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ORIGINAL RESEARCH

Associations of Menstrual Cycle Regularity and Length With Cardiovascular Diseases: A Prospective Study From UK Biobank

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BACKGROUND: The association between menstrual cycle characteristics and cardiovascular outcomes remains unclear. This study was undertaken to evaluate whether menstrual cycle regularity and length throughout the life course are associated with cardiovascular outcomes.

METHODS AND RESULTS: This cohort study included 58 056 women who had no cardiovascular disease (CVD) at baseline and reported their menstrual cycle regularity and length. Hazard ratios (HRs) and 95% CIs for CVD events were estimated using Cox proportional hazards models. During the median 11.8 years of follow-up, 1623 incident CVD cases were documented, including 827 incident cases of coronary heart disease, 199 myocardial infarctions, 271 strokes, 174 cases of heart failure, and 393 cases of atrial fibrillations. Compared with women with regular menstrual cycles, the HRs for women with irregular menstrual cycles were 1.19 (95% CI, 1.07–1.31) for CVD events and 1.40 (95% CI, 1.14–1.72) for atrial fibrillation. The multivariable-adjusted HRs for short (≤21 days) or long (35 days) menstrual cycles during follow-up were 1.29 (95% CI, 1.11–1.50) and 1.11 (95% CI, 0.98–1.56) for CVD events, respectively. Similarly, long or short cycle length were more likely to be associated with increased risk of atrial fibrillation (HR, 1.30 [95% CI, 1.01–1.66]; and HR, 1.38 [95% CI, 1.02–1.87]), and short cycle length was more likely to be associated with increased risk of coronary heart disease and myocardial infarction. However, these associations for stroke and heart failure were not significant.

CONCLUSIONS: Long or short menstrual cycle length was associated with increased risks of CVD and atrial fibrillation but not myocardial infarction, heart failure, or stroke. Short cycle length was associated with a greater risk of coronary heart disease and myocardial infarction.

Key Words: atrial fibrillation ■ cardiovascular diseases ■ coronary heart disease ■ menstrual cycle ■ regularity

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality for women worldwide.[1] It affects 45% of women aged >20 years in Western countries and accounts for one-third of all deaths in women.[2] It has gained great attention to unique sex-specific aspects for the prevention of CVD in women. It has been proposed that several sex-related risk factors, such as polycystic ovary syndrome and early menopause, have been associated with the occurrence of CVD and cardiovascular mortality.[3,4] Considering the increasing prevalence of CVD in women, novel risk factors should still be explored.

Regular menstrual cycles throughout the reproductive life that reflect normal functioning of the hypothalamic-pituitary-ovarian axis are a vital sign of women's general health.[5] Irregular and long menstrual

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CLINICAL PERSPECTIVE

What Is New?

- Menstrual cycle characteristics throughout the reproductive lifespan are associated with cardiovascular mortality.
- Whether menstrual cycle is prospectively associated with cardiovascular disease (CVD) and subsequent CVD events is unknown.
- This study investigated whether menstrual cycle regularity and length are associated with overall CVD and specific CVD events in women and explored modifying factors that might affect these associations by analyzing data from the UK Biobank.

What Are the Clinical Implications?

- Study findings indicated that irregular menstrual cycle is associated with incident CVD, long and short menstrual cycles are associated with atrial fibrillation, and short menstrual cycle is associated with a greater risk of coronary heart disease and myocardial infarction.
- There was a significant interaction on risk of CVD between irregular menstrual cycle and lower high-density lipoprotein cholesterol levels and smoking status.
- An irregular menstrual cycle throughout reproductive lifespan may be a previously unrecognized risk factor for atrial fibrillation over time.

Nonstandard Abbreviation and Acronym

SHBG	sex hormone–binding globulin

cycles are common endocrine disorders with prevalence of 20%, which are often attributed to the functional disruption of the hypothalamic-pituitary-ovarian axis among women of reproductive age.[6,7] It has been well established that irregular and long menstrual cycles are closely related with insulin resistance, metabolic disturbances, hyperandrogenism, and chronic inflammation.[8–11] These conditions have been associated with greater risk of coronary heart disease and related mortality, obesity, and type 2 diabetes.[12–15] Furthermore, a prior study reported that women with a history of short menstrual cycles had a nearly 2-fold increased risk of myocardial infarction in women aged <55 years.[16] Evidence linking menstrual cycle characteristics throughout the reproductive lifespan with CVD and cardiovascular mortality, however, is still limited. Therefore, data from large prospectives studies are still needed to fill the knowledge gaps.

To addressed this question, in this large population-based cohort study from UK Biobank, we hypothesize that short or long menstrual cycle length and irregular menstrual cycles were associated with overall CVD and specific CVD events in women, and we further explore modifying factors that might affect these associations.

METHODS

Publicly available data from UK Biobank study were analyzed in this study. All data analyzed in this study are available to researchers through an open application via https://www.ukbiobank.ac.uk/register-apply/.

Study Design and Population

The UK Biobank is a prospective cohort recruited of >500 000 participants, aged 40 to 69 years, across the United Kingdom between 2006 and 2010. Participants completed a touch-screen questionnaire, which included information on sociodemographic data, lifestyle factors, medical history, and medication use. In addition, participants received a physical assessment, including measurement of anthropomorphic data and vital signs, and provided biological samples. Participants were followed up for the development of incident diagnoses through national health records and follow-up visits. The UK Biobank study was approved by the North West Multicenter Research Ethical Committee, and all participants provided written informed consent.

At baseline, all female participants were asked to report the current menstrual cycle length and regularity. We excluded individuals who had reached menopause (n=208 272), those with missing data on menopause (n=534), and those who might be pregnant (n=136). We further excluded participants who did not fully report the menstrual cycle characteristics (n=4817), those who had missing data on menstrual cycle characteristics (n=476), or those who had a diagnosis of CVD (n=1038) at baseline. Finally, a total of 58 056 women were included in the current analysis.

Menstrual Cycle Characteristic Assessment

Menstrual cycle patterns were reported at baseline, including the usual regularity and length of the menstrual cycles. Women were asked "How many days is your usual menstrual cycle? (the number of days between each menstrual period)." The answer options were days of menstrual cycle, "irregular cycle," "do not know," and "prefer not to answer." Participants who had answered "do not know" or "prefer not to answer" were excluded from all analyses. Menstrual cycle regularity was defined as irregular if one of the following criteria

was met: self-report of irregular cycles; cycle length with ≤21 days; or cycle length with ≥35 days. Regular menstrual cycle was defined as cycle length with 22 to 34 days. Cycle length was categorized as ≤21, 22 to 27, 28 to 34, and ≥35 days or too irregular. Self-report of menstrual cycle characteristic has been validated in other studies, and it considered to be reliable.[7,17]

Ascertainment of Outcomes

The main outcomes of the current study included the incidence of CVD events, as well as incident coronary heart disease, myocardial infarction, heart failure, atrial fibrillation, and stroke. Data on hospital admissions were collected regularly through linkages to Health Episode Statistics, the Patient Episode Database, and the Scottish Morbidity Records. Information on death was obtained from National Health Service Digital for participants in England and Wales and from the National Health Service Central Register, part of the National Records of Scotland, for participants in Scotland. At the time of analysis, health outcome data were available up to November 30, 2020. For the analyses of cardiovascular outcomes and deaths, we used this date as the end of follow-up unless death or admission occurred first. Health outcomes were classified using *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes and self-reported codes (UK Biobank data coding 6) (Table S1). Coronary heart disease (CHD) was defined as fatal ischemic heart disease (*ICD-10* codes I20–I25) or nonfatal myocardial infarction (*ICD-10* codes I21–I23), atrial fibrillation and other cardiac arrhythmias (*ICD-10* codes I48–I49), and heart failure (*ICD-10* code I50); and stroke was defined as any cerebrovascular disease (*ICD-10* codes I60–I64 and I69).

Ascertainment of Covariates

The baseline questionnaire and physical assessment were used to assessed several possible confounding variables. Age and body mass index (BMI) were obtained at baseline. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Education level (university or college degree/others [including less than high school, high school, and other professional qualification]), race and ethnicity were based on the following question: "What is your ethnic group?" Categorized as White or others (including Asian, Black, Chinese, mixed [Irish, White and Black African, Pakistani, and African], and other racial or ethnic groups), and personal history of hypertension, diabetes, depression, and severe stress were collected from the health register using *ICD-10* codes, categorized as yes or no; parity was defined as the number of live-born births; family history of CVDs and stroke was categorized as yes or no; and menopausal status was obtained during the initial assessment center visit. Women were asked through touch-screen questionnaire: "Have you had your menopause (periods stopped)?" The answer options were "yes," "no," "not sure: had a hysterectomy," "not sure: other reason," and "prefer not to answer." Participants who had answered "yes" or "not sure: had a hysterectomy" or "not sure: other reason" or "prefer not to answer" were excluded from all analyses. Oral contraceptive and hormone replacement therapy (HRT) were based on participants' self-report, in answering the question "Have you ever taken the contraceptive pill? (include the "mini-pill")?" and "Have you ever used hormone replacement therapy?"; age at menarche was categorized as ≤10, 11, 12, 13, or ≥14 years. Total cholesterol, triglycerides, and sex hormone–binding globulin (SHBG) were gathered at baseline, considered as continuous variables. Information on smoking and alcohol consumption was gathered from the touch-screen questionnaire, and participants were classified as never, previous, and current. Physical activity level was determined according the following criteria ("International Physical Activity Questionnaire"): low physical activity (total score, <600 metabolic equivalent task/min per wk); moderate physical activity (total score, ≥600 metabolic equivalent task/min per wk); and high physical activity (total score, ≥3000 metabolic equivalent task/min per wk). Further details of covariate measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical Analysis

Continuous variables are presented as mean±SD or median/interquartile range (IQR), and categorial variables are presented as percentages. Baseline characteristics of study participants were compared according to menstrual cycle regularity and length using general linear models for continuous variables and χ^2 test for categorical variables. Cox proportional hazard ratio (HR) models were used to estimate the HRs and 95% CIs for the associations of menstrual cycle regularity and length with the risk of incident CVD and other cardiovascular outcomes; we checked the proportional hazards assumption by the Kolmogorov-type supremum test, and no violation of proportional hazards function assumptions was found (*P* values were all >0.05). The multivariable model (model 1) was adjusted for age; model 2 was additionally adjusted for education level (university or college degree/others), race and ethnicity (White/others), history of hypertension (yes or no), history of diabetes (yes or no), baseline total cholesterol level, baseline triglyceride level, baseline SHBG level, age at menarche (≤10, 11, 12, 13, or ≥14 years), parity (0, 1, or ≥2), family history of CVD and stroke (yes or no), history of contraceptive use (yes or

no), history of HRT (yes or no), and history of depression and severe stress (yes or no). Model 3 was further adjusted for BMI (<25 or ≥25 kg/m^2), smoking status (never, past, or current), drinking status (never, past, or current), and physical activity (low, moderate, or high).

Stratified analyses were performed according to BMI, SHBG, testosterone, ever use of oral contraceptives, parity, age at menarche, history of hypertension, and family history of CVD or stroke. To investigate whether the associations between menstrual cycle regularity and length and cardiovascular outcomes differed by these stratification variables, the potential effect modification was examined using the interaction models. Multiple imputation with chained equations was performed for participants with missing covariate data, assuming data were conditionally missing at random. Among 58 056 women, 221 had missing values for BMI, 114 had missing values for tobacco use, 25 had missing values for parity, 34 had missing values for alcohol use, 1604 had missing values for age at menarche, 122 had missing values for oral contraceptive use, 166 had missing values for HRT use, 3926 had missing values for triglycerides, 9752 had missing values for SHBG, and 3905 had missing values for cholesterol. The chained equation for each missing covariate was fully specified to capture nonlinearities and interactions in its association with other covariate. All data were analyzed using SAS version 9.4 (SAS Institute Inc), and 2-sided values of P<0.05 were considered statistically significant.

RESULTS

The study included 58 056 women, with mean age of 46.1 (range, 40–69) years at baseline. Table 1 presents the baseline characteristics of participants according to different menstrual cycle regularity and length. Women who reported irregular cycles had higher levels of BMI (26.7 [SD, 5.5] versus 26.2 [SD, 5.1] kg/m^2; P<0.001), total cholesterol (5.4 [IQR, 4.8–6.0] versus 5.3 [IQR, 4.7–5.9] mmol/L; P<0.001), and triglycerides (1.1 [IQR, 0.8–1.6] versus 1.1 [IQR, 0.8–1.5] mmol/L; P<0.001), and had lower levels of SHBG (60.5 [IQR, 42.3–83.3] versus 64.5 [IQR, 46.4–86.4] nmol/L; P<0.001) than women with regular menstrual cycles. Furthermore, women who reported irregular cycles were more likely to be current smokers and have histories of hypertension (12.2% versus 9.0%) and diabetes (2.5% versus 1.9%), as well as a higher prevalence of family history of CVD (35.2% versus 33.8%) and stroke (18.4% versus 16.9%) than women with regular menstrual cycles. Similar results were observed among women with short (≤21 days) or long (≥35 days) cycle length compared with women with cycle length between 22 and 34 days (Table 1).

During 678 625 person-years of follow-up, a total of 1623 CVD events were observed, including 827 incident CHD events, 199 myocardial infarctions, 271 strokes, 174 heart failure events, and 393 atrial fibrillations. The cumulative incidence of CVD was higher among women with irregular menstrual cycles than those with regular menstrual cycles (adjusted HR, 1.19 [95% CI, 1.07–1.31]) (Table 2). Similarly, women with menstrual cycle length ≤21 days or ≥35 days had higher risk of CVD than those with cycle length between 28 and 34 days (HR, 1.29 [95% CI, 1.11–1.50]; and HR, 1.11 [95% CI, 0.98–1.56], respectively) (Table 3). These associations remained statistically significant after further adjustment for education level, race and ethnicity, history of hypertension and diabetes, baseline total cholesterol, triglycerides, and baseline SHBG levels, age at menarche, parity, family history of CVD and stroke, history of oral contraceptive use, history of HRT, history of depression and severe stress, BMI, smoking status, drinking status, and physical activity among women with short cycle length (HR, 1.29 [95% CI, 1.11–1.50]). Furthermore, subgroup analyses in participants with follow-up menstrual cycle characteristics showed that women who maintained menstrual cycle irregularity during follow-up were significant associated with increased risk of CVD (adjusted HR, 2.32 [95% CI, 1.16–4.61]) (Figure S1). However, no significant associations of change in menstrual cycle regularity with CHD and atrial fibrillation were observed (Table S2).

With regard to subtypes of cardiovascular outcomes, women with irregular menstrual cycles were significantly associated with higher risks of atrial fibrillation (HR, 1.40 [95% CI, 1.14–1.72]) in the multivariable-adjusted models but not incident CHD, myocardial infraction, heart failure, and stroke (Table 2). Furthermore, women with short (≤21 days) or long (≥35 days) menstrual cycle length were significantly associated with higher atrial fibrillation risk (adjusted HRs, 1.38 [95% CI, 1.02–1.87] and 1.30 [95% CI, 1.01–1.66], respectively). In multivariate-adjusted models, participants with short menstrual cycles had a significantly higher likelihood of CHD and myocardial infarction than those with menstrual cycle length between 28 and 34 days (adjusted HRs, 1.41 [95% CI, 1.16–1.72] and 1.69 [95% CI, 1.13–2.52]), whereas the results were not significant in women with long cycles (adjusted HRs, 0.92 [95% CI, 0.76–1.10] and 1.08 [95% CI, 0.74–1.58]; Table 3). No significant associations of menstrual cycle length and regularity with stroke and heart failure were observed.

Stratified analyses were conducted according to potential CVD risk factors. The significant interactions on risk of CVD were observed between menstrual cycle characteristics and smoking status (P=0.007 and P=0.024 for interaction; Figure [A] and Table 4). Likewise, these associations were stronger in women who had lower levels of baseline high-density lipoprotein cholesterol (HDL-C) among those who with irregular menstrual cycles or short cycle length (all

Table 1. Baseline Characteristics of Women According to Menstrual Cycle Regularity and Length

Characteristics	Cycle regularity		Cycle length, d			
	Regular (n=39 582)	Irregular or no periods (n=18 474)	≤21 (n=6919)	22–27 (n=11 872)	28–34 (n=27 710)	≥35 or highly irregular (n=11 555)
Age, y	45.8 (3.8)	46.9 (4.1)	45.7 (3.9)	45.7 (3.5)	45.8 (3.9)	47.5 (4.1)
Race and ethnicity, %						
White	91.8	92.1	88.6	91.9	91.8	94.2
Asian	2.4	2.2	3.6	2.3	2.4	1.4
Black	2.5	2.7	4.0	2.5	2.6	1.9
Chinese	0.7	0.5	0.5	0.8	0.6	0.5
Mixed	1.2	1.4	1.7	1.2	1.2	1.2
Other*	1.4	1.2	1.7	1.4	1.5	0.9
University or college degree, %	60.5	55.9	50.9	61.7	59.9	58.8
Body mass index, kg/m^2	26.2 (5.1)	26.7 (5.5)	26.5 (5.2)	25.8 (4.9)	26.3 (5.2)	26.9 (5.7)
Current smoker, %	9.4	10.7	12.7	9.1	9.6	9.5
Alcohol consumption, %	92.8	92.2	90.1	93.0	92.7	93.4
Physical activity, %						
Low	51.9	54.3	51.5	50.8	52.4	55.9
Moderate	23.0	21.6	20.9	23.7	22.7	22.1
High	25.1	24.1	27.6	25.5	24.9	22.0
Total cholesterol, mmol/L	5.3 (4.7–5.9)	5.4 (4.8–6.0)	5.3 (4.8–6.0)	5.3 (4.7–5.9)	5.3 (4.7–6.0)	5.4 (4.8–6.1)
Triglycerides, mmol/L	1.1 (0.8–1.5)	1.1 (0.8–1.6)	1.1 (0.8–1.5)	1.0 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.6)
HDL-C, mmol/L	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.3–1.7)	1.5 (1.3–1.8)
SHBG, nmol/L	64.5 (46.4–86.4)	60.5 (42.3–83.3)	64.6 (45.7–89.4)	65.5 (47.8–86.5)	64.0 (45.9–86.4)	58.5 (40.6–80.1)
Testosterone, nmol/L	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.0 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
CRP, mg/L	1.0 (0.5–2.2)	1.1 (0.5–2.5)	1.2 (0.5–2.7)	0.9 (0.4–2.0)	1.0 (0.5–2.3)	1.1 (0.5–2.4)
Ever used oral contraceptives, %	87.7	91.0	91.1	87.6	87.8	91.0
Parity	1.6 (1.2)	1.6 (1.2)	1.6 (1.3)	1.5 (1.2)	1.6 (1.2)	1.6 (1.2)
Endometriosis, %	0.2	0.2	0.2	0.3	0.2	0.1
Age at menarche, y	13.0 (1.6)	13.1 (1.6)	13.1 (1.7)	13.0 (1.6)	13.1 (1.6)	13.0 (1.6)
Family history, %						
Cardiovascular disease	33.8	35.2	32.7	33.2	34.1	36.6
Stroke	16.9	18.4	17.8	16.7	17.0	18.8
Hypertension	9.0	12.2	10.2	8.4	9.3	13.3
Diabetes	1.9	2.5	2.3	1.6	2.0	2.6

Data are presented as the means (SDs), medians (interquartile ranges), or percentages. CRP indicates C-reactive protein; HDL-C, high-density lipoprotein cholesterol; and SHBG, sex hormone–binding globulin.
*For race and ethnicity, subjects categorized as "other" are those whose race or ethnicity was not categorized as White, mixed, Asian, Black, or Chinese, per the UK Biobank documentation.

Table 2. Adjusted HRs (95% CIs) for Risk of Cardiovascular Outcomes According to Menstrual Cycle Regularity

Variable	Cycle regularity		*P* value
	Regular	Irregular or no periods	
Total sample size	39582	18474	
CVD			
Total cases	987	636	
Model 1	1.00	1.28 (1.15–1.41)	<0.001
Model 2	1.00	1.20 (1.08–1.33)	<0.001
Model 3	1.00	1.19 (1.07–1.31)	0.001
CHD			
Total cases	506	321	
Model 1	1.00	1.24 (1.07–1.42)	0.003
Model 2	1.00	1.12 (0.97–1.29)	0.134
Model 3	1.00	1.11 (0.96–1.28)	0.173
Myocardial infarction			
Total cases	115	84	
Model 1	1.00	1.44 (1.09–1.92)	0.011
Model 2	1.00	1.26 (0.93–1.69)	0.130
Model 3	1.00	1.24 (0.92–1.67)	0.154
Atrial fibrillation			
Total cases	223	170	
Model 1	1.00	1.45 (1.18–1.77)	<0.001
Model 2	1.00	1.42 (1.15–1.74)	<0.001
Model 3	1.00	1.40 (1.14–1.72)	0.001
Heart failure			
Total cases	103	71	
Model 1	1.00	1.39 (1.02–1.88)	0.035
Model 2	1.00	1.28 (0.93–1.75)	0.128
Model 3	1.00	1.24 (0.90–1.70)	0.184
Stroke			
Total cases	167	104	
Model 1	1.00	1.27 (0.99–1.62)	0.062
Model 2	1.00	1.19 (0.93–1.54)	0.172
Model 3	1.00	1.18 (0.92–1.52)	0.193

Analyses were conducted with a multiple imputation approach for missing data.

Model 1 adjusted for age (continuous); model 2 additionally adjusted for education (university or college degree/others [including less than high school, high school, and other professional qualification]), race and ethnicity (White/others [including Asian, Black, Chinese, mixed {Irish, White and Black African, Pakistani, and African}, and other racial or ethnic group]), baseline hypertension (yes or no), baseline diabetes (yes or no), baseline total cholesterol level, baseline triglyceride level, baseline sex hormone–binding globulin level, age at menarche (≤10, 11, 12, 13, or ≥14 years), parity (0, 1, or ≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of hormone replacement therapy (yes or no), and history of depression or severe stress (yes or no). Model 3 further adjusted for body mass index (<25 or ≥25 kg/m^2), smoking status (never, past, or current), drinking status (never, past, or current), and physical activity (low, moderate, or high). CHD indicates coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.

P<0.001 for interaction) (Table S3). The significant interactions on risk of CVD were also observed between menstrual cycle characteristics and baseline CRP (C-reactive protein) levels (*P*=0.002 and *P*=0.010 for interaction) (Table S3). Furthermore, the association of short menstrual cycle length with incident atrial fibrillation was stronger among women who had an HDL-C ≥1.3 mmol/L (*P*=0.046 for interaction) (Table S4). However, there were no significant interactions between irregular menstrual cycles and atrial fibrillation in participants with other risk factors (*P*>0.05 for interaction) (Figure [B] and Table S4). In addition, no significant interactions were observed between menstrual cycle characteristics and risk of CVD in participants with or without history of oral contraceptive use (*P*>0.05 for interaction) (Table S5). Besides, no significant interactions were observed between menstrual cycle characteristics and risk of CVD among women aged <45 years and those who more likely experienced menopausal transition (aged ≥45 years) (adjusted HRs, 1.23 [95% CI, 1.00–1.51] and 1.17 [95% CI, 1.04–1.32], respectively; *P*>0.05 for interaction; Table S6).

DISCUSSION

In this large-scale prospective study with a median 11.8-year follow-up time, we found that irregular menstrual cycles were associated with increased risks of CVD independent of risk factors, including age, race and ethnicity, BMI, smoking status, drinking status, physical activity, history of oral contraceptive use, history of HRT, age at menarche, parity, baseline cholesterol levels, history of hypertension and diabetes, family history of CVD and stroke, and other confounding factors. Furthermore, long menstrual cycle length was associated with increased risks of atrial fibrillation but not myocardial infarction, heart failure, and stroke. Short menstrual cycle length was associated with a greater risk of CHD and myocardial infarction. In addition, we found the significant interaction on risk of CVD between irregular menstrual cycles and lower HDL-C levels and smoking status. These findings have important public health implications for the prevention of CVD in women.

Several prospective studies assessed the associations between menstrual cycle regularity and risk of CVD and mortality.[12,18] The NHS (Nurses' Health Study) reported that women who reported irregular cycles had an increased risk for CVD during 14 years of follow-up compared with those with regular menstrual cycles.[12] Another prospective study of 13534 female participants found that women with irregular menstrual cycles had 20% higher risk of heart disease.[18] In contrast, a cohort study of 15005 pregnant women found no significant association between menstrual cycle regularity and CVD risk.[13] To our knowledge, prospective high-quality evidence on the relationships between menstrual cycle characteristics and CVD and subsequent CVD in women's reproductive life is

Table 3. Adjusted HRs (95% CIs) for Risk of Cardiovascular Outcomes According to Menstrual Cycle Length

Variable	Cycle length, d				*P* value for trend
	≤21	22–27	28–34	≥35 or highly irregular	
Total sample size	6919	11 872	27 710	11 555	
CVD					
Total cases	237	270	717	399	
Model 1	1.34 (1.16–1.56)	0.89 (0.78–1.03)	1.00	1.18 (1.04–1.33)	<0.001
Model 2	1.33 (1.14–1.54)	0.96 (0.83–1.10)	1.00	1.11 (0.98–1.26)	0.012
Model 3	1.29 (1.11–1.50)	0.97 (0.84–1.12)	1.00	1.11 (0.98–1.56)	0.014
CHD					
Total cases	138	131	375	183	
Model 1	1.50 (1.23–1.82)	0.83 (0.68–1.01)	1.00	1.01 (0.84–1.20)	0.188
Model 2	1.45 (1.19–1.77)	0.94 (0.77–1.15)	1.00	0.91 (0.76–1.10)	0.807
Model 3	1.41 (1.16–1.72)	0.94 (0.77–1.16)	1.00	0.92 (0.76–1.10)	0.821
Myocardial infarction					
Total cases	35	33	82	49	
Model 1	1.73 (1.16–2.57)	0.96 (0.64–1.43)	1.00	1.26 (0.88–1.80)	0.055
Model 2	1.75 (1.17–2.61)	1.10 (0.73–1.65)	1.00	1.06 (0.72–1.55)	0.322
Model 3	1.69 (1.13–2.52)	1.09 (0.73–1.65)	1.00	1.08 (0.74–1.58)	0.331
Atrial fibrillation					
Total cases	58	55	168	112	
Model 1	1.40 (1.04–1.89)	0.79 (0.58–1.07)	1.00	1.34 (1.05–1.70)	0.005
Model 2	1.42 (1.05–1.92)	0.79 (0.58–1.08)	1.00	1.29 (1.01–1.65)	0.011
Model 3	1.38 (1.02–1.87)	0.80 (0.59–1.10)	1.00	1.30 (1.01–1.66)	0.012
Heart failure					
Total cases	26	25	78	45	
Model 1	1.34 (0.86–2.10)	0.76 (0.48–1.19)	1.00	1.26 (0.87–1.82)	0.130
Model 2	1.30 (0.82–2.06)	0.83 (0.53–1.31)	1.00	1.17 (0.80–1.72)	0.277
Model 3	1.20 (0.75–1.92)	0.87 (0.55–1.37)	1.00	1.19 (0.81–1.75)	0.293
Stroke					
Total cases	36	53	114	68	
Model 1	1.28 (0.88–1.86)	1.10 (0.79–1.52)	1.00	1.32 (0.97–1.78)	0.055
Model 2	1.20 (0.82–1.76)	1.12 (0.81–1.56)	1.00	1.26 (0.92–1.71)	0.129
Model 3	1.18 (0.80–1.74)	1.13 (0.81–1.58)	1.00	1.25 (0.92–1.71)	0.137

Analyses were conducted with a multiple imputation approach for missing data.

Model 1 adjusted for age (continuous); model 2 additionally adjusted for education (university or college degree/others [including less than high school, high school, and other professional qualification]), race or ethnicity (White/others [including Asian, Black, Chinese, mixed {Irish, White and Black African, Pakistani, and African}, and other racial or ethnic group]), baseline hypertension (yes or no), baseline diabetes (yes or no), baseline total cholesterol level, baseline triglyceride level, baseline sex hormone–binding globulin level, age at menarche (≤10, 11, 12, 13, or ≥14 years), parity (0, 1, or ≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of hormone replacement therapy (yes or no), and history of depression or severe stress (yes or no). Model 3 further adjusted for body mass index (<25 or ≥25 kg/m^2), smoking status (never, past, or current), drinking status (never, past, or current), and physical activity (low, moderate, or high). CHD indicates coronary heart disease; CVD, cardiovascular disease; and HR, hazard ratio.

scarce. A previous study reported that women who reported irregular cycles or menstrual cycle length of ≥32 days at the age of 29 to 46 years had an increased risk of cardiovascular mortality.[19] In this large prospective study using a nationally representative sample of women from UK Biobank, we found that irregular menstrual cycle was associated with higher risk of cardiovascular outcome. Our data indicated that women with cycle length ≤21 days or cycle length ≥35 days were significantly associated with increased risks of CVD events.

Notably, evidence on the relationship between menstrual cycle regularity and length and specific subtypes of CVD, such as atrial fibrillation, CHD, and myocardial infarction, was relatively limited. It has been well established that female sex is an independent risk factor for some types of arrhythmias because of hormonal fluctuations during menstrual cycle.[20–22] A prior study indicated that menstrual cycle and early menopause might affects P-wave dispersion or P-wave duration, which were identified as predictors of atrial fibrillation.[23,24] In contrast, the FHS (Framingham Heart Study) reported that women with

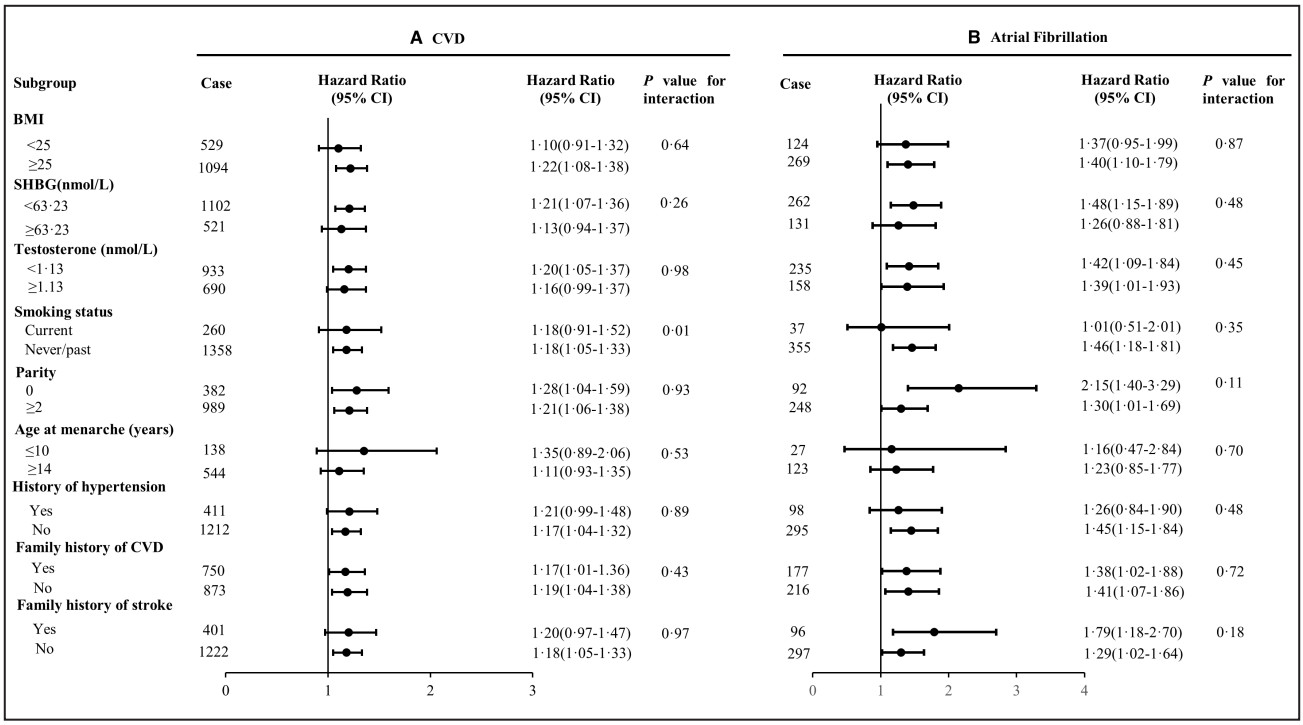

Figure. Adjusted hazard ratios and 95% CIs for the risk of cardiovascular disease (CVD) (A) and atrial fibrillation (B) according to menstrual cycle regularity, stratified by lifestyle factors and family history.
Analyses were conducted with a multiple imputation approach for missing data. Women with regular menstrual cycles are included as referent (1.00). A multivariable model was adjusted for age (continuous), education (university or college degree/others [including less than high school, high school, and other professional qualification]), race and ethnicity (White/others [including Asian, Black, Chinese, mixed {Irish, White and Black African, Pakistani, and African], and other racial or ethnic group]), baseline hypertension (yes or no), baseline diabetes (yes or no), baseline total cholesterol level, baseline sex hormone–binding globulin (SHBG) level, age at menarche (≤10, 11, 12, 13, or ≥14 years), parity (0, 1, or ≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of hormone replacement therapy (yes or no), history of depression or severe stress (yes or no), body mass index (BMI) (<25 or ≥25 kg/m^2), smoking status (never, past, or current), drinking status (never, past, or current), and physical activity (low, moderate, or high).

early menopausal age (<45 years) were not significantly associated with higher risk of atrial fibrillation than those with older menopausal ages.[25] In addition, prospective high-quality evidence on the relationships between another risk factor, menstrual cycle, and atrial fibrillation in premenopausal women is scare. To our knowledge, this is the first study to examine the relationships of menstrual cycle characteristic with atrial fibrillation risk. Our study indicated that irregular menstrual cycles, including long or short menstrual cycle length, were significantly associated with higher risk of atrial fibrillation. However, considering the relatively low prevalence of atrial fibrillation in the current study, further study needs to determine the relationships of menstrual cycle characteristics with atrial fibrillation in the large population at high risk. Furthermore, epidemiological studies reported a possible association of menstrual cycle characteristics and reproductive factors in CHD.[13,26] Our results showed that there was a significant association between short menstrual cycle length and increased risks of CHD, which was consistent with previous studies.[12,13] In addition, our data showed that short menstrual cycle length was significantly associated with the incidence of myocardial infarction. In the present study, no significant association was observed between cycle length and regularity and stroke and heart failure. Consistently, Solomon et al also reported no significant associations of irregular menstrual cycles with risks of overall stroke and ischemic stroke.[12] These findings might have implication for prevention of atrial fibrillation, myocardial infarction, and CHD in clinical practice among women.

In addition, we found that the relationships between menstrual cycle characteristic and CVD events were modified by smoking status. Likewise, the associations of short menstrual cycle length with incident CVD were significantly stronger among women with baseline HDL-C <1.3 mmol/L. Therefore, monitoring of menstrual cycle characteristics among those individuals may be particularly noteworthy.

Several potential mechanisms could explain the observed relationships between menstrual cycle regularity and incidence of CVD. First, irregular menstrual cycles are significantly related to multiple CVD risk factors, including obesity,[27,28] hyperinsulinemia, dyslipidemia,[29]

Table 4. Adjusted HRs (95% CIs) for the Risk of CVD According to Menstrual Cycle Length, Stratified by Lifestyle Factors and Family History

Stratified factors	Cycle length, d				*P* value for trend
	≤21	22–27	28–34	≥35 or highly irregular	
Body mass index, kg/m^2					
<25, n=529 cases	1.25 (0.96–1.63)	0.84 (0.66–1.07)	1.00	0.94 (0.74–1.18)	0.964
≥25, n=1094 cases	1.31 (1.09–1.57)	1.04 (0.88–1.24)	1.00	1.20 (1.03–1.40)	0.004
P value for interaction			0.270		
SHBG, nmol/L					
<63.23, n=1102 cases	1.30 (1.08–1.56)	0.93 (0.78–1.11)	1.00	1.12 (0.97–1.31)	0.029
≥63.23, n=521 cases	1.29 (0.99–1.68)	1.05 (0.83–1.34)	1.00	1.07 (0.84–1.35)	0.286
P value for interaction			0.337		
Testosterone, nmol/L					
<1.13, n=933	1.32 (1.09–1.61)	0.98 (0.82–1.19)	1.00	1.12 (0.95–1.33)	0.041
≥1.13, n=690	1.26 (0.99–1.59)	0.95 (0.76–1.18)	1.00	1.09 (0.90–1.33)	0.184
P value for interaction			0.996		
Smoking status					
Current, n=260 cases	1.07 (0.74–1.53)	0.77 (0.52–1.13)	1.00	1.13 (0.83–1.54)	0.393
Never/past, n=1358 cases	1.34 (1.13–1.58)	1.00 (0.86–1.17)	1.00	1.11 (0.96–1.27)	0.026
P value for interaction			0.024		
Parity					
0, n=382 cases	1.29 (0.94–1.76)	0.84 (0.63–1.13)	1.00	1.18 (0.91–1.53)	0.103
≥2, n=989 cases	1.38 (1.14–1.66)	1.03 (0.86–1.24)	1.00	1.14 (0.97–1.34)	0.021
P value for interaction			0.782		
Age at menarche, y					
≤10, n=138 cases	1.11 (0.61–2.04)	0.40 (0.18–0.89)	1.00	1.16 (0.70–1.90)	0.485
≥14, n=544 cases	1.24 (0.97–1.59)	0.85 (0.66–1.09)	1.00	0.96 (0.77–1.20)	0.773
P value for interaction			0.767		
History of hypertension					
Yes, n=411 cases	1.61 (1.21–2.14)	1.05 (0.78–1.43)	1.00	1.06 (0.83–1.36)	0.240
No, n=1212 cases	1.19 (1.00–1.42)	0.94 (0.80–1.11)	1.00	1.13 (0.98–1.31)	0.041
P value for interaction			0.931		
Family history of CVD					
Yes, n=750 cases	1.21 (0.96–1.52)	0.94 (0.76–1.16)	1.00	1.13 (0.94–1.35)	0.079
No, n=873 cases	1.35 (1.11–1.65)	0.98 (0.81–1.19)	1.00	1.09 (0.91–1.30)	0.099
P value for interaction			0.518		
Family history of stroke					
Yes, n=401 cases	1.22 (0.91–1.65)	0.80 (0.59–1.09)	1.00	1.08 (0.84–1.39)	0.320
No, n=1222 cases	1.32 (1.11–1.56)	1.02 (0.87–1.20)	1.00	1.12 (0.96–1.30)	0.028
P value for interaction			0.779		

Analyses were conducted with a multiple imputation approach for missing data.

A multivariable model was adjusted for age (continuous), education (university or college degree/others [including less than high school, high school, and other professional qualification]), race and ethnicity (White/others [including Asian, Black, Chinese, mixed {Irish, White and Black African, Pakistani, and African}, and other racial or ethnic group]), baseline hypertension (yes or no), baseline diabetes (yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10, 11, 12, 13, or ≥14 years), parity (0, 1, or ≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of hormone replacement therapy (yes or no), history of depression or severe stress (yes or no), body mass index (<25 or ≥25 kg/m^2), smoking status (never, past, or current), drinking status (never, past, or current), and physical activity (low, moderate, or high). CVD indicates cardiovascular disease; HR, hazard ratio; and SHBG, sex hormone–binding globulin.

diabetes,[30] hypertension,[31] and polycystic ovary syndrome.[32] Second, abnormalities in menstrual cycle length may have implications for reproductive health; cycle length is thought to be an indicator of cumulative exposure to ovarian steroids and to reflect underlying hormonal patterns. Long cycles and irregular cycles are thought to be associated with decreased estrogen exposure that can execute vasodilator function by augmentation of the β-adrenergic receptor, and reduction of oxidative stress, which might explain their

association with risk of CVD.[33] Women with irregular or long menstrual cycles were associated with higher levels of testosterone and lower levels of SHBG,[8] which has been established to be strongly related with the cause of CVDs.[34] In the current study, we found that women with long or irregular menstrual cycles had higher incidence rates of diabetes and hypertension, and had higher BMI, higher levels of total cholesterol, and lower levels of HDL-C, which are strong predictors of CVD events.[35,36] Collectively, these metabolic dysfunctions could contribute to an increased risk of incident CVD. In addition, oral contraceptives could play a potential modifying factor that could affect the associations between menstrual cycle characteristics and CVD risk, because they have been extensively used for treatment of irregular menstrual cycles or polycystic ovary syndrome in women.[37,38] However, they are unlikely to explain the association of menstrual cycle characteristics with risk of CVD now that no significant interaction was observed according to history of oral contraceptive use in the current analysis.

The strength of our study included its prospective design with a large sample size, and abundant CVD events over a long-term follow-up that provided sufficient power for the analyses in the current study. Furthermore, the detailed information was available on demographics, socioeconomic characteristics, lifestyle habits, comorbidity, medical status, and other covariates, which may enable us to perform comprehensive sensitivity analyses and subgroup analyses and enhance the validity of the conclusions in this study. Thus, our study provided the knowledge on how menstrual cycle regularity affects women's health and valuable guidance of future prevention among women.

Several potential limitations should also be considered in our study. First, because the cycle regularity question relied on the participant's interpretation of irregular and menstrual cycle length, some exposure misclassification might also be present. However, the assessment of menstrual cycle characteristics in our study was not subject to recall bias, avoiding potential bias away from the null. Second, participants with menopause at baseline were excluded from this study because early menopause might affect the menstrual cycle regularity, which may affect the generality of our study. Third, although we carefully control for multiple potential confounders, we cannot rule out the possibility of residual confounding. Fourth, a modest proportion of participants (8.4%) did not fully report their menstrual cycle characteristics across the entire reproductive lifespan and were excluded in the analyses, which might have resulted in selection bias. However, the baseline characteristics were similar between included and excluded women for incomplete cycle characteristic data. Fifth, we cannot rule out the possibility of some statistically significant results that may have occurred by chance. Finally, we cannot rule out that irregular menstrual cycles were attributable to menopausal transition in the present study because of lack of the history of menstrual cycle at early age and hormone data at baseline, such as follicular stage estradiol and follicle-stimulating hormones.

CONCLUSIONS

The results of this large prospective study indicate that women with irregular menstrual cycles were significantly associated with increased risks of CVD. Furthermore, long or short menstrual cycle length was associated with increased risks of CVD and atrial fibrillation but not myocardial infarction, heart failure, and stroke. Short menstrual cycle length was significantly associated with higher risks of CHD and myocardial infarction. These findings point out that women with menstrual cycle dysfunction might have adverse health consequences, and highlight the importance of monitoring menstrual cycle characteristics throughout women's reproductive life in the prevention of CVD and atrial fibrillation among women.

ARTICLE INFORMATION

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Author contributions: Dr H. Zhang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Drs C. Huang and H. Zhang; acquisition, analysis, or interpretation of data: Drs C. Huang, B. Lin, Yuan, Deng, Xu, and P. Zhang; drafting of the manuscript: Drs C. Huang, B. Lin, Yuan, and H. Zhang; critical revision of the manuscript for important intellectual content: Drs Wei, Wang, W. Liu, and Li; statistical analysis: Drs C. Huang, Yuan, D. Liu, and J. Lin; obtained funding: Dr H. Zhang; administrative, technical, or material support: Drs D. Liu, Y. Huang, and H. Zhang; and study supervision: Drs Deng, Xu, and H. Zhang.

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figure S1

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Supplemental Material

Table S1. Disease codes for CVD and subsequent CVD.

Diseases	ICD10 (UKB data field 41270)	Self-reported (UKB data field 20002)
CVD	I20, I21, I22, I23, I24, I25, I48, I49, I50, I60, I61, I62, I63, I64, I69	1491, 1583, 1074, 1075, 1076, 1077, 1081,1082, 1086
CHD	I20, I21, I22, I23, I24, I25	1074, 1075
Myocardial infarction	I21, I22, I23	1075
Atrial fibrillation	I48	-
Heart failure	I50	1076
stroke	I60, I61, I62, I63, I64, I69	1491, 1583, 1081, 1082,1086

Abbreviation: CVD, cardiovascular diseases; CHD, coronary heart disease.

Table S2. Adjusted hazard ratios and 95% confidence intervals for risk of CHD and atrial fibrillation according to changes in menstrual cycle characteristics (UK Biobank, 2006-2020) *.

Change in menstrual cycle characteristics	CHD		Atrial fibrillation	
	Cases/N	Hazard Ratio (95% CI)	Cases/N	Hazard Ratio (95% CI)
Change in regularity				
Regularity maintained	9/903	1.00	5/903	1.00
Regular to irregular	4/538	0.72(0.22-2.37)	4/538	0.99(0.25-3.95)
Irregular to regular	3/140	2.06(0.53-8.02)	1/140	1.71(0.19-15.81)
Irregularity maintained	6/243	2.52(0.86-7.35)	4/243	2.05(0.49-8.51)
P for trend		0.340		0.469

* Analyses are conducted with a multiple imputation approach for missing data.

A multivariable model was adjusted for age (continuous), education degree (university or college degree/others (including less than high school, high school, and other professional qualification)), ethnicity (white/others (including Asian, Black, Chinese, Mixed (Irish, White and Black African, Pakistani, and African), and other ethnic group)), baseline hypertension(yes or no), baseline diabetes(yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10,11,12,13,≥14), parity (0,1,≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of HRT (yes or no), history of depression or severe stress (yes or no), BMI (<25,≥25kg/m2), smoking status (never, past, or current), drink (never, past, or current), physical activity (low, moderate, high).

CHD, coronary heart disease.

Table S3. Adjusted hazard ratios and 95% confidence intervals for the risk of CVD according to menstrual cycle length and regularity, stratified by cardiovascular risk factors*.

Stratified factors	Cycle regularity		*P* for trend	Cycle length(days)				*P* for trend
	Regular	Irregular or no periods		≤21	22-27	28-34	≥35 or highly irregular	
History of diabetes								
Yes (n=112 cases)	1.00	1.05(0.71-1.55)	0.814	1.14(0.66-1.98)	0.90(0.48-1.68)	1.00	0.96(0.60-1.54)	0.996
No (n=1511 cases)	1.00	1.20(1.07-1.33)	0.001	1.30(1.11-1.52)	0.97(0.84-1.13)	1.00	1.13(0.99-1.29)	0.011
P for interaction	0.487					0.414		
Total cholesterol(mmol/L)								
<5.2 (n=685 cases)	1.00	1.15(0.97-1.37)	0.103	1.30(1.01-1.66)	0.96(0.77-1.21)	1.00	1.05(0.85-1.31)	0.290
≥5.2 (n=938 cases)	1.00	1.20(1.06-1.37)	0.006	1.29(1.06-1.57)	0.97(0.81-1.17)	1.00	1.14(0.97-1.34)	0.028
P for interaction	0.473					0.453		
Triglycerides(mmol/L)								
<1.7(n=1139 cases)	1.00	1.17(1.04-1.33)	0.012	1.26(1.05-1.51)	0.97(0.82-1.15)	1.00	1.11(0.95-1.30)	0.051
≥1.7(n=484 cases)	1.00	1.21(1.01-1.46)	0.044	1.37(1.05-1.79)	0.94(0.71-1.23)	1.00	1.10(0.87-1.38)	0.165
P for interaction	0.094					0.172		
HDL -C(mmol/L)								
<1.3 (n=789 cases)	1.00	1.22(1.06-1.42)	0.007	1.29(1.04-1.60)	0.99(0.80-1.22)	1.00	1.18(0.99-1.42)	0.022
≥1.3 (n=834 cases)	1.00	1.16(1.00-1.34)	0.044	1.31(1.06-1.61)	0.95(0.78-1.16)	1.00	1.06(0.88-1.26)	0.198
P for interaction	<0.001					<0.001		
Physical activity								
Low (n=969 cases)	1.00	1.18(1.03-1.35)	0.014	1.29(1.06-1.57)	0.98(0.81-1.18)	1.00	1.12(0.95-1.31)	0.058
Moderate (n=296 cases)	1.00	1.38(1.09-1.76)	0.008	1.50(1.04-2.18)	1.25(0.91-1.72)	1.00	1.47(1.09-1.97)	0.005
High (n=353 cases)	1.00	1.05(0.84-1.32)	0.654	1.19(0.88-1.61)	0.76(0.56-1.04)	1.00	0.84(0.63-1.13)	0.563
P for interaction	0.536					0.291		
CRP (mg/L)								
<3.0 (n=1164 cases)	1.00	1.21(1.07-1.37)	0.002	1.33(1.11-1.59)	1.02(0.87-1.20)	1.00	1.16(0.99-1.34)	0.011
≥3.0 (n=459 cases)	1.00	1.10(0.91-1.34)	0.313	1.18(0.89-1.54)	0.86(0.64-1.15)	1.00	1.01(0.80-1.27)	0.667
P for interaction	0.002					0.010		

* Analyses are conducted with a multiple imputation approach for missing data.

A multivariable model was adjusted for age (continuous), education degree (university or college degree/others (including less than high school, high school, and other professional qualification)), ethnicity (white/others (including Asian, Black, Chinese, Mixed (Irish, White and Black African, Pakistani, and African), and other ethnic group)), baseline hypertension(yes or no), baseline diabetes(yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10,11,12,13,≥14), parity (0,1,≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of HRT (yes or no), history of depression or severe stress (yes or no), BMI (<25,≥25kg/m2), smoking status (never, past, or current), drink (never, past, or current), physical activity (low, moderate, high).

Table S4. Adjusted hazard ratios and 95% confidence intervals for the risk of atrial fibrillation according to menstrual cycle length, stratified by cardiovascular risk factors*.

Stratified factors	Cycle length (days)				*P* for trend
	≤21	22-27	27-34	≥35 or highly irregular	
Body mass index					
<25 (n=124 cases)	1.33(0.76-2.33)	0.80(0.47-1.36)	1.00	1.27(0.81-1.98)	0.205
≥25 (n=269 cases)	1.39(0.97-2.00)	0.81(0.55-1.18)	1.00	1.30(0.97-1.74)	0.034
P for interaction			0.856		
SHBG (nmol/L)					
<63.23(n=262 cases)	1.35(0.93-1.95)	0.62(0.40-0.95)	1.00	1.31(0.98-1.75)	0.027
≥63.23(n=131 cases)	1.43(0.84-2.45)	1.16(0.73-1.86)	1.00	1.26(0.80-1.98)	0.213
P for interaction			0.603		
Testosterone (nmol/L)					
<1.13(n=235)	1.28(0.86-1.90)	0.67(0.44-1.03)	1.00	1.29(0.94-1.76)	0.056
≥1.13(n=158)	1.54(0.96-2.49)	1.00(0.63-1.60)	1.00	1.32(0.89-1.97)	0.086
P for interaction			0.528		
Smoking status					
Current (n=37 cases)	0.88(0.29-2.62)	0.87(0.32-2.38)	1.00	1.03(0.46-2.33)	0.994
Never/past (n=355 cases)	1.48(1.08-2.03)	0.81(0.58-1.12)	1.00	1.33(1.03-1.73)	0.007
P for interaction			0.352		
Parity					
0 (n=92 cases)	2.16(1.19-3.93)	0.77(0.39-1.54)	1.00	1.91(1.14-3.19)	0.003
≥2 (n=248 cases)	1.29(0.88-1.90)	0.75(0.50-1.13)	1.00	1.19(0.87-1.61)	0.160
P for interaction			0.110		
Age at menarche(years)					
≤10 (n=27 cases)	1.44(0.46-4.52)	0.18(0.02-1.37)	1.00	0.62(0.20-1.98)	0.592
≥14 (n=123 cases)	1.17(0.69-2.00)	0.69(0.39-1.24)	1.00	1.10(0.71-1.71)	0.543
P for interaction			0.363		
History of hypertension					
Yes (n=98 cases)	1.18(0.63-2.20)	0.60(0.29-1.24)	1.00	1.11(0.69-1.78)	0.508
No (n=295 cases)	1.46(1.03-2.07)	0.86(0.61-1.22)	1.00	1.36(1.02-1.81)	0.012
P for interaction			0.401		
History of diabetes					
Yes (n=16 cases)	1.23(0.35-4.39)	0.95(0.19-4.73)	1.00	0.17(0.02-1.42)	0.169
No (n=377 cases)	1.36(0.99-1.86)	0.80(0.58-1.10)	1.00	1.36(1.06-1.75)	0.005
P for interaction			0.068		
Family history of CVD					
Yes (n=177 cases)	1.38(0.86-2.21)	0.96(0.61-1.50)	1.00	1.36(0.95-1.96)	0.060
No (n=216 cases)	1.36(0.91-2.03)	0.68(0.44-1.06)	1.00	1.24(0.89-1.73)	0.093
P for interaction			0.989		
Family history of stroke					
Yes (n=96 cases)	2.06(1.18-3.59)	0.47(0.21-1.06)	1.00	1.29(0.79-2.12)	0.087
No (n=297 cases)	1.18(0.82-1.71)	0.90(0.64-1.26)	1.00	1.29(0.97-1.71)	0.058

P for interaction			0.515		
Total cholesterol(mmol/L)					
<5.2 (n=196 cases)	1.38(0.86-2.20)	0.85(0.55-1.33)	1.00	1.08(0.73-1.61)	0.440
≥5.2 (n=197 cases)	1.36(0.88-2.11)	0.76(0.48-1.19)	1.00	1.44(1.04-1.99)	0.014
P for interaction			0.502		
Triglycerides(mmol/L)					
<1.7(n=303 cases)	1.44(1.02-2.03)	0.83(0.59-1.18)	1.00	1.26(0.95-1.68)	0.038
≥1.7(n=90 cases)	1.20(0.62-2.30)	0.67(0.32-1.38)	1.00	1.38(0.85-2.24)	0.158
P for interaction			0.546		
HDL -C(mmol/L)					
<1.3 (n=191 cases)	1.12(0.71-1.77)	0.63(0.39-1.02)	1.00	1.28(0.91-1.80)	0.125
≥1.3 (n=202 cases)	1.66(1.10-2.51)	0.98(0.65-1.49)	1.00	1.34(0.94-1.90)	0.035
P for interaction			0.046		

* Analyses are conducted with a multiple imputation approach for missing data.

A multivariable model was adjusted for age (continuous), education degree (university or college degree/others (including less than high school, high school, and other professional qualification)), ethnicity (white/others (including Asian, Black, Chinese, Mixed (Irish, White and Black African, Pakistani, and African), and other ethnic group)), baseline hypertension(yes or no), baseline diabetes(yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10,11,12,13,≥14), parity (0,1,≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of HRT (yes or no), history of depression or severe stress (yes or no), BMI (<25,≥25kg/m2), smoking status (never, past, or current), drink (never, past, or current), physical activity (low, moderate, high).

Table S5. Adjusted hazard ratios and 95% confidence intervals for the risk of CVD between women never and past use contraceptives according to menstrual cycle length and regularity*.

Menstrual cycle characteristic	History of oral contraceptive use		*P* for interaction
	Never (n=6514)	Yes (n=51542)	
Cycle length (days)			
⩽21	1.06(0.66-1.69)	1.32(1.13-1.55)	0.884
22-27	1.12(0.77-1.63)	0.95(0.81-1.11)	
28-34	1.00	1.00	
⩾35	1.05(0.71-1.55)	1.11(0.97-1.27)	
Cycle regularity			
Regular	1.00	1.00	0.568
Irregular	1.02(0.74-1.39)	1.20(1.08-1.34)	

* Analyses are conducted with a multiple imputation approach for missing data.

A multivariable model was adjusted for age (continuous), education degree (university or college degree/others (including less than high school, high school, and other professional qualification)), ethnicity (white/others (including Asian, Black, Chinese, Mixed (Irish, White and Black African, Pakistani, and African), and other ethnic group)), baseline hypertension(yes or no), baseline diabetes(yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10,11,12,13,≥14), parity (0,1,≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of HRT (yes or no), history of depression or severe stress (yes or no), BMI (<25,≥25kg/m2), smoking status (never, past, or current), drink (never, past, or current), physical activity (low, moderate, high).

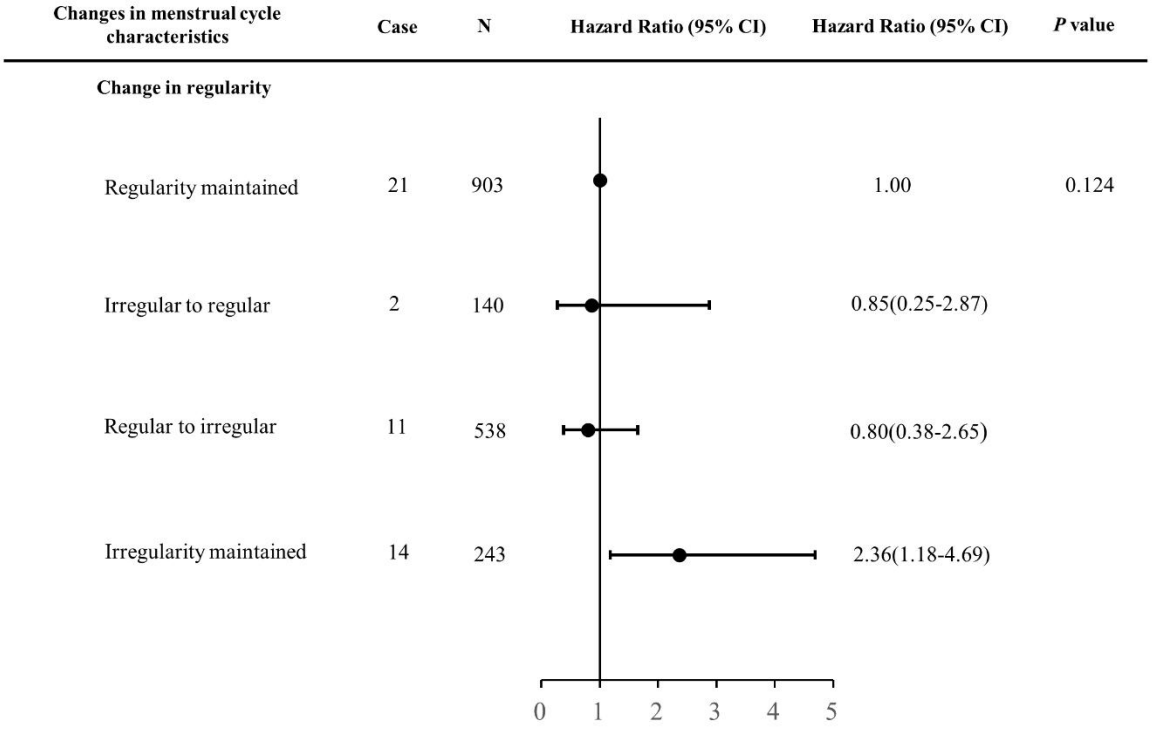
Table S6. Association between irregular menstrual cycles with the risk of CVD Stratified by Baseline Age Categories *

	Cycle regularity			*P* value
	Sample	**Regular**	**Irregular**	
Age(years)				
<45 (n=452 events)	22543	1.00	1.23(1.00-1.51)	0.047
⩾45 (n=1171 events)	35513	1.00	1.17(1.04-1.32)	0.010
P for interaction		0.740		

* Analyses are conducted with a multiple imputation approach for missing data.

A multivariable model was adjusted for age (continuous), education degree (university or college degree/others (including less than high school, high school, and other professional qualification)), ethnicity (white/others (including Asian, Black, Chinese, Mixed (Irish, White and Black African, Pakistani, and African), and other ethnic group)), baseline hypertension(yes or no), baseline diabetes(yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10,11,12,13,≥14), parity (0,1,≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of HRT (yes or no), history of depression or severe stress (yes or no), BMI (<25,≥25kg/m2), smoking status (never, past, or current), drink (never, past, or current), physical activity (low, moderate, high).

Figure S1. Multivariate adjusted hazard ratios and 95% confidence intervals for risk of cardiovascular diseases according to changes in menstrual cycle characteristics (UK Biobank, 2006-2020) *.



The vertical line indicates the reference value of 1. A multivariable model was adjusted for age (continuous), education degree (university or college degree/others (including less than high school, high school, and other professional qualification)), ethnicity (white/others (including Asian, Black, Chinese, Mixed (Irish, White and Black African, Pakistani, and African), and other ethnic group)), baseline hypertension(yes or no), baseline diabetes(yes or no), baseline total cholesterol level, baseline SHBG level, age at menarche (≤10,11,12,13,≥14), parity (0,1,≥2), family history of CVD or stroke (yes or no), history of oral contraceptive use (yes or no), history of HRT (yes or no), history of depression or severe stress (yes or no), BMI (<25,≥25kg/m2), smoking status (never, past, or current), drink (never, past, or current), physical activity (low, moderate, high).