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# Effect of exercise on symptoms of premenstrual syndrome in low and middle-income countries: a protocol for systematic review and meta-analysis



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# Effect of exercise on symptoms of premenstrual syndrome in low and middle-income countries: a protocol for systematic review and meta-analysis

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**ABSTRACT**

**Introduction**

Premenstrual syndrome (PMS) has the potential to affect the quality of life (QOL) adversely. Published guidelines recommend the use of exercise as part of the first-line management interventions for PMS. However, the published evidence related to the effectiveness of physical activity and PMS is inconclusive. This review will assess the effectiveness of exercise-based interventions in reducing PMS in women screened or diagnosed with PMS in low and middle-income countries (LMICs), where the prevalence of PMS is high.

**Methods and Analysis**

Electronic databases will be researched, including Embase, CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, PsycINFO, Web of Science, and Google Scholar. A standardized data extraction form will be used adapted from the Cochrane Handbook of Systematic Reviews of Interventions. Included articles will be assessed using the risk of bias tools based on study design. Data will be analysed using Review Manager, version 5.3. The Inverse-variance random-effects method will be used to report the standardized mean difference (SMD). A meta-analysis will be used only if studies are sufficiently homogenous. A narrative synthesis will be undertaken when studies are heterogenous. Methodological heterogeneity between studies will be evaluated by considering the study types. Statistical heterogeneity will be tested using the $I^2$ test. Subgroup analyses may be performed only for the primary outcome in case of sufficient studies. Sensitivity analysis will be conducted to assess the impact of intervention excluding studies without randomization and studies with a high risk of bias. Funnel plots will be used to assess the potential reporting bias and small-study effects only when there are more than ten studies included in the meta-analysis.

**Ethics and Dissemination**

This study does not require ethical approval, as the review is entirely based on published studies. The results will be published and/or will be presented in a pertinent conference.

**PROPERO registration:** CRD42020163377.

**Keywords:** Premenstrual syndrome, exercise, low and middle-income countries, systematic review, meta-analysis.

**Article Summary**

**Strengths**

- This systematic review will provide robust evidence related to the effectiveness of exercise-based interventions in reducing PMS symptoms in women screened or diagnosed with PMS in LMICs.
- The findings of this systematic review will provide an important reference for stakeholders and clinicians from LMICs when treating patients with PMS.

**Limitations**

- Since articles with relevant information published in languages other than English will be excluded, it may lead to publication bias.
- We may not be able to undertake anticipated sub-group analyses due to the range of different types of exercise, duration, intensity, etc.

## INTRODUCTION

Premenstrual syndrome (PMS) is a menstrual disorder characterized by repetitive physical, behavioural and psychological symptoms. It usually starts 5-7 days before menstruation (at the end of the secretion phase of the menstrual cycle) and rapidly resolves 2-4 days after menstruation (in the follicular phase) (1). Globally, PMS affects more than 40 million women of reproductive age (2), with the highest prevalence in low- and middle-income countries (LMICs). A systematic review reported a worldwide prevalence of PMS with the highest prevalence in Africa (85%) and South America (60%) (3). A recent study in Nepal reported that 72% of university students had at least one symptom of PMS (4).

The common clinical and psychological symptoms of PMS include depression, mood fluctuations, nervousness, irritability, fatigue, over-eating, weight gain, breast tenderness, muscle and joint pain, abdominal bloating, diarrhoea, and performance reduction (5–7). Most study findings show that 5-8% of women have mild to severe symptoms while some studies estimate 20% of all fertile women experience clinically significant premenstrual complaints (8). Although the etiology of PMS remains unclear (9–12), the prevalence of PMS is higher in women who do not exercise, are obese and perform poorly in academics while the prevalence is lower among hormonal contraception users (11). Therefore, PMS as a distressing experience of women needs attention when trying to achieve a healthy life and gender equality in resource-poor settings.

The current management of PMS mostly targets symptom relief that includes non-pharmacological treatment, surgery, and medication (13). The combination of oral

contraceptives, selective serotonin reuptake inhibitors (SSRIs) and gonadotropin-releasing hormone analogues are major pharmacological methods. Non-pharmacological methods include lifestyle modification, cognitive behavior therapy (CBT), and dietary supplementation (8,12,14,15). Although SSRIs are the first-line management option for PMS, side effects are evident (16). A study found that aerobic exercise improves PMS symptoms in women by reducing the serum aldosterone and increasing estrogen and progesterone (17). Physical exercise has minimal risks or side effects and is a suitable management tool in the context of LMICs. Therefore, attention has been paid to non-drug treatments, particularly physical activity (18). The National Institute for Health and Care Excellence (NICE) guideline in the UK suggests lifestyle modifications such as exercise and balanced meals for management of mild to severe PMS along with other medications (19). Likewise, the Royal College of Obstetricians and Gynecologists recommends exercise and CBT as first-line management for PMS (20).

Several systematic reviews on PMS have been published but their main focus was limited to CBT, acupuncture, dietary supplementation and herbal remedies (9,21–23). Some physicians recommend exercise as an intervention but emphasize it as non-evidence-based therapy (12,14). Lack of a well-organized review for health care providers increases the burden of proposing scientifically verified management for PMS. Furthermore, there is no systematic review on the effectiveness of physical exercise on PMS in the context of LMICs where PMS poses a great burden. This systematic review and meta-analysis, therefore, will assess the effectiveness of exercise-based interventions in reducing PMS symptoms in women screened or diagnosed with PMS in LMICs.

## METHODS AND ANALYSIS

The planned study was conceptualized in December 2019 and anticipate ending in November 2020.

### Protocol registration

This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) by following the guidelines. The protocol of this systematic review aligns with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (24), along with the recommendations adopted from the meta-analysis of observational studies in epidemiology group (25).

### Inclusion and exclusion criteria

We will include studies on women of reproductive age (15-49 years) who meet either the screening or diagnosis criteria for PMS.

We will exclude studies that included women who are not of reproductive age or postmenopausal. We will also exclude studies on pregnant women and reproductive-aged women with psychiatric disorders and chronic diseases like breast cancer and diabetes. Also, we will exclude studies on women who are on any medication or mineral supplements for PMS and non-English studies. Studies carried out in any high-income country setting and studies with interventions comparing two different exercises without a control arm will also be excluded.

**Intervention**

A pre-defined intervention for this review is exercise, which was defined for this review as "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" (26). The intervention can include any form of cardio or resistance exercise or a combination of both for at least six weeks. Interventions like yoga will also be included as it includes physical exercise (asanas) primarily and has been shown to reduce symptoms of menstrual distress (27). Studies with a combination of interventions like factorial trials or noninferiority trials with multiple parallel arms where exercise intervention can be considered as the experimental variable will be included for this review.

**Comparator**

The studies using no intervention or usual care, or no treatment or placebo will be considered as comparators in this review.

**Outcome**

**Primary outcome**

The studies with the outcome reported as total or overall PMS symptom score measured by any validated screening tool or questionnaire (e.g. Premenstrual Symptoms Screening Tool (PSST) questionnaire) will be the primary outcome in this review.

**Secondary outcome**

The secondary outcome will be the accrued score for physical, behavioural, emotional or psychological symptoms, as measured by validated tools. Studies reporting only secondary outcomes will also be considered for inclusion.

**Study design**

We will include randomized controlled trials (parallel, cluster or individual), quasi-experimental studies and cohort studies.

**Setting**

The studies conducted in the community, clinical or hospital settings in low-income, lower-middle-income, and upper-middle-income countries will be included.

**Patient and public involvement**

No patient is involved in this study.

**Data sources and search strategy**

Multiple databases will be searched for the relevant research articles which include Embase, CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, PsycINFO, Web of Science, and Google Scholar. The search strategy for this review will be developed by adapting, expanding, blending and updating search strategies from Cochrane Gynaecology and Fertility search strategies (28). The search strategy will use the search terms presented in the supplementary file. The researched articles will then be limited using the filters for LMICs and the English language. All the eligible studies published until March 2020 will be included. A search strategy developed for MEDLINE is shown in the supplementary file. This search will be updated until the above-mentioned timeline.

**Selection of studies**

All the retrieved search results will be stored in an EndNote library. The duplicates will be removed and stored in a separate library. Titles followed by the abstracts of the studies retrieved from the search and other sources will be screened independently by two review authors (SU and PLG) to identify relevant studies meeting the inclusion criteria. The full text of the selected studies will then be subsequently reviewed by two independent reviewers (AK and JM) for eligibility. Discrepancies, if any, will be resolved through discussion with the other two reviewers (PP and JR) and the explanations for the decisions taken with regards to inclusion or exclusion of studies will be well documented as per PRISMA reporting guidelines for systematic reviews (29).

**Data extraction**

A standard data extraction form will be adapted from the Cochrane Handbook of Systematic Reviews of Interventions (30). The data extraction will be carried out independently by three

reviewers (SU, AK, and PLG) after piloting. The following data will be extracted from each selected study: author and year; the economic level of the country; study design; start date and end date; study duration; ethical approval obtained; population description; setting; sample size; lost to follow up; PMS diagnosis method, time postdiagnosis of PMS; co-morbidities; intervention type; timing or frequency of intervention; intervention provider and provider settings; compliance; time points measured and reported; questionnaire used; primary and secondary outcomes reported.

The authors will be contacted in case of missing data. In studies where standard deviations are lacking, imputation may be done considering the similarity of the scale used, intervention and sample size and effect size. This will be done in agreement among the authors of the review.

**Risk of bias and quality assessment**

The Cochrane risk of bias tool(31) will be used for quality assessment in randomized controlled trials while the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I)(32) will be used to assess the risk of bias in quasi-experimental studies and cohort studies. The assessment will be performed independently by three reviewers (JM, SU and PP) and discrepancies resolved by consulting other reviewers (JR and RMI) when necessary. Risk of bias graph and summary will be generated.

**Statistical analysis**

**Data synthesis**

Data will be analysed using Review Manager, version 5.3. As the primary outcome of this intervention is usually measured on a continuous scale, we will synthesize data retained from primary studies by meta-analysis using an inverse-variance random-effects method to report the standardized mean difference (SMD). The SMD will be used because we anticipate the PMS symptom scores to be reported using different tools such as the premenstrual symptoms screening tool (PSST) or Penn Daily Symptom Report (DSR). The random-effects method will be used for this analysis to allow for between-study differences in intervention effects.

A meta-analysis will be used only if the studies are sufficiently homogenous. If studies are not sufficiently homogenous ($I^2$ statistic > 75.0%), we will adopt a narrative synthesis. After discussing the baseline characteristics, types of intervention and outcomes considered in the studies, we will describe patterns across studies in terms of the magnitude and direction of any observed effects. We will consider factors that may account for conflicting results; considering the complexity and heterogeneity of assessing psychological and behavioural outcomes. We will present the data on tables; including information on participants, intervention, outcome measures, and magnitude and direction of effects. We will use vote counting cautiously to

conclude, taking into account the sample size of the studies. Three authors forming two groups (JM, SU, and AK) and (PP, JR, and PLG) will synthesize data separately and discrepancies will be resolved by discussion with RMI.

**Assessment of heterogeneity**

Clinical heterogeneity will be evaluated by considering differences in participants (such as age, parity, and occupation), type of intervention (such as jogging, swimming, and yoga) and outcomes considered (such as physical, psychological, and behavioral symptoms) across studies. Study methodological heterogeneity between studies will be evaluated by considering the study types (RCTs vs non-RCTs). Statistical heterogeneity will be tested using the $I^2$ statistic (33,34). We will explain any observed heterogeneity using subgroup and/or sensitivity analysis.

**Subgroup analysis**

Subgroup analyses may be performed only for the primary outcome in case of sufficient studies. Subgroup analyses may be conducted based on the economic level of the country, e.g. low-income countries versus lower-middle-income and upper-middle-income countries. Other subgroup analyses may be carried out by categorizing exercise intervention into cardio and strength training or mixed depending upon sufficient study types.

**Sensitivity analysis**

We will conduct a sensitivity analysis to assess the impact of excluding studies without randomization (non-RCTs). We will also conduct sensitivity analyses to assess the impact of exercise by excluding studies with a high risk of bias.

**Assessment of reporting biases**

Funnel plots will be used to assess the potential reporting bias and small-study effects only when there are more than ten studies in the meta-analysis. The quantification of publication bias will be done using Egger's regression test method (35).

**Confidence in cumulative evidence**

The studies included in the review will be critically appraised and synthesized in terms of methodological quality along with the relevance, strength, and limitations of the evidence presented. The similarities and differences between the studies in terms of their characteristics, design, and execution will be identified and their potential impact on study outcome will be explored. The results of the review will be interpreted only after evaluating the quality of the evidence (GRADE) and its pertinence.

## DISCUSSION

We have proposed a systematic review with a transparent and reproducible methodology to assess the effectiveness of exercise-based interventions in the management of PMS in LMICs. The strengths of this review include well-defined study and report characteristics of studies to be included, well-defined data sources, search strategy, data extraction and management and quality assessment procedures, and pre-defined data synthesis strategies. Potential limitations of this review include the scarcity of RCTs involving exercise-based interventions for PMS in LIMCs, the methodological quality of available studies, and the possibility of publication bias. Also, potential heterogeneity of exercise-based interventions, measurement tools, and types of outcomes evaluated may hinder ease of data synthesis.

As clinicians strive to mitigate the physical and psychological burden of PMS in LMICs, our findings will provide a basis for practice guidelines on the use of low-cost exercise-based interventions in relieving PMS symptoms.

### Ethical considerations

This study does not require ethical approval, as the review is entirely based on published studies and there is no human or animal interaction involved.

### Dissemination

The findings of the review will be published in a suitable peer-review journal and will also be disseminated in relevant gynaecology and obstetrics conferences drawing stakeholders and clinicians from LMICs.

### Author Contributions

PP is the guarantor of this review and conceived the review. PP, JR, RMI, and JM designed the review further while PP and RMI contributed to the development of the search strategy. PP, JM, SI, AK, and PLG were involved in the initial draft of the manuscript. JR and RMI were involved in subsequent draft manuscript reviews. All authors edited, modified and approved the final version of this protocol. All authors will contribute equally to data extraction, synthesis and drafting of the final review.

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**Competing interests**

The authors declare that they have no competing interests.

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Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 2019>
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | exp Premenstrual Syndrome/ | 3995 |
| 2 | premenstrual.tw. | 4911 |
| 3 | (Premenstrua$ adj5 Syndrome$).tw. | 2518 |
| 4 | premenstrual tension.tw. | 476 |
| 5 | (premenstrua$ adj5 tension$).tw. | 495 |
| 6 | (premenstrua$ adj5 dysphor$).tw. | 965 |
| 7 | (PMS or PMT).mp. | 7497 |
| 8 | (premenstrua$ adj5 stress).mp. | 86 |
| 9 | premenstrual stress.tw. | 10 |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 | 12117 |
| 11 | exp Exercise/ | 187652 |
| 12 | exp Exercise Therapy/ | 48688 |
| 13 | exercis*.tw. | 283524 |
| 14 | physical activity.mp. | 104833 |
| 15 | physical activit*.tw. | 105541 |
| 16 | exp Physical Fitness/ | 28723 |
| 17 | physical training.tw. | 5620 |
| 18 | (exercise adj1 intervention$).tw. | 5903 |
| 19 | behavio?r* change intervention$.tw. | 1350 |
| 20 | aerobic exercise.tw. | 8792 |
| 21 | yoga.tw. | 4373 |
| 22 | or/11-21 | 469524 |
| 23 | Developing Countries.sh,kf. | 84770 |
| 24 | (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or | 3612694 |

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| 25 | (low-income or middle-income or lowincome or middleincome or LMIC* or resource-poor or limited-resource* or resource-constrain*).mp. | 65592 |
| 26 | ((less* developed or least-developed or less-economically developed or least-economically developed or less-affluent or least-affluent or developing or underdeveloped or under-developed or emerging or middle income or low* income or underserved or under served or deprived or poor) adj (nation? or region or regions or economy or economies or countr* or population? or world)).mp. | 156355 |
| 27 | (africa* or asia* or west indies or caribbean or central america* or latin america* or south america* or melanesia* or micronesia* or polynesia*).mp. | 551652 |
| 28 | (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab. | 237 |
| 29 | (low adj3 middle adj3 countr*).ti,ab. | 14870 |
| 30 | (lmic or lmics or third world or lami countr*).ti,ab. | 7038 |
| 31 | transitional countr*.ti,ab. | 157 |
| 32 | or/23-31 | 3984303 |
| 33 | 10 and 22 and 32 | 49 |

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Status |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | √ |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | √ |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | √ |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | √ |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | √ |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | √ |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | √ |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | √ |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | √ |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | √ |
| Study records: | | | |

| | | | |
|---|---|---|---|
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | √ |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | √ |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | √ |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | √ |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | √ |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | √ |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | √ |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's τ) | √ |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | √ |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | √ |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | √ |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | √ |

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

BMJ Open

# Effect of exercise on symptoms of premenstrual syndrome in low and middle-income countries: a protocol for systematic review and meta-analysis

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| Secondary Subject Heading: | Public health, Epidemiology |
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| | |

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# Effect of exercise on symptoms of premenstrual syndrome in low and middle-income countries: a protocol for systematic review and meta-analysis

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**ABSTRACT**

**Introduction**

Premenstrual syndrome (PMS) has the potential to affect the quality of life (QOL) adversely. Published guidelines recommend the use of exercise as part of the first-line management interventions for PMS. However, the published evidence related to the effectiveness of physical activity and PMS is inconclusive. This review will assess the effectiveness of exercise-based interventions in reducing PMS in women screened or diagnosed with PMS in low and middle-income countries (LMICs), where the prevalence of PMS is high.

**Methods and Analysis**

Electronic databases will be researched, including Embase, CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, PsycINFO, Web of Science, ClinicalTrials.gov, and Google Scholar. All the studies published until March 2020 will be included. A standardized data extraction form will be used adapted from the Cochrane Handbook of Systematic Reviews of Interventions. Included articles will be assessed using the risk of bias tools based on study design. Data will be analysed using Review Manager, version 5.3. The Inverse-variance random-effects method will be used to report the standardized mean difference (SMD). A meta-analysis will be used only if studies are sufficiently homogenous. A narrative synthesis will be undertaken when studies are heterogenous. Methodological heterogeneity between studies will be evaluated by considering the study types. Statistical heterogeneity will be tested using the $I^2$ test. Subgroup analyses may be performed only for the primary outcome in case of sufficient studies. Sensitivity analysis will be conducted to assess the impact of intervention excluding studies without randomization and studies with a high risk of bias. Funnel plots will be used to assess the potential reporting bias and small-study effects only when there are more than ten studies included in the meta-analysis.

**Ethics and Dissemination**

This study does not require ethical approval, as the review is entirely based on published studies. The results will be published and/or will be presented at a pertinent conference.

**PROPERO registration:** CRD42020163377.

**Keywords:** Premenstrual syndrome, exercise, low and middle-income countries, systematic review, meta-analysis.

**Article Summary**

**Strengths**

- This systematic review will provide robust evidence related to the effectiveness of exercise-based interventions in reducing PMS symptoms in women screened or diagnosed with PMS in LMICs.
- The findings of this systematic review will provide an important reference for stakeholders and clinicians from LMICs when treating patients with PMS.

**Limitations**

- Since articles with relevant information published in languages other than English will be excluded, it may lead to publication bias.
- We may not be able to undertake anticipated sub-group analyses due to the range of different types of exercise, duration, intensity, etc.

## INTRODUCTION

Premenstrual syndrome (PMS) is a menstrual disorder characterized by repetitive physical, behavioural and psychological symptoms. It usually starts 5-7 days before menstruation (at the end of the secretory phase of the menstrual cycle) and rapidly resolves 2-4 days after menstruation (in the follicular phase) (1). Globally, 90% women of reproductive age experience severe premenstrual symptoms while 20-40% experience PMS (2), with the highest prevalence reported in low- and middle-income countries (LMICs). A systematic review reported 30-99.5% prevalence of PMS in Iran(3). While, a recent study in Nepal reported that 72% of university students had at least one symptom of PMS (4).

The common clinical and psychological symptoms of PMS include depression, mood fluctuations, nervousness, irritability, fatigue, over-eating, weight gain, breast tenderness, muscle and joint pain, abdominal bloating, diarrhoea, and performance reduction (5–7). Most study findings show that 5-8% of women have mild to severe symptoms while some studies estimate 20% of all fertile women experience clinically significant premenstrual complaints (8). Although the etiology of PMS remains unclear (9–12), the prevalence of PMS is higher in women who do not exercise, are obese and perform poorly in academics while the prevalence is lower among hormonal contraception users (11). Therefore, PMS as a distressing experience of women needs attention when trying to achieve a healthy life and gender equality in resource-poor settings.

The current management of PMS mostly targets symptom relief that includes non-pharmacological treatment, surgery, and medication (13). The combination of oral contraceptives, selective serotonin reuptake inhibitors (SSRIs) and gonadotropin-releasing hormone analogues are major pharmacological methods. Non-pharmacological methods include lifestyle modification, cognitive behavior therapy (CBT), and dietary supplementation (8,12,14,15). Although SSRIs are the first-line management option for PMS, side effects are evident (16). A study found that aerobic exercise improves PMS symptoms in women by reducing the serum aldosterone and increasing estrogen and progesterone (17). Physical exercise has minimal risks or side effects and is a suitable management tool in the context of LMICs. Therefore, attention has been paid to non-drug treatments, particularly physical activity (18). The National Institute for Health and Care Excellence (NICE) guideline in the UK suggests lifestyle modifications such as exercise and balanced meals for management of mild to severe PMS along with other medications (19). Likewise, the Royal College of Obstetricians and Gynecologists recommends exercise and CBT as first-line management for PMS (20).

Several systematic reviews on PMS have been published but their main focus was limited to CBT, acupuncture, dietary supplementation and herbal remedies (9,21–23). Some physicians recommend exercise as an intervention but emphasize it as non-evidence-based therapy (12,14). Lack of a well-organized review for health care providers increases the burden of proposing scientifically verified management for PMS. Furthermore, there is no systematic review on the effectiveness of physical exercise on PMS in the context of LMICs where PMS poses a great burden. This systematic review and meta-analysis, therefore, will assess the effectiveness of exercise-based interventions in reducing PMS symptoms in women screened or diagnosed with PMS in LMICs.

## METHODS AND ANALYSIS

The planned study was conceptualized in December 2019 and anticipate ending in November 2020.

### Protocol registration

This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) by following the guidelines. The protocol of this systematic review aligns with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (24), along with the recommendations adopted from the meta-analysis of observational studies in epidemiology group (25).

**Inclusion and exclusion criteria**

We will include studies on women of reproductive age (15-49 years) who meet either the screening or diagnostic criteria for PMS. Validated symptom screening tool such as Premenstrual Symptoms Screening Tool (PSST) or established diagnostic tool such as DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) should have been used for inclusion.

We will exclude studies that included women who are either pregnant or of non-reproductive age. We will also exclude studies on reproductive-aged women with psychiatric disorders and chronic diseases like breast cancer and diabetes to reduce misclassification of symptoms due to other causes except PMS. Also, we will exclude studies on women who are on any medication or mineral supplements for PMS and non-English studies. Studies carried out in any high-income country setting and studies with interventions comparing two different exercises without a control arm will also be excluded. Countries will be classified as low, middle- or high-income according to World Bank's classification criteria (26).

**Intervention**

A pre-defined intervention for this review is exercise, which was defined for this review as "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" (27). The intervention can include any form of cardio or resistance exercise or a combination of both for at least six weeks. Interventions like yoga will also be included as it includes physical exercise (asanas) primarily and has been shown to reduce symptoms of menstrual distress (28). Hence, no limitation will be applied for exercise type. Studies with a combination of interventions like factorial trials or noninferiority trials with multiple parallel arms where exercise intervention can be considered as the experimental variable will be included for this review.

**Comparator**

The studies using no intervention or usual care, or no treatment or placebo will be considered as comparators in this review.

**Outcome**

**Primary outcome**

The studies with the outcome reported as total or overall PMS symptom score measured by any validated screening tool or questionnaire (e.g. PSST questionnaire) will be the primary outcome in this review.

**Secondary outcome**

The secondary outcome will be the Quality of Life (QoL) score and accumulated score for physical, behavioural, emotional or psychological symptoms, as measured by validated tools. Studies reporting only secondary outcomes will also be considered for inclusion.

**Study design**

We will include randomized controlled trials (parallel, cluster or individual), quasi-experimental studies and cohort studies.

**Setting**

The studies conducted in the community, clinical or hospital settings in low-income, lower-middle-income, and upper-middle-income countries will be included.

**Patient and public involvement**

No patient is involved in either the design or planning phase of this study.

**Data sources and search strategy**

Multiple databases will be searched for the relevant research articles which include Embase, CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, PsycINFO, Web of Science, ClinicalTrials.gov and Google Scholar. The search strategy for this review will be developed by adapting, expanding, blending and updating search strategies from Cochrane Gynaecology and Fertility search strategies (29). The search strategy will use the search terms presented in the Supplementary file 1. The researched articles will then be limited using the filters for LMICs and the English language. All the eligible studies published until March 2020 will be included. A search strategy developed for MEDLINE is shown in the supplementary file. This search will be updated until the above-mentioned timeline.

**Selection of studies**

All the retrieved search results will be stored in an EndNote library. The duplicates will be removed and stored in a separate library. Titles followed by the abstracts of the studies retrieved from the search and other sources will be screened independently by two review authors (SU and PLG) to identify relevant studies meeting the inclusion criteria. The full text of the selected studies will then be subsequently reviewed by two independent reviewers (AK and

JM) for eligibility. Discrepancies, if any, will be resolved through discussion with the other two reviewers (PP and JR) and the explanations for the decisions taken with regards to inclusion or exclusion of studies will be well documented as per PRISMA reporting guidelines for systematic reviews (30).

**Data extraction**

A standard data extraction form will be adapted from the Cochrane Handbook of Systematic Reviews of Interventions (31). The data extraction will be carried out independently by three reviewers (SU, AK, and PLG) after piloting. The following data will be extracted from each selected study: author and year; the economic level of the country; study design; start date and end date; study duration; ethical approval obtained; population description; setting; sample size; lost to follow up; PMS diagnosis method, time postdiagnosis of PMS; co-morbidities; intervention type; timing or frequency of intervention; intervention provider and provider settings; compliance; time points measured and reported; questionnaire used; primary and secondary outcomes reported.

The authors will be contacted in case of missing data. In studies where standard deviations are lacking, imputation may be done considering the similarity of the scale used, intervention and sample size and effect size. This will be done in agreement among the authors of the review.

**Risk of bias and quality assessment**

The Cochrane risk of bias tool(32) will be used for quality assessment in randomized controlled trials while the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I)(33) will be used to assess the risk of bias in quasi-experimental studies and cohort studies. The assessment will be performed independently by three reviewers (JM, SU and PP) and discrepancies resolved by consulting other reviewers (JR and RMI) when necessary. Risk of bias graph and summary will be generated.

**Statistical analysis**

**Data synthesis**

Data will be analysed using Review Manager, version 5.3. As the primary outcome of this intervention is usually measured on a continuous scale, we will synthesize data retained from primary studies by meta-analysis using an inverse-variance random-effects method to report the standardized mean difference (SMD). The SMD will be used because we anticipate the PMS symptom scores to be reported using different tools such as the premenstrual symptoms screening tool (PSST) or Penn Daily Symptom Report (DSR). The random-effects method will be used for this analysis to allow for between-study differences in intervention effects.

A meta-analysis will be used only if the studies are sufficiently homogenous. If studies are not sufficiently homogenous ($I^2$ statistic > 75.0%), we will adopt a narrative synthesis. After discussing the baseline characteristics, types of intervention and outcomes considered in the studies, we will describe patterns across studies in terms of the magnitude and direction of any observed effects. We will consider factors that may account for conflicting results; considering the complexity and heterogeneity of assessing psychological and behavioural outcomes. We will present the data on tables; including information on participants, intervention, outcome measures, and magnitude and direction of effects. We will use vote counting cautiously to conclude, taking into account the sample size of the studies. Three authors forming two groups (JM, SU, and AK) and (PP, JR, and PLG) will synthesize data separately and discrepancies will be resolved by discussion with RMI.

**Assessment of heterogeneity**

Clinical heterogeneity will be evaluated by considering differences in participants (such as age, parity, and occupation), type of intervention (such as jogging, swimming, and yoga) and outcomes considered (such as physical, psychological, and behavioral symptoms) across studies. Study methodological heterogeneity between studies will be evaluated by considering the study types (RCTs vs non-RCTs). Statistical heterogeneity will be tested using the $I^2$ statistic, to quantify discrepancy across studies. $I^2$ statistic of 75% and more indicates significant heterogeneity between studies (34,35). We will explain any observed heterogeneity using subgroup and/or sensitivity analysis.

**Subgroup analysis**

Subgroup analyses may be performed only for the primary outcome in case of sufficient studies. Subgroup analyses may be conducted based on the economic level of the country, e.g. low-income countries versus lower-middle-income and upper-middle-income countries. Other subgroup analyses may be carried out by categorizing exercise intervention into cardio and strength training or mixed depending upon sufficient study types.

**Sensitivity analysis**

We will conduct a sensitivity analysis to assess the impact of excluding studies without randomization (non-RCTs). We will also conduct sensitivity analyses to assess the impact of exercise by excluding studies with a high risk of bias.

**Assessment of reporting biases**

Funnel plots will be used to assess the potential reporting bias and small-study effects only when there are more than ten studies in the meta-analysis. The quantification of publication bias will be done using Egger's regression test method (36).

**Confidence in cumulative evidence**

The studies included in the review will be critically appraised and synthesized in terms of methodological quality along with the relevance, strength, and limitations of the evidence presented. The similarities and differences between the studies in terms of their characteristics, design, and execution will be identified and their potential impact on study outcome will be explored. The results of the review will be interpreted only after evaluating the quality of the evidence (GRADE) and its pertinence.

**DISCUSSION**

We have proposed a systematic review with a transparent and reproducible methodology to assess the effectiveness of exercise-based interventions in the management of PMS in LMICs. The strengths of this review include well-defined study and report characteristics of studies to be included, well-defined data sources, search strategy, data extraction and management and quality assessment procedures, and pre-defined data synthesis strategies. Potential limitations of this review include the scarcity of RCTs involving exercise-based interventions for PMS in LIMCs, the methodological quality of available studies, and the possibility of publication bias. Also, potential heterogeneity of exercise-based interventions, measurement tools, and types of outcomes evaluated may hinder ease of data synthesis.

As clinicians strive to mitigate the physical and psychological burden of PMS in LMICs, our findings will provide a basis for practice guidelines on the use of low-cost exercise-based interventions in relieving PMS symptoms.

**Ethics and dissemination**

This study does not require ethical approval, as the review is entirely based on published studies and there is no human or animal interaction involved.

The findings of the review will be published in a suitable peer-review journal and will also be disseminated in relevant gynaecology and obstetrics conferences drawing stakeholders and clinicians from LMICs.

**Author Contributions**

PP is the guarantor of this review and conceived the review. PP, JR, RMI, and JM designed the review further while PP and RMI contributed to the development of the search strategy. PP, JM,

SU, AK, and PLG were involved in the initial draft of the manuscript. JR and RMI were involved in subsequent draft manuscript reviews. All authors edited, modified and approved the final version of this protocol. All authors will contribute equally to data extraction, synthesis and drafting of the final review.

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**Competing interests**

The authors declare that they have no competing interests.

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Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 2019>
Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | exp Premenstrual Syndrome/ | 3995 |
| 2 | premenstrual.tw. | 4911 |
| 3 | (Premenstrua$ adj5 Syndrome$).tw. | 2518 |
| 4 | premenstrual tension.tw. | 476 |
| 5 | (premenstrua$ adj5 tension$).tw. | 495 |
| 6 | (premenstrua$ adj5 dysphor$).tw. | 965 |
| 7 | (PMS or PMT).mp. | 7497 |
| 8 | (premenstrua$ adj5 stress).mp. | 86 |
| 9 | premenstrual stress.tw. | 10 |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 | 12117 |
| 11 | exp Exercise/ | 187652 |
| 12 | exp Exercise Therapy/ | 48688 |
| 13 | exercis*.tw. | 283524 |
| 14 | physical activity.mp. | 104833 |
| 15 | physical activit*.tw. | 105541 |
| 16 | exp Physical Fitness/ | 28723 |
| 17 | physical training.tw. | 5620 |
| 18 | (exercise adj1 intervention$).tw. | 5903 |
| 19 | behavio?r* change intervention$.tw. | 1350 |
| 20 | aerobic exercise.tw. | 8792 |
| 21 | yoga.tw. | 4373 |
| 22 | or/11-21 | 469524 |
| 23 | Developing Countries.sh,kf. | 84770 |
| 24 | (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or | 3612694 |

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|---|---|---|
| | Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,kf,ti,ab,cp. | |
| 25 | (low-income or middle-income or lowincome or middleincome or LMIC* or resource-poor or limited-resource* or resource-constrain*).mp. | 65592 |
| 26 | ((less* developed or least-developed or less-economically developed or least-economically developed or less-affluent or least-affluent or developing or underdeveloped or under-developed or emerging or middle income or low* income or underserved or under served or deprived or poor) adj (nation? or region or regions or economy or economies or countr* or population? or world)).mp. | 156355 |
| 27 | (africa* or asia* or west indies or caribbean or central america* or latin america* or south america* or melanesia* or micronesia* or polynesia*).mp. | 551652 |
| 28 | (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab. | 237 |
| 29 | (low adj3 middle adj3 countr*).ti,ab. | 14870 |
| 30 | (lmic or lmics or third world or lami countr*).ti,ab. | 7038 |
| 31 | transitional countr*.ti,ab. | 157 |
| 32 | or/23-31 | 3984303 |
| 33 | 10 and 22 and 32 | 49 |