Research paper

Influence of chronotype on the incidence and severity of perinatal depression in the "Life-ON" study

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ARTICLE INFO

ABSTRACT

Background: Perinatal depression (PND) is a severe complication of pregnancy, but there are no established risk factors predicting the disease. Evening chronotype has been associated with unhealthy lifestyle habits and adverse outcomes during pregnancy. In this study, we aimed to clarify whether chronotype can predict symptoms and/or occurrence of PND.

Methods: Two hundred ninety-nine women were followed-up from the first trimester of pregnancy until 6 months postpartum. Chronotype was assessed at baseline using the MEQ, while mood was repeatedly assessed by depression rating scales (EPDS, HDRS, MADRS). The influence of time and chronotype on EPDS, HDRS and MADRS, was estimated by constructing multilevel linear mixed regression models. A Cox proportional-hazard regression model was built to evaluate the association between chronotype and incidence of depression.

Results: Chronotype modulated PND symptom severity depending on time of assessment, with evening chronotypes having a higher risk for developing PND symptoms, as assessed by EPDS, at postpartum visits V4 (5–12 days) and V5 (19–26 days). These also had less healthy lifestyle habits and were more likely to suffer from gestational diabetes mellitus and undergo cesarean delivery as compared to other chronotypes.

Limitations: Only a minority of women were classified as evening chronotypes. The long follow-up phase of the study led to missing data.

Conclusions: Pregnant evening chronotypes show unhealthy lifestyle habits and sociodemographic characteristics commonly associated with a higher risk for PND. They also have a higher risk of developing PND symptoms in the first month after delivery. Chronotype should therefore be routinely assessed during pregnancy to identify women potentially at risk for developing PND.

1. Introduction

Chronotype refers to the individual self-selected timing of sleep in relation to local time (Roenneberg, 2012). Chronotypes in the general population are normally distributed, ranging from morning types (early falling asleep in the evening and early wake up in the morning) to evening types (late falling asleep in the evening/night and late wake up in the morning), with intermediate types falling between these two extremes (Roenneberg et al., 2007).

Inter-individual differences in chronotype represent an important aspect of circadian regulation, reflecting a different phase relationship between daily biological and environmental events (Martin-Fairey et al., 2019). These also depend on age, gender, genetic variants, homeostatic sleep factors, as well as on the strength of external stimuli, known as *Zeitgebers* (e.g. temperature, nutrition, and particularly light), which synchronize the endogenous circadian clock to the 24-hour day (Roenneberg and Merrow, 2016).

Individual chronotypes can interfere with social demands related to school times, working hours, or leisure activities, generally leading evening and, to lesser extent, morning types to accumulate sleep debt on workdays and compensate for it by sleeping longer or midday napping on free days (Roenneberg et al., 2003). The degree of misalignment between biological and social time is normally referred to as social jetlag and can be quantified as the absolute difference between the timing of midsleep on workdays and on work-free days (Wittmann et al., 2006). There is a strong correlation between later chronotype and greater social jetlag (Wittmann et al., 2006), and both conditions are associated with adverse health consequences and unhealthy habits (Parsons et al., 2015). Evening chronotypes report a higher incidence of poor sleep quality and increased daytime sleepiness (Giannotti et al., 2002; Volk et al., 1994). They also have a higher risk for depression and suicides (Kitamura et al., 2010; Levandovski et al., 2011; Merikanto et al., 2015, 2013a; Selvi et al., 2011), as well as less healthy dietary habits (Kanerva et al., 2012; Malone et al., 2016). Moreover, evening chronotypes tend to consume more alcohol, nicotine, and caffeine (Adan, 1994; Hug et al., 2019) and are more likely to suffer from arterial hypertension, type 2 diabetes (Merikanto et al., 2013b) and bronchial asthma as compared to the other chronotypes (Merikanto et al., 2014).

In a nationwide Finnish study, evening types have been estimated to represent 11–13 % of the general adult population, with eveningness being slightly more prevalent among females than males (Merikanto et al., 2012). By contrast, a recent analysis of data recorded by using wearable devices in the Chinese population (n = 49,573) found no gender differences in chronotypes (Zhang et al., 2019). Another large-scale study estimating the distribution of individual chronotypes in the US population based on diary data, showed that women are on average earlier chronotypes than men until the age of 40, but later types thereafter (Fischer et al., 2017). The authors hypothesized hormonal changes in women to act as modulators for an aging circadian system, causing a shift to eveningness between 35 and 50 years. In women, chronotype also seems to modulate reproductive functions, such as the length of menstruation and the likelihood for pregnancy (Toffol et al., 2013). Furthermore, evidence suggests that, especially in women, a later chronotype might represent an unfavorable factor in the onset of physical or mental disorders (Fabbian et al., 2016) and be associated with adverse childhood experiences (Hug et al., 2019).

Very few studies examined the influence of chronotype on mood during the perinatal period. Overall, pregnant evening chronotypes reported greater seasonal variations in mood and behaviour than morning types (Merikanto et al., 2017), had a higher prevalence of insomnia and depression before and during pregnancy (Sampaio Facanha et al., 2021), and more symptoms of mania and obsessive-compulsive disorder in the postpartum period (Obeysekare et al., 2020).

In the present large-scale, prospective, cohort study on women during pregnancy and postpartum, we aimed to investigate whether chronotype is a risk factor for developing perinatal depression (PND).

PND is defined as a major depressive episode occurring during pregnancy or within 4 weeks after childbirth, up to one year, and represents a serious complication of pregnancy, affecting ca. 12 % of women (Dagher et al., 2021). Overall, perinatal mental disorders, including PND, are severe conditions that are associated with disruptive consequences on the health and well-being of mothers, children, and their families. Moreover, due to the induced socioeconomic burden, they represent a major public health problem for society as a whole, and are therefore considered a priority target of health prevention strategies at a global level. There is, in fact, general consensus among experts that perinatal mental disorders are still prevalent, underrecognized and undertreated (Howard and Khalifeh, 2020).

In this study, we hypothesized that a later chronotype might be predictive of PND occurrence and symptom severity. Secondarily, we examined the association between chronotype, maternal sociodemographic characteristics and lifestyle habits, in relation to PND. We hypothesized that evening chronotypes might present unfavorable social conditions and life attitudes predisposing them to develop PND.

2. Methods

2.1. Participants

Data presented here derive from a large cohort study on sleep and mood changes during the perinatal period (the "Life-ON" study) conducted between 2016 and 2020 in three centers in Italy (Milan, Turin, and Bologna) and one in Switzerland (Lugano). A detailed description of the "Life-ON" study protocol has been published previously (Baiardi et al., 2016). In summary, participating women were recruited during the first trimester of pregnancy and received 10 follow-up visits until 12 months postpartum. The time points of the consecutive visits (V) were scheduled as follows: V1 (10–15 gestational week); V2 (20–25 gestational week); V3 (34–36 gestational week); V4 (5–12 days postpartum); V5 (19–26 days postpartum); V6 (33–40 days postpartum); V7 (47–54 days postpartum); V8 (90–105 days postpartum); V9 (180–195 days postpartum); V10 (270–285 days postpartum); V11 (12 months postpartum). Sleep and mood parameters from both self-administered questionnaires and semi-structured interviews were regularly collected at every study visit (Baiardi et al., 2016). Women screened for study participation were excluded if they had a current or previous (one year) diagnosis of depressive disorder or were treated with any antidepressant medication in the previous 12 months. Twenty-three participants who developed PND, as assessed by an EPDS total score > 12 from visit 2 to visit 10, were offered to enter a randomized, controlled trial with 6-week bright light therapy (BLT) vs. placebo dim light (substudy "Life-ON2"). Seventy-eight women with an EPDS score ≤ 12 at visit 2, thus being considered not affected by PND, were also consecutively asked to participate in an open-label trial with 6-week BLT, to test its efficacy in preventing the onset of PND during the postpartum period (substudy "Life-ON3").

2.2. Chronotype assessment

Chronotype was assessed once at study entry (V1) using the 19-item Morningness–Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976). The MEQ is a self-administered rating scale developed to assess the individual differences in the degree to which respondents are active and alert at certain times of day (e.g. morning vs. evening). Each section of the questionnaire is assigned a value of 1 through 5. The sum of each item gives a global score ranging from 16 to 86, with scores ≤ 41 corresponding to "evening types", scores between 42 and 58 to "intermediate types" and scores ≥ 59 to "morning types".

2.3. Psychiatric assessment

Depressive symptoms during the study period were assessed using

one self-administered psychiatric scale and two semi-structured interviews:

- the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) is a 10-item self-administered screening tool used to identify women suffering from depressive symptoms during the perinatal period and was completed by participants at every study visit. Responses are scored 0, 1, 2, or 3 according to increased symptom severity. The total score ranges between 0 and 30 and a cut-off score higher than 12 was considered indicative of PND
- the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) is a semi-structured interview consisting of 21 items that are scored between 0 and 4 points and was administered at visits V1, V3, V6, V9, and V11. Total scores of 0–7 are considered as being normal, 8–16 suggest mild depression, 17–23 moderate depression and scores over 24 are indicative of severe depression.
- the Montgomery-Åsberg Depression Rating Scale (MADRS) is a semi-structured interview including 10 items aimed at evaluating symptoms of depression (Montgomery and Asberg, 1979). It was administered at the same time points as the HDRS, but differently from this, the MADRS does not focus predominantly on the somatic symptoms of depression, but rather addresses core mood symptoms, such as sadness, tension, lassitude, pessimistic thoughts, and suicidal thoughts. MADRS items are rated on a 0–6 continuum (0 = no abnormality, 6 = severe) and total scores in relation to the severity of depression are 0–8 (remission), 9–17 (mild depression), 18–34 (moderate depression), and ≥35 (severe depression).

2.4. Statistical analysis

2.4.1. Descriptive statistics for sociodemographic factors

All data analysis was performed using the R statistical software (R version 3.5.2). Demographic data of the whole study population (n = 299) and outcomes from the respective depression questionnaires on an ordinal scale were tested for normality with the Shapiro-Wilk-Test and for equality of variances using the Levene's test. Between-group differences for normally distributed data were calculated using a one-way-test of variance (ANOVA), reporting the corresponding effect size omega squared. Differences between groups for non-normally distributed data were calculated using the Kruskal-Wallis test. As the corresponding effect-size measure we chose epsilon squared (Kelley, 1935). Overall, between-group differences for demographic and questionnaire data on a categorical scale were calculated using Pearson's chi-squared test with corresponding effect size Cramér's V. The relationships between raw MEQ-values (unstratified for the different chronotypes) and depression rating-scale scores at the respective time-points of assessment were calculated using Spearman's rho (ρ) regression coefficient. As a cut-off value rejecting the null-hypothesis, $p < 0.05$ was considered statistically significant. Instead of correcting for multiple testing, we chose to report effect sizes for the respective statistical tests.

2.4.2. Multilevel linear mixed regression

We constructed multilevel linear mixed regression models with repeated measures to assess the influence of time (follow-up visits on an ordinal scale) and chronotype on the outcome of the EPDS, HDRS and MADRS on an ordinal scale, as well as divided into non-pathologic vs. pathologic values, based on the respective cut-off scores. We also considered a list of confounding factors that might be involved in the development of depression (including marital status, level of education, employment status, loss of employment (last 6 months), living situation, moving (last 6 months), if the pregnancy was planned/unplanned/undesired, number of children, personal history of depression and treatment or other psychiatric diseases, family history of depression, past or present alcohol intake and smoking). To assure optimal fit without inflating the number of included factors, definitive parameter selection was performed via backwards elimination based on Akaike information

criteria (AIC). Only parameters significantly improving the model fit were included in the construction of the definitive regression models, fitted with the restricted maximum likelihood method (see Supplemental Table 1). The inclusion of a parameter by backwards elimination can be interpreted as this having a meaningful influence on the observed variability in the data. However, this does not automatically mean that the variable will also result as a significant factor when constructing the definitive model. Chronotype, "time", as well as their interaction and confounding factors were considered as fixed effects, whereas participants were modelled as a random factor, taking into account the longitudinal dimension of the data with repeated-measure design, allowing for individual differences on the patient level. To assess model performance, we calculated the conditional R2 (R2c) representing the variance in the data attributable to the complete regression model.

Women entering at visit V2 the interventional substudy "Life-ON3" were excluded from this analysis, because of the possible impact of BLT on mood variables during the subsequent observation period. Data from participants of the "Life-ON2" substudy were also excluded from the beginning to preserve the longitudinal integrity of the dataset, as the time point of BLT start across the study was highly variable. Since excluding this subsample of women entails to omit circa half of the participants who developed a manifest depressive episode during the follow-up period, we repeated the multilevel linear regression including this cohort and obtained comparable results regarding parameter selection and overall model evaluation (not shown). The demographic characteristics of the untreated women did not differ significantly from the full sample.

2.4.3. Survival analysis

To investigate the association between chronotype and incidence of PND, we constructed cumulative incidence curves and calculated the difference between the curves for the different chronotypes using the log-rank test. A Cox proportional-hazard regression model was additionally constructed to extend the analysis to the effect of several risk-factors on event-free survival time (time until onset of meaningful depressive symptoms defined as EPDS >12 points). Participants in the interventional substudy "Life-ON3" were excluded from this analysis to avoid BLT as a possible factor influencing depressive symptomatology.

The list of possible confounding factors on the onset of PND was identical to that used in the multilevel linear mixed regression model (see Supplemental Table 1). Exhaustive model selection was performed assessing all possible regression models ranked by goodness-of-fit based on AIC, selecting the best possible model which also included chronotype as variable. We used the Schoenfeld test to examine Cox proportional hazards model assumptions.

2.5. Ethics

The "Life-ON" study has been approved by the respective ethics committee of the four participating centers in Italy and Switzerland. All participants gave a written informed consent prior to study entry.

3. Results

3.1. Chronotype distribution

A total of 438 women (age 34.1 ± 4.2 years) were enrolled in the "Life-ON" study during the first trimester of pregnancy (week 10–15). 409 participants (93.4 %) completed the MEQ at baseline visit, of which 6.36 % (n = 26) were classified as evening type, 55.5 % (n = 227) as intermediate type, and 38.14 % (n = 156) as morning type. After exclusion of premature dropouts and participants with insufficient data (n = 110), a sample of 299 women (age 34.1 ± 4.3 years), who provided sufficient data from visit 1 (baseline, 10–15 gestational week) to visit 9 (6 months postpartum) was considered for statistical analysis. Chronotype distribution in this sample was similar to the whole study

population, with 5.68 % (n = 17) being classified as evening types, 56.86 % (n = 170) as intermediate types, and 37.46 % (n = 112) as morning types. The graphic distribution of MEQ scores (chronotypes) followed a Gaussian curve, as shown in Fig. 1, similar to that known of the general population (Roenneberg et al., 2007).

3.2. Sociodemographic and health characteristics

Sociodemographic and health characteristics of the analyzed sample in relation to chronotype are listed in Table 1. Data showed no differences between the three chronotypes as regard to age and number of children, but only a small, non-significant, between group effect regarding weight and BMI, with no clinical relevance. Evening chronotypes were more likely to be in a relationship (64.7 %) than married (35.3 %) and to have a partner with restricted vs. unrestricted job, as compared to the other chronotypes. They were also more frequently smokers (p = 0.005) and alcohol consumers at study entry, and had a history of chronic alcohol and medication use in the past, as compared to the other chronotypes. Concerning health status, a small effect was observed for evening types regarding suffering from gestational diabetes mellitus (GDM) at study entry, with a 3.7 times higher risk as compared to morning chronotypes. Finally, regarding adverse pregnancy outcomes, evening type women were twice as likely to receive a cesarean section at delivery, as compared to morning chronotypes.

3.3. Depression rating scales

As depicted in Fig. 2, a clear change in median EPDS scores across the single follow-up visits is evident, with a peak at visits V4 and V5, directly after delivery. Within the full dataset (n = 299, Fig. 2a) we found a significant, moderate group effect for chronotype at visits V4 ($\chi2 = 15.2$, p = 0.0005, $\varepsilon2 = 0.05$; evening vs. intermediate: p = 0.017, evening vs. morning: p = 0.001, intermediate vs. morning: p = 0.014), and V5 ($\chi2 = 14.42$, p = 0.0007, $\varepsilon2 = 0.048$; evening vs. intermediate: p = 0.009, evening vs. morning: p = 0.0008, intermediate vs. morning: p = 0.043), with a weak group effect at V8 ($\chi2 = 6.81$, p = 0.03, $\varepsilon2 = 0.02$; evening vs. intermediate: p = ns., evening vs. morning: p = n.s., intermediate vs. morning: p = 0.03).

The same trend was also observed when excluding data from the substudies "Life-ON2" and "Life-ON3" (n = 224, Fig. 2b), with significant, weak to moderate group effects at the same time points V4 ($\chi2 = 7.74$, p = 0.02, $\varepsilon2 = 0.03$; evening vs. intermediate: p = n.s., evening vs. morning: p = n.s., intermediate vs. morning: p = 0.046), V5 ($\chi2 = 9.96$,

p = 0.007, $\varepsilon2 = 0.045$; evening vs. intermediate: p = 0.05, evening vs. morning: p = 0.009, intermediate vs. morning: p = 0.05) and V8 ($\chi2 = 6.21$, p = 0.04, $\varepsilon2 = 0.028$; evening vs. intermediate: p = n.s., evening vs. morning: p = n.s., intermediate vs. morning: p = 0.048). A less pronounced but comparable association was found when additionally including data from the "Life-ON2" participants, until the start of BLT (n = 242, Fig. 2c). Here, weak group effects emerged at visits V4 ($\chi2 = 7.02$, p = 0.03, $\varepsilon2 = 0.03$; post-hoc tests n.s.) and V5 ($\chi2 = 9.01$, p = 0.01, $\varepsilon2 = 0.037$; evening vs. intermediate: p = n.s., evening vs. morning: p = 0.01, intermediate vs. morning: p = n.s.), while a weak group effect not reaching statistical significance was observed at V8 ($\chi2 = 5.93$, p = 0.05, $\varepsilon2 = 0.025$).

Spearman's correlation only revealed a weak, monotonic correlation between EPDS values and MEQ for visit V4 ($\rho = -0.21$, p = 0.0014) and visit V5 ($\rho = -0.21$, p = 0.0015), while none of the other time-points or rating scales showed relevant relationships to raw MEQ values (Supplementary Figs. 1a and 1b).

When fitting the multilevel linear mixed regression model predicting the values of EPDS on an ordinal scale, time, chronotype, time-chronotype interaction, total number of children, employment status, relocating (previous 6 months), family history of depression, past alcohol intake, and smoking were selected as independent parameters to achieve best model fit based on AIC. The effect of time within the final model reached statistical significance at visit 5, 7, 8 and 9, with also a significant time-chronotype interaction at visit 4, 5 and 8, as shown in Fig. 3. Of the chosen confounding parameters, only relocating in the previous 6 months had a statistically significant influence on EPDS score. When examining overall model performance, 45 % ($R^2c = 0.45$) of global variation in the data was explained by the regression model.

Applying the same method to predict HDRS values on an ordinal scale, the parameters to achieve best model fit included time, total number of children, employment status, loss of employment (previous 6 months), relocating (previous 6 months), personal and family history of depression, level of education, past alcohol intake and smoking. Chronotype was not selected and therefore not included in the final model. Significant effects were found for time-restricted employment, loss of employment (previous 6 months), relocating (previous 6 months), medium-level education and for the time point visit 3 (Fig. 3). With an R^2c value of 0.42 the overall model accounted for 42 % of variability within the data.

Lastly, the parameters to achieve best model fit predicting MADRS values on an ordinal scale were employment status, loss of employment (previous 6 months), smoking, past and present alcohol intake, number
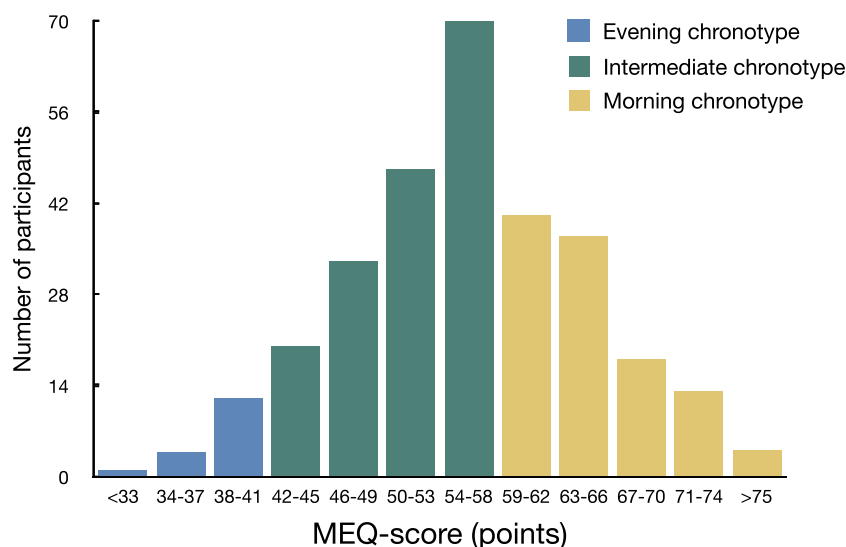

Fig. 1. Distribution of chronotypes in the study population based on MEQ-score. MEQ: Morningness-Eveningness Questionnaire.

Table 1

Sociodemographic characteristics of the study population (n = 299) stratified for chronotypes. ANOVA: analysis of variance. df: degrees of freedom. GDM: gestational diabetes mellitus. IVF: in-vitro fertilization. IQR: interquartile range, given as IQR (25th percentile|75th percentile). SD: standard deviation.

	Morning chronotype (n = 112)		Intermediate chronotype (n = 170)		Evening chronotype (n = 17)		ANOVA			Kruskal-Wallis			
	n	Mean (SD) or median (IQR)	n	Mean (SD) or median (IQR)	n	Mean (SD) or median (IQR)	F-value	p-Value	ω^2	χ^2	p-Value	ε^2	
Age (in years)	112	34.4 (4.3)	170	33.9 (4.2)	17	33.5 (4.8)	0.599	0.55	−0.002				
Weight (in kg)	110	58 (53|65)	167	61 (56|69)	17	57 (55|65)				5.71	0.06	0.0192[a]	
BMI	103	21.72 (20.23|23.5)	163	22.35 (20.865|24.61)	16	21.54 (20.315|24.715)				3.06	0.22	0.0103[a]	
Number of children	112	1 (0|1)	170	1 (0|1)	16	0 (0|1)				2.24	0.33	0.0075	

		Morning chronotype (n = 112)		Intermediate chronotype (n = 170)		Evening chronotype (n = 17)		Pearson's Chi-squared test			
		n	n (%)	n	n (%)	n	n (%)	χ^2	df	p-Value	Cramér's V
Pregnancy	Programmed	112	93 (83.0)	170	142 (83.5)	15	12 (70.6)	3.68	4	0.45	0.078
	Not programmed		19 (17.0)		26 (15.3)		5 (29.4)				
	Not desired		0 (0.0)		2 (1.2)		0 (0.0)				
Type of conception	Spontaneous	111	107 (96.4)	169	162 (95.9)	17	17 (100.0)	0.75	2	0.69	0.05
	IVF		4 (3.6)		7 (4.1)		0 (0.0)				
Time of delivery	Pre term	107	3 (2.8)	158	8 (5.1)	16	1 (6.3)	3.37	4	0.50	0.077
	At term		104 (97.2)		147 (93.0)		15 (93.7)				
	Post term		0 (0.0)		3 (1.9)		0 (0.0)				
Type of delivery	C-section	111	24 (21.6)	168	44 (26.2)	17	8 (47.1)	5.05	2	0.08	0.131[a]
	Vaginal		87 (78.4)		124 (73.8)		9 (52.9)				
Number of kids	None	112	78 (69.6)	167	110 (65.9)	15	13 (76.5)	1.84	4	0.77	0.056
	One		25 (22.3)		37 (22.2)		3 (17.6)				
	2 or more		9 (11.9)		20 (8.0)		1 (5.8)				
Marital status	Married	112	66 (58.9)	170	104 (61.2)	17	6 (35.3)	6.09	6	0.41	0.101[a]
	In a relationship		46 (41.1)		64 (37.7)		11 (64.7)				
	Divorced		0 (0.0)		1 (0.6)		0 (0.0)				
	Single		0 (0.0)		1 (0.6)		0 (0.0)				
Education level	College	112	82 (73.2)	170	113 (66.5)	15	10 (58.8)	4.09	4	0.39	0.083
	High school		27 (24.1)		48 (28.2)		5 (29.4)				
	Middle school		3 (2.7)		9 (5.3)		2 (11.8)				
Type of work (patient)	Unrestricted	107	68 (63.5)	156	113 (72.4)	17	13 (76.5)	3.17	4	0.53	0.075
	Restricted		24 (22.4)		25 (16.0)		3 (17.7)				
	Unemployed		15 (14.0)		18 (11.5)		1 (5.9)				
Type of work (partner)	Unrestricted	103	87 (84.5)	149	132 (88.6)	15	11 (73.3)	4.71	4	0.32	0.094
	Restricted		13 (12.6)		15 (10.0)		4 (26.7)				
	Unemployed		3 (2.9)		2 (1.3)		0 (0.0)				
Living situation	Own property	110	80 (72.7)	169	120 (71.0)	16	11 (68.8)	0.16	2	0.92	0.023
	Rent		30 (27.3)		49 (29.0)		5 (31.3)				
Perceived poverty	No	108	106 (98.2)	169	168 (99.4)	16	16 (100.0)	1.21	2	0.55	0.064
	Yes		2 (1.8)		1 (0.6)		0 (0.0)				
Loss of work (6 months)	No	111	103 (92.8)	169	153 (90.5)	17	16 (94.1)	0.59	2	0.74	0.045
	Yes		8 (7.2)		16 (9.5)		1 (5.9)				
Move (6 months)	No	111	100 (90.1)	168	149 (88.7)	17	17 (100.0)	2.18	2	0.34	0.086
	Yes		11 (9.9)		19 (11.3)		0 (0.0)				
GDM	No	111	104 (93.7)	168	155 (92.3)	17	13 (76.5)	5.94	2	0.05	0.142[a]
	Yes		7 (6.3)		13 (7.7)		4 (23.5)				
Iperemesis gravidarum	No	111	109 (98.2)	168	161 (95.8)	17	17 (100.0)	1.83	2	0.40	0.079
	Yes		2 (1.8)		7 (4.2)		0 (0.0)				
Family history of depression	No	111	74 (66.7)	170	110 (64.7)	17	9 (52.9)	1.22	2	0.54	0.064
	Yes		37 (33.3)		60 (35.3)		8 (47.0)				
Personal history of depression	No	111	96 (86.5)	170	147 (86.5)	15	14 (82.4)	0.23	2	0.89	0.028
	Yes		15 (13.5)		23 (13.5)		3 (17.6)				
Previous depression treatment	No	112	103 (92.0)	170	156 (91.8)	17	16 (94.1)	0.12	2	0.94	0.02
	Yes		9 (8.0)		14 (8.2)		1 (5.9)				
History other psychiatric disorders	No	112	95 (84.8)	170	140 (82.4)	17	16 (94.1)	1.69	2	0.43	0.075
	Yes		17 (15.2)		30 (17.6)		1 (5.9)				
Smoking	Ex-smoker	104	28 (26.9)	163	60 (36.8)	17	8 (47.0)	14.61	4	0.005**	0.16[a]
	Smoker		2 (1.9)		13 (8.0)		3 (17.7)				
	Non-smoker		74 (71.2)		90 (55.2)		6 (35.3)				
Chronic alcohol intake (current)	No	112	109 (97.3)	170	159 (93.5)	17	15 (88.2)	3.38	2	0.18	0.106[a]
	Yes		3 (2.7)		11 (6.5)		2 (11.8)				
Chronic alcohol intake (past)	No	88	86 (97.9)	128	119 (89.3)	10	10 (100.0)	3.09	2	0.24	0.117[a]
	Yes		2 (2.3)		9 (10.7)		0 (0.0)				
Chronic medication intake (present)	No	78	50 (64.1)	117	73 (62.3)	13	10 (76.9)	1.07	2	0.59	0.072
	Yes		28 (35.9)		44 (37.6)		3 (23.1)				
Chronic medication intake (past)	No	78	53 (68.0)	116	87 (75.0)	13	7 (53.8)	3.11	2	0.21	0.123[a]
	Yes		25 (31.5)		29 (25.0)		6 (46.2)				

[a] Weak group effect for epsilon squared ($\varepsilon2$) or Cramér's V, respectively.

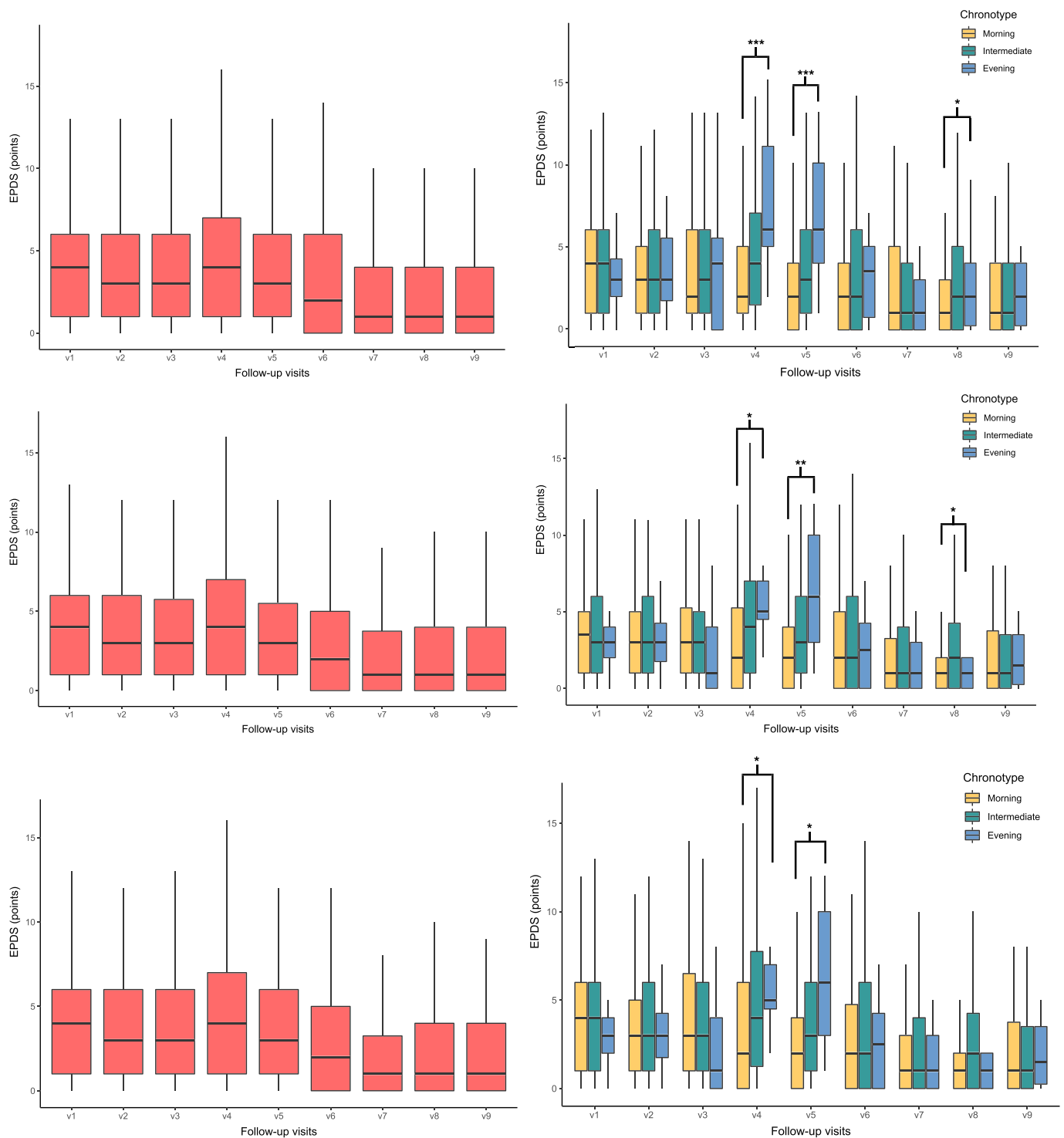** Statistically significant at the level p < 0.01.

Fig. 2. EPDS scores (median, IQR) during the follow-up visits, on the left-hand side unstratified for chronotype, on the right-hand side stratified for chronotype. a) Data regarding the whole study population (n = 299). b) Data from untreated women (n = 224), after exclusion of substudies "Life-ON2" and "Life-ON3" participants. c) Data from untreated women (n = 242), after exclusion of "Life-ON2" participants since start of BLT and exclusion of "Life-ON3" participants. Group effect assessed by Kruskal-Wallis test, with the respective overall p values: *p < 0.05, **p < 0.01, ***p < 0.001.

of children, personal history of depression and treatment, personal history of other psychiatric diseases and marital status. Chronotype and time were not selected and therefore not included in the final model. Within the final model, time-restricted employment, loss of employment in the previous 6 months, being divorced and previous treatment for depression had a significant influence predicting MADRS scores (Fig. 3). With an R^2c value of 0.28 the overall model accounted for 28 % of variability within the data.

Beta estimates for EPDS values

Beta estimates for HDRS values

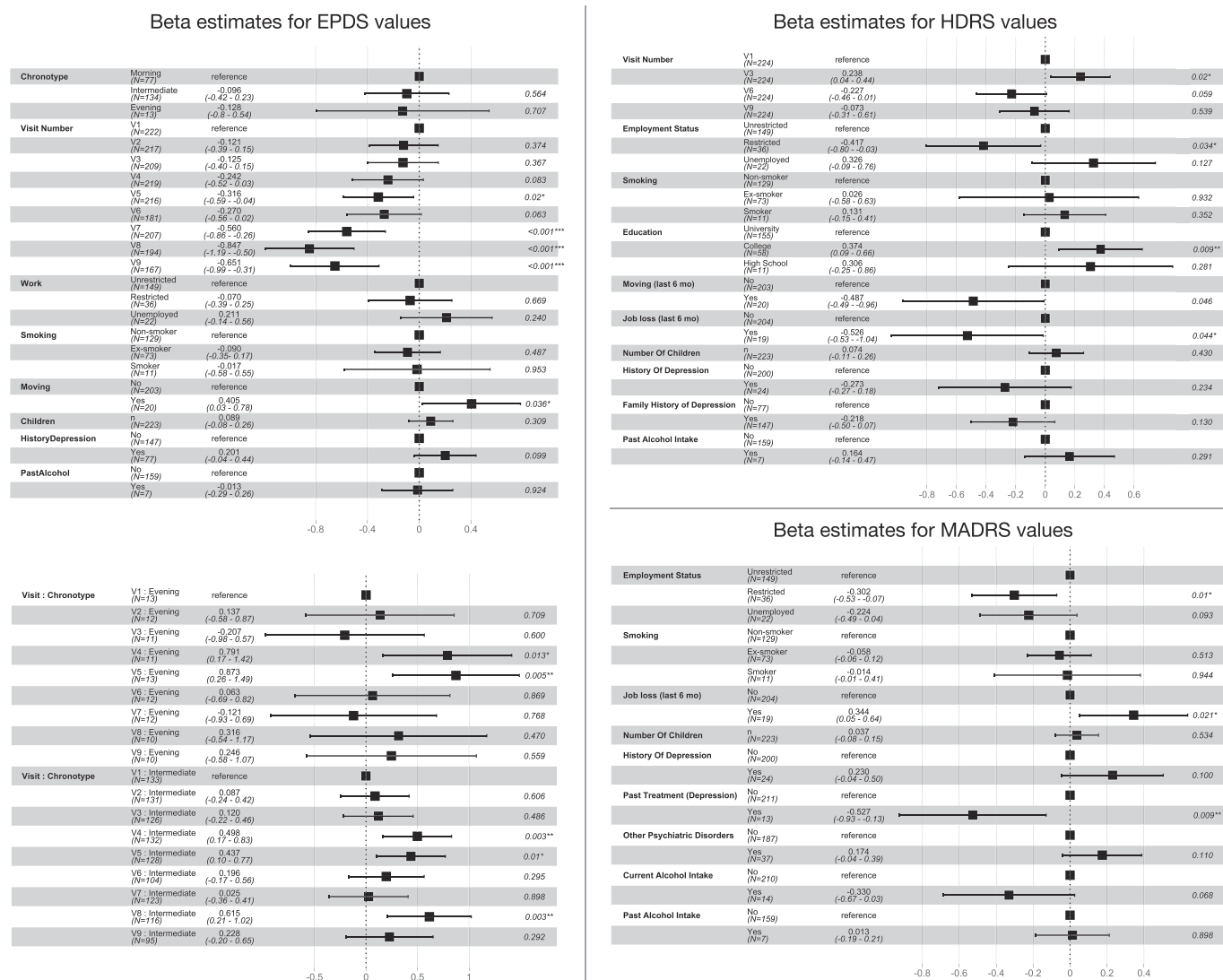## Beta estimates for MADRS values

Fig. 3. Beta estimate outcomes from the respective regression models predicting EPDS, HDRS and MADRS. EPDS time-chronotype interactions divided into effects for the single study visits for evening and intermediate chronotype are depicted in the bottom left-hand side. CI: confidence interval, given as 95 % CI. Overall p values: *p < 0.05, ** p < 0.01, ***p < 0.001.

3.4. Depression rating scales categorical

We also constructed a multilevel linear mixed regression model predicting non-pathologic vs. pathologic values of EPDS (cut-off for PND >12 points), HDRS (cut-off for "mild depression" >7 points) and MADRS (cut-off for "mild depression" >8 points) at the different follow-up time points, again using AIC based backwards elimination to select independent parameters for optimal model fit. Among our principal parameters of interest, chronotype was only selected for the model predicting HDRS and time for predicting MADRS, while those parameters were not included in the model predicting EPDS. None of the effect estimates of the selected parameters reached statistical significance when evaluating the different final models.

3.5. Overall depression incidence stratified for chronotype

During the follow-up period from inclusion to 6 months postpartum, out of 242 women considered in the survival analysis, 35 were classified as suffering from PND, corresponding to a cumulative incidence of 14.5 %. Evening chronotypes (20 %) showed a slightly higher percentage of cases compared to morning (13 %) and intermediate chronotypes (15

%), not reaching statistical significance ($\chi 2 = 0.36531$, df = 2, p-value = 0.8331, Cramer's V = 0.036).

When examining the constructed overall cumulative incidence curves for depression during the follow-up observations, a slight increase in cases can be observed across the perinatal period, with a steeper increment between 150 and 200 days of follow-up, which coincides with on-term delivery in our study population (Fig. 4). The same trend is observable when stratifying for chronotypes, with overall higher depression incidence among evening chronotypes, not reaching statistical significance (log-rank test, p = 0.86; Fig. 4). When only considering chronotype as predictor, evening chronotypes show a trend towards an increased risk of developing PND (HR 1.30, CI 0.37–4.52), while no clear trend in either direction can be observed for intermediate chronotypes, with neither of the associations reaching statistical significance.

Out of all possible Cox proportional-hazard models fitted when including the above mentioned confounding factors, the model with the lowest AIC, but still containing the variable "chronotype", also included total number of children, employment status, having relocated within the previous 6 months, loss of work within the previous 6 months, past history of depression, family history of depression and smoking, closely
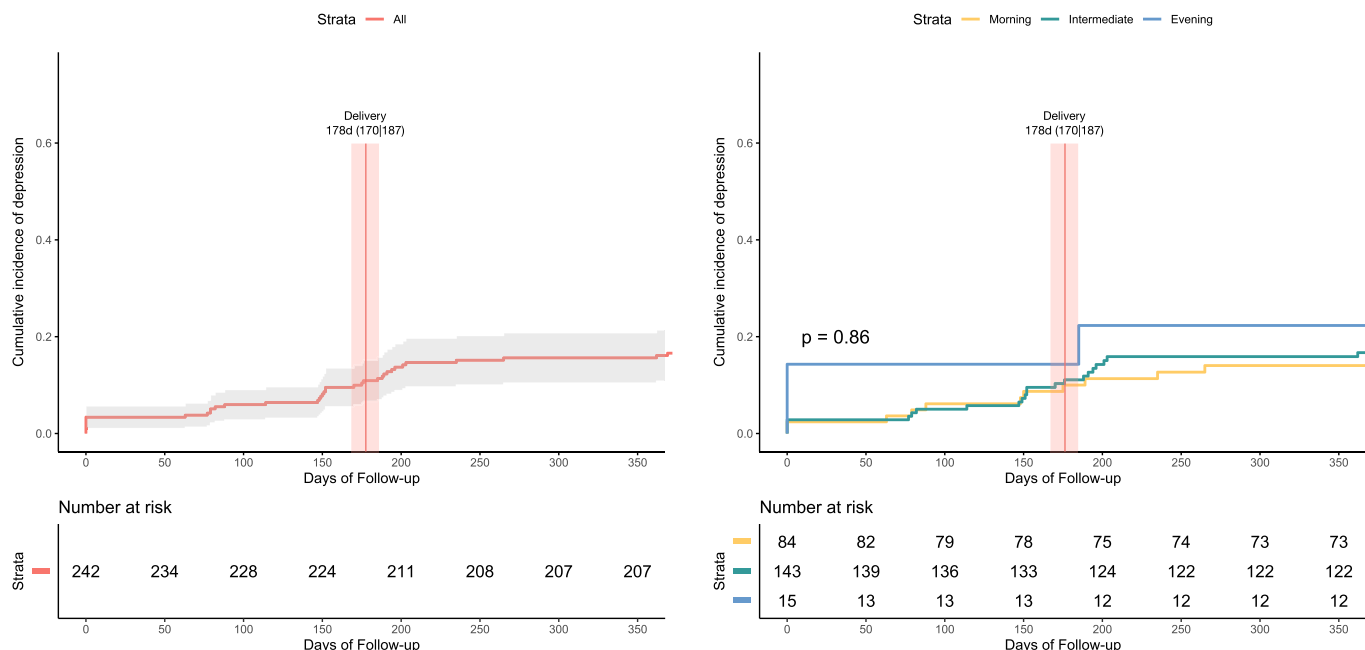
Fig. 4. Cumulative incidence curve for depression (EPDS > 12) in the follow-up period (days after study inclusion) in the untreated dataset, overall (left-hand side) and stratified for chronotype (right-hand side). Time of delivery is given in days after inclusion in the study with median (red line) and IQR (red transparent rectangle, given as IQR (25th percentile|75th percentile)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

resembling the parameters already selected in the regression model predicting EPDS values on an ordinal scale (Fig. 3).

Among the selected parameters, being an ex-smoker, having relocated within the previous 6 months, having more than one child, and having a previous diagnosis of depression yielded statistically significant results (Fig. 5). The overall model reached statistical significance (Score (log-rank) test = 32.11 on 11 df, p = 0.001). With a HR of 1.67 (CI 0.40–4.29), evening chronotypes show a trend towards an increased risk of developing a manifest depressive episode compared to morning chronotype, whereas, with an HR of 0.69 (CI 0.33–1.47), intermediate chronotypes show a trend towards a risk reduction, although neither of those associations reach statistical significance. Based on this model, the factors with the greatest influence on development of depression were relocation within the previous 6 months with a two-fold risk increase (HR 3.09, CI 1.25–7.60), having more than one child (HR 3.95, CI 1.54–10.18) and previous diagnosis of depression with an approximately three-fold risk increase (HR 4.21, CI 1.66–10.71).

4. Discussion

In our large cohort of pregnant women from the Life-ON study, chronotype was associated with PND symptom severity in the immediate postpartum period. A higher incidence of PND after delivery than during pregnancy is well-described in the literature and has been attributed to the complex interplay between genetic, hormonal, and psychosocial factors related to childbirth (Niel and Payne, 2020). However, even after constructing a regression model which carefully accounts for several, possible confounding factors in our sample, we found a statistically significant time-chronotype interaction for visits V4 and V5, scheduled in the first month postpartum. In particular, at these time points, both evening and intermediate chronotypes had significantly higher EPDS scores on an ordinal scale in respect to morning types. Evening chronotypes showed the most pronounced effect on EPDS values directly after delivery, suggesting that there is a time window during which they may be more vulnerable to PND compared to the other chronotypes. A weaker group effect was also observed at visit V8, corresponding to three months postpartum, when most women in our

study returned to work and probably experienced further stress in addition to childcare, which may have resulted in a worsening of mood. By contrast, chronotype was not predicting HDRS and MADRS values on an ordinal scale according to the multilevel linear mixed regression model. This should be interpreted taking into account that the EPDS is considered the most accurate tool to assess PND symptoms, as compared to other questionnaires (Levis et al., 2020). Moreover, HDRS and MADRS in our study were not administered in the immediate postpartum or at three months after delivery, which makes it difficult to compare the influence of chronotype on the values of the respective scales at the same time points. This furthermore seems to be the most vulnerable period for the influence of time and chronotype on EPDS values/mood and presumably also on the above-mentioned parameters. Among other variables with a significant influence on the EPDS, HDRS and MADRS scores, some conditions emerged as risk factors for developing depressive symptoms during the perinatal period. This corroborates earlier reports, that residential mobility in the previous 6 months (Grussu and Quatraro, 2009), restricted employment or loss of employment (Aochi et al., 2021), marital status (Urquia et al., 2013) and previous treatment for depression (Lancaster et al., 2010), are all associated with a higher risk for the onset of depression during the perinatal period.

The survival analysis did not show a statistically significant influence of chronotype on the overall risk of PND. However, a trend towards a risk increase for PND in evening chronotypes and a reduced risk for intermediate types, as compared to morning types, was observed.

As regards the sociodemographic characteristics of the study participants, evening chronotypes were significantly more often smokers than the other chronotypes, while small, non-significant effects were also found for chronic current and past alcohol consumption, as well as chronic past medication use. In the largest population-based study conducted so far on the association between chronotype, sociodemographic, socioeconomic and health-related characteristics in a cohort of 1646 pregnant women, evening-types were also more often smokers and had more illnesses or disabilities as compared to the other women (Merikanto et al., 2017). Other studies highlighted that pregnant women with an evening chronotype tend to have a poor diet quality (Gontijo

Hazard Ratio For Perinatal Depression (EPDS>12 points)

Variable	Category	HR (95% CI)	p-value
Chronotype	Morning (N=84)	reference	
	Intermediate (N=143)	0.69 (0.33 - 1.47)	0.34
	Evening (N=15)	1.67 (0.41 - 6.74)	0.471
Employment Status	Unrestricted (N=161)	reference	
	Restricted (N=40)	0.40 (0.12 - 1.33)	0.134
	Unemployed (N=24)	0.46 (0.12 - 1.73)	0.249
Smoking	Non-smoker (N=139)	reference	
	Ex-smoker (N=78)	0.34 (0.14 - 0.81)	0.015 *
	Smoker (N=12)	0.65 (0.13 - 3.28)	0.6
Loss Of Work (last 6 mo)	No (N=219)	reference	
	Yes (N=22)	2.36 (0.76 - 7.31)	0.138
Moving (last 6 mo)	No (N=217)	reference	
	Yes (N=24)	3.09 (1.26 - 7.60)	0.014 *
Number Of Children	none (N=163)	reference	
	one (N=55)	0.79 (0.33 - 1.90)	0.599
	>1 (N=23)	3.96 (1.54 - 10.17)	0.004 **
Family History Of Depression	No (N=158)	reference	
	Yes (N=84)	0.48 (0.21 - 1.07)	0.073
History Of Depression	No (N=210)	reference	
	Yes (N=32)	4.21 (1.66 - 10.71)	0.003 **

\# Events: 35; Global p-value (Log-Rank): 0.00459
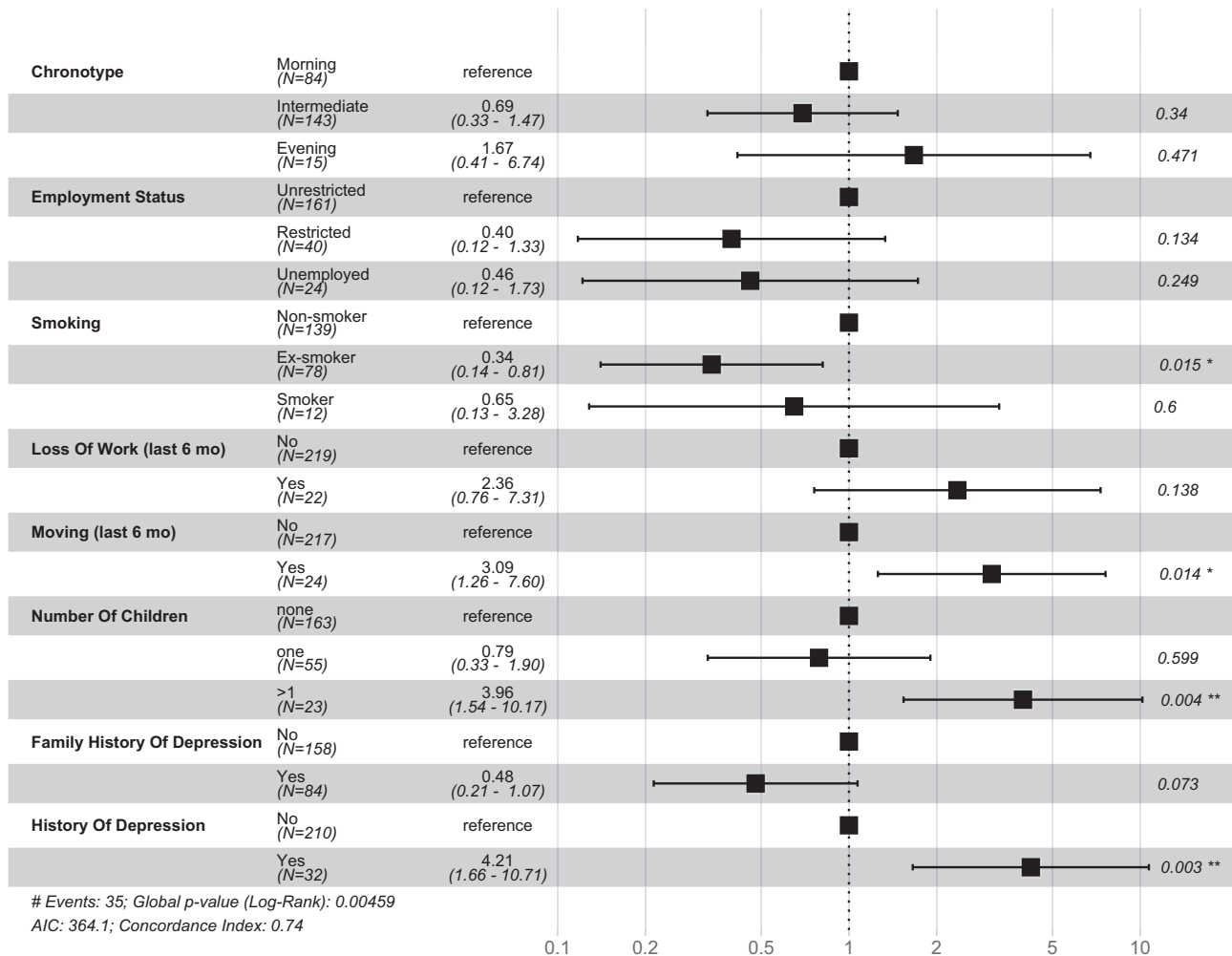AIC: 364.1; Concordance Index: 0.74

Fig. 5. Hazard ratio (CI) estimation for PND (EPDS >12) from the Cox proportional-hazard model. CI: Confidence-interval, given as 95 % CI. Overall p values: *p < 0.05, **p < 0.01.

et al., 2019), food craving traits, and to gain weight in the early gestational period (Teixeira et al., 2019) than other chronotypes. Our findings are therefore in line with the literature and confirm unhealthy lifestyle habits among evening chronotypes to be not only present in the general population (Roenneberg et al., 2019), but also in pregnant women, representing a serious risk for the health of the mothers and the fetus.

Finally, concerning the general health status of our participants and the risk of pregnancy complications, we found a small, yet non-significant effect in evening chronotypes for having GDM at study entry and undergoing cesarean section at delivery, as compared to the other chronotypes. Interestingly, a recent study conducted in 53 pregnant women with GDM showed that evening chronotypes have a more unstable marital status, a higher prevalence of insomnia and depression before and during pregnancy, and are more likely to develop adverse pregnancy outcomes, such as pre-eclampsia and neonatal ICU admission (Sampaio Facanha et al., 2021).

Overall, one of the strengths of our study is to analyze the influence of chronotype on mood not only during pregnancy, but at 9 consecutive time points during 12 months across the perinatal period, including both the pre- and postpartum. Moreover, our work provides data from a large sample of women from 4 different participating centers, located in two countries, thus reducing the risk of recruitment bias. Also, having adopted a more conservative cutoff value of the EPDS > 12, rather than smaller, has the advantage to increase specificity in identifying "real"

cases of PND and distinguishing them from milder forms of mood disturbances with common onset in the postpartum, sometimes referred to as "baby blues".

Some limitations must be considered in the interpretation of the reported findings. First, a relatively high drop-out or lost to follow-up rate led to missing data from a proportion of women in respect to the whole study sample. This is frequently observed in prospective studies with a long follow-up phase. Also, women participating in the randomized controlled trial with BLT "Life-ON2" were not considered in the regression analysis, thus excluding part of the women developing PND, which may have influenced our results as regards the identification of potential risk factors for PND. Chronotype assessment was performed using only the MEQ, which in chronobiological research has been questioned for its intrinsic property of evaluating the sleep-wake preferences of the individuals screened, rather than the effective time of sleeping (Roenneberg, 2015). Finally, only 17 women (5.68 %) among 299 participants were classified as evening chronotypes, representing a minority of cases, which may have influenced our findings. A recent investigation on chronotype, hormonal factors and activity levels changes during pregnancy in women and female mice, as measured by wrist actigraphy and running wheel activity respectively, showed that both groups had an earlier timing of sleep onset during the first and second gestational trimesters than before pregnancy and returned to the pre-pregnant state during the third trimester (Martin-Fairey et al.,

2019). As a possible explanation, the authors suggested a conserved mechanism among species based on coordinated increases in estrogen and/or progesterone during early pregnancy. Thus, considering that chronotype assessment in our study was performed during the first gestational trimester, it can even be hypothesized that the distribution of chronotypes in our sample, with a clearly higher prevalence of morning types over evening types, may have been influenced by the time of assessment.

In conclusion, pregnant women with evening chronotype in the Life-ON study present sociodemographic characteristics and lifestyle attitudes that are commonly associated with a higher risk for PND. Moreover, they are more likely subject to health problems and adverse pregnancy outcomes than the other chronotypes. Independently from all these factors, evening chronotype is significantly associated with more severe PND symptoms depending on time, with a higher incidence especially in the immediate postpartum, which is confirmed as the most vulnerable period for the mental health of new mothers. Overall, these findings urge clinicians to increase attention towards the circadian phenotype of pregnant women, by routinely assessing chronotype during pregnancy using a simple screening questionnaire. This might help to preventively identify women who are more prone to develop PND and to support them with targeted psychological, sleep hygiene or chronotherapeutic strategies, in order to prevent negative health consequences for mothers and newborns.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.08.064.

Contributors

All authors approved the final version of the manuscript and take public responsibility for its content. No conflicts of interest for any of the authors in relation to this work exist. This manuscript is an original research paper and has not been published previously.

Role of the funding source

CRediT authorship contribution statement

Corrado Garbazza: recruitment, data collection and analysis, paper writing. Sandra Hackethal, Enrica Migliore: data analysis, paper writing. Silvia Riccardi, Chiara Serrati, Valentina Fanti, Simone Baiardi: recruitment, data collection, paper revision. Armando D'Agostino, Alessandro Cicolin, Stefan Borgwardt, Fabio Cirignotta, Susanna Mondini, Christian Cajochen, Mauro Manconi: study design, research supervision, paper revision. Contribution to research for every member of the "Life-ON study group" is indicated in a separate file (Supplementary material).

Conflict of interest

None.

Acknowledgements

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