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Prevalence of and risk factors for self-reported menstrual changes following COVID-19 vaccination: a Danish cohort study

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ABSTRACT

STUDY QUESTION: Are there some characteristics that render individuals more susceptible to report menstrual changes following the Coronavirus disease 2019 (COVID-19) vaccination?

SUMMARY ANSWER: We found that 30% of menstruating women reported menstrual changes following COVID-19 vaccination and several potential risk factors including stress, vaccine concerns, severe COVID-19 infection, and immediate vaccine symptoms were associated with these reports.

WHAT IS KNOWN ALREADY: Studies suggest that COVID-19 vaccination might temporarily prolong menstrual cycle length by less than 1 day. Specific characteristics may trigger menstrual changes in temporal relation to the vaccination simply by chance or render women more vigilant to potential menstrual changes after being vaccinated. However, research investigating potential risk factors for reporting menstrual changes following COVID-19 vaccination is limited.

STUDY DESIGN, SIZE, DURATION: A population-based Danish cohort study. Data were collected from May 2021 to December 2021 as a part of the BiCoVac Cohort with the aim of examining non-specific effects following COVID-19 vaccination. The main study population included 13 648 menstruating women aged 16–65 years who completed all surveys, received their first dose of a COVID-19 vaccine during the data collection period, and completed questions related to their menstrual cycle.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Potential risk factors included 14 biological, physical, or psychological measures. Information on most potential risk factors was self-reported and collected before the participants' first COVID-19 vaccination. Information about any menstrual change following COVID-19 vaccination was self-reported at the end of the data collection period. Logistic regression analyses were used to estimate crude and adjusted odds ratios (ORs) with 95% CIs for the association between each potential risk factor and reporting menstrual changes following COVID-19 vaccination.

MAIN RESULTS AND THE ROLE OF CHANCE: Any menstrual change following COVID-19 vaccination was reported by 30% of menstruating women. Most of the potential risk factors were associated with reports of menstrual changes following COVID-19 vaccination. In particular, higher odds were found among women who reported ≥5 immediate vaccine symptoms; OR 1.67 [1.50–1.86], had had a prior severe COVID-19 infection; OR 2.17 [1.40–3.35], had a high-stress level at baseline; OR 1.67 [1.32–2.10], or were concerned about COVID-19 vaccines prior to vaccination; OR 1.92 [1.50–2.45]. Lower odds were found among women with regular menstrual cycles using hormonal contraception; OR 0.71 [0.65–0.78].

LIMITATIONS, REASONS FOR CAUTION: We were unable to address the causal effect of COVID-19 vaccination on the reported menstrual changes, as information about menstrual changes was not available among non-vaccinated women.

WIDER IMPLICATIONS OF THE FINDINGS: The study identified several potential risk factors for reporting menstrual changes following COVID-19 vaccination. Further studies are needed to establish causal associations and the clinical impact of self-reported menstrual changes.

STUDY FUNDING/COMPETING INTEREST(S): The BiCoVac data collection was funded by TrygFonden (id-number: 153678). No competing interests are declared.

Introduction

Vaccines against the novel Coronavirus disease 2019 (COVID-19) were introduced to reduce severity and mortality caused by COVID-19 infections (Haas *et al.*, 2021). However, following the rapid introduction of the COVID-19 vaccines (European Medicines Agency, 2021), public concerns of a potential association between COVID-19 vaccination and menstrual changes arose (Mcalpine, 2021). This was a contributory factor to vaccine hesitancy and fear of the impact of COVID-19 vaccines on fertility (Diaz *et al.*, 2022). Current literature addressing this concern is limited as clinical trials and most surveys do not actively inquire or collect information on menstrual cycles (Polack *et al.*, 2020).

Menstrual changes have previously been linked to vaccination. First in 1913, following the prophylactic typhoid vaccine (Lamb, 1913) and later reports of menstrual changes were found in relation to the vaccination against the human papillomavirus (HPV) (Gong *et al.*, 2020). Following the introduction of the COVID-19 vaccination programme, the Danish Medicines Agency had received approximately 6200 reports of menstrual changes by 31 December 2022 (Laegemiddelstyrelsen, 2023), and the UK Medicines and Healthcare products Regulatory Agency (MHRA)'s Yellow Card surveillance scheme had received more than 40 000 individual reports by October 2022 (Medicines and Healthcare products Regulatory Agency, 2022). These reports included cases of unexpected vaginal bleeding and changes in menstrual volume and frequency (Medicines and Healthcare products Regulatory Agency, 2022; Laegemiddelstyrelsen, 2023). In October 2022, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency stated that COVID-19 vaccines could potentially cause heavy menstrual bleeding (Pharmacovigilance Risk Assessment Committee, 2022). This changed the previous assessment from August 2021, which found no evidence suggesting any causal associations between COVID-19 vaccination and menstrual changes (Pharmacovigilance Risk Assessment Committee, 2021).

The menstrual cycle is a vital indicator of female health and fertility (Critchley *et al.*, 2020). Yet, menstrual cycles are flexible and short-term variability is natural and common and does not necessarily reflect health concerns or affect long-term fertility (Fehring *et al.*, 2006). The general prevalence of abnormal uterine bleeding among women of reproductive age varies between 3% and 30% (Munro *et al.*, 2018). Several plausible mechanisms may trigger menstrual changes, including older ages (Harlow and Paramsothy, 2011), lifestyle factors (e.g. low and high BMI (Jensen *et al.*, 1999), smoking (Rowland *et al.*, 2002)) and extreme exercise (Chen and Brzyski, 1999)), psychological distress (e.g. stress (Anto-Ocrah *et al.*, 2023) and mental disorders (Strine *et al.*, 2005)), general medical conditions (e.g. cardiovascular disease (Zhu *et al.*, 2019)), and viral infections (e.g. COVID-19 infection (Lebar *et al.*, 2022)). The mechanisms triggering menstrual changes might be happening in temporal relation to the vaccination simply by chance. When the underlying mechanisms leading to menstrual changes are not fully understood, affected individuals might mistakenly attribute the symptoms to the vaccine.

In the present study, we explored the prevalence of and potential risk factors for reporting menstrual changes following COVID-19 vaccination.

Materials and methods
Setting and data sources

The study was based on data from the Danish BiCoVac Cohort. BiCoVac was initiated in 2021 aiming to examine whether COVID-19 vaccines were associated with non-specific symptoms, i.e. effects beyond the reduction in COVID-19. A random sample of 911 613 Danish citizens (25% of all Danish citizens between 16 and 65 years of age living in Denmark in April 2021) were identified using the unique Danish civil personal registration (CPR) system. The identified sample was invited to participate by use of the Danish digital mailbox system 'e-boks' used for communication between authorities and Danish citizens. The sample included 440 992 women. Before May 2022, three surveys were distributed to the BiCoVac Cohort (baseline questionnaire in May 2021, first follow-up questionnaire in June–July 2021, and second follow-up questionnaire in October 2021). All surveys collected self-reported information on COVID-19 vaccination, COVID-19 infection, and associated symptoms, while the baseline survey also collected self-reported information on lifestyle behaviour as well as general health and well-being. The second follow-up survey was expanded to collect self-reported information on any changes in menstrual cycles.

Study population

This study included menstruating women and therefore, the study population was defined according to the second follow-up survey when information on menstrual status was obtained (see Supplementary Data File S1 for the definition of menstrual status). As information on menstrual changes following COVID-19 vaccination was only collected for COVID-19 vaccinated women, all non-vaccinated women were excluded. Individuals reporting not being biologically female or providing incomplete or conflicting information on COVID-19 vaccination status, menstrual status, or menstrual changes were also excluded. Furthermore, we excluded women who had received COVID-19 vaccines prior to the baseline survey, because information on most potential risk factors was obtained at baseline.

Supplementary analyses explored the prevalence of and potential risk factors for reporting menstrual changes following COVID-19 vaccination among postmenopausal women and women non-menstruating due to use of contraceptives, applying the same exclusion criteria as for the menstruating study population. Women who provided other reasons for not menstruating were not included due to a low number of responses.

Definition of measures

The primary outcome was any self-reported menstrual change. Information was obtained through a multiple-response categorical item in the second follow-up survey: '*Did your menstrual cycle change after the COVID-19 vaccination?*'. Possible response categories were: (i) '*No*', (ii) '*Menstrual cycle became longer*', (iii) '*Menstrual cycle became shorter*', (iv) '*Bleeding became heavier*', (v) '*Bleeding became lighter*', (vi) '*Menstrual cycle became regular*', (vii) '*Menstrual cycle became irregular*', (viii) '*Changed in other ways*', and (ix) '*Bleeding despite menopause*'. For menstruating women, any menstrual change was classified as one or more responses in the response categories two to eight (see Supplementary Data File S2 for classification among non-menstruating women). In case of response

Table 1. Definition of potential risk factors.

Potential risk factor	Categorization
Age	Years: 16–25, 26–35, 36–45, 46–55, or 56–65
BMI (kg/m^2)	Underweight (<18.5), normal weight (18.5–24.9) overweight (25–29.9), or obese ($\geq$30)
Physical activity level	Sedentary, light, moderate, or high
Weekly alcohol intake	Units: 0, 1–10, or >10
Smoking	Never, past, occasionally, or daily
Subjective overall health	Excellent, very good, good, or fair/poor
Stress (based on Cohen's perceived stress scale (PSS))	Low (0–13), moderate (14–26), or high (27–40)
General medical conditions (cancer, diabetes, heart attack, other heart diseases, stroke)	None or 1-or-more
Mental disorders (depression, anxiety)	None or 1-or-more
Pre-vaccination menstrual regularity	Irregular, regular without hormonal contraception, or regular using hormonal contraception
Vaccine attitude	Not concerned, sceptical, or concerned
Vaccine type	Pfizer-BioNTech, Moderna, other, or mixed
Number of immediate vaccine symptoms	<5 or $\geq$5
COVID-19 infection prior to last specified COVID-19 vaccination	No infection, asymptomatic infection, mild infection, moderate infection, or severe infection

category eight, participants were asked to indicate their experienced changes in writing. If a given menstrual change (not listed as a predefined change in the response categories) was reported by more than 25 women, a specific category was made for this change. Those who reported any menstrual change were asked about the duration of the menstrual change(s) using the following response categories: 'Less than two months', 'Two-four months', or 'More than four months'.

In addition to the question about any menstrual change, menstruating women were asked to recall intermenstrual bleeding both before and after the vaccination. Each question was reported as 'Yes' or 'No' and handled independently of any menstrual change reported.

The 14 variables listed in Table 1 were considered potential risk factors for reporting any menstrual change following COVID-19 vaccination (see Supplementary Data File S3 for operationalization of the potential risk factors). Definition of potential risk factors for supplementary analyses among postmenopausal and women not menstruating due to use of contraceptives can be found in Supplementary Data File S4.

Statistical analysis

Characteristics of the participants are presented with descriptive statistics (counts and frequencies). Descriptive statistics were also used to estimate the prevalence of women reporting both the individual menstrual changes as well as any menstrual change following COVID-19 vaccination (counts and frequencies with 95% CI).

The associations between potential risk factors and reporting any menstrual change following COVID-19 vaccination were analysed using simple and multiple logistic regression and presented as odds ratios (OR) with 95% CIs. Crude associations were estimated with two simple logistic regressions (1; based on full sample and 2; based on sample with complete information on covariates). In the multiple logistic regression, covariates were included for each exposure *a priori* based on a literature review and identified through exposure-specific directed acyclic graphs (DAGs). Covariates included in each multiple logistic regression are displayed in Supplementary Table S1.

In *post hoc* analyses, adjusted associations between potential risk factors and any menstrual change were stratified by age at baseline and pre-vaccination menstrual characteristics, respectively. In addition, menstrual changes related to menstrual

frequency, bleeding volume, menstrual cycle regularity, or reports of other changes were analysed separately.

All statistical analyses were performed using Stata Statistical Software, version 17 (StataCorp).

Ethical approval

The BiCoVac Cohort was approved by the Danish Data Protection Agency under the Aarhus University comment agreement (Aarhus University j.number 2016-051-000001, sequential number 2272, date: 25 March 2021). According to Danish law, ethical approval of survey studies is not required.

Role of the funding source

TrygFonden was not involved in either data collection, analysis, or interpretation nor in writing the report or submitting it for publication.

Results

Study population

In total, 34% (n = 150 606) of invited women participated in the baseline survey. Among the 96 794 women who were not vaccinated at baseline, 42% (n = 40 719) also completed the first and second follow-up surveys. Of these, 27 071 (67%) were excluded from the main study population of menstruating women because they remained un-vaccinated, were non-menstruating, or had incomplete or conflicting responses on sex, COVID-19 vaccination status, menstrual status, or menstrual changes. Thus, the main study population consisted of 13 648 menstruating and COVID-19 vaccinated women (Flowchart in Fig. 1). Women who participated in the baseline survey but not in the second follow-up survey were generally younger, reported higher stress levels, and were more concerned about COVID-19 vaccination compared with those who participated in the follow-up survey (data not shown).

Characteristics of the menstruating study population are provided in Table 2. Most women were between 36 and 55 years of age, had received two doses of COVID-19 vaccine (primarily Pfizer-BioNTech), and had no prior COVID-19 infection. The majority also had favourable health proxies, although 61% reported a low level of physical activity, 28% had a mental disorder, and 35% were moderately stressed. Furthermore, 35% were sceptical about COVID-19 vaccination. A regular menstrual cycle prior to COVID-19 vaccination was reported by 85% of which 29%-points used hormonal contraception. Women reporting any menstrual
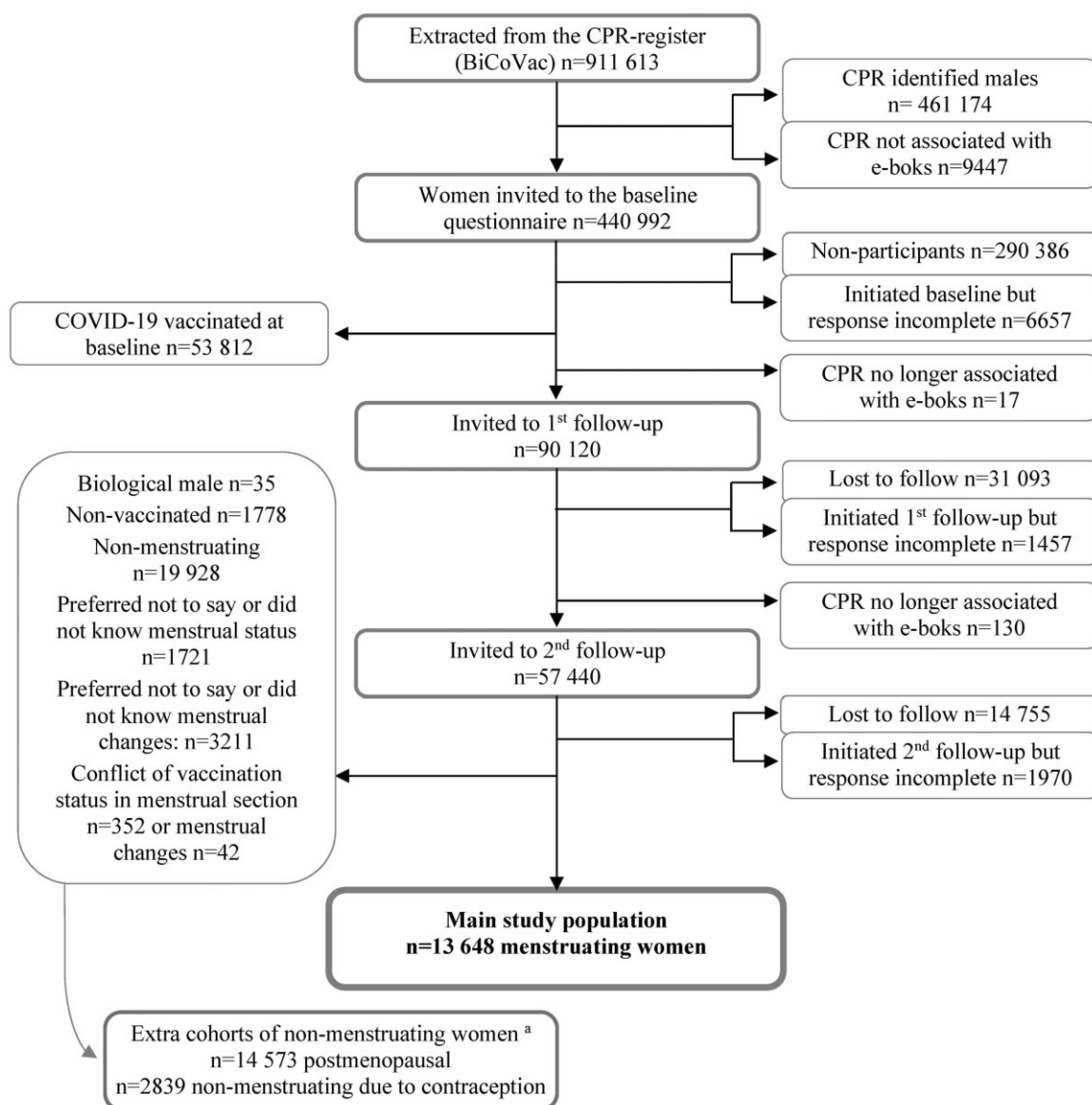
Figure 1. Flowchart of the study population. CPR, civil personal registration system (Denmark); E-boks, Danish digital-mailbox system. [a]Non-menstruating women due to pregnancy, pre-menarche, or provided other reasons (n = 2516) were not included in the extra cohort due to few responses per category.

change were more inclined to report moderate stress, be 46–55 years of age, have a general medical condition, be sceptical about the COVID-19 vaccine, and report ≥5 immediate vaccine symptoms. Women who did not report menstrual changes were more likely to use hormonal contraception, report excellent subjective overall health, and had never smoked.

Menstrual changes

Any menstrual change was reported by 4105 menstruating women, corresponding to 30% [29.31–30.86] of the main study population (Table 3). Among 3022 women with information on the duration of the menstrual change(s), 18% [16.61–19.34] reported a duration of more than 4 months. Change in menstrual cycle length was the most frequently reported change (9% [8.24–9.20] reported longer menstrual cycles and 7% [6.60–7.47] reported shorter menstrual cycles). Other frequently reported changes were heavier bleeding in 7% [6.31–7.15] and more irregular menstrual cycles in 7% [6.85–7.72]. Also, 8% [7.93–8.87] reported 'changed in other ways' of which menstrual absence,

intermenstrual bleeding, and prolonged bleeding were the most reported changes.

Independently of any menstrual change, pre-vaccination intermenstrual bleeding was reported by 19% (n = 2472) of the 13 348 women in whom this information was available, whereas intermenstrual bleeding post-vaccination was reported by 20% (n = 2574) of the 13 198 women in whom information about intermenstrual bleeding post-vaccination was available. Among women reporting pre-vaccination intermenstrual bleeding, 74% (n = 1716) also reported intermenstrual bleeding post-vaccination. Of those who did not report pre-vaccination intermenstrual bleeding, 8% (n = 819) reported intermenstrual bleeding post-vaccination.

Association between potential risk factors and reporting menstrual changes

The adjusted associations between potential risk factors and reporting any menstrual change following COVID-19 vaccination among menstruating women are shown in Fig. 2. OR for reporting

Table 2. Characteristics of the study population (menstruating women).

	Women who reported any menstrual change, n (%)	Women who did not report menstrual changes, n (%)	Total sample, n (%)
Total	4105 (100)	9543 (100)	13 648 (100)
Age			
16–25	549 (13)	1479 (16)	2028 (15)
26–35	856 (21)	2114 (22)	2970 (22)
36–45	1272 (31)	2976 (31)	4248 (31)
46–55	1393 (34)	2898 (30)	4291 (31)
56–65	35 (<1)	76 (<1)	111 (<1)
BMI (kg/m^2)			
Underweight (<18.5)	107 (3)	253 (3)	360 (3)
Normal weight (18.5–24.9)	2015 (49)	4806 (50)	6821 (50)
Overweight (25–29.9)	1006 (25)	2253 (24)	3259 (24)
Obese (≥30)	715 (17)	1582 (17)	2297 (17)
Missing	262 (6)	649 (7)	911 (7)
Physical activity			
Sedentary	588 (14)	1346 (14)	1934 (14)
Light	2508 (61)	5787 (61)	8295 (61)
Moderate	978 (24)	2310 (24)	3288 (24)
High	31 (<1)	100 (1)	131 (<1)
Smoking			
Never	2479 (60)	6261 (66)	8740 (64)
Past	1043 (25)	2093 (22)	3136 (23)
Occasionally	225 (6)	484 (5)	709 (5)
Daily	358 (9)	705 (7)	1063 (8)
Alcohol			
0 units a week	1674 (41)	3706 (39)	5380 (40)
1–10 units a week	2266 (55)	5405 (57)	7671 (56)
>10 units a week	165 (4)	432 (4)	597 (4)
Subjective overall health			
Poor/fair	331 (8)	515 (5)	846 (6)
Good	1213 (30)	2503 (26)	3716 (27)
Very good	1934 (47)	4624 (48)	6558 (48)
Excellent	627 (15)	1901 (20)	2528 (19)
PSS			
Low (0–13)	2357 (57)	6080 (64)	8437 (62)
Moderate (14–26)	1583 (39)	3210 (33)	4793 (35)
High (27–40)	165 (4)	253 (3)	418 (3)
General medical conditions[a]			
None	2743 (67)	6855 (72)	9598 (70)
1 or more	1227 (30)	2444 (26)	3671 (27)
Missing	135 (3)	244 (3)	379 (3)
Mental conditions[b]			
None	3749 (91)	8901 (93)	12 650 (93)
1 or more	304 (8)	566 (6)	870 (6)
Missing	52 (1)	76 (<1)	128 (<1)
Pre-vaccination menstrual regularity			
Irregular	657 (16)	1243 (13)	1900 (14)
Regular w/o using hormonal contraception[c]	2428 (59)	5192 (54)	7620 (56)
Regular using hormonal contraception[c]	997 (24)	3029 (32)	4026 (29)
Missing	23 (<1)	79 (<1)	102 (<1)
Vaccine attitude			
Not concerned	2258 (55)	6251 (66)	8509 (62)
Sceptical	1658 (40)	3015 (32)	4673 (34)
Concerned	144 (4)	193 (2)	337 (3)
Missing	45 (1)	84 (<1)	129 (<1)
Vaccine dose			
One	399 (10)	875 (9)	1274 (9)
Two	3694 (90)	8648 (91)	12 342 (90)
Three	12 (<1)	20 (<1)	32 (<1)
Vaccine type			
Pfizer-BioNTech	3190 (78)	7494 (79)	10 684 (78)
Moderna	821 (20)	1843 (19)	2664 (20)
Other	19 (<1)	50 (<1)	69 (<1)
Mixed	43 (1)	91 (1)	134 (1)
Missing	32 (<1)	65 (<1)	97 (<1)
Vaccine symptoms[d]			
<5 symptoms	3101 (76)	8040 (84)	11 141 (82)
≥5 symptoms	1004 (24)	1503 (16)	2507 (18)
COVID-19 infection			
No infection	3641 (89)	8696 (91)	12 337 (90)
Asymptomatic infection	21 (<1)	51 (<1)	72 (<1)
Mild infection	76 (2)	207 (2)	283 (2)

(continued)

Table 2. (continued)

	Women who reported any menstrual change, n (%)	Women who did not report menstrual changes, n (%)	Total sample, n (%)
Moderate infection	111 (3)	214 (2)	325 (2)
Severe infection	46 (1)	50 (<1)	96 (<1)
Missing	210 (5)	325 (3)	535 (4)

All numbers are counts and percentages of total values. The percentages were calculated vertically. PSS, perceived stress scale.
[a] General medical conditions include cancer, heart attack, other heart diseases, stroke, and diabetes.
[b] Mental disorders include depression and anxiety.
[c] Hormonal contraception includes contraceptive pills, mini-pills, IUD (intrauterine device), etc.
[d] Vaccine symptoms include 21 local and systemic symptoms in the immediate period following COVID-19 vaccination.

Table 3. Menstrual changes following COVID-19 vaccination (menstruating women).

	n	%	95% CI
Total	13 648	100	NA
Any menstrual changes[a]	4105	30	29.31–30.86
Longer menstrual cycle	1189	9	8.24–9.20
Shorter menstrual cycle	959	7	6.60–7.47
Heavier menstrual bleeding	917	7	6.31–7.15
Lighter menstrual bleeding	455	3	3.04–3.65
More regular menstrual cycle	102	1	0.61–0.91
More irregular menstrual cycle	993	7	6.85–7.72
Changed in other ways	1145	8	7.93–8.87
Menstrual absence[b]	264	2	1.71–2.18
Prolonged bleeding[b]	153	1	0.95–1.31
Shortened bleeding[b]	46	<1	0.25–0.45
Menstrual pain[b]	112	1	0.68–0.99
Intermenstrual bleeding[b]	188	1	1.19–1.59
Two monthly menstrual bleedings[b]	47	<1	0.25–0.46
Duration of any menstrual changes	3022	100	NA
<2 months	1037	34	32.62–36.04
2–4 months	1443	48	45.96–49.55
>4 months	542	18	16.58–19.35

All numbers are counts and percentages of non-missing values. The percentages were calculated vertically. NA, not applicable.
[a] Any menstrual change included one or more changes in menstrual frequency, bleeding volume, menstrual regularity, and changes reported as 'changed in other ways'.
[b] Menstrual change reported as 'changed in other ways' by more than 25 women.

any menstrual change was particularly high among women who reported ≥5 immediate vaccine symptoms; OR 1.67 [1.50–1.86], had a prior severe COVID-19 infection; OR 2.17 [1.40–3.35], were concerned about the COVID-19 vaccine prior to vaccination; OR 1.92 [1.50–2.45], or had a high perceived stress scale (PSS) at baseline; OR 1.67 [1.32–2.10] compared with reference categories. Statistically higher odds were also found with higher age (between 36 and 55 years of age), smoking, poor subjective overall health, and reporting a general medical or mental condition. Moreover, the use of hormonal contraception was associated with lower odds of reporting any menstrual change (OR 0.71 [0.65–0.78]). Though not statistically significant, lower or higher odds were also found for alcohol consumption of more than ten units per week (OR 0.84 [0.69–1.03]), a high level of physical activity (OR 0.75 [0.49–1.15]), and being underweight (OR 1.16 [0.91–1.47]). Pre-vaccination menstrual regularity and vaccine type were not associated with reporting any menstrual change. Crude and adjusted estimates can be seen in Supplementary Table S2.

In *post hoc* analyses, a statistically significant effect modification was found for age when stratified on pre-vaccination menstrual regularity (see Supplementary Table S3). Compared to the youngest age group, women between 26 and 55 years of age were more likely to report menstrual changes when using hormonal

contraception, whereas the opposite was found for women with pre-vaccination irregular menstrual cycles and women with regular menstrual cycles not using hormonal contraception. No statistically significant effect modification was found when stratifying the analyses by age at baseline (see Supplementary Table S4). The associations between potential risk factors and specific reported menstrual changes were generally similar to the estimates for any menstrual change (see Supplementary Table S5). However, minor differences were found in associations with age and pre-vaccination menstrual regularity.

Supplementary analyses

The extra cohorts included 14 577 postmenopausal women and 2839 non-menstruating women due to use of contraceptives. All women were COVID-19-vaccinated and complied with the same criteria as the menstruating study population. Characteristics can be seen in Supplementary Tables S6 and S7.

Any menstrual change was reported by 2% [2.14–2.64] (n = 347) of the postmenopausal women. Of the 273 women with information on duration of the menstrual change(s), 11% reported a duration of more than 4 months. Among non-menstruating women due to use of contraceptives, 10% [8.89–11.13] (n = 283) reported any menstrual change; of the 215 women with information on the duration of the menstrual change(s), 12% reported a duration of more than 4 months.

The adjusted associations between potential risk factors and reporting any menstrual change following COVID-19 vaccination were overall similar to those among menstruating women but estimated with more uncertainty due to lower numbers (see Supplementary Figs S1 and S2). Though, among non-menstruating women, higher age was associated with lower odds of reporting any menstrual change following COVID-19 vaccination (postmenopausal; aged 56–65 years; OR 0.19 [0.15–0.24], not menstruating due to use of contraceptives; aged 46–65 years; OR 0.59 [0.35–0.99]). Also, a prior COVID-19 infection (combined asymptomatic, mild, moderate, or severe symptoms) was not associated with reporting any menstrual change among postmenopausal women (OR 1.01 [0.59–1.71]), while there was a tendency of lower odds for those not menstruating due to use of contraceptives (OR 0.58 [0.30–1.12]).

Discussion
Main findings

In this sample of menstruating women, 30% reported menstrual changes following COVID-19 vaccination. Common reported changes were longer, shorter, and more irregular menstrual cycles, as well as heavier bleeding. The results indicated that women who had had a prior severe COVID-19 infection, were stressed at baseline, were concerned about COVID-19 vaccines prior to vaccination, or who after COVID-19 vaccination reported ≥5 immediate vaccine symptoms, more often reported any
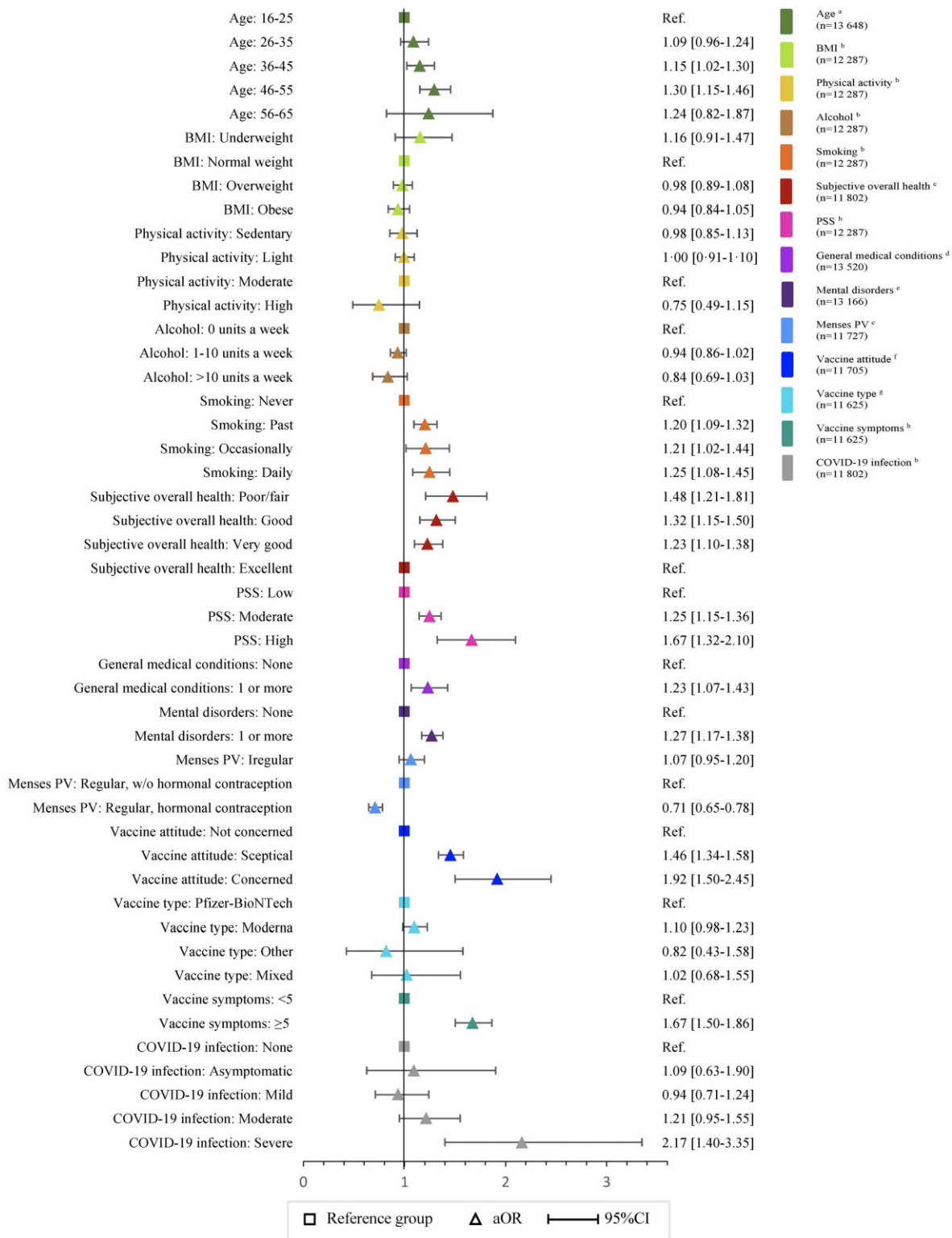
Figure 2. Association between potential risk factors and any menstrual change following COVID-19 vaccination (menstruating women). The forest plot exhibits the odds ratio with 95% CI of reporting any menstrual change following COVID-19 vaccination across 14 potential risk factors. The right-hand column of the forest plot displays the total number (n) and the covariates included in the analysis model for each of the 14 potential risk factors. aOR, adjusted odds ratio; menses PV, pre-vaccination menstrual regularity; PSS, perceived stress scale; Ref, reference category; W/o, without. General medical conditions include cancer, heart attack, other heart diseases, stroke, and diabetes. Mental disorders include depression and anxiety. Vaccine symptoms include 21 local and systemic immediate symptoms. [a]Unadjusted. [b]Adjusted for remaining lifestyle factors (BMI, physical activity, smoking, alcohol, and PSS), age, general medical conditions, and mental disorders. [c]Adjusted for age, lifestyle factors, general medical conditions, mental disorders, and COVID-19 infection. [d]Adjusted for age. [e]Adjusted for age and general medical conditions. [f]Adjusted for age, lifestyle factors, subjective overall health, general medical conditions, mental disorders, and COVID-19 infection. [g]Adjusted for age, lifestyle factors, subjective overall health, general medical conditions, mental disorders, vaccine attitude, and COVID-19 infection. [h]Adjusted for age, lifestyle factors, subjective overall health, general medical conditions, mental disorders, vaccine attitude, vaccine type, and COVID-19 infection.

menstrual change following COVID-19 vaccination compared with reference categories. This was also the case for women who had lower subjective overall health, were between 36 and 55 years of age, were smokers, or had reported a general medical condition or a mental disorder. Lower odds of reporting any menstrual change were seen among women with regular menstrual cycles using hormonal contraception.

Strengths and limitations

The strengths of this study include the large sample of the general Danish population and the possibility of controlling for a variety of relevant potential confounders in each analysis. Also, as information on most potential risk factors was collected prior to the participants' knowledge of the outcome, data from the BiCoVac Cohort is probably unique for the purpose of this study. However, the study also has some limitations. First, unvaccinated women were not asked about menstrual changes, and it was therefore not possible to compare frequencies of reported menstrual changes between COVID-19 vaccinated and unvaccinated women. This limits the study's ability to make causal interpretations about the role of the COVID-19 vaccine in the reported menstrual changes. Thus, the study was restricted to only evaluating the prevalence of and potential risk factors for self-reported menstrual changes following COVID-19 vaccination. Additionally, vaccinated women were not asked to quantify reported menstrual changes. This could otherwise have helped examine the clinical relevance according to the International Federation of Gynecology and Obstetrics classification of menstrual disturbances (Munro *et al.*, 2018).

Second, information on menstrual changes following COVID-19 vaccination was self-reported and collected retrospectively and thereby susceptible to both reporting and recall bias. A study by Bouchard *et al.* (2022) compared perceived menstrual changes with actual menstrual changes following COVID-19 vaccination. While the study did not have the statistical power to detect significant differences, results indicated that the reporting of perceived heavy menstrual bleeding following COVID-19 vaccination was inconsistent with actual bleeding volume. It is therefore important to consider the reported menstrual changes in the present study as subjective rather than objectively observed. In addition, it could be hypothesized that elements such as vaccine scepticism, vaccine symptoms, psychological challenges, and pre-vaccination menstrual irregularities could have an impact on the women's awareness of menstrual changes. This could lead to potential differential misclassification of the outcome and an under- or over-estimation of the association for these outcomes.

Third, selection bias cannot be excluded, as loss to follow-up in the BiCoVac Cohort could be associated with both the potential risk factors (e.g. age, stress, or vaccine scepticism) and outcome (e.g. more interest when having experienced menstrual changes). In this case, the prevalence of any menstrual change following COVID-19 vaccination found in this study could be overestimated.

Finally, although we controlled for various relevant potential confounders, residual confounding and unmeasured confounding cannot be excluded.

Interpretation

Menstrual changes following COVID-19 vaccination have been reported in the existing literature, including prolonged length of menstrual cycle (Alvergne *et al.*, 2022; Edelman *et al.*, 2022; Gibson *et al.*, 2022; Wang *et al.*, 2022), menstrual irregularities (Farland *et al.*, 2022; Laganà *et al.*, 2022), and heavy menstrual bleeding (Trogstad *et al.*, preprint; Lee *et al.*, 2022). The reported menstrual changes were generally temporary and tended to resolve within a few months in most of the affected individuals (Alvergne *et al.*, 2022; Edelman *et al.*, 2022; Farland *et al.*, 2022; Gibson *et al.*, 2022; Laganà *et al.*, 2022; Wang *et al.*, 2022). The prevalence of self-reported menstrual changes following COVID-19 vaccination in the present study was comparable to estimates found in the literature (Farland *et al.*, 2022). However, a notably lower prevalence was found in studies conducted in nations (e.g. Saudi Arabia) where awareness of female reproductive health is not necessarily comparable to Denmark due to cultural disparities (Alghamdi *et al.*, 2021; Dar-Odeh *et al.*, 2022) especially in a study where menstrual change had to be reported as an adverse event in general text fields rather than in pre-specified categories for registration of menstrual change (Alghamdi *et al.*, 2021). This suggests that inclusion of topic-specific questions increases the frequency of reporting menstrual changes. Studies identifying a notably higher prevalence were characterized by selective study populations where recruitment was made through social media and survey titles including the keywords menstrual cycle and COVID-19 vaccination (Laganà *et al.*, 2022; Lee *et al.*, 2022; Muhaidat *et al.*, 2022). A substantially higher prevalence was also found among non-menstruating women (Lee *et al.*, 2022). Lee *et al.* (2022) hypothesized that postmenopausal women reporting menstrual changes following COVID-19 vaccination presumably were women with dormant ovaries. The present study relied on women's self-reported menstrual status, which may pose a challenge in accurately determining their status during the perimenopausal period. Consequently, the menstrual status of some women may have been misclassified, and the reported menstrual changes might be attributed to natural reproductive decline.

An unpublished observation by the Norwegian Institute of Public Health found that nearly 38% of women between 18 and 30 years of age reported menstrual changes prior to COVID-19 vaccination (Trogstad *et al.*, preprint). In this context, the prevalence of any menstrual change following COVID-19 vaccination may not elicit concern, as other factors triggering symptoms might be happening in temporal relation to the vaccination simply by chance. However, the unpublished Norwegian observation found a significant increase in reports of menstrual changes following COVID-19 vaccination and as the observation only included women between 18 and 30 years of age (Trogstad *et al.*, preprint), it cannot be used to determine the background prevalence in the present study population.

As the prevalence of any menstrual change in the general population is unknown, it cannot be assessed whether the reported menstrual changes in the present study occurred more frequently than expected. Only few studies have compared menstrual cycles (bleeding duration and menstrual cycle length) between COVID-19 vaccinated and unvaccinated women. The most recent study by Edelman *et al.* (2022) found no association between COVID-19 vaccination and bleeding duration, but a temporary increase in the menstrual cycle length (of nearly 1 day). This temporary increase in menstrual cycle length was supported by findings reported by Gibson *et al.* (2022) who found that the menstrual cycle in which a vaccine was administered was longer (less than 1 day) than the pre-vaccination menstrual cycle. Also, Wang *et al.* (2022) found that vaccinated women had higher odds of a temporarily increased menstrual cycle length compared with non-vaccinated women.

The associations between severe COVID-19 infection and immediate vaccine symptoms, respectively, with any menstrual change have been reported in the literature, although inconsistencies in association with immediate vaccine symptoms exist

(Lee *et al.*, 2022; Muhaidat *et al.*, 2022). These differences could potentially be explained by differences in measures and categorizations. It is possible that individuals who experience a severe COVID-19 infection and more immediate symptoms following vaccination produce a stronger immune response. The immune response whether from COVID-19 vaccination or COVID-19 infection may transiently interfere with the hypothalamic–pituitary–ovarian (HPO) axis, which plays a key role in the regulation of the menstrual cycle (Turnbull and Rivier, 1999; Dellino *et al.*, 2023). This is in line with observations of menstrual changes found in relation to other immune responses, e.g. following vaccination against prophylactic typhoid and HPV (Lamb, 1913; Gong *et al.*, 2020).

To the best of our knowledge, no previous study has investigated associations between COVID-19 vaccine scepticism or mental disorders, respectively, and reporting of menstrual changes following COVID-19 vaccination. Yet, our results are in accordance with the literature addressing associations between psychological factors and reporting adverse events following COVID-19 vaccination (Geers *et al.*, 2022). The higher odds of reporting menstrual changes in women who were sceptical towards the vaccine might be amplified by the individual's expectations and selective attention towards their menstrual cycle.

The associations between self-reported menstrual changes and age, BMI, physical activity, vaccine type, stress, smoking, use of hormonal contraception, and pre-vaccination menstrual regularity have also been found by other studies, although with inconsistent results (Farland *et al.*, 2022; Lee *et al.*, 2022; Muhaidat *et al.*, 2022; Alvergne *et al.*, 2023). Different study designs, sample sizes, study populations, and content of categorizations could explain these inconsistencies. As far as we know, associations for alcohol consumption, subjective overall health, and the specific general medical conditions explored in this study with menstrual changes following COVID-19 vaccination have not previously been studied.

Overall, our results are in line with the literature addressing risk factors for reporting menstrual changes or other adverse events following COVID-19 vaccination. Most of the potential risk factors for reporting menstrual changes have also been identified before introducing the COVID-19 vaccines. This suggests that these potential risk factors are characteristics that generally contribute to menstrual changes independently of COVID-19 vaccination (Rowland *et al.*, 2002; Strine *et al.*, 2005; Harlow and Paramsothy, 2011; Zhu *et al.*, 2019).

Conclusion

Various self-reported menstrual changes following COVID-19 vaccination were identified. Most of the investigated potential risk factors were associated with reporting menstrual changes, particularly stress, vaccination concerns, severe COVID-19 infection, and ≥5 immediate vaccine symptoms. Hence, different characteristics may render some women to be more susceptible to reporting menstrual changes following COVID-19 vaccination. The reported menstrual changes might occur in temporal relation to the vaccination by chance or reflect women being more vigilant to detect/report potential menstrual changes after the vaccine. However, due to limitations in the study design, the results cannot be used to address the causal effect of COVID-19 vaccination on menstrual changes. Further studies are needed to establish causal associations and clinical impact of self-reported menstrual changes and COVID-19 vaccination.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The dataset is not publicly available due to national data security legislation on sensitive personal data. Licence to the data is subject to conditions stipulated by the Danish Data Protection Agency and Aarhus University.

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