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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

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3 1 Sociodemographic differences in symptom severity and duration amongst
4 2 women referred to secondary care for menorrhagia in England and Wales: a
5 3 cohort study from the National Heavy Menstrual Bleeding Audit
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1
2
3 22 **ABSTRACT**

4 23 **Objective** To examine symptom severity and duration at time of referral to secondary care for heavy
5
6 24 menstrual bleeding by socio-economic deprivation, age and ethnicity

7 25 **Design** Cohort analysis of data from the National Heavy Menstrual Bleeding Audit linked to Hospital
8
9 26 Episode Statistics data

10 27 **Setting** English and Welsh National Health Services (secondary care): February 2011 to January 2012

11 28 **Participants** 15,325 women aged 18 to 60 years in England and Wales who had a new referral for
12
13 29 heavy menstrual bleeding to a gynaecology outpatient department

14 30 **Methods** Multivariable linear regression to calculate adjusted differences in mean symptom severity
15
16 31 and quality of life scores at first outpatient visit. Multivariable logistic regression to calculate
17
18 32 adjusted odds ratios. Adjustment for body mass index, parity and co-morbidities.

19 33 **Primary Outcome Measures** Mean symptom severity score (0=best, 100=worst), mean condition-
20
21 34 specific quality of life score (0=worst, 100=best) and symptom duration (≥ 1 year).

22 35 **Results** Women were on average 42 years old and 12% were non-white. Mean symptom severity
23
24 36 and condition-specific quality of life scores were 61.8 and 34.7. Almost three-quarters of women
25
26 37 (74%) reported having had symptoms for ≥ 1 year. Women from more deprived areas had more
27
28 38 severe symptoms at their first outpatient visit (difference -6.1; 95%CI -7.2:-4.9, between least and
29
30 39 most deprived quintile) and worse condition-specific quality of life (difference 6.3; 95%CI 5.1:7.5).
31
32 40 Symptom severity declined with age whilst quality of life improved.

33 41 **Conclusions** Women living in more deprived areas reported more severe HMB symptoms and poorer
34
35 42 quality of life at the start of treatment in secondary care. Providers should examine referral practices
36
37 43 to explore if these differences reflect women's health-seeking behaviour or how providers decide
38
39 44 whether or not to refer.

40
41 46 **Funding** The National Heavy Menstrual Bleeding (HMB) Audit was funded by the Healthcare Quality
42
43 47 Improvement Partnership as part of the National Clinical Audit and Patient Outcomes Programme,
44
45 48 contract number HQIP NCA 004.

46 49 **Keywords** heavy menstrual bleeding, deprivation, ethnicity, health inequalities, patient-reported
47
48 50 outcomes, quality of life

49 51 **Tweetable abstract** Women from deprived areas referred with more severe heavy menstrual
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51 52 bleeding, potentially reflecting inequity

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3 55 **Strengths and limitations of this study**

- 4 56 • This study is the first to examine Heavy Menstrual Bleeding symptom severity and duration
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6 57 at time of referral to secondary care
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8 58 • The inclusion of patient-reported symptom severity and quality of life addresses a
9
10 59 knowledge gap about how women feel about their heavy menstrual bleeding
11
12 60 • As the data were collected by a national audit in England and Wales the sample is relatively
13
14 61 large, allowing comparisons between ethnic minority groups
15
16 62 • Even though the sample size is large, the National HMB Audit recruited approximately 30%
17
18 63 of eligible women. However, the characteristics of the women recruited were broadly
19
20 64 representative of the UK population in terms of ethnicity and age
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22 65 • Linking audit data to administrative hospital data also allowed comparisons between
23
24 66 socioeconomic groups
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68 INTRODUCTION

69 Heavy menstrual bleeding (HMB) is a common condition that affects one in four women of
70 reproductive age. In England and Wales, an estimated 50,000 women with HMB are referred to
71 secondary care provided by the National Health Service (NHS) every year¹. Menstrual disorders
72 account for approximately 20% of referrals to specialist gynaecology services² and studies have
73 found significant regional variations in use of surgical treatment within England³.

74
75 Women with HMB have significantly worse quality of life than women with normal menstrual
76 bleeding loss, in terms of their physical and mental health, as well as their emotional, social and
77 material quality of life⁴⁻⁷. More than a third of women with HMB report severe pain⁷. HMB is also
78 associated with morbidity, including anaemia and related fatigue^{8,9}. Women with HMB experience
79 reduced participation in social activities and their personal relationships and attendance at work can
80 be adversely affected¹⁰.

81
82 In order to improve the quality of life of women with HMB, it is important to understand both the
83 aetiology of this condition and its management in primary and secondary care¹¹. The prevalence of
84 HMB and conditions which affect symptom severity has been reported to vary by ethnicity¹²⁻¹⁵. In
85 addition, cultural norms and patient choice for treatment may vary between different groups^{16,17}.

86
87 In this study, we used data from the National HMB Audit to examine symptom severity, quality of
88 life and symptom duration at women's first gynaecology outpatient visit for HMB. The National HMB
89 Audit was a 4-year project (2010 - 2014) that assessed patient-reported outcomes and experiences
90 of care for women with HMB in England and Wales. Our objective is to examine symptom severity
91 and duration at the time of referral to secondary care by age, ethnicity and socio-economic
92 deprivation to get a better understanding of the burden of disease at the start of treatment in
93 secondary care.

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3 95 **METHODS**

4 96 **Data collection**

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6 97 Full details of the methods used in the National HMB Audit have been reported elsewhere^{1, 4, 18, 19}.

7 98 Women aged between 18 and 60 years in England and Wales who had a new referral for HMB to a
8
9 99 gynaecology outpatient department were eligible to participate in the National HMB Audit. Women
10
11 100 who had visited a gynaecology outpatient clinic for HMB within the previous 12 months were
12
13 101 excluded. Recruitment took place between 1 February 2011 and 31 January 2012^{1, 19}.

14 102
15 103 Women who consented to participate completed a baseline questionnaire (58 questions) on age,
16 104 ethnicity, duration of HMB symptoms, obstetric history, prior treatment received for HMB and co-
17 105 morbidities. The questionnaire also collected patient-reported HMB-specific and generic quality of
18 106 life measures. Scores for symptom severity and condition-specific health-related quality of life were
19 107 adapted from the Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire²⁰. A generic
20 108 health-related quality of life measure was derived from the EuroQol-5 (EQ-5D)²¹. Women completed
21 109 the questionnaire in hospital before their consultation. Using multiple sources of data, the
22 110 recruitment rate of the audit was estimated to be 31.9%¹. Descriptive results from the National HMB
23 111 Audit have been published elsewhere^{1, 4, 18, 19}.

24 112
25 113 Data from the prospective audit were linked at patient level to records from Hospital Episode
26 114 Statistics (HES) and Patient Episode Database for Wales (PEDW), administrative databases that
27 115 capture all inpatient and outpatient episodes in English and Welsh NHS hospitals. Data linkage was
28 116 performed using deterministic linkage criteria that included NHS number, sex and date of birth.

29 117
30 118 **Measures**

31 119 Symptom severity, condition-specific quality of life and generic quality of life scores and the
32 120 reported duration of symptoms at the first outpatient visit were used as outcomes in this study. The
33 121 severity and quality of life scores were analysed as continuous variables. Symptom severity scores
34 122 ranged from 0 (best possible score) to 100 (greatest symptom severity, worst possible score).
35 123 Condition-specific quality of life ranged from 0 (poorest quality of life) to 100 (best quality of life).
36 124 Generic quality of life is expressed on a scale with 0 representing death and 1 perfect health²².
37 125 Women were asked "How long have you had symptoms of heavy menstrual bleeding", with "2
38 126 months or less", "more than 2 months but less than 1 year", "more than 1 year" and "don't know" as
39 127 possible response categories. For analysis, duration of symptoms was grouped as "<1 year", "≥1
40 128 year" with "don't know" coded as missing. Levels of missing data on HMB symptoms and health-

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3 129 related quality of life were low (2.2% for severity, 4.8% for condition-specific and 9.9% for generic
4 130 quality of life and 3.0% for symptom duration).

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7 132 Age was categorised as 18-34, 35-39, 40-44, 45-49, ≥ 50 years for analysis. Women reported their
8 133 ethnicity as “white”, “mixed”, “Asian or Asian British”, “black or black British”, “Chinese” or “other”.
9 134 For analysis, the “mixed”, “Chinese” and “other” groups were combined as “other” due to small
10 135 numbers of women reporting these ethnicities. Self-reported height and weight data were used to
11 136 derive body mass index (BMI), categorised according to WHO groups as ≤ 25 , 25-30, and ≥ 30 ²³.

12 137 Women reported how many times they had seen their GP for HMB in the year prior to their first
13 138 outpatient visit, and this was grouped as 0, 1-2, 3-4, >4 for analysis (“don’t know” was coded as
14 139 missing).

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17 141 Women reported their parity, grouped for analysis as “nulliparous” or “parous”. Women were also
18 142 asked “Have you been told by a doctor that you have any of the following: “heart disease (for
19 143 example angina, heart attack or heart failure), high blood pressure, lung disease (for example
20 144 chronic bronchitis or emphysema), diabetes, depression, thyroid disorder, kidney disease, cancer
21 145 (within the last 5 years). For analysis, the number of co-morbidities reported was grouped as 0, 1,
22 146 ≥ 2 .

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24 147

25 148 Information on socio-economic deprivation (Index of Multiple Deprivation (IMD)) was extracted
26 149 from HES and PEDW. IMD is a relative measure of deprivation for small areas across a number of
27 150 domains, including income, employment, education and housing. We used quintiles of IMD (level 1 =
28 151 most deprived areas, level 5 = least deprived areas). The methods used to calculate IMD scores in
29 152 each country in the UK are similar but not directly comparable²⁴. For analysis, we generated a
30 153 combined measure of deprivation for England and Wales by assigning those in each country-specific
31 154 quintile to the same quintile in a combined measure. This preserved women’s relative deprivation
32 155 position within each country.

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35 157 **Statistical analysis**

36 158 Means and standard deviations (SD) and proportions were used to describe the cohort. Regression
37 159 analyses were used to examine the relationship between age, ethnicity and socio-economic
38 160 deprivation and each of the outcomes. For the scores representing symptom severity, condition
39 161 specific and generic quality of life, multivariable linear regression was used to calculate adjusted
40 162 differences in mean scores. For duration of symptoms (<1 year and ≥ 1 year), multivariable logistic
41 163 regression was used to calculate adjusted odds ratios (OR). Regression models included BMI, parity

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3 164 and number of co-morbidities as potential confounders. Levels of missing data were low (<3%) for
4 165 the majority of variables with the exception of ethnicity (7% missing) and BMI (approximately 23%
5 166 missing, Table 1). Missing values for explanatory variables were imputed using multiple imputation
6 167 by chained equations²⁵ and statistical coefficients were obtained using ten imputed datasets and
7 168 combined using Rubin's rules²⁶.

10 169

12 170 **FUNDING**

14 171 The National Heavy Menstrual Bleeding (HMB) Audit was funded by the Healthcare Quality
15 172 Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes
16 173 Programme (NCAPOP). The audit was led by the Royal College of Obstetricians and Gynaecologists.
17 174 The authors declare no funding for the writing of this manuscript.

20 175

22 176 **ETHICAL APPROVAL**

23 177 The data are from the National Heavy Menstrual Bleeding (HMB) Audit. Based on the Health
24 178 Research Authority's guidance, audits are regulated as standard clinical practice outside of the
25 179 Research Ethics Service²⁷.

28 180

30 181 **RESULTS**

31 182 **Patient Characteristics**

32 183 15,325 eligible women completed the questionnaire at their first visit to a gynaecology outpatient
33 184 department and 15,294 (99.8%) could be linked to HES or PEDW which provided information on
34 185 socioeconomic deprivation. The women's mean age was 42.3 years (SD 7.6) and BMI 27.3 (SD 5.4)
35 186 (Table 1). About one in five were nulliparous and one in three reported at least one co-morbidity.
36 187 11.7% of women reported a non-white ethnicity, with black or black British (5.4%) and Asian or Asian
37 188 British (4.3%) being the largest non-white groups. Women in the two least socioeconomically
38 189 deprived national quintile groups (18.7% in quintile 4 and 15.8% in quintile 5) were under-
39 190 represented given that per definition 20% of women are expected to be in each group. The
40 191 distribution of symptom severity, condition-specific and generic quality of life and symptom duration
41 192 by level of deprivation did not vary significantly between women in England and Wales (data not
42 193 shown).

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52 195 **Table 1: Patient characteristics at the first gynaecology outpatient visit for HMB**

53 196 **(% and number unless otherwise stated)**

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3 198 The mean score for symptom severity was 61.8 (standard error (SE) 0.17) with 74.0% of women
4 199 reporting that they had HMB symptoms for more than one year. The mean score for condition-
5 200 specific quality of life was 34.7 (SE: 0.18) and for generic quality of life 0.65 (SE: 0.28) (Table 2).
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202 **Severity of symptoms and quality-of-life by socioeconomic deprivation**

203 Symptom severity scores gradually increased with increasing socioeconomic deprivation (Table 2).
204 Condition-specific and generic quality of life scores also showed a worsening gradient according to
205 deprivation. In other words, women living in more deprived areas reported more severe symptoms
206 and a poorer quality of life at their first gynaecology outpatient visit for HMB than those living in less
207 deprived areas.
208

209

209 **Severity of symptoms and quality-of-life by age and ethnicity**

210 Symptom severity showed a gradual decrease with increasing age, indicating that older women
211 reported less severe symptoms at their first outpatient visit for HMB (Table 2). Quality of life scores
212 based on both the condition-specific and the generic measure increased with increasing age, which
213 shows that older women reported better quality of life at their first HMB outpatient visit. Symptom
214 severity also varied by ethnicity: black and Asian women reported less severe symptoms than white
215 women (Table 2). Condition-specific quality of life did not vary significantly by ethnicity, whereas
216 compared to white women, Asian woman reported lower generic quality of life scores (Table 2).
217

218

218 **Duration of symptoms**

219 Women living in the most deprived areas were slightly less likely to report having had HMB
220 symptoms for ≥ 1 year than those living in the less deprived areas. Women aged between 35 and 49
221 years were more likely to report having experienced HMB symptoms for ≥ 1 year than those younger
222 than 35. Compared to white women, black women were more likely than white women to report
223 symptoms for ≥ 1 year and Asian women were less likely.
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225 **Table 2. Severity and duration of symptoms at the first outpatient visit, by age group, ethnicity** 226 **and socioeconomic deprivation**

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3 227 **DISCUSSION**

4 228 **Main Findings**

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6 229 Women living in more socioeconomically deprived areas reported more severe HMB symptoms and
7 230 poorer quality of life at their first gynaecology outpatient visit. Older women reported less severe
8
9 231 symptoms and better quality of life than younger women. Reported symptom severity also varied by
10
11 232 ethnicity with black and Asian women reporting less severe symptoms than women from white
12
13 233 ethnic backgrounds.

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15 235 Three quarters of the women referred to secondary care reported that they had had symptoms of
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17 236 HMB for at least one year and women living in the most deprived areas were least likely to report
18
19 237 having had HMB symptoms for ≥ 1 year.

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22 239 **Interpretation**

23 240 More severe symptoms and poorer quality of life at first outpatient visit by socioeconomic
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25 241 deprivation, after adjustment for possible differences in age, ethnicity and body mass index, reflect
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27 242 that women from more deprived backgrounds report more severe problems at the start of
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29 243 treatment in secondary care but they were least likely to report that they had symptoms for ≥ 1 year.
30
31 244 There is evidence that people from more socioeconomically deprived backgrounds may be more
32
33 245 accepting of longstanding symptoms, chronic pain or poorer health-related quality of life²⁸, which is
34
35 246 a possible explanation for these finding. Conversely, those from more affluent socioeconomic
36
37 247 backgrounds have been found to report greater impact of health conditions on their health and their
38
39 248 quality of life, which may be linked to their higher expectations about health and life in general²⁹.

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41 250 Alternative explanations are that differences in symptom severity, quality of life and symptom
42
43 251 reflect inequitable access as well as differences in the nature and causes of HMB. Age is often found
44
45 252 to be associated with symptom severity^{15, 16, 30, 31}. Black women are 2-3 times more likely to have
46
47 253 fibroids and endometriosis³¹. Accepting heavy periods as normal vary by ethnicity and other social
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49 254 factors, which in turn can also lead to reluctance to seek care for HMB¹⁶. Ethnographic research
50
51 255 suggests that some women of South Asian ethnicity do not seek healthcare for HMB due to the
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53 256 belief that heavy periods cleanse the body¹⁷. We adjust for patient-level characteristics that may
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55 257 capture some of these differences but were unable to adjust for other unmeasured potential
56
57 258 confounders.

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3 260 The observation that women living in the most socio-economically deprived areas reported the most
4 261 severe symptoms but were least likely to report having had symptoms for ≥ 1 year is more difficult to
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6 262 explain. However, the question wording can have had an impact. Women were asked “How long
7
8 263 have you had symptoms of heavy menstrual bleeding?” and women whose symptom severity had
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10 264 worsened may have reported the duration of the most recent severity, rather than the overall
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12 265 duration.

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14 267 A key question is whether the observed differences in symptom severity and condition-specific
15
16 268 quality of life at the women’s first gynaecology outpatient visit are related to differences in women’s
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18 269 health seeking behaviour or to differences in how GPs and gynaecologists decide on whether to
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20 270 refer a woman with HMB. A study of self-reported health-care seeking behaviour in England did not
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22 271 find evidence that inequality in access to secondary care according to socioeconomic or ethnic
23
24 272 backgrounds is related to patients being less likely to go to their GP or a hospital’s emergency
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26 273 department³³. Similarly, a survey of patients with chronic joint pain found that the proportions of
27
28 274 patients who said that they were seeking help from their GP did not differ according to their
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30 275 socioeconomic background³⁴. On the other hand, a national study including 130,000 patients from
31
32 276 more than 300 primary care practices in England found that older patients and those from more
33
34 277 deprived areas were less likely to be referred to secondary care³⁵.

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36 279 **Implications for policy and practice**

37 280 In the UK, national guidelines for the management of HMB have been developed by the National
38
39 281 Institute for Health and Care Excellence and the Royal College of Obstetricians and Gynaecologists
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41 282 (RCOG)^{11, 36, 37}. The National HMB Audit carried out a survey of NHS hospitals in England and Wales to
42
43 283 find out how care for women with HMB is organised and delivered at local levels. It found that key
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45 284 systems such as the availability of local protocols, which specified local arrangements for patient
46
47 285 referral and management in response to the NICE guidelines, were reported only by 30% of
48
49 286 hospitals³⁸. Wide variation in the investigations and treatments that were offered to women with
50
51 287 HMB in primary care were also noted. The implementation of locally agreed referral pathways,
52
53 288 recommended by the RCOG, will help to reduce this variation³⁹.

54 289

55 290 Recent NICE guidelines recommend that interventions should focus on improving women’s quality of
56
57 291 life¹¹, although criteria for what constitutes a meaningful improvement in quality of life are less
58
59 292 clear. In highlighting differences in symptom severity at their first gynaecology outpatient visit, our
60
293 findings draw attention to the lack of an agreed threshold for referral of women with HMB to

294 secondary care in terms of symptom severity and quality of life. Routine measurement of both
295 symptom severity and quality of life may be required to stimulate greater consistency in referral
296 thresholds but validated instruments specific to HMB are currently lacking. As there is no widely
297 used condition-specific measure of condition-specific quality of life for HMB, the National HMB Audit
298 used the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, adapted for a UK
299 population of women with HMB¹⁸.

300

301 **Strengths and Limitations**

302 This study is the first to examine the relationship between sociodemographic factors and patient-
303 reported HMB symptom severity, quality of life and symptom duration in an outpatient setting. It
304 used data collected by a national audit carried out in England and Wales, which produced a relatively
305 large sample. We estimated that the National HMB Audit recruited about 30% of all eligible women.
306 There is no direct way to compare the characteristics of the women who were recruited and those
307 who were not. However, the characteristics of the women who were recruited were broadly
308 representative of the UK population in terms of the distributions of ethnicity and age^{40, 41}.

309

310 Survey questionnaires were only available in the English language, so non-English speakers are likely
311 to be under-represented. On the other hand, case ascertainment varied by provider and women
312 from providers with higher case ascertainment (ascertainment > 45%) were more often from a non-
313 white ethnic background and a more deprived areas than those referred to providers with lower
314 case ascertainment⁴ which suggests that the impact of not having questionnaires in other languages
315 is likely to be small.

316

317 **CONCLUSION**

318 About three in four women at their first visit to a gynaecological outpatient clinic for HMB in England
319 and Wales reported that they had symptoms at least one year before they were referred to
320 secondary care. Women from more deprived areas reported more severe HMB symptoms and a
321 poorer quality of life, which demonstrates a higher burden of disease at the time of referral to
322 secondary care. Primary and secondary care providers should examine to what extent these
323 differences reflect barriers in access to gynaecological secondary care services or women's
324 perceptions of their menstrual problems and health-seeking behaviour.

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9
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11
12 332 Healthcare Quality Improvement Partnership, who have no responsibility or liability for the accuracy,
13
14 333 currency, reliability and/or correctness of this publication.
15

16 334
17 335 **DATA SHARING STATEMENT**

18 336 The data analysed were collected as part of a national clinical audit and linked to administrative
19
20 337 hospital data (Hospital Episode Statistics). They were shared with the authors by the Healthcare
21
22 338 Quality Improvement Partnership, Health and Social Care Information Centre and the Royal College
23
24 339 of Surgeons of England. The data cannot be shared further without formal application to the data
25
26 340 providers.
27

28 341
29 342 **CONTRIBUTORS**

30 343 The research question was derived by TM and JvdM. Data collection was supported directly by AK,
31
32 344 IGU, DC, LBM and through advice by JS, TM, JvdM. Data analysis was performed by AK, IGU & RSG.
33
34 345 All authors contributed to the writing of the manuscript.
35

36 346
37 347 **COMPETING INTERESTS**

38 348 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf
39
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45
46 352 submitted work in the previous three years; no other relationships or activities that could appear to
47
48 353 have influenced the submitted work.
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449 **Table 1: Patient characteristics at the first gynaecology outpatient visit for HMB**
 450 **(% and number unless otherwise stated)**

	Full Cohort (n=15,325)
Age, mean (sd) in years	42.3 (7.6)
Age groups	
18-34	14.9 (2,283)
35-39	12.9 (1,971)
40-44	26.6 (4,071)
45-49	31.3 (4,794)
≥50	14.4 (2,206)
Body mass index, mean (sd) in kg/m ²	27.3 (5.4)
Body mass index, categories	
≤25	39.6 (4,681)
25-30	31.7 (3,739)
≥30	28.7 (3,392)
Missing	3,513
Parity	
Nulliparous	17.0 (2,530)
Parous	83.0 (12,338)
Missing	457
Number of reported comorbidities	
0	66.3 (10,165)
1	25.3 (3,878)
≥2	8.4 (1,282)
Ethnicity	
White	88.3 (12,614)
Asian or Asian British	4.3 (607)
Black or Black British	5.4 (770)
Other	2.0 (292)
Missing	1,042
Socioeconomic deprivation (IMD)	
Quintile 1 (most deprived)	23.5 (3,418)
Quintile 2	21.7 (3,159)
Quintile 3	20.2 (2,944)
Quintile 4	18.7 (2,720)
Quintile 5 (least deprived)	15.8 (2,304)
Missing	780

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Table 2. Severity and duration of symptoms at the first outpatient visit, by age group, ethnicity and socioeconomic deprivation

	Severity score (0 best and 100 worst) (n=14,990)			Condition-specific quality of life (0 worst and 100 best) (n=14,586)			Generic quality of life (0 death and 1 perfect health) (n=13,802)			Symptoms ≥1 year (n=14,866)		
	Mean score (se)	Adjusted ⁱ difference (95% CI)	p-value	Mean score (se)	Adjusted ⁱ difference (95% CI)	p-value	Mean score (se)	Adjusted ⁱ difference(95% CI)	p-value	% (se)	Adjusted ⁱ OR (95% CI)	p-value
11 Total	61.8 (0.17)			34.7 (0.18)			0.65 (0.28)			74.0 (0.36)		
12 Age group												
13 18-34	63.1 (0.44)	-		33.2 (0.48)	-		0.61 (0.007)	-		70.7 (0.98)	-	
14 35-39	62.9 (0.49)	-1.59 (-2.89, -0.29)		33.3 (0.51)	1.75 (0.39, 3.10)		0.63 (0.008)	0.03 (0.01, 0.05)		74.8 (1.00)	1.25 (1.09, 1.44)	
15 40-44	62.5 (0.33)	-2.17 (-3.30, -1.04)	p<0.001	33.7 (0.35)	2.59 (1.40, 3.77)	p<0.001	0.64 (0.005)	0.04 (0.02, 0.06)	p<0.001	76.8 (0.67)	1.39 (1.23, 1.58)	p<0.001
16 45-49	61.3 (0.31)	-3.36 (-4.47, -2.51)		35.4 (0.33)	4.23 (3.06, 5.39)		0.67 (0.005)	0.07 (0.05, 0.08)		74.2 (0.64)	1.20 (1.06, 1.35)	
17 ≥50	59.0 (0.47)	-5.88 (-7.19, -4.58)		38.2 (0.51)	7.31 (5.93, 8.68)		0.70 (0.007)	0.10 (0.07, 0.12)		70.9 (0.98)	1.01 (0.88, 1.16)	
18 Ethnicity												
19 White	61.9 (0.19)	-		34.8 (0.20)	-		0.66 (0.003)	-		74.1 (0.38)	-	
20 Black or Black British	61.5 (0.82)	-1.93 (-3.51, -0.35)		35.0 (0.86)	1.45 (-0.16, 3.06)		0.62 (0.01)	-0.01 (-0.08, 0.02)		79.4 (1.47)	1.34 (1.11, 1.62)	
21 Asian or Asian British	60.7 (1.02)	-2.38 (-4.25, -0.51)	P=0.011	34.2 (1.07)	1.32 (-0.59, 3.22)	0.1392	0.58 (0.02)	-0.05 (-0.88, -0.01)	p<0.001	66.1 (1.49)	0.70 (0.58, 0.85)	p<0.001
22 Other	61.5 (1.33)	-0.46 (-3.09, 2.16)		33.9 (1.41)	-1.01 (-3.54, 1.51)		0.60 (0.02)	-0.05 (-0.30, -0.20)		72.3 (2.67)	0.92 (0.70, 1.20)	
23 Socioeconomic deprivation (IMD)												
24 Quintile 1 (most deprived)	65.5 (0.37)	-		30.5 (0.39)	-		0.55 (0.007)	-		72.0 (0.78)	-	
25 Quintile 2	63.5 (0.38)	-1.53 (-2.57, 0.50)		33.1 (0.40)	1.82 (0.75, 2.90)		0.62 (0.006)	0.06 (0.05, 0.08)		73.6 (0.80)	1.11 (0.99, 1.24)	
26 Quintile 3	61.6 (0.39)	-4.22 (-4.30, -2.12)	p<0.001	35.0 (0.41)	3.44 (2.34, 4.54)	p<0.001	0.67 (0.006)	0.09 (0.08, 0.11)	p<0.001	75.1 (0.81)	1.20 (1.06, 1.34)	P=0.0091
27 Quintile 4	59.5 (0.41)	-6.02 (-6.02, -3.87)		36.8 (0.43)	4.78 (3.66, 5.90)		0.71 (0.006)	0.13 (0.12, 0.15)		74.5 (0.85)	1.16 (1.03, 1.31)	
28 Quintile 5 (least deprived)	58.2 (0.44)	-6.07 (-7.23, -4.91)		38.6 (0.46)	6.29 (5.10, 7.48)		0.73 (0.006)	0.14 (0.13, 0.16)		75.1 (0.91)	1.21 (1.07, 1.37)	

Footnote: All multivariable models were adjusted for body mass index, parity, and number of co-morbidities. P-values based on Wald test

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	7
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Only one stage
		(c) Consider use of a flow diagram	Only one stage
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	8 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	N/A (Baseline)
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A (Baseline results)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9 (Table 2)
		(b) Report category boundaries when continuous variables were categorized	8 (Table 2)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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Keywords:	GYNAECOLOGY, EPIDEMIOLOGY, PRIMARY CARE

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3 1 Sociodemographic differences in symptom severity and duration amongst
4 2 women referred to secondary care for menorrhagia in England and Wales: a
5 3 cohort study from the National Heavy Menstrual Bleeding Audit
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9 6 Kiran A^{1,2,†}, Geary RS^{1,2,†}, Gurol-Urganci I^{1,2}, Cromwell DA^{1,2}, Bansi-Matharu L³, Shakespeare J⁴,
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24 21

1
2
3 22 **ABSTRACT**

4 23 **Objective** To examine symptom severity and duration at time of referral to secondary care for heavy
5
6 24 menstrual bleeding by socio-economic deprivation, age and ethnicity

7 25 **Design** Cohort analysis of data from the National Heavy Menstrual Bleeding Audit linked to Hospital
8
9 26 Episode Statistics data

10 27 **Setting** English and Welsh National Health Services (secondary care): February 2011 to January 2012

11 28 **Participants** 15,325 women aged 18 to 60 years in England and Wales who had a new referral for
12
13 29 heavy menstrual bleeding to a gynaecology outpatient department

14 30 **Methods** Multivariable linear regression to calculate adjusted differences in mean symptom severity
15
16 31 and quality of life scores at first outpatient visit. Multivariable logistic regression to calculate
17
18 32 adjusted odds ratios. Adjustment for body mass index, parity and co-morbidities.

19 33 **Primary Outcome Measures** Mean symptom severity score (0=best, 100=worst), mean condition-
20
21 34 specific quality of life score (0=worst, 100=best) and symptom duration (≥ 1 year).

22 35 **Results** Women were on average 42 years old and 12% were non-white. Mean symptom severity
23
24 36 and condition-specific quality of life scores were 61.8 and 34.7. Almost three-quarters of women
25
26 37 (74%) reported having had symptoms for ≥ 1 year. Women from more deprived areas had more
27
28 38 severe symptoms at their first outpatient visit (difference -6.1; 95%CI -7.2:-4.9, between least and
29
30 39 most deprived quintile) and worse condition-specific quality of life (difference 6.3; 95%CI 5.1:7.5).
31
32 40 Symptom severity declined with age whilst quality of life improved.

33 41 **Conclusions** Women living in more deprived areas reported more severe HMB symptoms and poorer
34
35 42 quality of life at the start of treatment in secondary care. Providers should examine referral practices
36
37 43 to explore if these differences reflect women's health-seeking behaviour or how providers decide
38
39 44 whether or not to refer.

40
41 46 **Funding** The National Heavy Menstrual Bleeding (HMB) Audit was funded by the Healthcare Quality
42
43 47 Improvement Partnership as part of the National Clinical Audit and Patient Outcomes Programme,
44
45 48 contract number HQIP NCA 004.

46 49 **Keywords** heavy menstrual bleeding, deprivation, ethnicity, health inequalities, patient-reported
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48 50 outcomes, quality of life

49 51 **Tweetable abstract** Women from deprived areas referred with more severe heavy menstrual
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51 52 bleeding, potentially reflecting inequity

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3 55 **Strengths and limitations of this study**

- 4 56 • This study is the first to examine Heavy Menstrual Bleeding symptom severity and duration
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6 57 at time of referral to secondary care
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8 58 • The inclusion of patient-reported symptom severity and quality of life addresses a
9
10 59 knowledge gap about how women feel about their heavy menstrual bleeding
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12 60 • As the data were collected by a national audit in England and Wales the sample is relatively
13
14 61 large, allowing comparisons between ethnic minority groups
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16 62 • Even though the sample size is large, the National HMB Audit recruited approximately 30%
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18 63 of eligible women. However, the characteristics of the women recruited were broadly
19
20 64 representative of the UK population in terms of ethnicity and age
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22 65 • Linking audit data to administrative hospital data also allowed comparisons between
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24 66 socioeconomic groups
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68 INTRODUCTION

69 Heavy menstrual bleeding (HMB) is a common condition that affects one in four women of
70 reproductive age. In England and Wales, an estimated 50,000 women with HMB are referred from
71 primary care to secondary care gynaecology services provided by the National Health Service (NHS)
72 every year[1]. Menstrual disorders account for approximately 20% of referrals to specialist
73 gynaecology services[2] and studies have found significant regional variations in use of surgical
74 treatment within England[3].

75
76 Women with HMB have significantly worse quality of life than women with normal menstrual
77 bleeding loss, in terms of their physical and mental health, as well as their emotional, social and
78 material quality of life[4-7]. More than a third of women with HMB report severe pain[7]. HMB is
79 also associated with morbidity, including anaemia and related fatigue[8, 9]. Women with HMB
80 experience reduced participation in social activities and their personal relationships and attendance
81 at work can be adversely affected[10].

82
83 In order to improve the quality of life of women with HMB, it is important to understand both the
84 aetiology of this condition and its management in primary and secondary care[11]. The prevalence
85 of HMB and conditions which affect symptom severity has been reported to vary by ethnicity[12-15].
86 In addition, cultural norms and patient choice for treatment may vary between different groups[16,
87 17].

88
89 In this study, we used data from the National HMB Audit to examine symptom severity, quality of
90 life and symptom duration at women's first gynaecology outpatient visit for HMB. The National HMB
91 Audit was a 4-year project (2010 - 2014) that assessed patient-reported outcomes and experiences
92 of care for women with HMB in England and Wales. Our objective is to examine symptom severity
93 and duration at the time of referral to secondary care by age, ethnicity and socio-economic
94 deprivation to get a better understanding of the burden of disease at the start of treatment in
95 secondary care.

96

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2
3 97 **METHODS**

4 98 **Data collection**

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6 99 Full details of the methods used in the National HMB Audit have been reported elsewhere[1, 4, 18,
7 100 19]. Women aged between 18 and 60 years in England and Wales who had a new referral for HMB
8 101 to a gynaecology outpatient department were eligible to participate in the National HMB Audit.
9 102 Women who had visited a gynaecology outpatient clinic for HMB within the previous 12 months
10 103 were excluded. Recruitment took place between 1 February 2011 and 31 January 2012[1, 19].
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15 105 Women who consented to participate completed a baseline questionnaire (58 questions) on age,
16 106 ethnicity, duration of HMB symptoms, obstetric history, prior treatment received for HMB and co-
17 107 morbidities. The questionnaire also collected patient-reported HMB-specific and generic quality of
18 108 life measures.
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23 110 Scores for symptom severity and condition-specific health-related quality of life were adapted from
24 111 the Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire[20]. Of five candidate
25 112 questionnaires evaluated, only the UFS-QOL could be used throughout the care pathway, measured
26 113 HRQoL and was psychometrically strong[18]. The UFS-QOL was therefore adapted for HMB and a UK
27 114 population. We conducted semi-structured interviews with women ($n = 7$) and clinicians ($n = 5$) and
28 115 a mini focus group ($n = 3$) with local Heavy Menstrual Bleeding Audit coordinators to determine
29 116 suitable alternative words to describe HMB, and to identify words not clearly understood in UK
30 117 English. Based on this we changed the wording to refer to 'heavy menstrual bleeding' (i.e. heavy
31 118 periods) rather than 'fibroids', changed 'checking' to 'ticking'; 'soiling' to 'staining'; 'blue' to 'low';
32 119 and 'wiped out' to 'exhausted'. The adapted version performed acceptably in a psychometric
33 120 evaluation. Overall, the symptom severity subscale and the HRQL subscale of the UFS-QOL used as
34 121 outcomes demonstrated the strongest psychometric properties and have been used to report the
35 122 audit data. The UFS-QOL consists of eight symptom items and 29 HRQoL items. The symptom items
36 123 are scored to produce a severity subscale and the HRQoL items are scored into subscales (concern,
37 124 activities, energy/mood, control, self-consciousness and sexual function). The HRQoL sub-scales can
38 125 be used separately or combined into an overall HRQoL score. We use the overall HRQoL score in this
39 126 paper.
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53 129 A generic health-related quality of life measure was derived from the European Quality of Life-5
54 130 Dimensions (EuroQol-5 or EQ-5D)[21]. This generic measure was used because it is the instrument
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3 131 recommended by the Department of Health and allows comparisons with other national studies,
4 132 such as the Patient Reported Outcome Measures study of common elective surgical procedures[21].
5
6 133 Women completed the questionnaire in hospital before their consultation. Using multiple sources of
7
8 134 data, the recruitment rate of the audit was estimated to be 31.9%[1]. Descriptive results from the
9
10 135 National HMB Audit have been published elsewhere[1, 4, 18, 19].
11

12 136
13 137 Data from the prospective audit were linked at patient level to records from Hospital Episode
14 138 Statistics (HES) and Patient Episode Database for Wales (PEDW), administrative databases that
15 139 capture all inpatient and outpatient episodes in English and Welsh NHS hospitals. Data linkage was
16 140 performed using deterministic linkage criteria that included NHS number, sex and date of birth.
17
18 141

142 **Measures**

143 Symptom severity, condition-specific quality of life and generic quality of life scores and the
144 reported duration of symptoms at the first outpatient visit were used as outcomes in this study. The
145 severity and quality of life scores were analysed as continuous variables. Symptom severity scores
146 ranged from 0 (best possible score) to 100 (greatest symptom severity, worst possible score).
147 Condition-specific quality of life ranged from 0 (poorest quality of life) to 100 (best quality of life).
148 Generic quality of life is expressed on a scale with 0 representing death and 1 perfect health[22].
149 Women were asked "How long have you had symptoms of heavy menstrual bleeding", with "2
150 months or less", "more than 2 months but less than 1 year", "more than 1 year" and "don't know" as
151 possible response categories. For analysis, duration of symptoms was grouped as "<1 year", "≥1
152 year" with "don't know" coded as missing. Levels of missing data on HMB symptoms and health-
153 related quality of life were low (2.2% for severity, 4.8% for condition-specific and 9.9% for generic
154 quality of life and 3.0% for symptom duration).
155

156 Age was categorised as 18-34, 35-39, 40-44, 45-49, ≥50 years for analysis. Women reported their
157 ethnicity as "white", "mixed", "Asian or Asian British", "black or black British", "Chinese" or "other".
158 For analysis, the "mixed", "Chinese" and "other" groups were combined as "other" due to small
159 numbers of women reporting these ethnicities. Self-reported height and weight data were used to
160 derive body mass index (BMI), categorised according to WHO groups as ≤25, 25-30, and ≥30[23].
161 Women reported how many times they had seen their GP for HMB in the year prior to their first
162 outpatient visit, and this was grouped as 0, 1-2, 3-4, >4 for analysis ("don't know" was coded as
163 missing).
164

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3 165 Women reported their parity, grouped for analysis as “nulliparous” or “parous”. Women were also
4 166 asked “Have you been told by a doctor that you have any of the following: “heart disease (for
5 167 example angina, heart attack or heart failure), high blood pressure, lung disease (for example
6 168 chronic bronchitis or emphysema), diabetes, depression, thyroid disorder, kidney disease, cancer
7 169 (within the last 5 years). For analysis, the number of co-morbidities reported was grouped as 0, 1,
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10
11 170 ≥ 2 .

171

172 Information on socio-economic deprivation (Index of Multiple Deprivation (IMD)) was extracted
173 from HES and PEDW. IMD is a relative measure of deprivation for small areas across a number of
174 domains, including income, employment, education and housing. We used quintiles of IMD (level 1 =
175 most deprived areas, level 5 = least deprived areas). The methods used to calculate IMD scores in
176 each country in the UK are similar but not directly comparable[24]. For analysis, we generated a
177 combined measure of deprivation for England and Wales by assigning those in each country-specific
178 quintile to the same quintile in a combined measure. This preserved women’s relative deprivation
179 position within each country.

180

181 **Statistical analysis**

182 Means and standard deviations (SD) and proportions were used to describe the cohort. Regression
183 analyses were used to examine the relationship between age, ethnicity and socio-economic
184 deprivation and each of the outcomes. For the scores representing symptom severity, condition
185 specific and generic quality of life, multivariable linear regression was used to calculate adjusted
186 differences in mean scores. For duration of symptoms (<1 year and ≥ 1 year), multivariable logistic
187 regression was used to calculate adjusted odds ratios (OR). Regression models included BMI, parity
188 and number of co-morbidities as potential confounders. Levels of missing data were low (<3%) for
189 the majority of variables with the exception of ethnicity (7% missing) and BMI (approximately 23%
190 missing, Table 1). Missing values for explanatory variables were imputed using multiple imputation
191 by chained equations[25] and statistical coefficients were obtained using ten imputed datasets and
192 combined using Rubin’s rules[26].

193

194 **ETHICAL APPROVAL**

195 The data are from the National Heavy Menstrual Bleeding (HMB) Audit. Based on the Health
196 Research Authority’s guidance, audits are regulated as standard clinical practice outside of the
197 Research Ethics Service[27].

198

RESULTS**Patient Characteristics**

15,325 eligible women completed the questionnaire at their first visit to a gynaecology outpatient department and 15,294 (99.8%) could be linked to HES or PEDW which provided information on socioeconomic deprivation. The women's mean age was 42.3 years (SD 7.6) and BMI 27.3 (SD 5.4) (Table 1). About one in five were nulliparous and one in three reported at least one co-morbidity. 11.7% of women reported a non-white ethnicity, with black or black British (5.4%) and Asian or Asian British (4.3%) being the largest non-white groups. Women in the two least socioeconomically deprived national quintile groups (18.7% in quintile 4 and 15.8% in quintile 5) were under-represented given that per definition 20% of women are expected to be in each group. The distribution of symptom severity, condition-specific and generic quality of life and symptom duration by level of deprivation did not vary significantly between women in England and Wales (data not shown).

Table 1: Patient characteristics at the first gynaecology outpatient visit for HMB (% and number unless otherwise stated)

The mean score for symptom severity was 61.8 (standard error (SE) 0.17) with 74.0% of women reporting that they had HMB symptoms for more than one year. The mean score for condition-specific quality of life was 34.7 (SE: 0.18) and for generic quality of life 0.65 (SE: 0.28) (Table 2).

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

233 women reported better quality of life at their first HMB outpatient visit (difference 7.3; 95% CI: 5.9
234 to 8.7) between oldest and youngest age groups). Symptom severity also varied by ethnicity: black
235 and Asian women reported less severe symptoms than white women (difference compared to white
236 women -1.9 and -2.4 respectively, Table 2). Condition-specific quality of life did not vary significantly
237 by ethnicity, whereas compared to white women, Asian woman reported lower generic quality of
238 life scores (Table 2).

239

240 **Duration of symptoms**

241 Women living in the most deprived areas were slightly less likely to report having had HMB
242 symptoms for ≥ 1 year than those living in the less deprived areas. Women aged between 35 and 49
243 years were more likely to report having experienced HMB symptoms for ≥ 1 year than those younger
244 than 35. Compared to white women, black women were more likely than white women to report
245 symptoms for ≥ 1 year and Asian women were less likely.

246

247 **Table 2. Severity and duration of symptoms at the first outpatient visit, by age group, ethnicity 248 and socioeconomic deprivation**

249

250 **DISCUSSION**

251 **Main Findings**

252 Women living in more socioeconomically deprived areas reported more severe HMB symptoms and
253 poorer quality of life at their first gynaecology outpatient visit. Older women reported less severe
254 symptoms and better quality of life than younger women. Reported symptom severity also varied by
255 ethnicity with black and Asian women reporting less severe symptoms than women from white
256 ethnic backgrounds.

257

258 Three quarters of the women referred to secondary care reported that they had had symptoms of
259 HMB for at least one year and women living in the most deprived areas were least likely to report
260 having had HMB symptoms for ≥ 1 year.

261

262 **Interpretation**

263 More severe symptoms and poorer quality of life at first outpatient visit by socioeconomic
264 deprivation, after adjustment for possible differences in age, ethnicity and body mass index, reflect
265 that women from more deprived backgrounds report more severe problems at the start of
266 treatment in secondary care but they were least likely to report that they had symptoms for at least

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3 267 one year. The difference in the symptom severity score between women from the least and the
4 268 most deprived areas of about 6 is likely to be clinically significant, given that women who completed
5 269 a questionnaire one year after their first outpatient visit and reported that their symptoms were 'a
6 270 little better' had severity scores that were, on average, approximately 10 lower than women who
7 271 reported (in response to same questionnaire) that their symptoms were 'about the same'. There is
8 272 evidence that people from more socioeconomically deprived backgrounds may be more accepting of
9 273 symptoms, chronic pain or poorer health-related quality of life[28], which is a possible explanation
10 274 for these finding. Conversely, those from more affluent socioeconomic backgrounds have been
11 275 found to report greater impact of health conditions on their health and their quality of life, which
12 276 may be linked to their higher expectations about health and life in general[29].
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21 278 Alternative explanations are that differences in symptom severity, quality of life and symptom
22 279 reflect inequitable access as well as differences in the nature and causes of HMB. Age is often found
23 280 to be associated with symptom severity^{15, 16}[30, 31]. Black women are 2-3 times more likely to have
24 281 fibroids and endometriosis[31]. Accepting heavy periods as normal vary by ethnicity and other social
25 282 factors, which in turn can also lead to reluctance to seek care for HMB[16]. Ethnographic research
26 283 suggests that some women of South Asian ethnicity do not seek healthcare for HMB due to the
27 284 belief that heavy periods cleanse the body[17]. We adjust for patient-level characteristics that may
28 285 capture some of these differences but were unable to adjust for other unmeasured potential
29 286 confounders.
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36 287
37 288 The observation that women living in the most socio-economically deprived areas reported the most
38 289 severe symptoms but were least likely to report having had symptoms for ≥ 1 year may reflect the
39 290 wording of the question; women were asked "How long have you had symptoms of heavy menstrual
40 291 bleeding?" and women whose symptom severity had worsened may have reported the duration of
41 292 the most recent severity, rather than the overall duration.
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45 293
46 294 A key question is whether the observed differences in symptom severity and condition-specific
47 295 quality of life at the women's first gynaecology outpatient visit are related to differences in women's
48 296 health seeking behaviour or to differences in how GPs and gynaecologists decide on whether to
49 297 refer a woman with HMB. A study of self-reported health-care seeking behaviour in England did not
50 298 find evidence that inequality in access to secondary care according to socioeconomic or ethnic
51 299 backgrounds is related to patients being less likely to go to their GP or a hospital's emergency
52 300 department[32]. Similarly, a survey of patients with chronic joint pain found that the proportions of
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3 301 patients who said that they were seeking help from their GP did not differ according to their
4 302 socioeconomic background[33]. On the other hand, a national study including 130,000 patients from
5 303 more than 300 primary care practices in England found that older patients and those from more
6 304 deprived areas were less likely to be referred to secondary care[34].
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306 **Implications for policy and practice**

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11
12 307 In the UK, national guidelines for the management of HMB have been developed by the National
13 308 Institute for Health and Care Excellence and the Royal College of Obstetricians and Gynaecologists
14 309 (RCOG)[11, 35, 36]. The National HMB Audit carried out a survey of NHS hospitals in England and
15 310 Wales to find out how care for women with HMB is organised and delivered at local levels. It found
16 311 that key systems such as the availability of local protocols, which specified local arrangements for
17 312 patient referral and management in response to the NICE guidelines, were reported only by 30% of
18 313 hospitals[37]. Wide variation in the investigations and treatments that were offered to women with
19 314 HMB in primary care were also noted. The implementation of locally agreed referral pathways,
20 315 recommended by the RCOG, will help to reduce this variation[38].
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28 317 Women with HMB in this study reported substantially worse QoL (EQ-5D mean: 0.65, SD: 0.33) than
29 318 the population average for women in England (mean: 0.85, SD: 0.003), and compared to women
30 319 with incontinence (mean: 0.73, SD: 0.26)[39, 40]. This reinforces the need for interventions to focus
31 320 on improving women's quality of life, as recommended by recent NICE guidelines[11]. Obesity can
32 321 be associated with HMB so health promotion interventions around diet and exercise could
33 322 supplement HMB-specific interventions. Criteria for what constitutes a meaningful improvement in
34 323 quality of life are less clear. Awareness raising activities relating to the availability of treatments for
35 324 HMB could increase healthcare seeking before symptoms become severe. This may be particularly
36 325 beneficial for those from more deprived background who may be more accepting of chronic pain
37 326 and worse quality-of-life. In highlighting differences in symptom severity at their first gynaecology
38 327 outpatient visit, our findings draw attention to the lack of an agreed threshold for referral of women
39 328 with HMB to secondary care in terms of symptom severity and quality of life. Routine measurement
40 329 of both symptom severity and quality of life may be required to stimulate greater consistency in
41 330 referral thresholds but validated instruments specific to HMB are currently lacking. As there is no
42 331 widely used condition-specific measure of condition-specific quality of life for HMB, the National
43 332 HMB Audit used the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, adapted
44 333 for a UK population of women with HMB[18].
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3 335 **Strengths and Limitations**

4 336 This study is the first to examine the relationship between sociodemographic factors and patient-
5
6 337 reported HMB symptom severity, quality of life and symptom duration in an outpatient setting. It
7
8 338 used data collected by a national audit carried out in England and Wales, which produced a relatively
9
10 339 large sample. We estimated that the National HMB Audit recruited about 30% of all eligible women.
11
12 340 There is no direct way to compare the characteristics of the women who were recruited and those
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14 341 who were not. However, the characteristics of the women who were recruited were broadly
15
16 342 representative of the UK population in terms of the distributions of ethnicity and age[41, 42].
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18 343

19 344 Survey questionnaires were only available in the English language, so non-English speakers are likely
20
21 345 to be under-represented. On the other hand, case ascertainment varied by provider and women
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23 346 from providers with higher case ascertainment (ascertainment > 45%) were more often from a non-
24
25 347 white ethnic background and a more deprived areas than those referred to providers with lower
26
27 348 case ascertainment[4] which suggests that the impact of not having questionnaires in other
28
29 349 languages is likely to be small.

30 350

31 351 **CONCLUSION**

32 352 About three in four women at their first visit to a gynaecological outpatient clinic for HMB in England
33
34 353 and Wales reported that they had symptoms at least one year before they were referred to
35
36 354 secondary care. Women from more deprived areas reported more severe HMB symptoms and a
37
38 355 poorer quality of life, which demonstrates a higher burden of disease at the time of referral to
39
40 356 secondary care. Primary and secondary care providers should examine to what extent these
41
42 357 differences reflect barriers in access to gynaecological secondary care services or women's
43
44 358 perceptions of their menstrual problems and health-seeking behaviour.

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368 currency, reliability and/or correctness of this publication.

370 DATA SHARING STATEMENT

371 The data analysed were collected as part of a national clinical audit and linked to administrative
372 hospital data (Hospital Episode Statistics). They were shared with the authors by the Healthcare
373 Quality Improvement Partnership, Health and Social Care Information Centre and the Royal College
374 of Surgeons of England. The data cannot be shared further without formal application to the data
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380 All authors contributed to the writing of the manuscript.

382 COMPETING INTERESTS

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491 **Table 1: Patient characteristics at the first gynaecology outpatient visit for HMB**
 492 **(% and number unless otherwise stated)**

	Full Cohort (n=15,325)
Age, mean (sd) in years	42.3 (7.6)
Age groups	
18-34	14.9 (2,283)
35-39	12.9 (1,971)
40-44	26.6 (4,071)
45-49	31.3 (4,794)
≥50	14.4 (2,206)
Body mass index, mean (sd) in kg/m ²	27.3 (5.4)
Body mass index, categories	
≤25	39.6 (4,681)
25-30	31.7 (3,739)
≥30	28.7 (3,392)
Missing	3,513
Parity	
Nulliparous	17.0 (2,530)
Parous	83.0 (12,338)
Missing	457
Number of reported comorbidities	
0	66.3 (10,165)
1	25.3 (3,878)
≥2	8.4 (1,282)
Ethnicity	
White	88.3 (12,614)
Asian or Asian British	4.3 (607)
Black or Black British	5.4 (770)
Other	2.0 (292)
Missing	1,042
Socioeconomic deprivation (IMD)	
Quintile 1 (most deprived)	23.5 (3,418)
Quintile 2	21.7 (3,159)
Quintile 3	20.2 (2,944)
Quintile 4	18.7 (2,720)
Quintile 5 (least deprived)	15.8 (2,304)
Missing	780

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Table 2. Severity and duration of symptoms at the first outpatient visit, by age group, ethnicity and socioeconomic deprivation

	Severity score (0 best and 100 worst) (n=14,990)			Condition-specific quality of life (0 worst and 100 best) (n=14,586)			Generic quality of life (0 death and 1 perfect health) (n=13,802)			Symptoms ≥1 year (n=14,866)		
	Mean score (se)	Adjusted ⁱ difference (95% CI)	p-value	Mean score (se)	Adjusted ⁱ difference (95% CI)	p-value	Mean score (se)	Adjusted ⁱ difference(95% CI)	p-value	% (se)	Adjusted ⁱ OR (95% CI)	p-value
11 Total	61.8 (0.17)			34.7 (0.18)			0.65 (0.28)			74.0 (0.36)		
12 Age group												
13 18-34	63.1 (0.44)	-		33.2 (0.48)	-		0.61 (0.007)	-		70.7 (0.98)	-	
14 35-39	62.9 (0.49)	-1.59 (-2.89, -0.29)		33.3 (0.51)	1.75 (0.39, 3.10)		0.63 (0.008)	0.03 (0.01, 0.05)		74.8 (1.00)	1.25 (1.09, 1.44)	
15 40-44	62.5 (0.33)	-2.17 (-3.30, -1.04)	p<0.001	33.7 (0.35)	2.59 (1.40, 3.77)	p<0.001	0.64 (0.005)	0.04 (0.02, 0.06)	p<0.001	76.8 (0.67)	1.39 (1.23, 1.58)	p<0.001
16 45-49	61.3 (0.31)	-3.36 (-4.47, -2.51)		35.4 (0.33)	4.23 (3.06, 5.39)		0.67 (0.005)	0.07 (0.05, 0.08)		74.2 (0.64)	1.20 (1.06, 1.35)	
17 ≥50	59.0 (0.47)	-5.88 (-7.19, -4.58)		38.2 (0.51)	7.31 (5.93, 8.68)		0.70 (0.007)	0.10 (0.07, 0.12)		70.9 (0.98)	1.01 (0.88, 1.16)	
18 Ethnicity												
19 White	61.9 (0.19)	-		34.8 (0.20)	-		0.66 (0.003)	-		74.1 (0.38)	-	
20 Black or Black British	61.5 (0.82)	-1.93 (-3.51, -0.35)		35.0 (0.86)	1.45 (-0.16, 3.06)		0.62 (0.01)	-0.01 (-0.08, 0.02)		79.4 (1.47)	1.34 (1.11, 1.62)	
21 Asian or Asian British	60.7 (1.02)	-2.38 (-4.25, -0.51)	P=0.011	34.2 (1.07)	1.32 (-0.59, 3.22)	0.1392	0.58 (0.02)	-0.05 (-0.88, -0.01)	p<0.001	66.1 (1.49)	0.70 (0.58, 0.85)	p<0.001
22 Other	61.5 (1.33)	-0.46 (-3.09, 2.16)		33.9 (1.41)	-1.01 (-3.54, 1.51)		0.60 (0.02)	-0.05 (-0.30, -0.20)		72.3 (2.67)	0.92 (0.70, 1.20)	
23 Socioeconomic deprivation (IMD)												
24 Quintile 1 (most deprived)	65.5 (0.37)	-		30.5 (0.39)	-		0.55 (0.007)	-		72.0 (0.78)	-	
25 Quintile 2	63.5 (0.38)	-1.53 (-2.57, 0.50)		33.1 (0.40)	1.82 (0.75, 2.90)		0.62 (0.006)	0.06 (0.05, 0.08)		73.6 (0.80)	1.11 (0.99, 1.24)	
26 Quintile 3	61.6 (0.39)	-4.22 (-4.30, -2.12)	p<0.001	35.0 (0.41)	3.44 (2.34, 4.54)	p<0.001	0.67 (0.006)	0.09 (0.08, 0.11)	p<0.001	75.1 (0.81)	1.20 (1.06, 1.34)	P=0.0091
27 Quintile 4	59.5 (0.41)	-6.02 (-6.02, -3.87)		36.8 (0.43)	4.78 (3.66, 5.90)		0.71 (0.006)	0.13 (0.12, 0.15)		74.5 (0.85)	1.16 (1.03, 1.31)	
28 Quintile 5 (least deprived)	58.2 (0.44)	-6.07 (-7.23, -4.91)		38.6 (0.46)	6.29 (5.10, 7.48)		0.73 (0.006)	0.14 (0.13, 0.16)		75.1 (0.91)	1.21 (1.07, 1.37)	

Footnote: All multivariable models were adjusted for body mass index, parity, and number of co-morbidities. P-values based on Wald test

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	7
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Only one stage
		(c) Consider use of a flow diagram	Only one stage
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	8 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	N/A (Baseline)
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A (Baseline results)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9 (Table 2)
		(b) Report category boundaries when continuous variables were categorized	8 (Table 2)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

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3 1 Sociodemographic differences in symptom severity and duration amongst
4 2 women referred to secondary care for menorrhagia in England and Wales: a
5 3 cohort study from the National Heavy Menstrual Bleeding Audit
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9 6 Kiran A^{1,2,†}, Geary RS^{1,2,†}, Gurol-Urganci I^{1,2}, Cromwell DA^{1,2}, Bansi-Matharu L³, Shakespeare J⁴,
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3 22 **ABSTRACT**

4 23 **Objective** To examine symptom severity and duration at time of referral to secondary care for heavy
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6 24 menstrual bleeding by socio-economic deprivation, age and ethnicity

7 25 **Design** Cohort analysis of data from the National Heavy Menstrual Bleeding Audit linked to Hospital
8
9 26 Episode Statistics data

10 27 **Setting** English and Welsh National Health Services (secondary care): February 2011 to January 2012

11 28 **Participants** 15,325 women aged 18 to 60 years in England and Wales who had a new referral for
12
13 29 heavy menstrual bleeding to a gynaecology outpatient department

14 30 **Methods** Multivariable linear regression to calculate adjusted differences in mean symptom severity
15
16 31 and quality of life scores at first outpatient visit. Multivariable logistic regression to calculate
17
18 32 adjusted odds ratios. Adjustment for body mass index, parity and co-morbidities.

19 33 **Primary Outcome Measures** Mean symptom severity score (0=best, 100=worst), mean condition-
20
21 34 specific quality of life score (0=worst, 100=best) and symptom duration (≥ 1 year).

22 35 **Results** Women were on average 42 years old and 12% were non-white. Mean symptom severity
23
24 36 and condition-specific quality of life scores were 61.8 and 34.7. Almost three-quarters of women
25
26 37 (74%) reported having had symptoms for ≥ 1 year. Women from more deprived areas had more
27
28 38 severe symptoms at their first outpatient visit (difference -6.1; 95%CI -7.2:-4.9, between least and
29
30 39 most deprived quintile) and worse condition-specific quality of life (difference 6.3; 95%CI 5.1:7.5).
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32 40 Symptom severity declined with age whilst quality of life improved.

33 41 **Conclusions** Women living in more deprived areas reported more severe HMB symptoms and poorer
34
35 42 quality of life at the start of treatment in secondary care. Providers should examine referral practices
36
37 43 to explore if these differences reflect women's health-seeking behaviour or how providers decide
38
39 44 whether or not to refer.

40
41 46 **Funding** The National Heavy Menstrual Bleeding (HMB) Audit was funded by the Healthcare Quality
42
43 47 Improvement Partnership as part of the National Clinical Audit and Patient Outcomes Programme,
44
45 48 contract number HQIP NCA 004.

46 49 **Keywords** heavy menstrual bleeding, deprivation, ethnicity, health inequalities, patient-reported
47
48 50 outcomes, quality of life

49 51 **Tweetable abstract** Women from deprived areas referred with more severe heavy menstrual
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51 52 bleeding, potentially reflecting inequity

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3 55 **Strengths and limitations of this study**

- 4 56 • This study is the first to examine Heavy Menstrual Bleeding symptom severity and duration
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6 57 at time of referral to secondary care
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8 58 • The inclusion of patient-reported symptom severity and quality of life addresses a
9
10 59 knowledge gap about how women feel about their heavy menstrual bleeding
11
12 60 • As the data were collected by a national audit in England and Wales the sample is relatively
13
14 61 large, allowing comparisons between ethnic minority groups
15
16 62 • Even though the sample size is large, the National HMB Audit recruited approximately 30%
17
18 63 of eligible women. However, the characteristics of the women recruited were broadly
19
20 64 representative of the UK population in terms of ethnicity and age
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22 65 • Linking audit data to administrative hospital data also allowed comparisons between
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24 66 socioeconomic groups
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68 INTRODUCTION

69 Heavy menstrual bleeding (HMB) is a common condition that affects one in four women of
70 reproductive age. In England and Wales, an estimated 50,000 women with HMB are referred from
71 primary care to secondary care gynaecology services provided by the National Health Service (NHS)
72 every year[1]. Menstrual disorders account for approximately 20% of referrals to specialist
73 gynaecology services[2] and studies have found significant regional variations in use of surgical
74 treatment within England[3].

75
76 Women with HMB have significantly worse quality of life than women with normal menstrual
77 bleeding loss, in terms of their physical and mental health, as well as their emotional, social and
78 material quality of life[4-7]. More than a third of women with HMB report severe pain[7]. HMB is
79 also associated with morbidity, including anaemia and related fatigue[8, 9]. Women with HMB
80 experience reduced participation in social activities and their personal relationships and attendance
81 at work can be adversely affected[10].

82
83 In order to improve the quality of life of women with HMB, it is important to understand both the
84 aetiology of this condition and its management in primary and secondary care[11]. The prevalence
85 of HMB and conditions which affect symptom severity has been reported to vary by ethnicity[12-15].
86 In addition, cultural norms and patient choice for treatment may vary between different groups[16,
87 17].

88
89 In this study, we used data from the National HMB Audit to examine symptom severity, quality of
90 life and symptom duration at women's first gynaecology outpatient visit for HMB. The National HMB
91 Audit was a 4-year project (2010 - 2014) that assessed patient-reported outcomes and experiences
92 of care for women with HMB in England and Wales. Our objective is to examine symptom severity
93 and duration at the time of referral to secondary care by age, ethnicity and socio-economic
94 deprivation to get a better understanding of the burden of disease at the start of treatment in
95 secondary care.

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3 97 **METHODS**

4 98 **Data collection**

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6 99 Full details of the methods used in the National HMB Audit have been reported elsewhere[1, 4, 18,
7 100 19]. Women aged between 18 and 60 years in England and Wales who had a new referral for HMB
8 101 to a gynaecology outpatient department were eligible to participate in the National HMB Audit.
9 102 Women who had visited a gynaecology outpatient clinic for HMB within the previous 12 months
10 103 were excluded. Recruitment took place between 1 February 2011 and 31 January 2012[1, 19].
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15 105 Women who consented to participate completed a baseline questionnaire (58 questions) on age,
16 106 ethnicity, duration of HMB symptoms, obstetric history, prior treatment received for HMB and co-
17 107 morbidities. The questionnaire also collected patient-reported HMB-specific and generic quality of
18 108 life measures.
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23 110 Scores for symptom severity and condition-specific health-related quality of life were adapted from
24 111 the Uterine Fibroid Symptom and Quality of Life (UFS-QoL) questionnaire[20]. Of five candidate
25 112 questionnaires evaluated, only the UFS-QOL could be used throughout the care pathway, measured
26 113 HRQoL and was psychometrically strong[18]. The UFS-QOL was therefore adapted for HMB and a UK
27 114 population. We conducted semi-structured interviews with women ($n = 7$) and clinicians ($n = 5$) and
28 115 a mini focus group ($n = 3$) with local Heavy Menstrual Bleeding Audit coordinators to determine
29 116 suitable alternative words to describe HMB, and to identify words not clearly understood in UK
30 117 English. Based on this we changed the wording to refer to 'heavy menstrual bleeding' (i.e. heavy
31 118 periods) rather than 'fibroids', changed 'checking' to 'ticking'; 'soiling' to 'staining'; 'blue' to 'low';
32 119 and 'wiped out' to 'exhausted'. The adapted version performed acceptably in a psychometric
33 120 evaluation. Overall, the symptom severity subscale and the HRQL subscale of the UFS-QOL used as
34 121 outcomes demonstrated the strongest psychometric properties and have been used to report the
35 122 audit data. The UFS-QOL consists of eight symptom items and 29 HRQoL items. The symptom items
36 123 are scored to produce a severity subscale and the HRQoL items are scored into subscales (concern,
37 124 activities, energy/mood, control, self-consciousness and sexual function). The HRQoL sub-scales can
38 125 be used separately or combined into an overall HRQoL score. We use the overall HRQoL score in this
39 126 paper.
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53 129 A generic health-related quality of life measure was derived from the European Quality of Life-5
54 130 Dimensions (EuroQol-5 or EQ-5D)[21]. This generic measure was used because it is the instrument
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3 131 recommended by the Department of Health and allows comparisons with other national studies,
4 132 such as the Patient Reported Outcome Measures study of common elective surgical procedures[21].
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6 133 Women completed the questionnaire in hospital before their consultation. Using multiple sources of
7
8 134 data, the recruitment rate of the audit was estimated to be 31.9%[1]. Descriptive results from the
9
10 135 National HMB Audit have been published elsewhere[1, 4, 18, 19].
11

12 136

13 137 Data from the prospective audit were linked at patient level to records from Hospital Episode
14 138 Statistics (HES) and Patient Episode Database for Wales (PEDW), administrative databases that
15 139 capture all inpatient and outpatient episodes in English and Welsh NHS hospitals. Data linkage was
16 140 performed using deterministic linkage criteria that included NHS number, sex and date of birth.
17
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142 **Measures**

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21 143 Symptom severity, condition-specific quality of life and generic quality of life scores and the
22 144 reported duration of symptoms at the first outpatient visit were used as outcomes in this study. The
23 145 severity and quality of life scores were analysed as continuous variables. Symptom severity scores
24 146 ranged from 0 (best possible score) to 100 (greatest symptom severity, worst possible score).
25 147 Condition-specific quality of life ranged from 0 (poorest quality of life) to 100 (best quality of life).
26 148 Generic quality of life is expressed on a scale with 0 representing death and 1 perfect health[22].
27 149 Women were asked "How long have you had symptoms of heavy menstrual bleeding", with "2
28 150 months or less", "more than 2 months but less than 1 year", "more than 1 year" and "don't know" as
29 151 possible response categories. For analysis, duration of symptoms was grouped as "<1 year", "≥1
30 152 year" with "don't know" coded as missing. Levels of missing data on HMB symptoms and health-
31 153 related quality of life were low (2.2% for severity, 4.8% for condition-specific and 9.9% for generic
32 154 quality of life and 3.0% for symptom duration).
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43 156 Age was categorised as 18-34, 35-39, 40-44, 45-49, ≥50 years for analysis. Women reported their
44 157 ethnicity as "white", "mixed", "Asian or Asian British", "black or black British", "Chinese" or "other".
45 158 For analysis, the "mixed", "Chinese" and "other" groups were combined as "other" due to small
46 159 numbers of women reporting these ethnicities. Self-reported height and weight data were used to
47 160 derive body mass index (BMI), categorised according to WHO groups as ≤25, 25-30, and ≥30[23].
48 161 Women reported how many times they had seen their GP for HMB in the year prior to their first
49 162 outpatient visit, and this was grouped as 0, 1-2, 3-4, >4 for analysis ("don't know" was coded as
50 163 missing).
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3 165 Women reported their parity, grouped for analysis as “nulliparous” or “parous”. Women were also
4 166 asked “Have you been told by a doctor that you have any of the following: “heart disease (for
5 167 example angina, heart attack or heart failure), high blood pressure, lung disease (for example
6 168 chronic bronchitis or emphysema), diabetes, depression, thyroid disorder, kidney disease, cancer
7 169 (within the last 5 years). For analysis, the number of co-morbidities reported was grouped as 0, 1,
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11 170 ≥ 2 .

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14 172 Information on socio-economic deprivation (Index of Multiple Deprivation (IMD)) was extracted
15 173 from HES and PEDW. IMD is a relative measure of deprivation for small areas across a number of
16 174 domains, including income, employment, education and housing. We used quintiles of IMD (level 1 =
17 175 most deprived areas, level 5 = least deprived areas). The methods used to calculate IMD scores in
18 176 each country in the UK are similar but not directly comparable[24]. For analysis, we generated a
19 177 combined measure of deprivation for England and Wales by assigning those in each country-specific
20 178 quintile to the same quintile in a combined measure. This preserved women’s relative deprivation
21 179 position within each country.

22 180

23 181 **Statistical analysis**

24 182 Means and standard deviations (SD) and proportions were used to describe the cohort. Regression
25 183 analyses were used to examine the relationship between age, ethnicity and socio-economic
26 184 deprivation and each of the outcomes. For the scores representing symptom severity, condition
27 185 specific and generic quality of life, multivariable linear regression was used to calculate adjusted
28 186 differences in mean scores. For duration of symptoms (<1 year and ≥ 1 year), multivariable logistic
29 187 regression was used to calculate adjusted odds ratios (OR). Regression models included BMI, parity
30 188 and number of co-morbidities as potential confounders. Levels of missing data were low (<3%) for
31 189 the majority of variables with the exception of ethnicity (7% missing) and BMI (approximately 23%
32 190 missing, Table 1). Missing values for explanatory variables were imputed using multiple imputation
33 191 by chained equations[25] and statistical coefficients were obtained using ten imputed datasets and
34 192 combined using Rubin’s rules[26].

35 193

36 194 **ETHICAL APPROVAL**

37 195 The data are from the National Heavy Menstrual Bleeding (HMB) Audit. Based on the Health
38 196 Research Authority’s guidance, audits are regulated as standard clinical practice outside of the
39 197 Research Ethics Service[27].

40 198

RESULTS**Patient Characteristics**

15,325 eligible women completed the questionnaire at their first visit to a gynaecology outpatient department and 15,294 (99.8%) could be linked to HES or PEDW which provided information on socioeconomic deprivation. The women's mean age was 42.3 years (SD 7.6) and BMI 27.3 (SD 5.4) (Table 1). About one in five were nulliparous and one in three reported at least one co-morbidity. 11.7% of women reported a non-white ethnicity, with black or black British (5.4%) and Asian or Asian British (4.3%) being the largest non-white groups. Women in the two least socioeconomically deprived national quintile groups (18.7% in quintile 4 and 15.8% in quintile 5) were under-represented given that per definition 20% of women are expected to be in each group. The distribution of symptom severity, condition-specific and generic quality of life and symptom duration by level of deprivation did not vary significantly between women in England and Wales (data not shown).

Table 1: Patient characteristics at the first gynaecology outpatient visit for HMB (% and number unless otherwise stated)

The mean score for symptom severity was 61.8 (standard error (SE) 0.17) with 74.0% of women reporting that they had HMB symptoms for more than one year. The mean score for condition-specific quality of life was 34.7 (SE: 0.18) and for generic quality of life 0.65 (SE: 0.28) (Table 2).

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

233 women reported better quality of life at their first HMB outpatient visit (difference 7.3; 95% CI: 5.9
234 to 8.7) between oldest and youngest age groups). Symptom severity also varied by ethnicity: black
235 and Asian women reported less severe symptoms than white women (difference compared to white
236 women -1.9 and -2.4 respectively, Table 2). Condition-specific quality of life did not vary significantly
237 by ethnicity, whereas compared to white women, Asian woman reported lower generic quality of
238 life scores (Table 2).

239

240 **Duration of symptoms**

241 Women living in the most deprived areas were slightly less likely to report having had HMB
242 symptoms for ≥ 1 year than those living in the less deprived areas. Women aged between 35 and 49
243 years were more likely to report having experienced HMB symptoms for ≥ 1 year than those younger
244 than 35. Compared to white women, black women were more likely than white women to report
245 symptoms for ≥ 1 year and Asian women were less likely.

246

247 **Table 2. Severity and duration of symptoms at the first outpatient visit, by age group, ethnicity 248 and socioeconomic deprivation**

249

250 **DISCUSSION**

251 **Main Findings**

252 Women living in more socioeconomically deprived areas reported more severe HMB symptoms and
253 poorer quality of life at their first gynaecology outpatient visit. Older women reported less severe
254 symptoms and better quality of life than younger women. Reported symptom severity also varied by
255 ethnicity with black and Asian women reporting less severe symptoms than women from white
256 ethnic backgrounds.

257

258 Three quarters of the women referred to secondary care reported that they had had symptoms of
259 HMB for at least one year and women living in the most deprived areas were least likely to report
260 having had HMB symptoms for ≥ 1 year.

261

262 **Interpretation**

263 More severe symptoms and poorer quality of life at first outpatient visit by socioeconomic
264 deprivation, after adjustment for possible differences in age, ethnicity and body mass index, reflect
265 that women from more deprived backgrounds report more severe problems at the start of
266 treatment in secondary care but they were least likely to report that they had symptoms for at least

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3 267 one year. The difference in the symptom severity score between women from the least and the
4 268 most deprived areas of about 6 is likely to be clinically significant, given that a difference of 5 points
5 269 or more has been specified as clinically important in clinical trials[28]. There is evidence that people
6 270 from more socioeconomically deprived backgrounds may be more accepting of symptoms, chronic
7 271 pain or poorer health-related quality of life[29], which is a possible explanation for these finding.
8
9 272 Conversely, those from more affluent socioeconomic backgrounds have been found to report
10 273 greater impact of health conditions on their health and their quality of life, which may be linked to
11 274 their higher expectations about health and life in general[30].
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17 276 Alternative explanations are that differences in symptom severity, quality of life and symptom
18 277 reflect inequitable access as well as differences in the nature and causes of HMB. Age is often found
19 278 to be associated with symptom severity^{15, 16}[31, 32]. Black women are 2-3 times more likely to have
20 279 fibroids and endometriosis[32]. Accepting heavy periods as normal vary by ethnicity and other social
21 280 factors, which in turn can also lead to reluctance to seek care for HMB[16]. Ethnographic research
22 281 suggests that some women of South Asian ethnicity do not seek healthcare for HMB due to the
23 282 belief that heavy periods cleanse the body[17]. We adjust for patient-level characteristics that may
24 283 capture some of these differences but were unable to adjust for other unmeasured potential
25 284 confounders.
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33 286 The observation that women living in the most socio-economically deprived areas reported the most
34 287 severe symptoms but were least likely to report having had symptoms for ≥ 1 year may reflect the
35 288 wording of the question; women were asked "How long have you had symptoms of heavy menstrual
36 289 bleeding?" and women whose symptom severity had worsened may have reported the duration of
37 290 the most recent severity, rather than the overall duration.
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41 291
42 292 A key question is whether the observed differences in symptom severity and condition-specific
43 293 quality of life at the women's first gynaecology outpatient visit are related to differences in women's
44 294 health seeking behaviour or to differences in how GPs and gynaecologists decide on whether to
45 295 refer a woman with HMB. A study of self-reported health-care seeking behaviour in England did not
46 296 find evidence that inequality in access to secondary care according to socioeconomic or ethnic
47 297 backgrounds is related to patients being less likely to go to their GP or a hospital's emergency
48 298 department[33]. Similarly, a survey of patients with chronic joint pain found that the proportions of
49 299 patients who said that they were seeking help from their GP did not differ according to their
50 300 socioeconomic background[34]. On the other hand, a national study including 130,000 patients from
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301 more than 300 primary care practices in England found that older patients and those from more
302 deprived areas were less likely to be referred to secondary care[35].

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304 **Implications for policy and practice**

305 In the UK, national guidelines for the management of HMB have been developed by the National
306 Institute for Health and Care Excellence and the Royal College of Obstetricians and Gynaecologists
307 (RCOG)[11, 36, 37]. The National HMB Audit carried out a survey of NHS hospitals in England and
308 Wales to find out how care for women with HMB is organised and delivered at local levels. It found
309 that key systems such as the availability of local protocols, which specified local arrangements for
310 patient referral and management in response to the NICE guidelines, were reported only by 30% of
311 hospitals[38]. Wide variation in the investigations and treatments that were offered to women with
312 HMB in primary care were also noted. The implementation of locally agreed referral pathways,
313 recommended by the RCOG, will help to reduce this variation[39].

314

315 Women with HMB in this study reported substantially worse QoL (EQ-5D mean: 0.65, SD: 0.33) than
316 the population average for women in England (mean: 0.85, SD: 0.003), and compared to women
317 with incontinence (mean: 0.73, SD: 0.26)[40, 41]. This reinforces the need for interventions to focus
318 on improving women's quality of life, as recommended by recent NICE guidelines[11]. Obesity can
319 be associated with HMB so health promotion interventions around diet and exercise could
320 supplement HMB-specific interventions. Criteria for what constitutes a meaningful improvement in
321 quality of life are less clear. Awareness raising activities relating to the availability of treatments for
322 HMB could increase healthcare seeking before symptoms become severe. This may be particularly
323 beneficial for those from more deprived background who may be more accepting of chronic pain
324 and worse quality-of-life. In highlighting differences in symptom severity at their first gynaecology
325 outpatient visit, our findings draw attention to the lack of an agreed threshold for referral of women
326 with HMB to secondary care in terms of symptom severity and quality of life. Routine measurement
327 of both symptom severity and quality of life may be required to stimulate greater consistency in
328 referral thresholds but validated instruments specific to HMB are currently lacking. As there is no
329 widely used condition-specific measure of condition-specific quality of life for HMB, the National
330 HMB Audit used the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, adapted
331 for a UK population of women with HMB[18].

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3 333 **Strengths and Limitations**

4 334 This study is the first to examine the relationship between sociodemographic factors and patient-
5
6 335 reported HMB symptom severity, quality of life and symptom duration in an outpatient setting. It
7
8 336 used data collected by a national audit carried out in England and Wales, which produced a relatively
9
10 337 large sample. We estimated that the National HMB Audit recruited about 30% of all eligible women.
11
12 338 There is no direct way to compare the characteristics of the women who were recruited and those
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14 339 who were not. However, the characteristics of the women who were recruited were broadly
15
16 340 representative of the UK population in terms of the distributions of ethnicity and age[42, 43].
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18 341
19 342 Survey questionnaires were only available in the English language, so non-English speakers are likely
20
21 343 to be under-represented. On the other hand, case ascertainment varied by provider and women
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23 344 from providers with higher case ascertainment (ascertainment > 45%) were more often from a non-
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25 345 white ethnic background and a more deprived areas than those referred to providers with lower
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27 346 case ascertainment[4] which suggests that the impact of not having questionnaires in other
28
29 347 languages is likely to be small.
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31 348
32 349 **CONCLUSION**

33 350 About three in four women at their first visit to a gynaecological outpatient clinic for HMB in England
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35 351 and Wales reported that they had symptoms at least one year before they were referred to
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37 352 secondary care. Women from more deprived areas reported more severe HMB symptoms and a
38
39 353 poorer quality of life, which demonstrates a higher burden of disease at the time of referral to
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41 354 secondary care. Primary and secondary care providers should examine to what extent these
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43 355 differences reflect barriers in access to gynaecological secondary care services or women's
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45 356 perceptions of their menstrual problems and health-seeking behaviour.
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5
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7
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9
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11
12 365 Healthcare Quality Improvement Partnership, who have no responsibility or liability for the accuracy,
13
14 366 currency, reliability and/or correctness of this publication.

15 367
16 368 **DATA SHARING STATEMENT**

17 369 The data analysed were collected as part of a national clinical audit and linked to administrative
18
19 370 hospital data (Hospital Episode Statistics). They were shared with the authors by the Healthcare
20
21 371 Quality Improvement Partnership, Health and Social Care Information Centre and the Royal College
22
23 372 of Surgeons of England. The data cannot be shared further without formal application to the data
24
25 373 providers.

26 374
27 375 **CONTRIBUTORS**

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29
30 377 IGU, DC, LBM and through advice by JS, TM, JvdM. Data analysis was performed by AK, IGU & RSG.
31
32 378 All authors contributed to the writing of the manuscript.

33 379
34 380 **COMPETING INTERESTS**

35
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37
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39
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41
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54
55 392 Royal College of Obstetricians and Gynaecologists.

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492 **Table 1: Patient characteristics at the first gynaecology outpatient visit for HMB**
 493 **(% and number unless otherwise stated)**

	Full Cohort (n=15,325)
Age, mean (sd) in years	42.3 (7.6)
Age groups	
18-34	14.9 (2,283)
35-39	12.9 (1,971)
40-44	26.6 (4,071)
45-49	31.3 (4,794)
≥50	14.4 (2,206)
Body mass index, mean (sd) in kg/m ²	27.3 (5.4)
Body mass index, categories	
≤25	39.6 (4,681)
25-30	31.7 (3,739)
≥30	28.7 (3,392)
Missing	3,513
Parity	
Nulliparous	17.0 (2,530)
Parous	83.0 (12,338)
Missing	457
Number of reported comorbidities	
0	66.3 (10,165)
1	25.3 (3,878)
≥2	8.4 (1,282)
Ethnicity	
White	88.3 (12,614)
Asian or Asian British	4.3 (607)
Black or Black British	5.4 (770)
Other	2.0 (292)
Missing	1,042
Socioeconomic deprivation (IMD)	
Quintile 1 (most deprived)	23.5 (3,418)
Quintile 2	21.7 (3,159)
Quintile 3	20.2 (2,944)
Quintile 4	18.7 (2,720)
Quintile 5 (least deprived)	15.8 (2,304)
Missing	780

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Table 2. Severity and duration of symptoms at the first outpatient visit, by age group, ethnicity and socioeconomic deprivation

	Severity score (0 best and 100 worst) (n=14,990)			Condition-specific quality of life (0 worst and 100 best) (n=14,586)			Generic quality of life (0 death and 1 perfect health) (n=13,802)			Symptoms ≥1 year (n=14,866)		
	Mean score (se)	Adjusted ⁱ difference (95% CI)	p-value	Mean score (se)	Adjusted ⁱ difference (95% CI)	p-value	Mean score (se)	Adjusted ⁱ difference(95% CI)	p-value	% (se)	Adjusted ⁱ OR (95% CI)	p-value
11 Total	61.8 (0.17)			34.7 (0.18)			0.65 (0.28)			74.0 (0.36)		
12 Age group												
13 18-34	63.1 (0.44)	-		33.2 (0.48)	-		0.61 (0.007)	-		70.7 (0.98)	-	
14 35-39	62.9 (0.49)	-1.59 (-2.89, -0.29)		33.3 (0.51)	1.75 (0.39, 3.10)		0.63 (0.008)	0.03 (0.01, 0.05)		74.8 (1.00)	1.25 (1.09, 1.44)	
15 40-44	62.5 (0.33)	-2.17 (-3.30, -1.04)	p<0.001	33.7 (0.35)	2.59 (1.40, 3.77)	p<0.001	0.64 (0.005)	0.04 (0.02, 0.06)	p<0.001	76.8 (0.67)	1.39 (1.23, 1.58)	p<0.001
16 45-49	61.3 (0.31)	-3.36 (-4.47, -2.51)		35.4 (0.33)	4.23 (3.06, 5.39)		0.67 (0.005)	0.07 (0.05, 0.08)		74.2 (0.64)	1.20 (1.06, 1.35)	
17 ≥50	59.0 (0.47)	-5.88 (-7.19, -4.58)		38.2 (0.51)	7.31 (5.93, 8.68)		0.70 (0.007)	0.10 (0.07, 0.12)		70.9 (0.98)	1.01 (0.88, 1.16)	
18 Ethnicity												
19 White	61.9 (0.19)	-		34.8 (0.20)	-		0.66 (0.003)	-		74.1 (0.38)	-	
20 Black or Black British	61.5 (0.82)	-1.93 (-3.51, -0.35)		35.0 (0.86)	1.45 (-0.16, 3.06)		0.62 (0.01)	-0.01 (-0.08, 0.02)		79.4 (1.47)	1.34 (1.11, 1.62)	
21 Asian or Asian British	60.7 (1.02)	-2.38 (-4.25, -0.51)	P=0.011	34.2 (1.07)	1.32 (-0.59, 3.22)	0.1392	0.58 (0.02)	-0.05 (-0.88, -0.01)	p<0.001	66.1 (1.49)	0.70 (0.58, 0.85)	p<0.001
22 Other	61.5 (1.33)	-0.46 (-3.09, 2.16)		33.9 (1.41)	-1.01 (-3.54, 1.51)		0.60 (0.02)	-0.05 (-0.30, -0.20)		72.3 (2.67)	0.92 (0.70, 1.20)	
23 Socioeconomic deprivation (IMD)												
24 Quintile 1 (most deprived)	65.5 (0.37)	-		30.5 (0.39)	-		0.55 (0.007)	-		72.0 (0.78)	-	
25 Quintile 2	63.5 (0.38)	-1.53 (-2.57, 0.50)		33.1 (0.40)	1.82 (0.75, 2.90)		0.62 (0.006)	0.06 (0.05, 0.08)		73.6 (0.80)	1.11 (0.99, 1.24)	
26 Quintile 3	61.6 (0.39)	-4.22 (-4.30, -2.12)	p<0.001	35.0 (0.41)	3.44 (2.34, 4.54)	p<0.001	0.67 (0.006)	0.09 (0.08, 0.11)	p<0.001	75.1 (0.81)	1.20 (1.06, 1.34)	P=0.0091
27 Quintile 4	59.5 (0.41)	-6.02 (-6.02, -3.87)		36.8 (0.43)	4.78 (3.66, 5.90)		0.71 (0.006)	0.13 (0.12, 0.15)		74.5 (0.85)	1.16 (1.03, 1.31)	
28 Quintile 5 (least deprived)	58.2 (0.44)	-6.07 (-7.23, -4.91)		38.6 (0.46)	6.29 (5.10, 7.48)		0.73 (0.006)	0.14 (0.13, 0.16)		75.1 (0.91)	1.21 (1.07, 1.37)	

Footnote: All multivariable models were adjusted for body mass index, parity, and number of co-morbidities. P-values based on Wald test

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5, 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	7
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Only one stage
		(c) Consider use of a flow diagram	Only one stage
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	8 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	N/A (Baseline)
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A (Baseline results)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9 (Table 2)
		(b) Report category boundaries when continuous variables were categorized	8 (Table 2)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.