Received: 21 June 2024 | Revised: 6 September 2024 | Accepted: 3 October 2024

DOI: 10.1111/aogs.14991

ORIGINAL RESEARCH

Chronotypes in middle-aged women with polycystic ovary syndrome: A population-based study

Linnea Kroneld[1] | Päivi Polo-Kantola[1] | Meri-Maija Ollila[2] | Riikka K. Arffman[2] | Elisa Hurskainen[2] | Laure Morin-Papunen[2] | Varpu Jokimaa[1] | Terhi T. Piltonen[2]

[1]Department of Obstetrics and Gynecology, University of Turku and Turku University Hospital, Turku, Finland

[2]Department of Obstetrics and Gynecology, University of Oulu and Oulu University Hospital, Research Unit of Clinical Medicine, Medical Research Center, Oulu, Finland

Correspondence
Terhi T. Piltonen, Department of Obstetrics and Gynecology, University of Oulu and Oulu University Hospital, Research Unit of Clinical Medicine, Medical Research Center, Kajaanintie 50, 90220 Oulu, Finland.
Email: terhi.piltonen@oulu.fi

Abstract

Introduction: Circadian rhythm disruption has been associated with the risk of polycystic ovary syndrome (PCOS), as the evening chronotype (EC) shares several traits with PCOS, including metabolic disorders, cardiovascular diseases, and psychiatric disorders. It has been suggested that the biological clock could be targeted with new, preventive, and therapeutic strategies for PCOS in women with biorhythm disorders. We evaluated inner circadian rhythmicity in middle-aged women with PCOS in a population-based setting, focusing on whether women with PCOS and an EC have a specific subtype in relation to their clinical characteristics.

Material and Methods: The data derived from the Northern Finland Birth Cohort, a population-based longitudinal birth cohort of 12 058 individuals born in 1966. We compared the circadian phenotype between 314 women with PCOS (according to the Rotterdam criteria) and 1248 women without PCOS at age 46 years using the validated Finnish shortened 6-item Morningness-Eveningness Questionnaire (sMEQ) and the single-item self-assessed morningness-eveningness question.

Results: PCOS was not associated with the EC by the sMEQ ($p = 0.495$) or self-assessment ($p = 0.303$). The self-assessed morningness-eveningness values differed from the sMEQ chronotype distribution ($p < 0.001$), nevertheless, the most frequent chronotype was the intermediate chronotype (IC) determined by both chronotyping methods (sMEQ PCOS 47.7% vs. 45.2% non-PCOS; self-assessment PCOS 66.5% vs. 68.4% non-PCOS). The hyperandrogenic PCOS phenotypes A–C did not differ from the non-hyperandrogenic phenotype D as for the chronotype ($p = 0.271$). The EC was associated in both groups with depressive and anxiety symptoms (PCOS $p = 0.012$, non-PCOS $p < 0.001$) and the use of sleep medication (PCOS $p = 0.017$, non-PCOS $p < 0.001$).

Abbreviations: BMI, body mass index; EC, evening chronotype; FAI, free androgen index; IC, intermediate chronotype; MC, morning chronotype; MEQ, morningness-eveningness questionnaire; OA, oligo-amenorrhea; OR, odds ratio; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome; sMEQ, shortened Morningness-Eveningness Questionnaire.

Varpu Jokimaa and Terhi T. Piltonen shared senior authorship.

Conclusions: The EC was not over-represented in middle-aged women with PCOS or in the hyperandrogenic PCOS phenotypes A–C in our study. This does not support the need for chronotyping in the comprehensive assessment of women with PCOS. However, as chronotypes tend to change with aging, cross-sectional studies in different age groups are warranted to draw conclusions on the role of chronotypes in PCOS and the associated metabolic risks.

KEYWORDS
chronotype, circadian rhythm, MEQ, morningness-eveningness, PCOS, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder in women, affecting one woman out of eight worldwide. The diagnostics rely on the Rotterdam criteria, endorsed by the international PCOS guideline.[1] Typical symptoms include oligo-amenorrhea (OA), hirsutism, and anovulation, but the clinical phenotype varies significantly. Four different phenotypes have been identified: type A includes hyperandrogenism+ OA+polycystic ovarian morphology (PCOM), type B hyperandrogenism + OA, type C hyperandrogenism + PCOM and type D OA+PCOM.[2] PCOS, and especially hyperandrogenic phenotypes A–C, are associated with significant metabolic comorbidities, such as obesity, insulin resistance, and susceptibility to metabolic syndrome.[3,4] Therefore, PCOS is not only a gynecological disorder but a wider health issue that seems to prevail beyond menopause.[4–6]

The circadian rhythm is a natural internal process that regulates the sleep–wake cycle and repeats roughly every 24 h. It is driven by an endogenous circadian clock that is entrained by the light–dark cycle but also controlled by social habits. The chronotype determines an individual's circadian preference for behavioral and biological rhythms and is known to change with age.[7,8] Three chronobiological phenotypes are recognized: the morning chronotype (MC), the intermediate chronotype (IC), and the evening chronotype (EC). The prevalence of an EC is the highest in young adulthood and decreases with age.[7,8] Individuals with an EC have later sleep–wake schedules, later diurnal peaks of alertness and performance, and later sleep propensity rhythms than individuals with an MC.[9] Moreover, individuals with an EC have been linked to a higher risk of social jet lag and circadian rhythm misalignment caused by late sleep onset combined with early waking and accumulation of substantial sleep deprivation during the work week.[10] Mounting evidence suggests that eveningness and circadian clock disruption increase susceptibility to endocrine and metabolic disorders associated with obesity and diabetes.[11,12]

Previous studies have inferred that circadian genes and altered gene expression caused by circadian misalignment might be involved in the development of PCOS.[13–15] It has even been suggested that the biological clock could be a target for new, feasible preventive and therapeutic strategies for PCOS in women with biorhythm disorders.[13] To our knowledge, however, only one case–control study has investigated circadian rhythmicity in women with PCOS.[16] In that study, PCOS was associated with the EC, and the women of fertile age with PCOS and an EC were more likely to be obese, hyperandrogenic, and insulin-resistant, with unhealthier eating and lifestyle habits, than the women with PCOS and an MC or IC. This result underlined the relevance of including chronotype assessment in the evaluation and treatment of women with PCOS.[16] To the best of our knowledge, no studies have evaluated circadian rhythmicity in different PCOS phenotypes or in middle-aged PCOS population.

Key message

At age 46 years, women with PCOS did not differ in their chronotype distribution compared with women without PCOS. The hyperandrogenic (A–C) and non-hyperandrogenic (D) phenotypes showed similar chronotype distributions.

The main aim of our study was to evaluate the inner circadian rhythmicity of women with PCOS in a population-based setting. As PCOS and the EC are both associated with metabolic disorders, cardiovascular diseases, and psychiatric disorders,[17–21] we were especially interested in whether the EC is over-represented also among middle-aged women with PCOS and whether the different PCOS phenotypes differ as for their chronotypes. We hypothesized that in contrast to the general population in which the EC is known to decrease with age after reaching young adulthood, women with PCOS would still be more likely to represent the EC at the age of 46 years, and this would be seen especially in the hyperandrogenic phenotypes A-C.

2 | MATERIAL AND METHODS

2.1 | Study population

Our study was a substudy of the Northern Finland Birth Cohort study, a large population-based longitudinal birth cohort consisting of 12 058 individuals (5889 women and 6169 men) born in 1966 in the two northernmost provinces of Finland. More detailed

descriptions of the study population and the formation of the PCOS and reference groups have been published earlier.[21,22] In our study, the data collected at the age of 31 years were used to identify women with PCOS, and the data collected at the age of 46 years were used to determine the chronotype.

The definition of PCOS used in our study followed the 2023 international evidence-based guideline for the assessment and management of PCOS.[1] Thus, women with PCOS were identified at age 31 as having met at least two of the following criteria: OA, hirsutism/biochemical hyperandrogenism, or an anti-müllerian hormone level ≥3.2 ng/mL (surrogate for PCOM); the formation of the study population has been previously reported in detail.[23] Moreover, the women with PCOS were classified into phenotypes A–D. Information regarding hyperandrogenism, OA and anti-müllerian hormone was required to determine phenotype for women with PCOS.

The women without PCOS (i.e., the reference group) were selected from the cohort at the age of 31. A regular menstrual cycle, absence of hirsutism, and normal testosterone and free androgen index (FAI) as well as anti-müllerian hormone levels <3.2 ng/mL were required. At the age of 31 years, pregnant women ($n=277$), those using hormonal contraception ($n=858$), and, later, those not permitting the use of their data ($n=54$) or women without PCOS self-reporting PCOS diagnosis at the age of 46 years ($n=20$) were excluded. In addition, filling in at least one of the chronotype-related questions at the age of 46 years was required. With these criteria, altogether, 1562 women were included in the study, of which 314 women were defined as women with PCOS and 1248 women as women without PCOS (Figure 1). The PCOS phenotype could be determined for all women with PCOS.

2.2 | Chronotype and sleep variable analysis

For the chronotyping, we used both the Finnish version of the shortened Morningness-Eveningness Questionnaire (sMEQ)[24,25] and the single-item self-assessed morningness-eveningness question. The sMEQ includes six questions (items 4, 7, 9, 15, 17, and 19) drawn from the original 19-item MEQ[26] version: 1) easiness getting up in the morning, 2) tiredness during the first half hour in the morning, 3) anticipated quality of performance working out in the morning, 4) preferred time for 2 h of hard manual labor, 5) preferred consecutive 5 h work hours and 6) self-assessed morningness-eveningness (Appendix S1). The scoring of the sMEQ acts as a continuous descriptive variable but is also used to classify the participants into the three different groups of circadian rhythmicity. These three classes were used in the analyses: MC (19–27 points), IC (13–18 points), and EC (5–12 points). The self-reported bedtimes and waketimes were used to validate the sMEQ chronotype distribution on a three-point scale: <10 pm early bedtime, 10–12 pm average bedtime, >12 pm late bedtime and <6 am early waketime, 6–8 am average waketime, >8 am late waketime. The calculated Cronbach's alpha for the reliability of the sMEQ in the study population was 0.76 indicating a good internal consistency.

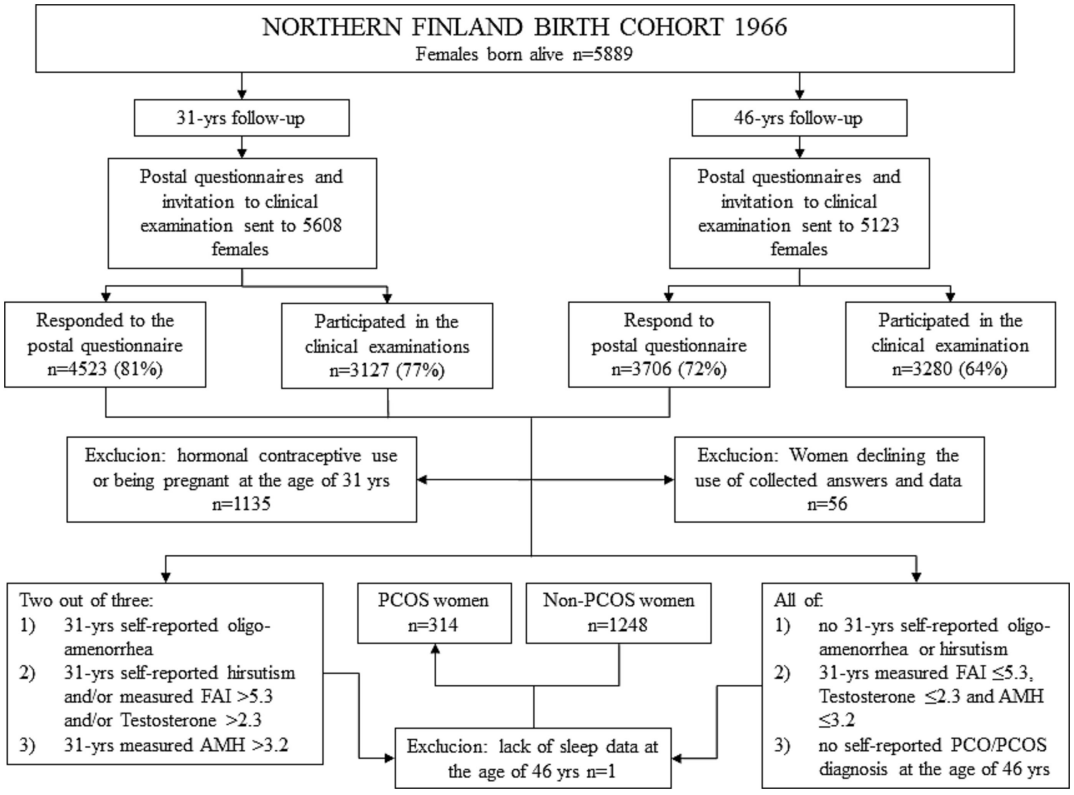

FIGURE 1 Flowchart: Formation of PCOS and non-PCOS groups. AMH, anti-müllerian hormone; FAI, free androgen index; PCOS, polycystic ovary syndrome.

Self-assessed morningness-eveningness was used as the single-item test for the chronotype. Similar to the sMEQ, the single-item morningness-eveningness was transformed into a three-category variable in response to the sMEQ chronotyping: MC (definitely a "morning" person), IC (more a "morning" than an "evening" person or more an "evening" than a "morning" person), and EC (definitely an "evening" person).

2.3 | Basic characteristics

The basic characteristics collected included body mass index (BMI, kg/m^2), smoking (yes/no), alcohol consumption (no use, light use <150 g/week, moderate use 150–210 g/week or heavy use >210 g/week), physical activity (low = no strenuous sports, moderate = everyday functional exercise ≥4 h/week, or high = fitness sports ≥2 h/week or competitive training several times a week), family status (other people living in the household or living alone) and educational level (low = basic education, middle = secondary education, or high = higher education degree). The women were classified as regular daytime workers (work hours between 6 am–6 pm) and shift workers. The shift workers had any other working hours than regular daytime workers, and shiftwork included evening, two-shift, and nighttime shift work.

The state of climacteric transition was assessed based on the menstrual cycle and climacteric vasomotor symptoms.[27] Women reported their climacteric vasomotor symptoms (hot flashes and/or night sweats) on a 5-point scale, which was dichotomized in the statistical analysis as yes (=some, quite a lot, or very much) or no (=not at all or hardly any). They were also asked whether they currently had a regular, irregular or no menstrual cycle. The depressive and anxiety symptoms were evaluated using the Hopkins symptom checklist-25,[28] in which cutoff points of ≥1.55 for milder and ≥1.75 for more serious and clinically relevant depressive and anxiety symptoms have previously been used.[28] Current medication was assessed, including use of sleep medications: drugs the women self-reported using as sleep medications and those nationally recommended for the use of insomnia were selected (Anatomical Therapeutic Chemical Classification codes: N05AA02, N05AA03, N05AF03, N05AH04, N05BA01, N05BA04, N05BB01, N05CD07, N05CF01, N05CF02, N05CH01, N06AA06, N06AA09, N06AA12, N06AX05, and N06AX11).[29] The FAI was calculated using the equation 100 × testosterone (nmol/liter)/sex hormone binding globulin, (nmol/liter). From the basic characteristics, the testosterone and FAI were clinically measured at the age of 31 and BMI at the age of 46 years. All other variables were self-reported in the questionnaire completed at 46 years of age.

2.4 | Statistical analyses

The normality of the continuous variables was assessed visually. Differences in characteristics among the study groups were analyzed with the Mann–Whitney *U*-test, Kruskal–Wallis test, or Chi-square test, as appropriate. The data are shown as medians with 25th and 75th percentiles or as counts and percentages. To investigate associations between the study groups and chronotype classifications, a multinomial logistic regression was used for an sMEQ-based three-class chronotype (MC/IC/EC). For a two-class self-assessed morningness-eveningness, a logistic regression model was applied. The sMEQ-score was also analyzed as a continuous variable with a linear regression model. Additionally, associations with preferred consecutive 5 h work hours were examined with a Poisson regression model. Univariate models, as well as multivariate models with adjustments for BMI (continuous), education, shiftwork status, and climacteric vasomotor symptoms (categorical), separately and combined, were fitted. The selection of the confounders was based on the literature[30,31] and statistical information. For the logistic and multinomial logistic regressions, the results are presented as odds ratios (ORs), for the Poisson regression as incidence rate ratios, and for the linear regression as regression coefficient betas, all with 95% confidence intervals and *p*-values. The linear multivariate regression models were checked for meeting the assumptions: the residuals were normally distributed and showed no patterns of heteroscedasticity or autocorrelation. With all adjusting variables added, variance inflation factor values ranged between 1.012 and 1.044, confirming the absence of multicollinearity. Spearman correlations between adjusting variables varied from −0.203 to 0.100. For the logistic regression models, the Hosmer-Lemeshow test *p*-values were non-significant, indicating that the models provided a good fit. Also, for multinomial logistic regression models, non-significant *p*-values from Pearson and Deviance goodness-of-fit tests confirmed that the models fit the data well. Likewise, for Poisson regression models, the non-significant Chi-square test *p*-values confirmed a good model fit.

The statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corporation, Armonk, NY, USA). A *p*-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Basic characteristics of women with PCOS and women without PCOS

Compared to the women without PCOS, the women with PCOS had a higher average BMI ($p = 0.001$). However, the majority (PCOS 72.4% and non-PCOS 78.8%) of the women in both groups had a BMI < 30 kg/m^2. Fewer women with PCOS reported having currently climacteric vasomotor symptoms ($p = 0.034$) or an irregular or no menstrual cycle ($p = 0.003$), and fewer of them lived alone ($p = 0.022$). A greater proportion of women with PCOS had lower levels of education ($p = 0.039$). The women with PCOS had higher testosterone ($p < 0.001$) and FAI ($p < 0.001$) levels at the age of 31 years, as expected. No differences were found in smoking, alcohol consumption, physical activity, number of shift workers, depressive and anxiety symptoms, or use of sleep medication between the groups (Table 1).

TABLE 1 Basic characteristics of women with PCOS and women without PCOS.

	n = 314	PCOS	*n* = 1248	non-PCOS	*p*-value
BMI (kg/m^2)					
Median (Q1, Q3)	272	26.5 (23.7, 30.4)	1049	25.3 (22.7, 29.2)	0.001
Smoking					
Yes, *n* (%)	310	59 (19.0)	1239	249 (20.1)	0.674
Alcohol consumption[a]	314		1247		0.172
No use, *n* (%)		46 (14.6)		144 (11.5)	
Light use, *n* (%)		245 (78.0)		1024 (82.1)	
Moderate use, *n* (%)		14 (4.5)		35 (2.8)	
Heavy use, *n* (%)		9 (2.9)		44 (3.5)	
Physical activity	310		1242		0.681
Low, *n* (%)		67 (21.6)		255 (20.5)	
Moderate, *n* (%)		134 (43.2)		517 (41.6)	
High, *n* (%)		109 (35.2)		470 (37.8)	
Family status					
Living alone, *n* (%)	314	19 (6.1)	1246	128 (10.3)	0.022
Educational level, *n* (%)	304		1205		0.039
Low, *n* (%)		20 (6.6)		69 (5.7)	
Middle, *n*(%)		205 (67.4)		731 (60.7)	
High, *n* (%)		79 (26.0)		405 (33.6)	
Shiftwork[b]					
Yes, *n* (%)	265	71 (26.8)	1057	225 (21.3)	0.055
Climacteric vasomotor symptoms					
Yes, *n* (%)	312	37 (11.9)	1242	208 (16.7)	0.034
Menstural cycle	309		1220		0.003
Regular, *n* (%)		194 (62.8)		634 (52.0)	
Irregular, *n* (%)		33 (10.7)		175 (14.3)	
No cycle, *n* (%)		82 (26.5)		411 (33.7)	
Hopkins symptom checklist-25					
Median (Q1, Q3)	296	1.3 (1.1,1.5)	1172	1.2 (1.1,1.5)	0.631
Sleep medication					
Yes, n (%)	278	20 (7.2)	1073	93 (8.7)	0.429
Testosterone[c]					
Median (Q1, Q3)	277	1.2 (0.9, 1.6)	754	0.9 (0.7, 1.1)	<0.001
FAI[d]					
Median (Q1, Q3)	244	2.4 (1.5, 3.9)	579	1.5 (1.0, 2.1)	<0.001

Note: Data is expressed as numbers (%).

Abbreviations: BMI, body mass index; FAI, free androgen index; PCOS, polycystic ovary syndrome; Q1, first quartile; Q3, third quartile.

[a]Light use <150 g/week; moderate use 150–210 g/week; heavy use >210 g/week.

[b]Any other than regular daytime work.

[c]Measured free serum testosterone (nmol/l) at age 31.

[d]Calculated free androen index at age 31.

When the basic characteristics in the three different sMEQ groups were compared separately among the women with PCOS and the women without PCOS, several differences were found between the women without PCOS as for their chronotype groups. A larger proportion of women without PCOS and an EC were smokers ($p = 0.038$), had more extensive alcohol consumption ($p = 0.031$), were physically less active ($p < 0.001$), were shift workers ($p = 0.014$), had more depressive and anxiety symptoms ($p < 0.001$), and used sleep medication more often ($p < 0.001$) compared with the women without PCOS and with an MC or IC. Furthermore, the women without PCOS and an EC had lower FAI levels ($p = 0.021$) at the age of 31 years than the women

TABLE 2 Basic characteristics of women with PCOS and women without PCOS by sMEQ.

	PCOS					Non-PCOS				
	n = 314	MC[a]	IC[a]	EC[a]	*p*-value	*n* = 1248	MC[a]	IC[a]	EC[a]	*p*-value
BMI (kg/m^2)										
Median (Q1, Q3)	268	27.2 (23.7, 30.5)	26.3 (23.4, 29.9)	27.2 (24.9, 30.7)	0.635	1031	25.1 (22.7, 28.7)	25.3 (22.7, 29.3)	25.5 (22.5, 29.7)	0.645
Smoking										
Yes, *n* (%)	306	15 (12.8)	31 (21.2)	12 (27.9)	0.061	1211	91 (17.8)	106 (19.4)	42 (27.1)	0.038
Alcohol consumption[b]	310				0.988	1220				0.031
No use, *n* (%)		19 (16.0)	21 (14.2)	6 (14.0)			50 (9.7)	74 (13.4)	18 (11.6)	
Light use, *n* (%)		92 (77.3)	115 (77.7)	34 (79.1)			439 (85.6)	440 (79.7)	123 (79.4)	
Moderate use, *n* (%)		4 (3.4)	8 (5.4)	2 (4.7)			13 (2.5)	18 (3.3)	3 (1.9)	
Heavy use, *n* (%)		4 (3.4)	4 (2.7)	1 (2.3)			11 (2.1)	20 (3.6)	11 (7.1)	
Physical activity	307				0.742	1214				<0.001
Low, *n* (%)		27 (22.9)	28 (19.2)	11 (25.6)			75 (14.7)	122 (22.3)	53 (34.2)	
Moderate, *n* (%)		47 (39.8)	68 (46.6)	19 (44.2)			219 (42.9)	237 (43.2)	46 (29.7)	
High, *n* (%)		44 (37.3)	50 (34.2)	13 (30.2)			217 (42.5)	189 (34.5)	56 (36.1)	
Family status										
Living alone, *n* (%)	310	9 (7.6)	6 (4.1)	4 (9.3)	0.319	1218	45 (8.8)	62 (11.3)	19 (12.3)	0.296
Educational level	300				0.509	1177				0.401
Low, *n* (%)		8 (7.0)	9 (6.2)	3 (7.5)			29 (5.9)	31 (5.8)	6 (4.1)	
Middle, *n* (%)		74 (64.3)	105 (72.4)	24 (60.0)			303 (61.3)	331 (61.9)	82 (55.4)	
High, *n* (%)		33 (28.7)	31 (21.4)	13 (32.5)			162 (32.8)	173 (32.3)	60 (40.5)	
Shiftwork[c]										
Yes, *n* (%)	261	25 (25.5)	31 (25.2)	14 (35.0)	0.446	1035	75 (17.0)	110 (23.6)	34 (26.6)	0.014
Climacteric vasomotor symptoms										
Yes, *n* (%)	308	15 (12.7)	18 (12.2)	4 (9.3)	0.835	1214	93 (18.3)	81 (14.7)	28 (18.2)	0.255
Menstural cycle	304				0.552	1194				0.736
Regular, *n* (%)		71 (61.2)	91 (62.8)	30 (69.8)			267 (53.3)	277 (51.2)	78 (51.3)	
Irregular, *n* (%)		11 (9.5)	15 (10.3)	6 (14.0)			63 (12.6)	83 (15.3)	24 (15.8)	
No cycle, *n* (%)		34 (29.3)	39 (26.9)	7 (16.3)			171 (34.1)	181 (33.5)	50 (32.9)	
Hopkins symptom checklist-25										
Median (Q1, Q3)	292	1.2 (1.1, 1.4)	1.3 (1.2, 1.5)	1.4 (1.2, 1.7)	0.012	1145	1.2 (1.1, 1.4)	1.3 (1.1, 1.5)	1.4 (1.2, 1.7)	<0.001

TABLE 2 (Continued)

	PCOS					Non-PCOS				
	n = 314	MC[a]	IC[a]	EC[a]	*p*-value	*n* = 1248	MC[a]	IC[a]	EC[a]	*p*-value
Sleep medication										
Yes, *n* (%)	274	5 (5.1)	8 (5.8)	7 (18.4)	0.017	1053	29 (6.7)	35 (7.3)	27 (19.1)	<0.001
Testosterone[d]										
Median (Q1, Q3)	273	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.2 (0.9, 1.5)	0.957	736	0.8 (0.6, 1.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.112
FAI[e]										
Median (Q1, 3)	241	2.2 (1.3, 4.1)	2.5 (1.5, 3.8)	2.5 (1.8, 3.8)	0.730	564	1.5 (1.0, 2.1)	1.5 (1.1, 2.1)	1.1 (0.9, 1.8)	0.021

Note: Data is expressed as numbers (%).

Abbreviations: BMI, body mass index; FAI, free androgen index; PCOS, polycystic ovary syndrome; Q1, first quartile; Q3, third quartile.

[a]Morning chronotype (MC) 19-27p, Intermediate chronotype (IC) 13-18p, Evening chronotype (EC) 5-12p in sMEQ.

[b]Light use <150 g/week; moderate use 150–210 g/week; heavy use >210 g/week.

[c]Any other than regular daytime work.

[d]Measured free serum testosterone (nmol/l) at age 31.

[e]Calculated free androgen index at age 31.

without PCOS and with an MC or IC, but the testosterone levels did not differ.

Fewer differences were found between the sMEQ groups in the women with PCOS than between the sMEQ groups in the women without PCOS. However, more women with PCOS and an EC had depressive and anxiety symptoms ($p = 0.012$) and were more likely to use sleep medication ($p = 0.017$) than the women with PCOS and an MC or IC (Table 2). Only one woman with PCOS, who participated in the survey at the age of 46, was excluded from the study due to lack of sleep data. No differences in the basic characteristics compared to the other women with PCOS were found.

3.2 | Chronotype distribution in the women with PCOS and the women without PCOS

Figure 2 shows the distribution of chronotypes by sMEQ and self-assessment. The mean sMEQ score in the women with PCOS was 17.1 (standard deviation 4.4), and in the women without PCOS, it was 17.5 (standard deviation 4.2) ($p = 0.199$). The most frequent chronotypes by the sMEQ were IC (PCOS 47.7% and non-PCOS 45.2%) and MC (PCOS 38.4% and non-PCOS 42.0%). Of the women with and without PCOS, 13.9% and 12.7%, respectively, had an EC. No differences were found in the risk for EC (OR 1.20, 95% confidence interval 0.81–1.77) or IC (OR 1.16, 95% confidence interval 0.88–1.51) in the women with PCOS compared to the women without PCOS. The results remained after adjustment for BMI, education, shiftwork, and climacteric vasomotor symptoms. (Tables 3 and 4).

The values of self-assessed morningness-eveningness differed from the sMEQ chronotype distribution ($p < 0.001$). Most of the women who perceived themselves as "definitely morning types" were also classified with an MC according to the sMEQ (97.2%). Of the self-assessed women with an IC, 34.0% were classified as having an MC, and 30.7% of the women with a self-assessed EC were classified as having an IC when chronotyped by the sMEQ. Both the women with PCOS and the women without PCOS were more likely to self-assess themselves as having an IC (PCOS 66.5% and non-PCOS 68.4%) than an MC (PCOS 17.6% and non-PCOS 18.9%) or EC (PCOS 16.0% and non-PCOS 12.6%). When comparing the self-assessed morningness-eveningness between the women with PCOS and the women without PCOS, no difference was found (OR 1.36, 95% confidence interval 0.88–2.10 for EC/MC and OR 1.05, 95% confidence interval 0.75–1.46 IC/MC, $p = 0.303$). After adjustments, the results remained (Tables 3 and 4).

The self-reported bedtimes and waketimes of the different sMEQ chronotype groups corresponded to the sMEQ chronotype distribution. The women with an EC were more likely to have a late bedtime on working days (EC 9.7%, IC 1.6%, MC 0.3%, $p < 0.001$), but especially on leisure days (EC 38.3%, IC 11.0%, MC 4.6%, $p < 0.001$) compared with the women with an IC or MC. The women with an EC were also more likely to have a late waketime on working days (EC 14.3%, IC 3.6%, IC 1.7%, $p < 0.001$) and especially on leisure days (EC 87.3%, IC 65.3%, MC 26.9%, $p < 0.001$), respectively.

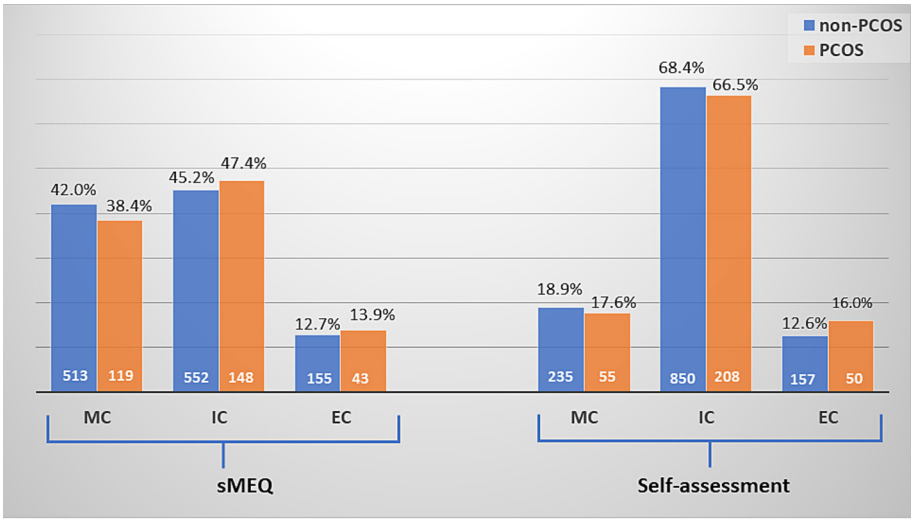

FIGURE 2 Chronotype distribution in women with PCOS and women without PCOS by sMEQ and Self-assessment. EC, evening chronotype; IC, intermediate chronotype; MC, morning chronotype; PCOS, polycystic ovary syndrome; sMEQ, shortened Morningness-Eveningness Questionnaire.

TABLE 3 Sleep and chronotype characteristics of women with PCOS and women without PCOS.

	n = 314	PCOS	n = 1248	non-PCOS	*p*-value
Easiness getting up in the morning	313		1246		0.404
Easy, *n* (%)		259 (82.7)		1055 (84.7)	
Not easy, *n* (%)		54 (17.3)		191 (15.3)	
Tiredness during the first half hour in the morning	314		*n*1246		0.896
Feeling tired, *n* (%)		101 (32.2)		396 (31.8)	
Feeling rested, *n* (%)		213 (67.8)		850 (68.2)	
Anticipated quality of performance working out in the morning	313		1248		0.562
Would be in a good shape, *n* (%)		146 (46.6)		605 (48.5)	
Would feel challenging, *n* (%)		167 (53.4)		643 (51.5)	
Preferred time for two hours of hard manual labor	*n*313		1247		0.223
Start at 8 or 11 am, *n* (%)		253 (80.8)		1044 (83.7)	
Start at 3 or 7 pm, *n* (%)		60 (19.2)		203 (16.3)	
Preferred consecutive five hour workhours					
Starting time, median (Q1, Q3)	*n*312	9.0 (8.0, 9.0)	1229	9.0 (8.0, 9.0)	0.860
Self-assessed morningness-eveningness	*n*313		1242		0.303
Morning chronotype, *n* (%)		55 (17.6)		235 (18.9)	
Intermediate chronotype, *n* (%)		208 (66.5)		850 (68.4)	
Evening chronotype, *n* (%)		50 (16.0)		157 (12.6)	
sMEQ score					
Mean (SD)	310	17.1 (4.4)	1220	17.5 (4.2)	0.199
Chronotype by sMEQ	310		1220		0.495
Morning chronotype[a], *n* (%)		119 (38.4)		513 (42.0)	
Intermediate chronotype[a], *n* (%)		148 (47.7)		552 (45.2)	
Evening chronotype[a], *n* (%)		43 (13.9)		155 (12.7)	

Note: Data is expressed as numbers (%).

Abbreviations: PCOS, polycystic ovary syndrome; sMEQ, shortened Morningness-Eveningness Questionnaire; SD, standard deviation; Q1, first quartile; Q3, third quartile.

[a]Morning chronotype 19-27p, intermediate chronotype 13-18p, evening chronotype 5-12p in sMEQ.

TABLE 4 Adjusted sleep and chronotype characteristics of women with PCOS and women without PCOS.

	Univariate analysis				Adjusted analysis[a]			
	n = 1530–1561	B or OR[b]	95% CI for B or OR	*p*-value	*n* = 1088–1106	B or OR[b]	95% CI for B or OR	*p*-value
Easiness getting up in the morning	1559	0.87	[0.62; 1.21]	0.404	1103	0.71	[0.48; 1.06]	0.091
Tiredness during the first half hour in the morning	1560	0.98	[0.75; 1.28]	0.896	1106	1.19	[0.86; 1.65]	0.300
Anticipated quality of performance working out in the morning	1561	1.08	[0.84; 1.38]	0.562	1105	1.01	[0.75; 1.35]	0.972
Preferred time for two hours of hard manual labor	1560	1.22	[0.89; 1.68]	0.223	1104	1.18	[0.80; 1.75]	0.398
Preferred consecutive five hour workhours	1541	1.00	[0.96; 1.05]	0.860	1096	1.00	[0.95; 1.05]	0.946
Self-assessed morningness-eveningness	1555	1.36/1.05	[0.88; 2.10]/ [0.75; 1.46]	0.303	1101	1.22/1.08	[0.71; 2.08]/ [0.73; 1.62]	0.777
sMEQ score, mean (SD)	1530	−0.35	[−0.87; 0.18]	0.199	1088	−0.30	[−0.92; 0.32]	0.341
Chronotype by sMEQ[c]	1530	1.20/1.16	[0.81; 1.77]/ [0.88; 1.51]	0.495	1088	1.32/1.19	[0.83; 2.11]/ [0.86; 1.64]	0.419

Abbreviations: CI, confidence interval; PCOS, polycystic ovary syndrome; sMEQ, shortened Morningness-Eveningness Questionnaire; OR, odds ratio; SD, standard deviation; Q1, first quartile; Q3, third quartile.

[a]Data adjusted with BMI, education, shiftwork and climacteric vasomotor symptoms.

[b]Unstandardised B for linear regression models, Exp(B) for logistic, Poisson and multinomial logistic regression models.

[c]Morning chronotype 19-27p, intermediate chronotype 13-18p, evening chronotype 5-12p in sMEQ.

3.3 | PCOS phenotypes and chronotype distribution

Most of the PCOS women represented phenotypes D or C (35.7%, *n* = 112 and 33.4% *n* = 105, respectively), whereas only 17.8% (*n* = 56) of the women were classified as phenotype A and 13.1% (*n* = 41) as phenotype B. The mean sMEQ score in the hyperandrogenic PCOS phenotypes A–C was 16.9 (standard deviation 4.4), and in phenotype D it was 17.6 (standard deviation 4.5) ($p = 0.433$). When comparing sMEQ and the self-assessed chronotype distribution between the PCOS phenotypes A–C and phenotype D, no differences between the groups were found (sMEQ $p = 0.452$ and self-assessed $p = 0.071$) (Table S1).

4 | DISCUSSION

The aim of our study was to investigate the association between PCOS and diurnal chronotypes. Contrary to our hypothesis, PCOS was not associated with an EC in middle-aged women. Further, the chronotypes of hyperandrogenic PCOS phenotypes A–C did not differ from those of PCOS phenotype D. Most of the women with PCOS and the women without PCOS were classified as IC both by the sMEQ and by self-assessment. An EC was associated with depressive and anxiety symptoms and the use of sleep medication both in the women with PCOS and the women without PCOS.

To the best of our knowledge, only one previous study[16] by an Italian study group has surveyed the possible association between diurnal preference and PCOS in a case–control study setting, but with no phenotype analysis. They showed that women of fertile age with PCOS had a higher prevalence of an EC, which was additionally associated with a worse hormonal and metabolic profile. Our study was not able to confirm this finding in our middle-aged population. In addition to the population-based differences, the differences may be explained by the different study designs. Although both were case–control studies, there were differences in the selection strategy and population characteristics. The population-based setting of our study made it likely that women with milder menstrual irregularity and hyperandrogenic symptoms were included in our PCOS population, however, thus reflecting the real-life range of PCOS phenotypes. The PCOS group in Barrea et al.'s study was selected from an endocrinology unit. A difference in patient characteristics has been shown in a previous systematic review and meta-analysis comparing referral versus unselected population studies.[32] Compared to our women with PCOS, the women with PCOS in Barrea et al.'s study were more likely to be obese, suggesting a possible dominance of the PCOS phenotype A. As for participant age, the women in our study were older and of similar age, whereas Barrea et al.ss study included women of fertile age with an age range of over 20 years. This is important, as there is a correlation between age and chronotype, with a decreasing probability of eveningness after reaching young adulthood and when women are approaching menopause.[7,8,30] Thus, taking the results of these studies together, one can hypothesize that the connection between PCOS and EC might be more related to younger women with PCOS, underlining the role of more hyperandrogenic phenotypes at a young age. Further, we used the shortened sMEQ alongside the self-assessed morningness-eveningness and not the original 19-item MEQ that Barrea et al. used. However, the

original MEQ and various shortened versions of the MEQ are widely used, as are validated scales to measure chronotypes, especially in epidemiological studies.[33–36]

Determining diurnal preference is a continuum that needs to be considered when evaluating different study results.[37] In our study, there was a difference between the number of women with an MC, IC, and EC based on the method used, as self-assessment showed a lower number of women with an MC than the sMEQ. Nevertheless, the chronotype distribution between the middle-aged women with and without PCOS was consistent with most of the women classified as IC, regardless of the method used. The distribution of chronotypes in our population correlated well with previously conducted chronotype studies in the Finnish general population at the age of 46,[8,25] as well as with the previous chronotype studies of the Northern Finland Birth Cohort 1966.[38,39] As Merikanto et al. showed,[37] the self-assessed single-item chronotyping method seems to result in a higher prevalence of evening preference compared with chronotyping by the sMEQ, suggesting that the distribution by sMEQ supported by the bedtimes and waketimes, could be considered closer to the true intrinsic chronotype of our study population.

The major strength of our study is its population-based study design. In addition, the response rates and the sample size were good, allowing us to evaluate a real spectrum of PCOS manifestations. Furthermore, we used the validated shortened 6-item Finnish version of the MEQ supported by the bedtimes and waketimes to determine the different chronotypes. Moreover, the strictly defined age of the study participants eliminated bias caused by age variations in the study population. As stated, the effect of age, approaching menopause, and sex on chronotype is well acknowledged,[7,8,30] and the impact of menopausal transition was taken into account in statistical adjustments. We also used anti-müllerian hormone as a PCOM marker in accordance with the latest PCOS guideline,[1] and thus, we were able to use the Rotterdam criteria to define women with PCOS, although individual ultrasound examinations were not available.

The study's limitations include missing data, as not all women who participated in the survey and clinical examination at the age of 31, participated in the survey at the age of 46 or answered the questions regarding chronotype. In addition, the women using contraceptive methods or being pregnant at the age of 31 years were excluded from the study to minimize the hormonal bias caused by these factors. This may have excluded some women with PCOS using contraception because of more severe PCOS symptoms. The chronotype was self-reported and no objective sleep measurements, such as actigraphy or polysomnography, were carried out. However, the 6-item sMEQ used has previously been shown to explain 83% of the variance in the full 19-item MEQ scale, with a Cronbach's alpha of 0.76–0.8, indicating an acceptable or good internal consistency.[24,25,37] The calculated Cronbach's alpha for our study population was 0.76 and we used self-reported sleep timing to confirm the sMEQ chronotype distribution. The sleep questions were answered at the age of 46 years, most likely entailing fewer PCOS symptoms at that age, when other women also start experiencing an increasing metabolic burden and climacteric symptoms that can affect the sleep patterns and circadian rhythms.[30,31] This and the generally smaller prevalence of an EC at the age of 46 years than in young adulthood[7,8] should be considered as possible factors overshadowing the plausible differences between women with and without PCOS, as well as PCOS phenotypes. On the other hand, as multimorbidity associated with PCOS and an EC has been shown to persist until later in life[5,6,20,39,40] and the general life expectancy of women is over 80 years in many countries, analyses at older ages and when the women are approaching menopause are especially warranted.

5 | CONCLUSION

In this population-based study, the EC was not over-represented in middle-aged women with PCOS. However, as research in the field is limited and the results are conflicting, further studies are warranted, especially since comorbidity and the risk profile connected with both PCOS and EC are similar. The present study does not support adding chronotyping to the routine evaluation of women with PCOS.

AUTHOR CONTRIBUTIONS

Linnea Kroneld, Päivi Polo-Kantola, Meri-Maija Ollila, Riikka K. Arffman, Elisa Hurskainen, Laure Morin-Papunen, Varpu Jokimaa, and Terhi T. Piltonen all conceived and designed the study. Linnea Kroneld carried out the literature search. Elisa Hurskainen analyzed the data. All authors contributed to the data interpretation and participated in the manuscript editing and writing.

ACKNOWLEDGMENTS

We thank all the cohort members and researchers who participated in the study. We also wish to acknowledge the work of the Northern Finland Birth Cohort Project Center.

FUNDING INFORMATION

The study was financially supported by Turku University Hospital (State Research Funding, VJ, PP-K), Finska Läkaresällskapet's personal grant (LK), the Academy of Finland (TTP, RKA), the Sigrid Jusélius Foundation (TTP), and Novo Nordisk (TTP).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ETHICS STATEMENT

The study followed the principles of the Declaration of Helsinki. The Ethics Committee of the Northern Ostrobothnia Hospital District approved the research on December 12, 2011 (decision number 94/2011). All participants took part on a voluntary basis and signed informed consent forms.

ORCID

Linnea Kroneld https://orcid.org/0000-0002-7069-3952
Päivi Polo-Kantola https://orcid.org/0000-0003-0665-0306
Meri-Maija Ollila https://orcid.org/0000-0002-6794-0369

Riikka K. Arffman https://orcid.org/0000-0003-3277-9293
Elisa Hurskainen https://orcid.org/0000-0002-1030-4417
Laure Morin-Papunen https://orcid.org/0000-0001-5987-7534
Varpu Jokimaa https://orcid.org/0000-0002-6405-488X
Terhi T. Piltonen https://orcid.org/0000-0002-9921-7300

REFERENCES

1. Teede HJ, Tay CT, Laven JJE, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Eur J Endocrinol*. 2023;189:G43-G64.
2. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertil Steril*. 2016;106:6-15.
3. Cinar N, Kizilarslanoglu MC, Harmanci A, et al. Depression, anxiety, and cardiometabolic risk in polycystic ovary syndrome. *Hum Reprod*. 2011;26:3339-3345.
4. Pinola P, Puukka K, Piltonen TT, et al. Normo- and hyperandrogenic women with polycystic ovary syndrome exhibit an adverse metabolic profile through life. *Fertil Steril*. 2017;107:788-795.e2.
5. Kujanpää L, Arffman RK, Pesonen P, et al. Women with polycystic ovary syndrome are burdened with multimorbidity and medication use independent of body mass index at late fertile age: a population-based cohort study. *Acta Obstet Gynecol Scand*. 2022;101:728-736.
6. Kujanpää L, Arffman RK, Vaaramo E, et al. Women with polycystic ovary syndrome have poorer work ability and higher disability retirement rate at midlife: a northern Finland birth cohort 1966 study. *Eur J Endocrinol*. 2022;187:479-488.
7. Fischer D, Lombardi DA, Marucci-Wellman H, Roenneberg T. Chronotypes in the US – influence of age and sex. *PLoS One*. 2017;12:e0178782.
8. Merikanto I, Partonen T. Increase in eveningness and insufficient sleep among adults in population-based cross-sections from 2007 to 2017. *Sleep Med*. 2020;75:368-379.
9. Horne JA, Brass CG, Petitt AN. Circadian performance differences between morning and evening 'types'. *Ergonomics*. 1980;23:29-36.
10. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. *Chronobiol Int*. 2006;23:497-509.
11. Plano SA, Casiraghi LP, Moro PG, Paladino N, Golombek DA, Chiesa JJ. Circadian and metabolic effects of light: implications in weight homeostasis and health. *Front Neurol*. 2017;8:558.
12. Montaruli A, Castelli L, Mulè A, et al. Biological rhythm and chronotype: new perspectives in health. *Biomol Ther*. 2021;11:487.
13. Li S, Zhai J, Chu W, Geng X, Chen ZJ, Du Y. Altered circadian clock as a novel therapeutic target for constant darkness-induced insulin resistance and hyperandrogenism of polycystic ovary syndrome. *Transl Res*. 2020;219:13-29.
14. Brzezinski A, Rai S, Purohit A, Pandi-Perumal SR. Melatonin, clock genes, and mammalian reproduction: what is the link? *Int J Mol Sci*. 2021;22:13240.
15. Wang F, Xie N, Wu Y, et al. Association between circadian rhythm disruption and polycystic ovary syndrome. *Fertil Steril*. 2021;115:771-781.
16. Barrea L, Verde L, Vetrani C, et al. Evening chronotype is associated with hormonal and metabolic disorders in polycystic ovary syndrome. *J Pineal Res*. 2023;74:e12844.
17. Zou H, Zhou H, Yan R, Yao Z, Lu Q. Chronotype, circadian rhythm, and psychiatric disorders: recent evidence and potential mechanisms. *Front Neurosci*. 2022;16:811771.
18. Makarem N, Paul J, Giardina EGV, Liao M, Aggarwal B. Evening chronotype is associated with poor cardiovascular health and adverse health behaviors in a diverse population of women. *Chronobiol Int*. 2020;37:673-685.
19. Wang Y, Ni Z, Li K. The prevalence of anxiety and depression of different severity in women with polycystic ovary syndrome: a meta-analysis. *Gynecol Endocrinol*. 2021;37:1072-1078.
20. Cooney LG, Dokras A. Beyond fertility: polycystic ovary syndrome and long-term health. *Fertil Steril*. 2018;110:794-809.
21. Ollila MM, Arffman RK, Korhonen E, et al. Women with PCOS have an increased risk for cardiovascular disease regardless of diagnostic criteria—a prospective population-based cohort study. *Eur J Endocrinol*. 2023;189:96-105.
22. Nordström T, Miettunen J, Auvinen J, et al. Cohort profile: 46 years of follow-up of the northern Finland birth cohort 1966 (NFBC1966). *Int J Epidemiol*. 2022;50:1786-1787.
23. Piltonen TT, Komsi E, Morin-Papunen LC, et al. AMH as part of the diagnostic PCOS workup in large epidemiological studies. *Eur J Endocrinol*. 2023;188(6):547-554.
24. Hätönen T, Forsblom S, Kieseppä T, Lönnqvist J, Partonen T. Circadian phenotype in patients with the co-morbid alcohol use and bipolar disorders. *Alcohol Alcohol*. 2008;43:564-568.
25. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Lahti T, Partonen T. Relation of chronotype to sleep complaints in the general Finnish population. *Chronobiol Int*. 2012;29:311-317.
26. Horne JA, Ostberg O. A self assessment questionnaire to determine morningness eveningness in human circadian rhythms. *Int J Chronobiol*. 1976;4:97-110.
27. Avis NE, Crawford SL, Green R. Vasomotor symptoms across the menopause transition: differences among women. *Obstet Gynecol Clin N Am*. 2018;45:629-640.
28. Veijola J, Jokelainen J, Läksy K, et al. The Hopkins symptom Checklist-25 in screening DSM-III-R axis-I disorders. *Nord J Psychiatry*. 2003;57:119-123.
29. Insomnia. Current Care Guidelines. *Working Group Set up by the Finnish Medical Society Duodecim and the Finnish Sleep Research Society*. The Finnish Medical Society Duodecim; 2023 Available online at: www.kaypahoito.fi
30. Verde L, Barrea L, Vetrani C, et al. Chronotype and sleep quality in obesity: how do they change after menopause? *Curr Obes Rep*. 2022;11:254-262.
31. Maki PM, Panay N, Simon JA. Sleep disturbance associated with the menopause. *Menopause*. 2024;31:724-733.
32. Lizneva D, Kirubakaran R, Mykhalchenko K, et al. Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis. *Fertil Steril*. 2016;106:1510-1520.e2.
33. Torsvall L, Akerstedt T. A diurnal type scale. Construction consistency and validation in shift work. *Scand J Work Environ Health*. 1980;6:283-290.
34. Di Milia L, Adan A, Natale V, Randler C. Reviewing the psychometric properties of contemporary circadian typology measures. *Chronobiol Int*. 2013;30:1261-1271.
35. Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C. Circadian typology: a comprehensive review. *Chronobiol Int*. 2012;29:1153-1175.
36. Danielsson K, Sakarya A, Jansson-Fröjmark M. The reduced Morningness–Eveningness questionnaire: psychometric properties and related factors in a young Swedish population. *Chronobiol Int*. 2019;36:530-540.
37. Merikanto I, Kantojärvi K, Partonen T, Pesonen AK, Paunio T. Genetic variants for morningness in relation to habitual sleep-wake behavior and diurnal preference in a population-based sample of 17,243 adults. *Sleep Med*. 2021;80:322-332.
38. Räihä T, Nerg I, Jurvelin H, Conlin A, Korhonen M, Ala-Mursula L. Evening chronotype is associated with poor work ability and disability pensions at midlife: a northern Finland birth cohort 1966 study. *Occup Environ Med*. 2021;78:567-575.

39. Nauha L, Jurvelin H, Ala-Mursula L, et al. Chronotypes and objectively measured physical activity and sedentary time at midlife. *Scand J Med Sci Sports*. 2020;30:1930-1938.
40. Kianersi S, Liu Y, Guash-Ferré M, et al. Chronotype, unhealthy lifestyle, and diabetes risk in middle-aged U.S. women: a prospective cohort study. *Ann Intern Med*. 2023;176:1330-1339.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kroneld L, Polo-Kantola P, Ollila M-M, et al. Chronotypes in middle-aged women with polycystic ovary syndrome: A population-based study. *Acta Obstet Gynecol Scand*. 2024;00:1-12. doi:10.1111/aogs.14991