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# Journal Pre-proof



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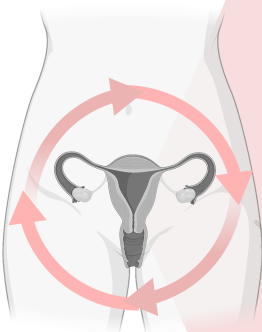
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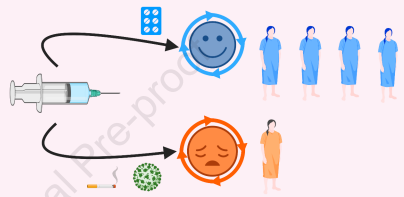
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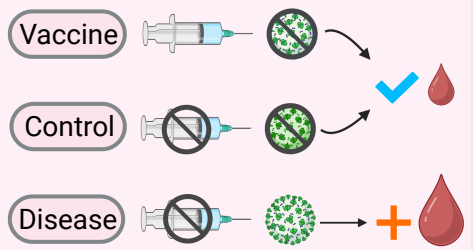
# Perceived changes to menstrual cycles following COVID-19 vaccination and disease



## Risk and protective factors



## Menses after vaccine & disease



1 A retrospective case-control study on menstrual cycle  
2 changes following COVID-19 vaccination and disease

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5  
6 Alexandra Alvergne<sup>1,2\*+</sup>, Gabriella Kountourides<sup>2\*</sup>, M. Austin Argentieri<sup>2,3</sup>, Lisa Agyen<sup>4</sup>,  
7 Natalie Rogers<sup>4</sup>, Dawn Knight<sup>4</sup>, Gemma C Sharp<sup>5,6</sup>, Jacqueline A Maybin<sup>7</sup>, Zuzanna  
8 Olszewska<sup>2\*</sup>

9  
10  
11  
12  
13 <sup>1</sup> ISEM, Univ Montpellier, CNRS, IRD, Montpellier, France

14 <sup>2</sup> School of Anthropology and Museum Ethnography, Oxford, UK

15 <sup>3</sup> Harvard/MGH Center on Genomics, Vulnerable Populations, and Health Disparities,  
16 Massachusetts General Hospital, Boston, USA

17 <sup>4</sup> Long COVID Support

18 <sup>5</sup> MRC Integrative Epidemiology Unit, University of Bristol, UK

19 <sup>6</sup> School of Psychology, University of Exeter

20 <sup>7</sup> MRC Centre for Reproductive Health, University of Edinburgh, UK

21  
22  
23  
24 + Lead contact : Alexandra Alvergne

25  
26 E-mail: alexandra.alvergne@umontpellier.fr

27  
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29 \* These authors contributed equally.

30

## 31 **Summary**

32

33 There has been increasing public concern that COVID-19 vaccination causes menstrual disturbance  
34 regarding the relative effect of vaccination compared to SARS-CoV-2 infection. Our objectives were to  
35 test potential risk factors for reporting menstrual cycle changes following COVID-19 vaccination and to  
36 compare menstrual parameters following COVID-19 vaccination and COVID-19 disease. We performed  
37 a secondary analysis of a retrospective online survey conducted in the UK in March 2021. In pre-  
38 menopausal vaccinated participants (n=4,989), 18% reported menstrual cycle changes after their first  
39 COVID-19 vaccine injection. The prevalence of reporting any menstrual changes was higher for women  
40 who smoke, have a history of COVID-19 disease, or are not using oestradiol-containing contraceptives.  
41 In a second sample including both vaccinated and unvaccinated participants (n=12,579), COVID-19  
42 vaccination alone was not associated with abnormal menstrual cycle parameters while a history of  
43 COVID-19 disease was associated with an increased risk of reporting heavier bleeding, 'missed' periods  
44 and inter-menstrual bleeding.

45

46

47

## 48 Introduction

49  
50

51 There has been substantial public concern that the COVID-19 pandemic has caused  
52 disruption of menstrual cycles due to vaccination,<sup>1-3</sup> infection with the SARS-CoV-2  
53 virus<sup>4</sup>, pandemic- related stress and lifestyle changes.<sup>5</sup> Yet, the independent  
54 contribution of each factor to menstrual cycle changes remains understudied,<sup>6,7</sup>  
55 particularly prior to media attention to the topic. This is despite rising awareness among  
56 clinicians that the menstrual cycle should be used as a vital sign of female health<sup>8,9</sup>  
57 and that sex is a biological variable which should be considered in immunological  
58 studies.<sup>10</sup> Ultimately, the lack of data for investigating independent associations  
59 between menstrual cycles and both COVID-19 vaccines and SARS-CoV-2 infection  
60 limit our ability to clarify the impact of the COVID-19 pandemic on menstruation.<sup>11</sup> Such  
61 knowledge is critical for advising women about the relative risk of experiencing  
62 menstrual disturbance when getting vaccinated against COVID-19 versus infected with  
63 SARS-CoV-2.

64

65 Before the COVID-19 pandemic, research on the relationship between vaccination and  
66 menstrual cycle health had been limited to the prophylactic typhoid<sup>12</sup>, HPV<sup>13,14</sup> and  
67 hepatitis B vaccines<sup>15</sup>. However, recent reports of menstrual disturbances following  
68 COVID-19 vaccination in the media<sup>1-3</sup> and surveillance schemes (e.g., in the UK<sup>16,17</sup>  
69 and France<sup>18</sup>) have led to a surge of research.<sup>7,19-23</sup> Prospective studies using samples  
70 of app users not using hormonal contraception found that COVID-19 vaccination  
71 changed cycle length by < 1 day,<sup>24-26</sup> with similar findings in a prospective study of  
72 3,858 pre-menopausal health professionals.<sup>7</sup> In a recent prospective study of 79

73 participants recruited via social media, the subsequent menstrual episode following  
74 COVID-19 vaccination occurred a mean of 2.3 days late after dose 1 and 1.3 days late  
75 after dose 2.<sup>20</sup> Beyond cycle length, other studies have reported various changes in  
76 regularity, duration and volume.<sup>19,20</sup> For instance, in a sample of young participants  
77 (18-30 years) drawn at random from the Norwegian National Population Registry,  
78 heavy bleeding increased from 7.6% to 13.6% in the first cycle after vaccination, and  
79 from 8.2% to 15.3% after the second vaccine dose<sup>23</sup>. Recent data from a gender-  
80 diverse sample receiving COVID-19 vaccination in the US suggests that changes in  
81 the form of heavy and breakthrough bleeding affect many people.<sup>22</sup> While there is  
82 accumulating evidence that COVID-19 vaccination-related menstrual symptoms are  
83 associated with small and temporary changes in cycle length<sup>19,24</sup>, there has been no  
84 quantitative assessment of the risk factors for menstrual disturbances following  
85 COVID-19 vaccination prior to widespread media attention.

86

87 Contrasting with the emerging picture showing a small effect of COVID-19 vaccine on  
88 cycle length, research on the associations between SARS-CoV-2 infection and  
89 menstrual cycle changes is scarce and inconsistent.<sup>11,27</sup> Early in the pandemic, a  
90 cross-sectional hospital-based study conducted in China and including COVID-19  
91 patients admitted to hospital (n=177) and controls (n=91), found that COVID-19  
92 patients reported more changes in menstrual blood volume (control versus COVID-19,  
93 5% versus 25%,  $P < 0.001$ ) and cycle length (control versus COVID-19, 6% versus  
94 28%,  $P < 0.001$ ).<sup>28</sup> Note that the external validity of this study has been questioned as  
95 the sample is biased towards women with multisystem dysfunction.<sup>29</sup> In a sub-sample  
96 of 127 participants aged 18-45 years taken from a prospective cohort study of SARS-

97 CoV-2 positive cases (Arizona CoVHORT study), 16% reported changes in their  
98 menstrual cycle, including irregular menstruation (60%), increase in premenstrual  
99 symptoms (45%) and infrequent menstruation (35%).<sup>30</sup> Yet causality cannot be inferred  
100 in this study due to the absence of a control group. Conversely, an association between  
101 SARS-CoV-2 infection and cycle changes was not observed in a prospective study of  
102 3,858 pre-menopausal health professionals taking part in the Nurses' Health Study 3.<sup>7</sup>  
103 In this sample, the prevalence of infection was low (n=421, 11%) compared to  
104 vaccination (n=3,527, 91%) and more than half of COVID positive individuals (n=223)  
105 were vaccinated prior to infection,<sup>7</sup> which may have limited the ability of the study to  
106 detect small to moderate effects. Finally, in a study of 187 American women, having  
107 detectable SARS-CoV-2 IgG antibodies was associated with a higher percentage of  
108 self-reported menstrual irregularities (cycles not between 26-35 days in the 3 months  
109 prior to survey) among unvaccinated women,<sup>31</sup> suggesting that SARS-CoV-2 may lead  
110 to abnormal cycle parameters. A study better powered to evaluate the independent  
111 association of SARS-CoV-2 and abnormal cycle changes is needed to inform  
112 vaccination decisions.

113

## 114 **Objectives of the study**

115 The objectives of this study were three-fold: (1) to identify the risk factors for reporting  
116 any menstrual changes following COVID-19 vaccination, (2) to evaluate the  
117 independent effect of COVID-19 disease and COVID-19 vaccination on menstrual  
118 parameters as defined by the International Federation of Gynaecologists and  
119 Obstetricians (FIGO),<sup>32</sup> including menstrual frequency, regularity, duration, volume  
120 and inter-menstrual bleeding, (3) to capture the types and breadth of menstrual



121 disturbances following COVID-19 vaccination in participants' written accounts. To do  
122 this, we used a large retrospective cross-sectional study on menstruation somewhat  
123 representative of those who menstruate in the UK. This was launched before UK media  
124 coverage of concerns over menstrual vaccine side-effects and includes both  
125 quantitative and textual data on menstrual cycle changes.

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## 126 **Results**

127

### 128 **Self-reported menstrual cycle changes following COVID-19**

#### 129 **vaccination**

##### 130 **Sample characteristics**

131 Out of the 26,710 individuals who completed the survey, 8,539 (31%) reported having  
132 been vaccinated, with either one (n=7,270) or two doses (n=1,269). Although the UK  
133 vaccination campaign began by targeting older and at-risk populations, we did not  
134 observe an over-representation of those over 40 years old. Of note, 54% of participants  
135 were nulliparous and 49% had a university or college degree. We excluded participants  
136 who did not have a period in the 12 months preceding the survey, those who were  
137 post-menopausal or transitioning, breastfeeding or pregnant, and among those who  
138 selected “Other changes”, those who contributed text to the effect of “too early to say”  
139 when describing menstrual disturbances following COVID-19 vaccination (n=369, 64%  
140 of those selecting the answer “Other changes”) (Figure 1). The final sample size of  
141 vaccinated individuals was 4,989, of which 53% received the Oxford-AstraZeneca and  
142 47% the Pfizer BioNTech vaccine (Table 1). The median age was 35 years old (IQR:  
143 28 to 43), with most participants living in England (81%), self-reporting as white (95%)  
144 and self-identifying as women (99%).

145

##### 146 **Risk factors for COVID-19 vaccine-related changes in menstrual cycles**

147 Eighty-two percent of eligible participants reported no changes to their menstrual  
148 cycles following COVID-19 vaccination. Only 6.2% reported more disruption, 1.6%  
149 reported less disruption and 10.2% reported “Other changes”, which could be

150 interpreted as any changes in cycle length and regularity, period duration and volume  
151 of menstrual bleeding as well as premenstrual symptoms.

152

153 The univariable analyses show that reporting any changes to menstrual cycles after  
154 COVID-19 vaccination is associated with contraceptive type, smoking behaviour,  
155 COVID-19 disease history and menstrual cycle changes over the last year (Figure 2).  
156 Reporting changes to menstrual cycles after COVID-19 vaccination was not associated  
157 with age, body mass index, ethnic group, gender, marital status, physical activity,  
158 income, education, place of residence, cycle length, period length, irregular cycles,  
159 heavy bleeding, vaccine type, vaccine timing, parity, life satisfaction changes,  
160 medication use, use of vitamins/supplements, endometriosis, polycystic ovary  
161 syndrome, thyroid disease, uterine polyps, uterine fibroids, inter cystitis and eating  
162 disorders (Figure 2; Table S1).

163

164 The multivariable analyses show that the prevalence of menstrual cycle changes after  
165 COVID-19 vaccination is 33% lower among users of combined contraceptives  
166 (PR=0.57, 95CI=[0.43 to 0.75], FDR P-value = 0.0002) while current smokers are 1.3  
167 times as likely to report any changes (PR=1.31, 95CI=[1.1 to 1.58], FDR P-value =  
168 0.006) and individuals with a positive COVID-19 disease history are 37 to 46% as likely  
169 to report menstrual changes post-vaccination [Long Covid (PR=1.46, 95CI=[1.22 to  
170 1.75], FDR P-value = 0.00009), acute COVID-19 (PR=1.40; 95CI=[1.20 to 1.62], FDR  
171 P-value=0.00003); self-diagnosed positive (PR=1.50, 95CI=[1.25 to 1.80], FDR P-  
172 value = 0.00005), tested positive (PR=1.37, 95CI=[1.16 to 1.62], FDR P-value =  
173 0.0008, Figure 3, Table S1). The effects remain significant after adjusting for self-

174 reported overall magnitude of menstrual cycle changes over the year preceding the  
175 survey which is positively associated with the risk of reporting any changes (PR=1.13,  
176 95CI=[1.05 to 1.21],  $P=0.003$ ). The findings were replicated when using complete case  
177 analyses with unimputed data, indicating that the results are not an artefact of the  
178 missing data imputation process (Table S2).

179  
180

## 181 **Risk for 'abnormal' menstrual characteristics**

### 182 **Sample characteristics**

183 To investigate independent effects of COVID-19 vaccination and COVID-19 disease  
184 on abnormal menstrual parameters as defined by the FIGO criteria for Abnormal  
185 Uterine Bleeding<sup>32</sup>, we conducted additional analyses including participants who were  
186 not vaccinated, leading to a final sample of 12,579 (Figure 4). We compared menstrual  
187 cycle parameters across 4 groups (Table 2): (1) participants vaccinated with 1 or 2  
188 doses but without a history of COVID-19 disease (Vax,  $n=3,635$ , 29%); (2) participants  
189 previously diagnosed with COVID-19 disease and vaccinated (Covax,  $n=1,354$ , 11%);  
190 (3) unvaccinated participants previously diagnosed with COVID-19 disease (Cov,  $n=$   
191  $1,802$ , 14%); (4) Participants neither vaccinated nor previously diagnosed with COVID-  
192 19 disease at the time of the survey (None,  $n=5,788$ , 46%). The relationships between  
193 cycle parameters and the history of COVID-19 disease and vaccination are adjusted  
194 for relevant cycle parameters before the pandemic, age, BMI, contraceptive use, and  
195 reproductive disease at baseline (Table S3).

196

197

198 **Cycle parameters**

199 **Cycle frequency** For this analysis we excluded participants who reported “Too  
200 irregular to say” for the outcome variable “*Cycle length during the pandemic*” (n=889),  
201 as we were interested in ascribing frequency. Across all groups of remaining  
202 participants (n=11,690), the most probable outcome is to report normal cycles  
203 (between 24 and 38 days, 70.2%), followed by frequent (<24 days, 26.4%) and  
204 infrequent cycles (>38 days, 3.3%, Figure 5). The relative risk of frequent vs. normal  
205 cycles and the relative risk of infrequent vs. normal cycles do not vary significantly  
206 between the vaccinated only group and the control group (no vaccination and no  
207 infection), suggesting vaccination alone does not associate with abnormal cycle  
208 frequency (Table S3, Figure 5). However, compared to being vaccinated only, a history  
209 of COVID-19 disease increases the relative risk of frequent vs. normal cycles by 30%  
210 (Cov: RRR = 1.3, 95CI = [1.06 to 1.6], FDR P-value = 0.050; Covax: OR = 1.32, 95CI  
211 = [1.06 to 1.64], FDR P-value = 0.052), the probability of reporting frequent cycles  
212 increasing from 26% in the vaccinated-only group to 34% in the COVID-19 disease  
213 groups. There are no significant differences between the vaccinated-only group and  
214 the COVID-19 disease-only group (Cov: RRR=1.06; 95CI = [0.91 to 1.25], FDR P-value  
215 = 0.618).

216

217 Finally, the odds for reporting “missed” and/or “stopped” periods do not vary between  
218 the control group and the vaccinated-only group (*Control*: PR = 0.96, 95CI = [0.82 to  
219 1.13], FDR P-value = 0.62), but increase by 27% in the COVID-19 disease-only group  
220 (Cov: PR = 1.27, 95CI = [1.05 to 1.54], FDR P-value = 0.032, Table S3), with the

221 probability of reporting missing or stopped periods increasing from 7% in the  
222 vaccinated-only group to 9% in the COVID-19 disease-only group (Figure 5). A  
223 significant increase is not observed for participants who are also both infected and  
224 vaccinated (Covax: PR = 1.14, 95CI = [0.92 to 1.41], FDR P-value = 0.296). Baseline  
225 cycle frequency and contraceptive and reproductive disease at baseline do not  
226 influence the association between a history of COVID-19 and cycle frequency during  
227 the pandemic (models including interaction effects are worse fits to the data than a  
228 model without interaction, Table S4).

229

230 **Cycle regularity** Across all groups of participants, the most probable outcome is to  
231 report regular cycles at the time of survey (less than 10 days difference between  
232 shortest and longest cycles, 79.7%), followed by highly irregular (over 20 days  
233 difference, 10.5%) and somewhat irregular (between 10-20 days difference, 9.8%,  
234 Figure 5). The relative risks of reporting irregular vs. regular cycles are not associated  
235 with COVID-19 vaccination and disease history in this sample (Table S3, Figure 5).

236

237 **Period duration** There are no significant differences in the prevalence of periods  
238 longer than 8 days between the vaccinated-only group and the control group (PR =  
239 1.05, 95CI [0.74; 1.49], FDR P-value = 0.8284, Table S3, Figure 5). Compared to the  
240 vaccinated-only group, the prevalence of periods longer than 8 days is increased by  
241 65% for the group combining both COVID-19 vaccination and disease (PR = 1.65, 95CI  
242 [1.08; 2.54], FDR P-value = 0.0474), a tendency not observed for those with a history  
243 of COVID-19 disease only (PR = 1.44, 95CI [0.94; 2.21], FDR P-value = 0.1446, Table  
244 S3). The associations do not depend on initial period length category, reproductive

245 disease at baseline or contraceptive uptake in this dataset as models including an  
246 interaction between any of those variables and COVID-19 vaccination and disease  
247 history are worse fits to the data than a model without interaction (Table S4).

248

249 **Flow volume** Across all groups of participants, the most probable outcome is 'No  
250 changes' (40.9%), followed by 'heavier' (25.1%), 'heavier and lighter' (19.1%) and  
251 'lighter' (14.9%). There are no significant differences between the vaccinated-only and  
252 the control groups for the relative risks of 'heavier' vs. 'normal' periods (RRR = 0.96,  
253 95CI = [0.85 to 1.1], FDR P-value = 0.752), 'lighter' vs. 'normal' periods or 'lighter and  
254 heavier' vs. 'normal' periods. As compared to being vaccinated only, a history of  
255 COVID-19 disease increases the risk of heavier vs. normal periods by ca. 38% (Cov:  
256 RRR = 1.38, 95CI = [1.17 to 1.63], FDR P-value = 0.0006; Covax: RRR = 1.39, 95CI  
257 = [1.16 to 1.66], FDR P-value = 0.0015) and the risk of 'lighter' periods vs. 'no changes'  
258 by 29% (Covax: RRR = 1.29, 95CI = [1.05 to 1.59], FDR P-value = 0.05). In absolute  
259 terms, the predicted probability of reporting heavier periods increases from 25% in the  
260 vaccinated-only group to 34% for participants in the COVID-19 only group (Figure 5).  
261 The associations do not depend on initial period flow, reproductive disease at baseline  
262 or contraceptive uptake in this dataset as models including an interaction between any  
263 of those variables and COVID-19 vaccination and disease history are worse fits to the  
264 data than a model without interaction (Table S4).

265

266 **Intermenstrual bleeding (IMB)** Across all groups of participants, the most probable  
267 outcome for spotting mid-cycle during the pandemic compared to before is 'no  
268 changes' (73%) followed by 'more' (18.5%), 'less' (3.1%) and 'sometimes more and

269 sometimes less' (5.4%). There are no significant differences between the vaccinated-  
270 only and the control groups for the relative risks of 'more' vs. 'no changes' for IMB  
271 (RRR = 0.99, 95CI = [0.85 to 1.15], FDR P-value = 0.953). As compared to the  
272 vaccinated-only group, the risk of reporting subjectively more spotting mid-cycle than  
273 pre-pandemic increases from 18% to 23% for participants with a history of COVID-19  
274 disease (Cov: RRR = 1.31, 95CI [1.09; 1.58],  $P = 0.0149$ ; Covax: RRR = 1.30, 95CI  
275 [1.06; 1.59], FDR P-value = 0.0338). The associations do not depend on reproductive  
276 disease at baseline or contraceptive uptake in this dataset as models including an  
277 interaction between any of those variables and COVID-19 vaccination and disease  
278 history are worse fits to the data than a model without interaction (Table S4). The  
279 findings remaining significant after Bonferroni correction (heavy bleeding and IMB)  
280 were replicated when using complete case analyses with unimputed data (Table S5).

281

## 282 **Textual description of menstrual cycle changes following COVID-19**

### 283 **vaccination**

#### 284 **Most common changes reported**

285 The analysis of text written by participants who selected "Other changes" (n= 574, 57%  
286 of those reporting any changes) rather than "MORE disruption" or "LESS disruption"  
287 showed concerns over cycle length and menstrual bleeding patterns. The most  
288 common unigrams (individual words) were "late", "bleed", "early", "long", "heavy",  
289 "spotting", "short", "pain" and "stop" and the most common bigrams (pairs of adjacent  
290 words) were "day late", "period start", "heavy bleed", and "late period" (Figure 6). While  
291 many reported menstrual cycle changes that entailed heavier bleeding/periods, there



292 was no one single pattern of symptoms, with changes including both early and late  
293 periods, and diverse experiences reported (from “miss period” to “heavy bleed”).

294

### 295 **Associations between symptoms**

296 Only a few symptoms are correlated ( $\phi < -0.2$  or  $\phi > 0.2$ ). “Cramps” positively correlate  
297 with “pain” and “heavy” and “bleed” negatively correlates with “late”. Further, “lighter”  
298 positively correlates with “normal”, as participants report that “*period was two days late,*  
299 *and lighter than normal*”. However, “lighter” and “late” do not co-occur more than  
300 expected by chance (Figure 7).

301

302

### 303 **Clusters of words**

304 Different clusters of symptoms emerge from the text, such as irregular periods, heavy  
305 cramps, and pain. However, the “pain” cluster encompassed many words that are  
306 weakly correlated, suggesting a diversity of pain experience. There was also some  
307 uncertainty regarding which changes do occur, with participants finding it “*hard to say*  
308 *if the irregular periods are still due to covid or the vaccination*”. When only correlations  
309  $>0.20$  were considered (Figure 8), 4 clusters emerged: “heavy, painful, cramps”,  
310 “irregular, disruption”, “lot, clot”, and an experiential cluster “symptom, experience,  
311 pain, increase, feel”. Notably, various pain experiences that do not directly relate to  
312 menstrual cramps were reported in the main text, including stomach pain and  
313 headache.

314

315

## 316 **Discussion**

317

318 There has been public concern over the possibility that vaccination against COVID-19  
319 leads to changes in menstrual cycles. Counselling women who are considering  
320 vaccination against COVID-19 thus requires identifying the risk factors for experiencing  
321 menstrual cycle changes following COVID-19 vaccination, as well as information on  
322 the relative risk of vaccines versus infection with SARS-CoV-2 for driving menstrual  
323 cycle changes. Using data collected in the UK prior to widespread media attention to  
324 menstrual disturbances following COVID-19 vaccination, this study found that (1)  
325 perceived menstrual cycle changes following vaccination are 'very common' given  
326 international pharmacovigilance standards (i.e. over 10%), (2) these perceived  
327 menstrual cycle changes are increased for participants reporting a history of COVID-  
328 19 disease, but decreased among those who use combined contraceptives, (3)  
329 vaccination alone does not lead to abnormal cycle parameters as defined by FIGO, but  
330 a history of COVID-19 disease is associated with an increased risk of reporting  
331 frequent cycles (<24 days), prolonged periods (>8 days), heavier period flow and more  
332 inter-menstrual bleeding and, (4) experiences of cycle changes after COVID-19  
333 vaccination are diverse, including light and heavy bleeding as well as early and late  
334 periods. The results have implications for evidence-based counselling tailored to  
335 individual circumstances.

336

### 337 **Meaning of the study**

338 Most menstruating people in our sample (82%) did not experience menstrual changes  
339 following COVID-19 vaccination. Further, we did not find vaccination to be associated

340 with “abnormal” cycle parameters, as defined by FIGO, and we found no difference in  
341 the risk of reporting frequent or infrequent cycles, irregular cycles, long period duration  
342 (+8 days), heavy periods or inter-menstrual bleeding between vaccinated-only  
343 participants and the control group (not vaccinated and without a history of COVID-19  
344 disease). This provides reassuring data suggesting that COVID-19 vaccination will not  
345 lead to menstrual changes in most people, which can be helpful when counselling  
346 reproductive-aged women about COVID-19 vaccination and menstrual changes.  
347 However, 18% did report menstrual disturbance following COVID-19 vaccination, a  
348 proportion that is above the threshold for a ‘very common’ ( $\geq 1/10$ ) adverse reaction  
349 according to international pharmacovigilance standards.<sup>33</sup> For instance, the rate of  
350 menstrual cycle changes assessed through self-report is more frequent than systemic  
351 side-effects after the first dose of the Pfizer vaccine (13.5%), according to data  
352 collected in the COVID Symptom Study app.<sup>34</sup> Given the retrospective nature of the  
353 survey, we cannot attribute changes to the vaccine as participants may have perceived  
354 normal menstrual variability. Nevertheless, clinicians should consider counselling  
355 women about possible menstrual effects following COVID-19 vaccination, while  
356 emphasising the need to seek medical advice if they are severe and lasting more than  
357 one cycle or involving “red flag” symptoms such as inter-menstrual bleeding, post-coital  
358 bleeding, or post-menopausal bleeding. This study also suggests that current smoking  
359 and having had COVID-19 increase the risk of experiencing menstrual disturbance  
360 following COVID-19 vaccination and that those on the combined oral contraceptive pill  
361 (COCP) are less likely to experience menstrual disturbance. Knowledge of risk factors  
362 may help tailor advice to individuals who menstruate prior to COVID-19 vaccination.  
363

**364 Risk factors for menstrual cycle changes following COVID-19 vaccination**

365 Our finding that using combined oral contraceptives decreases the risk of reporting  
366 menstrual changes post-vaccination by 50% contrasts with those obtained by similar  
367 online surveys in the US<sup>35</sup> and in the UK.<sup>36</sup> While a previous US study found “*very little*  
368 *difference between respondents with spontaneous and hormonally contracepting*  
369 *cycles in the rate of post-vaccine heavy menstrual flow*”,<sup>35</sup> a UK-based study found that  
370 “*people on hormonal contraception were more likely to report a change to menstrual*  
371 *flow*”.<sup>36</sup> The authors of the latter study attribute their finding to a reporting bias, where  
372 people using hormonal contraception to decrease their blood flow may be particularly  
373 motivated to respond to the survey.<sup>36</sup> Of note is that the effect of hormonal  
374 contraception is not directly comparable across samples, as our study distinguished  
375 between oestradiol-containing and progestogen-only contraceptives, noting a  
376 decreased risk of reporting any menstrual changes only for those using oestradiol-  
377 based contraceptives. The protective effect of combined contraceptives for cycle  
378 changes post-vaccination has been replicated in another study.<sup>37</sup>

379  
380 We found that smokers were more at risk of reporting menstrual disturbances following  
381 vaccination against COVID-19. Previous studies found that heavy smoking (> 20  
382 cigarettes/day) was associated with a shortening of the follicular phase, irregular cycles  
383 and possible increased risk of anovulation.<sup>38</sup> Thus, it could be that smokers  
384 misattribute cycle irregularity to the vaccine rather than to smoking if they are more  
385 attentive to their cycles after vaccination because they already experience irregular  
386 cycles. Alternatively, smoking could impact vaccine side-effects more generally  
387 through its impact on the immune system, although there is no link published on

388 vaccine side-effects and smoking. Yet, given that smoking induces systemic chronic  
389 inflammation, smokers may be at an increased risk of menstrual cycle disturbance due  
390 to an exacerbation of inflammation following vaccination against COVID-19.

391

392 Our study shows no association between the brand of vaccine (Pfizer vs. AstraZeneca)  
393 nor the number of doses (1 vs. 2) with post-vaccination menstrual changes. This result  
394 is in line with reports made on the Yellow Card surveillance scheme reporting, and with  
395 other studies comparing menstrual changes following the Pfizer and Moderna  
396 vaccines,<sup>35</sup> or between the Pfizer, AstraZeneca and Moderna vaccines.<sup>36</sup>

397

398 The absence of any association between pre-existing reproductive conditions and self-  
399 reported changes partly differs from the findings of other studies. In a previous UK  
400 study, participants with PCOS and endometriosis were “somewhat” more likely to  
401 report, respectively, a later and earlier timing of cycle after vaccination (borderline  
402 significance), but participants with a pre-existing diagnosis of fibroids and heavy  
403 menstrual bleeding were not more likely to report a change in flow as compared to  
404 others.<sup>36</sup> Conversely, in the US study,<sup>35</sup> participants diagnosed with fibroids were  
405 slightly more likely to experience heavier bleeding. Altogether, the findings indicate that  
406 there are no strong associations between pre-existing gynaecological conditions and  
407 menstrual cycle changes.

408

#### 409 **COVID-19 disease and risk of ‘abnormal’ cycle parameters**

410 The results from our analyses suggest that SARS-CoV-2 infection is potentially more  
411 concerning than COVID-19 vaccine for causing menstrual cycle changes categorized

412 as 'abnormal' in the FIGO System of nomenclature for abnormal uterine bleeding.<sup>32</sup>  
413 While participants who are vaccinated do not experience more abnormal cycle  
414 parameters than unvaccinated participants during the pandemic, a history of COVID-  
415 19 disease was associated with an increased tendency of reporting frequent cycles  
416 (<24 days), periods stopping and long period duration (8+ days), and a significant  
417 increased risk of reporting heavier flow and inter-menstrual bleeding. Those outcomes  
418 may result from various causes including ovarian irregularities, uterine issues,  
419 inflammation and hormonal imbalances. For instance, frequent cycles may suggest  
420 anovulatory cycles, short luteal phase (<10 days) and low progesterone levels, which  
421 may compromise fertility in the subsequent cycle immediately following the short luteal  
422 phase.<sup>39</sup> To date, there is no evidence that a history of asymptomatic or mild SARS-  
423 CoV-2 infection leads to negative outcomes of IVF treatments,<sup>40–42</sup> but results from IVF  
424 cannot be generalizable to populations without a history of Infertility or with severe  
425 COVID symptoms. This study also found that a history of COVID-19 disease increases  
426 the risk of reporting "missing" or "stopped" periods. This association must be  
427 interpreted with caution because the variable does not map onto the medical definition  
428 of amenorrhea (cessation of previously regular menses for 3 months) and merely  
429 captures participants' perception. Yet, this finding echoes a recently published case of  
430 secondary amenorrhea following SARS-CoV-2 infection in a 36-year-old healthy  
431 woman, suggesting greater attention should be focused on SARS-CoV-2-induced  
432 hypothalamic–pituitary dysfunction.<sup>43</sup> As compared to individuals who are vaccinated,  
433 a history of COVID-19 disease is significantly associated with an increased risk of  
434 reporting more inter-menstrual bleeding and heavier bleeding during the pandemic,  
435 which is in line with previous studies showing an association between abnormal uterine

436 bleeding and both subclinical Chlamydia infection<sup>44</sup> and dengue fever<sup>45</sup>. There is  
437 currently limited data on the associations between COVID-19 disease and human  
438 reproduction beyond the effect of SARS-CoV-2 infection during pregnancy and IVF  
439 treatments<sup>42</sup>. The results here suggest that a history of COVID-19 disease can, in  
440 some cases, lead to abnormal cycle parameters, whereas receiving a COVID-19  
441 vaccine does not. This is in line with a recent study showing a relationship between  
442 SARS-CoV-2 antibodies and menstrual irregularities<sup>31</sup>.

443

444

#### 445 **Unanswered questions and future research**

446 The association between a history of SARS-CoV-2 infection and menstrual  
447 disturbances post-vaccination in this study may be partly due to the effect of prior  
448 infection with SARS-CoV-2 on the immune response to vaccination, which has been  
449 found to be heightened<sup>46</sup>. Biological data would be needed to verify this hypothesis.  
450 Our findings also suggest that exogenous oestrogen may reduce post-vaccination  
451 menstrual disturbances through anti-inflammatory or anti-viral effects. This is  
452 consistent with the recent suggestion that an 'inflammatory' rather than an 'ovulatory'  
453 route might explain menstrual disturbances following COVID-19 vaccination given the  
454 high prevalence of breakthrough bleeding among users of long-acting reversible  
455 contraceptives (LARC)<sup>35</sup>. A protective effect of oestrogen<sup>47</sup> and oestradiol<sup>48</sup> has been  
456 suggested in relation to the severity of COVID-19, and randomized control trials on  
457 unbiased samples would be needed to establish causality between oestrogen and the  
458 reduced risk of menstrual disturbances following COVID-19 vaccination. Finally, the  
459 diversity of menstrual responses to COVID-19 vaccination might be partly explained

460 by the timing of vaccination in relation to the menstrual cycle. An analysis of the Apple  
461 Women's Health Study found that vaccination during the follicular phase was  
462 associated with longer cycles, while a second dose of an mRNA vaccine in the luteal  
463 phase was associated with slightly shorter cycles<sup>26</sup>. The findings thus call for routine  
464 menstrual data collection in COVID-19 and vaccination studies as well as research into  
465 the mechanisms of menstrual disturbance following vaccination.

466

### 467 **Limitations of the study**

468 Our analysis uses data from a survey not specifically designed to investigate the impact  
469 of COVID-19 vaccination on menstruation. It is retrospective in nature as well as  
470 sensitive to selection, recall and report biases, and does not systematically assess the  
471 full spectrum of menstrual disturbance defined by the International Federation of  
472 Gynaecology and Obstetrics Abnormal Uterine Bleeding System 1<sup>32</sup>. For instance, we  
473 cannot speak to abnormal uterine bleeding for heavy bleeding as the question was  
474 drafted in terms of changes (heavier). We took several steps to limit selection bias  
475 during sampling (see methods) and the initial survey is broadly representative of  
476 people infected with COVID in the UK (8.9% with a positive PCR test in our study  
477 compared to a national proportion of 6.6% at the time<sup>49</sup>). However, approximately 45%  
478 of the sample had received at least one dose of the vaccine, as compared to the  
479 national proportion of 59% by the time of the last survey entry<sup>50</sup>. In addition, menstrual  
480 changes may manifest later after vaccination, and our study does not have the time  
481 depth to evaluate this possibility. Among studies of other vaccines conducted on a  
482 longer timescale, no effect was found by 6-9 months<sup>12,51</sup>.

483



484 The history of COVID-19 disease in our study is self-reported and there are no  
485 biological data to confirm diagnosis. Therefore, there might be a number of  
486 asymptomatic individuals in our study population who may not have reported a history  
487 of COVID-19 disease although they were infected. However, our results are  
488 conservative because this bias would have reduced, rather than increased, differences  
489 between the groups of interest. Further, we are unable to fully ascertain that it is the  
490 virus, rather than its impact on people's lives, that is causing the associations, yet the  
491 associations between vaccination and menstrual changes remain after adjusting for  
492 changes in eating behaviour and physical exercise (analyses not shown). Finally, we  
493 are unable to evaluate if such changes are decreased or increased by vaccination  
494 (most individuals in the sample were likely vaccinated after COVID-19 disease rather  
495 than the other way around), if they are temporary or last in time, and the risk factors  
496 for experiencing menstrual cycle changes after infection. Yet, our findings point to the  
497 importance of routine assessment of reproductive health and time of last menstrual  
498 period as part of the health assessment of women with an infection.

499  
500 The survey is sensitive to recall bias, although this bias is limited compared to more  
501 recent surveys because sampling was conducted before widespread media attention  
502 to the topic<sup>23,35,36</sup>: the issue of menstrual disturbances was not reported by the British  
503 Broadcasting Corporation until May 13, 2021<sup>52</sup>, as compared to a flurry of attention in  
504 US media throughout April<sup>1-3</sup>. Further, we obtained the same results when we  
505 restricted the analysis to participants who completed the survey before the month of  
506 April 2021, suggesting our findings are less likely to be driven by individuals exposed  
507 to the idea of vaccine-related menstrual disturbances on social media. Finally,

508 compared to previous studies investigating both vaccination and infection<sup>40</sup>, this study  
509 is better powered to compare vaccination and infection.

510

## 511 **Author contributions**

512

513 AA, GK and ZO supervised the entire study, designed the survey, and wrote the  
514 original draft of the manuscript; GK conducted the text analysis; AA conducted the  
515 quantitative analysis and revised the manuscript; GS, MAA and JAM provided  
516 intellectual contributions to the survey design and analysis and revised the manuscript.  
517 LA, NR and DK provided patient feedback on the design of the survey and revised the  
518 manuscript.

519

## 520 **Acknowledgments**

521

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527

528

## 529 **Declaration of interests**

530

531 The authors declare no competing interests.

532

**533 Inclusion and diversity**

534

535 We worked to ensure gender balance, ethnic or other types of diversity in the  
536 recruitment of human subjects. We worked to ensure that the study questionnaires  
537 were prepared in an inclusive way. One or more of the authors of this paper self-  
538 identifies as an underrepresented ethnic minority in their field of research or within  
539 their geographical location.

540

Journal Pre-proof

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## 542 **Figure titles and legends**

543

544 **Figure 1. Flowchart of the sample selection for vaccinated individuals.**

545

546 **Figure 2. Prevalence-ratios from univariable analyses of the relationship**

547 **between multiple characteristics and menstrual cycle changes following COVID-**

548 **19 vaccination.** The figure depicts odds-ratio and 99%CI for 33 variables. \*\*: FDR P-

549 value < 0.01; \*\*\* FDR P-value < 0.001.

550

551 **Figure 3. Predicted probability of reporting any menstrual changes following**

552 **COVID-19 vaccination.** Predicted values and 99% confidence intervals given

553 contraceptive use, COVID-19 disease (based on type and certainty of diagnosis) and

554 menstrual cycle changes over the last year. Most individuals (82%) reported no

555 menstrual disturbances following COVID-19 vaccination. This probability was lower for

556 users of combined contraceptives and higher for current smokers and those who had

557 a history of COVID-19 infection.

558

559 **Figure 4. Flowchart of the sample selection for vaccinated and unvaccinated**

560 **individuals.**

561

562 **Figure 5. Predicted probabilities for cycle characteristics “during the pandemic”**

563 **given self-reported COVID-19 vaccination and disease history.** Discrete predictors

564 (cycle characteristics before the pandemic, contraceptive use, BMI, and reproductive

565 disease at baseline) are held constant at their proportions (not their reference level).

566 *Vax*: participants vaccinated with 1 or 2 doses but without a history of COVID-19  
567 disease; *Covax*: participants diagnosed with SARS-CoV-2 infection and vaccinated;  
568 *Cov*: unvaccinated participants diagnosed with history of COVID-19 disease; *None*:  
569 participants neither vaccinated nor diagnosed with SARS-CoV-2 infection. (A) *Cycle*  
570 *Frequency*: Normal: between 24-38 days; Frequent: <24 days; Infrequent: >38 days.  
571 The probability of reporting frequent cycle vs. normal cycles increases is higher in the  
572 *Cov* and *Covax* groups than in the *Vax* group (+30%). (B) *Cycle Regularity*. Regular  
573 (less than 10 days difference between the lengths of two cycles). Cycle regularity does  
574 not vary across groups. (C) *Period Flow*. The probability of reporting heavier flow is  
575 higher in the *Cov* and *Covax* groups compared to the *Vax* group (+38%), while the  
576 probability of reporting lighter vs. normal flow is higher in the *Covax* compared to the  
577 *Vax* group (+29%). (D) *Inter-menstrual bleeding*. The predicted probability of reporting  
578 more inter-menstrual bleeding is higher in the *Cov* and *Covax* groups compared to the  
579 *Vax* group (+31%). (E) *Period Duration*. A prolonged period is defined as >8 days. The  
580 predicted probability to report long periods is higher in the *Cov* group compared to the  
581 *Vax* group (+65%). (F) *Period "missed"*. Participants were asked whether they  
582 perceived having missed a period or whether their periods had stopped. The probability  
583 of reporting periods "stopping" or "missed" is higher in the *Cov* group compared to the  
584 *Vax* group (+31%).

585

586 **Figure 6. Most common words (unigrams) and pairs of adjacent words (bigrams)**  
587 **used to describe menstrual cycle changes following COVID-19 vaccination (n =**  
588 **574).**

589

590 **Figure 7. Correlation matrix between key words within sentences describing**  
591 **menstrual cycle changes following COVID-19 vaccination.** Numbers indicate the  
592 strength of the correlation (phi coefficient) between words. Colours indicate the  
593 direction (red: positive, blue: negative)

594

595 **Figure 8. Network of words describing menstrual cycle changes following**  
596 **vaccination with COVID-19.** Words have been lemmatised to the root of their words,  
597 for example “light” can represent both “lighter” and “light. Node size represents degree  
598 centrality (the commonality of words, only words with more than 5 occurrences are  
599 included). Edge thickness is a measure of correlation between words. When only  
600 correlations  $>0.20$  were considered, 4 clusters emerged (circled in colours)

601

602

603

604

**Tables with titles and legends**

605

606 **Table 1.** Characteristics of the sample of vaccinated individuals

607

<b>Characteristic</b>	N = 4,989
<b>Age, Median (IQR)</b>	35 (28 – 43)
<b>Body Mass Index, n (%)</b>	
Healthy weight	1,059 (34)
Obese	1,163 (37)
Overweight	836 (27)
Underweight	49 (1.6)
Unknown	1,882
<b>Hormonal contraceptive use at the time of the survey, n (%)</b>	
Combined oestrogen-progestin	441 (11)
Copper IUD	225 (5.4)
None	2,421 (58)
Other	84 (2.0)
Progestogen-only	854 (21)
Sterilization	130 (3.1)
Unknown	834
<b>COVID-19 disease (type), n (%)</b>	
COVID -	3,377 (75)
Long COVID	462 (10)
Acute COVID	687 (15)
Unknown	463
<b>COVID-19 disease (diagnosis), n (%)</b>	
Negative	3,377 (76)
Self diagnosed +	395 (8.9)
Tested +	671 (15)
Unknown	546
<b>Number of vaccination doses, n (%)</b>	
Yes, one dose	4,096 (82)
Yes, two doses	893 (18)
<b>Vaccine type, n (%)</b>	
Oxford-AstraZeneca	2,600 (53)
Pfizer-BioNTech	2,335 (47)
Unknown	54
<b>Timing of 1st dose, n (%)</b>	
Before 2021	331 (6.7)
January 2021	1,497 (30)
February 2021	1,469 (30)
March 2021	1,659 (33)
Unknown	33

608

609

610 **Table 2.** Characteristics of the sample of vaccinated and unvaccinated individuals by  
 611 COVID-19 status

612

Characteristic/Group	Covax <sup>1</sup> N = 1,354	Cov <sup>2</sup> N = 1,802	None <sup>3</sup> N = 5,788	Vax <sup>4</sup> N = 3,635	p-value <sup>5</sup>
<b>Age, Median (IQR)</b>	35.00 (28.00 – 43.00)	30.00 (24.00 – 38.00)	30.00 (24.00 – 37.00)	35.00 (28.00 – 43.00)	<0.001
<b>Body Mass Index, n (%)</b>					<0.001
Healthy weight	267 (31)	458 (42)	1,689 (48)	760 (34)	
Obese	354 (42)	288 (26)	728 (21)	832 (37)	
Overweight	225 (26)	316 (29)	942 (27)	616 (27)	
Underweight	6 (0.7)	36 (3.3)	124 (3.6)	38 (1.7)	
Unknown	502	704	2,305	1,389	
<b>Hormonal contraceptives, n (%)</b>					<0.001
Combined	120 (10)	217 (15)	768 (17)	305 (10)	
Copper IUD	58 (5.1)	87 (6.0)	257 (5.6)	169 (5.6)	
None	661 (58)	802 (56)	2,567 (56)	1,795 (59)	
Other	23 (2.0)	20 (1.4)	91 (2.0)	64 (2.1)	
Progestogen-only	257 (22)	292 (20)	861 (19)	599 (20)	
Sterilization	28 (2.4)	26 (1.8)	71 (1.5)	99 (3.3)	
Unknown	207	358	1,173	604	
<b>COVID type, n (%)</b>					<0.001
Acute COVID	848 (64)	1,169 (67)	0 (0)	0 (0)	
Long COVID	475 (36)	573 (33)	0 (0)	0 (0)	
No COVID	0 (0)	0 (0)	5,788 (100)	3,635 (100)	
Unknown	31	60	0	0	
<b>COVID diagnosis, n (%)</b>					<0.001
Negative	0 (0)	0 (0)	5,788 (100)	3,635 (100)	
Self-diagnosed +	208 (15)	416 (23)	0 (0)	0 (0)	
Tested +	1,146 (85)	1,386 (77)	0 (0)	0 (0)	
<b>Number of doses, n (%)</b>					<0.001
Unvaccinated	0 (0)	1,802 (100)	5,788 (100)	0 (0)	
1 dose	1,110 (82)	0 (0)	0 (0)	3,023 (83)	
2 doses	244 (18)	0 (0)	0 (0)	612 (17)	
<b>Vaccine type, n (%)</b>					0.66
Oxford-AstraZeneca	725 (54)	0 (NA)	0 (NA)	1,969 (55)	
Pfizer-BioNTech	616 (46)	0 (NA)	0 (NA)	1,626 (45)	
Unknown	13	1,802	5,788	40	
<b>Timing 1st dose, n (%)</b>					0.31
Before 2021	88 (6.5)	0 (NA)	0 (NA)	227 (6.3)	
February 2021	385 (29)	0 (NA)	0 (NA)	1,034 (29)	
January 2021	412 (31)	0 (NA)	0 (NA)	1,016 (28)	
March 2021	465 (34)	0 (NA)	0 (NA)	1,330 (37)	
Unknown	4	1,802	5,788	28	

613

614

615

<sup>1</sup>Participants both vaccinated and with a history of COVID-19 disease; <sup>2</sup>Unvaccinated participants with a history of COVID-19 disease; <sup>3</sup>Unvaccinated participants with no history of COVID-19 disease; <sup>4</sup>Unvaccinated participants with a history of COVID-19 disease; <sup>5</sup>Kruskal-Wallis rank sum test; Pearson's Chi-squared test.

616



## 617 **STAR★Methods**

### 618 **Resource availability**

619 **Lead contact:** Further information and requests for data and scripts should be directed  
620 to and will be fulfilled by the lead contact, Alexandra Alvergne  
621 (alexandra.alvergne@umontpellier.fr).

622 **Materials availability:** De-identified human data generated in this study have been  
623 deposited on the open science platform DOI 10.17605/OSF.IO/PQXY2

624 **Data and code availability:** De-identified human data have been deposited on the  
625 open science platform and are also available from Mendeley Data at  
626 <http://dx.doi.org/10.17632/xgmgnyknf.1>. They are publicly available as of the date of  
627 publication. All original code has been deposited on the open science platform and is  
628 publicly available as of the date of publication (<https://osf.io/pqxy2/>). Any additional  
629 information required to reanalyse the data reported in this paper is available from the  
630 lead contact upon request.

631  
632

### 633 **Experimental model and subject details**

634 **Human subjects:** The study, titled “The COVID-19 Pandemic and Women's  
635 Reproductive Health” was reviewed by and received ethical approval from the Oxford  
636 University School of Anthropology and Museum Ethnography Departmental Research  
637 Ethics Committee [SAME\_C1A\_20\_029].

638 Participants could only complete the survey if they were over 18, had ever  
639 menstruated, currently lived in the UK, and gave informed consent to the use of their  
640 data. The survey was written in English and disseminated through a Facebook

641 advertising campaign targeting all menstruators in the UK, and included images of  
642 women of diverse ethnicities, ages, and abilities, as well as images of breastfeeding  
643 and pregnant women; The title of the survey was kept general (“women’s reproductive  
644 health and the COVID pandemic”) so as not to oversample individuals with specific  
645 interest in menstrual cycles and COVID infection or vaccination. We fine-tuned the ad  
646 targeting (to the extent that Facebook allows) throughout the campaign to ensure even  
647 geographical and socio-economic spread. We also used a stratified sampling strategy  
648 to ensure that subgroups of the UK population in terms of age, income and ethnicity  
649 were represented in the final sample. In total, 695,543 people viewed the survey ad on  
650 their Facebook page and 26,710 with eligible criteria gave consent and completed it  
651 (there were no duplicates), leading to a 3.8% response rate. In this sample, participants  
652 were aged 18-45, 95% identified as White ethnicity and 99% identified as women.

653  
654  
655

## 656 **Method details**

657  
658

### 658 **Survey design**

659 Our online survey was designed to evaluate whether and how the COVID-19 pandemic  
660 influenced menstrual health. During the design of survey questions, input from a panel  
661 of women suffering from Long Covid, referred to us by the Long Covid Support  
662 (<https://www.longcovid.org/>), was incorporated. Retrospective and self-reported data  
663 on menstrual cycles, behaviour, life circumstances and health before and during the  
664 pandemic as well as COVID-19 disease and vaccination history were collected using  
665 an online survey hosted on the Qualtrics platform ([www.qualtrics.com](http://www.qualtrics.com)). All survey  
666 responses were anonymized using randomly generated IDs.

667

668 The online survey was launched on March 8, 2021. The survey included a maximum  
669 of 105 questions depending on individual circumstances and took an average of 24  
670 minutes to complete. Of the eligible participants who started the survey, 61% answered  
671 all questions after giving their consent (on average participants completed 80% of the  
672 questionnaire). In case of survey fatigue, progress could be saved for up to 14 days to  
673 allow participants to resume later. The survey ran from 08/03/21 to 01/06/21 and was  
674 closed when there had been no new entries for a week.

675

676

## 677 **Outcome variables**

### 678 ***Objective 1: Perceived vaccine side-effects on menstrual cycles***

679 While the survey did not initially aim to evaluate the impact of vaccination on menstrual  
680 cycles specifically, a question was included to assess participants' perception of their  
681 menstrual cycles following vaccination at the end of the survey. Specifically,  
682 participants who indicated that they had been menstruating in the past 12 months,  
683 received 1 or 2 doses of the COVID-19 vaccines and were not involved in a clinical  
684 trial were asked "*Have you noticed any changes to your menstrual cycles since you*  
685 *got vaccinated?*", to which 1 of 4 possible answers could be given: "No", "Yes, my  
686 menstrual cycles are MORE disrupted", "Yes, my menstrual cycles are LESS  
687 disrupted", "Other (please state)". Although "disruption" per se was not defined, by the  
688 time participants answered this question, they had already completed many questions  
689 on menstrual cycle regularity, duration, and symptoms. At the time of the survey  
690 design, anecdotal reports of menstrual effects of the vaccine were only just beginning  
691 to circulate. Participants could select the answer "Other", which in some cases may

692 not have been a different decision from choosing either “more disrupted” or “less  
693 disrupted”. For analysis, we thus transformed these variables to represent a binary  
694 outcome (“No changes” vs. “Any other changes”).

695

## 696 **Objective 2: Menstrual parameters**

697 We operationalized our outcome variables to approximate the FIGO classification  
698 system for normal and abnormal uterine bleeding in relation to 5 parameters:  
699 frequency, regularity, duration, volume, and inter-menstrual bleeding (FIGO System 1,  
700 <sup>32</sup>).

701 **Frequency** In the later part of the survey, participants were asked “*Over the last year,*  
702 *how many days long, on average, was your cycle (between the start of one bleed, and*  
703 *the start of the next bleed)?*”. Based on the number of days reported, we created a  
704 variable with 3 possible outcomes (Normal [24 to 38 days], Frequent [<24 days],  
705 Infrequent [>38 days], based on FIGO definitions).

706 Participants were also asked “*Over the last year, have your periods stopped?*” and  
707 “*Over the last year, did you miss your periods at least once?*” Although “stop” and  
708 “miss” were not defined, concerns over “missing periods” were being reported on social  
709 media and thus this variable was meant to capture people’s perception of their cycles  
710 from which we created a binary variable (perception of ‘missing’ or ‘stopped’ periods  
711 (0/1)).

712 **Regularity** Participants were asked “*Over the last year, how irregular was the length*  
713 *of your menstrual cycles on average?*”. We created a variable with 3 possible outcomes  
714 (Normal [>2 days; 2-5 days; 5-10 days], Somewhat irregular [10-20 days], Very  
715 irregular [>20 days]).

716 **Duration** Participants were asked “*Over the last year, have you noticed any changes*  
717 *in the length of your menstrual cycle? Days of bleeding (Period length)*” We created a  
718 binary variable with 2 possible outcomes (Normal  $\leq 8$  days; Prolonged  $>8+$  days]).

719 **Volume.** “*Over the last year, have you noticed any changes in your periods?*” There  
720 were 4 possible outcomes (“Heavier”, “Lighter”, “No Changes” and “Heavier and  
721 Lighter”).

722 **Inter-menstrual bleeding** *Over the last year, have you noticed any changes in*  
723 *spotting mid-cycle?* There were 4 possible outcomes (“No changes”, “More”,  
724 “Sometimes”, “Sometimes less and sometimes more”).

725

## 726 **Exposures**

727 A total of 33 variables were extracted for this analysis. In addition to socio-demographic  
728 variables (age, income, education, gender, ethnic group, marital status, parity),  
729 standard proxies for health (BMI, smoking status, physical activity, regular use of  
730 vitamins/supplements, regular use of medicine) and reproductive variables indicative  
731 of menstrual health before the pandemic (age at menarche, cycle length, period length,  
732 cycle irregularity, heavy bleeding and contraceptive use), the dataset included  
733 vaccine-related, COVID and pandemic-related variables. First, data on the type of  
734 vaccine received, of which only two had been approved for use in the UK at the time  
735 (Pfizer BioNTech/Oxford-AstraZeneca/Not sure), and the timing of the first vaccination  
736 (month/year) were included. Second, COVID-19 disease was operationalized in two  
737 ways: (i) based on whether people thought they had had COVID, as widespread testing  
738 had not been available in the UK in the early months of the pandemic which fell within  
739 the survey period, leading to three categories: *No COVID* (no tests or negative tests),

740 *acute COVID* (symptoms lasting less than 28 days) and *Long Covid* (symptoms lasting  
741 more than 28 days; we only included people who had symptoms more than a month  
742 before taking up the survey) as well as (ii) based on a combination of testing and self-  
743 diagnosis, leading to three categories: *No COVID* (no tests or negative tests), *COVID*  
744 *tested +* (positive test) and “*Self-diagnosed positive*” (referring to individuals who had  
745 a suspected or clinically diagnosed COVID infection but had not obtained positive PCR,  
746 antigen or antibody tests). We included this last category due to the unavailability of  
747 widespread testing in the UK in the first wave of the pandemic in 2020 and ongoing  
748 questions about the accuracy and optimal timing of antigen and antibody tests. Third,  
749 hormonal contraceptive use was categorized as progestogen-only (hormonal coil or  
750 IUS, implant, injectable, progestogen-only pill), combined oestrogen and progestin (the  
751 pill, the patch, vaginal ring), copper IUD, sterilization, none (fertility awareness,  
752 condom, female condom, diaphragm) and other. Fourth, a variable indicative of  
753 changes in life satisfaction compared to before the pandemic was included to adjust  
754 for changes experienced because of the pandemic and/or the infection rather than  
755 vaccination.

756

## 757 **Quantification and statistical analysis**

758

759 We restricted all analyses to pre-menopausal individuals living in the UK who had a  
760 period in the 12 months preceding the survey and who were not pregnant or  
761 breastfeeding. Further, we only included individuals who knew their COVID-19 disease  
762 and vaccination history at the time of the survey. In the sample, most individuals self-  
763 identify as white (95%) and as women (99%). We then grouped categories for the  
764 variables gender (women vs. other) and ethnic group (white vs. other) in univariable

765 analyses. We then applied several additional exclusions depending on the analysis.  
766 We reported prevalence-ratios and relative risk ratios in the text, and plotted predicted  
767 probabilities from adjusted models to represent absolute effects adjusted for  
768 confounders.

769

770 **What are the risk factors for perceiving menstrual cycle changes following**  
771 **COVID-19 vaccination ? (Objective 1)**

772 We first conducted a series of exploratory univariable analyses, investigating each of  
773 the 33 variables in relation to menstrual characteristics during the pandemic. We then  
774 retained all variables significant at the false discovery rate (FDR) threshold (FDR-  
775 corrected  $P < 0.05$ )<sup>53</sup> for consideration in multivariable analyses. We then conducted  
776 multivariable analyses for each potential risk factor adjusting for potential confounders,  
777 which were defined as variables significant in the univariable analyses and with a  
778 potential confounding (but not mediating) effect according to hypothesized directed  
779 acyclic graphs (Figure S1, Figure S2, Figure S3, Figure S4, Figure S5, Figure S6).  
780 Because the original outcome variable was nominal (two or more categories with no  
781 intrinsic order) but violated the IIA assumption (Independence or Irrelevant  
782 Alternatives) as options were not independent, we dichotomized the variable into two  
783 mutually exclusive categories (“No changes”, “Any other changes”) and performed log-  
784 binomial regressions, which are appropriate when the outcome is not rare (prevalence  
785  $> 10\%$ )<sup>54</sup>. Exponentiating the coefficients result in prevalence ratios (PR) displayed in  
786 tables and figures.

787

788 **Are COVID-19 vaccination and COVID-19 disease risk factors for ‘abnormal’**  
789 **menstrual parameters? (Objective 2)**

790 Our main exposure variable described participants’ self-reported COVID-19 disease  
791 and vaccination history and had 4 levels (1) vaccinated but not infected; (2) vaccinated  
792 and infected (unknown order); (3) infected only and (4) neither vaccinated nor infected.  
793 Our referent group was “vaccinated only”. We used multinomial models when the  
794 outcome variables were nominal (two or more categories with no intrinsic order) and  
795 log-binomial regressions when the outcome was dichotomous. To evaluate changes  
796 between menstrual cycle characteristics, we adjusted all models for menstrual  
797 characteristics before the pandemic, and included age, BMI, hormonal contraceptive  
798 use and presence of reproductive disease at baseline as confounders as per  
799 hypothesized directed acyclic graphs (Figure S6). Estimates and confidence intervals  
800 on the log-odds scale were converted to relative risk ratios (multinomial models) and  
801 those on the log-probability scale (log-binomial models) were converted to prevalence-  
802 ratios for reporting in tables and figures. To investigate if any associations between our  
803 exposure variable and menstrual cycle changes were influenced by confounders, we  
804 compared models with and without interaction effects using AIC. We reported variables  
805 significant at the false discovery rate (FDR) threshold (FDR-corrected  $P < 0.05$ )<sup>53</sup>

806

807 **Missing data**

808 The analysis of complete cases only by dropping missing cases can introduce bias and  
809 lead to a substantial reduction of statistical power<sup>55</sup>, especially if it is plausible that the  
810 data are not missing at random or not completely at random. An evaluation of the  
811 missing data suggested that multiple imputation was advisable (Figure S7). The



812 average proportion of missing values across all variables in the dataset was 3.8%,  
813 which was mostly accounted for by the variable BMI (38% of missing data, Figure S5).  
814 To handle missing data, we used a multiple imputation approach using the R package  
815 '*missRanger*<sup>56</sup>, which combines random forest imputation with predictive mean  
816 matching<sup>56</sup>. Prior to all analyses, we imputed 5 datasets, with a maximum of 10  
817 iterations specified for each imputation. Each imputation was also weighted by the  
818 degree of missing data for each participant, such that the contribution of data from  
819 participants with higher proportions of missingness was weighted down in the  
820 imputation. We set the maximum number of trees for the random forest to 200 but left  
821 all other random forest hyperparameters at their default. The average out-of-bag  
822 (OOB) error rate for multiple imputation across all imputed datasets was 0.08 (range:  
823 0 to 0.77). Parameter estimates for all five datasets were pooled to provide more  
824 accurate estimates. A sensitivity analysis was also performed on the complete cases  
825 without missing data imputation (Objective 1: n=1,548; Objective 2: n=936 to n=4,862,  
826 Table S2).

## 827 **Text analysis**

829 We first built a custom text cleaning function using the '*textclean*<sup>57</sup> and '*tidytext*<sup>58</sup> R  
830 packages to analyse the text written by participants selecting the "Other" category in  
831 the outcome variable (n=574). The resulting corpus was tokenized (broken into  
832 individual units) and lemmatized (words derived from others, such as "vaccine" and  
833 "vaccination" were grouped by their stem version "vaccine"). The corpus was analysed  
834 to answer the following three questions: (i) which single words (unigrams) and pairs of  
835 adjacent words (bigrams) are most frequent? (ii) which words co-occur in the same  
836 sentence? (iii) Are there clusters of symptoms? To investigate the commonality of

837 words, we explored the frequency of unigrams and bigrams within all responses. We  
838 performed a correlation analysis on the most important words for menstrual cycle  
839 descriptions to measure the association between words using the correlation index (phi  
840 coefficient ( $\phi$ ) displayed in Figure 7). To explore patterns of symptoms we examined  
841 which words commonly occur together (though not necessarily adjacent) to visualize  
842 groups of words that cluster together. Clusters were visualized by arranging correlated  
843 words into a combination of connected nodes (network graph) using the '*igraph*'  
844 package <sup>59</sup>.  
845

846

847 **Supplemental information titles and legends**

848 Table S1: Models output related to Figures 2 and 3.

849 Table S2: Complete cases analyses related to Figures 2 and 3

850 Table S3: Model outputs related to Figure 5

851 Table S5: Complete cases analyses related to Figure 5

852

853

Journal Pre-proof

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1044

Questionnaire filled by n=26,710 participants who gave consent → n=18,171 not-vaccinated

Participants vaccinated n=8,539 → n=2,587 who did not have a period in the last 12 months

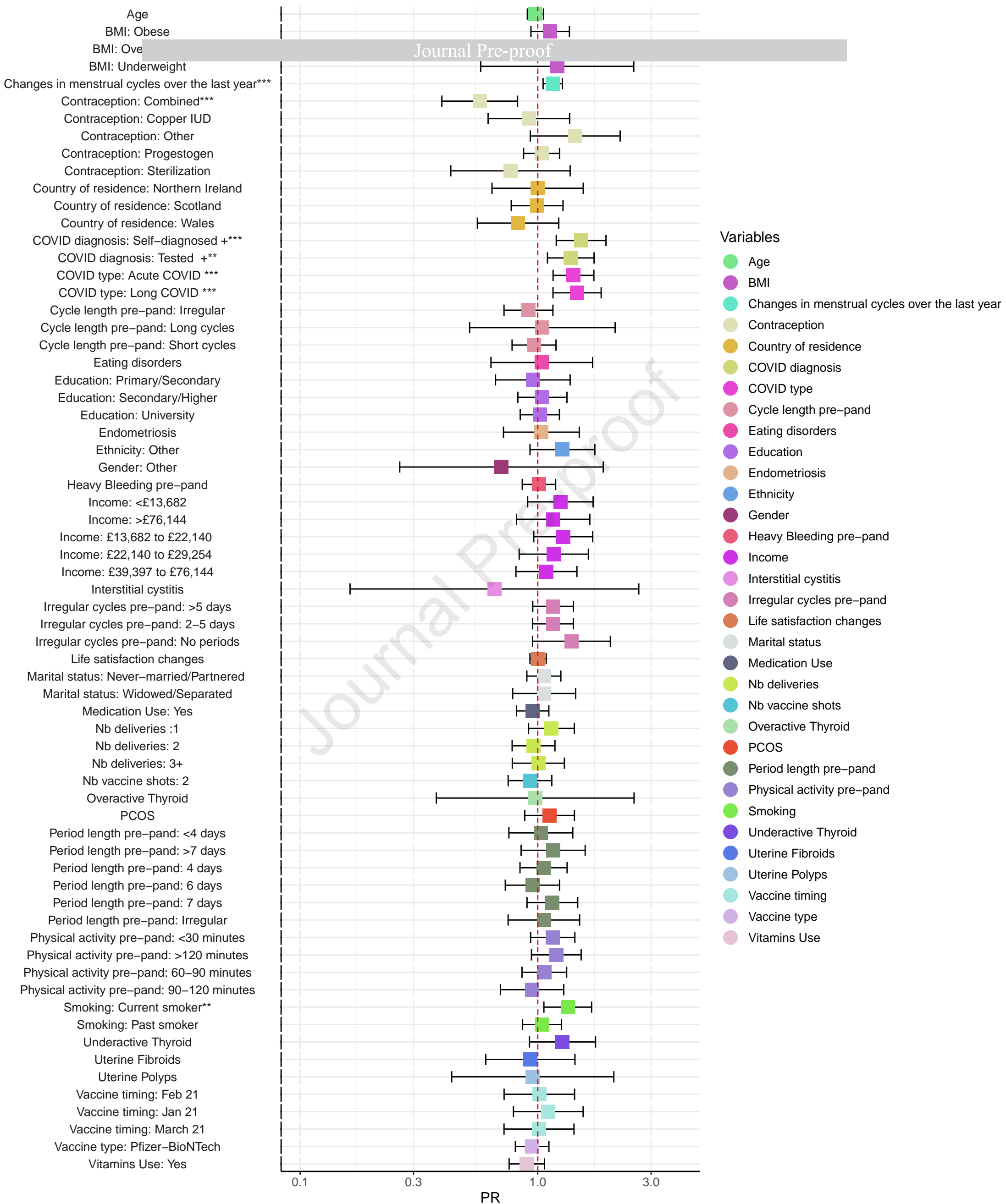
Participants who had a period in the last 12 months n=5,952 → n=537 post-menopausal or transitioning

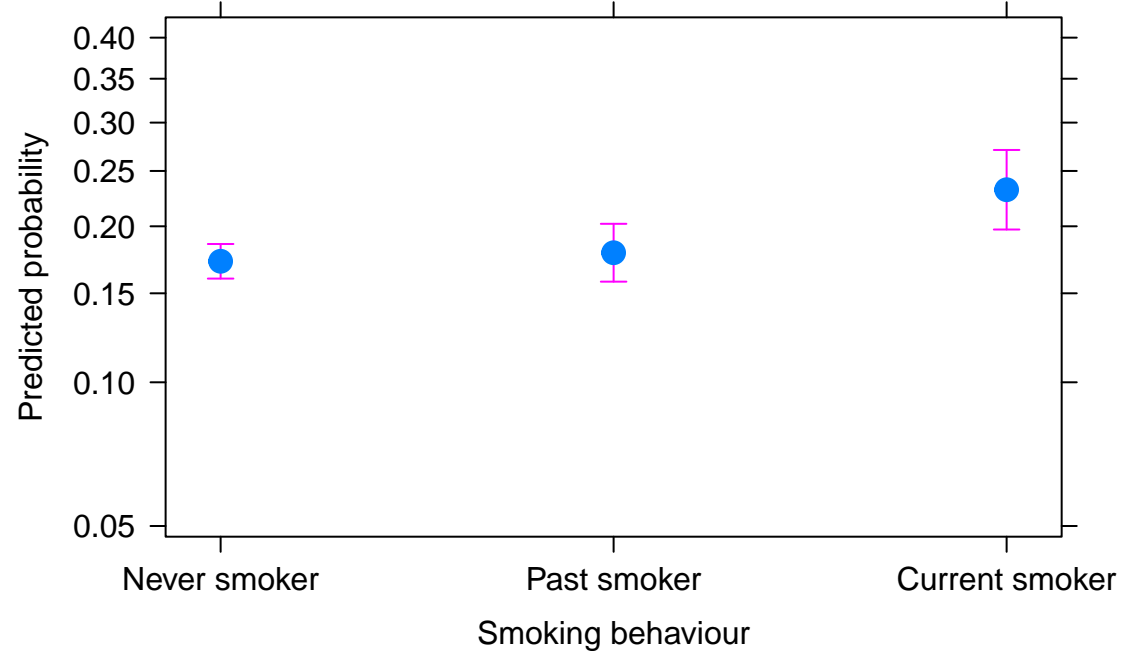
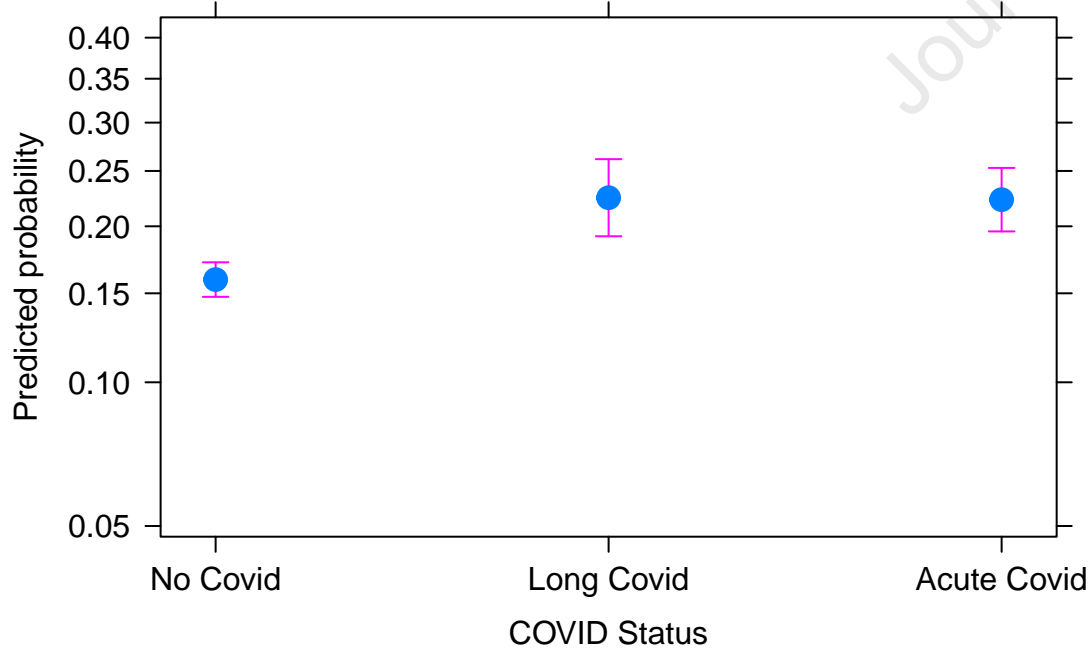
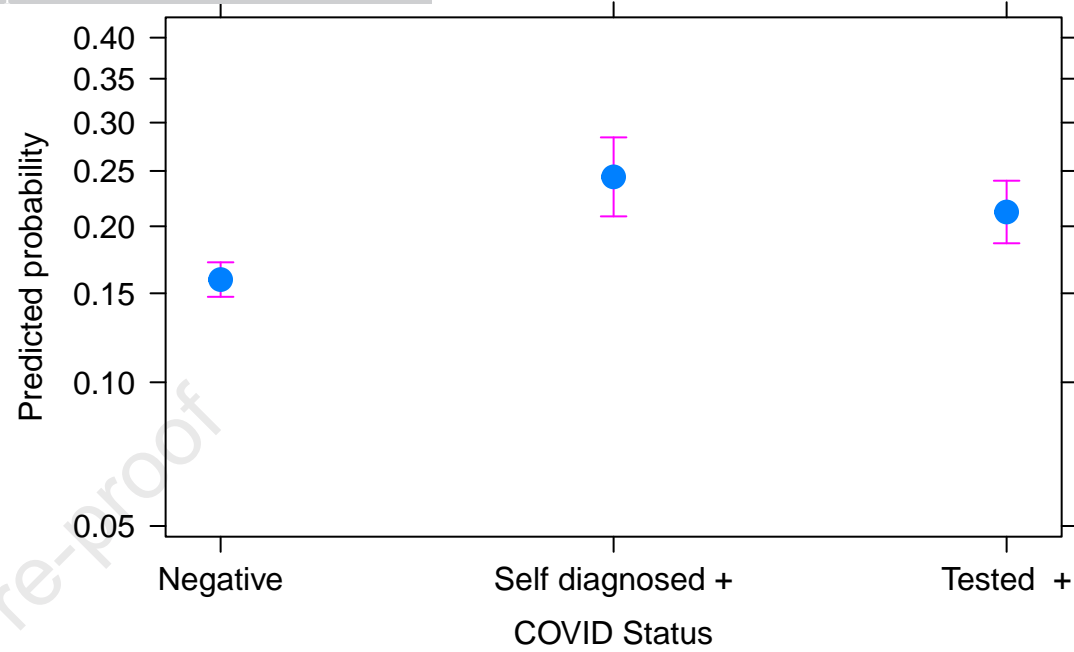
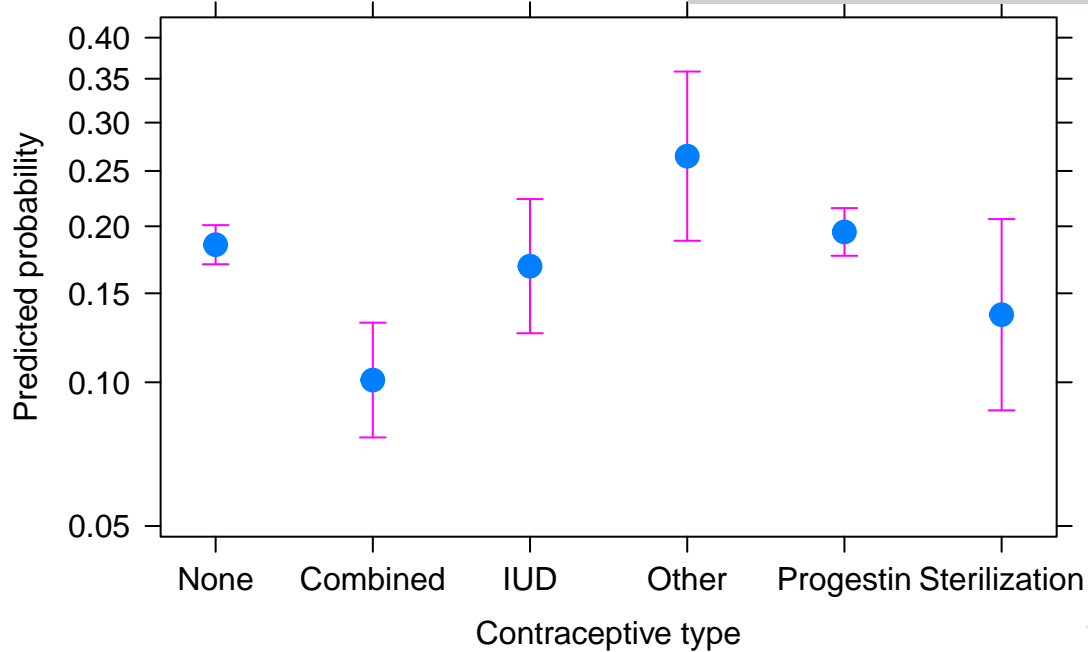
Participants who are pre-menopausal n=5,415 → n=57 who did not live in the UK

Participants living in the UK n=5,358 → n=369 reporting it is too early to evaluate changes

Final sample n=4,989

Journal Pre-proof





Questionnaire filled by n=26,710 participants who gave consent → n=18,171 not-vaccinated

Participants vaccinated n=8,539 → n=2,587 who did not have a period in the last 12 months

Participants who had a period in the last 12 months n=5,952 → n=537 post-menopausal or transitioning

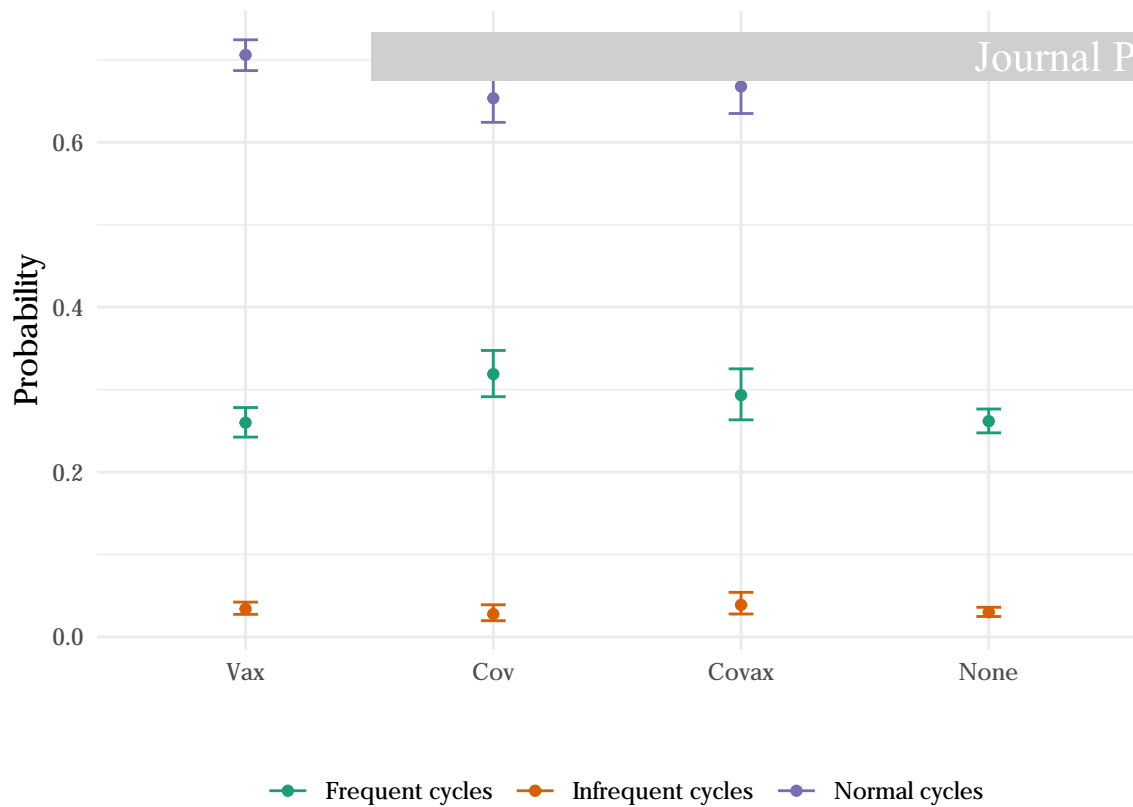
Participants who are pre-menopausal n=5,415 → n=57 who did not live in the UK

Participants living in the UK n=5,358 → n=369 reporting it is too early to evaluate changes

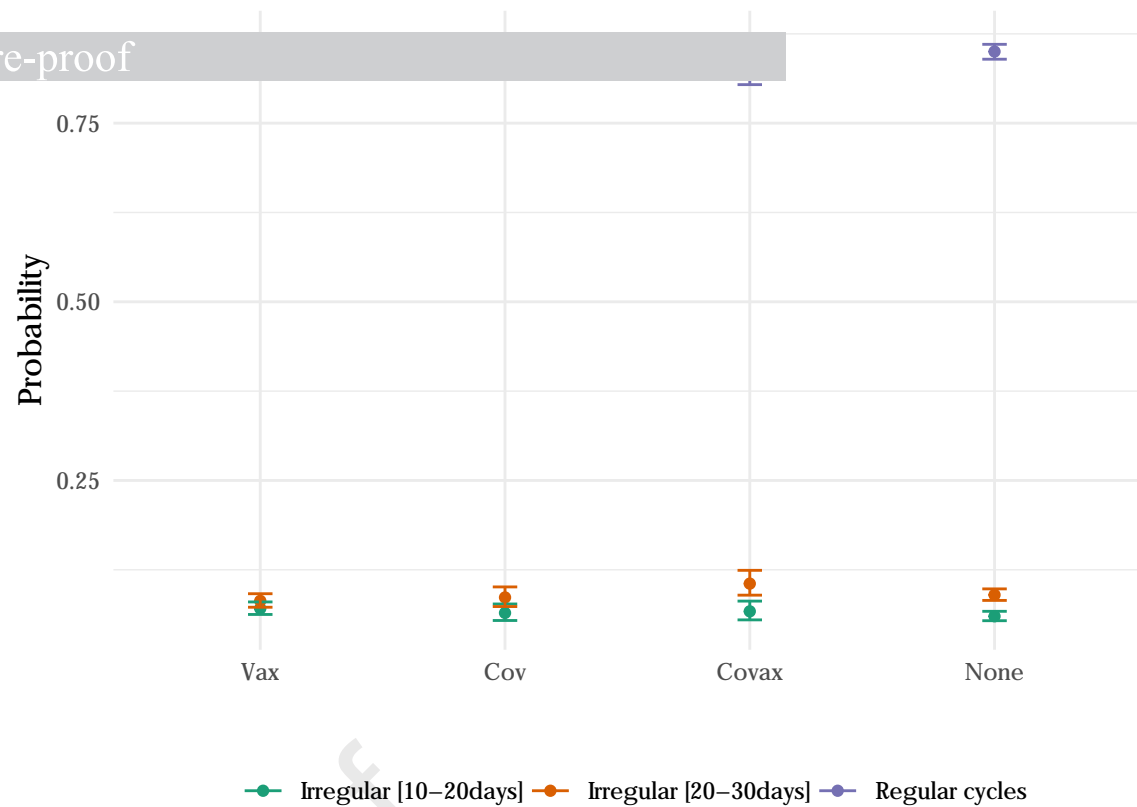
Final sample n=4,989

Journal Pre-proof

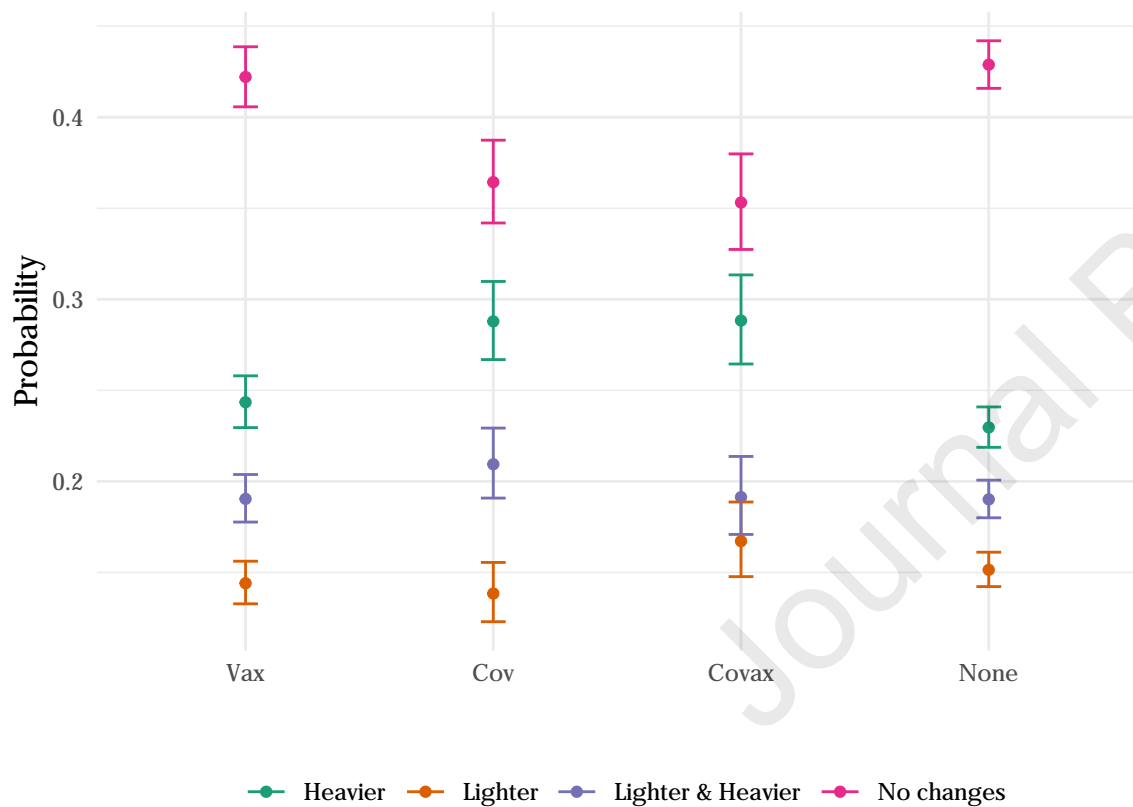
(A) Cycle frequency



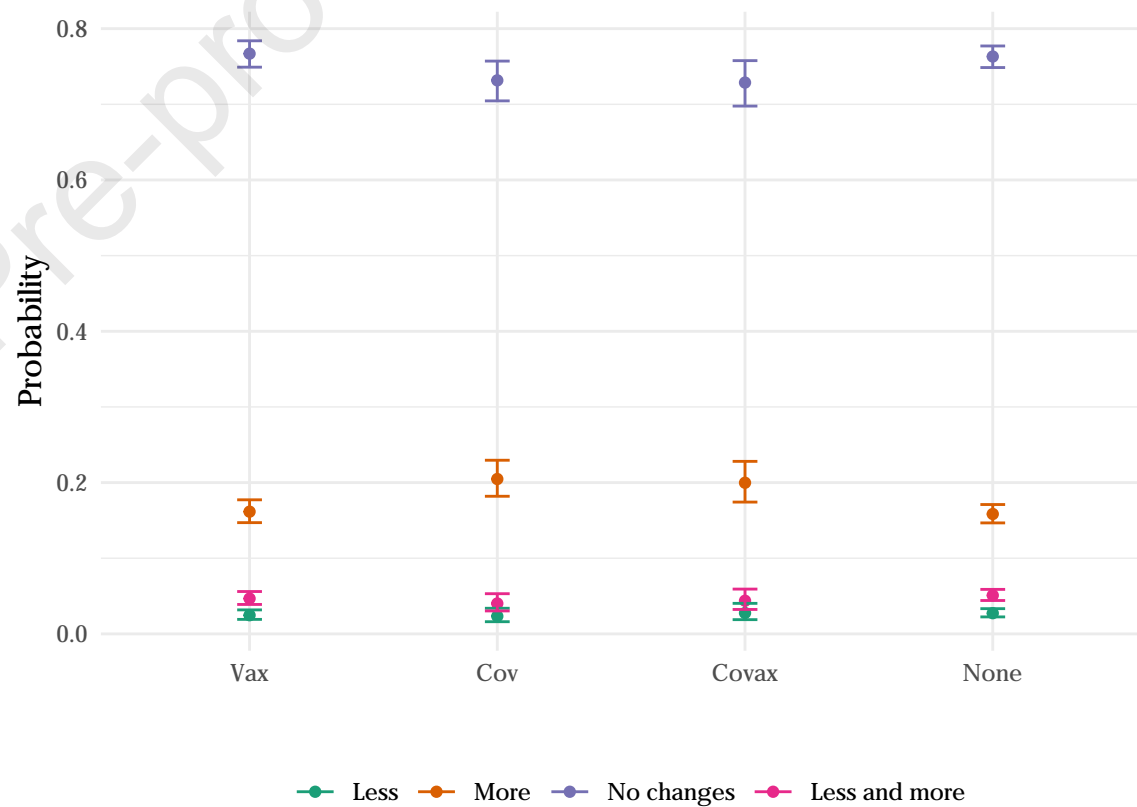
(B) Cycle regularity



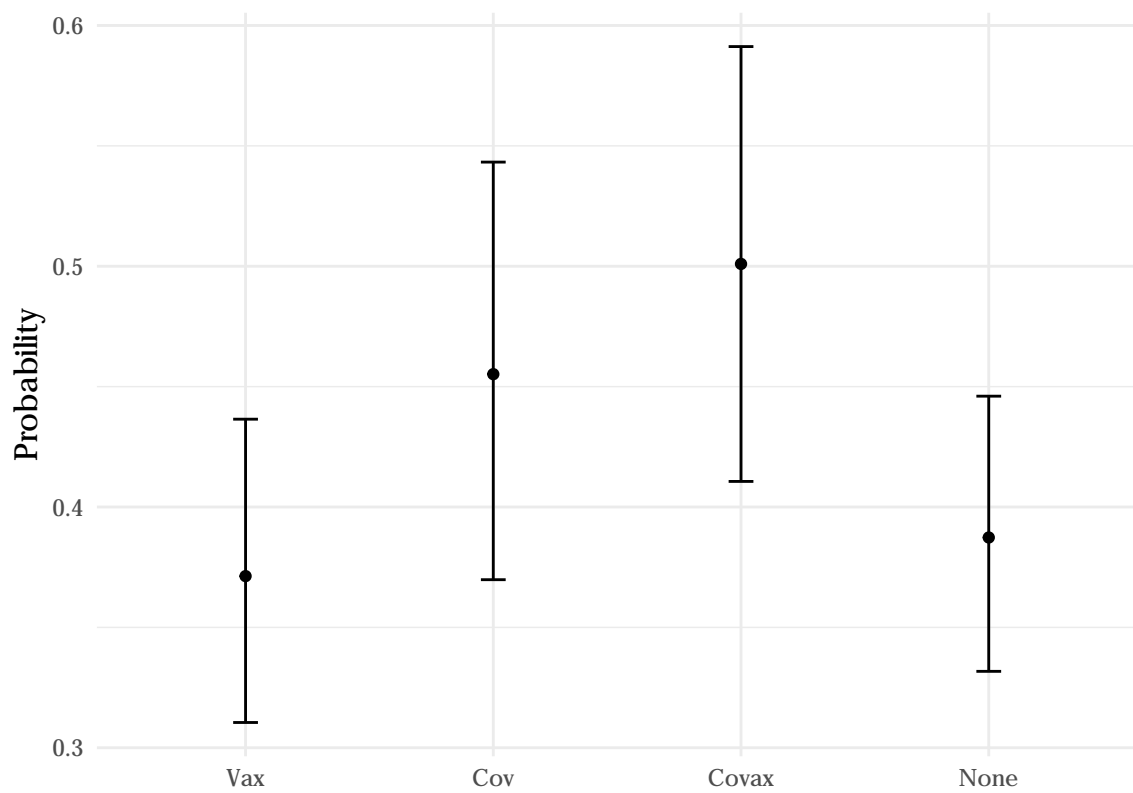
(C) Period flow



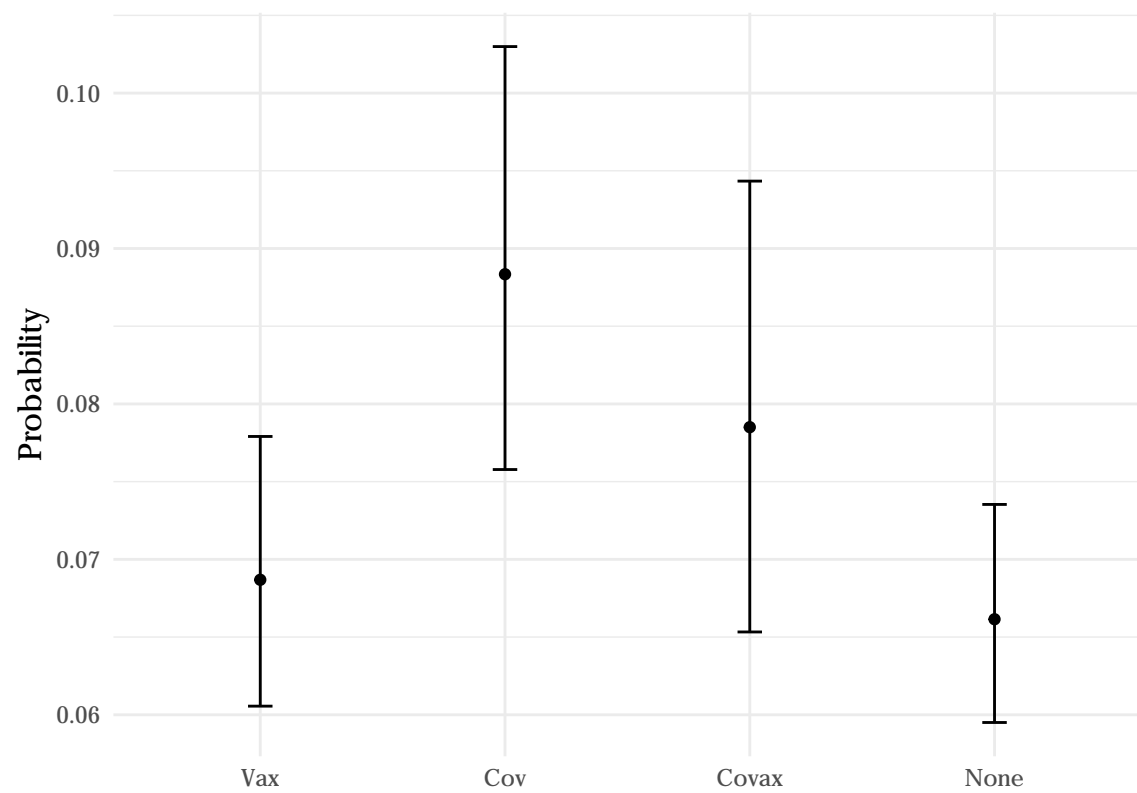
(D) Inter-menstrual bleeding

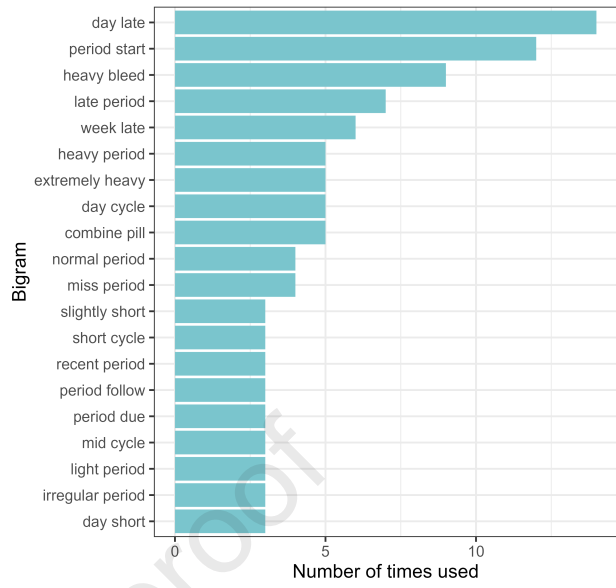
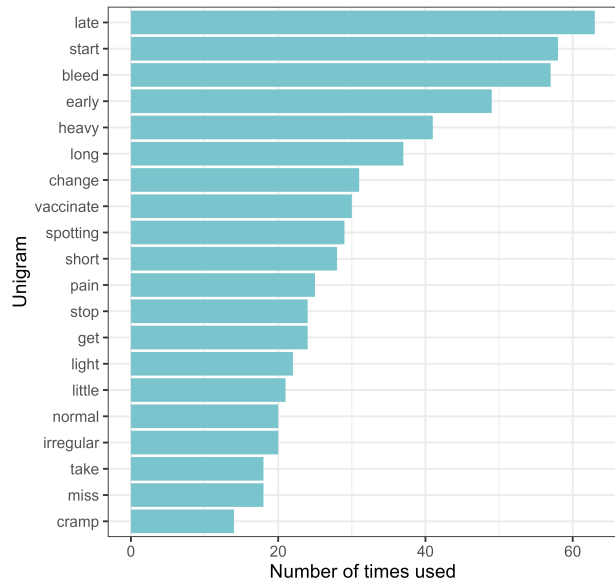


(E) Period duration (8+ days)



(F) Periods missed

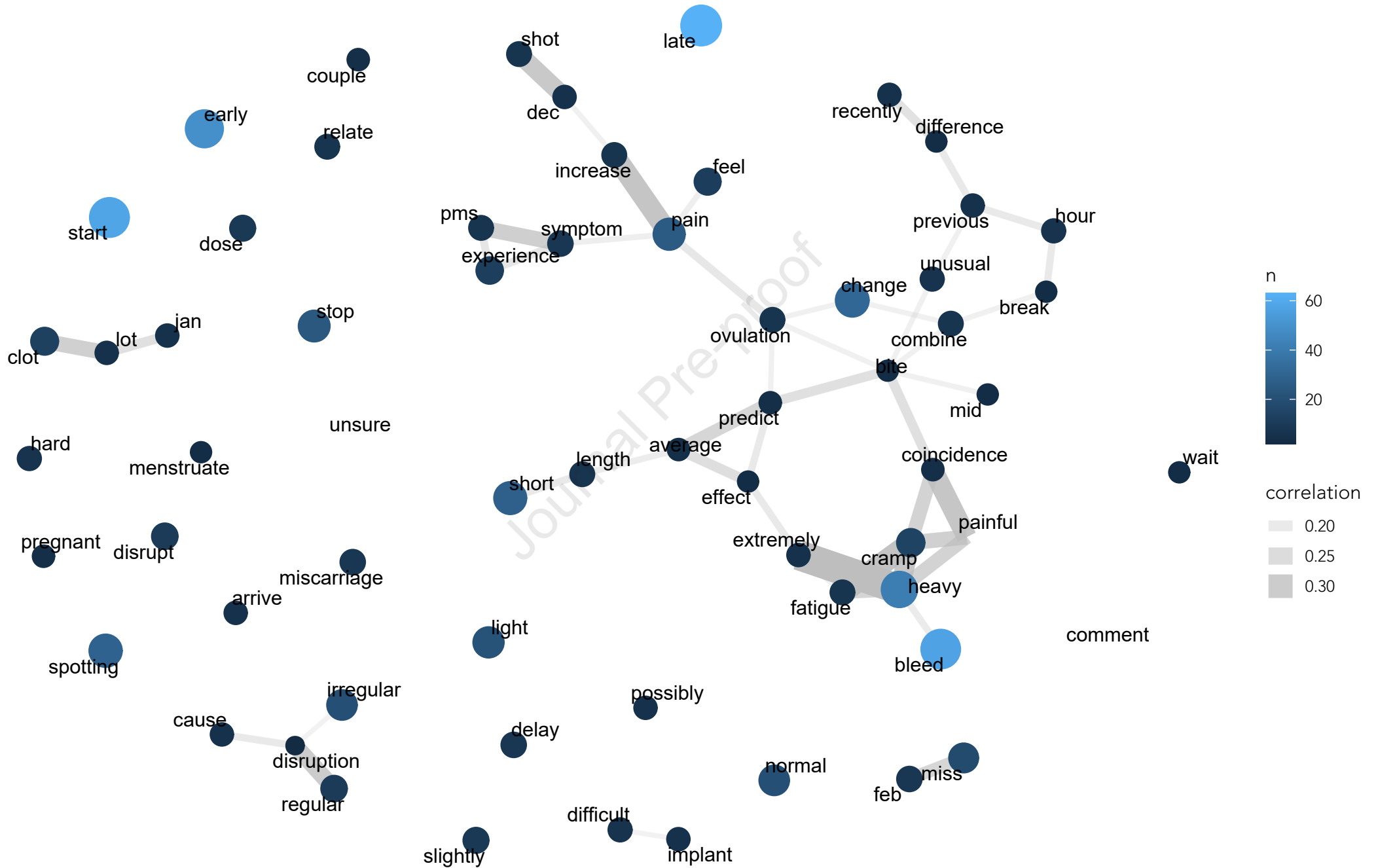




Journal Pre-proof







## Highlights

- Menstrual disturbances were reported by 1 in 5 people after COVID-19 vaccination
- Perceived vaccine-related menstrual changes decreased with combined contraceptives
- Vaccinated individuals were not at increased risk of abnormal uterine bleeding
- COVID-19 disease associated with heavier menstrual flow volume

**KEY RESOURCES TABLE**

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited Data		
Data and scripts	Open Science Framework	DOI 10.17605/OSF.IO/PQXY2
Data collection platform	Qualtrics XM	www.qualtrics.com
Software and Algorithms		
R version 4.2.2	The R Project for Statistical Computing	Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <a href="https://www.R-project.org/">https://www.R-project.org/</a> .