PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sociodemographic differences in symptom severity and duration amongst women referred to secondary care for menorrhagia in England and Wales: a cohort study from the National Heavy Menstrual Bleeding Audit
AUTHORS	Kiran, Amit; Geary, Rebecca; Gurol Urganci, Ipek; Cromwell, David; Bansi-Matharu, Loveleen; Shakespeare, Judy; Mahmood, Tahir; van der Meulen, Jan

VERSION 1 – REVIEW

REVIEWER	Mehmet Kağıtcı MD Mersin Şehir Hastanesi / Türkiye
REVIEW RETURNED	04-Jul-2017

GENERAL COMMENTS	This is a well designed and well written study on an important subject of gynocology. I believe that this study should be published as it is.

REVIEWER	Sarah O'Brien, MD Associate Professor of Pediatrics The Ohio State University Director of Experimental Therapeutics Nationwide Children's Hospital USA
REVIEW RETURNED	24-Jul-2017

GENERAL COMMENTS	Kiran and colleagues have linked 2 national databases in order to examine sociodemographic differences in symptom severity and duration among women referred to secondary care for heavy menses in England and Wales. The topic is important and understudied and the manuscript is well written. In general, the paper would be greatly strengthened if the authors could provide some clinical context and significance to the statistically significant differences that they identified in this large study population. Some specific comments for consideration: Lines 37-39 - Are these differences clinically significant? Lines 98-99 - For readers outside of the UK system it would be helpful to better understand practice patterns. In the US, for example, ob/gyn physicians are also considered primary care providers so a female could present to her ob/gyn for complaints of HMB without having to obtain a referral. Does this scenario ever apply in the UK, or were these all women

	who saw their GP initially for HMB and were then referred to ob/gyn? Lines 109-110 - What were the most common reasons for non-enrollment? Lines 142-145 - Was this information regarding co-morbidities confirmed by billing/diagnostic codes in HES and PEDW? Lines 198-200 - Results would be more compelling if readers had some sense of the symptoms behind the numbers. This reviewer, and many readers, may not be familiar with UFS-QOL. Also, what are population norms for EQ-SD? Putting these numbers into clinical context, either by including some example questions and/or means/ranges seen in prior studies will help the reader, and also help us determine if the current study's results are clinically significant. Lines 203-204 - Symptom severity scores and condition-specific QOL scores were both extracted from the same instrument (UFS-QOL). More details need to be provided on the methodology so that the study could be repeated. Line 209 - Keep in mind these are very large sample sizes. Again, differences are statistically different, but do they represent clinically significant differences? Lines 244-246 - How does this explain why poorer women were more likely to be seen less than one year from symptom onset?

REVIEWER	Georgie Bruinvels University College London, UK
REVIEW RETURNED	15-Oct-2017

GENERAL COMMENTS	Really interesting analysis and a very impactful study. A few points for consideration: Statistical analysis - were data assessed for normality? Obviously this will affect whether data is presented as median ± IQR or mean ± SD. Results - I would add in some of the key stats and p values. For example the lack of difference between England and Wales. Could also consider specifically showing where the differences were in age, ethnicity and socioeconomic deprivation. i.e. ages 18-34 and 45-49 in addition to looking at age as a whole. Discussion - I think it is really important to highlight both a potential lack of education and awareness of what is often deemed to be a very personal in those with a lower socioeconomic status. Accordingly, a future need to improve this should be highlighted. Although appreciably the seeking of medical help was actually faster in those of a lower socioeconomic status. While BMI has been considered, while difficult to evaluate, the influence of diet, exercise and healthy lifestyle choices could be outlined. As inflammatory conditions, the severity of HMB and dysmenorrhea could be reduced with healthier lifestyle choices which may be more common in those with a higher socioeconomic status.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 2
Lines 37-39 - Are these differences clinically significant?

Response: In the HMB Audit we assessed whether women's changes in severity scores from baseline to follow-up was of significance, calculating the minimal important difference (MID). The mean change in score among those who indicated their symptoms were 'about the same' prior to referral to secondary care was subtracted from the mean change in severity score among women who reported their symptoms were 'a little better'. The result was the minimum change required for an improvement in quality of life.
MID = mean change (symptoms 'a little better') − mean change (symptoms 'about the same') =
(−19.6) − (−10.6)
= 10.0 unit improvement
Based on this we find that the differences in symptom severity and HRQoL score of >6 units between women from the most and least deprived areas would be considered clinically significant. We have added the following to the third paragraph of the discussion.

"The difference in the symptom severity score between women from the least and the most deprived areas of about 6 is likely to be clinically significant, given that women who completed a questionnaire one year after their first outpatient visit and reported that their symptoms were 'a little better' had severity scores that were, on average, approximately 10 lower than women who reported (in response to same questionnaire) that their symptoms were 'about the same'."

Lines 98-99 - For readers outside of the UK system it would be helpful to better understand practice patterns. In the US, for example, ob/gyn physicians are also considered primary care providers so a female could present to her ob/gyn for complaints of HMB without having to obtain a referral. Does this scenario ever apply in the UK, or were these all women who saw their GP initially for HMB and were then referred to ob/gyn?

Response: In the UK, general practitioners and nurse practitioners provide primary care. OBGYN physicians are not considered primary care providers. We have amended the first paragraph of the manuscript to clarify this (added text in blue).
Line 69-72: "Heavy menstrual bleeding (HMB) is a common condition that affects one in four women of reproductive age. In England and Wales, an estimated 50,000 women with HMB are referred from primary care to secondary care gynaecology services provided by the National Health Service (NHS) every year."

Comment: What were the most common reasons for non-enrolment?

Response: Data are not available on reasons for non-enrolment. However, comparing the characteristics of the women who were recruited to the general UK population found that those enrolled were broadly representative of the general UK population in terms of the distributions of ethnicity and age as we indicate in the first paragraph of the Strengths and Limitation section in the Discussion (lines 361-364).

Lines 142-145 - Was this information regarding co-morbidities confirmed by billing/diagnostic codes in HES and PEDW?
Response: Information regarding co-morbidities was not confirmed by diagnostic codes in HES and PEDW as these would only have been available for those women who went onto have an inpatient episode, potentially introducing bias.

Lines 198-200 - Results would be more compelling if readers had some sense of the symptoms behind the numbers.

Response: This reviewer, and many readers, may not be familiar with UFS-QOL.

We have added the following information regarding the UFS-QOL to the methods section (line 111-126):
"Of five candidate questionnaires evaluated, only the UFS-QOL could be used throughout the care pathway, measured HRQoL and was psychometrically strong. The UFS-QOL was adapted for HMB and a UK population; we conducted semi-structured interviews with women (n = 7) and clinicians (n = 5) and a mini focus group (n = 3) with local Heavy Menstrual Bleeding Audit coordinators to determine suitable alternative words to describe HMB and to identify any words that were not clearly understood in UK English. Based on these interviews and mini focus group we changed the wording to refer to 'heavy menstrual bleeding (i.e. heavy periods)' rather than 'fibroids', changed 'checking' to 'ticking'; changed 'soiling' to 'staining'; changed 'blue' to 'low'; and changed 'wiped out' to 'exhausted'. The adapted version performed acceptably in a psychometric evaluation. Overall, the symptom severity subscale and the HRQL subscale of the UFS-QOL used as outcomes demonstrated the strongest psychometric properties and have been used to report the audit data. The UFS-QOL consists of eight symptom items and 29 HRQoL items. The symptom items are scored to produce a severity subscale and the HRQoL items are scored into subscales (concern, activities, energy/mood, control, self-consciousness and sexual function). The HRQoL sub-scales can be used separately or combined into an overall HRQoL score. We use the overall HRQoL score in this paper."

Comment: Also, what are population norms for EQ-SD? Putting these numbers into clinical context, either by including some example questions and/or means/ranges seen in prior studies will help the reader, and also help us determine if the current study's results are clinically significant.

Response: We have added the following text to lines 334-337.
"Women with HMB in this study reported substantially worse QoL (EQ-5D mean: 0.65, SD: 0.33) than the population average for women in England (mean: 0.85, SD: 0.003), and compared to women with incontinence (mean: 0.73, SD: 0.26). This reinforces the need for interventions to focus on improving women's quality of life, as recommended by recent NICE guidelines. "

Lines 203-204 - Symptom severity scores and condition-specific QOL scores were both extracted from the same instrument (UFS-QOL). More details need to be provided on the methodology so that the study could be repeated.

Response: We have added the following to lines 122-126:
"The UFS-QOL consists of eight symptom items and 29 HRQoL items. The symptom items are scored to produce a severity subscale and the HRQoL items are scored into subscales (concern, activities, energy/mood, control, self-consciousness and sexual function). The HRQoL sub-scales can be used separately or combined into an overall HRQoL score. We use the overall HRQoL score in this paper."

The patient questionnaire could be provided in an Appendix if desired.

Line 209 - Keep in mind these are very large sample sizes. Again, differences are statistically different, but do they represent clinically significant differences?
Response: As described above, in the HMB Audit we assessed whether women's changes in severity scores from baseline to follow-up was of significance, calculating the minimal important difference (MID). The mean change in score among those who indicated their symptoms were 'about the same' prior to referral to secondary care was subtracted from the mean change in severity score among women who reported their symptoms were 'a little better'. The result was the minimum change required for an improvement in quality of life.
MID = mean change (symptoms 'a little better') − mean change (symptoms 'about the same') = (−19.6) − (−10.6)
= 10.0 unit improvement

Based on this we find that the differences in symptom severity and HRQoL score of >6 units between women from the most and least deprived areas would be considered clinically significant. We have added the following to the third paragraph of the discussion.

“The difference in the symptom severity score between women from the least and the most deprived areas of about 6 is likely to be clinically significant, given that women who completed a questionnaire one year after their first outpatient visit and reported that their symptoms were ‘a little better’ had severity scores that were, on average, approximately 10 lower than women who reported (in response to same questionnaire) that their symptoms were ‘about the same’.”

Lines 244-246 - How does this explain why poorer women were more likely to be seen less than one year from symptom onset?

Response: The observation that women living in the most socio-economically deprived areas reported the most severe symptoms but were least likely to report having had symptoms for ≥1 year may reflect the wording of the question; women were asked “How long have you had symptoms of heavy menstrual bleeding?” and women whose symptom severity had worsened may have reported the duration of the most recent severity, rather than the overall duration. We have indicated this in lines 300-304.

Reviewer: 3
Statistical analysis - were data assessed for normality? Obviously this will affect whether data is presented as median ± IQR or mean ± SD.
We present the mean ± SD because we used linear regression to calculate adjusted differences in mean scores which will be will approximate a normal distribution (central limit theorem).

Results - I would add in some of the key stats and p values. For example the lack of difference between England and Wales. Could also consider specifically showing where the differences were in age, ethnicity and socioeconomic deprivation. i.e. ages 18-34 and 45-49 in addition to looking at age as a whole.

Response: We have added more detail to the body of the text of the result section as follows (lines 232-250): “Severity of symptoms and quality-of-life by socioeconomic deprivation
Symptom severity scores gradually increased with increasing socioeconomic deprivation (Table 2). Condition-specific and generic quality of life scores also showed a worsening gradient according to deprivation. In other words, women living in more deprived areas reported more severe symptoms (difference -6.1; 95%CI -7.2 to -4.9, between least and most deprived quintile) and a poorer quality of life (difference 6.3; 95%CI 5.1 to 7.5) at their first gynaecology outpatient visit for HMB than those living in less deprived areas.

Severity of symptoms and quality-of-life by age and ethnicity
Symptom severity showed a gradual decrease with increasing age, indicating that older women reported less severe symptoms at their first outpatient visit for HMB (difference -5.9; 95% CI: -7.2 to -4.6 between oldest and youngest age groups, Table 2). Quality of life scores based on both the condition-specific and the generic measure increased with increasing age, which shows that older women reported better quality of life at their first HMB outpatient visit (difference 7.3; 95% CI: 5.9 to 8.7) between oldest and youngest age groups). Symptom severity also varied by ethnicity: black and Asian women reported less severe symptoms than white women (difference compared to white women -1.9 and -2.4 respectively, Table 2). Condition-specific quality of life did not vary significantly by ethnicity, whereas compared to white women, Asian woman reported lower generic quality of life scores (Table 2).”

Discussion - I think it is really important to highlight both a potential lack of education and awareness of what is often deemed to be a very personal in those with a lower socioeconomic status. Accordingly, a future need to improve this should be highlighted. Although appreciably the seeking of medical help was actually faster in those of a lower socioeconomic status.

Response: We have added the following to lines 340-343:
“Awareness raising activities relating to the availability of treatments for HMB could increase healthcare seeking before symptoms become severe. This may be particularly beneficial for those from more deprived background who may be more accepting of chronic pain and worse quality-of-life.”
In addition, in lines 283-288 we discuss that people from more socioeconomically deprived backgrounds may be more accepting of longstanding symptoms, chronic pain or poorer health-related quality of life, which may explain women from more deprived areas reporting more severe symptoms and poorer quality of life at first outpatient visit.

Comment: While BMI has been considered, while difficult to evaluate, the influence of diet, exercise and healthy lifestyle choices could be outlined. As inflammatory conditions, the severity of HMB and dysmenorrhea could be reduced with healthier lifestyle choices which may be more common in those with a higher socioeconomic status.

Response: We have added the following to lines 337-339:
“Obesity can be associated with HMB so health promotion interventions around diet and exercise could supplement HMB-specific interventions.”

Once again, we thank the editors and reviewers for their comments on our manuscript.

VERSION 2 – REVIEW

REVIEWER	Sarah O'Brien, MD The Research Institute at Nationwide Children's Hospital and The Ohio State University, United States of America
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	In general, thorough response to the review and this paper is valuable to field. Still need additional clarification on response to Reviewer 2, #1 - If a change of 10 units is the minimum change required for improvement in QOL, then how is a change of 6 units clinically significant? This is a primary outcome and featured in the abstract so key to demonstrate that these QOL differences are not just statistically significant differences seen in very large sample size.

REVIEWER	Georgie Bruinvels UCL, UK
REVIEW RETURNED	26-Nov-2017

GENERAL COMMENTS	Happy with the updates made and clarification provided.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
In general, thorough response to the review and this paper is valuable to field. Still need additional clarification on response to Reviewer 2, #1 - If a change of 10 units is the minimum change required for improvement in QOL, then how is a change of 6 units clinically significant? This is a primary outcome and featured in the abstract so key to demonstrate that these QOL differences are not just statistically significant differences seen in very large sample size.

Response: We have edited lines 267-269 to provide further clarification as follows. “The difference in the symptom severity score between women from the least and the most deprived areas of about 6 is likely to be clinically significant, given that a difference of 5 points or more has been specified as clinically important in clinical trials.”

Once again, we thank the editors and reviewers for their comments on our manuscript.

VERSION 3 – REVIEW

REVIEWER	Sarah O'Brien, MD Nationwide Children's Hospital and The Ohio State University, USA
REVIEW RETURNED	18-Dec-2017

GENERAL COMMENTS	Authors have adequately addressed all concerns.