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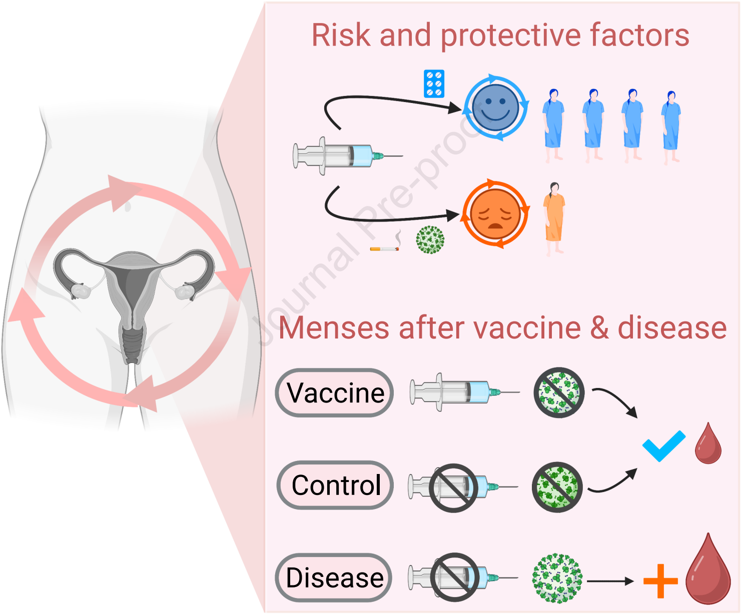
Perceived changes to menstrual cycles following COVID-19 vaccination and disease



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

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

[1] ISEM, Univ Montpellier, CNRS, IRD, Montpellier, France

[2] School of Anthropology and Museum Ethnography, Oxford, UK

[3] Harvard/MGH Center on Genomics, Vulnerable Populations, and Health Disparities, Massachusetts General Hospital, Boston, USA

[4] Long COVID Support

[5] MRC Integrative Epidemiology Unit, University of Bristol, UK

[6] School of Psychology, University of Exeter

[7] MRC Centre for Reproductive Health, University of Edinburgh, UK

+ Lead contact : Alexandra Alvergne

E-mail: alexandra.alvergne@umontpellier.fr

* These authors contributed equally.

Summary

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

Introduction

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

Before the COVID-19 pandemic, research on the relationship between vaccination and menstrual cycle health had been limited to the prophylactic typhoid[12], HPV[13,14] and hepatitis B vaccines[15]. However, recent reports of menstrual disturbances following COVID-19 vaccination in the media[1–3] and surveillance schemes (e.g., in the UK[16,17] and France[18]) have led to a surge of research.[7,19–23] Prospective studies using samples of app users not using hormonal contraception found that COVID-19 vaccination changed cycle length by < 1 day,[24–26] with similar findings in a prospective study of 3,858 pre-menopausal health professionals.[7] In a recent prospective study of 79 participants recruited via social media, the subsequent menstrual episode following COVID-19 vaccination occurred a mean of 2.3 days late after dose 1 and 1.3 days late after dose 2.[20] Beyond cycle length, other studies have reported various changes in regularity, duration and volume.[19,20] For instance, in a sample of young participants (18-30 years) drawn at random from the Norwegian National Population Registry, heavy bleeding increased from 7.6% to 13.6% in the first cycle after vaccination, and from 8.2% to 15.3% after the second vaccine dose[23]. Recent data from a gender-diverse sample receiving COVID-19 vaccination in the US suggests that changes in the form of heavy and breakthrough bleeding affect many people.[22] While there is accumulating evidence that COVID-19 vaccination-related menstrual symptoms are associated with small and temporary changes in cycle length[19,24], there has been no quantitative assessment of the risk factors for menstrual disturbances following COVID-19 vaccination prior to widespread media attention.

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

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

Objectives of the study

The objectives of this study were three-fold: (1) to identify the risk factors for reporting any menstrual changes following COVID-19 vaccination, (2) to evaluate the independent effect of COVID-19 disease and COVID-19 vaccination on menstrual parameters as defined by the International Federation of Gynaecologists and Obstetricians (FIGO),[32] including menstrual frequency, regularity, duration, volume and inter-menstrual bleeding, (3) to capture the types and breadth of menstrual disturbances following COVID-19 vaccination in participants' written accounts. To do this, we used a large retrospective cross-sectional study on menstruation somewhat representative of those who menstruate in the UK. This was launched before UK media coverage of concerns over menstrual vaccine side-effects and includes both quantitative and textual data on menstrual cycle changes.

Results

Self-reported menstrual cycle changes following COVID-19 vaccination

Sample characteristics

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

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

Eighty-two percent of eligible participants reported no changes to their menstrual cycles following COVID-19 vaccination. Only 6.2% reported more disruption, 1.6% reported less disruption and 10.2% reported "Other changes", which could be interpreted as any changes in cycle length and regularity, period duration and volume of menstrual bleeding as well as premenstrual symptoms.

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

The multivariable analyses show that the prevalence of menstrual cycle changes after COVID-19 vaccination is 33% lower among users of combined contraceptives (PR=0.57, 95CI=[0.43 to 0.75], FDR P-value = 0.0002) while current smokers are 1.3 times as likely to report any changes (PR=1.31, 95CI=[1.1 to 1.58], FDR P-value = 0.006) and individuals with a positive COVID-19 disease history are 37 to 46% as likely to report menstrual changes post-vaccination [Long Covid (PR=1. 46, 95CI=[1.22 to 1.75], FDR P-value = 0.00009), acute COVID-19 (PR=1.40; 95CI=[1.20 to 1.62], FDR P-value=0.00003); self-diagnosed positive (PR=1.50, 95CI=[1.25 to 1.80], FDR P-value = 0.00005), tested positive (PR=1.37, 95CI=[1.16 to 1.62], FDR P-value = 0.0008, Figure 3, Table S1). The effects remain significant after adjusting for self-reported overall magnitude of menstrual cycle changes over the year preceding the survey which is positively associated with the risk of reporting any changes (PR=1.13, 95CI=[1.05 to 1.21], *P*=0.003). The findings were replicated when using complete case analyses with unimputed data, indicating that the results are not an artefact of the missing data imputation process (Table S2).

Risk for 'abnormal' menstrual characteristics

Sample characteristics

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

Cycle parameters

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

Finally, the odds for reporting "missed" and/or "stopped" periods do not vary between the control group and the vaccinated-only group (*Control*: PR = 0.96, 95CI = [0.82 to 1.13], FDR P-value = 0.62), but increase by 27% in the COVID-19 disease-only group (*Cov*: PR = 1.27, 95CI = [1.05 to 1.54], FDR P-value = 0.032, Table S3), with the probability of reporting missing or stopped periods increasing from 7% in the vaccinated-only group to 9% in the COVID-19 disease-only group (Figure 5). A significant increase is not observed for participants who are also both infected and vaccinated (*Covax*: PR = 1.14, 95CI = [0.92 to 1.41], FDR P-value = 0.296). Baseline cycle frequency and contraceptive and reproductive disease at baseline do not influence the association between a history of COVID-19 and cycle frequency during the pandemic (models including interaction effects are worse fits to the data than a model without interaction, Table S4).

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

Period duration There are no significant differences in the prevalence of periods longer than 8 days between the vaccinated-only group and the control group (PR = 1.05, 95CI [0.74; 1.49], FDR P-value = 0.8284, Table S3, Figure 5). Compared to the vaccinated-only group, the prevalence of periods longer than 8 days is increased by 65% for the group combining both COVID-19 vaccination and disease (PR = 1.65, 95CI [1.08; 2.54], FDR P-value = 0.0474), a tendency not observed for those with a history of COVID-19 disease only (PR = 1.44, 95CI [0.94; 2.21], FDR P-value = 0.1446, Table S3). The associations do not depend on initial period length category, reproductive disease at baseline or contraceptive uptake in this dataset as models including an interaction between any of those variables and COVID-19 vaccination and disease history are worse fits to the data than a model without interaction (Table S4).

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

Intermenstrual bleeding (IMB) Across all groups of participants, the most probable outcome for spotting mid-cycle during the pandemic compared to before is 'no changes' (73%) followed by 'more' (18.5%), 'less' (3.1%) and 'sometimes more and sometimes less' (5.4%). There are no significant differences between the vaccinated-only and the control groups for the relative risks of 'more' vs. 'no changes' for IMB (RRR = 0.99, 95CI = [0.85 to 1.15], FDR P-value = 0.953). As compared to the vaccinated-only group, the risk of reporting subjectively more spotting mid-cycle than pre-pandemic increases from 18% to 23% for participants with a history of COVID-19 disease (*Cov*: RRR = 1.31, 95CI [1.09; 1.58], *P* = 0.0149; *Covax:* RRR = 1.30, 95CI [1.06; 1.59], FDR P-value = 0.0338). The associations do not depend on reproductive disease at baseline or contraceptive uptake in this dataset as models including an interaction between any of those variables and COVID-19 vaccination and disease history are worse fits to the data than a model without interaction (Table S4). The findings remaining significant after Bonferroni correction (heavy bleeding and IMB) were replicated when using complete case analyses with unimputed data (Table S5).

Textual description of menstrual cycle changes following COVID-19 vaccination

Most common changes reported

The analysis of text written by participants who selected "Other changes" (n= 574, 57% of those reporting any changes) rather than "MORE disruption" or "LESS disruption" showed concerns over cycle length and menstrual bleeding patterns. The most common unigrams (individual words) were "late", "bleed", "early", "long", "heavy", "spotting", "short", "pain" and "stop" and the most common bigrams (pairs of adjacent words) were "day late", "period start", "heavy bleed", and "late period" (Figure 6). While many reported menstrual cycle changes that entailed heavier bleeding/periods, there was no one single pattern of symptoms, with changes including both early and late periods, and diverse experiences reported (from “miss period” to “heavy bleed”).

Associations between symptoms

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

Clusters of words

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

Discussion

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

Meaning of the study

Most menstruating people in our sample (82%) did not experience menstrual changes following COVID-19 vaccination. Further, we did not find vaccination to be associated with "abnormal" cycle parameters, as defined by FIGO, and we found no difference in the risk of reporting frequent or infrequent cycles, irregular cycles, long period duration (+8 days), heavy periods or inter-menstrual bleeding between vaccinated-only participants and the control group (not vaccinated and without a history of COVID-19 disease). This provides reassuring data suggesting that COVID-19 vaccination will not lead to menstrual changes in most people, which can be helpful when counselling reproductive-aged women about COVID-19 vaccination and menstrual changes. However, 18% did report menstrual disturbance following COVID-19 vaccination, a proportion that is above the threshold for a 'very common' (≥ 1/10) adverse reaction according to international pharmacovigilance standards.[33] For instance, the rate of menstrual cycle changes assessed through self-report is more frequent than systemic side-effects after the first dose of the Pfizer vaccine (13.5%), according to data collected in the COVID Symptom Study app.[34] Given the retrospective nature of the survey, we cannot attribute changes to the vaccine as participants may have perceived normal menstrual variability. Nevertheless, clinicians should consider counselling women about possible menstrual effects following COVID-19 vaccination, while emphasising the need to seek medical advice if they are severe and lasting more than one cycle or involving "red flag" symptoms such as inter-menstrual bleeding, post-coital bleeding, or post-menopausal bleeding. This study also suggests that current smoking and having had COVID-19 increase the risk of experiencing menstrual disturbance following COVID-19 vaccination and that those on the combined oral contraceptive pill (COCP) are less likely to experience menstrual disturbance. Knowledge of risk factors may help tailor advice to individuals who menstruate prior to COVID-19 vaccination.

Risk factors for menstrual cycle changes following COVID-19 vaccination

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

We found that smokers were more at risk of reporting menstrual disturbances following vaccination against COVID-19. Previous studies found that heavy smoking (> 20 cigarettes/day) was associated with a shortening of the follicular phase, irregular cycles and possible increased risk of anovulation.[38] Thus, it could be that smokers misattribute cycle irregularity to the vaccine rather than to smoking if they are more attentive to their cycles after vaccination because they already experience irregular cycles. Alternatively, smoking could impact vaccine side-effects more generally through its impact on the immune system, although there is no link published on vaccine side-effects and smoking. Yet, given that smoking induces systemic chronic inflammation, smokers may be at an increased risk of menstrual cycle disturbance due to an exacerbation of inflammation following vaccination against COVID-19.

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

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

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

The results from our analyses suggest that SARS-CoV-2 infection is potentially more concerning than COVID-19 vaccine for causing menstrual cycle changes categorized as ‘abnormal’ in the FIGO System of nomenclature for abnormal uterine bleeding.[32] While participants who are vaccinated do not experience more abnormal cycle parameters than unvaccinated participants during the pandemic, a history of COVID-19 disease was associated with an increased tendency of reporting frequent cycles (<24 days), periods stopping and long period duration (8+ days), and a significant increased risk of reporting heavier flow and inter-menstrual bleeding. Those outcomes may result from various causes including ovarian irregularities, uterine issues, inflammation and hormonal imbalances. For instance, frequent cycles may suggest anovulatory cycles, short luteal phase (<10 days) and low progesterone levels, which may compromise fertility in the subsequent cycle immediately following the short luteal phase.[39] To date, there is no evidence that a history of asymptomatic or mild SARS-CoV-2 infection leads to negative outcomes of IVF treatments,[40–42] but results from IVF cannot be generalizable to populations without a history of Infertility or with severe COVID symptoms. This study also found that a history of COVID-19 disease increases the risk of reporting “missing” or “stopped” periods. This association must be interpreted with caution because the variable does not map onto the medical definition of amenorrhea (cessation of previously regular menses for 3 months) and merely captures participants’ perception. Yet, this finding echoes a recently published case of secondary amenorrhea following SARS-CoV-2 infection in a 36-year-old healthy woman, suggesting greater attention should be focused on SARS-CoV-2-induced hypothalamic–pituitary dysfunction.[43] As compared to individuals who are vaccinated, a history of COVID-19 disease is significantly associated with an increased risk of reporting more inter-menstrual bleeding and heavier bleeding during the pandemic, which is in line with previous studies showing an association between abnormal uterine bleeding and both subclinical Chlamydia infection[44] and dengue fever[45]. There is currently limited data on the associations between COVID-19 disease and human reproduction beyond the effect of SARS-CoV-2 infection during pregnancy and IVF treatments[42]. The results here suggest that a history of COVID-19 disease can, in some cases, lead to abnormal cycle parameters, whereas receiving a COVID-19 vaccine does not. This is in line with a recent study showing a relationship between SARS-CoV-2 antibodies and menstrual irregularities[31].

Unanswered questions and future research

The association between a history of SARS-CoV-2 infection and menstrual disturbances post-vaccination in this study may be partly due to the effect of prior infection with SARS-CoV-2 on the immune response to vaccination, which has been found to be heightened[46]. Biological data would be needed to verify this hypothesis. Our findings also suggest that exogenous oestrogen may reduce post-vaccination menstrual disturbances through anti-inflammatory or anti-viral effects. This is consistent with the recent suggestion that an 'inflammatory' rather than an 'ovulatory' route might explain menstrual disturbances following COVID-19 vaccination given the high prevalence of breakthrough bleeding among users of long-acting reversible contraceptives (LARC)[35]. A protective effect of oestrogen[47] and oestradiol[48] has been suggested in relation to the severity of COVID-19, and randomized control trials on unbiased samples would be needed to establish causality between oestrogen and the reduced risk of menstrual disturbances following COVID-19 vaccination. Finally, the diversity of menstrual responses to COVID-19 vaccination might be partly explained by the timing of vaccination in relation to the menstrual cycle. An analysis of the Apple Women's Health Study found that vaccination during the follicular phase was associated with longer cycles, while a second dose of an mRNA vaccine in the luteal phase was associated with slightly shorter cycles[26]. The findings thus call for routine menstrual data collection in COVID-19 and vaccination studies as well as research into the mechanisms of menstrual disturbance following vaccination.

Limitations of the study

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

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

The survey is sensitive to recall bias, although this bias is limited compared to more recent surveys because sampling was conducted before widespread media attention to the topic[23,35,36]: the issue of menstrual disturbances was not reported by the British Broadcasting Corporation until May 13, 2021[52], as compared to a flurry of attention in US media throughout April[1–3]. Further, we obtained the same results when we restricted the analysis to participants who completed the survey before the month of April 2021, suggesting our findings are less likely to be driven by individuals exposed to the idea of vaccine-related menstrual disturbances on social media. Finally, compared to previous studies investigating both vaccination and infection[40], this study is better powered to compare vaccination and infection.

Author contributions

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

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Declaration of interests

The authors declare no competing interests.

Inclusion and diversity

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

Figure titles and legends

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

Figure 2. Prevalence-ratios from univariable analyses of the relationship between multiple characteristics and menstrual cycle changes following COVID-19 vaccination. The figure depicts odds-ratio and 99%CI for 33 variables. **: FDR P-value < 0.01; *** FDR P-value < 0.001.

Figure 3. Predicted probability of reporting any menstrual changes following COVID-19 vaccination. Predicted values and 99% confidence intervals given contraceptive use, COVID-19 disease (based on type and certainty of diagnosis) and menstrual cycle changes over the last year. Most individuals (82%) reported no menstrual disturbances following COVID-19 vaccination. This probability was lower for users of combined contraceptives and higher for current smokers and those who had a history of COVID-19 infection.

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

Figure 5. Predicted probabilities for cycle characteristics "during the pandemic" given self-reported COVID-19 vaccination and disease history. Discrete predictors (cycle characteristics before the pandemic, contraceptive use, BMI, and reproductive disease at baseline) are held constant at their proportions (not their reference level).

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

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

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

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

Tables with titles and legends

Table 1. Characteristics of the sample of vaccinated individuals

Characteristic	N = 4,989
Age, Median (IQR)	35 (28 – 43)
Body Mass Index, n (%)	
Healthy weight	1,059 (34)
Obese	1,163 (37)
Overweight	836 (27)
Underweight	49 (1.6)
Unknown	1,882
Hormonal contraceptive use at the time of the survey, n (%)	
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
COVID-19 disease (type), n (%)	
COVID -	3,377 (75)
Long COVID	462 (10)
Acute COVID	687 (15)
Unknown	463
COVID-19 disease (diagnosis), n (%)	
Negative	3,377 (76)
Self diagnosed +	395 (8.9)
Tested +	671 (15)
Unknown	546
Number of vaccination doses, n (%)	
Yes, one dose	4,096 (82)
Yes, two doses	893 (18)
Vaccine type, n (%)	
Oxford-AstraZeneca	2,600 (53)
Pfizer-BioNTech	2,335 (47)
Unknown	54
Timing of 1st dose, n (%)	
Before 2021	331 (6.7)
January 2021	1,497 (30)
February 2021	1,469 (30)
March 2021	1,659 (33)
Unknown	33

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

Characteristic\Group	**Covax**[1] **N = 1,354**	**Cov**[2] **N = 1,802**	**None**[3] **N = 5,788**	**Vax**[4] **N = 3,635**	p-value[5]
Age, Median (IQR)	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
Body Mass Index, n (%)					<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	
Hormonal contraceptives, n (%)					<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	
COVID type, n (%)					<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	
COVID diagnosis, n (%)					<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)	
Number of doses, n (%)					<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)	
Vaccine type, n (%)					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	
Timing 1st dose, n (%)					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	

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

STAR★Methods

Resource availability

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

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

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

Experimental model and subject details

Human subjects: The study, titled "The COVID-19 Pandemic and Women's Reproductive Health" was reviewed by and received ethical approval from the Oxford University School of Anthropology and Museum Ethnography Departmental Research Ethics Committee [SAME_C1A_20_029].

Participants could only complete the survey if they were over 18, had ever menstruated, currently lived in the UK, and gave informed consent to the use of their data. The survey was written in English and disseminated through a Facebook advertising campaign targeting all menstruators in the UK, and included images of women of diverse ethnicities, ages, and abilities, as well as images of breastfeeding and pregnant women; The title of the survey was kept general ("women's reproductive health and the COVID pandemic") so as not to oversample individuals with specific interest in menstrual cycles and COVID infection or vaccination. We fine-tuned the ad targeting (to the extent that Facebook allows) throughout the campaign to ensure even geographical and socio-economic spread. We also used a stratified sampling strategy to ensure that subgroups of the UK population in terms of age, income and ethnicity were represented in the final sample. In total, 695,543 people viewed the survey ad on their Facebook page and 26,710 with eligible criteria gave consent and completed it (there were no duplicates), leading to a 3.8% response rate. In this sample, participants were aged 18-45, 95% identified as White ethnicity and 99% identified as women.

Method details

Survey design

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

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

Outcome variables

Objective 1: Perceived vaccine side-effects on menstrual cycles

While the survey did not initially aim to evaluate the impact of vaccination on menstrual cycles specifically, a question was included to assess participants' perception of their menstrual cycles following vaccination at the end of the survey. Specifically, participants who indicated that they had been menstruating in the past 12 months, received 1 or 2 doses of the COVID-19 vaccines and were not involved in a clinical trial were asked "*Have you noticed any changes to your menstrual cycles since you got vaccinated?*", to which 1 of 4 possible answers could be given: "No", "Yes, my menstrual cycles are MORE disrupted", "Yes, my menstrual cycles are LESS disrupted", "Other (please state)". Although "disruption" per se was not defined, by the time participants answered this question, they had already completed many questions on menstrual cycle regularity, duration, and symptoms. At the time of the survey design, anecdotal reports of menstrual effects of the vaccine were only just beginning to circulate. Participants could select the answer "Other", which in some cases may not have been a different decision from choosing either “more disrupted” or “less disrupted”. For analysis, we thus transformed these variables to represent a binary outcome (“No changes” vs. “Any other changes”).

Objective 2: Menstrual parameters

We operationalized our outcome variables to approximate the FIGO classification system for normal and abnormal uterine bleeding in relation to 5 parameters: frequency, regularity, duration, volume, and inter-menstrual bleeding (FIGO System 1, [32]).

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

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

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

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

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

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

Exposures

A total of 33 variables were extracted for this analysis. In addition to socio-demographic variables (age, income, education, gender, ethnic group, marital status, parity), standard proxies for health (BMI, smoking status, physical activity, regular use of vitamins/supplements, regular use of medicine) and reproductive variables indicative of menstrual health before the pandemic (age at menarche, cycle length, period length, cycle irregularity, heavy bleeding and contraceptive use), the dataset included vaccine-related, COVID and pandemic-related variables. First, data on the type of vaccine received, of which only two had been approved for use in the UK at the time (Pfizer BioNTech/Oxford-AstraZeneca/Not sure), and the timing of the first vaccination (month/year) were included. Second, COVID-19 disease was operationalized in two ways: (i) based on whether people thought they had had COVID, as widespread testing had not been available in the UK in the early months of the pandemic which fell within the survey period, leading to three categories: *No COVID* (no tests or negative tests), *acute COVID* (symptoms lasting less than 28 days) and *Long Covid* (symptoms lasting more than 28 days; we only included people who had symptoms more than a month before taking up the survey) as well as (ii) based on a combination of testing and self-diagnosis, leading to three categories: *No COVID* (no tests or negative tests), *COVID tested +* (positive test) and "*Self-diagnosed positive"* (referring to individuals who had a suspected or clinically diagnosed COVID infection but had not obtained positive PCR, antigen or antibody tests). We included this last category due to the unavailability of widespread testing in the UK in the first wave of the pandemic in 2020 and ongoing questions about the accuracy and optimal timing of antigen and antibody tests. Third, hormonal contraceptive use was categorized as progestogen-only (hormonal coil or IUS, implant, injectable, progestogen-only pill), combined oestrogen and progestin (the pill, the patch, vaginal ring), copper IUD, sterilization, none (fertility awareness, condom, female condom, diaphragm) and other. Fourth, a variable indicative of changes in life satisfaction compared to before the pandemic was included to adjust for changes experienced because of the pandemic and/or the infection rather than vaccination.

Quantification and statistical analysis

We restricted all analyses to pre-menopausal individuals living in the UK who had a period in the 12 months preceding the survey and who were not pregnant or breastfeeding. Further, we only included individuals who knew their COVID-19 disease and vaccination history at the time of the survey. In the sample, most individuals self-identify as white (95%) and as women (99%). We then grouped categories for the variables gender (women vs. other) and ethnic group (white vs. other) in univariable analyses. We then applied several additional exclusions depending on the analysis. We reported prevalence-ratios and relative risk ratios in the text, and plotted predicted probabilities from adjusted models to represent absolute effects adjusted for confounders.

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

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

Are COVID-19 vaccination and COVID-19 disease risk factors for 'abnormal' menstrual parameters? (Objective 2)

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

Missing data

The analysis of complete cases only by dropping missing cases can introduce bias and lead to a substantial reduction of statistical power [55], especially if it is plausible that the data are not missing at random or not completely at random. An evaluation of the missing data suggested that multiple imputation was advisable (Figure S7). The average proportion of missing values across all variables in the dataset was 3.8%, which was mostly accounted for by the variable BMI (38% of missing data, Figure S5). To handle missing data, we used a multiple imputation approach using the R package '*missRanger*'[56], which combines random forest imputation with predictive mean matching[56]. Prior to all analyses, we imputed 5 datasets, with a maximum of 10 iterations specified for each imputation. Each imputation was also weighted by the degree of missing data for each participant, such that the contribution of data from participants with higher proportions of missingness was weighted down in the imputation. We set the maximum number of trees for the random forest to 200 but left all other random forest hyperparameters at their default. The average out-of-bag (OOB) error rate for multiple imputation across all imputed datasets was 0.08 (range: 0 to 0.77). Parameter estimates for all five datasets were pooled to provide more accurate estimates. A sensitivity analysis was also performed on the complete cases without missing data imputation (Objective 1: n=1,548; Objective 2: n=936 to n=4,862, Table S2).

Text analysis

We first built a custom text cleaning function using the '*textclean*'[57] and '*tidytext*'[58] R packages to analyse the text written by participants selecting the "Other" category in the outcome variable (n=574). The resulting corpus was tokenized (broken into individual units) and lemmatized (words derived from others, such as "vaccine" and "vaccination" were grouped by their stem version "vaccine"). The corpus was analysed to answer the following three questions: (i) which single words (unigrams) and pairs of adjacent words (bigrams) are most frequent? (ii) which words co-occur in the same sentence? (iii) Are there clusters of symptoms? To investigate the commonality of words, we explored the frequency of unigrams and bigrams within all responses. We performed a correlation analysis on the most important words for menstrual cycle descriptions to measure the association between words using the correlation index (phi coefficient (φ) displayed in Figure 7). To explore patterns of symptoms we examined which words commonly occur together (though not necessarily adjacent) to visualize groups of words that cluster together. Clusters were visualized by arranging correlated words into a combination of connected nodes (network graph) using the '*igraph*' package [59].

Supplemental information titles and legends

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

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

Table S3: Model outputs related to Figure 5

Table S5: Complete cases analyses related to Figure 5

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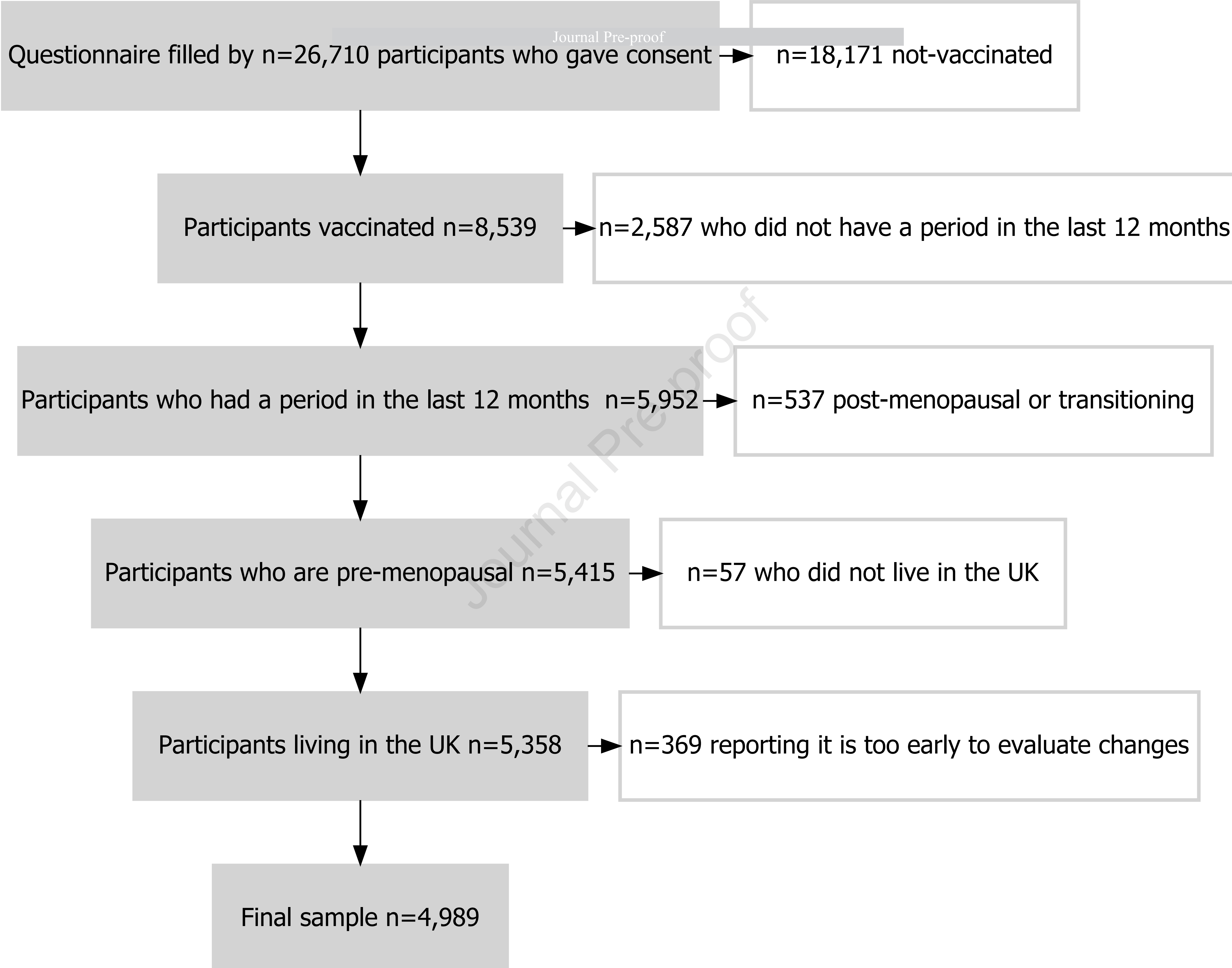
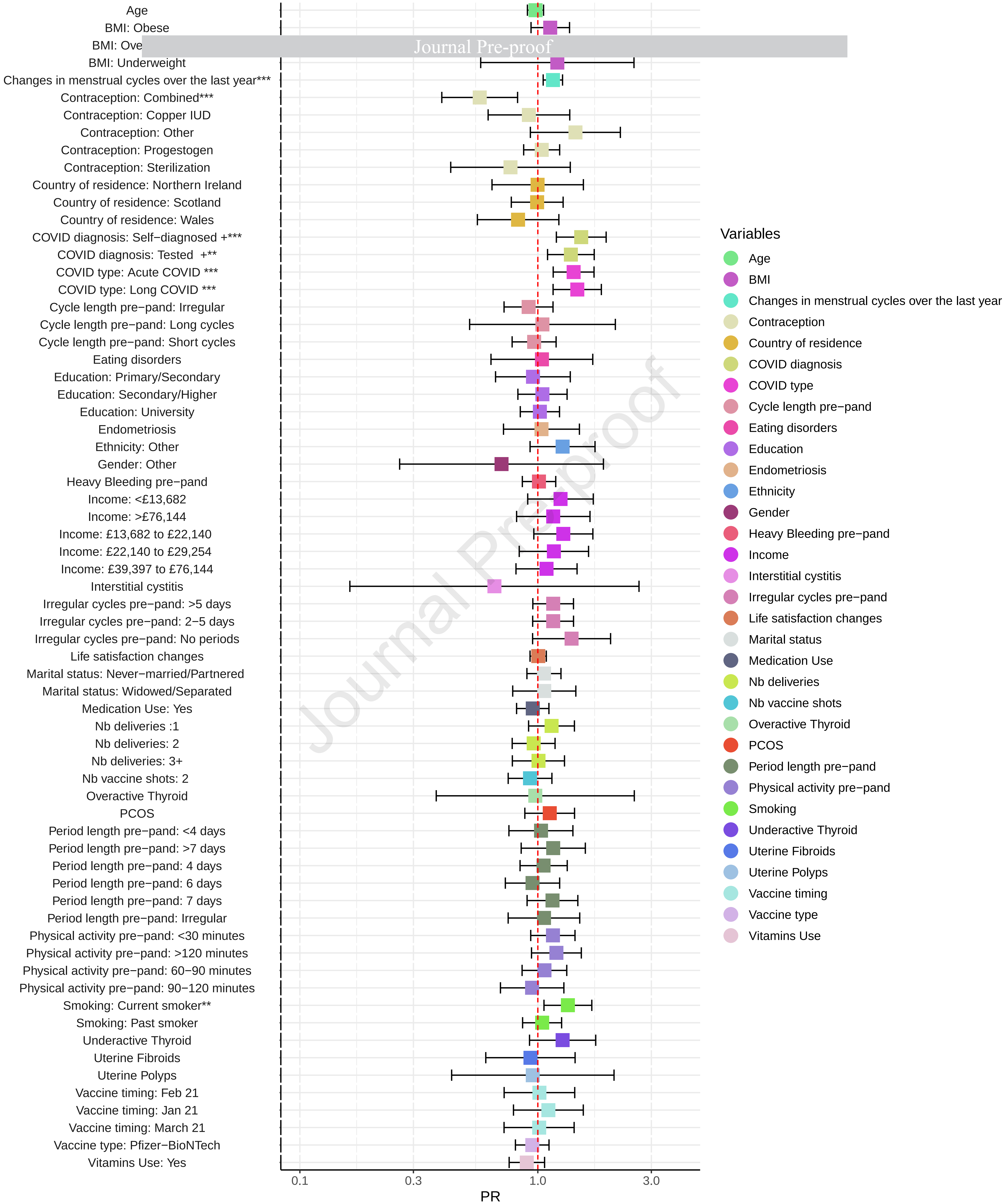
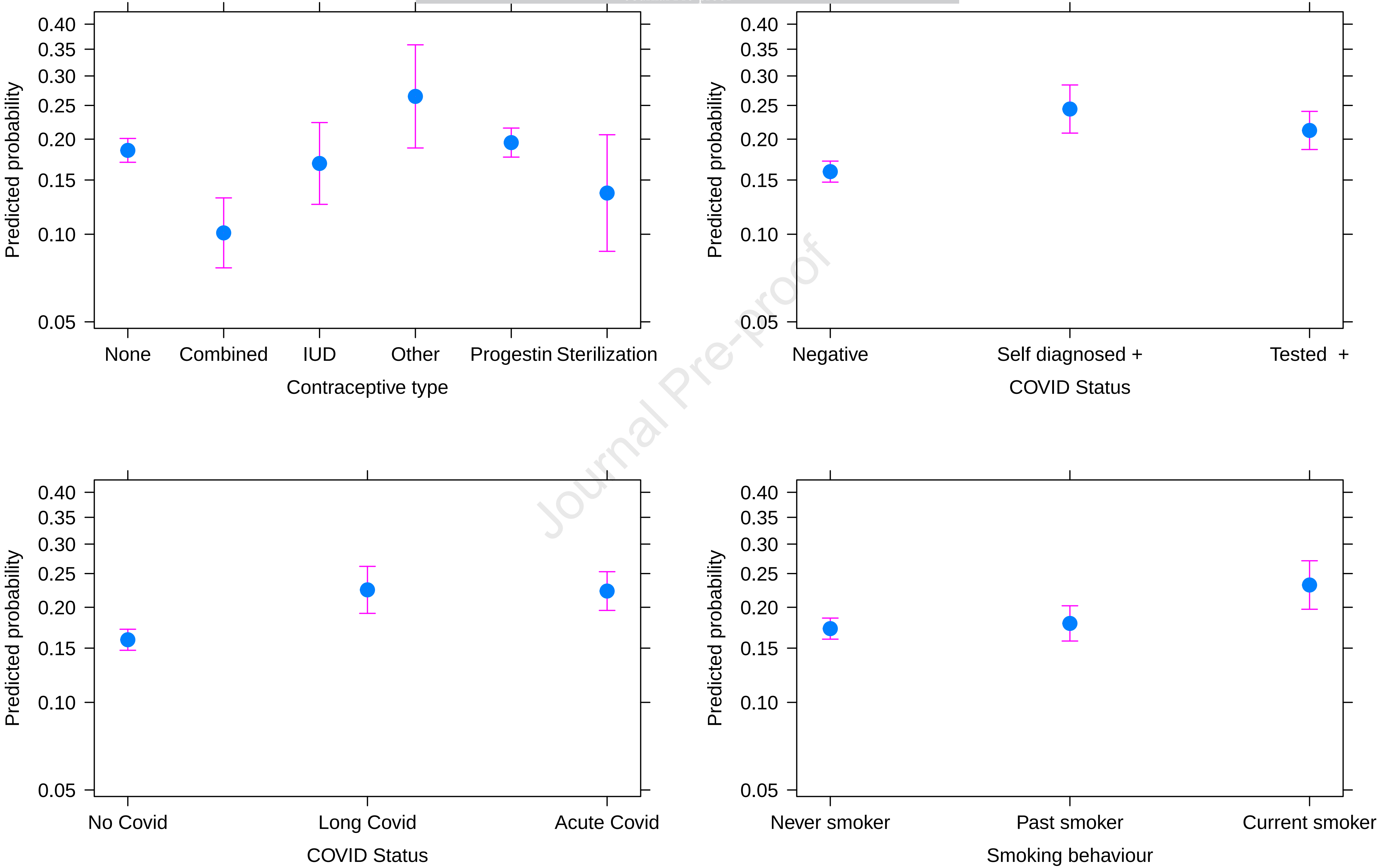
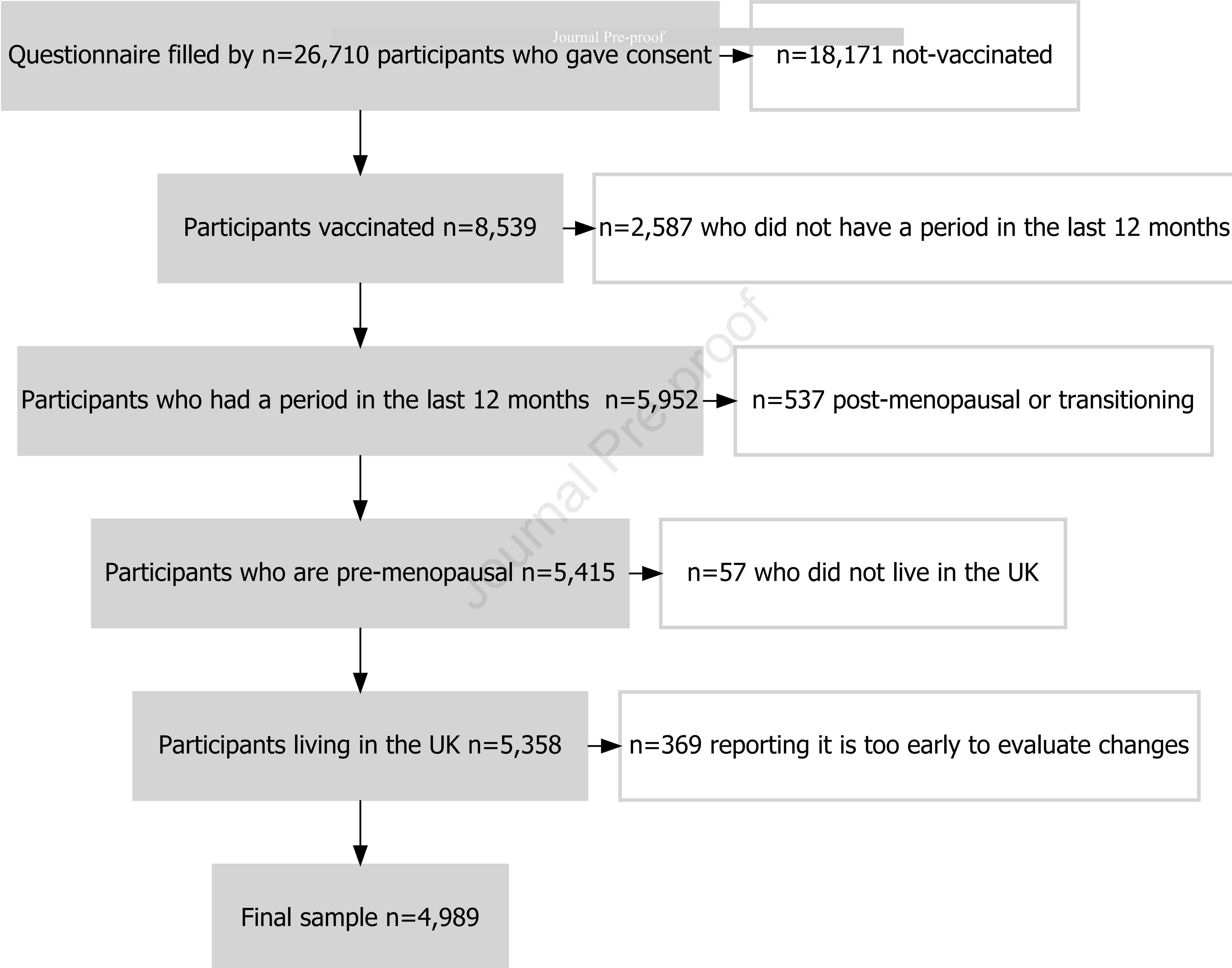

Questionnaire filled by n=26,710 participants who gave consent
n=18,171 not-vaccinated
Participants vaccinated n=8,539
n=2,587 who did not have a period in the last 12 months
Participants who had a period in the last 12 months n=5,952
n=537 post-menopausal or transitioning
Participants who are pre-menopausal 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


Age
BMI: Obese
BMI: Ove
BMI: Underweight
Changes in menstrual cycles over the last year***
Contraception: Combined***
Contraception: Copper IUD
Contraception: Other
Contraception: Progestogen
Contraception: Sterilization
Country of residence: Northern Ireland
Country of residence: Scotland
Country of residence: Wales
COVID diagnosis: Self−diagnosed +***
COVID diagnosis: Tested +**
COVID type: Acute COVID ***
COVID type: Long COVID ***
Cycle length pre−pand: Irregular
Cycle length pre−pand: Long cycles
Cycle length pre−pand: Short cycles
Eating disorders
Education: Primary/Secondary
Education: Secondary/Higher
Education: University
Endometriosis
Ethnicity: Other
Gender: Other
Heavy Bleeding pre−pand
Income: <£13,682
Income: >£76,144
Income: £13,682 to £22,140
Income: £22,140 to £29,254
Income: £39,397 to £76,144
Interstitial cystitis
Irregular cycles pre−pand: >5 days
Irregular cycles pre−pand: 2−5 days
Irregular cycles pre−pand: No periods
Life satisfaction changes
Marital status: Never−married/Partnered
Marital status: Widowed/Separated
Medication Use: Yes
Nb deliveries :1
Nb deliveries: 2
Nb deliveries: 3+
Nb vaccine shots: 2
Overactive Thyroid
PCOS
Period length pre−pand: <4 days
Period length pre−pand: >7 days
Period length pre−pand: 4 days
Period length pre−pand: 6 days
Period length pre−pand: 7 days
Period length pre−pand: Irregular
Physical activity pre−pand: <30 minutes
Physical activity pre−pand: >120 minutes
Physical activity pre−pand: 60−90 minutes
Physical activity pre−pand: 90−120 minutes
Smoking: Current smoker**
Smoking: Past smoker
Underactive Thyroid
Uterine Fibroids
Uterine Polyps
Vaccine timing: Feb 21
Vaccine timing: Jan 21
Vaccine timing: March 21
Vaccine type: Pfizer−BioNTech
Vitamins Use: Yes
0.1
0.3
1.0
3.0
PR
Variables
Age
BMI
Changes in menstrual cycles over the last year
Contraception
Country of residence
COVID diagnosis
COVID type
Cycle length pre−pand
Eating disorders
Education
Endometriosis
Ethnicity
Gender
Heavy Bleeding pre−pand
Income
Interstitial cystitis
Irregular cycles pre−pand
Life satisfaction changes
Marital status
Medication Use
Nb deliveries
Nb vaccine shots
Overactive Thyroid
PCOS
Period length pre−pand
Physical activity pre−pand
Smoking
Underactive Thyroid
Uterine Fibroids
Uterine Polyps
Vaccine timing
Vaccine type
Vitamins Use


Predicted probability
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
None
Combined
IUD
Other
Progestin
Sterilization
Contraceptive type
Negative
Self diagnosed +
Tested +
COVID Status
No Covid
Long Covid
Acute Covid
COVID Status
Never smoker
Past smoker
Current smoker
Smoking behaviour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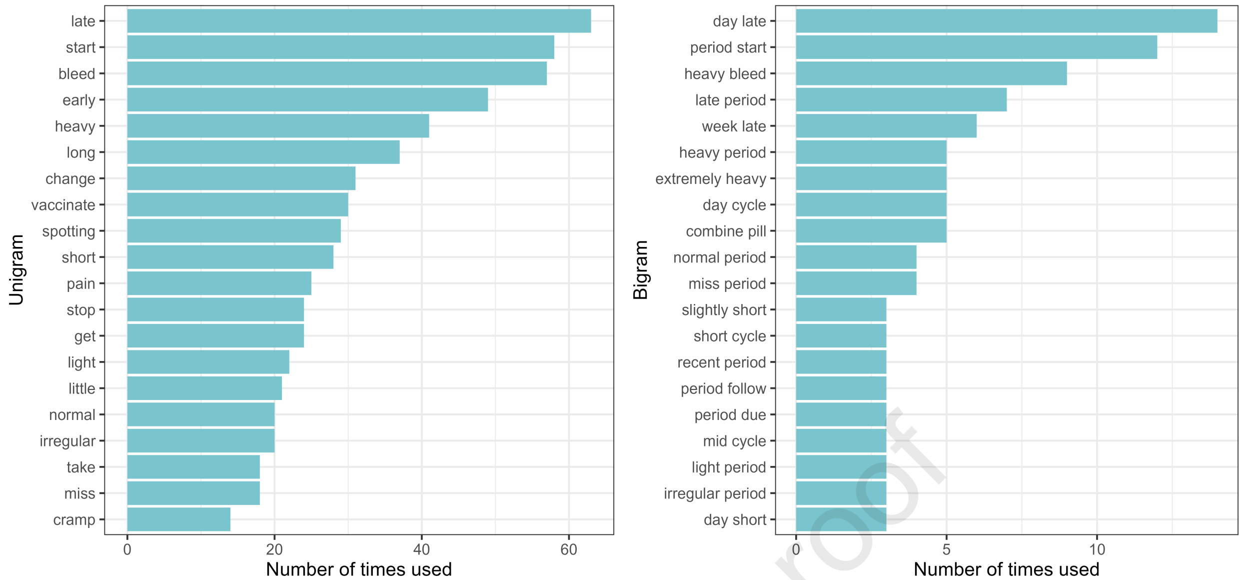
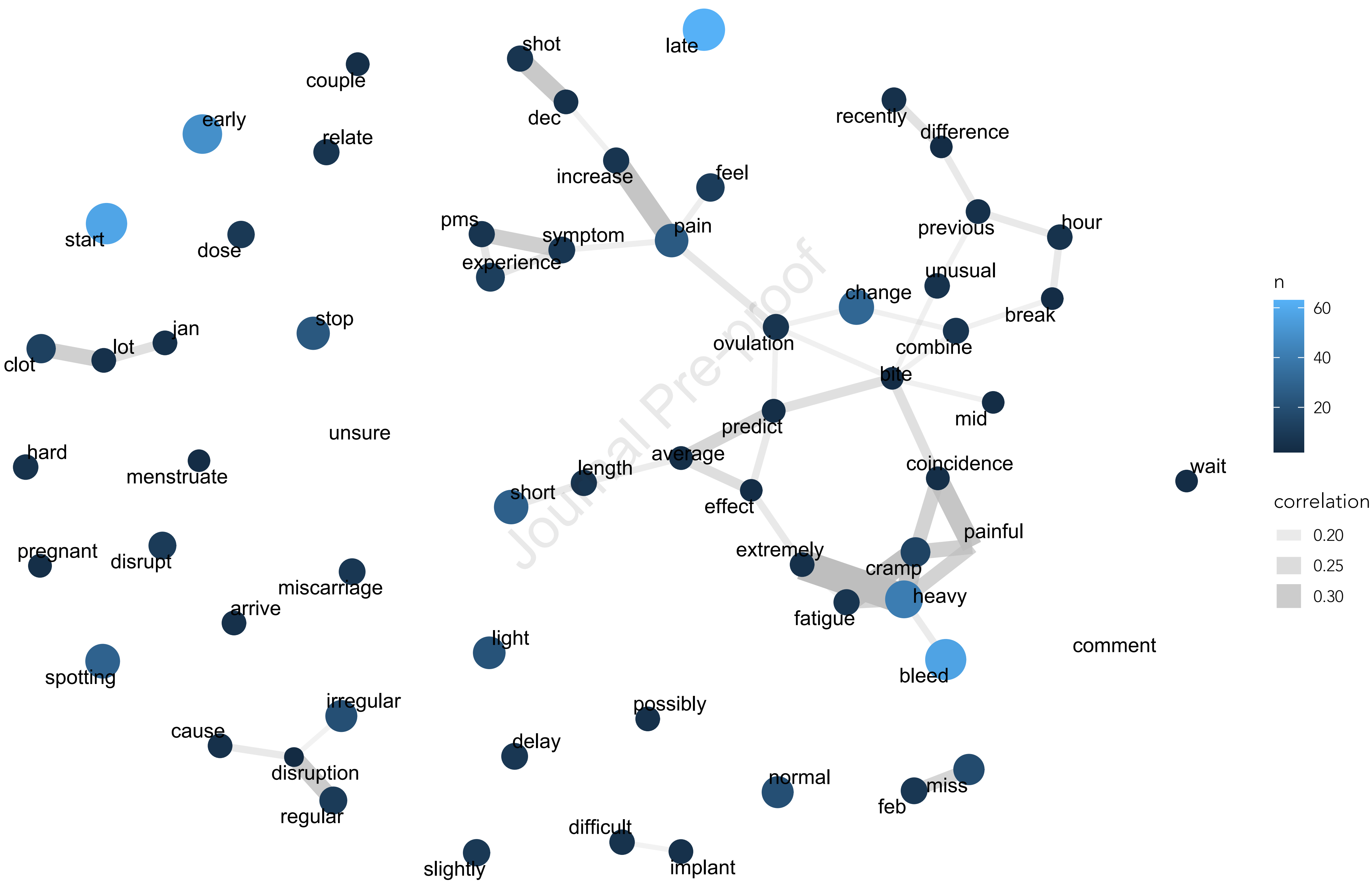
Final sample n=4,989

(A) Cycle frequency
Probability
Vax
Cov
Covax
None
Frequent cycles
Infrequent cycles
Normal cycles
(B) Cycle regularity
Probability
Irregular [10−20days]
Irregular [20−30days]
Regular cycles
(C) Period flow
Probability
Heavier
Lighter
Lighter & Heavier
No changes
(D) Inter−menstrual bleeding
Probability
Less
More
No changes
Less and more
(E) Period duration (8+ days)
Probability
(F) Periods missed
Probability


Unigram
late
start
bleed
early
heavy
long
change
vaccinate
spotting
short
pain
stop
get
light
little
normal
irregular
take
miss
cramp
0
20
40
60
Number of times used
Bigram
day late
period start
heavy bleed
late period
week late
heavy period
extremely heavy
day cycle
combine pill
normal period
miss period
slightly short
short cycle
recent period
period follow
period due
mid cycle
light period
irregular period
day short
0
5
10
Number of times used

	unsure	regular	late	feb	miss	change	shot	bleed	slightly	short	recently	irregular	menstruate	light	normal	experience	pain	clot	painful	cramp	heavy	disrupt	stop	dose	spotting	start	relate	early
unsure	0																											
regular	0.04	0																										
late	0.05	0.11	0																									
feb	-0.03	0.06	0.03	0																								
miss	-0.04	-0.04	0	0.21	0																							
change	0.02	-0.04	-0.01	-0.04	0.01	0																						
shot	-0.04	-0.03	0.03	-0.03	-0.04	0.03	0																					
bleed	-0.09	0.03	-0.16	0.05	-0.07	-0.11	-0.08	0																				
slightly	-0.03	0.06	0.03	0.07	-0.04	-0.04	-0.03	0.1	0																			
short	-0.06	0	-0.11	-0.05	-0.06	-0.07	-0.05	0.11	0.14	0																		
recently	0.03	0.03	-0.08	-0.04	-0.05	0.01	-0.04	-0.07	-0.04	-0.06	0																	
irregular	-0.06	0.01	-0.04	-0.05	-0.01	-0.06	-0.05	-0.07	-0.05	-0.08	-0.01	0																
menstruate	-0.03	-0.03	-0.06	-0.03	-0.03	-0.04	-0.03	0.02	-0.03	-0.05	-0.03	0.02	0															
light	-0.05	-0.05	-0.03	0.02	0	-0.06	-0.05	0.09	0.09	0.14	-0.06	-0.07	-0.04	0														
normal	-0.05	0.09	-0.02	-0.04	0.01	0	-0.04	0.01	-0.04	-0.07	-0.05	0.03	0.04	0.13	0													
experience	0.04	-0.04	-0.03	-0.03	-0.04	-0.04	-0.03	0.03	-0.03	0	-0.04	-0.05	-0.03	0.01	-0.05	0												
pain	-0.04	-0.04	-0.08	-0.04	0.02	0.02	-0.04	-0.06	-0.04	-0.06	-0.05	-0.06	-0.03	0	0.07	0.11	0											
clot	-0.04	-0.04	-0.08	-0.03	-0.04	-0.04	-0.03	0.03	0.06	0.11	-0.04	-0.05	-0.03	0.01	-0.05	0.04	0.03	0										
painful	-0.03	-0.03	-0.07	-0.03	-0.04	-0.04	-0.03	0.05	-0.03	0.01	-0.04	0.08	-0.03	0.02	0.03	0.06	-0.04	0.06	0									
cramp	-0.04	-0.04	-0.04	-0.03	-0.04	-0.05	-0.04	0.06	0.05	-0.06	-0.04	0	-0.03	0.01	0.01	0.04	0.03	0.11	0.23	0								
heavy	-0.07	-0.06	-0.11	0	-0.07	-0.08	-0.06	0.15	0.05	-0.07	-0.03	-0.06	-0.06	0.02	0.11	0.13	0.02	0.13	0.22	0.26	0							
disrupt	-0.03	-0.03	-0.07	-0.03	-0.04	-0.04	-0.03	-0.08	-0.03	-0.05	-0.04	-0.05	-0.03	-0.04	-0.04	-0.03	-0.04	-0.03	-0.03	-0.03	-0.06	0						
stop	-0.05	-0.05	-0.07	-0.05	-0.06	-0.06	-0.05	-0.01	-0.05	-0.08	-0.06	-0.03	-0.04	-0.02	-0.07	-0.05	-0.06	0.01	0.02	0	-0.02	0.02	0					
dose	-0.04	0.05	0.02	0.06	0.03	-0.04	-0.03	0.03	0.06	-0.05	-0.04	-0.05	-0.03	-0.05	-0.05	-0.04	-0.04	-0.04	-0.03	-0.04	-0.06	-0.03	0.07	0				
spotting	-0.01	0	-0.06	0.01	-0.07	-0.02	-0.05	-0.06	0.01	-0.09	-0.07	-0.01	-0.05	-0.04	-0.03	0.1	-0.01	-0.06	-0.05	0.1	-0.04	-0.05	-0.04	0	0			
start	-0.05	-0.04	-0.05	-0.04	-0.05	-0.05	0.03	-0.08	-0.04	-0.02	-0.05	0.03	-0.04	0.09	-0.06	0.02	-0.05	0.02	0.04	-0.05	0.04	-0.04	0.04	-0.04	0.06	0		
relate	-0.03	-0.03	-0.07	0.07	-0.04	-0.04	-0.03	-0.03	-0.03	-0.05	-0.04	0.02	-0.03	-0.04	-0.04	-0.03	-0.04	0.06	-0.03	0.05	-0.06	-0.03	-0.05	-0.03	0.01	0.04	0	
early	-0.04	-0.04	-0.08	-0.03	-0.04	-0.05	-0.04	-0.06	-0.03	-0.06	-0.04	-0.06	-0.03	-0.05	0.01	0.04	-0.04	-0.04	-0.03	-0.04	-0.02	-0.03	-0.05	-0.04	-0.01	-0.05	0.05	0


shot
late
couple
dec
recently
difference
early
relate
increase
feel
pain
pms
symptom
experience
start
dose
previous
hour
unusual
change
break
combine
ovulation
stop
jan
lot
clot
bite
mid
predict
unsure
average
length
hard
menstruate
coincidence
wait
short
effect
painful
extremely
pregnant
disrupt
cramp
miscarriage
heavy
arrive
fatigue
light
comment
bleed
spotting
irregular
cause
possibly
delay
disruption
normal
miss
feb
regular
difficult
implant
slightly
n
60
40
20
correlation
0.20
0.25
0.30

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. https://www.R-project.org/.