Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study

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ABSTRACT

OBJECTIVE

To evaluate whether irregular or long menstrual cycles throughout the life course are associated with all cause and cause specific premature mortality (age <70 years).

DESIGN

Prospective cohort study.

SETTING

Nurses' Health Study II (1993-2017).

PARTICIPANTS

79 505 premenopausal women without a history of cardiovascular disease, cancer, or diabetes and who reported the usual length and regularity of their menstrual cycles at ages 14-17 years, 18-22 years, and 29-46 years.

MAIN OUTCOME MEASURES

Hazard ratios and 95% confidence intervals for all cause and cause specific premature mortality (death before age 70 years) were estimated from multivariable Cox proportional hazards models.

RESULTS

During 24 years of follow-up, 1975 premature deaths were documented, including 894 from cancer and 172 from cardiovascular disease. Women who reported always having irregular menstrual cycles experienced higher mortality rates during follow-up than women who reported very regular cycles in the same age ranges. The crude mortality rate per 1000 person years of follow-up for women reporting very regular cycles and women reporting always irregular cycles were 1.05 and 1.23 for cycle characteristics at ages 14-17 years, 1.00 and 1.37 for cycle characteristics at ages 18-22 years, and 1.00 and 1.68 for cycle characteristics at ages 29-46 years. The corresponding multivariable adjusted hazard ratios for premature death during follow-up were 1.18 (95% confidence interval 1.02 to 1.37), 1.37 (1.09 to 1.73), and 1.39 (1.14 to 1.70), respectively. Similarly, women who reported that their usual cycle length was 40 days or more at ages 18-22 years and 29-46 years were more likely to die prematurely than women who reported a usual cycle length of 26-31 days in the same age ranges (1.34, 1.06 to 1.69; and 1.40, 1.17 to 1.68, respectively). These relations were strongest for deaths related to cardiovascular disease. The higher mortality associated with long and irregular menstrual cycles was slightly stronger among current smokers.

CONCLUSIONS

Irregular and long menstrual cycles in adolescence and adulthood are associated with a greater risk of premature mortality (age <70 years). This relation is slightly stronger among women who smoke.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Irregular and long menstrual cycles are common among women of reproductive age and have been associated with a higher risk of major chronic diseases

Evidence linking irregular or long menstrual cycles with mortality is sparse

WHAT THIS STUDY ADDS

Irregular and long menstrual cycles in adolescence and throughout adulthood are associated with a greater risk of premature mortality, which is slightly stronger among women who currently smoke

These relations were strongest for deaths due to cardiovascular disease when cause specific mortality was tested

The results emphasize the need for primary care providers to include menstrual cycle characteristics throughout the reproductive life span as additional vital signs in assessing women's general health status

Introduction

Age specific mortality in most countries has steadily improved with advances in medical and public health.[1] However, all countries still face an appreciable burden of premature mortality, defined by the World Health Organization as death before age 70 years,[2 3] accounting for 52.4% of the 56.9 million deaths globally in 2016.[3] Non-communicable diseases, including cardiovascular disease and cancer,[4] are the leading cause of premature death worldwide, contributing 57.0% (17.0 million) of the total premature deaths in 2016.[3] To curb the rising global burden of non-communicable diseases, the United Nations has launched, as part of the Sustainable Development Goals, a global goal of reducing the total premature mortality (deaths before age 70 years) from non-communicable diseases by one third by 2030.[5]

Regular menstrual cycles reflect normal functioning of the hypothalamic-pituitary-ovarian axis, a vital sign of women's general health.[6] Irregular and long menstrual cycles, often attributed to the functional disruption of the hypothalamic-pituitary-ovarian axis, are, however, common among women of reproductive age.[7] They have been associated with greater risk of non-communicable diseases, including ovarian cancer,[8] coronary heart disease,[9] type 2 diabetes,[10] and mental health problems,[11] through mechanisms probably related to a disrupted hormonal environment (eg, hyperinsulinemia),[12] chronic inflammation,[13] and metabolic disturbances (eg, insulin resistance, dyslipidemia, and metabolic syndrome).[14] Evidence linking irregular or long menstrual cycles with

mortality is, however, limited.[8 15] As deaths occurring before age 70 years result in a greater number of life years lost, we evaluated whether irregular or long menstrual cycles during adolescence and throughout premenopausal adulthood were associated with all cause and cause specific premature mortality among women participating in a large ongoing prospective cohort study. Moreover, because compelling evidence has shown that lifestyle factors (eg, overweight, smoking, diet, physical activity), mental health status, and reproductive characteristics are important determinants of mortality risk and might directly impact some of the underlying metabolic disturbances associated with long or irregular menstrual cycles,[16-18] we also examined whether the relations between menstrual cycle characteristics and premature mortality were modified by lifestyle, psychological, and reproductive factors.

Methods

Study design

The Nurses' Health Study II is an ongoing prospective cohort started in 1989 with the recruitment of 116 429 female US registered nurses aged 25 to 42 years.[19] Participants are followed biennially through mailed or electronic questionnaires, which collect information on lifestyle, diet, medical history, and incident diseases. Response rates in each follow-up cycle exceed 90%. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard TH Chan School of Public Health, and those of participating registries as required. Return of completed questionnaires by participants indicated continued informed consent.

At baseline in 1989, participants recalled the characteristics of their menstrual cycles during adolescence (age 14-17 years) and at ages 18-22 years. In 1993, participants (then aged 29-46 years) were asked to report the current usual length and regularity of their menstrual cycles. For the present analysis, we defined baseline as the date of completion of the 1993 questionnaire. We excluded women who never returned follow-up questionnaires (n=860), had missing data on birthday (n=17), had reached menopause (n=5454), had died (n=139), or had received a diagnosis of cancer (n=2363), cardiovascular disease (n=78), or type 2 diabetes (n=351) by 1993. We further excluded 27 662 women who did not fully report the characteristics of their menstrual cycles on the 1989 and 1993 questionnaires, leaving 79 505 women in the analysis. The baseline age standardized characteristics were similar between included (n=79 505) and excluded women resulting from incomplete data on menstrual cycle characteristics (n=27 662) (supplemental table 1).

Menstrual cycle characteristics in adolescence and adulthood

The women reported the usual regularity and length of their menstrual cycles, excluding during pregnancy and lactation, on the 1989 and 1993 questionnaires. Cycle regularity was reported as very regular (within 3-4 days), regular (within 5-7 days), usually irregular, and always irregular or no periods. Cycle length was reported as 21 days or less, 21-25 days, 26-31 days, 32-39 days, 40-50 days, or more than 50 days or too irregular to estimate. Self-report of menstrual cycle characteristics has been validated in other studies and is considered to be reliable.[7 20] To assess the reliability of self-reported menstrual cycle characteristics in our cohort, we cross classified participants by the cycle regularity and length reported in 1993.[9] Among women with a regular cycle, 75% had a cycle length of 26-31 days and only 1.5% reported an extreme cycle length (<21 days, ≥40 days or too irregular to estimate). Similarly, among women reporting irregular cycles or no cycles, 70.3% had an extreme cycle length and 7.4% had a normal cycle length.[9] Moreover, the distribution of cycle patterns reported in this cohort is highly consistent with that reported in a similar cohort (n=26 421),[9] the Nurses' Health Study, as well as with observations among other populations of women of similar age.[21]

Assessment of covariates

Self-reported height and race were gathered at baseline. Lifestyle factors and health related characteristics (eg, age, parity, age at menopause, body weight, smoking status, family histories of diseases) were obtained at baseline and updated biennially. We calculated body mass index (BMI) at each follow-up period. Alcohol consumption and physical activity were ascertained at baseline and then updated about every four years. Dietary intake was assessed every four years using a validated semiquantitative food frequency questionnaire; we computed the alternative healthy eating index (AHEI) 2010 as a summary measure of diet quality (higher scores indicate healthier diets).[22] The AHEI-2010 consists of 11 components (vegetables, fruit, whole grains, nuts and legumes, long chain omega-3 fatty acids, polyunsaturated fatty acids, alcohol, sugar sweetened drinks and fruit juice, red and processed meat, trans fatty acids, and sodium), each of which was scored on a 0 to 10 point scale. The component scores were summed to obtain the total AHEI-2010 score, which ranged from 0 (non-adherence) to 110 (perfect adherence). Starting in 1993, participants were asked on each biennial questionnaire if they ever received a physician diagnosis of uterine fibroids or endometriosis. Phobic anxiety symptom scores, as measured by the Crown-Crisp index, were calculated from eight questions administered in 1993 and 2005.[23] Clinician diagnosed depression has been collected through biennial questionnaires since 2003.[24]

Premature death ascertainment

Deaths were ascertained from state vital statistics records, periodic searches of the national death index, or by reports from next of kin or the postal authorities. This method has been found to ascertain more than 98% of deaths.[25] The cause of death was

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ascertained by physician review of medical records, autopsy reports, or death certificates. We used ICD-8 (international classification of diseases, eighth revision) to distinguish deaths from cardiovascular disease (including heart failure, coronary heart disease, stroke, and any other vascular causes; ICD-8 codes 390-458), cancers (140-207), and any other reasons (supplemental table 2). Premature mortality was defined as death before age 70 years.[2]

Data analysis

We calculated person years of follow-up from the date of return of the 1993 questionnaire to the date of premature death, or the end of follow-up (30 June 2017), whichever came first. Three women died at or after age 70 years and were treated as censored observations in all analyses. We fit Cox proportional hazard models to estimate the hazard ratios for the associations of menstrual cycle regularity and length within each of the three reported age ranges with the risk of all cause and cause specific premature mortality, while simultaneously adjusting for time varying confounders and risk factors. The Anderson-Gill data structure was used to handle time varying covariates efficiently,[26] when a new data record is created for every questionnaire cycle at which a participant is at risk, with covariates set to the values at the time the questionnaire is returned. To control as finely as possible for confounding by age, calendar time, and any possible interactions between these two timescales, we stratified the analysis jointly by age in months at the start of follow-up and calendar year of the current questionnaire cycle. The timescale for the analysis was months since the start of the current questionnaire cycle, which is equivalent to age in months. Covariates were selected a priori based on past findings and were included in Cox models if their inclusion changed the age adjusted hazard ratio by 5% or more.[27] Multivariable Cox models were adjusted for age; calendar time; age at menarche; race; baseline hypertension and high blood cholesterol level; family history of myocardial infarction, stroke, or diabetes; and time varying menopausal status and parity. In a secondary analysis, we further adjusted multivariable models for time varying alcohol consumption, BMI, physical activity, smoking status, and diet (AHEI-2010 score). For the covariates with missing values at a given time point (<5% for any covariates), information from the most recent questionnaire was carried forward; otherwise, a missing indicator was used in the analysis.[28]

Because oral contraceptives affect menstrual cycle characteristics and also might be used as a treatment for common ovulation disorders,[29] we examined women who used oral contraceptives for more than two months during each age range in a separate cycle characteristics category. To assess the effect of change in menstrual cycle patterns across the reproductive lifespan, we repeated the Cox regressions by cross classifying participants according to menstrual cycle regularity and length at ages 14-22 years and 29-46 years. We also estimated the hazard ratios according to the joint categories of menstrual cycle regularity and length and examined interactions on both multiplicative and additive scales. The additive interaction was assessed by calculating the relative excess risk due to interaction.[30] We also tested for effect modification by lifestyle and reproductive factors by performing analyses stratified by BMI, diet quality, physical activity, smoking status, phobic anxiety symptom scores, depression, parity, and age at menopause.

Several sensitivity analyses were conducted. First, to minimize the possibility of misclassifying women who experienced menstrual irregularity from early menopause we reanalyzed the Cox models by excluding women older than 40 years in 1993. Second, we defined premature mortality as deaths before age 65 years to allow comparison with other studies.[31] Third, we excluded women who received a diagnosis of type 2 diabetes during follow-up to assess if associations between menstrual cycle characteristics and mortality are fully explained by the subsequent development of type 2 diabetes. Fourth, we used only baseline values of all covariates to examine whether adjusting for time varying variables could have biased the results. Fifth, we excluded women who reported hirsutism, endometriosis, or uterine fibroids to test if the relation was accounted for by these other gynecologic conditions or polycystic ovary syndrome (PCOS). Sixth, we excluded women who reported no periods and a cycle of more than 50 days or too irregular to estimate from the analysis to reduce exposure misclassification. Finally, we included women in the analyses who provided partial data on menstrual cycle characteristics at the ages of 14-17 years, 18-22 years, and 29-46 years. All data were analyzed using SAS 9.4 for UNIX (SAS Institute).

Patient and public involvement

This research was done without patient involvement. Patients and the public were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients and the public were not invited to contribute to the writing or editing of this document for readability or accuracy. The study did not receive funds to train or involve members of the community in the study design or interpretation of the results.

Results

The study included 79 505 premenopausal women, with a mean age of 37.7 (range 29-46) years at baseline in 1993. Table 1 presents the participants' age adjusted characteristics according to menstrual cycle regularity and length in 1993 (ages 29-46 years). Compared with women who reported very regular menstrual cycles, those reporting irregular cycles or no periods had a higher BMI (28.2 (SD 7.8) *v* 25.0 (5.3)) and were more likely to have hypertension (13.2% *v* 6.2%), high blood cholesterol levels (23.9% *v* 14.9%), hirsutism (8.4% *v* 1.8%), endometriosis (5.9% *v* 4.5%), and uterine

Table 1 | Age standardized characteristics of women at baseline according to menstrual cycle regularity and length at ages 29-46 years (Nurses' Health Study II, 1993-2017).* Values are means (SDs), medians (interquartile ranges) unless stated otherwise

	Cycle regularity†				Cycle length (days)†			
Characteristics	Very regular (n=43 695)	Regular (n=18 787)	Usually irregular (n=4571)	Always irregular or no periods (n=2685)	≤25 (n=11 743)	26-31 (n=46 969)	32-39 (n=7522)	≥40 or highly irregular (n=3504)
Age (years)‡	38.1 (4.4), 38.0 (35.0-41.0)	38.3 (4.5), 38.0 (35.0-42.0)	38.5 (5.0), 39.0 (35.0-43.0)	37.7 (4.9), 38.0 (34.0-42.0)	39.4 (4.2), 40.0 (37.0-43.0)	38.1 (4.4), 38.0 (35.0-42.0)	36.8 (4.4), 37.0 (33.0-40.0)	37.9 (5.1), 37.0 (34.0-42.0)
White race (%)	96.0	95.2	94.5	94.9	95.1	95.9	95.7	94.5
Current smoker (%)	10.4	10.9	11.2	11.8	14.8	10.1	8.3	10.6
Body mass index	25.0 (5.3), 23.5 (21.3-27.3)	25.1 (5.6), 23.6 (21.3-27.5)	26.6 (6.9), 24.6 (21.6-29.9)	28.2 (7.8), 25.8 (22.3-32.3)	24.8 (5.3), 23.5 (21.3-27.4)	25.0 (5.4), 23.6 (21.3-27.4)	26.1 (6.4), 24.0 (21.4-28.5)	27.9 (7.7), 25.6 (22.2-31.7)
Physical activity (h/wk)	2.7 (3.8), 1.4 (0.3-3.5)	2.6 (3.7), 1.3 (0.2-3.3)	2.5 (3.8), 1.3 (0.2-3.2)	2.5 (4.0), 1.1 (0.1-3.1)	2.7 (4.0), 1.3 (0.3-3.5)	2.6 (3.8), 1.4 (0.3-3.5)	2.5 (3.6), 1.3 (0.3-3.2)	2.4 (3.6), 1.1 (0.2-3.1)
Hypertension (%)	6.2	7.2	11.1	13.2	7.1	6.5	8.3	12.1
High blood cholesterol (%)	14.9	16.6	20.0	23.9	15.4	15.3	18.8	23.1
Family history:								
Diabetes (%)	15.8	16.7	17.5	19.4	16.4	16.0	16.8	18.6
Myocardial infarction (%)	13.4	13.7	14.1	14.8	14.3	13.3	14.3	14.2
Stroke (%)	11.2	11.5	12.1	12.2	11.7	11.3	11.3	12.4
Alcohol consumption (g/d)	3.6 (6.8), 0.9 (0-4.4)	3.2 (6.3), 0.9 (0-3.7)	2.9 (6.4), 0.9 (0-2.9)	2.8 (6.3), 0 (0-2.8)	3.3 (6.2), 0.9 (0-3.9)	3.6 (6.8), 0.9 (0-4.3)	3.0 (5.9), 0.9 (0-3.3)	2.8 (6.3), 0.9 (0-2.8)
Total calories (kcal)	1820 (550), 1760 (1410-2160)	1830 (560), 1760 (1420-2170)	1850 (560), 1800 (1440-2190)	1840 (580), 1780 (1420-2220)	1800 (550), 1730 (1390-2130)	1820 (550), 1760 (1420-2170)	1850 (560), 1810 (1450-2190)	1870 (570), 1800 (1440-2230)
AHEI-2010 score	44.9 (10.1), 44.5 (37.8-51.6)	44.3 (10.1), 43.9 (37.4-50.9)	44.0 (10.0), 43.7 (37.0-50.7)	43.7 (10.5), 42.7 (36.5-50.3)	44.6 (10.2), 44.6 (37.8-51.6)	44.7 (10.1), 44.3 (37.7-51.3)	44.4 (10.2), 43.7 (37.3-50.8)	43.9 (10.3), 43.3 (36.7-50.6)
Parity	1.7 (1.2), 2.0 (1.0-3.0)	1.8 (1.2), 2.0 (1.0-3.0)	1.6 (1.2), 2.0 (1.0-2.0)	1.6 (1.2), 2.0 (0-2.0)	1.7 (1.2), 2.0 (1.0-2.0)	1.7 (1.2), 2.0 (1.0-3.0)	1.8 (1.2), 2.0 (1.0-3.0)	1.6 (1.3), 2.0 (1.0-2.0)
Hirsutism (%)	1.8	2.8	4.9	8.4	2.1	2.0	4.2	8.0
Phobic anxiety symptom scores ≥3 (%)	23.9	27.6	28.8	29.2	27.4	24.7	26.5	27.7
Endometriosis (%)	4.5	4.5	5.4	5.9	5.1	4.6	4.0	4.2
Uterine fibroids (%)	7.8	8.3	9.6	10.0	9.0	7.9	7.8	8.5
Aspirin use (%)	8.3	8.7	9.3	9.6	9.0	8.3	9.0	8.9

AHEI-2010=alternative healthy eating index 2010.
1 kcal=4.18 kJ.
*Medians (interquartile ranges) are not standardized to the age distribution of the study population.
†Age standardized characteristics of oral contraceptive users (n=9767) are not shown.
‡Not adjusted for age.

fibroids (10.0% *v* 7.8%), as well as a higher prevalence of family history of diabetes (19.4% *v* 15.8%). Similar results were observed among women who reported that their usual cycle length was 40 days or more or too irregular to estimate compared with women who had a normal cycle length of between 26 and 31 days (table 1). In addition, smoking was more common among women who reported a usual cycle length of 25 days or less than among women reporting a normal cycle length (14.8% *v* 10.1%).

During 1 879 769 person years of follow-up, 1975 deaths were documented before age 70 years, including 894 from cancer and 172 from cardiovascular disease. The crude cumulative incidence of premature mortality was higher among women who experienced irregular or long menstrual cycles than those with regular or short cycles (supplemental fig 1). Multivariable Cox models further showed a greater risk of premature mortality across categories of decreasing menstrual cycle regularity in all age ranges (fig 1). These associations were substantially unchanged after additional adjustment for time varying dietary and lifestyle factors (fig 1). In the fully adjusted models, women who reported always having irregular menstrual cycles or no periods between the ages of 14 and 17 years, 18 and 22 years, and 29 and 46 years had hazard ratios for premature death during follow-up of 1.18 (95% confidence interval 1.02 to 1.37), 1.37 (1.09 to 1.73), and 1.39 (1.14 to 1.70), respectively, compared with women reporting a very regular menstrual cycle in the same age range. A similar pattern was found across categories of increasing cycle length at the ages of 18-22 years and 29-46 years (fig 1). In the fully adjusted models, women who reported a usual cycle length of 40 days or more or too irregular to estimate between the ages of 18 and 22 years and 29 and 46 years had hazard ratios for premature death during follow-up of 1.34 (1.06 to 1.69) and 1.40 (1.17 to 1.68), respectively, compared with women reporting a cycle length of 26-31 days in the same age range. When the effect of changes in menstrual cycle patterns across the reproductive lifespan was tested, the risk of premature mortality was strongest among women who consistently reported long or irregular cycles (table 2).

Women who used oral contraceptives between the ages of 14 and 17 years were also more likely to die prematurely than women who reported very regular menstrual cycles during this age range (fig 1). Oral

Menstrual cycle regularity and length	Deaths/ person years	Crude incidence/ 1000 person years	Multivariable models* Hazard ratio (95% CI)	Multivariable models* Hazard ratio (95% CI)	Models adjusted for lifestyle factors† Hazard ratio (95% CI)	Models adjusted for lifestyle factors† Hazard ratio (95% CI)
Cycle regularity						
14-17 years						
Oral contraceptive use	190/172 391	1.10		1.30 (1.11 to 1.53)		1.19 (1.01 to 1.40)
Very regular	674/641 862	1.05		1.00		1.00
Regular	560/586 613	0.95		0.94 (0.84 to 1.06)		0.95 (0.85 to 1.06)
Usually irregular	287/264 550	1.08		1.10 (0.96 to 1.26)		1.10 (0.95 to 1.26)
Always irregular or no period	264/214 354	1.23		1.22 (1.06 to 1.41)		1.18 (1.02 to 1.37)
P for trend				0.006		0.02
18-22 years						
Oral contraceptive use	1222/1 150 886	1.06		1.10 (0.97 to 1.25)		1.05 (0.92 to 1.19)
Very regular	304/303 126	1.00		1.00		1.00
Regular	232/246 996	0.94		0.95 (0.80 to 1.13)		0.97 (0.82 to 1.15)
Usually irregular	119/107 126	1.11		1.17 (0.95 to 1.45)		1.18 (0.95 to 1.46)
Always irregular or no period	98/71 636	1.37		1.39 (1.11 to 1.75)		1.37 (1.09 to 1.73)
P for trend				0.004		0.005
29-46 years						
Oral contraceptive use	167/230 177	0.73		0.89 (0.75 to 1.05)		0.93 (0.78 to 1.10)
Very regular	1038/1 034 464	1.00		1.00		1.00
Regular	492/444 306	1.11		1.07 (0.96 to 1.19)		1.05 (0.94 to 1.17)
Usually irregular	172/107 632	1.60		1.41 (1.20 to 1.66)		1.35 (1.14 to 1.58)
Always irregular or no period	106/63 190	1.68		1.50 (1.22 to 1.83)		1.39 (1.14 to 1.70)
P for trend				<0.001		<0.001
Cycle length (days)						
18-22 years						
Oral contraceptive use	1222/1 150 886	1.06		1.09 (0.98 to 1.22)		1.03 (0.93 to 1.15)
≤25	72/64 115	1.12		1.03 (0.81 to 1.32)		1.03 (0.81 to 1.33)
26-31	476/471 549	1.01		1.00		1.00
32-39	122/129 612	0.94		1.02 (0.84 to 1.25)		1.03 (0.84 to 1.26)
≥40 or too irregular to estimate	83/63 608	1.30		1.37 (1.08 to 1.73)		1.34 (1.06 to 1.69)
P for trend				0.05		0.07
29-46 years						
Oral contraceptive use	167/230 177	0.73		0.87 (0.74 to 1.03)		0.91 (0.77 to 1.08)
≤25	340/277 378	1.23		1.03 (0.91 to 1.17)		0.99 (0.88 to 1.12)
26-31	1143/1 111 668	1.03		1.00		1.00
32-39	187/177 990	1.05		1.17 (1.00 to 1.37)		1.17 (1.00 to 1.37)
≥40 or too irregular to estimate	138/82 557	1.67		1.47 (1.23 to 1.76)		1.40 (1.17 to 1.68)
P for trend				0.002		0.002

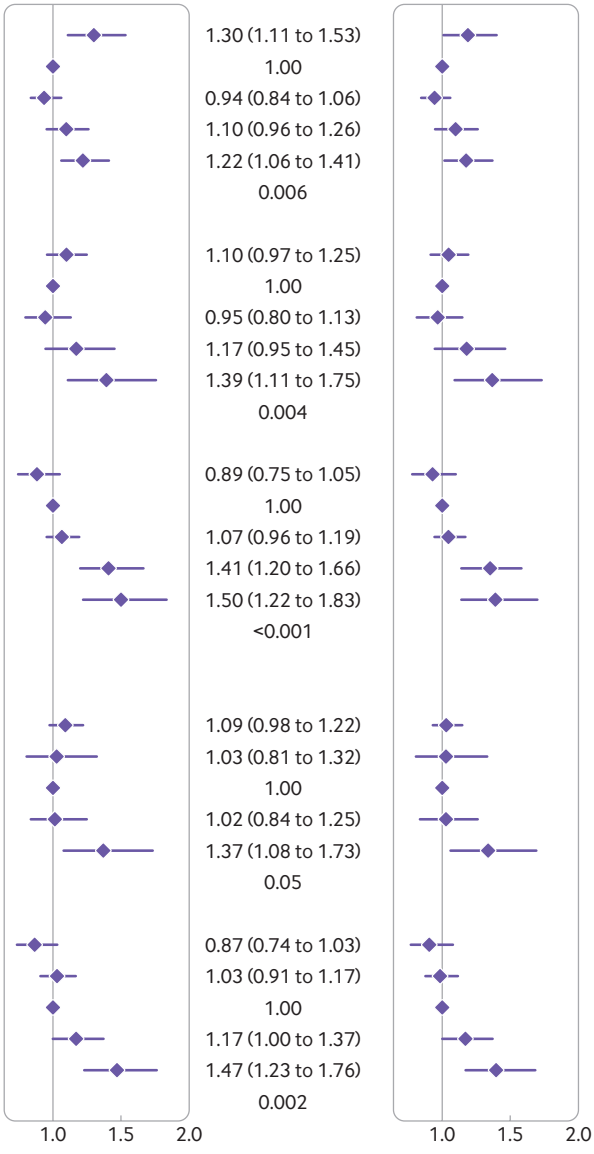

Fig 1 | Adjusted hazard ratios and 95% confidence intervals for risk of premature mortality (<70 years) according to menstrual cycle regularity (at ages 14-17 years, 18-22 years, and 18-48 years) and length (ages 18-22 years and 29-46 years) among 79 505 women (Nurses' Health Study II, 1993-2017). *Multivariable models were adjusted for age (continuous); menopausal status (premenopausal, never, past, or current menopausal hormone use); age at menarche (≤10, 11, 12, 13, or ≥14 years); race (white or other); family history of myocardial infarction, stroke, or diabetes (yes or no); baseline hypertension or high blood cholesterol level (yes or no); and updated parity (0, 1, or ≥2). †Multivariable models were further adjusted for updated alcohol consumption (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30 g/day), body mass index (<23, 23-24.9, 25-29.9, 30-34.9, or ≥35), physical activity (0, 0.1-0.9, 1.0-3.4, 3.5-5.9, or ≥6 hours/week), smoking consumption (never smoker, former smoker, current smoker: 1-14, 15-24, or ≥25 cigarettes/day), and fifths of alternative healthy eating index 2010 score. P values for trend were calculated across the categories of menstrual cycle regularity or length, excluding women who used oral contraceptives

contraceptive use at the ages of 18-22 years or 29-46 years, however, was not associated with premature mortality. When women were cross classified according to menstrual cycle length and regularity at ages of 18-22 years and 29-46 years, no evidence was found for an interaction between cycle regularity and length in relation to premature mortality (supplemental table 3).

Analyses of cause specific premature mortality showed that the higher risk of premature mortality among oral contraceptive users during adolescence was restricted to cancer related deaths (table 3). Women who reported irregular menstrual cycles at ages 14-17 years or 18-22 years had a higher risk of cancer mortality but no increased risk of premature

mortality due to cardiovascular disease or other causes (table 3). Among women who reported irregular cycles at ages 29-46 years, the risk of premature mortality was slightly higher for cardiovascular disease mortality than for cancer mortality or death from other causes (table 3). A similar pattern was observed for menstrual cycle length (supplemental table 4). In analyses with cause of death disaggregated and analyzed separately for diagnostic categories with at least 100 deaths attributed, irregular or long menstrual cycles were associated with a greater risk of death due to malignant neoplasm of digestive organs and peritoneum and external causes (eg, accidents, injury, or poisoning; supplemental table 5).

The associations of irregular and long cycles with premature mortality did not seem to be modified by diet quality, BMI, physical activity levels, phobic anxiety symptom scores, depression, parity, or age at menopause. However, the association of long cycles with premature mortality was slightly stronger among current smokers (table 4). Sensitivity analyses showed that findings remained unchanged when women older than 40 years in 1993 or those with a diagnosis of type 2 diabetes during follow-up were excluded, when premature mortality was redefined as death before age 65 years, and when only baseline values of all covariates were used (supplemental table 6). The findings were also robust after excluding women who reported hirsutism, endometriosis, or uterine fibroids, or menstrual cycles of more than 50 days or too irregular to estimate or no periods; and when including those who provided partial information on menstrual cycle characteristics during adolescence or adulthood (supplemental table 7).

Discussion

In this large prospective study, we found that women who experienced irregular or long menstrual cycles in adolescence and throughout adulthood were more likely to die before age 70 years than women reporting regular or short cycles. These associations were stronger for irregular and long cycles continuously present in adolescence and adulthood. Moreover, although irregular and long cycles during adulthood were associated with a higher risk of death due to cancer and cardiovascular disease, these relations were stronger for cardiovascular disease mortality. Our findings also suggest that the increased risk of premature mortality associated with long cycle length was slightly stronger among women who currently smoked.

Comparison with other studies

Irregular and long menstrual cycles have been associated with a greater risk of coronary heart disease, cancer, mental health problems, and multiple other common chronic conditions.[8-10] PCOS, a common endocrinologic disorder characterized by androgen excess and ovarian dysfunction,[32] has also been associated with a higher risk of type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease, coagulation disorders, and possibly cardiovascular disease.[33 34] Although these data collectively indicate that menstrual cycle dysfunction might accelerate the risk of premature mortality, few population based studies have explored the association between menstrual cycle characteristics and mortality. In support of our findings, a prospective US cohort of 15 005 mothers followed over 40 years[15] reported a higher risk of death due to cardiovascular disease among women with an irregular menstrual cycle. In the same cohort, another study found that women with irregular menstrual cycles had a greater risk of death due to ovarian cancer.[8] The association between PCOS and all cause mortality is less consistent,[35] which could in part be related to differences in study

Table 2 | Adjusted hazard ratios and 95% confidence intervals for risk of premature mortality (<70 years) according to changes in menstrual cycle characteristics (Nurses' Health Study II, 1993-2017)

Changes in menstrual cycle characteristics	Deaths/person years	Hazard ratio (95% CI)	
		Multivariable models*	Further adjusted for lifestyle factors†
Change in regularity from ages 14-17 years to 29-46 years:			
Regularity maintained	1032/1 024 460	1.00 (reference)	1.00 (reference)
Regular to irregular	105/63 816	1.22 (1.00 to 1.50)	1.15 (0.93 to 1.40)
Irregular to regular	361/327 749	1.10 (0.98 to 1.25)	1.08 (0.96 to 1.22)
Irregularity maintained	143/89 451	1.64 (1.38 to 1.96)	1.57 (1.32 to 1.88)
Change in regularity from ages 18-22 years to 29-46 years:			
Regularity maintained	465/469 499	1.00 (reference)	1.00 (reference)
Regular to irregular	37/24 609	1.05 (0.75 to 1.46)	0.98 (0.70 to 1.37)
Irregular to regular	133/115 847	1.16 (0.96 to 1.41)	1.15 (0.94 to 1.39)
Irregularity maintained	66/40 630	1.78 (1.37 to 2.30)	1.71 (1.32 to 2.22)
Change in length from ages 18-22 years to 29-46 years:			
Maintained <32 days	465/442 301	1.00 (reference)	1.00 (reference)
<32 to ≥32 days	44/36 327	1.03 (0.76 to 1.41)	1.00 (0.73 to 1.36)
≥32 to <32 days	109/101 055	1.02 (0.82 to 1.25)	1.01 (0.82 to 1.24)
Maintained ≥32 days	83/70 902	1.41 (1.12 to 1.79)	1.42 (1.12 to 1.80)

*Multivariable models were adjusted for age (continuous); menopausal status (premenopausal, never, past, or current menopausal hormone use); age at menarche (≤10, 11, 12, 13, or ≥14 years); race (white or other); family history of myocardial infarction, stroke, or diabetes (yes or no); baseline hypertension or high blood cholesterol level (yes or no); and updated parity (0, 1, or ≥2).
†Multivariable models were further adjusted for updated alcohol consumption (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30 g/day), body mass index (<23, 23-24.9, 25-29.9, 30-34.9, or ≥35), physical activity (0, 0.1-0.9, 1.0-3.4, 3.5-5.9, or ≥6 hours/week), smoking consumption (never smoker, former smoker, current smoker: 1-14, 15-24, or ≥25 cigarettes/day), and fifths of alternative healthy eating index 2010 score.

design, sample size, and diverging definitions of PCOS across studies. In our present study, the association of irregular and long menstrual cycles with higher risk of premature mortality persisted when we excluded women with hirsutism, endometriosis, or uterine fibroids, indicating that these relations were not solely driven by PCOS or other common gynaecologic conditions.

Underlying mechanisms of the observed relations

The mechanisms underlying the associations of irregular and long menstrual cycles with premature mortality are likely related to the disrupted hormonal environment. Irregular and long menstrual cycles are strong predictors of hyperinsulinemia, which synergize with pituitary gonadotropins to stimulate androgen production in ovarian theca cells, further exacerbating insulin resistance.[12] Hyperinsulinemia also inhibits sex hormone binding globulin production in women, resulting in higher levels of free testosterone.[12] This hormonal milieu has been hypothesised to play a critical role in the cause of cancer,[36] diabetes,[37] and cardiovascular disease.[38] Furthermore, results from small but rigorously phenotyped clinical cohorts strongly suggest that PCOS is related to markers of metabolic and cardiovascular risk,[13 14] including greater insulin resistance, dyslipidemia, coronary calcium deposition, carotid intima-media thickness, and prevalence of metabolic syndrome. Collectively, these metabolic disarrangements could contribute not only to an increased risk of cardiometabolic diseases and some cancers but also eventually to premature mortality.[39 40]

Unexpectedly, we found an increased risk of premature mortality among women who used oral contraceptives in adolescence (age 14-17 years), which might represent confounding by indication. It could be that a higher proportion of women who self-reported oral contraceptive use at these younger ages are comprised of women who used oral contraceptives to manage symptoms and signs of PCOS (acne, hirsutism, irregular menses) and other medical conditions (eg, endometriosis),[29 41] rather than to prevent pregnancy. These indications for oral contraceptive use (ie, PCOS and endometriosis) have been linked to higher risks of cardiovascular disease and some cancers,[16 42] which might explain our observed association at these younger ages. As the proportion of women using oral contraceptives solely for contraception increases from adolescence into adulthood, using oral contraceptives likely becomes a weaker proxy for severe presentations of PCOS or endometriosis related pelvic pain resulting in no association, as seen in our study. However, we cannot rule out the possibility that early use of oral contraceptives might result in an increased risk of premature mortality related to the drug itself.[43]

We found a joint effect of long cycle length and smoking on mortality, suggesting that menstrual cycle dysfunction might interact synergistically with smoking to further increase the risk of premature mortality. This is not surprising given the well documented protective effect of abstinence from smoking on premature mortality.[44 45] This interaction is also biologically plausible. Women with long and irregular cycles already have an adverse metabolic,

Table 3 | Adjusted hazard ratios and 95% confidence intervals for risk of cause specific premature mortality (<70 years) according to menstrual cycle pattern at ages of 14-17 years, 18-22 years, and 29-46 years among 79 505 women (Nurses' Health Study II, 1993-2017)*

Menstrual cycle pattern and oral contraceptive use by age group	Cancer		Cardiovascular disease		Other causes	
	Deaths/person years	Hazard ratio (95% CI)	Deaths/person years	Hazard ratio (95% CI)	Deaths/person years	Hazard ratio (95% CI)
14-17 years						
Oral contraceptive use	89/172 464	1.35 (1.06 to 1.72)	18/172 535	1.21 (0.71 to 2.07)	83/172 488	1.05 (0.82 to 1.34)
Cycle pattern:						
Very regular	293/642 188	1.00 (reference)	64/642 415	1.00 (reference)	317/642 197	1.00 (reference)
Regular	266/586 866	1.04 (0.88 to 1.23)	39/587 077	0.71 (0.48 to 1.06)	255/586 906	0.91 (0.77 to 1.08)
Irregular or no period	246/479 185	1.19 (1.00 to 1.41)	51/479 359	1.11 (0.76 to1.61)	254/479 182	1.09 (0.92 to 1.29)
P for trend†		0.06		0.70		0.40
18-22 years						
Oral contraceptive use	546/1 151 478	1.08 (0.89 to 1.31)	108/1 151 900	0.95 (0.63 to 1.45)	568/1 151 511	1.04 (0.86 to 1.25)
Cycle pattern:						
Very regular	134/303 266	1.00 (reference)	29/303 368	1.00 (reference)	141/303 276	1.00 (reference)
Regular	117/247 095	1.10 (0.86 to 1.41)	14/247 189	0.63 (0.33 to 1.19)	101/247 120	0.91 (0.70 to 1.17)
Irregular or no period	97/178 864	1.33 (1.02 to 1.73)	21/178 930	1.24 (0.70 to 2.18)	99/178 865	1.20 (0.93 to 1.55)
P for trend†		0.05		0.66		0.19
29-46 years						
Oral contraceptive use	64/230 269	0.78 (0.60 to 1.02)	8/230 318	0.62 (0.29 to 1.31)	95/230 241	1.11 (0.88 to 1.40)
Cycle pattern:						
Very regular	497/1 034 926	1.00 (reference)	80/1 035 315	1.00 (reference)	461/1 035 002	1.00 (reference)
Regular	213/444 549	0.96 (0.82 to 1.13)	54/444 701	1.45 (1.02 to 2.05)	225/444 561	1.08 (0.92 to 1.26)
Irregular or no period	120/170 958	1.33 (1.09 to 1.63)	30/171 052	1.59 (1.04 to 2.45)	128/170 968	1.35 (1.10 to 1.65)
P for trend†		0.05		0.01		0.006

*Multivariable models were adjusted for age (continuous); menopausal status (premenopausal, never, past, or current menopausal hormone use); age at menarche (≤10, 11, 12, 13, or ≥14 years); age at menarche (≤10, 11, 12, 13, or ≥14 years); race (white or other); family history of myocardial infarction, stroke, or diabetes (yes or no); baseline hypertension or high blood cholesterol level (yes or no); as well as updated parity (0, 1, or ≥2), alcohol consumption (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30 g/day), body mass index (<23, 23-24.9, 25-29.9, 30-34.9, or ≥35), physical activity (0, 0.1-0.9, 1.0-3.4, 3.5-5.9, or ≥6 hours/week), smoking status (never smoker, former smoker, current smoker: 1-14, 15-24, or ≥25 cigarettes/day), and fifths of alternative healthy eating index 2010 score.
†P values for trend were calculated across the categories of menstrual cycle regularity, excluding women who were oral contraceptive users.

Table 4 | Adjusted hazard ratios and 95% confidence intervals for the risk of premature mortality (<70 years) according to irregular and long menstrual cycles at ages of 29-46 years, stratified by lifestyle factors, mental health status, and reproductive characteristics (Nurses' Health Study II, 1993-2017)*

	Cycle regularity		Cycle length (days)	
Stratified factors	Very regular or regular	Irregular or no period	<32	≥32
Diet quality:				
Top 40% (n=594 deaths)	1.00 (reference)	1.44 (1.14 to 1.81)	1.00 (reference)	1.20 (0.96 to 1.49)
Bottom 60% (n=1214 deaths)	1.00 (reference)	1.30 (1.11 to 1.52)	1.00 (reference)	1.29 (1.12 to 1.49)
P for multiplicative interaction	0.34		0.63	
RERI (95% CI)	−0.15 (−0.54 to 0.23)		0.10 (−0.22 to 0.42)	
P for additive interaction	P=0.43		0.53	
Smoking status:				
Non-current smokers (n=1501 deaths)	1.00 (reference)	1.28 (1.10 to 1.48)	1.00 (reference)	1.19 (1.04 to 1.36)
Current smokers (n=307 deaths)	1.00 (reference)	1.66 (1.24 to 2.23)	1.00 (reference)	1.71 (1.28 to 2.27)
P for multiplicative interaction	0.22		0.03	
RERI (95% CI)	0.70 (−0.04 to 1.44)		0.93 (0.18, 1.68)	
P for additive interaction	0.07		0.02	
Body mass index:				
<25 (n=700 deaths)	1.00 (reference)	1.39 (1.11 to 1.74)	1.00 (reference)	1.42 (1.17 to 1.74)
≥25 (n=1108 deaths)	1.00 (reference)	1.31 (1.12 to 1.54)	1.00 (reference)	1.16 (1.00 to 1.36)
P for multiplicative interaction	0.45		0.07	
RERI (95% CI)	−0.16 (−0.52 to 0.20)		−0.30 (−0.63, 0.02)	
P for additive interaction	0.38		0.07	
Physical activity:				
≥30 min/day (n=342 deaths)	1.00 (reference)	1.32 (0.96 to 1.82)	1.00 (reference)	1.32 (0.99 to 1.76)
<30 min/day (n=1466 deaths)	1.00 (reference)	1.36 (1.18 to 1.57)	1.00 (reference)	1.25 (1.10 to 1.44)
P for multiplicative interaction	0.97		0.47	
RERI (95% CI)	0.14 (−0.34 to 0.63)		−0.05 (−0.49 to 0.39)	
P for additive interaction	0.56		0.81	
Phobic anxiety symptom scores:				
<3 (n=1335 deaths)	1.00 (reference)	1.37 (1.18 to 1.60)	1.00 (reference)	1.23 (1.06 to 1.42)
≥3 (n=473 deaths)	1.00 (reference)	1.24 (0.97 to 1.59)	1.00 (reference)	1.35 (1.08 to 1.71)
P for multiplicative interaction	0.52		0.39	
RERI (95% CI)	−0.07 (−0.48 to 0.35)		0.22 (−0.17 to 0.61)	
P for additive interaction	P=0.76		0.26	
Depression:				
No (n=1346 deaths)	1.00 (reference)	1.30 (1.12 to 1.52)	1.00 (reference)	1.28 (1.11 to 1.47)
Yes (n=462 deaths)	1.00 (reference)	1.40 (1.09 to 1.79)	1.00 (reference)	1.21 (0.95 to 1.54)
P for multiplicative interaction	0.87		0.47	
RERI (95% CI)	0.13 (−0.31 to 0.58)		−0.07 (−0.47 to 0.32)	
P for additive interaction	P=0.56		0.72	
Parity:				
≤1 (n=770 deaths)	1.00 (reference)	1.49 (1.23 to 1.80)	1.00 (reference)	1.21 (1.00 to 1.46)
≥2 (n=1038 deaths)	1.00 (reference)	1.23 (1.03 to 1.47)	1.00 (reference)	1.31 (1.12 to 1.54)
P for multiplicative interaction	0.24		0.57	
RERI (95% CI)	0.40 (−0.02 to 0.82)		0.01 (−0.37 to 0.39)	
P for additive interaction	0.06		0.95	
Age at menopause:				
<45 years (n=725 deaths)	1.00 (reference)	1.21 (0.99 to 1.47)	1.00 (reference)	1.15 (0.96 to 1.38)
≥45 years (n=1083 deaths)	1.00 (reference)	1.42 (1.19 to 1.69)	1.00 (reference)	1.38 (1.17 to 1.63)
P for multiplicative interaction	0.59		0.29	
RERI (95% CI)	−0.11 (−0.44 to 0.22)		−0.17 (−0.46 to 0.12)	
P for additive interaction	0.50		0.25	

RERI=relative excess risk due to interaction.
*Multivariable models were adjusted for age (continuous); menopausal status (premenopausal, never, past, or current menopausal hormone use); age at menarche (≤10, 11, 12, 13, or ≥14 years); age at menarche (≤10, 11, 12, 13, or ≥14 years); race (white or other); family history of myocardial infarction, stroke, or diabetes (yes or no); baseline hypertension or high blood cholesterol level (yes or no); as well as updated parity (0, 1, or ≥2), alcohol consumption (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, or ≥30 g/day), body mass index (<23, 23-24.9, 25-29.9, 30-34.9, or ≥35), physical activity (0, 0.1-0.9, 1.0-3.4, 3.5-5.9, or ≥6 hours/week), smoking status (never smoker, former smoker, current smoker: 1-14, 15-24, or ≥25 cigarettes/day), and fifths of alternative healthy eating index 2010 score, excluding the stratifying variable.

cardiovascular, and inflammatory risk profile, which can be further exacerbated by smoking. This interaction, however, should be interpreted with caution given the marginal statistical significance of the tests. Interestingly, we did not find any convincing evidence of effect modification by dietary quality, BMI, physical activity, phobic anxiety symptom scores, depression, parity, and age at menopause, despite accumulating evidence consistently suggesting that these lifestyle, psychological, and reproductive factors are important determinants of premature mortality, probably by affecting the hormonal environment and metabolic conditions.[16 18 46]

Strengths and limitations of this study

Although several authors have documented the validity of self-report of menstrual cycle characteristics,[7 20 47] some misclassification is still expected, particularly for

recalled menstrual cycle characteristics at the ages of 14-17 years and 18-22 years. Since the cycle regularity question relied on the participant's interpretation of irregular, some exposure misclassification might also be present. In this case, however, the misclassification is likely non-differential for mortality, resulting in associations biased towards the null. We found that the risk of premature mortality was higher among women who reported long or irregular cycles later in life, which might partly be explained by diminished recall accuracy for earlier age ranges. Second, menstrual cycle characteristics in mid-adulthood were only assessed at one time point, which could misclassify women who experienced menstrual irregularity from early menopause. Our findings were, however, unchanged when we excluded women older than 40 years in 1993. Third, a large proportion of participants (26%) did not fully report their menstrual cycle characteristics across the entire reproductive lifespan, which might have resulted in selection bias. The baseline characteristics were, however, similar between included and excluded women for incomplete cycle characteristics data. Additionally, when we included women in the analyses who provided partial information on cycle characteristics (<0.1%, <3%, and <23% who had missing data at ages 14-17 years, 18-22 years, and 29-46 years, respectively), most of the findings remained materially unchanged. Fourth, despite our control for multiple potential confounders, we cannot rule out the possibility of residual confounding. Fifth, our study participants were mostly white women and shared a common profession and educational attainment, which might limit the generalizability of our findings. Sixth, the cause of death could not be determined in a high proportion of women who died during follow-up (15%), which hampered our ability to generate precise estimates for disease specific mortality.

Strengths of the study include its prospective design with a high follow-up rate, enough premature deaths, and the availability of information on various updated covariates. Additionally, the availability of menstrual cycle characteristics at three different points across the reproductive lifespan enabled us to detect subtle association patterns likely reflecting how the same phenotype might represent an expected physiological transition in one point in life and be a proxy for underlying metabolic disease in another. Importantly, as it is not possible to randomize women to different menstrual cycle characteristics, long term observational studies with thorough control for confounding, such as this one, are and will be the best available evidence for understanding the long term health consequences of menstrual cycle characteristics. Additional research, expanding on these findings, as well as research aimed at understanding risk factors for long and irregular cycles, will be important to consolidate the knowledge of how menstrual cycle characteristics impact women's health and point towards potential risk management interventions.

Conclusions and policy implications

We found that long and irregular menstrual cycles are associated with an increased risk of death before age 70 years. This relation was independent of BMI and was present in women without other signs of PCOS, suggesting that menstrual cycle characteristics might serve as an independent proxy for overall health status in women of reproductive age. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have emphasized the need for considering menstrual cycle as a vital sign of general health in adolescents.[6] The results of this study suggest that these considerations are not exclusive to adolescence and might span women's entire reproductive life. Our study found that irregular and long menstrual cycles, whether in adolescence or adulthood, are associated with a greater risk of premature mortality, which is slightly stronger among women who currently smoke. These relations were also stronger when long and irregular cycles were consistently present during adolescence and throughout adulthood. Our results emphasize the need for primary care providers to include menstrual cycle characteristics throughout the reproductive years as additional vital signs in assessing women's general health status and point to potential lifestyle interventions to manage risk among women with menstrual cycle disorders that might have long term adverse health consequences.

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Data sharing: Data described in the manuscript, code book, and analytic code will not be made publicly available. Further information including the procedures for obtaining and accessing data from the Nurses' Health Studies II is described at www.nurseshealthstudy.org/researchers (email nhsaccess@channing.harvard.edu).

The senior author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary information: supplemental tables 1-7 and figure 1