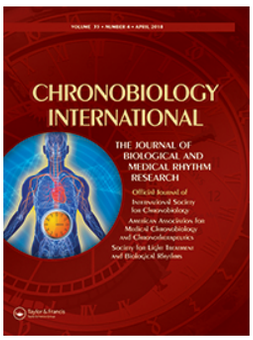

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Premature birth and circadian preference in young adulthood: evidence from two birth cohorts

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ABSTRACT

A preference for eveningness (being a "night owl") and preterm birth (<37 weeks of gestation) are associated with similar adversities, such as elevated blood pressure, impaired glucose regulation, poorer physical fitness, and lower mood. Yet, it remains unclear if and how preterm birth is associated with circadian preference. The aim of this study was to assess this association across the whole gestation range, using both objective and subjective measurements of circadian preference.

Circadian preference was measured among 594 young adults (mean age 24.3 years, SD 1.3) from two cohorts: the ESTER study and the Arvo Ylppö Longitudinal Study. We compared 83 participants born early preterm (<34 weeks) and 165 late preterm (34 to <37 weeks) with those born at term (≥37 weeks, $n = 346$). We also compared very low birth weight (VLBW, <1500 g) participants with term-born controls. We obtained objective sleep data with actigraphs that were worn for a mean period of 6.8 (SD 1.4) nights. Our primary outcome was sleep midpoint during weekdays and weekend. The sleep midpoint is the half-way time between falling asleep and waking up, and it represents sleep timing. We also investigated subjective chronotype with the Morningness–Eveningness Questionnaire (MEQ) in 688 ($n = 138/221/329$) ESTER participants. The MEQ consists of 19 questions, which estimates the respondent to be of a "morning", "evening," or "intermediate" chronotype, based on the Morningness–Eveningness Score (MES). We analyzed the data from the actigraphs and the MES with three linear regression models, and analyzed distribution of the chronotype class with Pearson $\chi 2$.

There were no consistent differences across the study groups in sleep midpoint. As compared with those born at term, the mean differences in minutes:seconds and 95% confidence intervals for the sleep midpoint were: early preterm weekdays 11:47 (−8:34 to 32:08), early preterm weekend 4:14 (−19:45 to 28:13), late preterm weekdays −10:28 (−26:16 to 5:21), and late preterm weekend −1:29 (−20:36 to 17:37). There was no difference in sleep timing between VLBW-participants and controls either. The distribution of chronotype in the MEQ among all participants was 12.4% morningness, 65.4% intermediate, and 22.2% eveningness. The distribution of the subjective chronotype class did not differ between the three gestational age groups ($p = 0.98$). The linear regression models did not show any influence of gestational age group or VLBW status on the MES (all $p > 0.5$).

We found no consistent differences between adults born early or late preterm and those born at term in circadian preference. The earlier circadian preference previously observed in those born smallest is unlikely to extend across the whole range of preterm birth.

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Introduction

The adversities of the ~14.9 million (Blencowe et al. 2012) infants who are born preterm every year are not limited to the perilous beginning of their lives. Studies have shown that adults born preterm (<37 weeks), in particular those born very preterm (<32 weeks) or with a very or extremely low birth weight (VLBW <1500 g and ELBW <1000 g), have higher blood pressure (Hovi et al.

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Supplemental data for this article can be accessed here.

2016), higher prevalence of dysglycemia (Morrison et al. 2016), they exercise less (Kajantie et al. 2010), and some studies report more depression (Mathewson et al. 2017; Nosarti et al. 2012).

Recent studies have indicated that individual circadian preference is also associated with health and wellbeing. Later circadian preference (being a "night owl") has been linked to many of the same risk factors that are associated with prematurity: higher blood pressure (Merikanto et al. 2013a), higher prevalence of diabetes (Merikanto et al. 2013a), less physical activity (Wennman et al. 2015; Wong et al. 2015), and more depression (Merikanto et al. 2013b).

The similarity of outcomes originally raised the question of whether preterm birth is associated with later circadian preference. Intriguingly, the few studies that have studied this association, have suggested the opposite, as children and adults born preterm have shown an *earlier* circadian preference (being a "morning lark"). These studies have used both objective and subjective measurements, and they report findings from different age groups. Two actigraphy studies in a cohort of VLBW adults, performed at ages 22.5 and 25 years (Björkqvist et al. 2014; Strang-Karlsson et al. 2008), together showed an earlier bed time and getting up time in the VLBW-group. A cohort of 16–19-year-old adolescents born preterm (mean birth weight 1514g and gestational age 31 weeks) displayed a similar finding with actigraphy and self-report (Hibbs et al. 2014). At younger ages, a one-night, in-home polysomnography study found that 6–13-year-olds born very preterm had 13 minutes earlier sleep onset time compared to controls, but they also had a trend toward longer sleep duration (9.0 h versus 8.9 h, $p = 0.066$) (Maurer et al. 2016). Using actigraphy, even 12-month-old VLBW-infants born preterm have displayed earlier sleep onset and offset times than term-born controls (Asaka & Takada 2010).

In studies exclusively measuring self-reported chronotype, VLBW-adults reported a propensity for morningness in the Morningness–Eveningness Questionnaire (MEQ) (Strang-Karlsson et al. 2010). Also, among 13-year-old preterms (<37 weeks), a larger proportion were "morning types" compared to controls when assessed with the Junior MEQ and Junior Composite Scale (Natale et al. 2005). A Norwegian questionnaire study (Stangenes et al. 2017) of extremely preterm (<28 weeks or ELBW) 11-year-olds displayed 0.4h earlier bedtime, but correspondingly longer time in bed.

Most participants of the aforementioned studies are characterized by a very low birth weight and/or very short gestational age. However, most preterm infants, e.g. >70% of those born in the US (Engle et al. 2007), are born late preterm (34 to <37 weeks of gestation). Late preterm population is also subject to increased morbidity, mortality (Crump et al. 2011; Engle 2011), and cardiometabolic risk (Sipola-Leppänen et al. 2014), however whether this is related to circadian preference is not known.

Accordingly, the aim of the current study was to investigate if adults born preterm across the whole gestation range have different circadian preference than controls. To determine circadian preference, we used actigraphs to measure objective sleep timing and the Morningness–Eveningness Questionnaire to measure subjective chronotype. Based on the previous studies, we hypothesized an earlier circadian preference among the preterm participants of two large birth cohorts.

Materials and methods

Participants

Two cohorts provided the participants for the present analysis: the ESTER study, and the Arvo Ylppö Longitudinal Study (AYLS) (Supplemental Figure 1). The 1980 subjects of the ESTER study (Preterm Birth and Early-Life Programming of Adult Health and Disease) come from two cohorts: 1) the Northern Finland Birth Cohort 1986 (49.8%) born in 1985–1986, and 2) a cohort of participants born 1987–1989 (50.2%) in the same area, identified via the Finnish Medical Birth Register. In 2009–2011, 753 subjects (38.0%) participated in a clinical study at 23.3 (SD 1.3) years. The study is based in Northern Finland, between latitudes 63.9 to 70.0. Comparison of participants and non-participants has been described in detail previously (Sipola-Leppänen et al. 2015). Of the clinical study participants 330 (43.8%) participated in the actigraphy study. After exclusion of participants with night shifts ($n = 9$), sickness during the sleep registration period ($n = 14$, of whom two also belonged to each other group) and insufficient amount of nights (<3 nights, $n = 18$), the

participant number was 291, with altogether 1890 measured nights.

Additionally, in the ESTER study, 690 participants filled in the Morningness–Eveningness Questionnaire (MEQ) (Horne & Östberg 1976). Two participants returned incomplete questionnaires, leaving 688 available for analysis (Supplemental Table 1).

AYLS is a part of a multicenter follow-up study conducted in Uusimaa, Finland, and Bavaria, Germany, called the Bavarian-Finnish longitudinal study (Heinonen et al. 2008; Riegel et al. 1995; Salonen et al. 2015). Participants in Finland were recruited from a total of 15,311 deliveries in the seven maternity hospitals in Uusimaa province 1985–1986. The sample comprised 2193 infants, of whom 1535 were admitted to neonatal wards within obstetric units or transferred to the Neonatal Intensive Care Unit (NICU) of the Children's Hospital within 10 days of birth. An additional 658 non-hospitalized controls were prospectively recruited, from births after every second hospitalized infant in the three largest maternity hospitals of Uusimaa. Of the 2193 infants, 1913 subjects (87.2%) could be traced as adults, and were invited to a follow-up study performed 2009–2012. A total of 1136 subjects (hospitalized n = 754, controls n = 382, 59.4% of the invited) participated at the mean age of 25.2 (SD 0.6) years. AYLS is based around Helsinki, at latitude 60.2. To evaluate the effects of preterm birth, we restricted the study to preterm adults (n = 175, of whom 166 were hospitalized as described above), and corresponding term-born (≥37 weeks) adults from the control group (n = 314), a sum of 489 participants. Of these 489 individuals, 340 (69.5%) participated in the actigraphy study After exclusion of participants with night shifts (n = 14), sickness during the sleep registration period (n = 5), and insufficient amount of nights (<3 nights, n = 18), the participant amount was 303 with altogether 2128 measured nights.

Therefore, for the pooled actigraphy data, we had a final total of 594 participants (291 from ESTER and 303 from AYLS) available for sleep analysis. These participants wore the actigraph for a mean period of 6.8 (SD = 1.4) nights (ESTER 6.5, AYLS 7.0). We compared these final 594 subjects, who provided actigraphy data, with non-actigraphy participants and those who were excluded in the process. Among the final total of actigraphy study subjects, there were less preterm participants and less current smokers, and the participants were 0.45 years older (all $p < 0.014$). There was no statistically significant difference in maternal body mass index (BMI, kg/m^2) before pregnancy, exposure to maternal smoking during pregnancy, gestational diabetes, gestational hypertension, preeclampsia, being the first-born child, parental educational attainment or current own BMI. The 688 participants from the ESTER study who completed the MEQ did not differ in any significant way from the 65 participants who did not complete the MEQ.

Both studies were approved by the Coordinating Ethics Committee at Helsinki and Uusimaa Hospital District. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Actigraphy

Wrist-worn actigraphs were used to objectively measure sleep duration and timing. Actigraphs are well validated for measuring circadian rhythms when compared to polysomnography (Littner et al. 2003; Van De Water et al. 2011). The actigraph uses piezoelectric beams to detect movement, and records these counts digitally. If the movement count reaches a certain threshold during an epoch, an algorithm scores the epoch as awake. If the movement count does not surpass the threshold during several consecutive epochs, the algorithm considers the participant to be asleep. In both the ESTER and AYLS studies, participants documented in a sleep diary the times for going to bed and getting up, any exceptional events or nights, and any interruptions in the recording (e.g. when showering). Additionally, the participants pressed an event marker on the actigraph at bed- and get up times, which helped in identifying the analysis windows for each night. In the ESTER study, we used ActiGraph GT1M (ActiGraph, LLC), with the software Actilife 4.1.1, and the Sadeh algorithm. In the AYLS, we used Actiwatch AW7 (Cambridge Neurotechnology Ltd., UK), with the software Sleep Analysis 7.

We report the following sleep variables with these descriptions: *bed time*, the time when the participant closed the eyes and pressed the event marker; *get up time*, the time when the participant got up and pressed the event marker; *actual sleep time*, the sleep duration after subtracting the time awake; *wake after sleep onset (WASO)*, the amount of time the participant is awake between falling asleep and getting up; *sleep midpoint weekday*, the midpoint in time between falling asleep and getting up during weekday nights (Sunday–Thursday); *sleep midpoint weekend*, the midpoint in time between falling asleep and getting up during weekend nights (Friday–Saturday); *catch-up* sleep, the difference in sleep duration between weekend- and weekday nights. Our primary outcomes were sleep midpoint during weekday and weekend nights. These two outcomes represent objectively measured sleep timing, and thus circadian preference.

The actigraphy data was scrutinized and compared with the participant's sleep diary. Individual nights were disqualified if 1) there was no activity during the registration, 2) if all documentation was missing from the sleep diary, 3) if bedtime was missing from both event markers and sleep diary, 4) if get up time was undocumented, and the event marker was not unequivocal, 5) if an aberrant activity influenced the sleep (e.g. trip), and 6) if the event markers and the sleep diary did not correspond to each other. Nights were also disqualified if the participant reported napping, drinking alcohol or taking medication that influenced sleep.

Morningness–eveningness questionnaire

The MEQ is a self-report instrument used for establishing a subjective chronotype. The questionnaire consists of 19 questions that produce a Morningness–Eveningness Score (MES), ranging from 16 to 86. A higher score is indicative of morningness, and a lower of eveningness, with specific thresholds for the categories (42 to 58 for "intermediate"). This three-group categorization can be further divided into a "definite" morning (70 to 86) and evening (16 to 30) type. The questionnaire is validated in young adults (Horne & Östberg 1976), and it correlates well with physiological markers of circadian rhythm, such as body temperature and melatonin level (Griefahn 2002).

Background variables

The original medical records provided the gestational age of the participants, based on ultrasonography or last menstrual period (Sipola-Leppänen et al. 2014), as well as providing information about birth weight standard deviation (SD) score, parity, maternal gestational disorders, smoking during pregnancy and BMI before pregnancy. Small for gestational age (SGA) was defined as ≤ −2 SD for sex and length of gestation, based on Finnish birth weight standards (Pihkala et al. 1989). At the clinical visit, the participant reported the educational attainment of the higher educated parent, and the current participant BMI was calculated from measured height and weight. Self-report questionnaires provided information about daily smoking (yes/no) and the amount of paid work in a week.

Statistical methods

The participants were divided into three groups based on gestational age: for the actigraphy study 83 early preterm (<34 weeks of gestation), 165 late preterm (34 to <37 weeks) and 346 controls (≥37 weeks), as defined by the American Academy of Pediatrics (Engle et al. 2007). The number of participants for the MEQ analysis was 138, 221, and 329, respectively. Also, to allow comparison with previous studies (Björkqvist et al. 2014; Strang-Karlsson et al. 2008), we separately investigated VLBW participants (actigraphy n = 33, MEQ n = 49).

Analysis of descriptive characteristics was done with t-test if the variable was continuous, and with Pearson χ^2 if categorical. Means were calculated for sleep variables and MES. We analyzed and presented the results in three linear regression models; *model 1* adjusting for age, sex and cohort; *model 2* further adjusting for parental educational attainment, birth weight SD score, parity, maternal smoking during pregnancy, maternal BMI before pregnancy, gestational hypertension and diabetes; and *model 3* further adjusting for participant BMI.

Model 1 is a minimally adjusted model (Roenneberg et al. 2007), and the alternative models 2 and 3 adjust for factors related to preterm birth (Goldenberg et al. 2008) and current lifestyle. Because the two actigraph models were used exclusively in each cohort, their effect was taken into account with the cohort adjustment in model 1. Interaction terms (sex x study group) in relation to the sleep outcomes were not significant ($p > 0.2$). 69 participants (7/23/39) did not provide weekend data. To study the effect of paid employment, we analysed separately participants who reported <20 hours ($n = 351$) or ≥20 hours ($n = 243$) of paid work during the week. As a sensitivity analysis we investigated if exclusion of participants who reported having children in the family changed the main outcomes. Additionally, we calculated sleep midpoint corrected by sleep debt MSFsc (Roenneberg et al. 2004). We analyzed distribution of both the three-group chronotype (morning/intermediate/evening) and five-group chronotype (definite morning/moderate morning/intermediate/moderate evening/definite evening) with Pearson χ^2. The α-level was set to 0.05. SPSS 22.0 was used for the statistical analyses.

Results

Background characteristics

The early and late preterm groups were compared to the control group regarding background variables (Table 1). In the pooled actigraphy data from both cohorts, the preterm participants were younger than the controls. There was no statistically significant difference in distribution of maternal smoking during pregnancy, maternal BMI before pregnancy, gestational diabetes or hypertension, being first-born, parental educational attainment, sex, current BMI or smoking. By design the early and late preterm groups were born at a lower birth weight, smaller for

Table 1. Characteristics of actigraphy study participants, $n = 594$.

			Control, $n = 346$		Late preterm, $n = 165$		Early preterm, n = 83	
				Missing		P-value		P-value
Number of participants				0/0/0		0.009		<0.001
	AYLS	*n* (% in cohort)	200 (66.0)		75 (24.8)		28 (9.2)	
	ESTER	*n* (% in cohort)	146 (50.2)		90 (30.9)		55 (18.9)	
Male		*n* (%)	150 (43.4)	0/0/0	84 (50.9)	0.109	38 (45.8)	0.689
Gestational age, weeks		mean (SD)	40.14 (1.18)	0/0/0	35.81 (0.79)	<0.001	31.71 (2.16)	<0.001
Birth Weight, grams		mean (SD)	3589.80 (488.72)	0/0/0	2711.64 (547.91)	<0.001	1729.22 (471.81)	<0.001
Small for gestational age		*n* (%)	4 (1.2)	0/0/0	20 (12.1)	<0.001	14 (16.9)	<0.001
First-born child		*n* (%)	139 (40.2)	0/0/0	76 (46.1)	0.207	40 (48.2)	0.183
Maternal BMI before pregnancy		mean (SD)	22.22 (2.99)	5/2/0	22.20 (3.32)	0.952	22.57 (3.84)	0.439
Maternal gestational diabetes		*n* (%)	8 (2.3)	2/10/14	5 (3.0)	0.559	0 (0.0)	0.201
Maternal gestational hypertension		*n* (%)	40 (11.6)	16/8/1	16 (9.7)	0.528	12 (14.5)	0.468
Maternal pre-eclampsia		*n* (%)	8 (2.3)	16/8/1	22 (13.3)	<0.001	16 (19.3)	<0.001
Maternal smoking during pregnancy		*n* (%)	52 (15.2)	3/3/2	29 (17.9)	0.433	18 (22.2)	0.124
Participant age, years		mean (SD)	24.50 (1.20)	0/0/0	24.04 (1.46)	0.001	23.98 (1.53)	0.004
Participant BMI	Men	mean (SD)	24.30 (3.60)	0/0/0	24.39 (4.00)	0.851	24.03 (4.43)	0.699
	Women	mean (SD)	23.75 (4.51)	0/0/0	22.64 (4.16)	0.06	23.79 (5.95)	0.952
Participant smoking		*n* (%)	72 (21.1)	5/4/0	36 (22.4)	0.751	16 (19.3)	0.711
Parental education				11/3/0		0.633		0.763
Basic		*n* (%)	26 (7.8)		11 (6.8)		6 (7.2)	
Secondary		*n* (%)	180 (53.7)		82 (50.6)		47 (56.6)	
Lower-level tertiary		*n* (%)	42 (12.5)		18 (11.1)		7 (8.4)	
Upper-level tertiary		*n* (%)	87 (26.0)		51 (31.5)		23 (27.7)	

Control ≥37 weeks of gestation, late preterm 34 to <37 weeks of gestation, early preterm <34 weeks of gestation.
P-values were calculated with t-test if the variable was continuous, and χ^2 if categorical.
SD, standard deviation; BMI, body mass index (kg/m^2).

gestational age, and a larger proportion were exposed to maternal preeclampsia.

As described above, the participants who completed the MEQ were all from the ESTER study. The differences in background characteristics between preterm and control group participants in the MEQ participant analysis were similar to the comparison outlined above, except that the late preterm group had proportionally more first-born participants and exposure to maternal diabetes and hypertension during pregnancy than the control group (Supplemental Table 1).

Objective sleep timing: early and late prematurity

The early and late preterm groups did not differ from the controls regarding the sleep timing measured by sleep midpoint (all $p > 0.14$), in any of the three models (Table 2). The same was true for MSFsc (all $p > 0.28$). The only significant difference we found in any of the sleep variables was that the late preterm group had more catch-up sleep, but only in model 2 (MD 20 min 17 s, $p = 0.048$). Exclusion of 59 participants who reported having children did not impact the main outcomes.

When we studied the participants based on their working schedules (<20 or ≥20 hours of paid work during the week), we found that in the group with more work, the late preterm participants had 25 min 12 s earlier bed time (model 1, $p = 0.028$) than controls. Otherwise, there were no significant differences between the two preterm groups and the control group (Supplemental Table 2A and 2B).

Objective sleep timing: VLBW

The 33 adults born preterm at VLBW had 22 min 8 s longer actual sleep time than controls (model 1 $p = 0.017$, $p > 0.62$ in models 2 and 3), and a 47 min 25 s longer catch-up sleep (model 1 $p = 0.057$, models 2 and 3 $p \leq 0.031$), but no association was found regarding the sleep midpoint or other sleep variables (Supplemental Table 3). Analysis of MSFsc did not reveal a significant difference either (all $p > 0.47$).

Subjective chronotype: early and late prematurity and VLBW

Of all 688 participants who completed the MEQ, 12.4% were of morning, 65.4% of intermediate and 22.2% of evening type. 0.7% were definite morning and 3.5% definite evening types. Neither the three- nor five-group distribution differed between early preterm, late preterm and control group (unadjusted χ^2 $p = 0.98$ and $p = 0.61$). The MES was also similar among groups, and was unaffected by adjustment for variables in our models (Supplemental Table 4; all $p > 0.5$). Exclusion of 75 participants who reported having children did not impact the results. Furthermore, the distribution of chronotype and the MES did not differ between the VLBW-group and controls (all $p > 0.69$).

Discussion

Our aim was to investigate if being born early or late preterm was associated with an earlier circadian preference in adult life. We used actigraphy and self-reported chronotype to obtain objective and subjective data. Against the hypothesis grounded on previous reports, we found no significant and consistent differences in the circadian preferences between the term and preterm groups, neither using actigraphy nor subjective chronotype assessment. Nor were we able to replicate previous findings of an earlier circadian preference among the group of adults born preterm at VLBW.

Previous studies have presented reasons why prematurity might be associated with an earlier sleep–wake rhythm. Many of the components that primarily drive the circadian rhythm: the retinal photoreceptors, their connections to the suprachiasmatic nucleus, key developments of the central pacemaker itself, and the efferent connections to the periphery, are matured postnatally in animal models (Brooks & Canal 2013). The development and onset of melatonin rhythmicity depends on neuroanatomical maturation, not environmental cues. So, the transient melatonin deficiency of 2–4 months that term-born infants experience after birth is longer with preterm birth, and commencement of pineal secretion is even further postponed by possible brain insults (Jan et al. 2007). Animal models have also

Table 2. Linear regression models of sleep variables, all participants.

			Controls (n = 341)	Late preterm (n = 163)		Early preterm (n = 83)	
n = 587	Model	Units	Mean (SD)	B (95% CI)	p	B (95% CI)	p
Bed Time							
		h:min:sec	00:09:50 (1:17:23)				
	1	h:min:sec		-0:11:24 (-0:26:03 to 0:03:14)	0.126	0:06:43 (-0:12:07 to 0:25:34)	0.484
	2	h:min:sec		-0:11:34 (-0:26:46 to 0:03:38)	0.136	0:10:05 (-0:10:23 to 0:30:33)	0.334
	3	h:min:sec		-0:10:55 (-0:26:05 to 0:04:14)	0.158	0:09:41 (-0:10:43 to 0:30:04)	0.352
Get up time							
		h:min:sec	8:23:55 (1:31:30)				
	1	h:min:sec		-0:09:52 (-0:27:03 to 0:07:20)	0.260	0:14:12 (-0:07:56 to 0:36:20)	0.208
	2	h:min:sec		-0:13:35 (-0:31:21 to 0:04:12)	0.134	0:12:26 (-0:11:30 to 0:36:22)	0.308
	3	h:min:sec		-0:13:05 (-0:30:51 to 0:04:42)	0.149	0:12:07 (-0:11:47 to 0:36:02)	0.320
Actual sleep time							
		h:min:sec	7:03:02 (0:51:14)				
	1	h:min:sec		0:01:05 (-0:08:18 to 0:10:28)	0.820	0:06:38 (-0:05:26 to 0:18:43)	0.281
	2	h:min:sec		-0:02:26 (-0:12:00 to 0:07:08)	0.617	0:01:24 (-0:11:29 to 0:14:17)	0.805
	3	h:min:sec		-0:02:47 (-0:12:20 to 0:06:46)	0.567	0:01:37 (-0:11:14 to 0:14:28)	0.831
Wake after sleep onset							
		h:min:sec	0:59:48 (0:28:26)				
	1	h:min:sec		-0:00:58 (-0:05:51 to 0:03:56)	0.699	0:01:08 (-0:05:10 to 0:07:26)	0.723
	2	h:min:sec		-0:00:39 (-0:05:45 to 0:04:27)	0.803	0:01:40 (-0:05:12 to 0:08:33)	0.633
	3	h:min:sec		-0:00:28 (-0:05:34 to 0:04:38)	0.857	0:01:34 (-0:05:18 to 0:08:25)	0.655
Sleep midpoint weekday							
		h:min:sec	04:06:48 (1:22:06)				
	1	h:min:sec		-0:10:28 (-0:26:16 to 0:05:21)	0.194	0:11:47 (-0:08:34 to 0:32:08)	0.256
	2	h:min:sec		-0:12:19 (-0:28:42 to 0:04:04)	0.141	0:12:58 (-0:09:06 to 0:35:01)	0.249
	3	h:min:sec		-0:11:47 (-0:28:10 to 0:04:35)	0.158	0:12:38 (-0:09:23 to 0:34:40)	0.260
			Controls (n = 302)	Late preterm (n = 140)		Early preterm (n = 76)	
n = 518	Model	Units	Mean (SD)	B (95% CI)	p	B (95% CI)	p
Sleep midpoint weekend							
		h:min:sec	05:14:09 (1:32:40)				
	1	h:min:sec		-0:01:29 (-0:20:36 to 0:17:37)	0.878	0:04:14 (-0:19:45 to 0:28:13)	0.729
	2	h:min:sec		-0:04:13 (-0:24:17 to 0:15:51)	0.680	0:01:33 (-0:24:43 to 0:27:49)	0.908
	3	h:min:sec		-0:02:58 (-0:23:00 to 0:17:03)	0.771	0:01:35 (-0:24:36 to 0:27:45)	0.906
Catch-up							
		h:min:sec	0:20:34 (1:31:40)				
	1	h:min:sec		0:18:36 (-0:00:29 to 0:37:41)	0.056	0:04:34 (-0:19:22 to 0:28:30)	0.708
	2	h:min:sec		0:20:17 (0:00:13 to 0:40:20)	0.048	0:06:27 (-0:19:49 to 0:32:42)	0.630
	3	h:min:sec		0:19:04 (-0:00:58 to 0:39:05)	0.062	0:06:25 (-0:19:46 to 0:32:35)	0.631

Control ≥37 weeks of gestation, late preterm 34 to <37 weeks of gestation, early preterm <34 weeks of gestation.
The times shown in the early and late preterm group are relative to the time in the control group, a negative value is earlier and a positive value is later.
Model 1 = adjusted for age, sex and cohort (AYLS, Northern Finland Birth Cohort, 1987–1989 cohort).
Model 2 = adjusted for variables in model 1 + parental education level (14 missing) + maternal smoking during pregnancy (8 missing) + maternal BMI before pregnancy (7 missing) + birth weight standard deviation score + being the first-born child + maternal hypertension during pregnancy (25 missing) + maternal diabetes during pregnancy (26 missing).
Model 3 = adjusted for variables in model 2 + participant BMI.
SD, standard deviation; CI, confidence interval; BMI, body mass index(kg/m^2).

demonstrated that prenatal hypoxia (Joseph et al., 2002) and protein malnutrition (Durán et al. 2005) may induce a possible phase advance of activity. These are also characteristics of the very preterm or VLBW groups rather than those born across the whole range of preterm birth, as in the present study. Moreover, those born very preterm or at VLBW are more likely to be admitted to NICUs (Marchofdimes.org 2011), where the infant is often subjected to abnormal lighting conditions, or even continuous lighting which was the norm for our VLBW participants in the 1980s. One possible reason why we did not observe differences between groups could be that the perinatal conditions were not as disruptive for our participants, who were born across the whole range of gestational ages, as they were for the VLBW survivors in studies that have reported an earlier circadian rhythm. That we did not observe a difference between adults

born preterm at VLBW and controls should be interpreted with caution, as our study was not powered for this smaller group.

Strengths of this study were the use of objective data which was gathered with actigraphy, avoiding recall bias. The data was collected from two separate, well-described cohorts of adult preterms of different degrees of gestational age. The average length of wearing the actigraph was almost seven days, which can be considered good. This together with the substantial number of participants resulted in adequate power; the confidence intervals in sleep midpoint between the early preterm and term groups (−8 to 32 min) and between late preterm and term groups (−26 to 5 min) indicate that we were able to exclude moderate or large differences between the study groups. Furthermore, for an $\alpha = 0.05$ and $1\text{-}\beta = 0.8$, even our weakest main comparison between the early preterm group ($n = 83$) and controls ($n = 341$) in the actigraphy analysis would be able to detect or exclude a mean difference of 0.34 SD. This is charitable considering that the mean effect size in studies that investigate preterm circadian preference (Asaka & Takada 2010; Björkqvist et al. 2014; Hibbs et al. 2014; Maurer et al. 2016; Natale et al. 2005; Stangenes et al. 2017; Strang-Karlsson et al. 2008; Strang-Karlsson et al. 2010), and in adult VLBW studies in general, tend to be around the order of magnitude of ~0.5 (Hovi et al. 2007; Pyhälä et al. 2011). The few formally statistically significant differences showed no consistent pattern and are likely to have arisen by chance, or are possibly related to issues not studied here. In addition, we were able to complement the objective sleep data with information about subjective chronotype using the MEQ. As a weakness, we did not specifically ask the participants to specify work days and free days, or ask if the participant shared a bed with a partner or with children.

To summarize, we investigated if there was an observable difference in circadian preference between early and late preterm adults and controls born at term. Earlier studies have mainly focused on VLBW or very preterm groups. This study provided information about late preterm participants, who constitute the overwhelming majority of the prematurely born population (Engle et al. 2007). Contrary to our hypothesis, our analysis did not reveal any consistent findings of an earlier circadian preference or a pronounced morningness in preterm groups or subgroups among young adults. Therefore, in conclusion, we estimate that the earlier circadian preference that has been observed in those born smallest is unlikely to extend across the whole range of preterm birth.

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