## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Protocol: a systematic review and meta-analysis of prevalence of, and risk factors for, pelvic floor disorders in community-dwelling women in low-and-middle income countries |
| **AUTHORS** | Islam, Rakibul; Oldroyd, John; Karim, Md; Hussain, Monira; Hoque, Dewan; Romero, Lorena; Fisher, Jane |

## VERSION 1 - REVIEW

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| **REVIEWER** | Karen D Cowgill, PhD, MSc<br>Assistant Professor<br>University of Washington Tacoma<br>USA |
| **REVIEW RETURNED** | 07-Jan-2017 |

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| **GENERAL COMMENTS** | This article presents the protocol for a proposed systematic review of pelvic-floor disorders in community-dwelling women in low- and middle-income countries.<br>A strength of the proposed study is the inclusion of a librarian and the creation of a powerful search strategy.<br>Issues that should be addressed or elaborated on include the background and justification for the study and the statistical analyses.<br>Below are some specific comments and questions:<br>The background could go into greater detail about the mechanisms of injuries that lead to pelvic-floor disorders. Although age, parity, obesity, and vaginal birth are listed as the main risk factors, how the disorders are related to these and how they arise would be important for the general reader to know. This explanation would also provide better support for the statement (p. 4, lines 21-28) about reasons that PFD may be more prevalent among women in LMICs than in HICs, which is the main justification for the proposed systematic review.<br>p. 4, line 24 – please clarify how increasing life expectancy of women in LMICs would be expected to raise these women's risk of PFDs relative to women in HICs.<br>p. 4, lines 30-40 – please discuss further the results of the earlier review. You state that the proposed review will describe reasons for variations in reported prevalence, but it is not clear from the Statistical analysis section how it will achieve this.<br>p. 5, line 1 – why use MEDLINE instead of PubMed, when PubMed includes all of MEDLINE and more?<br>p. 5, lines 34-39 – the terms listed here don't quite align with the search strategy shown in Table 1 (e.g., no permutation of the term "anal incontinence" appears in the search strategy)<br>Table 1, title – what is the scientific rationale for searching MEDLINE all the way back to its inception in 1946? How would articles from the 40s, 50s, or 60s address the stated objectives of the review, |

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| | given that both demographic and epidemiological transitions have occurred in many countries over the past 70 years?<br>Table 1, line 9 – has this line been truncated? Presumably the search strategy includes all World Bank-classified LMICs by name, and not just the 7 shown here?<br>p. 6, line 37 – since PFD is itself a "debilitating condition", how are you defining "healthy" here? Perhaps it would be clearer to omit this criterion and rely on the exclusion of women with co-morbidities as shown at the top of p. 7.<br>p. 7, lines 19-20 – please clarify the reasons for excluding employed women. Does this apply only to employment in the formal sector? Is it education per se, or access to / use of health care services that distinguishes these women?<br>p. 7, line 30 – earlier you state that conference websites will be searched for grey literature, but here you say conference abstracts and posters will be excluded. Please clarify which conference resources, if any, would be included.<br>p. 7, line 40 – "will be distributed among [sic] two review authors" – does this mean the studies will be divided and each paper will be reviewed for inclusion by only one author? Recommended practice is for all studies to be reviewed by at least 2 authors.<br>p. 8, line 10 – PRISMA-P is appropriate for the current article. The review itself should follow guidelines of a checklist like MOOSE.<br>p. 8, lines 22-23 – why specify restricted access to data when the study does not include confidential data and is exempt from IRB review?<br>p. 8, line 56 – I suggest you include the "criteria" column for each item in the Hoy tool to facilitate and optimize reliability of the review.<br>p. 9, lines 42-45 – the description of the meta-regression and its purpose is confusing and seems incomplete. How will the meta-regression identify sources of heterogeneity? How does this differ from the subgroup analysis described on the following page? Please refer to Cochrane Handbook part 2, section 9.6.4, and please cite a methodological reference for this method rather than, or in addition to, reference [17]. Also note that meta-regression should be used only if there are 10 or more studies in the meta-analysis.<br>p. 10, lines 8-10 – the description of the assessment of heterogeneity is confusing. The actual value of I2 should be used to assess the degree of heterogeneity, and the cut-offs for low, moderate, and high heterogeneity should be specified. The significance can be determined by a chi-squared for Q, but the null hypothesis is that there is no heterogeneity, so a p-value > 0.05 (or 0.10 if there are few studies, since Q has low power in this case) would be a desirable result.<br>p. 11, line 16 – it seems that the results of the review are a foregone conclusion?<br>p. 11, line 23 – the protocol has not adequately addressed how the risk factors for PFDs will be elucidated.<br>Throughout the manuscript, there are minor grammatical and typographical errors that should be corrected (for example, incorrect subject-verb agreement on p. 1 at lines 10, 12, 17; "detail" on p. 9 at line 29 should be corrected to "detailed" "obtained" on p. 11 at line 6 should be corrected to "obtain"; "perspective" on p. 11 at line 28 should be corrected to "prospective"; typos and internal notes in Data Extraction Form; a space should be entered before each bracketed number where references are cited). |

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| **REVIEWER** | Ewa Barcz<br>Ist Department and Clinic of Obstetrics and Gynecology Medical University of Warsaw<br>Poland |
| **REVIEW RETURNED** | 26-Feb-2017 |

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| **GENERAL COMMENTS** | Interesting subject with well design protocol |

## VERSION 1 – AUTHOR RESPONSE

REVIEWER:1

Reviewer:1

This article presents the protocol for a proposed systematic review of pelvic-floor disorders in community-dwelling women in low- and middle-income countries.
A strength of the proposed study is the inclusion of a librarian and the creation of a powerful search strategy. Issues that should be addressed or elaborated on include the background and justification for the study and the statistical analyses. Below are some specific comments and questions:
Comment: The background could go into greater detail about the mechanisms of injuries that lead to pelvic-floor disorders. Although age, parity, obesity, and vaginal birth are listed as the main risk factors, how the disorders are related to these and how they arise would be important for the general reader to know. This explanation would also provide better support for the statement (p. 4, lines 21-28) about reasons that PFD may be more prevalent among women in LMICs than in HICs, which is the main justification for the proposed systematic review.
Authors' Response: Thank you very much. We have now included a sentence which describes the mechanisms of injuries and the interrelationship between risk factors that lead to pelvic floor disorders.

Comment: p. 4, line 24 – please clarify how increasing life expectancy of women in LMICs would be expected to raise these women's risk of PFDs relative to women in HICs.
Authors' Response: Increasing life expectancy of women in LMICs would be expected to raise these women's risk of PFDs because increased age is a risk factor for PFDs. This has been clarified in the text.

Comment: p. 4, lines 30-40 – please discuss further the results of the earlier review. You state that the proposed review will describe reasons for variations in reported prevalence, but it is not clear from the Statistical analysis section how it will achieve this.
Authors' Response: Thank you for your comment. The reasons for variations in reported prevalence between studies will be explained descriptively first taking into account differences in methodologies of the studies. For instance, we will see whether the variation in reported prevalence is due to sampling procedures (random vs non-random), representativeness of the study (representative vs non-representative), validation of the questionnaires (validated vs non-validated), duration of symptoms over which question was asked (short vs long) and so on. In addition, reasons for variations will be addressed using heterogeneity test of I2, which is discussed under the relevant section in the protocol.

Comment: p. 5, line 1 – why use MEDLINE instead of PubMed, when PubMed includes all of MEDLINE and more?
Authors' Response: We use 3 segments of Medline all via the OVID search software. The 3 segments total over 26 million records) whereas PubMed has 25 million records so we believe we are not missing out on records. In addition to OVID Medline we will also search Embase which has over 29

million records. Added to these 2 are the other databases we will search such as CINAHL, PSYCINFO and Maternity & Infant Care. The combined results from all of these databases will be well in excess of what PubMed covers.
We use the OVID search platform as it has extensive software functionality that is essential for systematic review searches. We need to do Proximity searches and inword truncation and various other advanced techniques that the PubMed search platform cannot perform.

Comment: p. 5, lines 34-39 – the terms listed here don't quite align with the search strategy shown in Table 1 (e.g., no permutation of the term "anal incontinence" appears in the search strategy)
Table 1, title – what is the scientific rationale for searching MEDLINE all the way back to its inception in 1946? How would articles from the 40s, 50s, or 60s address the stated objectives of the review, given that both demographic and epidemiological transitions have occurred in many countries over the past 70 years?
Authors' Response: Table 1 has had the right-hand-side cut off so not all the lines are shown completely.
In line 5 of the search strategy are the Mesh terms for incontinence. These will retrieve articles on these subjects
5 Urinary Incontinence, Urge/ or Fecal Incontinence/ or Urinary Incontinence, Stress/ or Urinary Incontinence/
In line 6 we use the free text term of incontinence on its own as the OVID software knows to pick up any words on either side of it.
6 incontinence.mp.
This line will automatically pick up any phrases that include the word incontinence such as urinary incontinence, stress/urge/mixed urinary incontinence, faecal incontinence or fecal incontinence or anal incontinence etc.

Many systematic review searches are performed from database inception. The screening criteria will eliminate what does not meet the objectives.

Comment: Table 1, line 9 – has this line been truncated? Presumably the search strategy includes all World Bank-classified LMICs by name, and not just the 7 shown here?
Authors' Response: Table 1 has had the right-hand-side cut off so not all the lines are shown completely. We have replaced table1 with new table.
This is what the complete line 9 will cover.
9 (Afghanistan* or Albania* or Algeria* or Angola* or Argentina* or Armenia* or Azerbaijan* or Bangladesh* or Belarus* or Beliz* or Benin* or Bhutan* or Bolivia* or Bosnia* or Herzegovin* or Botswan* or Brazil* or Bulgaria* or Burkina* or Burundi* or Cabo Verde* or Cape Verde* or Cambodia* or Cameroon* or Central African or Chad* or China or Chinese or Colombia* or Comor* or Congo* or Costa Rica* or Cote d'Ivoir* or Ivory Coast or Cuba* or Djibouti* or Dominica* or Ecuador* or Egypt* or El Salvador* or Eritrea* or Ethiopia* or Fiji* or Gabon* or Gambia* or Georgia* or Ghana* or Grenad* or Guatemala* or Guinea* or Guyan* or Haiti* or Hondura* or Hungar* or India* or Indonesia* or Iran* or Iraq* or Jamaica* or Jordan* or Kazakhstan* or Kenya* or Kiribati* or Korea* or Kosov* or Kyrgyz Republic or Lao* or Leban* or Lesotho* or Liberia* or Libya* or Macedonia* or Madagascar* or Malawi* or Malaysia* or Maldiv* or Mali* or Marshall Island* or Mauritania* or Mauriti* or Mexic* or Micronesia* or Moldova* or Mongolia* or Montenegr* or Morocc* or Mozambi* or Myanma* or Burmese or Namibia* or Nepal* or Nicaragua* or Niger* or Nigeria* or Pakistan* or Palau* or Panama* or Papua New Guinea* or Paraguay* or Peru* or Philippines or Filipino or Romania* or Rwanda* or Samoa* or Sao Tome* or Senegal* or Serbia* or Seychell* or Sierra Leon* or Solomon Island* or Somalia* or South Africa* or Sudan* or Sri Lanka* or St Lucia* or St Vincent or Grenadines or Surinam* or Swazi* or Syria* or Tajikistan* or Tanzania* or Thai* or Timor* or Togo* or Tonga* or Tunisia* or Turk* or Turkmenistan* or Tuvalu* or Uganda* or Ukrain* or Uzbekistan* or Vanuatu* or Venezuela* or Vietnam* or West Bank or Gaza or Yemen* or Zambia* or

Zimbabwe*).mp.

Comment: p. 6, line 37 – since PFD is itself a “debilitating condition”, how are you defining “healthy” here? Perhaps it would be clearer to omit this criterion and rely on the exclusion of women with co-morbidities as shown at the top of p. 7.
Authors’ Response: We think it is important to be clear that women with PFD, who are otherwise healthy, are included. Therefore, we have changed the inclusion criteria (p6) to read “…studies of women with PFDs who were otherwise healthy…”. This is still consistent the exclusion criteria that women with comorbidities are excluded. We hope this is acceptable.

Comment: p. 7, lines 19-20 – please clarify the reasons for excluding employed women. Does this apply only to employment in the formal sector? Is it education per se, or access to / use of health care services that distinguishes these women?
Authors’ Response: Thank you very much. The reviewer is right. In LMICs, professional women means those are working in the formal sector. They tend to be more educated and use health care services more frequently when compared with non-professional women. In the revised manuscript, we have updated the text to reflect this.

Comment: p. 7, line 30 – earlier you state that conference websites will be searched for grey literature, but here you say conference abstracts and posters will be excluded. Please clarify which conference resources, if any, would be included.
Authors’ Response: We have added the following text in the revised manuscript: “However, a full-length article will be included if any are found in the conference websites”.

Comment: p. 7, line 40 – “will be distributed among [sic] two review authors” – does this mean the studies will be divided and each paper will be reviewed for inclusion by only one author? Recommended practice is for all studies to be reviewed by at least 2 authors.
Authors’ Response: Thank you very much. No, two other authors will cross-check all studies which is reflected in the protocol now, “Two other review authors (MNK, DMEH) will reassess all studies.”

Comment: p. 8, line 10 – PRISMA-P is appropriate for the current article. The review itself should follow guidelines of a checklist like MOOSE.
Authors’ Response: Thank you very much. We will the follow MOOSE guidelines for the review article.

Comment: p. 8, lines 22-23 – why specify restricted access to data when the study does not include confidential data and is exempt from IRB review?
Authors’ Response: Thank you very much. This is as per Monash University data management guidelines.

Comment: p. 8, line 56 – I suggest you include the “criteria” column for each item in the Hoy tool to facilitate and optimize reliability of the review.
Authors’ Response: Thank you very much. Yes, we have used the Hoy tool’s criteria which is described under ‘risk-of-bias and quality assessment’ section in the protocol. Please see also criteria at the end of the data extraction form.

Comment: p. 9, lines 42-45 – the description of the meta-regression and its purpose is confusing and seems incomplete. How will the meta-regression identify sources of heterogeneity? How does this differ from the subgroup analysis described on the following page? Please refer to Cochrane Handbook part 2, section 9.6.4, and please cite a methodological reference for this method rather than, or in addition to, reference [17]. Also note that meta-regression should be used only if there are 10 or more studies in the meta-analysis.

p. 9, lines 42-45 – the description of the meta-regression and its purpose is confusing and seems incomplete. How will the meta-regression identify sources of heterogeneity?

Authors' Response: Thank you very much. It would be helpful if we distinguish between different types of heterogeneity; Clinical heterogeneity and Statistical heterogeneity.

Clinical heterogeneity arises due to different methodological characteristics which are not usually quantified. An example of clinical heterogeneity is, differences in selection of patients, severity of disease, and management across studies. Variability in the participants, interventions and outcomes studied may be described as clinical diversity are also called clinical heterogeneity. Judgments about clinical heterogeneity are qualitative, do not involve any calculations. Conventional ways to address them is meta-regression (Fletcher 2007).

If heterogeneity (Clinical heterogeneity) is found or is suspected to exist, the common approach used in meta-analysis is to fit a meta-regression model that explains the heterogeneity in terms of study-level covariates (Morton et al 2004). Meta-regression, investigates the extent to which heterogeneity between results of multiple studies can be related to one or more characteristics of the studies (Thompson and Higgins 2002).

Fletcher, J. (2007). What is heterogeneity and is it important? BMJ: British Medical Journal, 334(7584), 94–96. http://doi.org/10.1136/bmj.39057.406644.68

Morton SC, Adams JL, Suttorp MJ, et al. 2004. Meta-regression Approaches: What, Why, When, and How? Rockville (MD): Agency for Healthcare Research and Quality (US); Mar. (Technical Reviews, No. 8.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK43894/

Thompson SG, Higgins JPT. 2002. How should meta-regression analyses be undertaken and interpreted? Statistics in Medicine 21: 1559–1573.

How does this differ from the subgroup analysis described on the following page?

Authors' Response: Thank you very much. Meta-regression is an extension to subgroup analyses that allows the effect of continuous, as well as categorical, characteristics to be investigated, and in principle allows the effects of multiple factors to be investigated simultaneously. In contrast, sub group analysis, can only be performed for categorical study characteristics and only one at a time. (Cochrane Handbook part 2, section 9.6.4)

Please refer to Cochrane Handbook part 2, section 9.6.4, and please cite a methodological reference for this method

Authors' Response: The reference has been added in the appropriate section of the text.

Also note that meta-regression should be used only if there are 10 or more studies in the meta-analysis.

Authors' Response: Thanks for the comment. We are completely aware of concern made by the reviewer that Meta-regression should generally require more than ten studies as our preliminary assessment shows that we may find double the required number of studies.

In the revised manuscript, the section has been re written and the following text have been added.

“A meta regression will be performed using the effect estimate (prevalence) as depended variable and study characteristics as explanatory variables. The regression coefficient obtained from a meta-regression analysis will be interpreted as how changes with a unit increase in the explanatory variable affects the outcome variable. The P value of each regression coefficient will be generated to assess the statistical significance of the effect of individual study characteristics”.

Comment: p. 10, lines 8-10 – the description of the assessment of heterogeneity is confusing. The actual value of I2 should be used to assess the degree of heterogeneity, and the cut-offs for low, moderate, and high heterogeneity should be specified. The significance can be determined by a chi-squared for Q, but the null hypothesis is that there is no heterogeneity, so a p-value > 0.05 (or 0.10 if there are few studies, since Q has low power in this case) would be a desirable result.

Authors’ Response: Many thanks for the comment. Variability in the intervention effects being evaluated in the different studies is known as statistical heterogeneity, and is a consequence of clinical or methodological diversity, or both, among the studies. Statistical heterogeneity manifests itself in the observed intervention effects being more different from each other than one would expect due to random error (chance) alone. For example, individual studies in a systematic review may seem to measure the same outcome but may have results that are not consistent with each other. Some studies show a benefit while others show harm, or the trials are inconsistent in the size of benefit or harm. This heterogeneity can be quantified by I2 and the significance can be determined by a chi-squared for Q.

In the revised manuscript, the section has been re written and the following text have been added under ‘Assessment of heterogeneity’ section.
“To examine the magnitude of the variation between studies, we will quantify the heterogeneity by using the I2 measure and its confidence interval (Higgins 2002). We will consider a two-sided probability value ≤0.05 as significant. To assess the degree of heterogeneity I2 value will be used, and the cut-offs for low, moderate, and high heterogeneity considered are a) between 0% to 40%: might not be important; b) 30% to 60%: may represent moderate heterogeneity; c) 50% to 90%: may represent substantial heterogeneity; d0 75% to 100%: considerable heterogeneity (Higgins 2003). The significance will be determined by a chi-squared for Q, so a p-value > 0.05 will be considered as significant”.

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 2002;21:1539-1558.

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British Medical Journal 2003;327:557-560.

Comment: p. 11, line 16 – it seems that the results of the review are a foregone conclusion?

Authors’ Response: The text on p 11 lines 15 to 19 says: “This systematic review and meta-analysis will provide pooled prevalence estimates of PFDs among women in LMICs. This study will also provide evidence of reasons for the substantial variation of prevalence reporting of PFDs in this context.”

This highlights our intention to account for difference in prevalence of PFDs between published studies, and also report new pooled estimates using meta-analysis. Both the reasons for differences in prevalence and the new estimate are currently unknown. We don't think they are a forgone conclusion. For this reason we would refer to leave the text as it is.

Comment: p. 11, line 23 – the protocol has not adequately addressed how the risk factors for PFDs will be elucidated.
Authors' Response: We anticipate that parity or vaginal delivery will be the key risk factors for PFDs in LMICS. However, we do not consider age as a key risk factor for PFDs since it is a non-modifiable risk factor and as such, has limited scope for modification by policy intervention. Thus, the following sentences have now been added in the protocol under statistical analysis section to clarify how the risk factors for PFDs will be elucidated: "Risk factors of PFDs from all included studies will be synthesised descriptively to understand the key risk factors for PFDs in LMICs. Then, meta-regression of the odds ratios of the key risk factors will be conducted to identify the individual effects of each risk factor for PFD."

Comment: Throughout the manuscript, there are minor grammatical and typographical errors that should be corrected (for example, incorrect subject-verb agreement on p. 1 at lines 10, 12, 17; "detail" on p. 9 at line 29 should be corrected to "detailed" "obtained" on p. 11 at line 6 should be corrected to "obtain"; "perspective" on p. 11 at line 28 should be corrected to "prospective"; typos and internal notes in Data Extraction Form; a space should be entered before each bracketed number where references are cited).
Authors' Response: All grammatical and typographical errors have been corrected in the corresponding lines. However, we have kept the word "perspective" on p. 11 at line 28 as we mean "perspective" as context not "prospective".
A space have been entered before each bracketed number where references are cited.

REVIEWER:2

Reviewer:2
Comment: Interesting subject with well design protocol
Authors' Response: Thank you very much for the approval of the manuscript.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Karen D Cowgill, PhD, MSc<br>University of Washington Tacoma, USA |
| **REVIEW RETURNED** | 01-Apr-2017 |

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| **GENERAL COMMENTS** | Thanks to the authors for their thorough responses to questions and issues raised in the review. For the most part, they have addressed my concerns, but there are two minor issues that should be addressed before publication:<br>1. Although the authors state that they will follow MOOSE criteria for the study, the ms has not been updated to reflect this – it still states they will follow PRISMA-P, which is not appropriate for this review.<br>2. Thank you for clarifying that the stat test will apply to Q. I suggest you delete the sentence "We will consider a two-sided probability value ≤0.05 as significant." |

**VERSION 2 – AUTHOR RESPONSE**

Authors' reply to reviewers' comments:
Thanks to the authors for their thorough responses to questions and issues raised in the review. For the most part, they have addressed my concerns, but there are two minor issues that should be addressed before publication:

1. Although the authors state that they will follow MOOSE criteria for the study, the ms has not been updated to reflect this – it still states they will follow PRISMA-P, which is not appropriate for this review.
Authors' Response: Thank you very much. We have now updated with the following text "The manuscript will be structured using the MOOSE guidelines". The reference has also been updated accordingly.

2. Thank you for clarifying that the stat test will apply to Q. I suggest you delete the sentence "We will consider a two-sided probability value ≤0.05 as significant."
Authors' Response: Thank you very much. The sentence "We will consider a two-sided probability value ≤0.05 as significant" has now been deleted.