

Chronotype in very low birth weight adults – a sibling study

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Abbreviations:

AGA: Appropriate for gestational age

ELBW: Extremely low birth weight, ≤ 1500 grams

FMBR: Finnish Medical Birth Registry

HeSVA: Helsinki Study of Very low birth weight Adults

MSFsc: Midsleep on free days, corrected for sleep debt

SGA: Small for gestational age, ≤ -2 SD

VLBW: Very low birth weight, ≤ 1500 grams

Abstract

Chronotype is the temporal preference for activity and sleep during the 24h day and is linked to mental and physical health, quality of life, and mortality. Later chronotypes, so called “night owls”, consistently display poorer health outcomes than “larks”. Previous studies have suggested that preterm birth (<37 weeks of gestation) is associated with an earlier chronotype in children, adolescents, and young adults, but studies beyond this age are absent. Our aim was to determine if adults born preterm at very low birth weight (VLBW, ≤ 1500 grams) display different chronotypes than their siblings. We studied VLBW adults, aged 29.9 years (SD 2.8), matched with same-sex term-born siblings as controls. A total of 123 participants, consisting of 53 sibling pairs and 17 unmatched participants, provided actigraphy-derived data on the timing, duration, and quality of sleep from 1640 nights (mean 13.3 per participant, SD 2.7). Mixed effects models provided estimates and significance tests. Compared to their siblings, VLBW adults displayed 27 min earlier sleep midpoint during free days (95% CI: 3 to 51 min, $p = .029$). This was also reflected in timing of falling asleep, waking up, and sleep-debt corrected sleep midpoint. The findings were emphasized in VLBW participants born small for gestational age. VLBW adults displayed an earlier chronotype than their siblings still at age 30, which suggests that the earlier chronotype is an enduring individual trait not explained by shared family factors. This preference could provide protection from risks associated with preterm birth.

Keywords: actigraphy, sleep midpoint, midsleep, MSFsc, VLBW, very low birth weight, preterm, prematurity

Introduction

Preterm birth is globally the main cause of death in children under five years (Liu et al. 2016). Although most prematurely born children survive without severe disabilities (March of Dimes et al. 2012), a disruptive start to life may leave long-lasting effects. Decades-long follow-up studies on preterm survivors with very or extremely low birth weight (VLBW \leq 1500 grams, ELBW \leq 1000 grams) show increased blood pressure (Hovi et al. 2016), dysglycaemia (Hovi et al. 2007; Morrison et al. 2016), less exercise (Kajantie et al. 2010), more anxiety (Mathewson et al. 2017), and more internalizing (Pyhälä et al. 2017). Interestingly, in the field of chronobiology, some of these vulnerabilities are displayed by people with late chronotypes, so called night owls (Anothaisintawee et al. 2017; Merikanto et al. 2013; Hisler et al. 2017; Taylor and Hasler 2018). Chronotype is the partly heritable (37-50%, Koskenvuo et al. 2007; Watson et al. 2013) preference in timing for activity or sleep; it is a behavioral manifestation of the internal circadian clock, and it impacts most aspects of human life, from DNA repair (Sancar et al. 2010) and physiology (Pilorz et al. 2018) to personality and behavior (Adan et al. 2012; Fabbian et al. 2016). The resemblance in outcomes of preterm survivors and night owls has generated studies investigating whether chronotype contributes to prematurity-related morbidity. Counterintuitively, studies have suggested an earlier chronotype in extremely preterm children (Stangenes et al. 2017), preterm adolescents (Hibbs et al. 2014), and VLBW preterm adults in their early twenties (Strang-Karlsson et al. 2010; Björkqvist et al. 2014), but not in a young adult cohort with subjects from all degrees of prematurity (Björkqvist, Pesonen, et al. 2018). Thus, current evidence is inconclusive whether the reported earlier chronotype of preterm survivors persists into adulthood.

We investigated whether adult VLBW survivors, aged on average 30 years, display an earlier chronotype in a sibling design, which allows better control for heritability and familial environment than case-control studies. This is important because VLBW young

adults initiate independent lives later than term-born controls (Kajantie et al. 2008), and report more protective upbringing (Pyhälä et al. 2011), which can affect sleep-wake patterns (Randler et al. 2009). To answer these questions, we measured sleep patterns of VLBW survivors and their siblings with actigraphy for two weeks.

Materials and methods

Recruitment

We recruited VLBW subjects from the Helsinki Study of Very Low Birth Weight Adults (HeSVA, Hovi et al. 2007), the ESTER Preterm Birth Study (Sipola-Leppänen et al. 2015), and through the Finnish Medical Birth Registry (FMBR). HeSVA includes 166 VLBW survivors treated 1978-85 at the neonatal intensive care unit of the Children's Hospital at Helsinki University Central Hospital (Figure 1, map, supplemental), who underwent clinical examinations 2004-05. ESTER includes 376 preterm subjects (55 VLBW) either from the Northern Finland Birth Cohort 1986 (NFBC1986, born 1985–86) or identified through the Finnish Medical Birth Register (FMBR; born 1987–89), who underwent clinical examinations 2009-11. Subjects in NFBC1986 undergo regular assessments, so to avoid participation fatigue we only recruited subjects born 1987-89. After recruitments from HeSVA and ESTER, we identified through the FMBR VLBW survivors from live births between 1.1.1987-30.9.1990 in hospitals serving the provinces of Uusimaa, Varsinais-Suomi, and Northern Häme/Pirkanmaa, and physicians from these birth hospitals contacted the subjects.

The aim was to recruit 80 sibling pairs for three-day testing, including MRI scans, metabolic tests, tissue biopsies, exercise tests, neurocognitive assessment, and accelerometry. In power calculations 80 pairs, given $1-\beta = .8$ and $\alpha = .05$, allow detection of effect sizes of 0.32 in two-way comparisons (Faul et al. 2007).

Between July 2014 and February 2017, we successfully contacted 186 VLBW adults (Figure 2) whose population records indicated having a same-sex sibling born within 10 years. If records indicated a multiple birth, we randomly contacted one survivor. If willing to participate, each VLBW adult sought participation of a sibling with the least age difference. The term-born, same-sex sibling had to be 18 years of age or older, with less than 10 years age difference. If either potential participant presented with pregnancy, cerebral palsy, mental retardation, motor or sensory impairment, or endocrine disorder, we excluded both. Sixty-four potential pairs (34.4% of contacted) declined participation and 43 (23.1%) warranted exclusion, so the recruitment process netted 79 sibling pairs (42.5%): 22 via HeSVA, 6 via ESTER and 51 via FMBR. Participation analysis was possible with pseudonymized registry data (FMBR, ESTER) and previously collected data from HeSVA. For all variables in Table 2 and three-tiered parental education (lower secondary or less or unknown, upper secondary, tertiary) the 79 participants differed from the 175 non-participants only in less maternal smoking during pregnancy ($p = 0.009$) and more highly educated fathers ($p = 0.004$, Table 1, supplemental).

Three sibling-controls dropped out of the clinical studies, performed 2014-17, and 8 subjects declined actigraphy participation (Figure 3). One VLBW subject's exclusion criterion became apparent at the clinical visit, and scrutiny of birth records revealed 4 siblings born preterm, which warranted their exclusion. Of the 142 actigraphy participants, 19 (13.4%) returned invalid measurements due to technical errors or non-compliance, leaving 123 participants with analyzable data (53 pairs, 17 unmatched participants). These participants did not differ significantly from the 27 study participants without actigraphy data regarding sex distribution, age, gestational age, birth weight, or relative birth weight.

Perinatal data for HeSVA and ESTER participants has been previously collected from hospital or maternity clinic records (Hovi et al. 2007; Sipola-Leppänen et al. 2015). For

their siblings and all new subjects we similarly collected data about birth weight, gestational age, parity, mother's age, maternal smoking during pregnancy, and multiple pregnancy. Our primary source for gestational age was the noted weeks on birth certificate or records. If it differed by over two weeks from gestational age derived from last menstrual period we checked whether it was due to ultrasonography correction, which it was in all cases. Based on gestational age, Pihkala et al.'s (1989) standards converted birth weight into standard deviation units, with small for gestational age (SGA) defined as ≤ -2 SD.

The study followed accepted ethical practices (Portaluppi et al. 2010), the ethics committee of the Hospital District of Helsinki and Uusimaa approved the study, and all participants provided informed signed consent. Participants completing the study received ~84 EUR reimbursement per visit, plus travel costs and overnight lodging if required.

Sleep measurement

Wrist-worn accelerometers called actigraphs (Actiwatch2, Philips-Respironics, Murrysville, PA) measured sleep with 1-minute epochs and medium sensitivity setting. Both siblings received instructions to wear the device simultaneously for at least 14 days and to report in a diary sleep times, work hours, use of alcohol or sleeping medication, temporary removals of the device, and abnormal occurrences like illnesses or travel. To help recognize these situations the participants kept sleep logs and pressed an event marker on the device, which showed up on the recording.

Actigraphy is the most appropriate tool for objectively measuring sleep-wake patterns in non-laboratory settings due to its minimal invasiveness, good validity, and ease of use (Van De Water et al. 2011). Actigraphs measure sleep timing and duration accurately, but tend to misclassify wake (Pesonen and Kuula 2018). The technology in Actiwatch2 is based on piezo-electric sensors that detect movement, which the device stores as activity counts.

Based on these counts, an algorithm (Respironics Actiware v5.59) analyzed the data and scored each minute as wake or sleep.

The 123 participants recorded 1726 nights, of which 86 (5.0%) had to be excluded based on technical criteria: (a) the actigraph was not used; (b) bedtime information was missing; (c) sleep data indicated the participant was already asleep at the self-reported time; or (d) self-reported awakening time was missing and the activity pattern was ambiguous. The final accepted nights numbered 1640 (participant mean 13.3, SD 2.7). Participants reported use of alcohol in 272 cases, sleeping medication in 37, and daytime naps in 49. Parents reported being woken up by children during 74 nights. Three participants reported ailments more disruptive than the common cold, which was our cut-off point for labelling illness. Self-reported free- or workday status for next morning was available for 1396 nights (85.1%), and we assumed free weekend mornings for 242 nights (14.9%). We excluded 11 nights with shift work. Free day comparisons were available for 51 pairs (VLBW n = 59, control = 60), and work day comparisons for 47 pairs (VLBW n = 61, control = 56).

The main outcome for chronotype was free day sleep midpoint, because sleep is constrained during workdays. Sleep midpoint is the half-way time between falling asleep and waking up, and it serves as proxy for dim light melatonin onset (Terman et al. 2001), the gold standard of circadian markers (Klerman et al. 2002). A further refinement is free day sleep midpoint corrected for sleep debt, $MSF_{sc} = \text{free day sleep midpoint} - 0.5 * (\text{free day sleep duration} - \text{average weekly sleep duration})$ (Roenneberg et al. 2004), because sleep deprivation accrued during work days manifests itself on free days as longer sleep duration and later sleep midpoint.

We also report: *sleep start*, when the participant fell asleep; *sleep end*, when the participant woke up; *duration*, time between sleep start and end; *actual sleep time*, time spent asleep after sleep start; *wake after sleep onset*, time spent awake after sleep start; *wake*

percentage, proportion of duration that is awake; *catch-up sleep*, difference in sleep duration between free and work days, indicating possible sleep debt; and *social jet lag*, difference in sleep midpoint between free and work days (Wittmann et al. 2006) or difference in sleep start between free and work days (Jankowski 2017).

Statistical analysis

We assessed background variables on a group level with independent samples t-tests and χ^2 , and pairs with paired t-tests and McNemar's test. We used linear mixed effects models to study if VLBW status explained potential group differences in sleep outcomes, with repeated measurements nested within subjects, and subjects nested within families. The following variables were fixed effects: model 1 included the minimal chronobiological variables, age, and sex (Roenneberg et al. 2007), and model 2 further adjusted for use of alcohol and sleep medication, naps, child-related awakenings, and illness. Unmatched subjects remained in the analysis to improve model accuracy.

Calculation of MSFsc, catch-up sleep, and social jet lag involves mean values from work and free days. For these outcomes, we 1) excluded nights with preceding naps, alcohol use, or sleep medication use to omit their effect, 2) calculated mean values separately for free-and work days, 3) computed MSFsc, catch-up sleep, and social jet lag, and 4) compared outcomes with paired t-test. This exclusion process caused attrition, leaving 41 pairs for comparisons of MSFsc, catch-up sleep, and social jet lag.

We performed different post hoc mixed effects analyses to the free day sleep midpoint (model 2). To test for possible effect of relative birth weight on sleep outcomes we compared separately VLBW small for gestational age (SGA) and appropriate for gestational age (AGA) subgroups to their AGA siblings. We also examined possible sex interaction with a sex*VLBW interaction term and ran the analysis separately according to sex. Further, we

examined if birth or testing season (Vollmer et al. 2012; Didikoglu et al. 2019) influenced the VLBW-control difference in free day sleep midpoint. This was done by introducing photoperiod variables to model 2 (spring [Feb-April], summer [May-July], autumn [Aug-Oct], and winter [Nov-Jan]). Finally, as a sensitivity analysis we excluded subjects who had participated in the earlier HeSVA (n = 19) and ESTER (n = 3) studies.

We performed all statistical analyses using SPSS (IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp). We rounded time differences to minutes in the text for brevity, but the tables also display seconds.

Results

The VLBW subjects ($n = 63$) were on average 29.9 (SD 2.8) years old, and the siblings 29.7 years (SD 5.2, $n = 60$, Table 2). Men comprised 50.8% of VLBW and 48.3% of control participants. Of the 53 whole sibling pairs 26 were men (49.1%). Besides having a lower birth weight, a larger proportion of VLBW subjects were born SGA (36.5% vs 3.3%), and from a multiple pregnancy (11.1% vs 1.7%). No differences emerged between groups for mother's age at delivery, maternal smoking during pregnancy, or being firstborn.

On free days the VLBW subjects displayed significantly earlier chronotype than their siblings, as evidenced by the earlier sleep midpoint (-27 min, $p = .029$, Table 3, model 2), sleep start (-25 min, $p = .040$), and sleep end (-28 min, $p = .043$). No differences in sleep duration, actual sleep time, wake after sleep onset, or wake percentage emerged on free days.

On work days sleep timing did not differ between groups. Although not statistically significant, the VLBW subjects displayed 22 min earlier sleep start ($p = .108$), 18 min longer duration ($p = .068$), and 11 min longer actual sleep time ($p = .197$). The VLBW subjects displayed more nocturnal wake after sleep onset (6 min, $p = .023$), for a wake percentage difference of 1.06 % ($p = .05$).

VLBW subjects displayed 41 min earlier MSFsc than their siblings (95% CI: -78 to -5 minutes, $p = .029$, not in tables). No difference emerged for catch-up sleep (0 min, 95% CI: -31 to 31 min) or social jet lag (sleep midpoint difference -20 min, 95% CI: -51 to 10 min, sleep start difference -20 min, 95% CI: -52 min to 12 min).

For post hoc analysis we separately compared free day sleep midpoint of VLBW SGA ($n = 21$) and VLBW AGA ($n = 38$) subjects to their siblings born AGA ($n = 58$, 50 complete pairs [19 SGA, 31 AGA]). This revealed a stronger tendency for earlier chronotype in the VLBW SGA group (-48 min, 95% CI: -75 to -21 min, $p = .001$, model 2, Figure 4) than in the VLBW AGA group (-21 min, 95% CI: -52 to 10 min, $p = .18$). The sex interaction term

introduced to free day sleep midpoint model 2 was not statistically significant, but analysis by sex revealed that free day sleep midpoint in the VLBW group was more pronounced among women (-41 min, 95% CI: -6 to -76 min, $p = 0.023$) than among men (-15 min earlier, 95% CI: -49 to 21 min, $p = 0.4$). Addition of birth or testing season shifted the free day sleep midpoint difference by less than a minute, so our results remained. Exclusion of previous HeSVA and ESTER participants from the analysis did not meaningfully impact our finding.

Discussion

Our study is the first to compare VLBW subjects' chronotype and sleep to that of their term-born siblings. The analysis revealed clear differences in sleep timing on free days, and subtle differences on work days. First, on free mornings the earlier sleep start, midpoint, sleep end, and the earlier sleep-debt-corrected midpoint MSFsc suggest that VLBW adults displayed an earlier chronotype than their term-born siblings. Second, on work mornings with more forced schedules both groups woke up at similar times, but VLBW subjects possibly went to bed earlier (sleep start -22 min, $p = .108$, sleep duration 18 min, $p = .068$). This anticipation of a scheduled early morning might explain why VLBW subjects displayed 6 min more wake after sleep onset during work nights.

Our findings align well with previous studies in children, adolescents, and younger adults. However, direct comparisons are often difficult due to diversity of subject age and outcomes; only few studies have reported sleep midpoints or MSFsc. The strongest support comes from a large actigraphy study of preterm adolescents (mean birth weight 1514 grams, gestational age 31 weeks), which showed 24 min earlier sleep midpoint during weekends (Hibbs et al. 2014), compared to 27 min in the current study. Other actigraphy studies also show earlier sleep start or sleep end among VLBW young adults and toddlers (Strang-Karlsson et al. 2007; Asaka and Takada 2010; Björkqvist et al. 2014). One overnight

polysomnography study on very preterm (<32 weeks) school-aged children showed 13 min earlier sleep onset (Maurer et al. 2016), but in an earlier study by the same team found sleep onset was non-significantly (6 min) earlier (Perkinson-Gloor et al. 2015). The current findings were in disagreement with a study of only 33 VLBW subjects covering the entire preterm range, which did not discover difference in chronotype between preterm and term-born groups (Björkqvist, Pesonen, et al. 2018). The phenomenon of an earlier chronotype may, therefore, be restricted to those born smallest, i.e., SGA.

Supporting this notion, a post hoc analysis by relative birth weight revealed much earlier chronotype (free day sleep midpoint -48 min, $p = 0.001$) in VLBW subjects born SGA. Possible developmental programming would arguably be strongest among those most exposed to impaired intrauterine environments, and the combined pathology of prematurity and SGA is stronger than either condition alone (Katz et al. 2013). However, the association between intrauterine growth and chronotype remains inconclusive: Strang-Karlsson et al. (2010) found pronounced self-evaluated morningness in VLBW young adults born AGA rather than SGA. Although the sex interaction was not statistically significant, we found a more pronounced difference among women than among men. While this is an interesting finding, it is post hoc and should be confirmed in further studies.

Compared to night owls, larks display better mental and physical health (Adan et al. 2012; Fabbian et al. 2016), higher academic achievement (Tonetti et al. 2015) and quality of life (Prieto et al. 2012; Suh et al. 2017), and reduced mortality (Knutson and von Schantz 2018). Thus, a natural assumption is that earlier chronotype might be a protective factor. Paradoxically, the reported difference could also be a consequence of developmental programming due to fetal distress. Several animal studies indicate that early life exposure to stress (Koehl et al. 1997; Koehl et al. 1999), hypoxia (Joseph et al. 2002), malnutrition (Durán et al. 2005), alcohol (Handa et al. 2007), or postnatal continuous lighting (Brooks et al. 2014)

also might advance the internal clock, so confirming possible protective effects requires further study. It is possible the chronotype of the mother may be transferred through an imprinting signal caused by maternal circadian melatonin pattern in utero (Serón-Ferré et al. 2012) and during breastfeeding (McKenna and Reiss 2018). If so, preterm birth could disrupt this transfer.

Our study had several strengths. Using siblings as controls not only increased statistical power but allowed circumvention of unmeasured family-based confounders. Also, the mean recording period of almost two weeks is, to our knowledge, unparalleled in this field. Furthermore, the detailed information about free and work days allowed determination of unforced circadian rhythms. As weaknesses we note that over 13% of participants failed to return valid measurements, which is unfortunate because minimal drop-out was important due to the delicate study setting. Also, the family environment might have changed during the decade that we allowed as age difference between siblings, and we lacked detailed information about family composition and changes in living conditions and location. We placed strong emphasis in recruiting whole sibling pairs, which may lead to selective participation of behaviorally similar sibling pairs. This would, if anything, lead to more conservative findings.

Adults born preterm at VLBW display an earlier chronotype than their siblings at almost 30 years of age. This indicates that the phenomenon persists with age and more independent living and seems most pronounced after disruptive perinatal conditions, such as VLBW and SGA. Although this study reports robust results, the actual explanation of this phenomenon remains elusive. We suggest future studies investigate possible mechanisms, such as differences in light exposure, personality type, length of the internal day, or possible genetic variation or epigenetic modification of clock genes. Our findings should also be replicated in other parts of the world in order to determine whether regional or cultural

differences in sleep timing play any part in explaining these results. These mechanisms may shed light to early life programming of chronotype and to potential protective factors in children and adults born preterm.

Declaration of interest

The authors report no conflict of interest.

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Figure legends

Figure 1. Map of recruitment areas

Figure 2. Flowchart of participant recruitment

Figure 3. Flowchart of actigraphy participants

Figure 4. Mean difference and 95% confidence interval of free day sleep midpoint of very low birth weight (VLBW) adults born small for gestational age (SGA, n = 21) and appropriate for gestational age (AGA, n = 38) compared to term siblings born appropriate for gestational age (AGA, n = 58). Complete pairs numbered n = 50 (19 SGA, 31 AGA).