Med.* 1993;38(8):630-636.
6
7
8
9
10 31. Chuong CJ, Burgos DM. Medical history in women with premenstrual syndrome. *J*
11 *Psychosom Obstet Gynaecol.* 1995;16(1):21-27.
12
13
14
15 32. Hourani LL, Yuan H, Bray RM. Psychosocial and lifestyle correlates of
16 premenstrual symptoms among military women. *J Womens Health (Larchmt).*
17 2004;13(7):812-821.
18
19
20
21
22
23 33. Forrester-Knauss C, Zemp Stutz E, Weiss C, Tschudin S. The interrelation between
24 premenstrual syndrome and major depression: Results from a population-based sample.
25 *BMC Public Health.* 2011;11:795-2458-11-795.
26
27
28
29
30 34. Pinar G, Colak M, Oksuz E. Premenstrual syndrome in Turkish college students and
31 its effects on life quality. *Sex Reprod Health.* 2011;2(1):21-27.
32
33
34
35
36 35. Hong JP, Park S, Wang HR, et al. Prevalence, correlates, comorbidities, and suicidal
37 tendencies of premenstrual dysphoric disorder in a nationwide sample of Korean
38 women. *Soc Psychiatry Psychiatr Epidemiol.* 2012;47(12):1937-1945.
39
40
41
42
43 36. Cheng SH, Shih CC, Yang YK, Chen KT, Chang YH, Yang YC. Factors associated
44 with premenstrual syndrome - a survey of new female university students. *Kaohsiung J*
45 *Med Sci.* 2013;29(2):100-105.
46
47
48
49
50 37. Kritz-Silverstein D, Wingard DL, Garland FC. The association of behavior and
51 lifestyle factors with menstrual symptoms. *J Womens Health Gen Based Med.*
52
53
54
55
56
57

1
2
3 1999;8(9):1185-1193.

4
5
6 38. Harvey SM, Beckman LJ. Cyclic fluctuation in alcohol consumption among female
7
8 social drinkers. *Alcohol Clin Exp Res*. 1985;9(5):465-467.

9
10
11 39. Schechter D, Bachmann GA, Vaitukaitis J, Phillips D, Saperstein D. Perimenstrual
12
13 symptoms: Time course of symptom intensity in relation to endocrinologically defined
14
15 segments of the menstrual cycle. *Psychosom Med*. 1989;51(2):173-194.

16
17
18 40. McLeod DR, Foster GV, Hoehn-Saric R, Svikis DS, Hipsley PA. Family history of
19
20 alcoholism in women with generalized anxiety disorder who have premenstrual
21
22 syndrome: Patient reports of premenstrual alcohol consumption and symptoms of
23
24 anxiety. *Alcohol Clin Exp Res*. 1994;18(3):664-670.

25
26
27 41. Svikis DS, Miles DR, Haug NA, Perry B, Hoehn-Saric R, McLeod D. Premenstrual
28
29 symptomatology, alcohol consumption, and family history of alcoholism in women with
30
31 premenstrual syndrome. *J Stud Alcohol*. 2006;67(6):833-836.

32
33
34 42. Wood C, Larsen L, Williams R. Social and psychological factors in relation to
35
36 premenstrual tension and menstrual pain. *Aust N Z J Obstet Gynaecol*. 1979;19(2):111-
37
38 115.

39
40
41 43. Charette L, Tate DL, Wilson A. Alcohol consumption and menstrual distress in
42
43 women at higher and lower risk for alcoholism. *Alcohol Clin Exp Res*. 1990;14(2):152-1
44
45

46
47
48 44. Gannon L, Luchetta T, Pardie L, Rhodes K. Perimenstrual symptoms: Relationships
49
50 with chronic stress and selected lifestyle variables. *Behav Med*. 1989;15(4):149-159.

51
52
53 45. Marks JL, Hair CS, Klock SC, Ginsburg BE, Pomerleau CS. Effects of menstrual
54
55

- 1
2
3 phase on intake of nicotine, caffeine, and alcohol and nonprescribed drugs in women
4
5 with late luteal phase dysphoric disorder. *J Subst Abuse*. 1994;6(2):235-243.
6
7
8 46. Wittchen H-, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of
9
10 premenstrual dysphoric disorder in the community. *Psychol Med*. 2002;32(1):119-132.
11
12
13 47. Kim SH, Lee JH. Study on Relation between Premenstrual Syndrome (PMS) and
14
15 Nutritional Intake, Blood Composition of Female College Students. *Korean J*
16
17 *Community Nutr*. 2005;10(5):603-614.
18
19
20
21 48. Bertone-Johnson ER, Hankinson SE, Willett WC, Johnson SR, Manson JE.
22
23 Adiposity and the development of premenstrual syndrome. *J Womens Health (Larchmt)*.
24
25 2010;19(11):1955-1962.
26
27
28 49. Tobin MB, Schmidt PJ, Rubinow DR. Reported alcohol use in women with
29
30 premenstrual syndrome. *Am J Psychiatry*. 1994;151(10):1503-1504.
31
32
33
34 50. Christensen AP, Oei TP, Callan VJ. The relationship between premenstrual
35
36 dysphoria and daily ratings dimensions. *J Affect Disord*. 1989;16(2-3):127-132.
37
38
39 51. Mello NK, Mendelson JH, Lex BW. Alcohol use and premenstrual symptoms in
40
41 social drinkers. *Psychopharmacology (Berl)*. 1990;101(4):448-455.
42
43
44
45 52. Song JE. The relationship between life style, menstrual attitude and premenstrual
46
47 syndrome in nursing students. *Health Nurs*. 2013;19(2):119-128.
48
49
50 53. Perry BL, Miles D, Burruss K, Svikis DS. Premenstrual symptomatology and
51
52 alcohol consumption in college women. *J Stud Alcohol*. 2004;65(4):464-468.
53
54
55
56
57

1
2
3 54. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
4 epidemiology: A proposal for reporting. meta-analysis of observational studies in
5 epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.
6
7

8
9
10 554. Rothman KJ. *Modern Epidemiology*. Boston: Little, Brown and Co;1986. p.39.
11

12
13 56. Halbreich U. The etiology, biology, and evolving pathology of premenstrual
14 syndromes. *Psychoneuroendocrinology*. 2003;28 Suppl 3:55-99.
15

16
17 57. Rapkin A. A review of treatment of premenstrual syndrome and premenstrual
18 dysphoric disorder. *Psychoneuroendocrinology*. 2003;28 Suppl 3:39-53.
19
20

21
22 58. Pakharensko L. Effect of estrogen receptor gene ESR1 polymorphism on
23 development of premenstrual syndrome. *Georgian Med News* 2014; (235):37-41.
24
25

26
27 59. Yen JY, Tu HP, Chen CS, Yen CF, Long CY, Ko CH. The effect of serotonin 1A
28 receptor polymorphism on the cognitive function of premenstrual dysphoric disorder.
29 *Eur Arch Psychiatry Clin Neurosci*. 2014;264(8):729-39].
30
31

32
33 60. Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol*.
34 1996;25(6):1107-1116.
35
36

37
38 61. Berlin JA. Invited commentary: Benefits of heterogeneity in meta-analysis of data
39 from epidemiologic studies. *Am J Epidemiol*. 1995;142(4):383-387.
40
41

42
43 62. Higgins JP. Commentary: Heterogeneity in meta-analysis should be expected and
44 appropriately quantified. *Int J Epidemiol*. 2008;37(5):1158-1160.
45
46
47
48
49
50
51
52
53
54
55
56
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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	Students 18-22 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	Students 18-28 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 \geq 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

Fernández MM

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

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7 Figure 1. Flow diagram for study selection

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

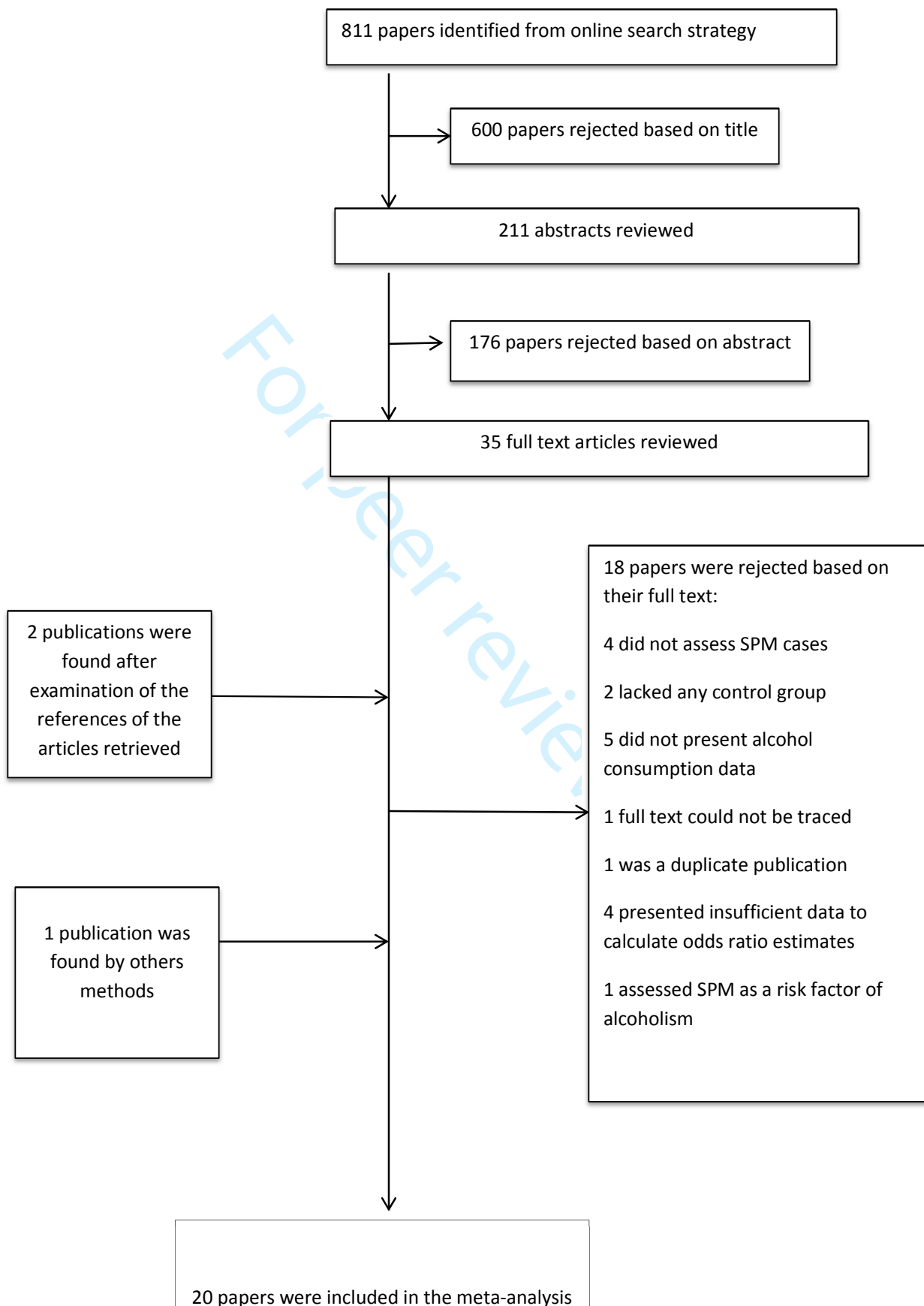
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11 Figure 3. Study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: heavy drinking

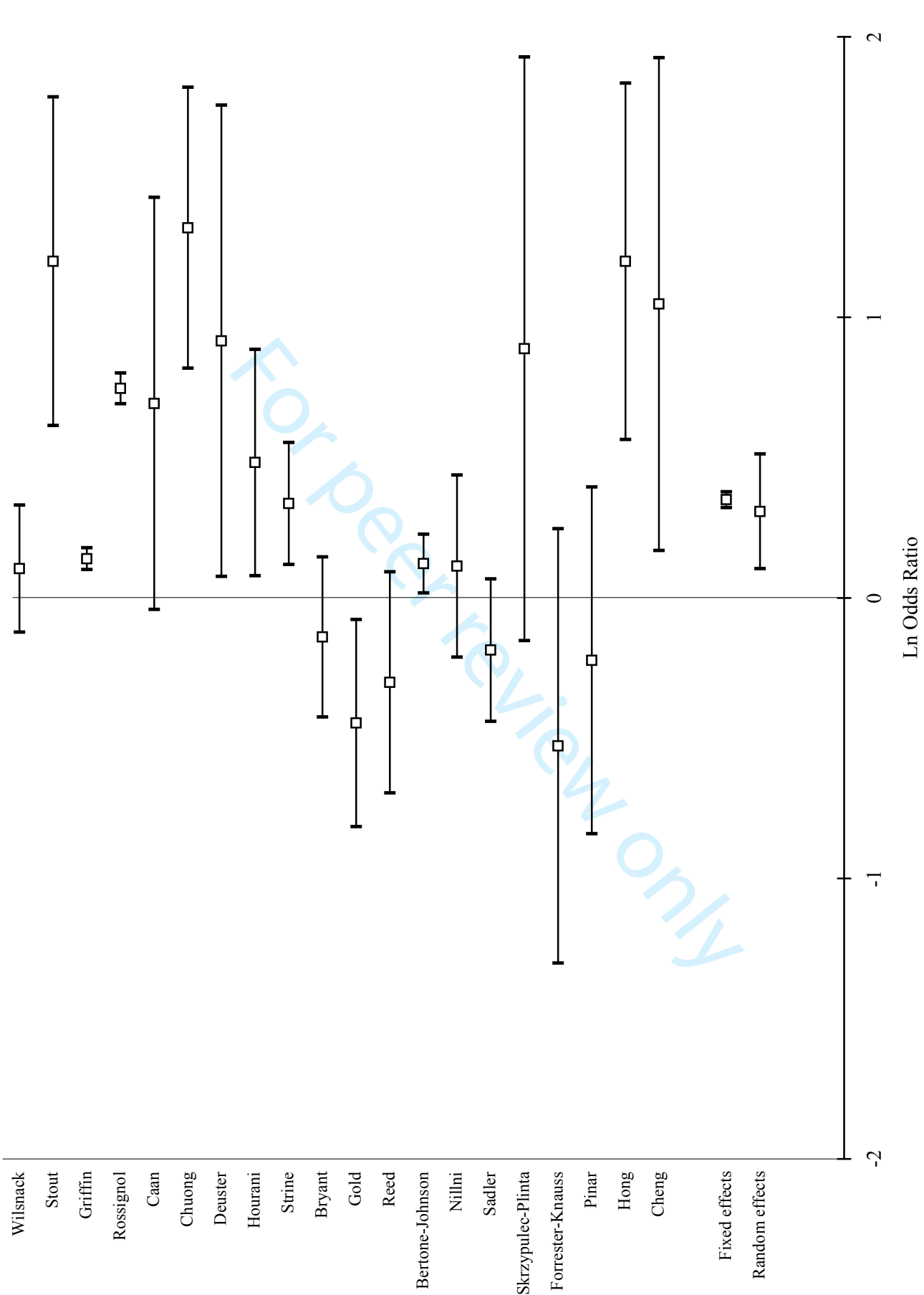
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13 Figure 4: Funnel plot of Odds Ratios versus standard error of Odds Ratios of alcohol drinking and premenstrual syndrome

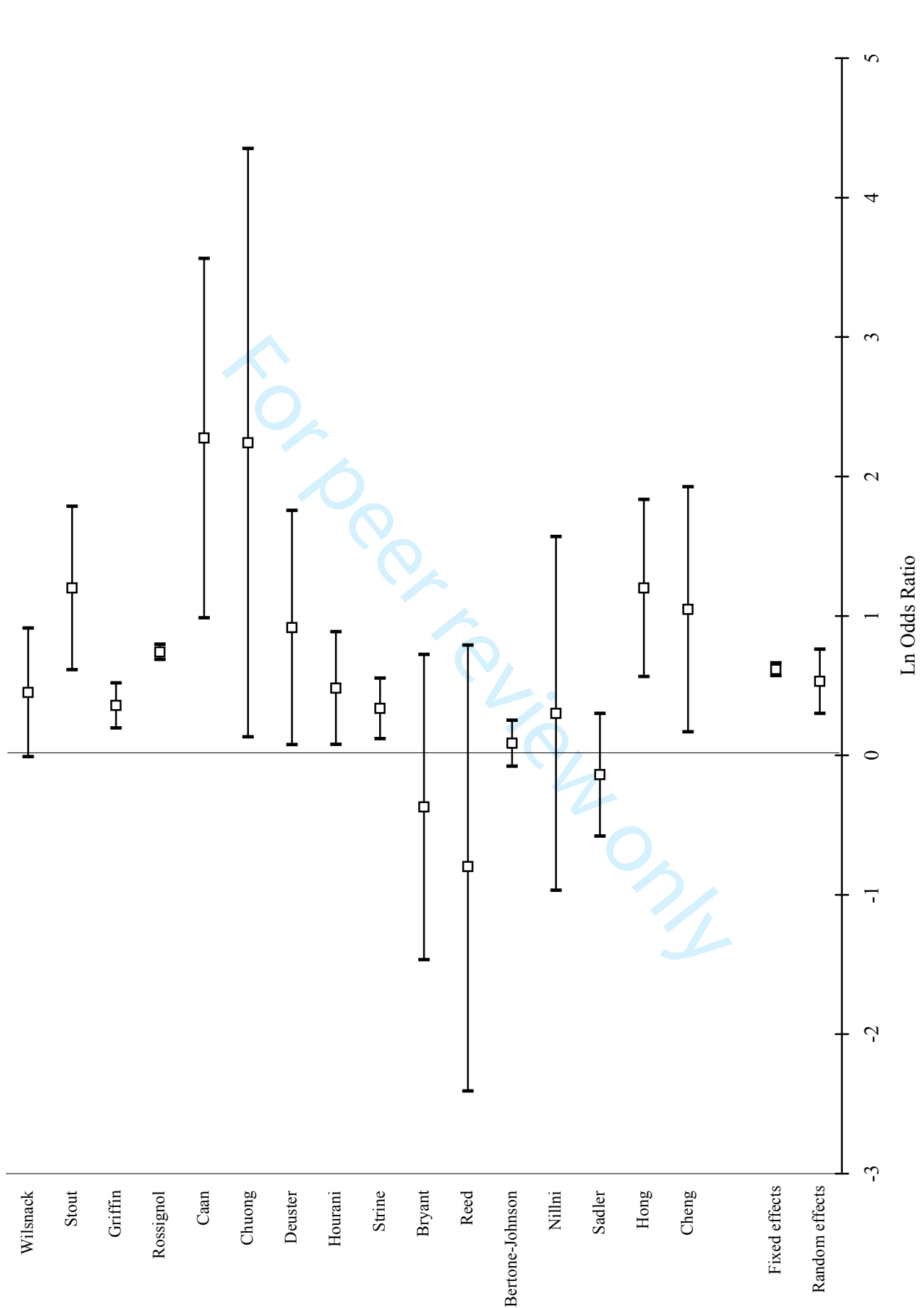
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For peer review only

Fernández MM

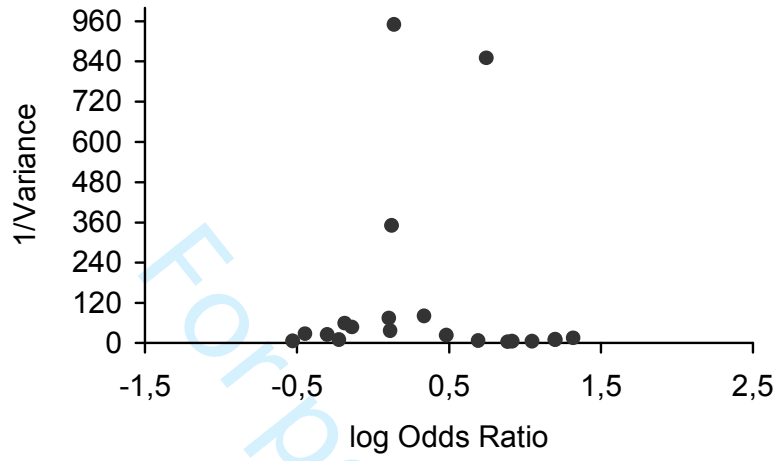




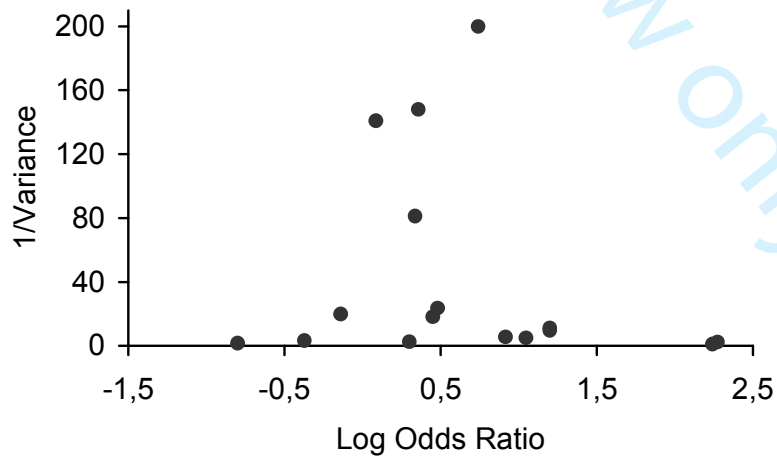


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Any drinking



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

Page 1 of 2

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

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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

For more information, visit: www.prisma-statement.org.

Page 2 of 2

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019490.R1
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	meta-analysis, Premenstrual syndrome, Alcohol

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Manuscripts

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 cases², 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

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

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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

1
2 regional bibliographic databases of the WHO (AIM, LILACS, IMEMR, IMSEAR,
3 WPRIM), the Conference Proceedings Citation Index, the Open Access Thesis and
4 Dissertations (OATD), from inception to May 2017.
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8 For Medline, we used the following algorithm both in Medical Subject Heading and in
9 free text words: ("premenstrual syndrome"[MeSH Terms] OR "premenstrual
10 syndrome"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR
11 "alcohol"[All Fields]). An example of this search is given in Supplement 1. Similar
12 strategies were used for the other databases.
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19 We also reviewed the references of every article retrieved. Furthermore, we established
20 personal contact with researchers to trace further publications or reports. We did not
21 include any language limitations. All searches were carried out independently by two
22 researchers and results were merged.
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28 The review protocol of this meta-analysis was registered in Prospero.¹⁵
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33 **Study selection**

34 Studies were included if: 1) they presented original data from cohort, case-control or
35 cross-sectional studies, 2) PMS or its more severe form, Premenstrual Dysphoric
36 Disorder (PMDD), were clearly defined as the outcome of interest, 3) one of the
37 exposure factors was alcohol consumption, 4) they provided estimates of odds ratios
38 (OR), rate ratios (RR), or prevalence odds ratios and their confidence intervals, or
39 enough data to calculate them.
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47 If data on the same population were duplicated in more than one publication, the most
48 recent study was included in the analysis.
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51 We developed a standard data-recording form in which we recorded authors, year of
52 publication, study location, study design, sample size, outcome, outcome measurement
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3 details, effect estimator (OR, RR, other), effect estimate, 95% Confidence Intervals, and
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5 adjustment, restriction or matching factors used.

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7 When further clarification was necessary, we attempted to contact the authors.^{14,16,17}
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10 11 *Quality Assessment*

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13 Study quality was assessed using a five-point binary scale specifically developed for
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15 this study. The scale is based on the Newcastle-Ottawa scale with modifications in view
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17 of standard guidelines and our own judgment.¹⁸ The Newcastle-Ottawa scale is a
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19 scoring system that assesses every aspect of an observational epidemiologic study from
20
21 a methodological point of view. For this meta-analysis, we tried to use those elements
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23 that were common to all epidemiological designs and thus shortened the scale
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25 considerably. We used the following criteria labelled as “1” or “0”: 1) Measurement of
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27 alcohol intake: through standard or validated questionnaire which includes quantity
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29 and/or frequency: 1, else (simple question, no data on frequency or quantity) or not
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31 explained: 0; 2) PMS diagnosis: through standard or validated questionnaire: 1, else or
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33 not explained: 0; 3) Confounding assessment: results adjusted at least for age and
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35 smoking, either in the design phase or in the analysis: 1, else: 0; 4) Participation:
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37 participation exceeded 80% of the people initially approached: 1, else or data not
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39 provided: 0; 5) Target population: target population clearly defined: 1, based on
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41 convenience sampling of subjects such as patients of a single consultation or volunteers
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43 or not explained: 0
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48 Throughout this assessment, when the information on a specific item was not provided
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50 by the authors, we graded this item as “0”. We carried out a pooled analysis on those
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52 studies that fulfilled at least 3 criteria and compared with those that fulfilled fewer than
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54 3. Furthermore, we did not grade cross-sectional studies differently from the case-
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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

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3 drinkers).²⁴ As drinking patterns vary widely between countries, we calculated the
4 content in ethanol of an average drink using data on consumption of beer, wine and
5 spirits, specific to each country and used different sources to define low, moderate and
6 heavy drinking.^{8,12} We considered a consumption of less than 10g/day of ethanol as low
7 intake, a consumption between 10g/day and the content in ethanol of 1 average
8 drink/day as moderate intake, and a consumption equal or higher than the content in
9 ethanol of 1 average drink/day as heavy intake. To compute an estimate for the category
10 “any drinking”, we pooled the odds ratios obtained in the 3 categories (low, moderate
11 and heavy intake).
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24 We used the DerSimonian and Laird Q test to check for heterogeneity. To quantify this
25 heterogeneity we calculated the proportion of the total variance due to between-study
26 variance (I² statistic).²⁵ Large values (>0.75) indicate large amount of heterogeneity,
27 values between 0.4 and 0.75 suggest a moderate amount while small values (<0.4)
28 indicate low heterogeneity. We later explored the origin of heterogeneity by restricting
29 the analysis to subgroups of studies defined by study characteristics such as study
30 design, adjustment, origin and quality score. All secondary analyses were planned a
31 priori.
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44 We assessed publication bias, first visually, using funnel plots and then, more formally,
45 using the test proposed by Egger et al.²⁶ We also used the trim-and-fill method to
46 correct for potential publication bias. All analyses were performed with the software
47 HEpiMA® version 2.1.3²⁷ and STATA version 12. The transformation of standardized
48 mean differences into odds ratios was performed with the software Comprehensive
49 Meta-Analysis (Englewood, New Jersey, USA).
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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 consumption⁴³⁻⁴⁶ and one of them did not present a confidence interval,⁴⁷ the full text of one could not be traced⁴⁸, 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

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3 studies was higher than that of cross-sectional studies both for any drinking and heavy
4 drinking. When we restricted our analysis to those studies that presented odds ratio
5 estimates, i.e. when we excluded studies that computed standardized mean differences,
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7 the pooled estimates were higher: pooled OR= 1.51; 95%CI 1.22-1.88 for any drinking
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9 and 1.90; 95%CI 1.45-2.49 for heavy drinking.
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13 The pooled estimate of studies with high quality scores was lower than that from low
14 quality studies.
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17 Except for the criteria “validated diagnosis” and the criteria “high response rate” in the
18 any drinking group for which the estimates were similar, when we considered the
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20 quality criteria individually instead of just as a global quality score, as recommended by
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22 the MOOSE guidelines,⁵⁵ the studies that fulfilled the criteria yielded lower pooled
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24 estimates than studies which did not.
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29 About two-thirds of the studies included in this meta-analysis were carried out in US
30 populations. The estimates from American studies were higher than those from other
31 countries, both in the any drinking group and the heavy drinking group.
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36 37 *Publication Bias*

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39 The funnel plot (figure 4) for the any drinking group did not suggest asymmetry, a
40 result confirmed by a p-value of the Egger’s test of 0.85. However, the trim-and-fill
41 procedure indicated 2 potentially missing studies though the corrected random effects
42 pooled odds ratio, OR=1.31 (95%CI 1.08-1.61), was very close to the odds ratio we
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44 obtained. Again, the funnel plot for heavy drinking did not suggest any publication bias
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46 (p-value Egger’s test = 0.61) and the trim-and-fill method indicated 2 potentially
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48 missing studies and a corrected pooled estimate that was very similar to that obtained
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3 before correction (random effects pooled OR= 1.68; 95%CI: 1.30-2.16).
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6 7 8 *Sensitivity Analysis*

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

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33 The results of our systematic review and meta-analysis suggest that alcohol drinking is
34 associated with a moderate increase in the risk of PMS. This increase is more
35 pronounced for heavy drinking, which favours a causal explanation of the relation
36 between alcohol intake and PMS.
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43 These findings are important given that the worldwide prevalence of alcohol drinking
44 among women is not negligible. Worldwide, the proportion of current female drinkers is
45 28.9%, while that of heavy female drinkers is 5.7%. In Europe and America these
46 figures are much higher and reach 59.9% for current drinking and 12.6% for heavy
47 drinking in Europe.⁸ Based on the figures above and on our results we estimate that 11%
48 of the PMS cases may be associated to alcohol intake worldwide and 21% in Europe.⁵⁶
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3 Furthermore, heavy drinking may be associated with 4% of the PMS cases in the world
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5 and over 9% in Europe. If this association is of causal nature, eliminating heavy
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7 drinking in women would then prevent one in every twelve cases of PMS in Europe.
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10 Alcohol use may plausibly increase the risk of PMS by altering levels of sex steroid
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12 hormones and gonadotropin during the menstrual cycle. PMS was previously found to
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14 be linked to fluctuations of these sex hormones during the cycle.^{12,57} Furthermore,
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16 alcohol intake may increase the risk of PMS through its effect on serotonin and gamma-
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18 amino butyric acid (GABA) activity. On the one hand, women who present alterations
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20 in the serotonin and GABA systems may be more sensitive to alcohol. On the other
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22 hand it is known that the activity of both serotonin and GABA is altered among subjects
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24 with PMS.¹² In fact, selective serotonin reuptake inhibitors (SSRIs) as well as the
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26 GABA-ergic anxiolytic alprazolam may represent effective treatments in PMS cases.^{57,58}
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30 The relatively large number of studies conducted and the consistency of the results
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32 across study designs and settings provide substantial epidemiological evidence that
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34 alcohol drinking may be associated with an increase in the risk of PMS. However, non-
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36 causal explanations of the relation should be carefully evaluated.
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39 First, publication bias is a highly unlikely explanation for our results, as the association
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41 between alcohol drinking and PMS remained strong even after extremely conservative
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43 assumptions regarding the number, size, and findings of studies potentially conducted
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45 and not included in our meta-analysis. Also, the findings of the asymmetry tests of the
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47 funnel plot as well as those of the trim-and-fill method did not alter our results.
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51 Second, residual confounding (confounding from unknown variables that is not
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53 eliminated by adjustment) may have introduced bias as in any meta-analysis of
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3 observational studies. It is remarkable that only one-third of the studies included in this
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5 meta-analysis considered tobacco smoking in their adjustment in spite of the potential
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7 for confounding of this factor.¹² In our meta-analysis, restricting our analysis to studies
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9 that adjusted for potential confounders, including tobacco smoking, did not introduce
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11 any substantial modification in the estimate corresponding to any intake of alcohol. The
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13 estimate corresponding to heavy intake decreased substantially after restriction to
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15 studies with complete adjustment but still shows a 38% increase in the risk.
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17 Furthermore, other confounders that were not measured in the studies of this meta-
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19 analysis could explain our results. Recently, some genetic polymorphisms, such as those
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21 of the ESR1 gene and those associated to the serotonin 1A receptor have been
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23 implicated in the occurrence of PMS.^{59,60} Such genetic factors could theoretically play a
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25 role of confounders and explain the results of this meta-analysis concerning alcohol
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27 drinking. However, this hypothesis is highly unlikely to be true. First, to act as a
28
29 confounder, a genetic factor must be related to PMS on the one hand and to alcohol
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31 drinking on the other hand. No such factor has been described so far. Second, even if
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33 this hypothetical factor could double the risk of PMS among subjects exposed to it (OR
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35 confounder–disease = 2) and, simultaneously, this factor happened to be twice as
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37 prevalent among alcohol drinkers than among non-drinkers (OR confounder–exposure =
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39 2), the adjusted OR of the relation between any alcohol drinking and PMS would still be
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41 1.21 and that of the relation between heavy drinking and PMS would still be 1.51
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43 (assuming one-third of people are exposed to this unknown factor).⁶¹ The existence of
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45 an unknown factor so strongly related to alcohol intake and to PMS is highly
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47 improbable.
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53 Third, measurement error and misclassification of alcohol intake is likely to occur since
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3 women may understate their intake of alcohol as many societies hold more negative
4 attitudes towards women's alcohol drinking than men's drinking.⁸ However, this
5 misclassification is probably non differential regarding PMS, i.e. women with PMS do
6 not underestimate their drinking habits in a different fashion from women who do not
7 suffer PMS. In this case, the bias introduced is then towards the null value. The true OR
8 is then even higher than the one we report in our meta-analysis. Similarly,
9 misclassification of the outcome is also possible (i.e. women with PMS who are
10 diagnosed as non-cases, and conversely non-diseased women who are erroneously
11 diagnosed as PMS cases). As previously, this possible misclassification is unlikely to
12 occur differently in women who consume alcohol and in those women who do not. The
13 bias introduced, if any, is towards the null value.
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27 Fourth, given that a substantial proportion of the studies included in this meta-analysis
28 used a cross-sectional design, a reverse causation process, in which PMS-affected
29 women use alcohol to mitigate the effect of this syndrome, could introduce what is
30 known as protopathic bias and thus, explain the results observed. Although in theory
31 this hypothesis should be rejected due to the fact that the pooled estimates for both
32 categories of drinking are higher for case-control studies than for cross-sectional
33 studies, it should be noted that, in several case-control studies included in this meta-
34 analysis, the assessment of alcohol intake was probably concomitant to the assessment
35 of PMS. This hypothesis remains then plausible.
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47 Furthermore, in our subgroup analyses, we were unable to identify any factors that
48 accounted for study heterogeneity. This situation is extremely frequent and for meta-
49 analysis experts, heterogeneity should be viewed more as the rule rather than the
50 exception.⁶² As recommended by experts when heterogeneity is present, in order to deal
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3 with this issue, we focused our interpretation on the random effects estimates that are, in
4
5 general, more conservative.⁶³
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8 Our meta-analysis shows that alcohol intake is moderately associated with PMS risk.
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10 The consistency of the results and the existence of a plausible biologic mechanism
11
12 strengthen our conclusions. Future studies should minimize measurement error in the
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14 exposure by using validated questionnaires. These studies should avoid cross-sectional
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16 designs and focus on determining whether there is a threshold of alcohol intake under
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18 which the harmful effect on PMS is non-existent.
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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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16 17 18 **Contributorship statement**

19
20 **María del Mar Fernández** performed the computerized systematic search, literature
21
22 revision, risk of bias assessment, meta-analysis and redaction of the manuscript, figures
23
24 and tables.
25

26
27 **Jurgita Saulyte** assessed the risk of bias and revised the manuscript.

28
29 **Hazel Inskip** provided unpublished data and participated in the redaction of the
30
31 manuscript
32

33
34 **Bahi Takkouche** did the complementary searches, assessment of the publication bias
35
36 and revision of the final manuscript, figures and tables. He acts as a guarantor of the
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38 study.
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References

1. O'Brien PM, Bäckström T, Brown C, Dennerstein L, Epperson CN, et al. Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: The IPMSD Montreal Consensus. *Arch Womens Ment Health*. 2011;14(1):13-21.
2. Rapkin AJ, Winer SA. Premenstrual syndrome and premenstrual dysphoric disorder: Quality of life and burden of illness. *Expert Rev Pharmacoecon Outcomes Res*. 2009;9(2):157-170.
3. Sternfeld B, Swindle R, Chawla A, Long S, Kennedy S. Severity of premenstrual symptoms in a health maintenance organization population. *Obstet Gynecol*. 2002;99(6):1014-1024.
4. Direkvand-Moghadam A, Sayehmiri K, Delpisheh A, Kaikhavandi S. Epidemiology of premenstrual syndrome (PMS)-A systematic review and meta-analysis study. *J Clin Diagn Res*. 2014;8(2):106-109
5. Borenstein JE, Dean BB, Endicott J, Wong J, Brown C, Dickerson V et al. Health and economic impact of the premenstrual syndrome. *J Reprod Med*. 2003;48(7):515-524.
6. Futterman LA, Rapkin AJ. Diagnosis of premenstrual disorders. *J Reprod Med*. 2006;51(4 Suppl):349-358.
7. Bertone-Johnson ER, Whitcomb BW, Rich-Edwards JW, Hankinson SE, Manson JE. Premenstrual syndrome and subsequent risk of hypertension in a prospective study. *Am J Epidemiol*. 2015;182(12):1000-1009.

- 1
2
3 8. World Health Organization. Global status report on alcohol and health 2014.
4
5 Available at:
6
7 http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf. Accessed
8
9 December 11, 2017.
10
11
12 9. Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors
13 associated with premenstrual syndrome. *Arch Fam Med*. 1999;8(2):122-128.
14
15
16 10. Strine TW, Chapman DP, Ahluwalia IB. Menstrual-related problems and
17 psychological distress among women in the United States. *J Womens Health (Larchmt)*.
18 2005;14(4):316-323.
19
20
21
22
23 11. Skrzypulec-Plinta V, Droszol A, Nowosielski K, Plinta R. The complexity of
24 premenstrual dysphoric disorder--risk factors in the population of polish women.
25 *Reprod Biol Endocrinol*. 2010;8:141-7827-8-141.
26
27
28
29
30
31
32 12. Bertone-Johnson ER, Hankinson SE, Johnson SR, Manson JE. Timing of alcohol
33 use and the incidence of premenstrual syndrome and probable premenstrual dysphoric
34 disorder. *J Womens Health (Larchmt)*. 2009;18(12):1945-1953.
35
36
37
38
39
40 13. Gold EB, Bair Y, Block G, Greendale GA, Harlow SD, Johnson S et al. Diet and
41 lifestyle factors associated with premenstrual symptoms in a racially diverse community
42 sample: Study of Women's Health Across the Nation (SWAN). *J Womens Health*
43 *(Larchmt)*. 2007;16(5):641-656.
44
45
46
47
48
49 14. Sadler C, Smith H, Hammond J, Bayly R, Borland S, Panay N et al. Lifestyle
50 factors, hormonal contraception, and premenstrual symptoms: The United Kingdom
51
52
53
54
55
56
57

- 1
2
3 Southampton Women's Survey. *J Womens Health (Larchmt)*. 2010;19(3):391-396.
4
5
6 15. Chien PF, Khan KS, Siassakos D. Registration of systematic reviews: PROSPERO.
7
8 *BJOG*. 2012;119(8):903-905.
9
10
11 16. Wilsnack SC, Klassen AD, Wilsnack RW. Drinking and reproductive dysfunction
12
13 among women in a 1981 national survey. *Alcohol Clin Exp Res*. 1984;8(5):451-458.
14
15
16 17. Kiesner J. Affective response to the menstrual cycle as a predictor of self-reported
17
18 affective response to alcohol and alcohol use. *Arch Womens Ment Health*.
19
20 2012;15(6):423-432.
21
22
23 18. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. (2012) The
24
25 Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in
26
27 meta-analyses. Ottawa Health Research Institute Web site. Available at:
28
29 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December
30
31 11, 2017.
32
33
34 19. Rothman KJ, Greenland S, Lash TL. Measure of effect and measures of association.
35
36 In: *Modern Epidemiology* (3rd ed). Philadelphia: Lippincott, Williams and Wilkins;
37
38 2008. p.61.
39
40
41 20. Griffin ML, Mello NK, Mendelson JH, Lex BW. Alcohol use across the menstrual
42
43 cycle among marijuana users. *Alcohol*. 1987;4(6):457-462.
44
45
46 21. Nillni YI, Rohan KJ, Bernstein A, Zvolensky MJ. Premenstrual distress predicts
47
48 panic-relevant responding to a CO2 challenge among young adult females. *J Anxiety*
49
50 *Disord*. 2010;24(4):416-422.
51
52
53
54
55
56
57

- 1
2
3 22. Bryant M, Truesdale KP, Dye L. Modest changes in dietary intake across the
4 menstrual cycle: Implications for food intake research. *Br J Nutr*. 2006;96(5):888-894.
5
6
7
8 23. Reed SC, Levin FR, Evans SM. Changes in mood, cognitive performance and
9 appetite in the late luteal and follicular phases of the menstrual cycle in women with and
10 without PMDD (premenstrual dysphoric disorder). *Horm Behav*. 2008;54(1):185-193.
11
12
13
14
15 24. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Converting among effect
16 sizes. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-*
17 *Analysis*. Chichester, UK: John Wiley & Sons; 2009. p 45-49
18
19
20
21
22
23 25. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of
24 heterogeneity in epidemiologic meta-analysis. *Am J Epidemiol*. 1999;150(2):206-215.
25
26
27
28
29 26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected
30 by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
31
32
33
34 27. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, Spiegelman D. HEpiMA:
35 Software for the identification of heterogeneity in meta-analysis. *Comput Methods*
36 *Programs Biomed*. 2001;64(2):101-107.
37
38
39
40
41
42 28. Stout AL, Steege JF, Blazer DG, George LK. Comparison of lifetime psychiatric
43 diagnoses in premenstrual syndrome clinic and community samples. *J Nerv Ment Dis*.
44 1986;174(9):517-522.
45
46
47
48
49 29. Rossignol AM, Bonnländer H. Prevalence and severity of the premenstrual
50 syndrome. Effects of foods and beverages that are sweet or high in sugar content. *J*
51 *Reprod Med*. 1991;36(2):131-136.
52
53
54
55
56
57

- 1
2
3 30. Caan B, Duncan D, Hiatt R, Lewis J, Chapman J, Armstrong MA. Association
4 between alcoholic and caffeinated beverages and premenstrual syndrome. *J Reprod*
5 *Med.* 1993;38(8):630-636.
6
7
8
9
10 31. Chuong CJ, Burgos DM. Medical history in women with premenstrual syndrome. *J*
11 *Psychosom Obstet Gynaecol.* 1995;16(1):21-27.
12
13
14
15 32. Hourani LL, Yuan H, Bray RM. Psychosocial and lifestyle correlates of
16 premenstrual symptoms among military women. *J Womens Health (Larchmt).*
17 2004;13(7):812-821.
18
19
20
21
22 33. Forrester-Knauss C, Zemp Stutz E, Weiss C, Tschudin S. The interrelation between
23 premenstrual syndrome and major depression: Results from a population-based sample.
24 *BMC Public Health.* 2011;11:795-2458-11-795.
25
26
27
28
29 34. Pinar G, Colak M, Oksuz E. Premenstrual syndrome in Turkish college students and
30 its effects on life quality. *Sex Reprod Health.* 2011;2(1):21-27.
31
32
33
34
35 35. Hong JP, Park S, Wang HR, et al. Prevalence, correlates, comorbidities, and suicidal
36 tendencies of premenstrual dysphoric disorder in a nationwide sample of Korean
37 women. *Soc Psychiatry Psychiatr Epidemiol.* 2012;47(12):1937-1945.
38
39
40
41
42 36. Cheng SH, Shih CC, Yang YK, Chen KT, Chang YH, Yang YC. Factors associated
43 with premenstrual syndrome - a survey of new female university students. *Kaohsiung J*
44 *Med Sci.* 2013;29(2):100-105.
45
46
47
48
49 37. Ju H, Jones M, Mishra GD. Illicit drug use, early age at first use and risk of
50 premenstrual syndrome: a longitudinal study. *Drug Alcohol Depend.* 2015; 152: 209-17
51
52
53
54
55
56
57

- 1
2
3 38. Kritz-Silverstein D, Wingard DL, Garland FC. The association of behavior and
4 lifestyle factors with menstrual symptoms. *J Womens Health Gen Based Med*.
5 1999;8(9):1185-1193.
6
7
8
9
10 39. Harvey SM, Beckman LJ. Cyclic fluctuation in alcohol consumption among female
11 social drinkers. *Alcohol Clin Exp Res*. 1985;9(5):465-467.
12
13
14
15 40. Schechter D, Bachmann GA, Vaitukaitis J, Phillips D, Saperstein D. Perimenstrual
16 symptoms: Time course of symptom intensity in relation to endocrinologically defined
17 segments of the menstrual cycle. *Psychosom Med*. 1989;51(2):173-194.
18
19
20
21
22
23 41. McLeod DR, Foster GV, Hoehn-Saric R, Svikis DS, Hipsley PA. Family history of
24 alcoholism in women with generalized anxiety disorder who have premenstrual
25 syndrome: Patient reports of premenstrual alcohol consumption and symptoms of
26 anxiety. *Alcohol Clin Exp Res*. 1994;18(3):664-670.
27
28
29
30
31
32
33 42. Svikis DS, Miles DR, Haug NA, Perry B, Hoehn-Saric R, McLeod D. Premenstrual
34 symptomatology, alcohol consumption, and family history of alcoholism in women with
35 premenstrual syndrome. *J Stud Alcohol*. 2006;67(6):833-836.
36
37
38
39
40
41 43. Wood C, Larsen L, Williams R. Social and psychological factors in relation to
42 premenstrual tension and menstrual pain. *Aust N Z J Obstet Gynaecol*. 1979;19(2):111-
43 115.
44
45
46
47
48 44. Charette L, Tate DL, Wilson A. Alcohol consumption and menstrual distress in
49 women at higher and lower risk for alcoholism. *Alcohol Clin Exp Res*. 1990;14(2):152-1
50
51
52
53 45. Gannon L, Luchetta T, Pardie L, Rhodes K. Perimenstrual symptoms: Relationships
54
55
56
57

- 1
2
3 with chronic stress and selected lifestyle variables. *Behav Med*. 1989;15(4):149-159.
4
5
6 46. Marks JL, Hair CS, Klock SC, Ginsburg BE, Pomerleau CS. Effects of menstrual
7
8 phase on intake of nicotine, caffeine, and alcohol and nonprescribed drugs in women
9
10 with late luteal phase dysphoric disorder. *J Subst Abuse*. 1994;6(2):235-243.
11
12
13 47. Wittchen H-, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of
14
15 premenstrual dysphoric disorder in the community. *Psychol Med*. 2002;32(1):119-132.
16
17
18 48. Kim SH, Lee JH. Study on Relation between Premenstrual Syndrome (PMS) and
19
20 Nutritional Intake, Blood Composition of Female College Students. *Korean J*
21
22 *Community Nutr*. 2005;10(5):603-614.
23
24
25
26 49. Bertone-Johnson ER, Hankinson SE, Willett WC, Johnson SR, Manson JE.
27
28 Adiposity and the development of premenstrual syndrome. *J Womens Health (Larchmt)*.
29
30 2010;19(11):1955-1962.
31
32
33
34 50. Tobin MB, Schmidt PJ, Rubinow DR. Reported alcohol use in women with
35
36 premenstrual syndrome. *Am J Psychiatry*. 1994;151(10):1503-1504.
37
38
39 51. Christensen AP, Oei TP, Callan VJ. The relationship between premenstrual
40
41 dysphoria and daily ratings dimensions. *J Affect Disord*. 1989;16(2-3):127-132.
42
43
44
45 52. Mello NK, Mendelson JH, Lex BW. Alcohol use and premenstrual symptoms in
46
47 social drinkers. *Psychopharmacology (Berl)*. 1990;101(4):448-455.
48
49
50 53. Song JE. The relationship between life style, menstrual attitude and premenstrual
51
52 syndrome in nursing students. *Health Nurs*. 2013;19(2):119-128.
53
54
55
56
57

- 1
2
3 54. Perry BL, Miles D, Burruss K, Svikis DS. Premenstrual symptomatology and
4
5 alcohol consumption in college women. *J Stud Alcohol*. 2004;65(4):464-468.
6
7
8 55. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
9
10 epidemiology: A proposal for reporting. meta-analysis of observational studies in
11
12 epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012.
13
14
15 56. Rothman KJ. *Modern Epidemiology*. Boston: Little, Brown and Co;1986. p.39.
16
17
18 57. Halbreich U. The etiology, biology, and evolving pathology of premenstrual
19
20 syndromes. *Psychoneuroendocrinology*. 2003;28 Suppl 3:55-99.
21
22
23 58. Rapkin A. A review of treatment of premenstrual syndrome and premenstrual
24
25 dysphoric disorder. *Psychoneuroendocrinology*. 2003;28 Suppl 3:39-53.
26
27
28 59. Pakhareno L. Effect of estrogen receptor gene ESR1 polymorphism on
29
30 development of premenstrual syndrome. *Georgian Med News*. 2014; (235):37-41.
31
32
33 60. Yen JY, Tu HP, Chen CS, Yen CF, Long CY, Ko CH. The effect of serotonin 1A
34
35 receptor polymorphism on the cognitive function of premenstrual dysphoric disorder.
36
37 *Eur Arch Psychiatry Clin Neurosci*. 2014;264(8):729-39].
38
39
40 61. Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol*.
41
42 1996;25(6):1107-1116.
43
44
45 62. Berlin JA. Invited commentary: Benefits of heterogeneity in meta-analysis of data
46
47 from epidemiologic studies. *Am J Epidemiol*. 1995;142(4):383-387.
48
49
50 63. Higgins JP. Commentary: Heterogeneity in meta-analysis should be expected and
51
52
53
54
55
56
57

1
2
3 appropriately quantified. *Int J Epidemiol.* 2008;37(5):1158-1160.
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
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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	Students 18-22 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	Students 18-28 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 \geq 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

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7 Figure 1. Flow diagram for study selection

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

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

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

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For peer review only

Fernández MM

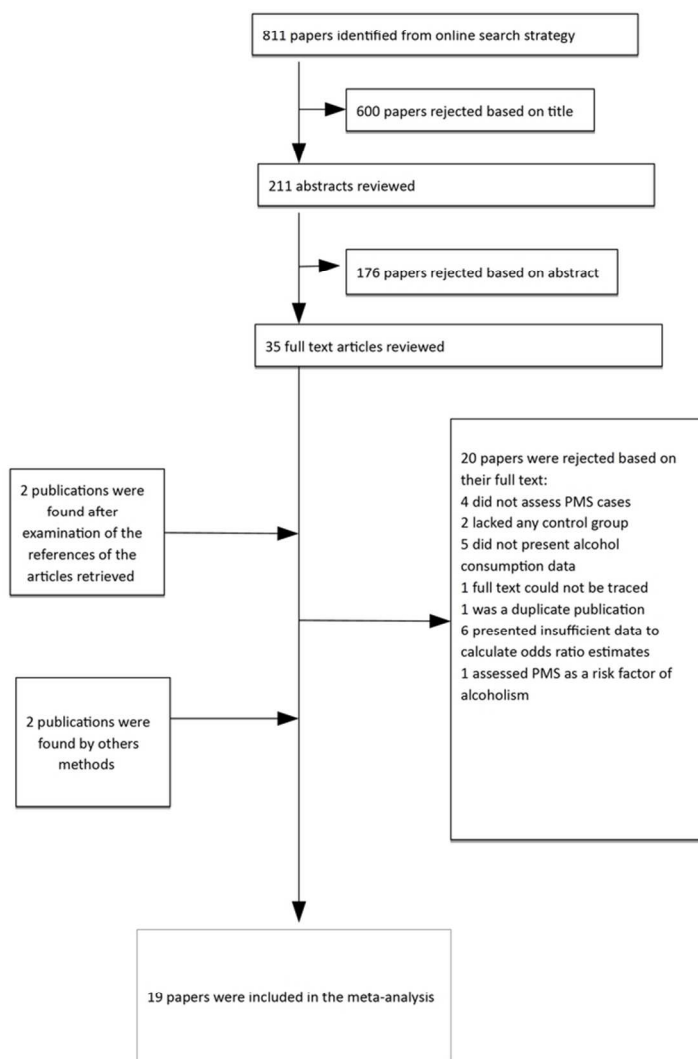


Figure 1. Flow diagram for study selection

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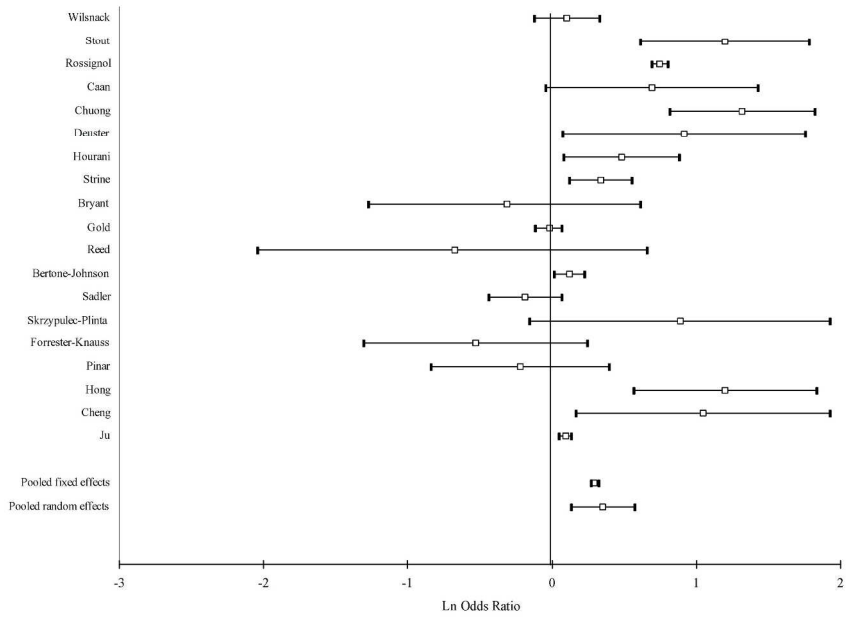


Figure 2. Forest plot of study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: any drinking

328x254mm (300 x 300 DPI)

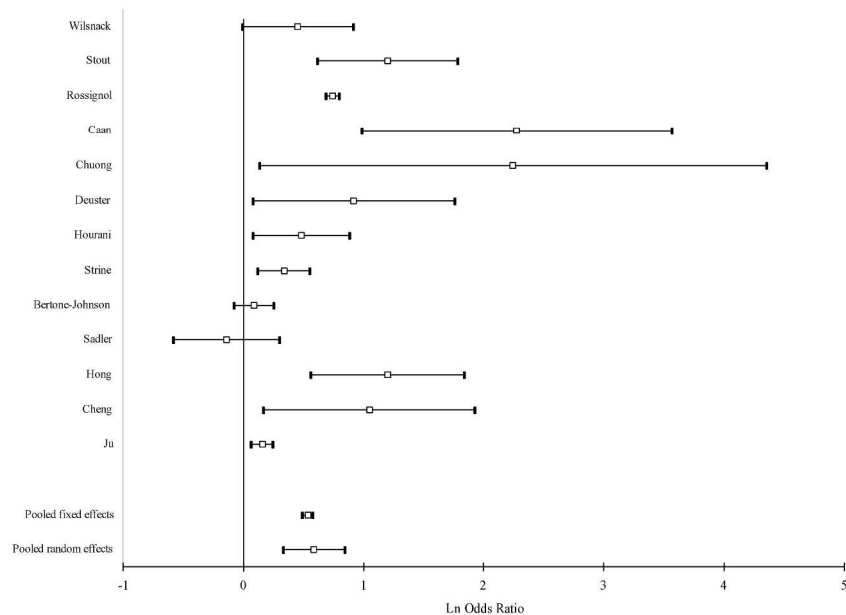


Figure 3. Forest plot of study-specific and pooled Odds Ratios of alcohol drinking and premenstrual syndrome: heavy drinking

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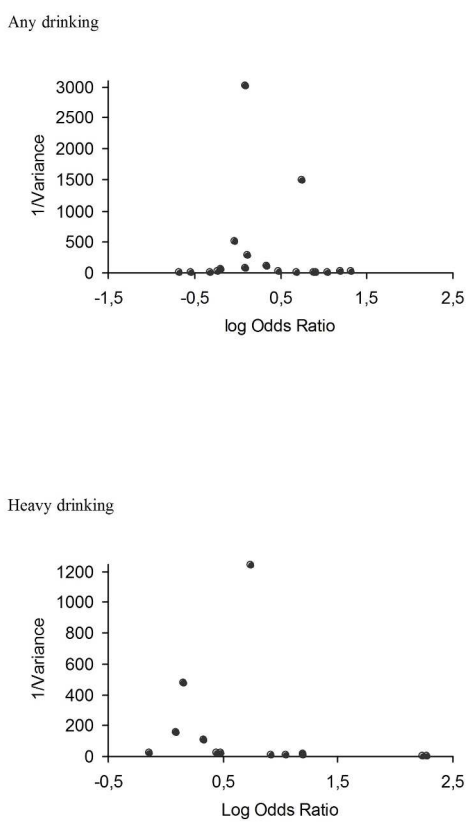


Figure 4: Funnel plot of log Odds Ratios versus standard error of log Odds Ratios of alcohol drinking and premenstrual syndrome

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.

2: Blainski A, Gionco B, Oliveira AG, Andrade G, Scarminio IS, Silva DB, Lopes NP, Mello JC. Antibacterial activity of Limonium brasiliense (Baicuru) against multidrug-resistant bacteria using a statistical mixture design. J Ethnopharmacol. 2017 Feb 23;198:313-323. doi: 10.1016/j.jep.2017.01.013. Epub 2017 Jan 13. PubMed PMID: 28089736.

3: İşik H, Ergöl Ş, Aynioğlu Ö, Şahbaz A, Kuzu A, Uzun M. Premenstrual syndrome and life quality in Turkish health science students. Turk J Med Sci. 2016 Apr 19;46(3):695-701. doi: 10.3906/sag-1504-140. PubMed PMID: 27513243.

4: Kepple AL, Lee EE, Haq N, Rubinow DR, Schmidt PJ. History of postpartum depression in a clinic-based sample of women with premenstrual dysphoric disorder. J Clin Psychiatry. 2016 Apr;77(4):e415-20. doi: 10.4088/JCP.15m09779. PubMed PMID: 27035701.

1
2
3 5: Timby E, Bäckström T, Nyberg S, Stenlund H, Wihlbäck AC, Bixo M. Women with
4 premenstrual dysphoric disorder have altered sensitivity to allopregnanolone over
5 the menstrual cycle compared to controls-a pilot study. *Psychopharmacology*
6 (Berl). 2016 Jun;233(11):2109-17. doi: 10.1007/s00213-016-4258-1. Epub 2016 Mar
7
8
9
10 10. PubMed PMID: 26960697.

11
12
13
14
15
16
17 6: Kim K, Hong JP, Cho MJ, Fava M, Mischoulon D, Lee DW, Heo JY, Jeon HJ. Loss of
18 sexual interest and premenstrual mood change in women with postpartum versus
19 non-postpartum depression: A nationwide community sample of Korean adults. *J*
20 *Affect Disord*. 2016 Feb;191:222-9. doi: 10.1016/j.jad.2015.11.050. Epub 2015 Dec
21
22
23 2. PubMed PMID: 26682491.

24
25
26
27
28
29
30
31 7: Doyle C, Swain WA, Ewald HA, Cook CL, Ewald PW. Sexually Transmitted Pathogens,
32 Depression, and Other Manifestations Associated with Premenstrual Syndrome. *Hum*
33 *Nat*. 2015 Sep;26(3):277-91. doi: 10.1007/s12110-015-9238-3. PubMed PMID:
34
35 26272230.

36
37
38
39
40
41
42 8: Ju H, Jones M, Mishra GD. Illicit drug use, early age at first use and risk of
43 premenstrual syndrome: A longitudinal study. *Drug Alcohol Depend*. 2015 Jul
44
45 1;152:209-17. doi: 10.1016/j.drugalcdep.2015.03.037. Epub 2015 Apr 17. PubMed
46
47
48 PMID: 25920763.

49
50
51
52
53
54 9: Goker A, Artunc-Ulkumen B, Aktenk F, Ikiz N. Premenstrual syndrome in Turkish
55
56
57
58
59
60

1
2
3 medical students and their quality of life. *J Obstet Gynaecol*. 2015 Apr;35(3):275-8.

4 doi: 10.3109/01443615.2014.948820. Epub 2014 Aug 20. PubMed PMID:

5
6 25140580.
7
8
9
10
11

12
13 10: Bäckström T, Bixo M, Johansson M, Nyberg S, Ossewaarde L, Ragagnin G,

14 Savic I, Strömberg J, Timby E, van Broekhoven F, van Wingen G. Allopregnanolone

15 and mood disorders. *Prog Neurobiol*. 2014 Feb;113:88-94. doi:

16
17 10.1016/j.pneurobio.2013.07.005. Epub 2013 Aug 23. Review. PubMed PMID: 23978486.
18
19
20
21
22

23
24 11: Cheng SH, Shih CC, Yang YK, Chen KT, Chang YH, Yang YC. Factors associated

25 with premenstrual syndrome - a survey of new female university students.

26
27 Kaohsiung J Med Sci. 2013 Feb;29(2):100-5. doi: 10.1016/j.kjms.2012.08.017.
28
29

30 Epub 2013 Jan 3. PubMed PMID: 23347812.
31
32
33
34
35
36

37 12: Kiesner J. Affective response to the menstrual cycle as a predictor of self-

38 reported affective response to alcohol and alcohol use. *Arch Womens Ment Health*.

39 2012 Dec;15(6):423-32. doi: 10.1007/s00737-012-0303-1. Epub 2012 Aug 23.
40
41

42 PubMed PMID: 22915027.
43
44
45
46
47
48

49 13: Li X, Gan Y, Zhang H, Qiao M, Hou Z, Guan Z, Liang M. [Study on preparation

50 method of Yueanjian for treatment of premenstrual syndrome]. *Zhongguo Zhong Yao*

51 *Za Zhi*. 2012 Apr;37(7):925-8. Chinese. PubMed PMID: 22792790.
52
53
54
55
56
57
58
59
60

1
2
3
4
5 14: Hong JP, Park S, Wang HR, Chang SM, Sohn JH, Jeon HJ, Lee HW, Cho SJ, Kim BS,
6 Bae JN, Cho MJ. Prevalence, correlates, comorbidities, and suicidal tendencies of
7 premenstrual dysphoric disorder in a nationwide sample of Korean women. Soc
8 Psychiatry Psychiatr Epidemiol. 2012 Dec;47(12):1937-45. doi:
9
10
11
12 10.1007/s00127-012-0509-6. Epub 2012 Apr 27. PubMed PMID: 22538387.
13
14

15
16
17
18
19 15: Wöber C. [Trigger factors in headache and migraine: myths and facts]. MMW
20 Fortschr Med. 2012 Feb 9;154(2):65-7. German. PubMed PMID: 22352256.
21
22
23
24
25

26
27 16: Forrester-Knauss C, Zemp Stutz E, Weiss C, Tschudin S. The interrelation
28 between premenstrual syndrome and major depression: results from a
29 population-based sample. BMC Public Health. 2011 Oct 12;11:795. doi:
30
31
32 10.1186/1471-2458-11-795. PubMed PMID: 21992230; PubMed Central PMCID:
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
PMC3209462.

17: Bäckström T, Haage D, Löfgren M, Johansson IM, Strömberg J, Nyberg S, Andréen L,
Ossewaarde L, van Wingen GA, Turkmen S, Bengtsson SK. Paradoxical effects of GABA-
A modulators may explain sexsteroid induced negative mood symptoms in some
persons. Neuroscience. 2011 Sep 15;191:46-54. doi:
10.1016/j.neuroscience.2011.03.061. Epub 2011 May 13. Review. PubMed PMID:
21600269.

1
2
3 18: Pinar G, Colak M, Oksuz E. Premenstrual Syndrome in Turkish college students
4 and its effects on life quality. Sex Reprod Healthc. 2011 Jan;2(1):21-7. doi:
5 10.1016/j.srhc.2010.10.001. Epub 2010 Oct 15. PubMed PMID: 21147455.
6
7
8
9

10
11
12 19: Nillni YI, Rohan KJ, Bernstein A, Zvolensky MJ. Premenstrual distress
13 predicts panic-relevant responding to a CO2 challenge among young adult females.
14 J Anxiety Disord. 2010 May;24(4):416-22. doi: 10.1016/j.janxdis.2010.02.006. Epub
15 2010 Feb 20. PubMed PMID: 20226625; PubMed Central PMCID: PMC2865427.
16
17
18
19
20
21
22
23

24
25 20: Sadler C, Smith H, Hammond J, Bayly R, Borland S, Panay N, Crook D, Inskip H;
26 Southampton Women's Survey Study Group. Lifestyle factors, hormonal contraception,
27 and premenstrual symptoms: the United Kingdom Southampton Women's Survey. J
28 Womens Health (Larchmt). 2010 Mar;19(3):391-6. doi:
29 10.1089/jwh.2008.1210. PubMed PMID: 20156129; PubMed Central PMCID: PMC3091016.
30
31
32
33
34
35
36
37
38

39 21: Bertone-Johnson ER, Hankinson SE, Johnson SR, Manson JE. Timing of alcohol
40 use and the incidence of premenstrual syndrome and probable premenstrual
41 dysphoric disorder. J Womens Health (Larchmt). 2009 Dec;18(12):1945-53. doi:
42 10.1089/jwh.2009.1468. PubMed PMID: 20044856; PubMed Central PMCID: PMC2828255.
43
44
45
46
47
48
49

50
51 22: Martini J, Wittchen HU, Soares CN, Rieder A, Steiner M. New women-specific
52 diagnostic modules: the Composite International Diagnostic Interview for
53 Women (CIDI-VENUS). Arch Womens Ment Health. 2009 Oct;12(5):281-9. doi:
54
55
56
57
58
59

1
2
3 10.1007/s00737-009-0077-2. Epub 2009 Jun 16. PubMed PMID: 19533302.
4
5
6
7

8
9 23: Nakade M, Takeuchi H, Kurotani M, Harada T. Effects of meal habits and
10 alcohol/cigarette consumption on morningness-eveningness preference and sleep
11 habits by Japanese female students aged 18-29. *J Physiol Anthropol*. 2009
12 Mar;28(2):83-90. PubMed PMID: 19346668.
13
14
15
16

17
18
19
20
21 24: Andréen L, Nyberg S, Turkmen S, van Wingen G, Fernández G, Bäckström T. Sex
22 steroid induced negative mood may be explained by the paradoxical effect mediated
23 by GABAA modulators. *Psychoneuroendocrinology*. 2009 Sep;34(8):1121-32. doi:
24 10.1016/j.psyneuen.2009.02.003. Epub 2009 Mar 9. Review. PubMed PMID: 19272715.
25
26
27
28

29
30
31
32 25: Fukui PT, Gonçalves TR, Strabelli CG, Lucchino NM, Matos FC, Santos JP,
33 Zukerman E, Zukerman-Guendler V, Mercante JP, Masruha MR, Vieira DS, Peres MF.
34 Trigger factors in migraine patients. *Arq Neuropsiquiatr*. 2008 Sep;66(3A):494-9.
35 PubMed PMID: 18813707.
36
37
38
39

40
41
42
43
44 26: Brozic P, Turk S, Lanisnik Rizner T, Gobec S. Discovery of new inhibitors of
45 aldo-keto reductase 1C1 by structure-based virtual screening. *Mol Cell*
46 *Endocrinol*. 2009 Mar 25;301(1-2):245-50. doi: 10.1016/j.mce.2008.08.002. Epub
47 2008 Aug 14. PubMed PMID: 18765269.
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 27: Reed SC, Levin FR, Evans SM. Changes in mood, cognitive performance and
4 appetite in the late luteal and follicular phases of the menstrual cycle in women with
5 and without PMDD (premenstrual dysphoric disorder). *Horm Behav*. 2008
6 Jun;54(1):185-93. doi: 10.1016/j.yhbeh.2008.02.018. Epub 2008 Mar 7. PubMed PMID:
7 18413151; PubMed Central PMCID: PMC2491904.
8
9
10
11
12

13
14
15
16
17 28: Hu Y, Hou TT, Zhang QY, Xin HL, Zheng HC, Rahman K, Qin LP. Evaluation of the
18 estrogenic activity of the constituents in the fruits of *Vitex rotundifolia* L.
19 for the potential treatment of premenstrual syndrome. *J Pharm Pharmacol*. 2007
20 Sep;59(9):1307-12. PubMed PMID: 17883902.
21
22
23
24
25
26
27

28
29 29: Gold EB, Bair Y, Block G, Greendale GA, Harlow SD, Johnson S, Kravitz HM,
30 Razor MO, Siddiqui A, Sternfeld B, Utts J, Zhang G. Diet and lifestyle factors associated
31 with premenstrual symptoms in a racially diverse community sample: Study of
32 Women's Health Across the Nation (SWAN). *J Womens Health (Larchmt)*. 2007
33 Jun;16(5):641-56. Erratum in: *J Womens Health (Larchmt)*. 2007 Jul-Aug;16(6):934.
34 PubMed PMID: 17627400.
35
36
37
38
39
40
41
42
43
44

45 30: Allsworth JE, Clarke J, Peipert JF, Hebert MR, Cooper A, Boardman LA. The
46 influence of stress on the menstrual cycle among newly incarcerated women.
47 *Womens Health Issues*. 2007 Jul-Aug;17(4):202-9. Epub 2007 Jun 7. PubMed PMID:
48 17560123; PubMed Central PMCID: PMC2170522.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 31: Shaver JL, Wilbur J, Robinson FP, Wang E, Buntin MS. Women's health issues
4 with fibromyalgia syndrome. *J Womens Health (Larchmt)*. 2006 Nov;15(9):1035-
5
6 45. PubMed PMID: 17125422.
7
8
9

10
11
12
13 32: Bryant M, Truesdale KP, Dye L. Modest changes in dietary intake across
14 the menstrual cycle: implications for food intake research. *Br J Nutr*. 2006
15 Nov;96(5):888-94. PubMed PMID: 17092378.
16
17
18

19
20
21
22
23 33: Svikis DS, Miles DR, Haug NA, Perry B, Hoehn-Saric R, McLeod D. Premenstrual
24 symptomatology, alcohol consumption, and family history of alcoholism in women
25 with premenstrual syndrome. *J Stud Alcohol*. 2006 Nov;67(6):833-6. PubMed PMID:
26
27 17060999.
28
29

30
31
32
33
34 34: Latthe P, Mignini L, Gray R, Hills R, Khan K. Factors predisposing women to
35 chronic pelvic pain: systematic review. *BMJ*. 2006 Apr 1;332(7544):749-55. Epub
36
37 2006 Feb 16. Review. PubMed PMID: 16484239; PubMed Central PMCID: PMC1420707.
38
39
40

41
42
43
44 35: N-Wihlbäck AC, Sundström-Poromaa I, Bäckström T. Action by and sensitivity to
45 neuroactive steroids in menstrual cycle related CNS disorders. *Psychopharmacology*
46 (Berl). 2006 Jun;186(3):388-401. Epub 2005 Dec 15. Review. PubMed PMID: 16362406.
47
48
49
50

51
52
53
54 36: Sein Anand J, Chodorowski Z, Ciechanowicz R, Wiśniewski M, Pankiewicz P. The
55
56
57

1
2 relationship between suicidal attempts and menstrual cycle in women. *Przegl Lek.*
3
4 2005;62(6):431-3. PubMed PMID: 16225087.
5
6
7
8
9

10
11 37: Nyberg S, Andersson A, Zingmark E, Wahlström G, Bäckström T, Sundström-
12 Poromaa I. The effect of a low dose of alcohol on allopregnanolone serum
13 concentrations across the menstrual cycle in women with severe premenstrual
14 syndrome and controls. *Psychoneuroendocrinology.* 2005 Oct;30(9):892-901. PubMed
15
16 PMID: 15979810.
17
18
19
20
21
22
23

24 38: Perry BL, Miles D, Burruss K, Svikis DS. Premenstrual symptomatology and
25 alcohol consumption in college women. *J Stud Alcohol.* 2004 Jul;65(4):464-8.
26
27 PubMed PMID: 15376821.
28
29
30
31
32
33

34 39: Smith SS, Ruderman Y, Hua Gong Q, Gulinello M. Effects of a low dose of
35 ethanol in an animal model of premenstrual anxiety. *Alcohol.* 2004 May;33(1):41-9.
36
37 PubMed PMID: 15353172; PubMed Central PMCID: PMC4168969.
38
39
40
41
42
43

44 40: Casanueva E. [Non-pregnant women's nutrition and its impact in life quality].
45
46 *Ginecol Obstet Mex.* 1999 Mar;67:104-12. Review. Spanish. PubMed PMID: 15338580.
47
48
49
50
51

52 41: Nyberg S, Wahlström G, Bäckström T, Sundström Poromaa I. Altered sensitivity
53
54 to alcohol in the late luteal phase among patients with premenstrual dysphoric
55
56
57
58
59
60

1
2
3 disorder. Psychoneuroendocrinology. 2004 Jul;29(6):767-77. PubMed PMID: 15110926.
4
5
6
7

8
9 42: Bäckström T, Andersson A, Andréé L, Birzniece V, Bixo M, Björn I, Haage D,
10 Isaksson M, Johansson IM, Lindblad C, Lundgren P, Nyberg S, Odmark IS,
11 Strömberg J, Sundström-Poromaa I, Turkmen S, Wahlström G, Wang M, Wihlbäck
12 AC, Zhu D, Zingmark E. Pathogenesis in menstrual cycle-linked CNS disorders. Ann
13 N Y Acad Sci. 2003 Dec;1007:42-53. Review. PubMed PMID: 14993039.
14
15
16
17
18
19
20
21
22

23 43: Kouri EM, Halbreich U. Effects of alcohol and other drugs in women of
24 reproductive age: hormonal interactions. Drugs Today (Barc). 1998
25 Oct;34(10):837-43. PubMed PMID: 14743255.
26
27
28
29
30
31
32

33 44: Peters TJ, Deacon AC. International air travel: a risk factor for attacks in
34 acute intermittent porphyria. Clin Chim Acta. 2003 Sep;335(1-2):59-63. PubMed
35 PMID: 12927685.
36
37
38
39
40
41
42

43 45: Bäckström T, Andreen L, Birzniece V, Björn I, Johansson IM, Nordenstam-Haghjo
44 M, Nyberg S, Sundström-Poromaa I, Wahlström G, Wang M, Zhu D. The role of
45 hormones and hormonal treatments in premenstrual syndrome. CNS Drugs.
46 2003;17(5):325-42. Review. PubMed PMID: 12665391.
47
48
49
50
51
52
53

54 46: Rothman RB, Baumann MH. Therapeutic and adverse actions of serotonin
55
56
57
58
59
60

1
2
3 transporter substrates. *Pharmacol Ther.* 2002 Jul;95(1):73-88. Review. PubMed
4 PMID: 12163129.
5
6
7
8
9

10
11 47: Sundstrom-Poromaa I, Smith DH, Gong QH, Sabado TN, Li X, Light A, Wiedmann M,
12 Williams K, Smith SS. Hormonally regulated alpha(4)beta(2)delta GABA(A) receptors
13 are a target for alcohol. *Nat Neurosci.* 2002 Aug;5(8):721-2. PubMed PMID: 12118257;
14 PubMed Central PMCID: PMC2887346.
15
16
17
18
19
20
21

22
23 48: Ottley C. Food and mood. *Nurs Stand.* 2000 Sep 27-Oct 3;15(2):46-52; quiz
24 54-5. Review. PubMed PMID: 11971416.
25
26
27
28
29
30

31 49: Rothman RB, Baumann MH. Serotonin releasing agents. Neurochemical,
32 therapeutic and adverse effects. *Pharmacol Biochem Behav.* 2002 Apr;71(4):825-36.
33 Review. PubMed PMID: 11888573.
34
35
36
37
38
39
40

41 50: Limosin F, Ades J. [Psychiatric and psychological aspects of premenstrual
42 syndrome]. *Encephale.* 2001 Nov-Dec;27(6):501-8. Review. French. PubMed
43 PMID: 11865558.
44
45
46
47
48
49
50

51 51: Johnson S. The multifaceted and widespread pathology of magnesium deficiency.
52 *Med Hypotheses.* 2001 Feb;56(2):163-70. PubMed PMID: 11425281.
53
54
55
56
57
58
59
60

1
2
3
4
5 52: Pollock BG. Citalopram: a comprehensive review. Expert Opin
6 Pharmacother. 2001 Apr;2(4):681-98. Review. PubMed PMID: 11336616.
7
8
9

10
11
12
13 53: Li C, Samsioe G, Lidfelt J, Nerbrand C, Agardh CD; Women's Health in Lund Area
14 (WHILA) Study. Important factors for use of hormone replacement therapy: a
15 population-based study of Swedish women. The Women's Health in Lund Area (WHILA)
16 Study. Menopause. 2000 Jul-Aug;7(4):273-81. PubMed PMID: 10914621.
17
18
19
20
21
22
23

24
25 54: Kritz-Silverstein D, Wingard DL, Garland FC. The association of behavior and
26 lifestyle factors with menstrual symptoms. J Womens Health Gen Based Med.
27 1999 Nov;8(9):1185-93. PubMed PMID: 10595332.
28
29
30
31
32
33

34
35 55: Deuster PA, Adera T, South-Paul J. Biological, social, and behavioral factors
36 associated with premenstrual syndrome. Arch Fam Med. 1999 Mar-Apr;8(2):122-8.
37 PubMed PMID: 10101982.
38
39
40
41
42
43

44
45 56: Smith SS, Gong QH, Li X, Moran MH, Bitran D, Frye CA, Hsu FC. Withdrawal from
46 3alpha-OH-5alpha-pregnan-20-One using a pseudopregnancy model alters the
47 kinetics of hippocampal GABAA-gated current and increases the GABAA receptor
48 alpha4 subunit in association with increased anxiety. J Neurosci. 1998 Jul
49 15;18(14):5275-84. PubMed PMID: 9651210.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5 57: Smith SS, Gong QH, Hsu FC, Markowitz RS, French-Mullen JM, Li X. GABA(A)
6
7 receptor alpha4 subunit suppression prevents withdrawal properties of an
8
9 endogenous steroid. *Nature*. 1998 Apr 30;392(6679):926-30. PubMed PMID: 9582073.
10
11
12
13

14
15 58: Allen D. Are alcoholic women more likely to drink premenstrually? *Alcohol*
16
17 *Alcohol*. 1996 Mar;31(2):145-7. PubMed PMID: 8737009.
18
19
20
21
22

23 59: Ragan PW. Greater alcohol use in women with PMS. *Am J Psychiatry*. 1995
24
25 Oct;152(10):1539-40. PubMed PMID: 7573607.
26
27
28
29
30

31 60: Chuong CJ, Burgos DM. Medical history in women with premenstrual syndrome.
32
33 *J Psychosom Obstet Gynaecol*. 1995 Mar;16(1):21-7. PubMed PMID: 7787954.
34
35
36
37
38

39 61: Tobin MB, Schmidt PJ, Rubinow DR. Reported alcohol use in women with
40
41 premenstrual syndrome. *Am J Psychiatry*. 1994 Oct;151(10):1503-4. PubMed PMID:
42
43 8092343.
44
45
46
47
48

49 62: McLeod DR, Foster GV, Hoehn-Saric R, Svikis DS, Hipsley PA. Family history of
50
51 alcoholism in women with generalized anxiety disorder who have premenstrual
52
53 syndrome: patient reports of premenstrual alcohol consumption and symptoms
54
55 of anxiety. *Alcohol Clin Exp Res*. 1994 Jun;18(3):664-70. PubMed PMID: 7943673.
56
57
58
59
60

1
2
3
4
5
6
7 63: Marks JL, Hair CS, Klock SC, Ginsburg BE, Pomerleau CS. Effects of menstrual
8 phase on intake of nicotine, caffeine, and alcohol and nonprescribed drugs in
9 women with late luteal phase dysphoric disorder. *J Subst Abuse*. 1994;6(2):235-43.
10 PubMed PMID: 7804022.
11
12
13
14

15
16
17
18
19 64: Caan B, Duncan D, Hiatt R, Lewis J, Chapman J, Armstrong MA. Association
20 between alcoholic and caffeinated beverages and premenstrual syndrome. *J Reprod*
21 *Med*. 1993 Aug;38(8):630-6. PubMed PMID: 8410870.
22
23
24
25

26
27
28
29 65: Fark AR. A pilot study of white-coat and labile hypertension: associations
30 with diagnoses of psychosocial dysfunction. *Fam Pract Res J*. 1993
31 Mar;13(1):71-80. PubMed PMID: 8484344.
32
33
34
35

36
37
38
39 66: Shibasaki M, Takeda K, Sumazaki R, Nogami T, Takita H. Premenstrual asthma
40 with seasonal variation. *Ann Allergy*. 1992 Apr;68(4):315-8. PubMed PMID: 1348404.
41
42
43
44

45
46
47 67: Tarczyoska-Nosal S, Ekiert M, Kostrzewska E. [Factors inducing clinical
48 symptoms of acute hepatic porphyria 1986-1990]. *Acta Haematol Pol*.
49 1991;22(1):100-4. Polish. PubMed PMID: 1823950.
50
51
52
53

1
2
3 68: Charette L, Tate DL, Wilson A. Alcohol consumption and menstrual distress
4 in women at higher and lower risk for alcoholism. *Alcohol Clin Exp Res*. 1990
5 Apr;14(2):152-7. PubMed PMID: 2190478.
6
7
8
9

10
11
12
13 69: Mello NK, Mendelson JH, Lex BW. Alcohol use and premenstrual symptoms
14 in social drinkers. *Psychopharmacology (Berl)*. 1990;101(4):448-55. PubMed
15 PMID: 2388970.
16
17
18
19

20
21
22
23 70: Christensen AP, Oei TP, Callan VJ. The relationship between
24 premenstrual dysphoria and daily ratings dimensions. *J Affect Disord*. 1989
25 Mar-Jun;16(2-3):127-32. PubMed PMID: 2522111.
26
27
28
29

30
31
32
33 71: Gannon L, Luchetta T, Pardie L, Rhodes K. Perimenstrual symptoms:
34 relationships with chronic stress and selected lifestyle variables. *Behav Med*.
35 1989 Winter;15(4):149-59. PubMed PMID: 2597778.
36
37
38
39

40
41
42
43 72: Garber MR, Kovalenko AE. [Effect of female sexsteroids on levels of
44 endogenous ethanol]. *Probl Endokrinol (Mosk)*. 1988 Jan-Feb;34(1):31-4.
45 Russian. PubMed PMID: 3362808.
46
47
48
49

50
51
52
53 73: Massil HY, O'Brien PM. Approach to the management of premenstrual
54 syndrome. *Clin Obstet Gynecol*. 1987 Jun;30(2):443-52. PubMed PMID: 3608284.
55
56
57
58

1
2
3
4
5
6
7 74: Mello NK, Mendelson JH, Palmieri SL. Cigarette smoking by women:
8 interactions with alcohol use. *Psychopharmacology (Berl)*. 1987;93(1):8-15.
9 PubMed PMID: 3114817.
10
11
12

13
14
15
16
17 75: Griffin ML, Mendelson JH, Mello NK, Lex BW. Marihuana use across the
18 menstrual cycle. *Drug Alcohol Depend*. 1986 Oct;18(2):213-24. PubMed PMID:
19 3780416.
20
21
22

23
24
25
26
27 76: Stout AL, Steege JF, Blazer DG, George LK. Comparison of lifetime psychiatric
28 diagnoses in Premenstrual Syndrome Clinic and community samples. *J Nerv Ment*
29 *Dis*. 1986 Sep;174(9):517-22. PubMed PMID: 3746277.
30
31
32

33
34
35
36
37 77: Halliday A, Bush B, Cleary P, Aronson M, Delbanco T. Alcohol abuse in women
38 seeking gynecologic care. *Obstet Gynecol*. 1986 Sep;68(3):322-6. PubMed PMID:
39 3737053.
40
41
42

43
44
45
46
47 78: Mello NK. Drug use patterns and premenstrual dysphoria. *NIDA Res*
48 *Monogr*. 1986;65:31-48. Review. PubMed PMID: 3090443.
49
50

51
52
53
54 79: Sutker PB, Allain AN, Brantley PJ, Randall CL. Acute alcohol intoxication,
55
56
57

1
2
3 negative affect, and autonomic arousal in women and men. *Addict Behav.*
4
5 1982;7(1):17-25. PubMed PMID: 7200716.
6
7
8
9

10
11 80: Wood C, Larsen L, Williams R. Social and psychological factors in relation to
12
13 premenstrual tension and menstrual pain. *Aust N Z J Obstet Gynaecol.* 1979
14
15 May;19(2):111-5. PubMed PMID: 292427.
16
17
18
19

20
21 81: Weissman MM, Klerman GL. Sex differences and the epidemiology of depression.
22
23 *Arch Gen Psychiatry.* 1977 Jan;34(1):98-111. Review. PubMed PMID: 319772.
24
25
26
27

28
29 82: Beckman LJ. Women alcoholics. A review of social and psychological studies. *J*
30
31 *Stud Alcohol.* 1975 Jul;36(7):797-824. Review. PubMed PMID: 240065.
32
33
34
35

36
37 83: Belfer ML, Shader RI, Carroll M, Harmatz JS. Alcoholism in women. *Arch Gen*
38
39 *Psychiatry.* 1971 Dec;25(6):540-4. PubMed PMID: 5168854.
40
41
42
43

44
45 84: Cermak I, Ringel R. [Clinical experiences with the new psychoactivator
46
47 *Deanxit (Melitracen and Flupenthixol)*]. *Schweiz Rundsch Med Prax.* 1971 Jun
48
49 8;60(23):757-62. German. PubMed PMID: 5104765.
50
51
52
53

54
55 85: Gerlach E. [What is the place for a depot sympathomimetic in gynecologic
56
57
58
59
60

1
2
3 practice?]. Hippokrates. 1969 Sep;40(18):727-31. German. PubMed PMID: 4390995.
4
5
6
7

8
9 86: AKERMAN R. [The efficacy of Vasculat in premenstrual, menstrual, pelviopathic
10 and climacteric disorders]. Wien Med Wochenschr. 1962 Mar 31;112:254-5.
11
12 German. PubMed PMID: 13859908.
13
14
15

16
17
18
19 87: AKERMAN R. [The effect of Vasculat in premenstrual, menstrual, pelviopathic
20 and climacteric disorders]. Wien Med Wochenschr. 1962 Mar 31;112:254-5.
21
22 German. PubMed PMID: 13859907.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
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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

Page 1 of 2

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

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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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