Supplemental Online Content

Wang Z, Jukic AMZ, Baird DD, et al. Irregular cycles, ovulatory disorders, and cardiometabolic conditions in a US-based digital cohort. *JAMA Netw Open*. 2024;7(5):e249657. doi:10.1001/jamanetworkopen.2024.9657

eMethods.

eReference

eTable 1. Survey Questions Relevant to Exposure Variables in This Study

eTable 2. Baseline Characteristics in the Full Study Population for This Analysis vs Participants Who Responded to the Hormonal Symptoms Survey

eTable 3. Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions

eTable 4. Associations Between Having Irregular Cycles at Enrollment and Prevalent Cardiometabolic Conditions Among Participants Who Responded to the Hormonal Symptoms Survey

eTable 5. Covariate-Adjusted Associations of PCOS With Prevalent Cardiometabolic Conditions, Tests for Effect Modification by BMI on the Additive Scale (With BMI <25 as the Referent Group)

eTable 6. Covariate-Adjusted Associations Between Irregular Cycles and Prevalent Cardiometabolic Conditions Among Those Without PCOS, Tests for Effect Modification by BMI on the Additive Scale (With BMI <25 as the Referent Group)

eTable 7. Covariate-Adjusted Associations of PCOS With Prevalent Cardiometabolic Conditions, Tests for Effect Modification by Physical Activity on the Additive Scale (Low vs High)

eTable 8. Covariate-Adjusted Associations Between Irregular Cycles and Prevalent Cardiometabolic Conditions Among Those Without PCOS, Tests for Effect Modification by Physical Activity on the Additive Scale (Low vs High)

eTable 9. Age at Diagnosis for Each Cardiometabolic Condition, Overall and Stratified by PCOS Diagnosis or Time to Regularity, Among a Subset of Participants Who Provided Data of Age at Diagnosis

eTable 10. Covariate-Adjusted Associations of Combined Information on Cycle Irregularity, PCOS, and BMI With Prevalent Cardiometabolic Conditions Among the Subset of Participants Who Responded to the Hormonal Symptoms Survey (n = 25 399)

eTable 11. Covariate-Adjusted Associations of Categorical Time to Cycle Regularity With Prevalent Cardiometabolic Conditions

eTable 12. Covariate-Adjusted Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions, Comparing Results From the Main Analysis to Sensitivity Analyses That Removed 409 Individuals With Potentially Misclassified/Inaccurate Time to Regularity

eTable 13. Associations of Having PCOS With Prevalent Cardiometabolic Conditions, Adjusted for Covariates, Comparing Results From Complete Case Analyses to Pooled Results From Multiple Imputations

eTable 14. Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions, Adjusted for Covariates, Comparing Results From Complete Cases Analyses to Pooled Results From Multiple Imputation

eTable 15. Associations of Having Irregular Cycles With Prevalent Cardiometabolic Conditions Among 25 115 Participants Who Responded to the Relevant Survey Question for Irregular Cycles, Adjusted for Covariates, Comparing Results From Complete Case Analyses to Pooled Results From Multiple Imputation

eTable 16. Associations of Having Irregular Cycles With Prevalent Cardiometabolic Conditions Among 25 115 Participants Who Responded to the Relevant Survey Question for Irregular Cycles, Adjusted for Covariates, Comparing Results From Main Analyses to Sensitivity Analyses Excluding Those With Possible PCOS

eTable 17. Associations of Having PCOS With Prevalent Cardiometabolic Conditions, Comparing Results From Main Analyses Adjusted for Gravidity to Results Adjusted for Parity

eTable 18. Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions, Comparing Results From Main Analyses Adjusted for Gravidity to Results Adjusted for Parity

eTable 19. Associations of Having Irregular Cycles With Prevalent Cardiometabolic Conditions Among 25 115 Participants Who Responded to the Relevant Survey Question for Irregular Cycles, Comparing Results From Main Analyses Adjusted for Gravidity to Results Adjusted for Parity

eFigure 1. Flowchart of Participants in This Study

eFigure 2. Conceptual Model for the Study Questions

eFigure 3. Associations of 1-Year Increase in Time to Cycle Regularity With Prevalent Cardiometabolic Conditions Among a Subset of 37 259 Participants Who Have Reached Cycle Regularity at Enrollment (Not Due to Hormone Use)

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

We defined **metabolic syndrome** using the WHO 1998 criteria with modification based on data availability:

> Having insulin resistance (diagnosed prediabetes/type 2 diabetes); AND
> Having at least two of (1) obesity (BMI ≥ 30 kg/m^2), (2) dyslipidemia (diagnosed high cholesterol), or (3) diagnosed hypertension.

We performed exploratory **secondary/sensitivity analyses**, and details of the Methods are described here as supplemental materials below.

First, for each of the cardiometabolic conditions, a subset of participants who had that condition at baseline further provided information on **age at diagnosis**. The survey questions on age at diagnosis were added at a later timepoint during the study, so not all participants provided this information. The proportion of participants who had a condition and further provided age at diagnosis (out of all participants who had that condition) ranged between 15% and 25% (depending on the condition). Within these subsets, we calculated the mean ± SD of age at diagnosis for each cardiometabolic condition, overall as well as further stratified by: (1) PCOS diagnosis (yes vs. no); and (2) Time to regularity (Prolonged vs. within 4 years since menarche). Due to the small number of participants (especially for the less common cardiovascular conditions) who provided age at diagnosis information, we were not able to adjust for covariates. Instead, for the stratified results, we tested for statistical significance using Kruskal-Wallis tests, where p-value < 0.05 were considered as having significantly different mean age at diagnosis.

Second, as **other forms of the time-to-regular-cycles variables**, we derived the following to use in sensitivity analyses for their associations with the cardiometabolic conditions: (1) Time to cycle regularity (in years): Among participants who reported reaching cycle regularity at enrollment, not due to hormone use (N = 37,259), we assigned the following values to each category of response: “Less than 1 year” = 0.5 year; “1-2 years” = 1.5 years; “3-4 years” = 3.5 years; “more than 5 years” = 5.5 years. (2) Time to cycle regularity (categorical): we grouped time to cycle regularity as 2 years or less (referent group), 3-4 years, 5 or more years, not yet regular, or regular after using hormones.

Third, we evaluated the independent associations between each of cycle irregularity, PCOS, and BMI while controlling for others, and assessed their associations with the cardiometabolic conditions. With this combined information, we were able to evaluate another ovulatory disorder - possible hypothalamic amenorrhea (HA), in an exploratory way based on the available data we have. Given we do not have hormonal lab results, we used self-reported data to explore **possible HA** based on the following criteria:

(1) having irregular cycles (among those who completed the Hormone Symptom Survey), AND

(2) without PCOS, AND

(3) with BMI < 21 kg/m^2, AND

(4) did not have other endocrinopathies that may also lead to irregular cycles, including hyperprolactinemia, hyperthyroidism, hypothyroidism and early menopause.

The cutoff for BMI was based on prior literature on the optimal BMI threshold to differentiate HA from PCOS.[1]

Fourth, we performed sensitivity analysis adjusted for parity instead of gravidity.

Fifth, we performed sensitivity analysis where we removed a total of N = 409 individuals who may have the potential of a misclassified or inaccurate self-reported time to regularity. Specifically, these 409 individuals include: 1) N = 202 individuals whose age difference between enrollment and self-reported age at menarche was less than 5 years (i.e., making them ineligible to select certain category/categories for the time to regularity survey question); and 2) N = 207 individuals with a self-reported age at menarche of “16 years old or older” and age at enrollment ≤ 25 years old (i.e., these participants might also be at risk of misclassifying time to regularity if the difference between age at enrollment and menarche was less than 5 years). In the sensitivity analysis, these 409 individuals were removed from the covariate-adjusted regression models for the association between prolonged time to regularity and cardiometabolic conditions, and we compared the effect estimates to the estimates from the main analysis.

Sixth, we performed sensitivity analysis using multiple imputation by chained equations (MICE) with 50 imputations to impute the missing values (exposures, covariates, outcomes) instead of using a complete

case approach for all our main analyses. One exception is that irregular cycles information is only available among a subset of 25,115 participants who completed the Hormonal Symptoms Survey. To ensure the accuracy of the estimates for the associations between this variable and the cardiometabolic conditions, pooled regressions estimate from the 50 imputed datasets remains restricted to this subset of 25,115 participants. Results from MICE are pooled with appropriate effect estimates and 95% CIs calculated.

Lastly, for the association between irregular cycles and cardiometabolic conditions among those without PCOS, we excluded 1252 participants who reported both irregular cycles AND signs of hirsutism (including being trouble by growth of thick, coarse hair on the body, reported “several” or “a lot” for hair growth on the upper lip, or reported “several” or “a lot” for hair growth on the chin) from the participants without a self-reported PCOS diagnosis.

eReference

1. Phylactou M, Clarke SA, Patel B, Baggaley C, Jayasena CN, Kelsey TW, Comninos AN, Dhillo WS, Abbara A. Clinical and biochemical discriminants between functional hypothalamic amenorrhoea (FHA) and polycystic ovary syndrome (PCOS). *Clinical Endocrinology*. 2021;95(2):239–252.

eTable1. Survey Questions Relevant to Exposure Variables in This Study

Survey	Questions	Answer choices	Conditions
Medical History Survey	Gynecologic Conditions - Have you ever been diagnosed with any of the following by a doctor or other care provider? Select all that apply.	Abnormal Pap smear Adenomyosis Endometriosis Fibroids Infertility **Polycystic ovarian syndrome (PCOS)** Polyps (Uterus or cervix) Premenstrual syndrome (PMS) or Premenstrual dysphoric disorder (PMDD) None of the above I prefer not to answer	Given to all participants
Reproductive History Survey	At what age did you have your first menstrual period? It's okay to estimate.	7 years old or younger 8 years old 9 years old 10 years old 11 years old 12 years old 13 years old 14 years old 15 years old 16 years old or older I don't know I prefer not to answer	Given to all participants
	After your first menstrual cycle, how long did it take for your cycle to become regular? In other words, when could you start predicting the beginning of your next menstrual cycle?	**Less than 1 year** **1-2 years** **3-4 years** **More than 5 years** **After using hormones (e.g., birth control pills)** **They're not yet regular** I don't know I prefer not to answer	
Hormonal Symptoms Survey	Are you troubled by any of the following symptoms?	Being over your ideal weight **Growth of thick, course, and dark hair on parts of your body** Hair loss on your head Acne	Survey distributed since November 2021 & Given to all participants

	SELECT ALL THAT APPLY	Nipple discharge **Unpredictable periods** Difficulty detecting ovulation None of the above I don't know I prefer not to answer	
	How much coarse or thick hair do you have on your upper lip? (with associated images) SELECT ONE	○ None ○ A few ○ Several ○ A lot ○ I prefer not to answer 	
	How much coarse or thick hair do you have on your chin? (with associated images) SELECT ONE	○ None ○ A few ○ Several ○ A lot ○ I prefer not to answer 	

eTable 2. Baseline Characteristics in the Full Study Population for This Analysis vs Participants Who Responded to the Hormonal Symptoms Survey

		Among participants who responded to the Hormonal Symptoms Survey			
Characteristics	**Full study population**	***Overall***	***No PCOS & no irregular cycles***	***No PCOS & with irregular cycles***	***PCOS***
N	***60789***	***25399***	***16459 (64.8%)***	***4754 (18.7%)***	***2925 (11.5%)***
Age at enrollment (years):					
Mean ± SD	34.5 ± 11.1	35.8 ± 11.3	36.7 ± 11.8	33.1 ± 10.1	35.1 ± 9.3
Median (IQR)	33 (26 – 41)	34 (27 – 43)	35 (28 – 44)	32 (24 – 41)	34 (28 – 41)
Race/ethnicity, n (%):					
Non-Hispanic white	43404 (71.4)	18905 (74.4)	12364 (75.1)	3512 (73.9)	2157 (73.7)
Non-Hispanic Black	3294 (5.4)	1240 (4.9)	839 (5.1)	197 (4.1)	118 (4.0)
Asian	1942 (3.2)	718 (2.8)	461 (2.8)	151 (3.2)	75 (2.6)
Hispanic	4411 (7.3)	1593 (6.3)	1008 (6.1)	290 (6.1)	199 (6.8)
More than one	6131 (10.1)	2378 (9.4)	1434 (8.7)	502 (10.6)	308 (10.5)
Other	1602 (2.6)	565 (2.2)	353 (2.1)	102 (2.1)	68 (2.3)
Socioeconomic status, n (%):					
0-3	16284 (26.8)	6322 (24.9)	3619 (22.0)	1503 (31.6)	887 (30.3)
4-5	25590 (42.1)	10735 (42.3)	7036 (42.7)	1912 (40.2)	1293 (44.2)
6-9	18596 (30.6)	8238 (32.4)	5752 (34.9)	1321 (27.8)	731 (25.0)
Missing	319 (0.5)	104 (0.4)	52 (0.3)	18 (0.4)	14 (0.5)
Employment status, n (%):					
Employed	43752 (72.0)	18741 (73.8)	12255 (74.5)	3361 (70.7)	2200 (75.2)
Unemployed	3382 (5.6)	1161 (4.6)	716 (4.4)	259 (5.4)	116 (4.0)
Other	13090 (21.5)	5322 (21.0)	3402 (20.7)	1100 (23.1)	587 (20.1)
Missing	565 (0.9)	175 (0.7)	86 (0.5)	34 (0.7)	22 (0.8)
Education level, n (%):					
High school and below	9923 (16.3)	3578 (14.1)	2125 (12.9)	895 (18.8)	366 (12.5)
Some college or college	37399 (61.5)	15530 (61.1)	9979 (60.6)	2915 (61.3)	1888 (64.5)
Graduate school	13023 (21.4)	6141 (24.2)	4275 (26.0)	913 (19.2)	662 (22.6)
Missing	444 (0.7)	150 (0.6)	80 (0.5)	31 (0.7)	11 (0.4)
Body mass index (categorical), n (%):					
Underweight (< 18.5 kg/m^2)	1590 (2.6)	619 (2.4)	370 (2.2)	181 (3.8)	35 (1.2)
Healthy weight (18.5 to <25 kg/m^2)	20063 (33.0)	8348 (32.9)	5765 (35.0)	1631 (34.3)	495 (16.9)
Overweight (25 to <30 kg/m^2)	15033 (24.7)	6403 (25.2)	4416 (26.8)	1124 (23.6)	554 (18.9)
Obesity (30 kg/m^{2}or higher)	22555 (37.1)	9497 (37.3)	5607 (34.1)	1702 (35.8)	1787 (61.1)
Missing	1548 (2.5)	532 (2.1)	301 (1.8)	116 (2.4)	54 (1.8)
Age at menarche, n (%):					

11 or younger	17738 (29.2)	7601 (29.9)	4749 (28.9)	1418 (29.8)	1056 (36.1)
12-13	29396 (48.4)	13037 (51.3)	8657 (52.6)	2449 (51.5)	1334 (45.6)
14-15	8191 (13.5)	3561 (14.0)	2327 (14.1)	688 (14.5)	373 (12.8)
16 or older	1914 (3.1)	790 (3.1)	471 (2.9)	147 (3.1)	138 (4.7)
Missing	3550 (5.8)	410 (1.6)	255 (1.5)	52 (1.1)	24 (0.8)
Gravidity, n (%):					
0	25466 (41.9)	10985 (43.2)	6892 (41.9)	2287 (48.1)	1288 (44.0)
1	8028 (13.2)	3489 (13.7)	2244 (13.6)	618 (13.0)	472 (16.1)
2+	23798 (39.1)	10579 (41.7)	7145 (43.4)	1802 (37.9)	1131 (38.7)
Missing	3497 (5.8)	346 (1.4)	178 (1.1)	47 (1.0)	34 (1.2)
Family history of any metabolic conditions, n (%)	35094 (57.7)	16717 (65.8)	10995 (66.8)	3239 (68.1)	2298 (78.6)
Time to cycle regularity, n (%):					
Regular within 4 years	34326 (56.5)	15111 (59.5)	10903 (66.2)	2398 (50.4)	1118 (38.2)
Regular after 5+ years, after using hormones, or not yet regular	15977 (26.3)	6847 (27.0)	3128 (19.0)	1827 (38.4)	1573 (53.8)
Missing	10486 (17.2)	3441 (13.5)	2428 (14.8)	529 (11.1)	234 (8.0)
Ever used hormone, n (%)	43781 (72.0)	19516 (76.8)	12455 (75.7)	3579 (75.3)	2570 (87.9)

IQR: interquartile range.

eTable 3. Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions

Conditions	Among all participants in this study[a] (N = 50303)			Among participants with PCOS[a] (N = 5725)			Among participants without PCOS[a] (N = 37707)			Among participants without PCOS and with irregular cycles (within those who completed the Hormonal Symptoms Survey)[a] (N = 4225)		
	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]
N	**50303**	**50147**	**41424**	**5725**	**5708**	**5454**	**37707**	**37592**	**35872**	**4225**	**4214**	**4010**
Obesity	1.16 (1.11, 1.20)	1.23 (1.18, 1.28)	1.21 (1.16, 1.27)	0.96 (0.86, 1.07)	0.96 (0.86, 1.07)	1.03 (0.91, 1.16)	0.95 (0.90, 1.00)	1.02 (0.97, 1.07)	1.02 (0.97, 1.08)	1.03 (0.91, 1.07)	1.12 (0.98, 1.28)	1.14 (0.99, 1.31)
Prediabetes	1.34 (1.25, 1.43)	1.61 (1.49, 1.72)	1.49 (1.38, 1.61)	0.94 (0.83, 1.06)	1.00 (0.88, 1.13)	1.01 (0.89, 1.16)	0.95 (0.87, 1.05)	1.20 (1.08, 1.32)	1.20 (1.08, 1.33)	0.88 (0.69, 1.11)	1.13 (0.88, 1.46)	1.15 (0.87, 1.50)
Type 1 diabetes	1.49 (1.19, 1.84)	1.56 (1.25, 1.95)	1.54 (1.21, 1.95)	1.14 (0.70, 1.87)	1.26 (0.77, 2.09)	1.34 (0.78, 2.35)	1.41 (1.09, 1.81)	1.47 (1.13, 1.89)	1.52 (1.16, 1.99)	0.95 (0.45, 1.93)	0.80 (0.37, 1.66)	0.94 (0.42, 2.05)
Type 2 diabetes	1.16 (1.03, 1.30)	1.59 (1.41, 1.79)	1.45 (1.28, 1.65)	0.91 (0.75, 1.11)	1.12 (0.91, 1.37)	1.11 (0.89, 1.38)	0.89 (0.76, 1.03)	1.25 (1.06, 1.46)	1.24 (1.05, 1.46)	0.80 (0.54, 1.18)	1.12 (0.74, 1.69)	1.06 (0.68, 1.64)
High cholesterol	0.97 (0.92, 1.04)	1.26 (1.18, 1.35)	1.17 (1.09, 1.25)	0.94 (0.82, 1.07)	1.11 (0.97, 1.27)	1.10 (0.95, 1.28)	0.85 (0.79, 0.91)	1.10 (1.02, 1.19)	1.06 (0.98, 1.15)	0.77 (0.63, 0.93)	1.02 (0.83, 1.25)	1.00 (0.81, 1.24)
Hypertension	0.93 (0.87, 0.98)	1.21 (1.13, 1.29)	1.16 (1.08, 1.24)	0.81 (0.71, 0.92)	0.96 (0.83, 1.11)	1.00 (0.86, 1.16)	0.82 (0.76, 0.89)	1.08 (1.00, 1.17)	1.09 (1.01, 1.19)	0.72 (0.59, 0.88)	0.93 (0.75, 1.15)	0.93 (0.74, 1.17)
Metabolic syndrome	1.12 (1.02, 1.24)	1.54 (1.39, 1.71)	1.45 (1.30, 1.62)	0.89 (0.75, 1.04)	1.06 (0.90, 1.25)	1.07 (0.89, 1.28)	0.76 (0.66, 0.87)	1.09 (0.94, 1.25)	1.14 (0.98, 1.33)	0.59 (0.41, 0.84)	0.83 (0.57, 1.21)	0.78 (0.52, 1.17)
Arrhythmia	1.10 (1.00, 1.22)	1.25 (1.13, 1.38)	1.20 (1.08, 1.33)	0.86 (0.68, 1.08)	0.96 (0.76, 1.21)	1.02 (0.79, 1.31)	1.09 (0.97, 1.22)	1.25 (1.11, 1.40)	1.20 (1.06, 1.35)	1.03 (0.76, 1.39)	1.12 (0.82, 1.53)	1.16 (0.84, 1.60)

Congestive heart failure	1.12 (0.85, 1.47)	1.47 (1.10, 1.94)	1.31 (0.96, 1.76)	0.92 (0.48, 1.77)	1.31 (0.67, 2.58)	1.36 (0.64, 2.93)	1.09 (0.79, 1.48)	1.40 (1.00, 1.92)	1.30 (0.92, 1.81)	1.05 (0.40, 2.67)	1.10 (0.39, 2.93)	1.19 (0.42, 3.25)
Coronary artery disease	0.86 (0.60, 1.19)	1.37 (0.95, 1.93)	1.10 (0.74, 1.61)	0.64 (0.33, 1.20)	0.95 (0.49, 1.84)	0.99 (0.47, 2.06)	0.77 (0.49, 1.15)	1.20 (0.76, 1.83)	0.96 (0.59, 1.52)	/ [d]	/ [d]	/ [d]
Heart attack	0.90 (0.66, 1.20)	1.18 (0.87, 1.59)	1.09 (0.78, 1.50)	0.58 (0.32, 1.08)	0.74 (0.39, 1.38)	0.91 (0.45, 1.81)	0.90 (0.63, 1.25)	1.18 (0.82, 1.67)	1.05 (0.71, 1.52)	0.60 (0.21, 1.53)	0.60 (0.19, 1.65)	0.68 (0.21, 1.91)
Heart valve disease	1.05 (0.85, 1.31)	1.26 (1.00, 1.57)	1.16 (0.91, 1.46)	1.27 (0.73, 2.25)	1.42 (0.81, 2.55)	1.45 (0.81, 2.66)	1.00 (0.78, 1.27)	1.20 (0.93, 1.53)	1.08 (0.82, 1.40)	0.51 (0.24, 1.00)	0.59 (0.27, 1.20)	0.56 (0.25, 1.15)
Stroke	1.22 (0.96, 1.55)	1.54 (1.19, 1.97)	1.40 (1.07, 1.81)	0.93 (0.54, 1.61)	1.11 (0.64, 1.94)	1.27 (0.71, 2.29)	1.17 (0.88, 1.55)	1.49 (1.11, 1.98)	1.34 (0.98, 1.81)	1.32 (0.62, 2.79)	2.04 (0.92, 4.50)	2.36 (1.00, 5.59)
Transient ischemic attack	1.12 (0.90, 1.38)	1.45 (1.17, 1.80)	1.43 (1.14, 1.79)	0.92 (0.60, 1.42)	1.08 (0.70, 1.69)	1.33 (0.82, 2.17)	1.03 (0.80, 1.32)	1.37 (1.05, 1.76)	1.33 (1.01, 1.73)	0.63 (0.30, 1.23)	0.77 (0.36, 1.57)	0.70 (0.31, 1.48)
Deep vein thrombosis	0.94 (0.79, 1.11)	1.14 (0.95, 1.36)	1.07 (0.89, 1.29)	0.60 (0.42, 0.87)	0.70 (0.48, 1.01)	0.74 (0.49, 1.09)	0.94 (0.76, 1.15)	1.15 (0.93, 1.41)	1.13 (0.91, 1.39)	1.04 (0.60, 1.80)	1.24 (0.69, 2.19)	1.02 (0.55, 1.88)
Pulmonary embolism	1.09 (0.89, 1.34)	1.30 (1.05, 1.61)	1.23 (0.98, 1.53)	0.77 (0.52, 1.15)	0.94 (0.62, 1.41)	0.88 (0.57, 1.38)	0.99 (0.77, 1.27)	1.17 (0.90, 1.51)	1.21 (0.92, 1.58)	1.12 (0.58, 2.14)	1.30 (0.65, 2.56)	1.41 (0.68, 2.89)

POR: prevalence odds ratio; CI: confidence interval

[a] Excluded those who did not respond to the time to cycle regularity question. Prolonged time to cycle regularity defined as those who reported time to cycle regularity of 5 or more years, regular after using hormone, or not yet regular.

[b] Adjusted for age and race/ethnicity. Data from participants with missing covariates were excluded from the analysis.

[c] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[d] Model unable to converge due to small N.

eTable 4. Associations Between Having Irregular Cycles at Enrollment and Prevalent Cardiometabolic Conditions Among Participants Who Responded to the Hormonal Symptoms Survey

Conditions	Among all participants who responded to the Hormonal Symptoms Survey[a] (N = 25115)			Among participants with PCOS[a] (N = 2971)			Among participants without PCOS[a] (N = 21213)		
	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]	POR (95% CI), unadjusted	POR (95% CI), adjusted model 1[b]	POR (95% CI), adjusted model 2[c]
N	**25115**	**25050**	**22964**	**2917**	**2911**	**2786**	**21213**	**21159**	**20130**
Obesity	1.33 (1.26, 1.41)	1.44 (1.36, 1.53)	1.38 (1.29, 1.47)	1.39 (1.19, 1.62)	1.45 (1.24, 1.70)	1.42 (1.20, 1.68)	1.09 (1.02, 1.17)	1.18 (1.10, 1.26)	1.13 (1.05, 1.21)
Prediabetes	1.60 (1.45, 1.75)	2.01 (1.82, 2.22)	1.78 (1.60, 1.98)	1.26 (1.07, 1.50)	1.43 (1.20, 1.72)	1.36 (1.12, 1.64)	1.12 (0.99, 1.27)	1.47 (1.28, 1.67)	1.38 (1.20, 1.58)
Type 1 diabetes	1.24 (0.88, 1.74)	1.24 (0.87, 1.74)	1.07 (0.73, 1.54)	1.25 (0.57, 2.83)	1.33 (0.58, 3.11)	1.12 (0.46, 2.77)	1.14 (0.76, 1.68)	1.13 (0.75, 1.66)	1.04 (0.67, 1.57)
Type 2 diabetes	1.14 (0.97, 1.33)	1.62 (1.37, 1.92)	1.38 (1.15, 1.64)	0.67 (0.51, 0.87)	0.94 (0.71, 1.25)	0.82 (0.61, 1.11)	1.00 (0.81, 1.22)	1.46 (1.18, 1.81)	1.36 (1.08 1.69)
High cholesterol	1.01 (0.93, 1.10)	1.39 (1.27, 1.52)	1.29 (1.18, 1.41)	0.93 (0.78, 1.11)	1.29 (1.06, 1.57)	1.29 (1.05, 1.59)	0.90 (0.81, 0.99)	1.22 (1.10, 1.35)	1.17 (1.05, 1.30)
Hypertension	1.01 (0.93, 1.10)	1.39 (1.26, 1.52)	1.20 (1.09, 1.32)	0.86 (0.71, 1.03)	1.22 (1.00, 1.49)	1.13 (0.91, 1.40)	0.93 (0.84, 1.03)	1.25 (1.12, 1.39)	1.14 (1.02, 1.28)
Metabolic syndrome	1.34 (1.18, 1.53)	2.03 (1.77, 2.33)	1.73 (1.49, 2.01)	1.04 (0.84, 1.30)	1.48 (1.17, 1.88)	1.35 (1.05, 1.75)	0.94 (0.79, 1.12)	1.49 (1.23, 1.80)	1.36 (1.11, 1.66)
Arrhythmia	1.07 (0.93, 1.23)	1.28 (1.11, 1.49)	1.21 (1.04, 1.41)	0.80 (0.57, 1.11)	1.06 (0.74, 1.50)	1.15 (0.80, 1.67)	1.09 (0.92, 1.28)	1.28 (1.08, 1.51)	1.21 (1.02, 1.43)
Congestive heart failure	0.81 (0.52, 1.23)	1.20 (0.75, 1.86)	1.04 (0.63, 1.66)	0.76 (0.27, 2.04)	1.57 (0.51, 4.78)	1.85 (0.51, 6.85)	0.77 (0.46, 1.24)	1.07 (0.62, 1.77)	1.00 (0.56, 1.68)
Coronary artery disease	0.38 (0.18, 0.69)	0.81 (0.37, 1.59)	0.78 (0.35, 1.56)	0.39 (0.11, 1.17)	0.85 (0.22, 2.89)	0.83 (0.20, 3.10)	0.32 (0.12, 0.68)	0.63 (0.22, 1.47)	0.63 (0.21, 1.48)
Heart attack	1.18 (0.77, 1.76)	1.91 (1.21, 2.94)	1.80 (1.11, 2.85)	1.09 (0.44, 2.75)	1.87 (0.70, 5.15)	1.57 (0.55, 4.59)	1.07 (0.64, 1.72)	1.68 (0.97, 2.79)	1.72 (0.97, 2.92)
Heart valve disease	0.96 (0.69, 1.30)	1.23 (0.88, 1.70)	1.27 (0.90, 1.76)	0.91 (0.42, 1.95)	0.95 (0.43, 2.10)	1.07 (0.46, 2.50)	0.96 (0.67, 1.35)	1.23 (0.84, 1.76)	1.26 (0.86, 1.82)
Stroke	0.95 (0.65, 1.35)	1.30 (0.88, 1.89)	1.13 (0.75, 1.67)	0.73 (0.30, 1.73)	0.98 (0.38, 2.46)	0.87 (0.32, 2.31)	0.98 (0.64, 1.45)	1.33 (0.86, 2.01)	1.14 (0.71, 1.76)

Transient ischemic attack	1.15 (0.85, 1.55)	1.64 (1.19, 2.23)	1.53 (1.09, 2.11)	0.88 (0.46, 1.67)	1.09 (0.55, 2.16)	0.99 (0.49, 2.03)	1.13 (0.79, 1.58)	1.63 (1.12, 2.32)	1.56 (1.06, 2.26)
Deep vein thrombosis	0.96 (0.75, 1.23)	1.25 (0.96, 1.61)	1.05 (0.79, 1.37)	0.81 (0.47, 1.39)	1.25 (0.70, 2.22)	1.14 (0.61, 2.12)	0.90 (0.67, 1.19)	1.13 (0.83, 1.52)	0.99 (0.72, 1.35)
Pulmonary embolism	1.04 (0.77, 1.39)	1.26 (0.92, 1.70)	1.10 (0.79, 1.50)	0.77 (0.42, 1.42)	1.07 (0.55, 2.04)	0.98 (0.48, 1.99)	0.98 (0.68, 1.37)	1.15 (0.79, 1.63)	1.10 (0.75, 1.58)

POR: prevalence odds ratio; CI: confidence interval

[a] Excluded those who did not respond to the question that was used to define irregular cycles.

[b] Adjusted for age and race/ethnicity. Data from participants with missing covariates were excluded from the analysis.

[c] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[d] Model unable to converge due to small N.

eTable 5. Covariate-Adjusted Associations of PCOS With Prevalent Cardiometabolic Conditions, Tests for Effect Modification by BMI on the Additive Scale (With BMI <25 as the Referent Group)

Conditions	Among BMI < 25 kg/m^2	Among BMI 25-<30 kg/m^2	Among BMI ≥ 30 kg/m^2
		Tests for effect modification (BMI 25-<30 kg/m^2 vs. < 25 kg/m^2)	Tests for effect modification (BMI ≥ 30 kg/m^2 vs. < 25 kg/m^2)
Total N	**21653**	**15033**	**22555**
Obesity	/	/	/
Prediabetes	REF	RERI (95% CI) = 1.25 (-0.29, 2.78)	**RERI (95% CI) = 8.31 (6.49, 10.14)**
Type 1 diabetes	REF	RERI (95% CI) = -0.52 (-2.02, 0.99)	RERI (95% CI) = -0.25 (-1.52, 1.03)
Type 2 diabetes	REF	**RERI (95% CI) = 5.53 (2.29, 8.77)**	**RERI (95% CI) = 11.67 (7.78, 15.55)**
High cholesterol	REF	RERI (95% CI) = 0.35 (-0.21, 0.90)	RERI (95% CI) = 0.40 (-0.06, 0.86)
Hypertension	REF	RERI (95% CI) = 0.08 (-0.46, 0.62)	**RERI (95% CI) = 1.24 (0.70, 1.78)**
Metabolic syndrome	REF	RERI (95% CI) = 1.37 (-3.12, 5.86)	**RERI (95% CI) = 55.29 (36.42, 74.16)**
Arrhythmia	REF	/[a]	/[a]
Congestive heart failure	REF	/[a]	RERI (95% CI) = 0.42 (-0.95, 1.79)
Coronary artery disease	REF	RERI (95% CI) = 1.54 (-2.29, 5.36)	RERI (95% CI) = 1.66 (-1.36, 4.69)
Heart attack	REF	/[a]	/[a]
Heart valve disease	REF	/[a]	/[a]
Stroke	REF	/[a]	RERI (95% CI) = -0.48 (-1.76, 0.81)
Transient ischemic attack	REF	/[a]	RERI (95% CI) = -0.01 (-1.18, 1.16)
Deep vein thrombosis	REF	RERI (95% CI) = -0.43 (-1.62, 0.76)	RERI (95% CI) = -0.79 (-1.89, 0.32)
Pulmonary embolism	REF	RERI (95% CI) = 0.29 (-1.56, 2.14)	RERI (95% CI) = 0.47 (-1.14, 2.09)

Models adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, ever hormone use, and family history of metabolic conditions.

RERI: relative excess risk due to interaction, which indicates the difference between the joint risk ratio and the separate contributions by the exposure and modifier. RERI = 0 means no interaction or exactly additivity; RERI > 0 means positive interaction or more than additivity; RERI < 0 means negative interaction or less than additivity; RERI can go from −infinity to +infinity. The 95% CIs for RERI were calculated based on the delta method. We used the R function developed by: *Mathur MB & VanderWeele TJ (2018). R function for additive interaction measures. Epidemiology 29(1), e5-e6.*

[a] Additive interaction measures are typically conceptualized for settings in which both the exposure and the modifier are positively associated with the outcome. In this data, negative association(s) occurred, so we do not present the effect modification on the additive scale.

eTable 6. Covariate-Adjusted Associations Between Irregular Cycles and Prevalent Cardiometabolic Conditions Among Those Without PCOS, Tests for Effect Modification by BMI on the Additive Scale (With BMI <25 as the Referent Group)

Conditions	Among BMI < 25 kg/m^2	Among BMI 25-<30 kg/m^2	Among BMI ≥ 30 kg/m^2
		Tests for effect modification (BMI 25-<30 kg/m^2 vs. < 25 kg/m^2)	Tests for effect modification (BMI ≥ 30 kg/m^2 vs. < 25 kg/m^2)
Total N	**7947**	**5540**	**7309**
Obesity	/	/	/
Prediabetes	REF	RERI (95% CI) = 0.03 (-0.89, 0.96)	RERI (95% CI) = 0.96 (-0.22, 2.13)
Type 1 diabetes	REF	RERI (95% CI) = 0.27 (-1.12, 1.65)	RERI (95% CI) = - 0.38 (-1.74, 0.97)
Type 2 diabetes	REF	RERI (95% CI) = 0.07 (-2.28, 2.43)	RERI (95% CI) = 3.15 (-0.61, 6.91)
High cholesterol	REF	RERI (95% CI) = 0.36 (-0.08, 0.81)	RERI (95% CI) = 0.23 (-0.20, 0.65)
Hypertension	REF	RERI (95% CI) = -0.08 (-0.55, 0.39)	**RERI (95% CI) = 0.62 (0.02, 1.22)**
Metabolic syndrome	REF	RERI (95% CI) = 0.83 (-2.03, 3.69)	**RERI (95% CI) = 8.56 (0.65, 16.47)**
Arrhythmia	REF	/[a]	/[a]
Congestive heart failure	REF	RERI (95% CI) = - 2.42 (-5.72, 0.88)	RERI (95% CI) = -2.25 (-5.75, 1.25)
Coronary artery disease	REF	/[a]	/[a]
Heart attack	REF	RERI (95% CI) = - 0.34 (-3.42, 2.73)	RERI (95% CI) = 0.51 (-3.34, 4.36)
Heart valve disease	REF	/[a]	/[a]
Stroke	REF	/[a]	RERI (95% CI) = -0.67 (-2.02, 0.67)
Transient ischemic attack	REF	RERI (95% CI) = -0.18 (-1.61, 1.25)	RERI (95% CI) = 0.02 (-1.26, 1.31)
Deep vein thrombosis	REF	/[a]	/[a]
Pulmonary embolism	REF	/[a]	/[a]

Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, ever hormone use, and family history of metabolic conditions.

RERI: relative excess risk due to interaction, which indicates the difference between the joint risk ratio and the separate contributions by the exposure and modifier. RERI = 0 means no interaction or exactly additivity; RERI > 0 means positive interaction or more than additivity; RERI < 0

means negative interaction or less than additivity; RERI can go from −infinity to +infinity. The 95% CIs for RERI were calculated based on the delta method. We used the R function developed by: *Mathur MB & VanderWeele TJ (2018). R function for additive interaction measures. Epidemiology 29(1), e5-e6.*

[a] Additive interaction measures are typically conceptualized for settings in which both the exposure and the modifier are positively associated with the outcome. In these data, negative association(s) occurred, so we do not present the effect modification on the additive scale.

eTable 7. Covariate-Adjusted Associations of PCOS With Prevalent Cardiometabolic Conditions, Tests for Effect Modification by Physical Activity on the Additive Scale (Low vs High)

Conditions	Moderate/vigorous/strenuous physical activity	None/light physical activity: Tests for effect modification (none/light vs. moderate/vigorous/strenuous physical activity)
Total N	**36750**	**17985**
Obesity	REF	**RERI (95% CI) = 1.97 (1.35, 2.59)**
Prediabetes	REF	RERI (95% CI) = 0.22 (-0.33, 0.77)
Type 1 diabetes	REF	RERI (95% CI) = 0.24 (-0.61, 1.08)
Type 2 diabetes	REF	**RERI (95% CI) = 1.19 (0.37, 2.01)**
High cholesterol	REF	RERI (95% CI) = 0.24 (-0.05, 0.53)
Hypertension	REF	**RERI (95% CI) = 0.41 (0.13, 0.69)**
Metabolic syndrome	REF	**RERI (95% CI) = 1.22 (0.47, 1.97)**
Arrhythmia	REF	RERI (95% CI) = 0.13 (-0.24, 0.51)
Congestive heart failure	REF	/[a]
Coronary artery disease	REF	RERI (95% CI) = 0.08 (-2.32, 2.48)
Heart attack	REF	RERI (95% CI) = 1.01 (-0.55, 2.58)
Heart valve disease	REF	RERI (95% CI) = -0.16 (-0.92, 0.60)
Stroke	REF	RERI (95% CI) = 0.05 (-1.07, 1.17)
Transient ischemic attack	REF	RERI (95% CI) = 0.18 (-0.92, 1.28)
Deep vein thrombosis	REF	RERI (95% CI) = 0.05 (-0.63, 0.72)
Pulmonary embolism	REF	RERI (95% CI) = 0.54 (-0.42, 1.50)

Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use.

RERI: relative excess risk due to interaction, which indicates the difference between the joint risk ratio and the separate contributions by the exposure and modifier. RERI = 0 means no interaction or exactly additivity; RERI > 0 means positive interaction or more than additivity; RERI < 0 means negative interaction or less than additivity; RERI can go from −infinity to +infinity. The 95% CIs for RERI were calculated based on the delta method. We used the R function developed by: *Mathur MB & VanderWeele TJ (2018). R function for additive interaction measures. Epidemiology 29(1), e5-e6.*

[a] Additive interaction measures are typically conceptualized for settings in which both the exposure and the modifier are positively associated with the outcome. In these data, negative association(s) occurred, so we do not present the effect modification on the additive scale.

eTable 8. Covariate-Adjusted Associations Between Irregular Cycles and Prevalent Cardiometabolic Conditions Among Those Without PCOS, Tests for Effect Modification by Physical Activity on the Additive Scale (Low vs High)

Conditions	Moderate/vigorous/strenuous physical activity OR (95% CI)	None/light physical activity Tests for effect modification (none/light vs. moderate/vigorous/strenuous physical activity)
Total N	**14696**	**6430**
Obesity	REF	RERI (95% CI) = 0.01 (-0.30, 0.32)
Prediabetes	REF	RERI (95% CI) = 0.14 (-0.26, 0.54)
Type 1 diabetes	REF	/[a]
Type 2 diabetes	REF	RERI (95% CI) = 0.16 (-0.64, 0.97)
High cholesterol	REF	RERI (95% CI) = -0.06 (-0.36, 0.24)
Hypertension	REF	RERI (95% CI) = 0.10 (-0.21, 0.41)
Metabolic syndrome	REF	RERI (95% CI) = 0.43 (-0.24, 1.10)
Arrhythmia	REF	RERI (95% CI) = -0.13 (-0.59, 0.33)
Congestive heart failure	REF	/[a]
Coronary artery disease	REF	/[a]
Heart attack	REF	RERI (95% CI) = -0.25 (-2.75, 2.26)
Heart valve disease	REF	RERI (95% CI) = -0.54 (-1.65, 0.57)
Stroke	REF	RERI (95% CI) = -0.81 (-2.19, 0.58)
Transient ischemic attack	REF	RERI (95% CI) = 0.23 (-1.33, 1.79)
Deep vein thrombosis	REF	/[a]
Pulmonary embolism	REF	/[a]

Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use.

RERI: relative excess risk due to interaction, which indicates the difference between the joint risk ratio and the separate contributions by the exposure and modifier. RERI = 0 means no interaction or exactly additivity; RERI > 0 means positive interaction or more than additivity; RERI < 0 means negative interaction or less than additivity; RERI can go from −infinity to +infinity. The 95% CIs for RERI were calculated based on the delta method. We used the R function developed by: *Mathur MB & VanderWeele TJ (2018). R function for additive interaction measures. Epidemiology 29(1), e5-e6.*

[a] Additive interaction measures are typically conceptualized for settings in which both the exposure and the modifier are positively associated with the outcome. In these data, negative association(s) occurred, so we do not present the effect modification on the additive scale.

eTable 9. Age at Diagnosis for Each Cardiometabolic Condition, Overall and Stratified by PCOS Diagnosis or Time to Regularity, Among a Subset of Participants Who Provided Data of Age at Diagnosis

Cardiometabolic condition	N with condition at baseline and provided age at diagnosis (% among those with condition at baseline)	Mean ± SD of age at diagnosis, years old				
		Overall	With PCOS diagnosis	No PCOS diagnosis	Prolonged time to regularity (5+ years, never regular, or regular after hormone use)	Time to regularity within 4 years
Prediabetes	910 (20.5)	35.6 ± 12.8	29.4 ± 9.4[a]	38.4 ± 13.1[a]	30.8 ± 11.4[b]	37.3 ± 13.2[b]
Type 1 diabetes	58 (14.5)	19.1 ± 14.1	18.6 ± 11.7	19.1 ± 14.4	18.3 ± 11.3	19.9 ± 14.8
Type 2 diabetes	385 (24.6)	37.4 ± 11.1	32.4 ± 9.5[a]	39.6 ± 11.1[a]	34.0 ± 11.0[b]	38.8 ± 11.2[b]
High cholesterol	1589 (24.0)	35.5 ± 13.3	31.5 ± 10.9[a]	36.3 ± 13.6[a]	31.0 ± 12.3[b]	37.0 ± 13.5[b]
Hypertension	1425 (22.7)	36.3 ± 11.9	32.0 ± 10.2[a]	37.1 ± 12.0[a]	32.6 ± 11.2[b]	37.6 ± 12.0[b]
Arrhythmia	387 (18.1)	32.3 ± 16.6	32.5 ± 14.2	32.3 ± 17.1	28.8 ± 16.3[b]	33.2 ± 16.5[b]
Congestive heart failure	62 (22.4)	40.2 ± 13.5	47.9 ± 13.5	39.0 ± 13.3	40.2 ± 18.4	38.8 ± 11.5
Coronary artery disease	39 (20.6)	49.9 ± 12.9	42.6 ± 11.4	51.7 ± 12.8	41.3 ± 13.5	50.2 ± 13.0
Heart attack	47 (18.1)	42.5 ± 12.9	38.0 ± 6.0	43.5 ± 13.9	34.7 ± 12.2	42.8 ± 11.6
Heart valve disease	82 (17.7)	27.5 ± 18.3	15.0 ± 11.4	28.5 ± 18.4	26.9 ± 20.3	27.4 ± 17.1
Stroke	69 (20.4)	39.3 ± 15.7	33.6 ± 13.3	40.5 ± 16.0	34.5 ± 14.4	41.9 ± 15.9
Transient ischemic attack	90 (19.5)	38.4 ± 13.4	33.5 ± 11.4	39.5 ± 13.6	35.9 ± 13.7	39.9 ± 13.1
Deep vein thrombosis	145 (19.9)	35.1 ± 10.9	36.8 ± 11.3	34.7 ± 10.9	31.4 ± 10.5[b]	36.3 ± 10.6[b]
Pulmonary embolism	107 (22.5)	35.0 ± 11.0	34.8 ± 10.2	35.0 ± 11.3	33.3 ± 12.1	35.8 ± 10.6

[a] Results with p-value < 0.05 from Kruskal-Wallis test for the mean age at diagnosis of each condition when comparing the PCOS vs. no PCOS group.

[b] Results with p-value < 0.05 from Kruskal-Wallis test for the mean age at diagnosis of each condition when comparing the prolonged time to regularity group vs. time to regularity within 4 years.

eTable 10. Covariate-Adjusted Associations of Combined Information on Cycle Irregularity, PCOS, and BMI With Prevalent Cardiometabolic Conditions Among the Subset of Participants Who Responded to the Hormonal Symptoms Survey (n = 25399)

	No PCOS & no irregular cycles	No PCOS & with irregular cycles [POR (95% CI)]					PCOS [POR (95% CI)]
		Overall	BMI < 21 kg/m^2		BMI between 21-25 kg/m^2	BMI > 25 kg/m^2	
			All	Possible HA[a]			
N	**16459**	**4754**	**703**	**636**	**1109**	**2826**	**2925**
Obesity	REF	1.12 (1.04, 1.21)	/	/	/	/	3.04 (2.78, 3.32)
Prediabetes	REF	1.33 (1.16, 1.53)	1.30 (0.71, 2.20)	1.49 (0.77, 2.63)	1.53 (1.03, 2.22)	1.31 (1.13, 1.52)	4.02 (3.56, 4.52)
Type 1 diabetes	REF	1.04 (0.67, 1.57)	1.42 (0.47, 3.48)	1.38 (0.39, 3.69)	0.77 (0.23, 1.98)	1.04 (0.61, 1.70)	1.24 (0.75, 1.95)
Type 2 diabetes	REF	1.36 (1.09, 1.70)	1.76 (0.41, 5.07)	1.32 (0.21, 4.64)	1.45 (0.49, 3.90)	1.35 (1.07, 1.70)	3.28 (2.72, 3.96)
High cholesterol	REF	1.16 (1.04, 1.29)	0.88 (0.59, 1.27)	0.83 (0.54, 1.24)	1.14 (0.88, 1.45)	1.20 (1.06, 1.36)	1.75 (1.56, 1.96)
Hypertension	REF	1.14 (1.02, 1.28)	0.76 (0.45, 1.19)	0.78 (0.46, 1.26)	1.25 (0.93, 1.67)	1.16 (1.02, 1.31)	1.50 (1.33, 1.68)
Metabolic syndrome	REF	1.32 (1.08, 1.61)	/[b]	/[b]	1.51 (0.45, 3.89)	1.34 (1.09, 1.63)	3.75 (3.18, 4.42)
Arrhythmia	REF	1.22 (1.02, 1.44)	1.34 (0.88, 1.96)	1.38 (0.89, 2.07)	1.19 (0.85, 1.63)	1.20 (0.96, 1.49)	1.40 (1.15, 1.70)
Congestive heart failure	REF	1.05 (0.59, 1.77)	1.16 (0.06, 6.13)	1.47 (0.08, 8.10)	3.01 (0.95, 8.10)	0.80 (0.40, 1.49)	1.10 (0.59, 1.91)
Coronary artery disease	REF	0.64 (0.22, 1.50)	/[b]	/[b]	1.12 (0.06, 5.86)	0.63 (0.19, 1.59)	2.12 (1.09, 3.89)
Heart attack	REF	1.68 (0.95, 2.84)	1.35 (0.07, 7.50)	2.27 (0.12, 12.96)	2.60 (0.58, 8.61)	1.59 (0.85, 2.83)	2.08 (1.16, 3.58)
Heart valve disease	REF	1.22 (0.83, 1.76)	0.80 (0.27, 1.88)	0.81 (0.24, 2.09)	1.06 (0.46, 2.13)	1.43 (0.89, 2.22)	1.33 (0.84, 2.03)
Stroke	REF	1.13 (0.71, 1.74)	1.14 (0.27, 3.35)	0.89 (0.14, 3.08)	1.69 (067, 3.69)	0.98 (0.55, 1.67)	1.17 (0.69, 1.89)
Transient ischemic attack	REF	1.51 (1.03, 2.18)	1.42 (0.41, 3.69)	1.18 (0.28, 3.44)	1.65 (0.71, 3.42)	1.48 (0.94, 2.27)	1.86 (1.24, 2.73)

Deep vein thrombosis	REF	1.01 (0.73, 1.37)	0.48 (0.11, 1.34)	0.41 (0.07, 1.35)	1.11 (0.51, 2.15)	1.07 (0.74, 1.51)	1.34 (0.96, 1.84)
Pulmonary embolism	REF	1.13 (0.77, 1.61)	0.31 (0.02, 1.49)	/[b]	0.41 (0.07, 1.37)	1.36 (0.91, 1.99)	1.42 (0.96, 2.05)

POR: prevalence odds ratio; CI: confidence interval. Models adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[a] Possible HA defined as: (1) having irregular cycles, and (2) without PCOS, and (3) with BMI < 21 kg/m^2, and (4) without any of the following other endocrinopathies: hyperprolactinemia, hyperthyroidism, hypothyroidism, or early menopause.

[b] Model unable to converge due to small N.

eTable 11. Covariate-Adjusted Associations of Categorical Time to Cycle Regularity With Prevalent Cardiometabolic Conditions

	Among all participants in this study[a,b] [POR (95% CI)] (N = 50303)					Among participants without PCOS[a,b] [POR (95% CI)] (N = 37707)				
	≤ 2 years	3-4 years	≥ 5 years	Not yet regular	Regular after using hormones	≤ 2 years	3-4 years	≥ 5 years	Not yet regular	Regular after using hormones
N	**31138**	**3188**	**2933**	**5752**	**7292**	**24863**	**2459**	**2002**	**3433**	**4950**
Obesity	REF	0.90 (0.83, 0.97)	1.00 (0.92, 1.09)	1.51 (1.42, 1.61)	1.10 (1.04, 1.17)	REF	0.89 (0.81, 0.98)	0.89 (0.80, 0.98)	1.18 (1.09, 1.28)	0.96 (0.90, 1.03)
Prediabetes	REF	1.17 (0.99, 1.36)	1.40 (1.21, 1.61)	1.76 (1.58, 1.96)	1.40 (1.27, 1.56)	REF	1.15 (0.96, 1.38)	1.22 (1.01, 1.46)	1.28 (1.09, 1.50)	1.16 (1.00, 1.33)
Type 1 diabetes	REF	0.90 (0.52, 1.45)	2.04 (1.40, 2.89)	1.49 (1.07, 2.05)	1.27 (0.91, 1.74)	REF	0.92 (0.50, 1.53)	1.91 (1.22, 2.87)	1.68 (1.15, 2.41)	1.10 (0.73, 1.61)
Type 2 diabetes	REF	0.96 (0.72, 1.26)	1.49 (1.20, 1.85)	1.73 (1.44, 2.06)	1.27 (1.06, 1.51)	REF	0.93 (0.67, 1.27)	1.36 (1.03, 1.78)	1.46 (1.13, 1.86)	1.03 (0.80, 1.31)
High cholesterol	REF	0.97 (0.85, 1.11)	0.95 (0.83, 1.08)	1.35 (1.22, 1.49)	1.18 (1.08, 1.29)	REF	1.01 (0.87, 1.17)	0.85 (0.72, 0.99)	1.22 (1.07, 1.39)	1.10 (0.99, 1.22)
Hypertension	REF	1.05 (0.91, 1.20)	0.95 (0.83, 1.09)	1.23 (1.11, 1.37)	1.18 (1.07, 1.29)	REF	1.08 (0.93, 1.25)	0.90 (0.76, 1.05)	1.13 (0.99, 1.29)	1.14 (1.01, 1.27)
Metabolic syndrome	REF	1.08 (0.85, 1.35)	1.21 (0.98, 1.48)	1.82 (1.55, 2.12)	1.31 (1.13, 1.53)	REF	1.27 (0.97, 1.63)	1.08 (0.82, 1.41)	1.12 (0.87, 1.43)	1.18 (0.95, 1.44)
Arrhythmia	REF	1.01 (0.82, 1.24)	0.95 (0.77, 1.17)	1.27 (1.08, 1.49)	1.03 (1.11, 1.45)	REF	1.02 (0.81, 1.27)	0.87 (0.67, 1.10)	1.23 (1.01, 1.48)	1.33 (1.14, 1.54)
Congestive heart failure	REF	0.87 (0.42, 1.58)	1.54 (0.93, 2.42)	1.78 (1.17, 2.64)	0.99 (0.62, 1.52)	REF	1.03 (0.50, 1.88)	1.18 (0.61, 2.06)	1.78 (1.08, 2.83)	1.16 (0.70, 1.83)

Coronary artery disease	REF	0.94 (0.41, 1.87)	1.27 (0.66, 2.26)	1.48 (0.80, 2.55)	1.11 (0.65, 1.81)	REF	1.04 (0.43, 2.15)	1.15 (0.51, 2.28)	1.16 (0.47, 2.43)	1.12 (0.58, 1.98)
Heart attack	REF	1.31 (0.73, 2.18)	1.15 (0.64, 1.90)	1.42 (0.89, 2.18)	1.03 (0.63, 1.61)	REF	1.49 (0.81, 2.54)	1.22 (0.63, 2.14)	1.36 (0.76, 2.29)	1.08 (0.60, 1.79)
Heart valve disease	REF	1.20 (0.77, 1.78)	1.13 (0.73, 1.69)	1.47 (1.04, 2.04)	1.17 (0.85, 1.58)	REF	1.28 (0.81, 1.93)	1.11 (0.67, 1.72)	1.30 (0.85, 1.93)	1.15 (0.80, 1.60)
Stroke	REF	0.88 (0.47, 1.49)	1.19 (0.71, 1.87)	1.88 (1.31, 2.66)	1.34 (0.92, 1.90)	REF	0.97 (0.50, 1.69)	1.27 (0.71, 2.11)	1.80 (1.15, 2.73)	1.31 (0.84, 1.96)
Transient ischemic attack	REF	1.31 (0.73, 2.18)	1.15 (0.64, 1.90)	1.42 (0.89, 2.18)	1.03 (0.63, 1.61)	REF	1.25 (0.76, 1.95)	1.51 (0.96, 2.26)	1.28 (0.81, 1.94)	1.26 (0.86, 1.80)
Deep vein thrombosis	REF	1.20 (0.77, 1.78)	1.13 (0.73, 1.69)	1.47 (1.04, 2.04)	1.17 (0.85, 1.58)	REF	1.18 (0.81, 1.68)	1.24 (0.85, 1.76)	1.29 (0.91, 1.79)	1.00 (0.73, 1.33)
Pulmonary embolism	REF	0.88 (0.47, 1.49)	1.19 (0.71, 1.87)	1.88 (1.31, 2.66)	1.34 (0.92, 1.90)	REF	1.19 (0.72, 1.84)	1.78 (1.17, 2.62)	1.17 (0.74, 1.77)	0.96 (0.64, 1.39)

POR: prevalence odds ratio; CI: confidence interval. Unable to evaluate among participants with PCOS due to small N in each category of time to cycle regularity that led to model non-convergence.

[a] Excluded those who did not respond to the time to cycle regularity question.

[b] Models adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

eTable 12. Covariate-Adjusted Associations of Prolonged Time to cycle Regularity With Prevalent Cardiometabolic Conditions, Comparing Results From the Main Analysis to Sensitivity Analyses That Removed 409 Individuals With Potentially Misclassified/Inaccurate Time to Regularity

Conditions	Among all participants in this study [POR (95% CI)] (N = 50303)		Among participants with PCOS [POR (95% CI)] (N = 5725)		Among participants without PCOS [POR (95% CI)] (N = 37707)	
	OR (95% CI) from main analysis	OR (95% CI) from sensitivity analysis[a]	OR (95% CI) from main analysis	OR (95% CI) from sensitivity analysis[a]	OR (95% CI) from main analysis	OR (95% CI) from sensitivity analysis[a]
Obesity	1.21 (1.16, 1.27)	1.21 (1.15, 1.27)	1.03 (0.91, 1.16)	1.03 (0.91, 1.16)	1.02 (0.97, 1.08)	1.02 (0.97, 1.07)
Prediabetes	1.49 (1.38, 1.61)	1.50 (1.38, 1.62)	1.01 (0.89, 1.16)	1.01 (0.89, 1.16)	1.20 (1.08, 1.33)	1.20 (1.08, 1.33)
Type 1 diabetes	1.54 (1.21, 1.95)	1.53 (1.20, 1.94)	1.34 (0.78, 2.35)	1.33 (0.76, 2.34)	1.52 (1.16, 1.99)	1.52 (1.16, 1.99)
Type 2 diabetes	1.45 (1.28, 1.65)	1.46 (1.28, 1.66)	1.11 (0.89, 1.38)	1.13 (0.91, 1.42)	1.24 (1.05, 1.46)	1.23 (1.04, 1.45)
High cholesterol	1.17 (1.09, 1.25)	1.17 (1.09, 1.25)	1.10 (0.95, 1.28)	1.10 (0.95, 1.28)	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
Hypertension	1.16 (1.08, 1.24)	1.16 (1.08, 1.25)	1.00 (0.86, 1.16)	1.00 (0.86, 1.16)	1.09 (1.01, 1.19)	1.10 (1.02, 1.19)
Metabolic syndrome	1.45 (1.30, 1.62)	1.45 (1.30, 1.61)	1.07 (0.89, 1.28)	1.07 (0.89, 1.28)	1.14 (0.98, 1.33)	1.14 (0.98, 1.32)
Arrhythmia	1.20 (1.08, 1.33)	1.21 (1.09, 1.35)	1.02 (0.79, 1.31)	1.03 (0.80, 1.33)	1.20 (1.06, 1.35)	1.21 (1.07, 1.36)
Congestive heart failure	1.31 (0.96, 1.76)	1.33 (0.98, 1.79)	1.36 (0.64, 2.93)	1.36 (0.64, 2.92)	1.30 (0.92, 1.81)	1.32 (0.94, 1.84)
Coronary artery disease	1.10 (0.74, 1.61)	1.10 (0.74, 1.61)	0.99 (0.47, 2.06)	0.99 (0.47, 2.05)	0.96 (0.59, 1.52)	0.96 (0.59, 1.52)
Heart attack	1.09 (0.78, 1.50)	1.09 (0.78, 1.50)	0.91 (0.45, 1.81)	0.91 (0.45, 1.81)	1.05 (0.71, 1.52)	1.05 (0.71, 1.53)
Heart valve disease	1.16 (0.91, 1.46)	1.17 (0.92, 1.47)	1.45 (0.81, 2.66)	1.44 (0.80, 2.65)	1.08 (0.82, 1.40)	1.09 (0.83, 1.41)
Stroke	1.40 (1.07, 1.81)	1.39 (1.07,1.81)	1.27 (0.71, 2.29)	1.26 (0.71, 2.29)	1.34 (0.98, 1.81)	1.34 (0.98, 1.81)
Transient ischemic attack	1.43 (1.14, 1.79)	1.42 (1.13, 1.78)	1.33 (0.82, 2.17)	1.33 (0.82, 2.17)	1.33 (1.01, 1.73)	1.32 (1.01, 1.72)
Deep vein thrombosis	1.07 (0.89, 1.29)	1.07 (0.89, 1.29)	0.74 (0.49, 1.09)	0.73 (0.49, 1.09)	1.13 (0.91, 1.39)	1.13 (0.90, 1.39)
Pulmonary embolism	1.23 (0.98, 1.53)	1.24 (0.99, 1.54)	0.88 (0.57, 1.38)	0.92 (0.59, 1.44)	1.21 (0.92, 1.58)	1.21 (0.92, 1.58)

POR: prevalence odds ratio; CI: confidence interval. Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[a] Sensitivity analysis: Removing a total of N = 409 individuals who may have the potential of a misclassified/inaccurate self-reported time to regularity: 1) whose age difference between enrollment and menarche was less than 5 years, and/or 2) who reported age at menarche ≥ 16 years old and were ≤ 25 years old upon enrollment.

eTable 13. Associations of Having PCOS With Prevalent Cardiometabolic Conditions, Adjusted for Covariates, Comparing Results From Complete Case Analyses to Pooled Results From Multiple Imputation

Conditions	POR (95% CI)[a]	
	Complete case analyses	Multiple imputation with chained equations
Total N	**47152**	**60789**
Obesity	2.94 (2.77, 3.12)	2.81 (2.65, 2.97)
Prediabetes	3.75 (3.47, 4.06)	3.94 (3.65, 4.24)
Type 1 diabetes	1.43 (1.07, 1.90)	1.52 (1.17, 1.96)
Type 2 diabetes	2.76 (2.43, 3.15)	2.85 (2.52, 3.22)
High cholesterol	1.68 (1.55, 1.81)	1.72 (1.60, 1.85)
Hypertension	1.57 (1.45, 1.70)	1.58 (1.47, 1.71)
Metabolic syndrome	3.28 (2.94, 3.66)	3.32 (3.00, 3.69)
Arrhythmia	1.37 (1.20, 1.55)	1.41 (1.24, 1.59)
Congestive heart failure	1.23 (0.83, 1.76)	1.30 (0.93, 1.82)
Coronary artery disease	2.92 (1.95, 4.29)	2.52 (1.74, 3.64)
Heart attack	1.79 (1.23, 2.54)	1.70 (1.21, 2.40)
Heart valve disease	1.21 (0.89, 1.62)	1.30 (0.99, 1.70)
Stroke	1.66 (1.21, 2.24)	1.68 (1.25, 2.26)
Transient ischemic attack	1.87 (1.44, 2.40)	1.90 (1.49, 2.43)
Deep vein thrombosis	1.54 (1.24, 1.89)	1.57 (1.29, 1.91)
Pulmonary embolism	1.83 (1.43, 2.32)	1.90 (1.51, 2.39)

POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use.

eTable 14. Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions, Adjusted for Covariates, Comparing Results From Complete Case Analyses to Pooled Results From Multiple Imputation

Conditions	POR (95% CI)[a]					
	Among all participants in this study		Among participants with PCOS		Among participants without PCOS	
	Complete case analyses	Multiple imputation with chained equations	Complete case analyses	Multiple imputation with chained equations	Complete case analyses	Multiple imputation with chained equations
N	**41424**	**60789**	**5454**	**7514**	**35872**	**53275**
Obesity	1.21 (1.16, 1.27)	1.21 (1.16, 1.26)	1.03 (0.91, 1.16)	1.12 (1.01, 1.25)	1.02 (0.97, 1.08)	1.03 (0.98, 1.08)
Prediabetes	1.49 (1.38, 1.61)	1.47 (1.36, 1.58)	1.01 (0.89, 1.16)	1.09 (0.96, 1.23)	1.20 (1.08, 1.33)	1.13 (1.02, 1.26)
Type 1 diabetes	1.54 (1.21, 1.95)	1.52 (1.20, 1.93)	1.34 (0.78, 2.35)	1.29 (0.80, 2.08)	1.52 (1.16, 1.99)	1.49 (1.14, 1.94)
Type 2 diabetes	1.45 (1.28, 1.65)	1.46 (1.29, 1.65)	1.11 (0.89, 1.38)	1.17 (0.94, 1.45)	1.24 (1.05, 1.46)	1.21 (1.04, 1.42)
High cholesterol	1.17 (1.09, 1.25)	1.17 (1.10, 1.24)	1.10 (0.95, 1.28)	1.10 (0.96, 1.25)	1.06 (0.98, 1.15)	1.06 (0.99, 1.14)
Hypertension	1.16 (1.08, 1.24)	1.12 (1.05, 1.20)	1.00 (0.86, 1.16)	1.01 (0.88, 1.16)	1.09 (1.01, 1.19)	1.05 (0.97, 1.13)
Metabolic syndrome	1.45 (1.30, 1.62)	1.40 (1.26, 1.55)	1.07 (0.89, 1.28)	1.12 (0.94, 1.33)	1.14 (0.98, 1.33)	1.07 (0.93, 1.23)
Arrhythmia	1.20 (1.08, 1.33)	1.19 (1.07, 1.33)	1.02 (0.79, 1.31)	1.00 (0.79, 1.26)	1.20 (1.06, 1.35)	1.17 (1.04, 1.32)
Congestive heart failure	1.31 (0.96, 1.76)	1.34 (1.02, 1.76)	1.36 (0.64, 2.93)	1.22 (0.65, 2.30)	1.30 (0.92, 1.81)	1.32 (0.97, 1.80)
Coronary artery disease	1.10 (0.74, 1.61)	1.23 (0.88, 1.74)	0.99 (0.47, 2.06)	0.97 (0.50, 1.86)	0.96 (0.59, 1.52)	1.11 (0.73, 1.69)
Heart attack	1.09 (0.78, 1.50)	1.15 (0.86, 1.52)	0.91 (0.45, 1.81)	0.90 (0.49, 1.67)	1.05 (0.71, 1.52)	1.12 (0.80, 1.55)
Heart valve disease	1.16 (0.91, 1.46)	1.21 (0.98, 1.50)	1.45 (0.81, 2.66)	1.40 (0.82, 2.40)	1.08 (0.82, 1.40)	1.13 (0.89, 1.44)
Stroke	1.40 (1.07, 1.81)	1.47 (1.15, 1.89)	1.27 (0.71, 2.29)	1.22 (0.72, 2.07)	1.34 (0.98, 1.81)	1.26 (0.97, 1.62)
Transient ischemic attack	1.43 (1.14, 1.79)	1.37 (1.11, 1.69)	1.33 (0.82, 2.17)	1.22 (0.79, 1.88)	1.33 (1.01, 1.73)	1.42 (1.06, 1.90)
Deep vein thrombosis	1.07 (0.89, 1.29)	1.08 (0.90, 1.30)	0.74 (0.49, 1.09)	0.80 (0.56, 1.15)	1.13 (0.91, 1.39)	1.08 (0.87, 1.33)
Pulmonary embolism	1.23 (0.98, 1.53)	1.20 (0.97, 1.48)	0.88 (0.57, 1.38)	0.95 (0.64, 1.41)	1.21 (0.92, 1.58)	1.12 (0.88, 1.44)

POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use.

eTable 15. Associations of Having Irregular Cycles With Prevalent Cardiometabolic Conditions Among 25 115 Participants Who Responded to the Relevant Survey Question for Irregular Cycles, Adjusted for Covariates, Comparing Results From Complete Case Analyses to Pooled Results From Multiple Imputation

Conditions	POR (95% CI)[a]					
	Among all 25,115 participants		Among participants with PCOS		Among participants without PCOS	
	Complete case analyses	Multiple imputation with chained equations	Complete case analyses	Multiple imputation with chained equations	Complete case analyses	Multiple imputation with chained equations
N	**22964**	**25115**	**2786**	**3038**	**20130**	**22077**
Obesity	1.38 (1.29, 1.47)	1.35 (1.26, 1.44)	1.42 (1.20, 1.68)	1.49 (1.27, 1.75)	1.13 (1.05, 1.21)	1.10 (1.03, 1.18)
Prediabetes	1.78 (1.60, 1.98)	1.76 (1.59, 1.95)	1.36 (1.12, 1.64)	1.47 (1.22, 1.76)	1.38 (1.20, 1.58)	1.33 (1.17, 1.52)
Type 1 diabetes	1.07 (0.73, 1.54)	1.16 (0.82, 1.64)	1.12 (0.46, 2.77)	1.21 (0.55, 2.70)	1.04 (0.67, 1.57)	1.10 (0.74, 1.65)
Type 2 diabetes	1.38 (1.15, 1.64)	1.37 (1.16, 1.63)	0.82 (0.61, 1.11)	0.82 (0.62, 1.09)	1.36 (1.08 1.69)	1.32 (1.06, 1.65)
High cholesterol	1.29 (1.18, 1.41)	1.29 (1.18, 1.41)	1.29 (1.05, 1.59)	1.23 (1.02, 1.49)	1.17 (1.05, 1.30)	1.18 (1.06, 1.31)
Hypertension	1.20 (1.09, 1.32)	1.21 (1.10, 1.33)	1.13 (0.91, 1.40)	1.09 (0.89, 1.33)	1.14 (1.02, 1.28)	1.15 (1.03, 1.28)
Metabolic syndrome	1.73 (1.49, 2.01)	1.72 (1.49, 1.99)	1.35 (1.05, 1.75)	1.36 (1.07, 1.73)	1.36 (1.11, 1.66)	1.34 (1.11, 1.63)
Arrhythmia	1.21 (1.04, 1.41)	1.24 (1.07, 1.44)	1.15 (0.80, 1.67)	1.02 (0.73, 1.42)	1.21 (1.02, 1.43)	1.25 (1.06, 1.47)
Congestive heart failure	1.04 (0.63, 1.66)	1.09 (0.70, 1.71)	1.85 (0.51, 6.85)	1.13 (0.43, 2.98)	1.00 (0.56, 1.68)	1.06 (0.63, 1.78)
Coronary artery disease	0.78 (0.35, 1.56)	0.83 (0.42, 1.66)	0.83 (0.20, 3.10)	0.80 (0.25, 2.61)	0.63 (0.21, 1.48)	0.72 (0.30, 1.71)
Heart attack	1.80 (1.11, 2.85)	1.77 (1.14, 2.76)	1.57 (0.55, 4.59)	1.83 (0.74, 4.50)	1.72 (0.97, 2.92)	1.61 (0.96, 2.70)
Heart valve disease	1.27 (0.90, 1.76)	1.21 (0.87, 1.68)	1.07 (0.46, 2.50)	1.25 (0.58, 2.69)	1.26 (0.86, 1.82)	1.18 (0.82, 1.69)
Stroke	1.13 (0.75, 1.67)	1.21 (0.83, 1.77)	0.87 (0.32, 2.31)	1.01 (0.42, 2.42)	1.14 (0.71, 1.76)	1.24 (0.81, 1.89)
Transient ischemic attack	1.53 (1.09, 2.11)	1.50 (1.09, 2.06)	0.99 (0.49, 2.03)	1.21 (0.63, 2.33)	1.56 (1.06, 2.26)	1.47 (1.03, 2.12)
Deep vein thrombosis	1.05 (0.79, 1.37)	1.15 (0.89, 1.49)	1.14 (0.61, 2.12)	1.10 (0.64, 1.90)	0.99 (0.72, 1.35)	1.10 (0.81, 1.48)
Pulmonary embolism	1.10 (0.79, 1.50)	1.17 (0.86, 1.59)	0.98 (0.48, 1.99)	0.95 (0.52, 1.73)	1.10 (0.75, 1.58)	1.14 (0.80, 1.64)

POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use.

eTable 16. Associations of Having Irregular Cycles With Prevalent Cardiometabolic Conditions Among 25 115 Participants Who Responded to the Relevant Survey Question for Irregular Cycles, Adjusted for Covariates, Comparing Results From Main Analyses to Sensitivity Analyses Excluding Those With Possible PCOS

Conditions	POR (95% CI)[a]	
	Among participants without PCOS	
	Main analyses	Sensitivity analyses, excluding those with possible PCOS[b]
N	20130	18878
Obesity	1.13 (1.05, 1.21)	0.98 (0.90, 1.07)
Prediabetes	1.38 (1.20, 1.58)	1.25 (1.06, 1.48)
Type 1 diabetes	1.04 (0.67, 1.57)	0.91 (0.52, 1.50)
Type 2 diabetes	1.36 (1.08 1.69)	1.35 (1.02, 1.75)
High cholesterol	1.17 (1.05, 1.30)	1.13 (1.00, 1.29)
Hypertension	1.14 (1.02, 1.28)	1.02 (0.89, 1.17)
Metabolic syndrome	1.36 (1.11, 1.66)	1.10 (0.85, 1.41)
Arrhythmia	1.21 (1.02, 1.43)	1.10 (0.90, 1.35)
Congestive heart failure	1.00 (0.56, 1.68)	0.90 (0.43, 1.69)
Coronary artery disease	0.63 (0.21, 1.48)	0.39 (0.06, 1.29)
Heart attack	1.72 (0.97, 2.92)	1.58 (0.77, 3.00)
Heart valve disease	1.26 (0.86, 1.82)	1.17 (0.74, 1.79)
Stroke	1.14 (0.71, 1.76)	1.26 (0.74, 2.04)
Transient ischemic attack	1.56 (1.06, 2.26)	1.56 (1.00, 2.37)
Deep vein thrombosis	0.99 (0.72, 1.35)	0.98 (0.66, 1.40)
Pulmonary embolism	1.10 (0.75, 1.58)	1.18 (0.76, 1.78)

POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[b] Based on self-reported irregular cycles AND signs of hirsutism.

eTable 17. Associations of Having PCOS With Prevalent Cardiometabolic Conditions, Comparing Results From Main Analyses Adjusted for Gravidity to Results Adjusted for Parity

Conditions	POR (95% CI)	
	Adjusted model [a]	Adjusted model [b]
Total N	**47152**	**47562**
Obesity	2.94 (2.77, 3.12)	2.92 (2.75, 3.10)
Prediabetes	3.75 (3.47, 4.06)	3.74 (3.46, 4.05)
Type 1 diabetes	1.43 (1.07, 1.90)	1.44 (1.07, 1.90)
Type 2 diabetes	2.76 (2.43, 3.15)	2.75 (2.41, 3.13)
High cholesterol	1.68 (1.55, 1.81)	1.68 (1.55, 1.81)
Hypertension	1.57 (1.45, 1.70)	1.57 (1.45, 1.70)
Metabolic syndrome	3.28 (2.94, 3.66)	3.25 (2.91, 3.63)
Arrhythmia	1.37 (1.20, 1.55)	1.37 (1.20, 1.55)
Congestive heart failure	1.23 (0.83, 1.76)	1.24 (0.84, 1.78)
Coronary artery disease	2.92 (1.95, 4.29)	2.92 (1.96, 4.28)
Heart attack	1.79 (1.23, 2.54)	1.76 (1.22, 2.49)
Heart valve disease	1.21 (0.89, 1.62)	1.25 (0.92, 1.66)
Stroke	1.66 (1.21, 2.24)	1.70 (1.24, 2.30)
Transient ischemic attack	1.87 (1.44, 2.40)	1.90 (1.47, 2.44)
Deep vein thrombosis	1.54 (1.24, 1.89)	1.55 (1.26, 1.91)
Pulmonary embolism	1.83 (1.43, 2.32)	1.84 (1.44, 2.33)

POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[b] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, parity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

eTable 18. Associations of Prolonged Time to Cycle Regularity With Prevalent Cardiometabolic Conditions, Comparing Results From Main Analyses Adjusted for Gravidity to Results Adjusted for Parity

Conditions	POR (95% CI)[a]					
	Among all participants in this study		Among participants with PCOS		Among participants without PCOS	
	Adjusted model [a]	Adjusted model [b]	Adjusted model [a]	Adjusted model [b]	Adjusted model [a]	Adjusted model [b]
N	**41424**	**41768**	**5454**	**5725**	**35872**	**5708**
Obesity	1.21 (1.16, 1.27)	1.21 (1.15, 1.26)	1.03 (0.91, 1.16)	1.03 (0.91, 1.15)	1.02 (0.97, 1.08)	1.02 (0.97, 1.08)
Prediabetes	1.49 (1.38, 1.61)	1.49 (1.38, 1.60)	1.01 (0.89, 1.16)	1.01 (0.88, 1.15)	1.20 (1.08, 1.33)	1.20 (1.08, 1.33)
Type 1 diabetes	1.54 (1.21, 1.95)	1.48 (1.17, 1.88)	1.34 (0.78, 2.35)	1.22 (0.71, 2.13)	1.52 (1.16, 1.99)	1.49 (1.13, 1.94)
Type 2 diabetes	1.45 (1.28, 1.65)	1.45 (1.27, 1.64)	1.11 (0.89, 1.38)	1.11 (0.89, 1.39)	1.24 (1.05, 1.46)	1.23 (1.04, 1.45)
High cholesterol	1.17 (1.09, 1.25)	1.17 (1.10, 1.25)	1.10 (0.95, 1.28)	1.11 (0.96, 1.29)	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
Hypertension	1.16 (1.08, 1.24)	1.15 (1.07, 1.23)	1.00 (0.86, 1.16)	0.99 (0.85, 1.15)	1.09 (1.01, 1.19)	1.09 (1.00, 1.18)
Metabolic syndrome	1.45 (1.30, 1.62)	1.43 (1.28, 1.60)	1.07 (0.89, 1.28)	1.07 (1.28, 1.60)	1.14 (0.98, 1.33)	1.12 (0.97, 1.30)
Arrhythmia	1.20 (1.08, 1.33)	1.19 (1.07, 1.32)	1.02 (0.79, 1.31)	1.00 (0.78, 1.28)	1.20 (1.06, 1.35)	1.19 (1.06, 1.34)
Congestive heart failure	1.31 (0.96, 1.76)	1.33 (0.98, 1.79)	1.36 (0.64, 2.93)	1.30 (0.62, 2.80)	1.30 (0.92, 1.81)	1.34 (0.95, 1.86)
Coronary artery disease	1.10 (0.74, 1.61)	1.15 (0.78, 1.67)	0.99 (0.47, 2.06)	0.98 (0.47, 2.05)	0.96 (0.59, 1.52)	1.05 (0.65, 1.64)
Heart attack	1.09 (0.78, 1.50)	1.08 (0.78, 1.49)	0.91 (0.45, 1.81)	0.84 (0.42, 1.68)	1.05 (0.71, 1.52)	1.07 (0.73, 1.54)
Heart valve disease	1.16 (0.91, 1.46)	1.17 (0.93, 1.47)	1.45 (0.81, 2.66)	1.38 (0.77, 2.53)	1.08 (0.82, 1.40)	1.10 (0.84, 1.42)
Stroke	1.40 (1.07, 1.81)	1.42 (1.13, 1.78)	1.27 (0.71, 2.29)	1.26 (0.78, 2.05)	1.34 (0.98, 1.81)	1.34 (1.02, 1.74)
Transient ischemic attack	1.43 (1.14, 1.79)	1.41 (1.08, 1.83)	1.33 (0.82, 2.17)	1.21 (0.67, 2.19)	1.33 (1.01, 1.73)	1.38 (1.01, 1.85)
Deep vein thrombosis	1.07 (0.89, 1.29)	1.07 (0.89, 1.29)	0.74 (0.49, 1.09)	0.71 (0.47, 1.05)	1.13 (0.91, 1.39)	1.14 (0.91, 1.40)
Pulmonary embolism	1.23 (0.98, 1.53)	1.22 (0.97, 1.52)	0.88 (0.57, 1.38)	0.87 (0.56, 1.36)	1.21 (0.92, 1.58)	1.21 (0.92, 1.57)

POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

[b] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, parity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

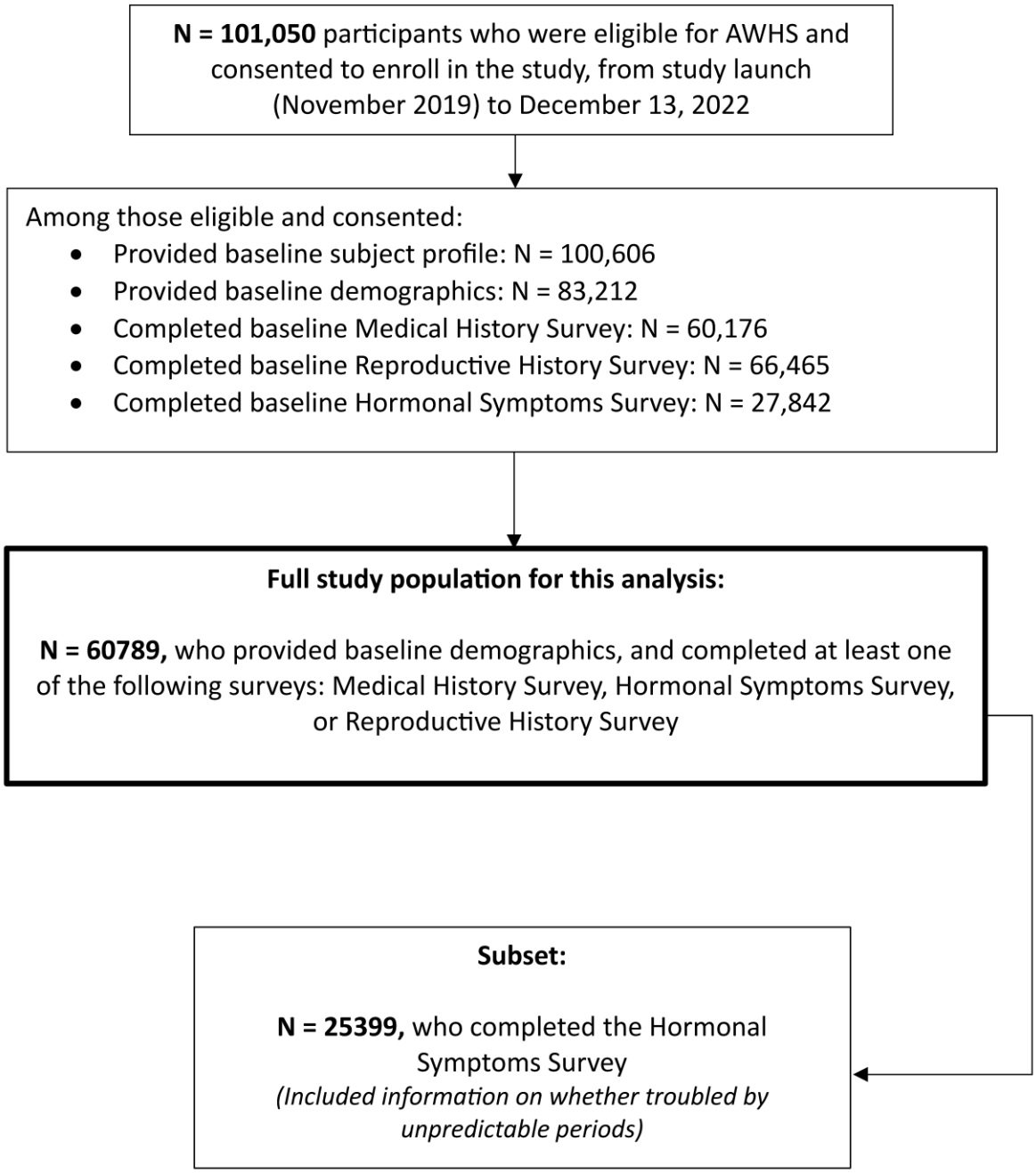
eTable 19. Associations of Having Irregular Cycles With Prevalent Cardiometabolic Conditions Among 25 115 Participants Who Responded to the Relevant Survey Question for Irregular Cycles, Comparing Results From Main Analyses Adjusted for Gravidity to Results Adjusted for Parity

Conditions	POR (95% CI)[a]					
	Among all participants		Among participants with PCOS		Among participants without PCOS	
	Adjusted model [a]	Adjusted model [b]	Adjusted model [a]	Adjusted model [b]	Adjusted model [a]	Adjusted model [b]
N	**22964**	**23136**	**2786**	**2810**	**20130**	**20271**
Obesity	1.38 (1.29, 1.47)	1.38 (1.29, 1.47)	1.42 (1.20, 1.68)	1.43 (1.21, 1.69)	1.13 (1.05, 1.21)	1.12 (1.05, 1.21)
Prediabetes	1.78 (1.60, 1.98)	1.77 (1.69, 1.96)	1.36 (1.12, 1.64)	1.34 (1.11, 1.62)	1.38 (1.20, 1.58)	1.36 (1.19, 1.56)
Type 1 diabetes	1.07 (0.73, 1.54)	1.08 (0.74, 1.54)	1.12 (0.46, 2.77)	1.10 (0.45, 2.69)	1.04 (0.67, 1.57)	1.06 (0.69, 1.59)
Type 2 diabetes	1.38 (1.15, 1.64)	1.38 (1.16, 1.64)	0.82 (0.61, 1.11)	0.83 (0.62, 1.13)	1.36 (1.08 1.69)	1.35 (1.07, 1.68)
High cholesterol	1.29 (1.18, 1.41)	1.28 (1.17, 1.41)	1.29 (1.05, 1.59)	1.30 (1.06, 1.60)	1.17 (1.05, 1.30)	1.16 (1.04, 1.29)
Hypertension	1.20 (1.09, 1.32)	1.20 (1.09, 1.32)	1.13 (0.91, 1.40)	1.12 (0.90, 1.39)	1.14 (1.02, 1.28)	1.14 (1.02, 1.28)
Metabolic syndrome	1.73 (1.49, 2.01)	1.72 (1.48, 2.00)	1.35 (1.05, 1.75)	1.36 (1.05, 1.75)	1.36 (1.11, 1.66)	1.35 (1.10, 1.65)
Arrhythmia	1.21 (1.04, 1.41)	1.20 (1.03, 1.40)	1.15 (0.80, 1.67)	1.16 (0.80, 1.68)	1.21 (1.02, 1.43)	1.20 (1.01, 1.42)
Congestive heart failure	1.04 (0.63, 1.66)	1.03 (0.62, 1.64)	1.85 (0.51, 6.85)	1.94 (0.54, 7.33)	1.00 (0.56, 1.68)	0.98 (0.55, 1.66)
Coronary artery disease	0.78 (0.35, 1.56)	0.75 (0.34, 1.48)	0.83 (0.20, 3.10)	0.81 (0.19, 2.98)	0.63 (0.21, 1.48)	0.59 (0.20, 1.38)
Heart attack	1.80 (1.11, 2.85)	1.67 (1.03, 2.64)	1.57 (0.55, 4.59)	1.49 (0.52, 4.37)	1.72 (0.97, 2.92)	1.58 (0.90, 2.67)
Heart valve disease	1.27 (0.90, 1.76)	1.27 (0.90, 1.76)	1.07 (0.46, 2.50)	1.05 (0.45, 2.46)	1.26 (0.86, 1.82)	1.25 (0.85, 1.80)
Stroke	1.13 (0.75, 1.67)	1.16 (0.77, 1.71)	0.87 (0.32, 2.31)	0.87 (0.32, 2.33)	1.14 (0.71, 1.76)	1.17 (0.74, 1.80)
Transient ischemic attack	1.53 (1.09, 2.11)	1.52 (1.09, 2.10)	0.99 (0.49, 2.03)	0.97 (0.47, 1.99)	1.56 (1.06, 2.26)	1.55 (1.05, 2.24)
Deep vein thrombosis	1.05 (0.79, 1.37)	1.07 (0.82, 1.40)	1.14 (0.61, 2.12)	1.19 (0.64, 2.20)	0.99 (0.72, 1.35)	1.01 (0.73, 1.36)
Pulmonary embolism	1.10 (0.79, 1.50)	1.08 (0.78, 1.48)	0.98 (0.48, 1.99)	0.91 (0.45, 1.82)	1.10 (0.75, 1.58)	1.10 (0.75, 1.57)

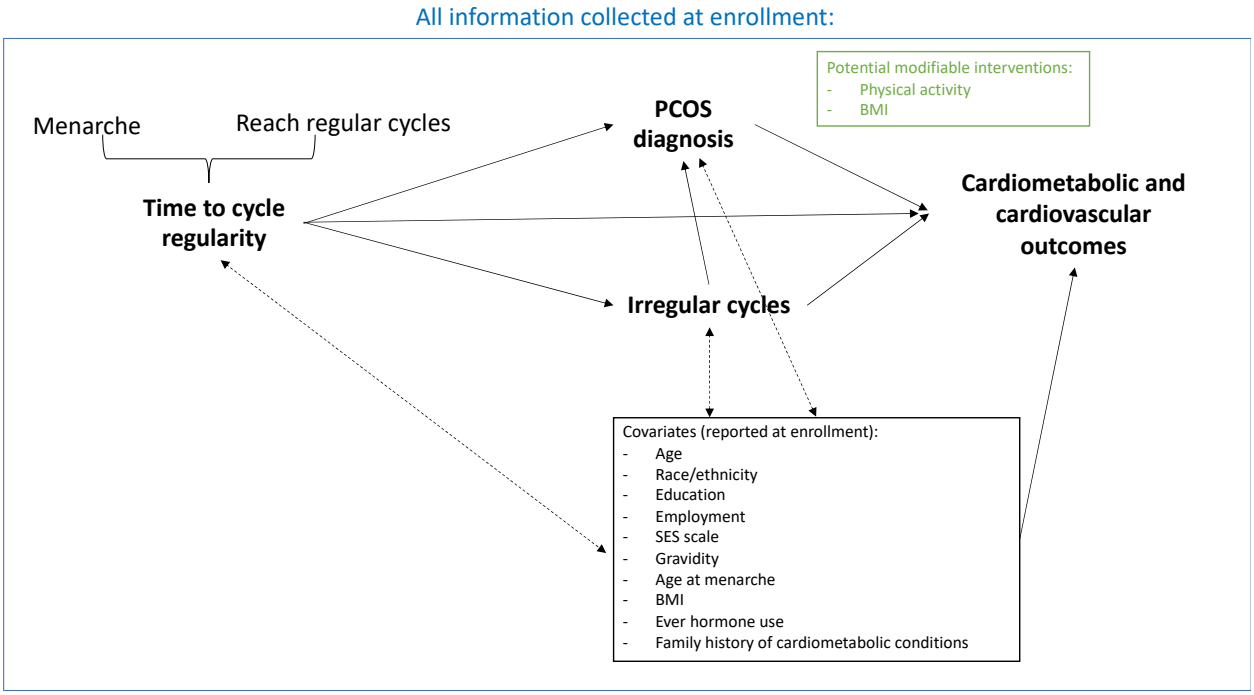
POR: prevalence odds ratio; CI: confidence interval.

[a] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, gravidity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.

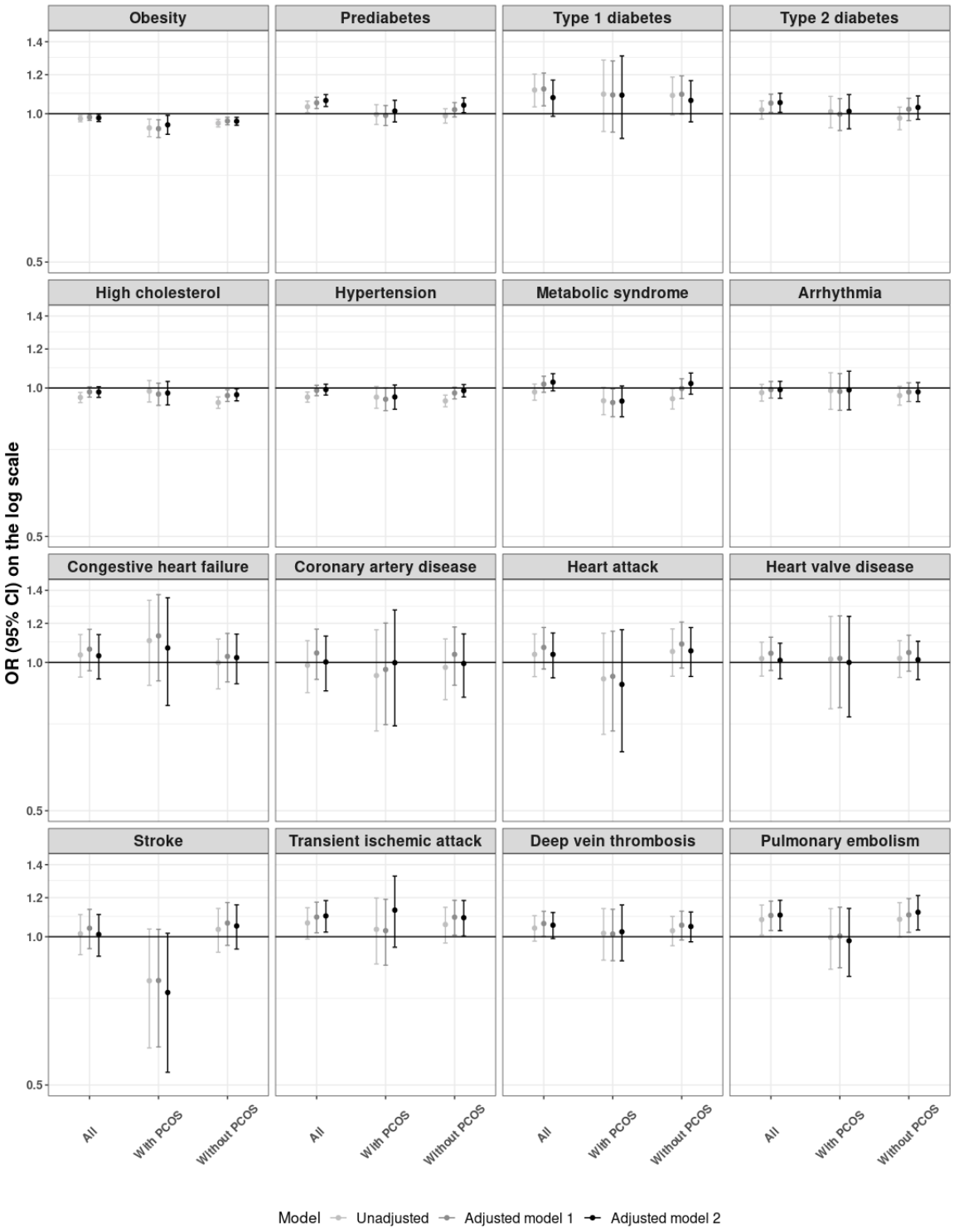
[b] Adjusted for age, race/ethnicity, SES, employment, education, age at menarche, parity, BMI (for outcomes other than obesity), family history of metabolic conditions, and ever hormone use. Data from participants with missing covariates were excluded from the analysis.



eFigure 1. Flowchart of Participants in This Study



eFigure 2. Conceptual Model for the Study Questions
Dashed lines indicate potential correlations or associations, although current evidence might be inconclusive.



eFigure 3. Associations of 1-Year Increase in Time to Cycle Regularity With Prevalent Cardiometabolic Conditions Among a Subset of 37 259 participants Who Have Reached Cycle Regularity at Enrollment (Not Due to Hormone Use)

OR: prevalence odds ratio; CI: confidence interval.