Genetic variants for morningness in relation to habitual sleep-wake behavior and diurnal preference in a population-based sample of 17,243 adults

Merikanto, Ilona

2021-04

Merikanto , I , Kantojärvi , K , Partonen , T , Pesonen , A-K & Paunio , T 2021 , ' Genetic variants for morningness in relation to habitual sleep-wake behavior and diurnal preference in a population-based sample of 17,243 adults ' , Sleep Medicine , vol. 80 , pp. 322-332 . https://doi.org/10.1016/j.sle

http://hdl.handle.net/10138/332033
https://doi.org/10.1016/j.sleep.2021.01.054

Sleep Medicine 80 (2021) 322–332

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Genetic variants for morningness in relation to habitual sleep-wake behavior and diurnal preference in a population-based sample of 17,243 adults

Ilona Merikanto [a, b, c, *], Katri Kantojärvi [a, d], Timo Partonen [a], Anu-Katriina Pesonen [b], Tiina Paunio [a, d]

[a] Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland
[b] Department of Psychology and Logopedics and SleepWell Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[c] Orton Orthopaedics Hospital, Helsinki, Finland
[d] Department of Psychiatry and SleepWell Research Program, University of Helsinki and Helsinki University Hospital, Finland

ARTICLE INFO

Article history:
Received 5 November 2020
Accepted 27 January 2021
Available online 30 January 2021

Keywords:
Chronotype
Eveningness
MEQ
Polygenic risk score
Population-based
Sleep midpoint

ABSTRACT

Objective: Associations of eveningness with health hazards benefit from analyzing to what extent the polygenic score for morningness correlates with the assessments of the behavioral trait of morningness-eveningness and chronotype.

Methods: With a population-based sample of 17,243 Finnish adults, aged 25–74 years, this study examines the associations of four feasible assessment methods of chronotype, a) biological the genetic liability based on the polygenic score for morningness (PGS_{morn}), b) the widely-used single item for self-assessed morningness/eveningness (MEQ_{i19}) of the original Morningness-Eveningness Questionnaire (MEQ), c) the behavioral trait of morningness-eveningness as assessed with the score on the shortened version (sMEQ) of the original MEQ, and d) the phase of entrainment as assessed with the habitual midpoint of sleep based on the self-reported sleep-wake schedule during weekend ($Sleep_{mid\text{-}wknd}$) as well as the sleep debt corrected midpoint of sleep ($Sleep_{mid\text{-}corr}$).

Results: All self-report measures correlated with each other, but very weakly with the PGS_{morn}, which explained 1–2% of the variation in diurnal preference or habitual sleep-wake schedule. The influence of age was greater on $Sleep_{mid\text{-}wknd}$ and $Sleep_{mid\text{-}corr}$ than on the sMEQ or MEQ_{i19}, indicating that the diurnal preference might be a more stable indicator for morningness-eveningness than the sleep-wake schedule. Analyses of the discrepancies between sMEQ and MEQ_{i19} indicated that eveningness can be over-estimated when relying on only the single-item self-assessment.

Conclusions: The current polygenic score for morningness explains only a small proportion of the variation in diurnal preference or habitual sleep-wake schedule. The molecular genetic basis for morningness-eveningness needs further elucidation.

1. Introduction

Many of the physiological functions and behavioral activity patterns, such as sleep onset and awakening times, blood pressure, hormone secretion and body temperature, operate according to individual circadian rhythms [1] that follow approximately a 24 h period [2]. Based on the variation in the timing of circadian rhythms individuals differ by their chronotype with earlier or later timed peaks in their physiological and behavioral functions [3–5]. Twin studies have given heritability estimates of 44%–57% for diurnal preference [6–8] and chronotype is considered to be a fairly

Abbreviations: GWAS, Genome-wide association study; MEQ, Morningness-Eveningness Questionnaire; MEQ_{i19}, Self-assessed morningness/eveningness based on item 19 from the original MEQ; PGS, Polygenic score; PGS_{morn}, Polygenic score for morningness; $PGS_{morn\text{-}best\text{-}fit}$, Polygenic score for morningness with best fit p-value threshold; $Sleep_{mid\text{-}wknd}$, Midpoint of sleep on weekends; $Sleep_{mid\text{-}corr}$, Midpoint of sleep corrected for sleep debt; sMEQ, 6-item shortened version of the original MEQ.

* Corresponding author. Department of Psychology and Logopedics, Faculty of Medicine, PL21, 00014, University of Helsinki, Finland.
E-mail address: ilona.merikanto@helsinki.fi (I. Merikanto).

https://doi.org/10.1016/j.sleep.2021.01.054

unchangeable biological character in healthy individuals across the adulthood [9,10]. Understanding the mechanisms and variation in individual chronotype has become increasingly relevant as a growing number of epidemiological studies have found an association between chronotype and various health outcomes [11,12]. For instance, eveningness has been associated with increased risk for poorer mental health and depression [13,14], cardiovascular diseases and type 2 diabetes [15,16], respiratory disorders [17] and spinal diseases as compared to diurnal preference for morningness [18,19]. However, the chronotype assessment method can differ greatly between epidemiological studies, as there are different subjective or objective ways to determine diurnal behavioral or physiological rhythms. This challenges comparisons of different study outcomes especially eg regarding diverse estimations on population-level chronotype prevalence.

Individual chronotype can be operationalized as eg, timing of diurnal body temperature [20–22] or melatonin secretion [23], sleep-wake behavior assessed either with actigraphy [24] or by questionnaires [25], or as questionnaires on diurnal preference [5,26]. Of these, dim-light melatonin onset is considered a reliable circadian marker, but it is not feasible in large cohort studies [27,28]. Measuring body temperature rhythm from wrist or sleep-wake patterns with accelerometers are practical solutions for chronotype measurements, but can also easily be influenced by current physical and environmental conditions [20,24,29,30].

However, for large epidemiological studies, a subjective assessment, such as questionnaires assessing chronotype via sleep-wake behavior vs. via diurnal activity preferences is a feasible tool to assess representative samples at a population-level. Both Munich ChronoType Questionnaire (MCTQ) for sleep-wake behavior [25] and Morningness-Eveningness Questionnaire (MEQ) for diurnal preference [5] correlate strongly with dim light melatonin onset [31]. Of these, MEQ is more widely used and has also a high reliability [32] and reproducibility [33]. MEQ has also been shown to correlate with the circadian period length and core body temperature phase [4]. However, 19-item original MEQ can be lengthy to respond. Thus shorter MEQ versions have been introduced, including 4 items [34], 5 items [35] or 6 items [36]. All shortened scales consist of slightly different original MEQ items. Of the shortened versions, the 6-item version explains most, 83%, of the total variation of the full MEQ [36] and is therefore used here to describe diurnal preference along with single item self-assessment of diurnal preference. Regarding sleep-wake schedule, midpoint of sleep on work-free days describes individual circadian sleep-wake rhythm better than when measured on working days when sleep habits are more governed by the societal schedules [37].

Recently, results from genome-wide association study (GWAS) on very large samples have given estimates for the polygenic variation of diurnal preferences based on a single item of MEQ [38–40]. GWAS is a powerful tool in search of multiple genetic single-nucleotide variants across genome that associate with certain traits and diseases [41]. GWASs on morningness/eveningness thus enable calculation of polygenic scores (PGS) for a genetic tendency towards morningness/eveningness in any sample comprising genetic information. Using polygenic scores (PGS) for summarized genetic effects of multiple single nucleotide polymorphism (SNP), the effect of which would individually be too weak to reach significance in relation to the studied phenomenon, has become a popular approach in health research [42].

Researchers must thus make decisions on which assessment method to choose for studying chronotype. In epidemiological studies targeting large sample sizes, it is an attractive solution to reduce questionnaire items in order to reach better response rates or to use data from existing biologic samples, such as genetic information, which are becoming more readily available from an increasing number of people in Biobank repositories. In national health examination studies or surveys examining the association of multiple possible factors regarding a specific health issue, the number of instruments used for chronotype assessment is likely restricted into one or few low-cost and feasible methods. In those situations, the use of a single item on the self-reported diurnal profile or the calculation of PGS for morningness/eveningness may be the most likely candidates for assessment instruments. It is, however, largely unknown how well PGS for morningness/eveningness derived from one study can be translated to assess chronotype in other cohorts, with different genotypic variation. Thus far, only one longitudinal study [43] showed an association between higher PGS for morningness, consisting of the SNPs reaching the level of genome-wide significance in a previous GWAS [44], and earlier timed midpoint of sleep from childhood to adolescence. It is also elusive how well the single question for self-assessed morningness/eveningness, which is used when diurnal preference has been assessed in the large-scale GWA studies [38–40], corresponds to different assessments of diurnal preference at a population level among adults.

Accordingly, the current study examines the population-based correlation between the polygenic score for morningness (PGS_{morn}) and the self-reported preference to daily activities and timing of sleep. These self-reports include a) the single item for self-assessed morningness/eveningness (MEQ_{i19}) of the original MEQ on which the most recent and the largest GWAS on morningness/eveningness [39] was based, b) the 6-item shortened version (sMEQ) of the original MEQ, and c) the midpoint of sleep based on the self-reported sleep-wake schedule on weekends ($Sleep_{mid\text{-}wknd}$) along with the midpoint of sleep corrected for sleep debt ($Sleep_{mid\text{-}corr}$). We also monitor the differences between average bedtimes, wake-up times and midpoint of sleep between the diurnal preference types separately in 10-year age groups. Finally, discrepancies between diurnal preference assessments and the contribution of the PGS_{morn} on the total variance in diurnal preference (sMEQ) and sleep-wake behavior ($Sleep_{mid\text{-}wknd}$) are analyzed in more detail.

2. Methods

2.1. Participants

The combined analytic samples used in this study are derived from three population-based studies on Finnish adults, The National FINRISK 2007 Study, The National FINRISK 2012 Study and The FinHealth 2017 Study. All these studies used sex- and 10-year age-group stratified random sample from five large geographical areas in Finland, from 25 years old to 74 in 2007 and 2012 and from 18 years old onwards without upper age limit in 2017. More detailed description of The National FINRISK 2007 and 2012 Studies is given in our previous research [14]. For the purpose of this study, we selected from The FinHealth 2017 Study only the participants with similar age range than in previous population-based datasets, from 25 to 74 years old. Total of 17,243 participants with information on self-assessed diurnal preference were included in this study. The mean age between the analytic samples ranged from Mean = 50.67 (SD = 13.99) years in FINRISK 2007, Mean = 51.02 (SD = 14.09) years in FINRISK 2012 to Mean = 52.12 (SD = 13.80) years in FinHealth 2017 Study ($p < 0.0001$ in one-way ANOVA). The sex distribution differed somewhat between the analytic samples (46.4% women in FINRISK 2007, 47.3% women in FINRISK 2012 and 44.1% women in FinHealth 2017 Study, $p = 0.002$ in chi-square).

The National FINRISK 2007 and 2012 Studies and The FinHealth 2017 Study were approved by the Coordinating Ethics

Committee of the Hospital District of Helsinki and Uusimaa, Finland. They were conducted according to accepted international ethical standards in accordance with the Declaration of Helsinki and its amendments. All the participants gave written informed consent.

2.2. Diurnal preference

Diurnal preference was assessed in FINRISK 2007 and 2012 Studies by shortened 6-item version of the 19-item Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) [5]. The shortened MEQ (sMEQ) consist of items 4, 7, 9, 15, 17 and 19 from the original MEQ, as the combination of these items explained 83% of the variance in the full MEQ scale [36]. The sum score of the sMEQ items ranges from 5 (extreme eveningness) to 27 (extreme morningness). The sum score was categorized into three classes, including the definite or moderate Morning-types (19–27 points), the Intermediate-type (13–18 points), and the definite or moderate Evening-types (5–12 points), reflecting the original MEQ sum score scaling. We analyzed the Cronbach alpha for the MEQ items in the combined datasets of FINRISK 2007 and 2012 and it was an acceptable 0.76.

Only the MEQ item 19 (MEQ_{i19}) was available in The FinHealth 2017 Study, whereas it was included as one of the six items in FINRISK 2007 and 2012 Studies. This question requests individuals to estimate their diurnal preference as either Definitely a 'morning' person, More a 'morning' than an 'evening' person, More an 'evening' than a 'morning' person or Definitely an 'evening' person. This item was used in this study to indicate self-assessed morningness/eveningness.

2.3. Habitual sleep-wake behavior: midpoint of sleep

Midpoint of sleep was calculated based on self-reported bedtimes and wake up times, available in FINRISK 2012 Study and The FinHealth 2017 Study, to indicate general sleep rhythm habits. Midpoint of sleep was determined by the half of the time passed in sleep since going to bed in local time separately for weekdays and weekends [25]. Sleep-wake schedule on weekends was used here as a chronotype measurement. We also calculated the corrected midpoint of sleep ($Sleep_{mid\text{-}corr}$) that accounts for the influence of sleep debt for those sleeping longer on weekends than on weekdays [37]. The mean midpoint of sleep in weekdays ($Sleep_{mid\text{-}wk}$) in our combined analytic sample was at 2:45 AM (SD = 1 h 33 min), in weekends ($Sleep_{mid\text{-}wknd}$) at 3:44 AM (SD = 1 h 18 min) and for $Sleep_{mid\text{-}corr}$ at 3:33 AM (SD = 1 h 15 min).

2.4. Genetic liability: polygenic score for morningness

FINRISK 2007 and 2012 and FinHealth 2017 samples were genotyped with Illumina (Illumina Inc., San Diego, CA, USA) and Affymetrix arrays (Thermo Fisher Scientific, Santa Clara, CA, USA). Quality control has been described elsewhere [45]. Genotyped samples were pre-phased with Eagle 2.3.5 [46] and imputed with Beagle 4.1 [47] at the Institute for Molecular Medicine Finland (FIMM) using the population-specific SISu v3 imputation reference panel.

PGS for morningness (PGS_{morn}) was derived from GWAS where 697,828 UK Biobank and 23andMe samples were studied (Jones 2019, PMID: 30696823). To generate the PGS we used UK Biobank sample where full set of chronotype GWAS for 449,734 individuals, 40–69 years old, were available. PGS was constructed by calculating the weighted sum of risk alleles, which an individual carry. The weight was determined by an effect size of an individual allele. We used PRSice program [48] to estimate polygenic risks scores for studied individuals. In this study we used p-value thresholds 5×10^{-8}, 0.001, 0.01, 0.03, 0.1 and 1. We tested the best fit p-value threshold for PGS_{morn} with an occupational cohort [49,50] where information about the chronotype was collected with the same question (MEQ_{i19}) as in UK Biobank study. Best fit p-value threshold was 0.01 ($PGS_{morn\text{-}best\text{-}fit}$).

2.5. Control variables

The effect of sex and age on the associations between diurnal preference measurements were taken into account in the statistical analyses, as there are age and sex related differences in sleep and diurnal preference in the Finnish adult population reported previously in FINRISK 2007 Study [51]. Information on the sex was received from the Population Information System of the national Population Register Centre. The age at the participation was calculated based on the year of birth given from the Population Information System of the national Population Register Centre.

2.6. Statistical analyses

First, chi-square tests and one-way ANOVA were used for comparing the distribution of diurnal preference types by sex or age.

Second, partial correlation analyses, adjusted with sex and age, were used for analyzing the associations between continuous chronotype measurements. Additionally, partial correlations adjusted with sex between different $PGSs_{morn}$ and other chronotype measurements were performed separately for those of ages 40–69 years old representing the age range used in the original GWAS [39] and in comparison for younger ages in our data, ages from 25 to 39 years old. These additional analyses were performed in order to find out if the correlations were similar or stronger between $PGSs_{morn}$ and other chronotype measurements among the age range used in the original GWAS as compared to younger ages.

Third, one-way ANCOVAs, adjusted with sex and age, were used for analyzing the differences in $Sleep_{mid\text{-}wknd}$ and the $PGS_{morn\text{-}best\text{-}fit}$ between those answering to MEQ_{i19} in line with or contradictory against their sMEQ-based diurnal preference. Additionally, one-way ANCOVAs, adjusted with sex, were used for analyzing this also separately for each 10-year age-group.

Fourth, we divided the $PGS_{morn\text{-}best\text{-}fit}$ into decile groups in order to analyze with one-way ANOVA whether the mean sMEQ sum differed between $PGS_{morn\text{-}best\text{-}fit}$ decile groups. These analyses were performed for all ages together and also separately for each 10-year age-group. The mean age between the decile groups did not differ in one-way ANOVA (p = 0.50), being 50.8–51.9 years.

Finally, we used hierarchical regression analyses to analyze the contribution of the $PGS_{morn\text{-}best\text{-}fit}$ on the variation in sMEQ sum, MEQ_{i19}, and $Sleep_{mid\text{-}wknd}$. In these analyses, age was included in the first step, sex in the second step and $PGS_{morn\text{-}best\text{-}fit}$ in the final step.

3. Results

3.1. Prevalence of diurnal preference types and self-assessed morningness/eveningness in Finnish adult population

As shown in Table 1, based on the sMEQ, Morning-type was the most common diurnal type in the combined FINRISK 2007 and

Table 1
Prevalence of diurnal types in Finnish adult population aged 25–74 years.

Diurnal types based on sMEQ				
	Morning-types	Intermediate-types	Evening-types	p-value
% (N)	45.6 (4833)	41.9 (4436)	12.5 (1323)	
Mean age in years (SD)	53.8 (12.9)	49.2 (14.2)	44.8 (13.6)	<0.0001
% separately by sex				<0.0001
Men	48.4 (2334)	40.8 (1967)	10.8 (520)	
Women	43.3 (2499)	42.8 (2469)	13.9 (803)	
Diurnal types based on MEQ_{i19}				
	Definite Morning-types	More Morning-oriented	More Evening-oriented	Definite Evening-types	p-value
% (N)	21.5 (3664)	32.3 (5586)	31.3 (5415)	14.9 (2578)	
Mean age in years (SD)	55.7 (12.4)	52.0 (13.6)	49.2 (14.2)	47.0 (14.4)	<0.0001
% (N) separately by sex					0.25
Men	21.0 (1741)	32.6 (2705)	31.8 (2645)	14.6 (1214)	
Women	21.9 (2130)	32.1 (3125)	30.9 (3007)	15.1 (1472)	

2012 dataset. Eveningness was more common among women than among men, while morningness was emphasized more among men than among women ($p < 0.0001$). Morning-types were significantly older than Intermediate-types or Evening-types ($p < 0.0001$).

Based on the MEQ_{i19} in the combined FINRISK 2007, 2012 and FinHealth 2017 datasets, Finnish adults self-assessed themselves more often as definite Morning-types than definite Evening-types although the prevalence difference between these diurnal types was not as steep as when compared to sMEQ Morning-and Evening-type prevalence (Table 1). The prevalence of more Morning-oriented or more Evening-oriented types were higher than of the definite diurnal types. There were no significant differences between men and women in self-assessment of morningness/eveningness ($p = 0.25$). Similar to the sMEQ, mean age was progressively older among those self-assessing themselves more Morning-types than Evening-types ($p < 0.0001$).

3.2. Partial correlations between chronotype measurements

As shown in Table 2, all the correlations between sMEQ sum score, MEQ_{i19}, $Sleep_{mid\text{-}wknd}$ and $PGSs_{morn}$ were significant (all $p < 0.01$). Of the chronotype measures, the correlation between sMEQ and MEQ_{i19} was the strongest.

sMEQ correlated better than MEQ_{i19} with $Sleep_{mid\text{-}wknd}$. The moderate correlations between $Sleep_{mid\text{-}wknd}$ and questionnaire-based diurnal preference indicated that those with more evening preference had later weekend $Sleep_{mid\text{-}wknd}$ than those more towards morning preference. $Sleep_{mid\text{-}wknd}$ shown as standardized z-scores in Fig. 1 illustrates the progressively later sleep rhythm in younger and more Evening-oriented adults as both by sMEQ (Fig. 1a) and by MEQ_{i19} (Fig. 1b).

MEQ_{i19} correlated consistently slightly better than sMEQ sum with the $PGSs_{morn}$, although overall the correlations were weak. Correlations between different $PGSs_{morn}$ and $Sleep_{mid\text{-}wknd}$ were

Table 2
Partial correlations adjusted with sex and age between circadian assessments. MEQ refers to Morningness/Eveningness Questionnaire, $Sleep_{mid\text{-}wknd}$ refers to midpoint of sleep on weekends, $Sleep_{mid\text{-}corr}$ refers to corrected midpoint of sleep and PGS_{morn} refers to polygenic score for morningness. $PGS_{morn\text{-}best\text{-}fit}$ with p-threshold 0.01 was the best fit p-value threshold for PGS_{morn} in a separate occupational cohort. **** = p-value <0.0001.

	sMEQ sum	MEQ item 19: Self-assessed Morning/ Evening-type	$Sleep_{mid\text{-}wknd}$	$Sleep_{mid\text{-}corr}$	PGS_{morn} p-threshold 5×10^{-8}	PGS_{morn} p-threshold 0.001	$PGS_{morn\text{-}best\text{-}fit}$ p-threshold 0.01	PGS_{morn} p-threshold 0.03	PGS_{morn} p-threshold 0.1
	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)	Pearson coefficient *r* (p-value)
MEQ item 19	0.867 ****								
$Sleep_{mid\text{-}wknd}$	−0.554 ****	−0.470 ****							
$Sleep_{mid\text{-}corr}$	−0.543 ****	−0.462 ****	0.980 ****						
PGS_{morn} p-threshold 5×10^{-8}	0.077 ****	0.095 ****	−0.091 ****	−0.084 ****					
PGS_{morn} p-threshold 0.001	0.109 ****	0.131 ****	−0.104 ****	−0.099 ****	0.549 ****				
$PGS_{morn\text{-}best\text{-}fit}$ p-threshold 0.01	0.111 ****	0.129****	−0.101 ****	−0.096 ****	0.403 ****	0.775 ****			
PGS_{morn} p-threshold 0.03	0.116 ****	0.133 ****	−0.106 ****	−0.102 ****	0.352 ****	0.693 ****	0.893 ****		
PGS_{morn} p-threshold 0.1	0.107 ****	0.124 ****	−0.101 ****	−0.095 ****	0.294 ****	0.609 ****	0.796 ****	0.881 ****	
PGS_{morn} p-threshold 1	0.106 ****	0.116 ****	−0.093 ****	−0.086 ****	0.252 ****	0.546 ****	0.728 ****	0.818 ****	0.922 ****

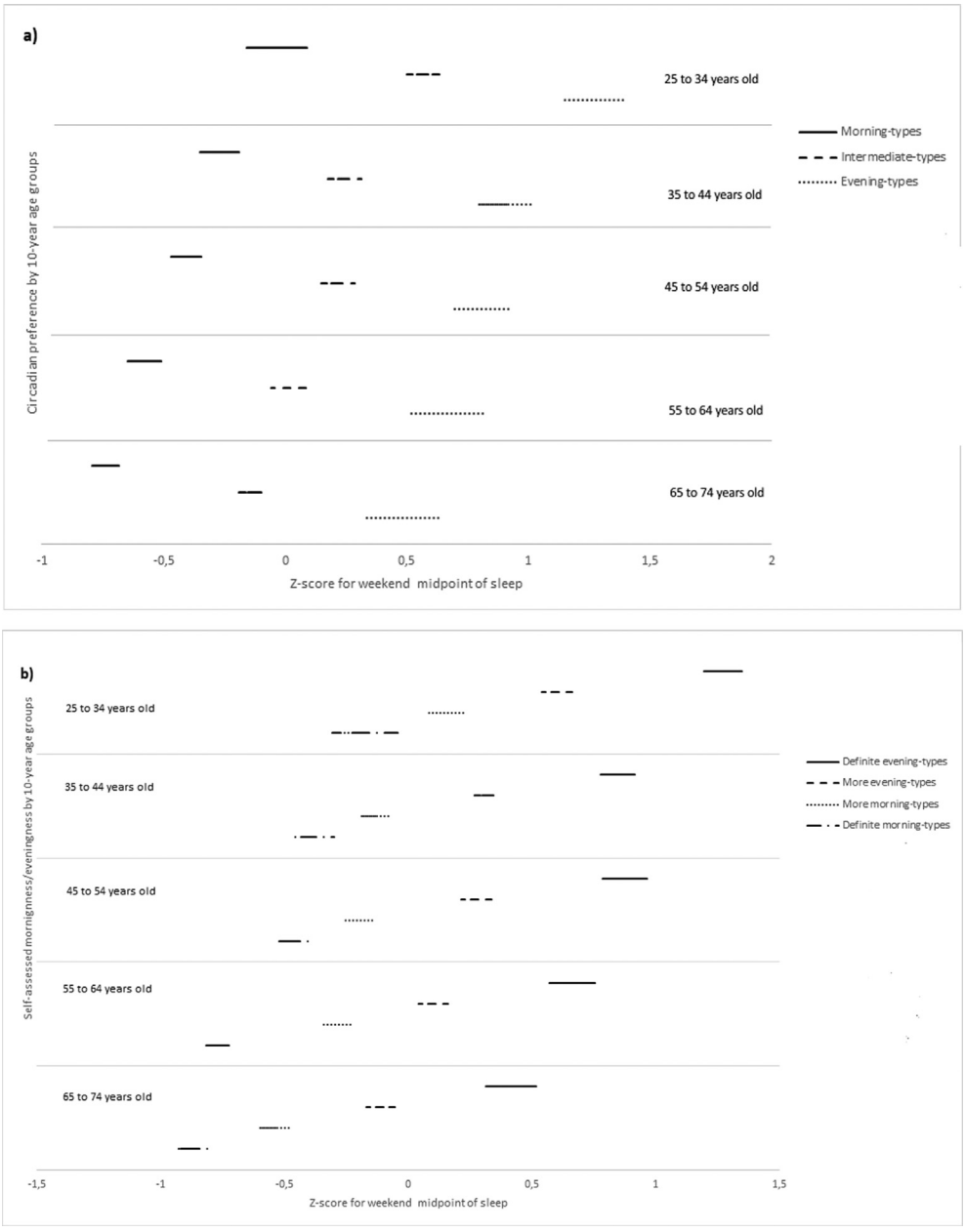

Fig. 1. $Sleep_{mid\text{-}wknd}$ as standardized z-scores for each 10-year age group by a) diurnal preference types based on the sMEQ sum score, and by b) the self-assessed morningness/eveningness based on MEQ_{i19}.

weaker than with sMEQ sum or MEQ_{i19}. Those with questionnaire-based diurnal preference more towards morning than evening or earlier timed midpoints of sleep had higher $PGSs_{morn}$.

3.3. Partial correlations between chronotype measurements on adults aged 25–39 years old and 40–69 years old

The correlations between $PGS_{morn\text{-}best\text{-}fit}$ and sMEQ sum were somewhat stronger among the combined older age groups resembling the age range of the original GWAS sample (Jones et al., 2019), 40–69 years old ($r = 0.113$, $p < 0.0001$), relative to 25–39 years old ($r = 0.108$, $p < 0.0001$). The same was seen regarding the correlations between $PGS_{morn\text{-}best\text{-}fit}$ and $Sleep_{mid\text{-}wknd}$ (for 40–69 years old $r = -0.104$, $p < 0.0001$; for 25–39 years old $r = -0.091$, $p < 0.0001$) and for $Sleep_{mid\text{-}corr}$ (for 40–69 years old $r = -0.100$, $p < 0.0001$; for 25–39 years old $r = -0.081$, $p < 0.0001$). The correlations between $PGS_{morn\text{-}best\text{-}fit}$ and MEQ_{i19} was, on the other hand, slightly stronger among 25–39 years old ($r = 0.129$, $p < 0.0001$) than among 40–69 years old ($r = 0.126$, $p < 0.0001$).

3.4. Self-assessed morningness-eveningness by sMEQ diurnal preference types

Although sMEQ and MEQ_{i19} diurnal types correlated significantly ($r = 0.871$, $p < 0.0001$), there was some discrepancy in diurnal classification when the self-assessment of different diurnal types was analyzed in more detail. As shown in Fig. 2, while 99.5% of the sMEQ Evening-types self-assessed themselves consistently as either definite Evening-types or more Evening-oriented, ~5% of the sMEQ Morning-types self-assessed themselves contradictory as more

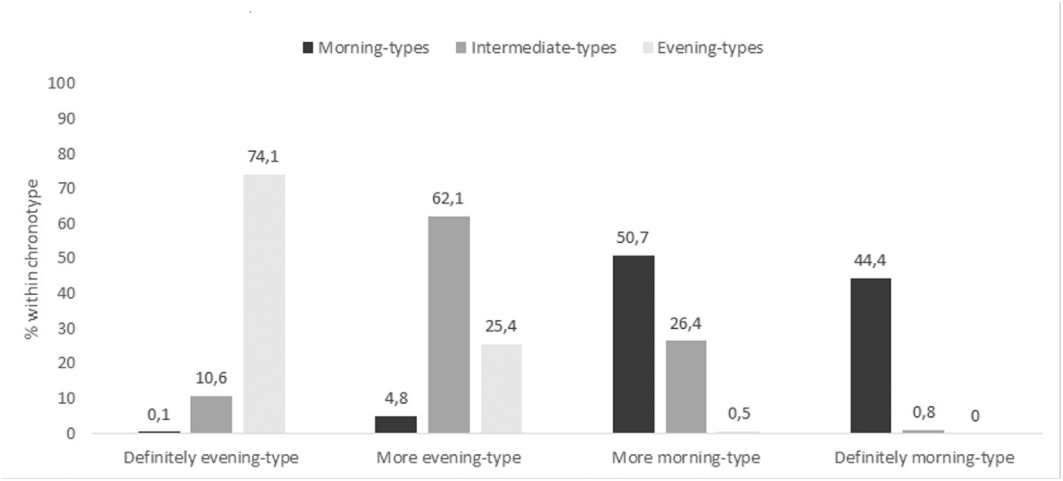

Fig. 2. Distribution of MEQ_{i19} self-assessed diurnal preference types by sMEQ diurnal types.

Evening-than Morning-oriented. In addition, 74.1% of the sMEQ Evening-types self-assessed themselves as definite Evening-types, while only 44.4% of the Morning-types self-assessed themselves as definite Morning-types. Of the sMEQ Intermediate-types, about 73% self-assess themselves as either definite or more Evening-types. As shown in Fig. S1, sMEQ Morning-type men self-assessed themselves more often contradictory as Evening-types than Morning-women.

3.5. Midpoint of sleep and PGS_{morn} among morning-types with discrepancies in self-assessed diurnal preference

Table 3 shows that after controlling for sex and age, sMEQ Morning-types self-assessing themselves contradictory to their diurnal type had 26 min later weekend sleep midpoint and 25 min later sleep debt corrected midpoint of sleep than consistently self-assessing sMEQ Morning-types (both $p = 0.001$). When $Sleep_{mid\text{-}wknd}$ and $Sleep_{mid\text{-}corr}$ were analyzed separately for each 10-year-age-group, $Sleep_{mid\text{-}wknd}$ was significantly later among sMEQ Morning-types self-assessing themselves contradictory to their diurnal type by 29 min among 45–54 years old ($p = 0.03$) and by 34 min among 55–64 years old ($p = 0.009$) as compared to consistently self-assessing sMEQ Morning-types. $Sleep_{mid\text{-}corr}$ was significantly later among sMEQ Morning-types self-assessing themselves contradictory to their diurnal type by 35 min among 55–64 years old ($p = 0.009$) as compared to consistently self-assessing sMEQ Morning-types.

As shown in Fig. 3a, $PGS_{morn\text{-}best\text{-}fit}$ was lower among sMEQ Morning-types self-assessing themselves contradictory to their diurnal type as compared to consistently self-assessing sMEQ Morning-types ($p = 0.003$). When $PGS_{morn\text{-}best\text{-}fit}$ was analyzed separately for each 10-year-age-group, this was evident among 55 to 64 ($p = 0.001$, Fig. 3b) and 65 to 74 years old ($p = 0.03$, Fig. 3c). $PGS_{morn\text{-}best\text{-}fit}$ did not differ significantly in other age groups between contradictory or consistently self-assessing sMEQ Morning-types ($p \geq 0.12$).

3.6. Diurnal preference sum score and midpoint of sleep by PGS_{morn}

As shown in Fig. 4a, where $PGS_{morn\text{-}best\text{-}fit}$ was divided in to deciles, mean sMEQ sum was higher for higher deciles of the $PGS_{morn\text{-}best\text{-}fit}$ indicating that stronger genetic tendency for morningness corresponded in higher diurnal preference for morningness as well ($p < 0.0001$). Fig. S2 illustrates the mean sMEQ sum by $PGS_{morn\text{-}best\text{-}fit}$ decile groups separately for each 10-year-age-group. For each age group, a similar trend was seen where mean sMEQ sum was higher for higher $PGS_{morn\text{-}best\text{-}fit}$ deciles although this was not a purely linear trend (for each age group $p < 0.02$). In general, mean sMEQ sums were lower for younger ages

Table 3
Mean midpoint of sleep on weekends ($Sleep_{mid\text{-}wknd}$) and corrected midpoint of sleep ($Sleep_{mid\text{-}corr}$) by 6-item MEQ (sMEQ) Morning-types self-assessing their diurnal type in line as Morning-types or contradictory as Evening-types in MEQ item 19 answers (MEQ_{i19}). SD refers to standard deviation.

	Morning-types self-assessing themselves as definitely or more morning-oriented	Morning-types self-assessing themselves as definitely or more evening-oriented	p-value
	Mean ± SD (h:min)	Mean ± SD (h:min)	
$Sleep_{mid\text{-}wknd}$			
For all ages between 25 and 69	3:18 ± 1:17	3:44 ± 0:57	0.001
Ages 25 to 34	4:08 ± 1:23	4:17 ± 1:15	0.85
Ages 35 to 44	3:37 ± 1:00	3:56 ± 1:03	0.24
Ages 45 to 54	3:23 ± 0:56	3:52 ± 0:44	0.03
Ages 55 to 64	3:06 ± 1:02	3:40 ± 0:49	0.009
Ages 65 to 74	2:55 ± 1:38	3:22 ± 0:53	0.19
$Sleep_{mid\text{-}corr}$			
For all ages between 25 and 69	3:07 ± 1:09	3:32 ± 0:55	0.001
Ages 25 to 34	3:51 ± 1:21	3:55 ± 1:14	0.97
Ages 35 to 44	3:20 ± 0:57	3:43 ± 1:01	0.12
Ages 45 to 54	3:10 ± 0:53	3:34 ± 0:43	0.05
Ages 55 to 64	2:55 ± 1:01	3:30 ± 0:52	0.009
Ages 65 to 74	2:50 ± 1:23	3:16 ± 0:53	0.17

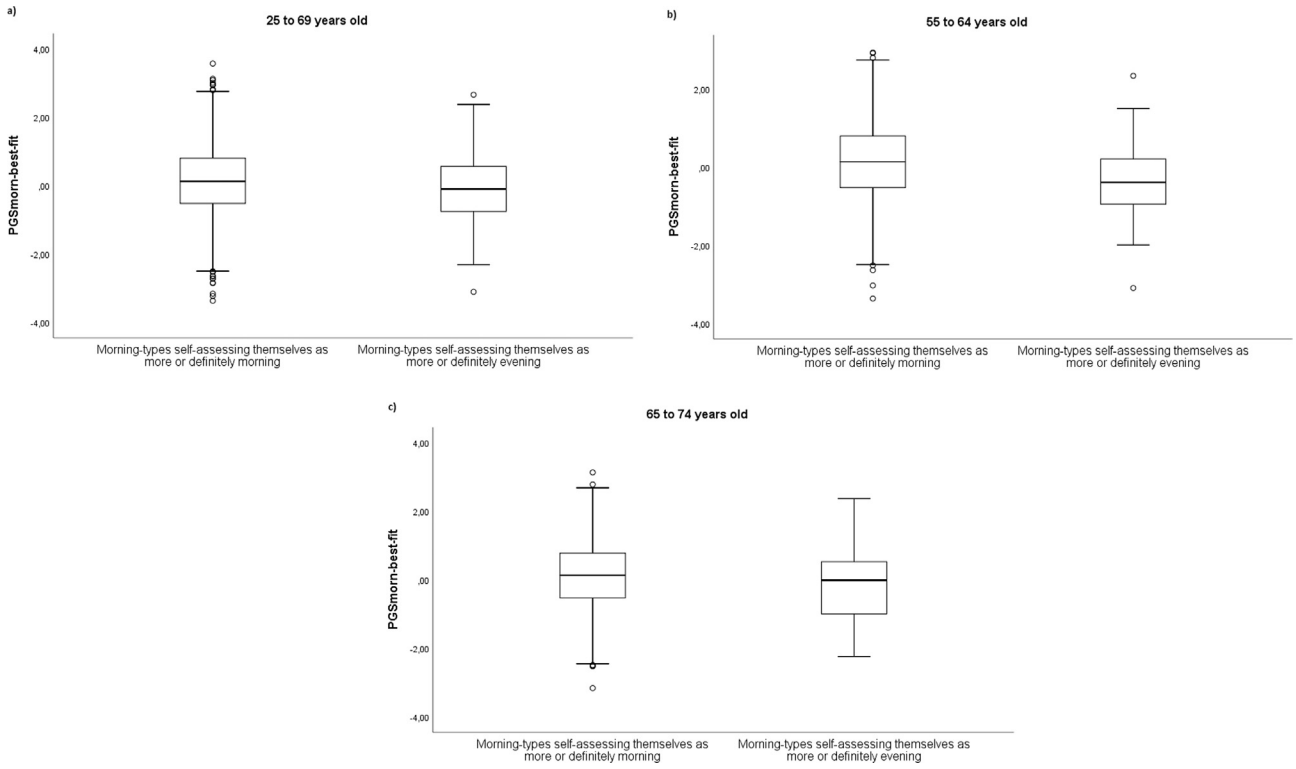

Fig. 3. Box plots for $PGS_{morn\text{-}best\text{-}fit}$ by Morning-types self-assessing themselves contradictory as definitely or more evening-oriented and Morning-types self-assessing themselves in line as definitely or more morning-oriented for the participants aged a) 25–69 years, b) 55–64 years, and c) 65–74 years.

regarding all $PGS_{morn\text{-}best\text{-}fit}$ decile groups as compared to older ages, diurnal preference progressively being more towards morningness for older age groups.

As shown in Fig. 4b, mean $Sleep_{mid\text{-}wknd}$ was earlier for higher deciles of $PGS_{morn\text{-}best\text{-}fit}$ indicating that stronger genetic tendency for morningness corresponded in earlier sleep-wake rhythm ($p < 0.0001$). Fig. S3 illustrates mean $Sleep_{mid\text{-}wknd}$ by $PGS_{morn\text{-}best\text{-}fit}$ decile groups separately for each 10-year-age-group. For ages above 34 years (for each 10-year age group above 34 years $p < 0.003$), a similar trend was seen where mean $Sleep_{mid\text{-}wknd}$ was earlier for higher $PGS_{morn\text{-}best\text{-}fit}$ deciles although this was not a purely linear trend. In general, mean $Sleep_{mid\text{-}wknd}$ was later for younger ages regarding all $PGS_{morn\text{-}best\text{-}fit}$ decile groups as compared to older ages, sleep-wake rhythm being progressively earlier for older age groups. Fig. 4c and Fig. S4 show essentially similar results for $Sleep_{mid\text{-}corr}$ as for $Sleep_{mid\text{-}wknd}$. For ages above 34 years (for each 10-year age group above 34 years $p < 0.008$), a similar trend was seen where mean $Sleep_{mid\text{-}corr}$ was earlier for higher $PGS_{morn\text{-}best\text{-}fit}$ deciles although this was not a purely linear trend.

As Table 4 shows, higher age was associated in hierarchical regression model with diurnal preference towards morningness, age explaining 6% of the variance in diurnal preference based on sMEQ sum and 4% of the variance in MEQ_{i19}. Age explained 11% of the variance in $Sleep_{mid\text{-}wknd}$ and 8% of the variance in $Sleep_{mid\text{-}corr}$, indicating that younger age was associated with later midpoint of sleep. Sex explained additional 0.3% of the variance in sMEQ indicating slightly stronger diurnal preference towards morningness on men than women. Sex did not significantly contribute to the variance in MEQ_{i19}, $Sleep_{mid\text{-}wknd}$ or $Sleep_{mid\text{-}corr}$. Higher genetic tendency towards morningness associated with stronger diurnal preference towards morningness, $PGS_{morn\text{-}best\text{-}fit}$ explaining additional 1% of the variance in sMEQ and additional 2% of the variance in MEQ_{i19}. Earlier $Sleep_{mid\text{-}wknd}$ and $Sleep_{mid\text{-}corr}$ associated with higher $PGS_{morn\text{-}best\text{-}fit}$, $PGS_{morn\text{-}best\text{-}fit}$ explaining additional 1% of the variance in midpoint of sleep.

4. Discussion

In the current study, we explored the correlations of different types of chronotype assessments. Understanding the overlap between different measurement modes is important to evaluation of different study outcomes in relation to chronotype. We found that even though all the chronotype assessment methods studied here correlated significantly, some of the correlations were very weak and there were discrepancies between assessments. Also, the effect of age on the total variation in chronotype assessment varied between assessments. In addition, in line with previous studies [51,52], both the diurnal preference and habitual sleep-wake rhythm among Finnish adults were progressively more morning-oriented along older age-groups.

As expected, $PGSs_{morn,}$ as based on the single diurnal preference question, correlated best with MEQ_{i19} than with other measures [39]. However, all the associations between $PGSs_{morn}$ and other chronotype measures were very weak, especially regarding $Sleep_{mid\text{-}wknd}$ and $Sleep_{mid\text{-}corr}$. One explanation for the weak correlations between $PGSs_{morn}$ and other chronotype measures here could be that the original GWAS had a more limited participant's age range, from 40 to 69 year old in the UK Biobank sample [39], than is in this study. Previous studies have found that the genetic influences on diurnal preference can differ between generations [6,8]. It is possible that calculating PGS_{morn} based on genetic polymorphism and phenotypes from participants of certain age range influences how well the PGS fits for different ages. However, examining adults of the same age than the participants in the original GWAS [39] separately from younger adults in our sample improved these correlations only slightly among the older

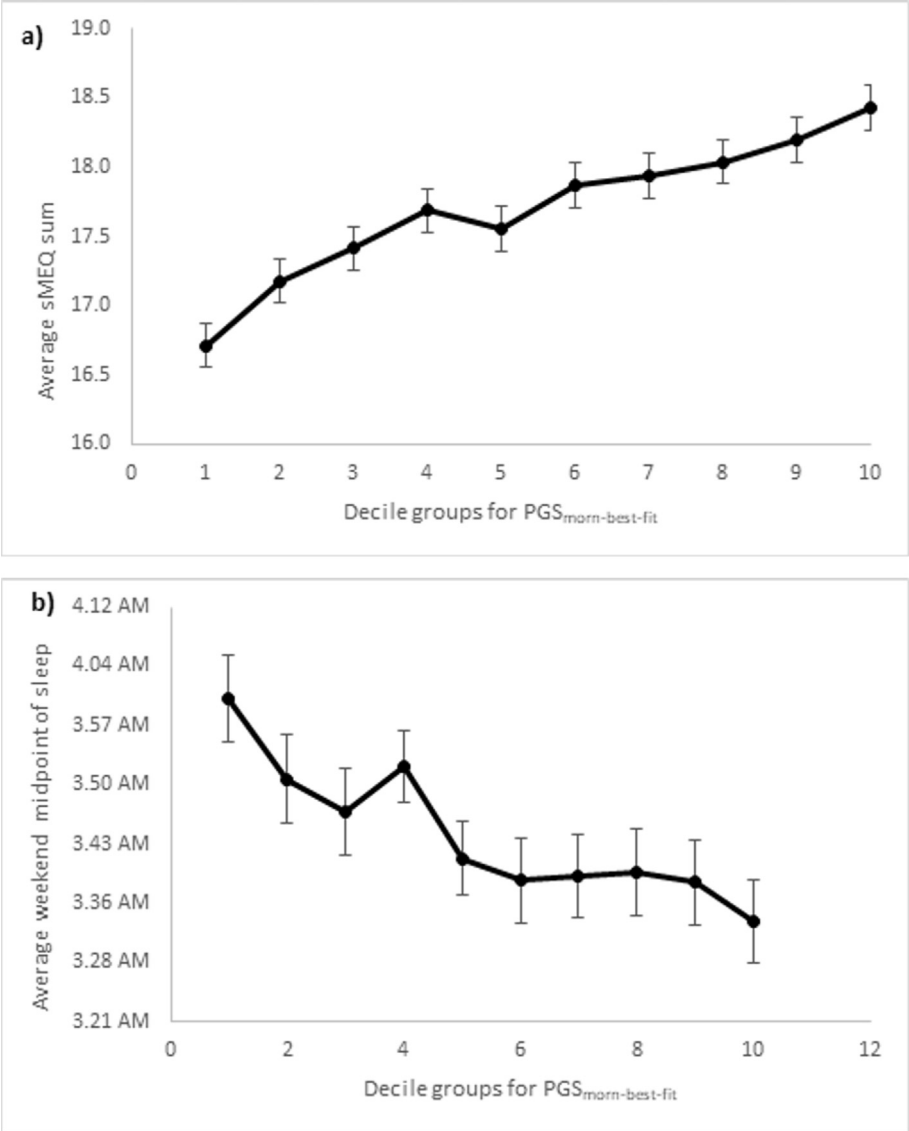

Fig. 4. a) Average sMEQ sum and b) average $Sleep_{mid\text{-}wknd}$ by decile groups for $PGS_{morn\text{-}best\text{-}fit}$ for those aged 25–69 years. 1 = decile group with lowest $PGS_{morn\text{-}best\text{-}fit}$ and 10 = decile group with highest $PGS_{morn\text{-}best\text{-}fit}$.

participants. Another explanation for the weak associations between $PGSs_{morn}$ and MEQ_{i19} in our study could be the difference in the genetic make-up of the UK and Finnish populations. Finnish population has a unique genetic background due to the long isolated history and a small population size with multiple possible bottlenecks [53], which can limit the similarity of polymorphisms with other populations. Furthermore, GWAS have been criticized in presenting mostly arbitrary genetic associations that do not explain heritability of complex traits very well or pinpoint the actual genes contributing to the trait phenotype [54]. For instance, the genetic feedback loops that contribute to the functioning of the circadian clock are known to be complex [55,56] and the genetic influence on chronotype variation substantial [6–8]. Yet, in this study the $PGSs_{morn}$ contributed only 1–2% to the variation in self-reported diurnal preference, or habitual sleep-wake rhythm.

Of all chronotype assessment measurements, the $Sleep_{mid\text{-}wknd}$ correlated strongest with the diurnal preference based on the sMEQ. The 6-item MEQ might thus predict better the habitual sleep-wake behavior than the self-assessed morningness-eveningness based on the single item. The correlation between the sMEQ and the $Sleep_{mid\text{-}wknd}$ presented here was very close to previously reported correlation between the full MEQ and the self-reported midpoint of sleep on free days [57]. The findings of this study showed that age explained only 6% of the variation in diurnal preference, while explaining 11% of the variance in $Sleep_{mid\text{-}wknd}$ indicating that the $Sleep_{mid\text{-}wknd}$ varied more with the age than diurnal preference among Finnish adults.

The correlation between the sum score of the sMEQ and the MEQ_{i19} in this study was strong, which is not surprising as MEQ_{i19} was included in the sMEQ as one of the six MEQ items. However, there was some discrepancy in how Morning-types self-assessed their diurnal type. Approximately 5% of the sMEQ Morning-types self-assessed themselves as more evening-oriented. This was slightly emphasized in men among whom approximately 6% considered themselves as more evening-oriented even though being classified as Morning-types based on the sMEQ. Average $Sleep_{mid\text{-}wknd}$ was almost half an hour later on those Morning-types considering themselves as more evening oriented, and this was

Table 4
Hierarchical Regression Model for sMEQ sum, MEQ_{i19} and $Sleep_{mid\text{-}wknd}$ by $PGS_{morn\text{-}best\text{-}fit}$.

	sMEQ sum by $PGS_{morn\text{-}best\text{-}fit}$			MEQ_{i19} by $PGS_{morn\text{-}best\text{-}fit}$			$Sleep_{mid\text{-}wknd}$ by $PGS_{morn\text{-}best\text{-}fit}$			$Sleep_{mid\text{-}corr}$ by $PGS_{morn\text{-}best\text{-}fit}$		
	r/R^2	R^2 *Change* (p-value[a])	β (p-value[b])	r/R^2	R^2 *Change* (p-value[a])	β (p-value[b])	r/R^2	R^2 *Change* (p-value[a])	β (p-value[b])	r/R^2	R^2 *Change* (p-value[a])	β (p-value[b])
Step 1 Variables entered: age	0.24/ 0.06			0.21/ 0.04			0.33/ 0.11			0.29/ 0.08		
Age			0.24 (<0.0001)			0.21 (<0.0001)			−0.33 (<0.0001)			−0.29 (<0.0001)
Step 2 Variables entered: sex	0.25/ 0.06	0.003 (<0.0001)		0.21/ 0.04	0.00002 (0.56)		0.33/ 0.11	0.0001 (0.29)		0.29/ 0.08	0.0004 (0.06)	
Age			0.24 (<0.0001)			0.21 (<0.0001)			−0.33 (<0.0001)			−0.29 (<0.0001)
Sex			−0.05 (<0.0001)			0.005 (0.56)			−0.01 (0.29)			−0.02 (0.06)
Step 3 Variables entered: $PGS_{morn\text{-}best\text{-}fit}$	0.27/ 0.07	0.01 (<0.0001)		0.24/ 0.06	0.02 (<0.0001)		0.34/ 0.12	0.01 (<0.0001)		0.30/ 0.09	0.008 (<0.0001)	
Age			0.24 (<0.0001)			0.21 (<0.0001)			−0.33 (<0.0001)			−0.29 (<0.0001)
Sex			−0.05 (<0.0001)			0.004 (0.59)			−0.01 (0.31)			−0.02 (0.06)
$PGS_{morn.03}$			0.11 (<0.0001)			0.13 (<0.0001)			−0.10 (<0.0001)			−0.09 (>0.0001)

r = *Pearson correlation coefficient*, R^2 = Variance in dependent variable explained by the model, R^2 *Change* = Additional variance in dependent variable explained by the novel variable entered in the step, p-value[a] = Significance for additional variance in dependent variable explained by the novel variable entered in the step, β = Standardized coefficient, p-value[b] = Significance of the association between independent variable and dependent variable.

emphasized among older age-groups, even though habitual sleep-wake rhythms were still earlier-timed than for Intermediate or Evening types of persons. In addition, the $PGS_{morn\text{-}best\text{-}fit}$ was lower for Morning-types considering themselves as evening oriented, and this was emphasized on those aged 55 years and above. Furthermore, less than half of the Morning-types considered themselves as definite morning-types, while nearly three quarters of the Evening-types considered themselves as definite evening-types. These findings support the notion that crude classifications to specific diurnal preference types are not strict, but that the circadian typology is more of a continuum. It is possible, although this can only be speculated based on results here, that the presence of more later-timed Morning-types, especially among men, reflects the tendency of the circadian clock to run slower as the human pacemaker averages slightly above 24 h [2], this being emphasized in men [58].

The results presented here suggest that assessing diurnal preference by single question can be unreliable criterion for classification of individuals into either Evening-types or Morning-types, as some individuals considering themselves as more Evening-types actually fall in the morningness spectrum of the diurnal preference variation and, based on the findings presented in this study, Intermediate-types would mostly be classified as Evening-types. For instance, prevalence of eveningness at the Finnish adult population level, aged 25–74 years, increased from 12.5% based on sMEQ to 46.2% based on MEQ_{i19}. As adult GWAS for polymorphisms in morningness-eveningness have conducted based on the single-item self-assessment of diurnal types, they might not be well suited for describing the actual variation in diurnal preference types or sleep-wake rhythms among adults.

4.1. Strengths and limitations

Strengths of this study include the large sample of adults representing population level variation in individual chronotype variation at the wide age range of 25–74 years. As a limitation, information on diurnal preference as based on sMEQ was not available from the 2017 sample, and information on the sleep-wake schedule was not available from the 2007 sample. Another limitation to the study is the lack of data on physiological measurements such as melatonin onset or body temperature rhythm, which would not been feasible to collect from such as large population-based sample.

5. Conclusion

Even though all the chronotype assessment methods correlated with each other, the correlations with especially $PGSs_{morn}$ were weak. In addition, even though the diurnal preference as based on sMEQ and the MEQ_{i19} correlated strongly, using the self-assessed morningness-eveningness based on MEQ_{i19} might classify the chronotype variation falsely, especially by leading to overestimation of the prevalence of Evening-types in a study population. The habitual $Sleep_{mid\text{-}wknd}$, on the other hand, varied more with age than diurnal preference indicating that diurnal preference based on full MEQ or sMEQ could be more reliable in describing long-term trends in chronotype. When only few or one assessment method for individual chronotype are available for examining the health outcomes by chronotype, these differences between the feasible chronotype assessment methods should be kept in mind as the associations are likely to differ depending on which assessment method is used.

Disclosure statement and funding

This study was funded by The Academy of Finland (projects 322312), The Paulo Foundation and Helsinki University Hospital (Grant TYH2019315). The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication. There are no competing financial interests. Financial Disclosure: none. Non-financial Disclosure: none.

Acknowledgements

We want to thank all the participants in FINRISK 2007, FINRISK 2012 and FinHealth 2017 cohorts. The genetic data used for the research was obtained from THL Biobank. We thank all study participants for their generous participation at THL Biobank. THL Biobank is thanked for handling and FinnGen for imputation of samples. The data used for the research was imputed with the THL Biobank's SISu v3 Imputation reference panel. We also thank the Sequencing Informatics Team, FIMM Human Genomics, University of Helsinki, for the work done in preparation of the reference panel data.

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link https://doi.org/10.1016/j.sleep.2021.01.054.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.01.054.

References

[1] Czeisler CA, Gooley JJ. Sleep and circadian rhythms in humans. Cold Spring Harbor Symp Quant Biol 2007;72:579–97. https://doi.org/10.1101/sqb.2007.72.064.
[2] Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 1999;284:2177–81.
[3] Duffy J, Dijk D, Hall E, et al. Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. J Invest Med: The Official Publication of the American Federation for Clinical Research 1999;47:141–50.
[4] Duffy JF, Rimmer DW, Czeisler CA. Association of intrinsic circadian period with morningness–eveningness, usual wake time, and circadian phase. Behav Neurosci 2001;115:895.
[5] Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1975;4:97–110.
[6] Barclay NL, Watson NF, Buchwald D, et al. Moderation of genetic and environmental influences on diurnal preference by age in adult twins. Chronobiol Int 2014;31:222–31. https://doi.org/10.3109/07420528.2013.842924.
[7] Koskenvuo M, Hublin C, Partinen M, et al. Heritability of diurnal type: a nationwide study of 8753 adult twin pairs. Journal of Sleep Research 2007;16:156–62.
[8] Vink JM, Vink JM, Groot AS, et al. Genetic analysis of morningness and eveningness. Chronobiol Int 2001;18:809–22.
[9] Barclay NL, Rowe R, O'Leary R, et al. Longitudinal stability of genetic and environmental influences on the association between diurnal preference and sleep quality in young adult twins and siblings. J Biol Rhythm 2016;31:375–86. https://doi.org/10.1177/0748730416653533.
[10] Broms U, Pitkäniemi J, Bäckmand H, et al. Long-term consistency of diurnal-type preferences among men. Chronobiol Int 2014;31:182–8.
[11] Basnet S, Merikanto I, Lahti T, et al. Associations of common non-communicable medical conditions and chronic diseases with chronotype in a population-based health examination study. Chronobiol Int 2017;34:462–70. https://doi.org/10.1080/07420528.2017.1295050.
[12] Fabbian F, Zucchi B, De Giorgi A, et al. Chronotype, gender and general health. Chronobiol Int 2016;33:863–82. https://doi.org/10.1080/07420528.2016.1176927.
[13] Kitamura S, Hida A, Watanabe M, et al. Evening preference IS related to the incidence OF depressive states independent OF sleep-wake conditions. Chronobiol Int 2010;27:1797–812. https://doi.org/10.3109/07420528.2010.516705.
[14] Merikanto I, Kronholm E, Peltonen M, et al. Circadian preference links to depression in general adult population. J Affect Disord 2015;188:143–8. https://doi.org/10.1016/j.jad.2015.08.061.
[15] Merikanto I, Lahti T, Puolijoki H, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiol Int 2013;30:470–7. https://doi.org/10.3109/07420528.2012.741171.
[16] Yu JH, Yun C-H, Ahn JH, et al. Evening chronotype is associated with metabolic disorders and body composition in middle-aged adults. J Clin Endocrinol Metab 2015;100:1494–502. https://doi.org/10.1210/jc.2014-3754.
[17] Merikanto I, Englund A, Kronholm E, et al. Evening chronotypes have the increased odds for bronchial asthma and nocturnal asthma. Chronobiol Int 2014;31:95–101. https://doi.org/10.3109/07420528.2013.826672.
[18] Merikanto I, Lahti T, Seitsalo S, et al. Behavioral trait of morningness-eveningness in association with articular and spinal diseases in a population. PloS One 2014;9:e114635.
[19] Merikanto I, Lahti T, Seitsalo S, et al. Eveningness has the increased odds for spinal diseases but the decreased odds for articular diseases with prospective hospital treatments. Biol Rhythm Res 2017;48(2):263–74.
[20] Bonmati-Carrion MA, Middleton B, Revell V, et al. Circadian phase asessment by ambulatory monitoring in humans: correlation with dim light melatonin onset. Chronobiol Int 2014;31:37–51. https://doi.org/10.3109/07420528.2013.820740.
[21] Kerkhof GA, Van Dongen HP. Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. Neurosci Lett 1996;218:153–6.
[22] Martinez-Nicolas A, Ortiz-Tudela E, Rol MA, et al. Uncovering different masking factors on wrist skin temperature rhythm in free-living subjects. PloS One 2013;8.
[23] Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. J Biol Rhythm 1999;14:227–36. https://doi.org/10.1177/074873099129000641.
[24] Ancoli-Israel S, Cole R, Alessi C, et al. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003;26:342–92.
[25] Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythm 2003;18:80–90. https://doi.org/10.1177/0748730402239679.
[26] Torsvall L, Åkerstedt T. A diurnal type scale: construction, consistency and validation in shift work. Scand J Work Environ Health 1980;6(4):283–90.
[27] Arendt J. Importance and relevance of melatonin to human biological rhythms. J Neuroendocrinol 2003;15:427–31.
[28] Benloucif S, Burgess HJ, Klerman EB, et al. Measuring melatonin in humans. Journal of Clinical Sleep Medicine 2008;4:66–9. https://doi.org/10.5664/jcsm.27083.
[29] Littner M, Kushida CA, Anderson WM, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep 2003;26:337–41. https://doi.org/10.1093/sleep/26.3.337.
[30] Vanmarkenlichtenbelt W, Daanen H, Wouters L, et al. Evaluation of wireless determination of skin temperature using iButtons. Physiol Behav 2006;88:489–97. https://doi.org/10.1016/j.physbeh.2006.04.026.
[31] Kantermann T, Sung H, Burgess HJ. Comparing the morningness-eveningness questionnaire and munich ChronoType questionnaire to the dim light melatonin onset. J Biol Rhythm 2015;30:449–53. https://doi.org/10.1177/0748730415597520.
[32] Di Milia L, Adan A, Natale V, et al. Reviewing the psychometric properties of contemporary circadian typology measures. Chronobiol Int 2013;30:1261–71. https://doi.org/10.3109/07420528.2013.817415.
[33] Kantermann T, Eastman CI. Circadian phase, circadian period and chronotype are reproducible over months. Chronobiol Int 2018;35:280–8. https://doi.org/10.1080/07420528.2017.1400979.
[34] Jankowski KS. Polish version of the reduced morningness–eveningness questionnaire. Biol Rhythm Res 2013;44:427–33.
[35] Adan A, Almirall H. Horne & Östberg morningness-eveningness questionnaire: a reduced scale. Pers Indiv Differ 1991;12:241–53. https://doi.org/10.1016/0191-8869(91)90110-W.
[36] Hätönen T, Forsblom S, Kieseppä T, et al. Circadian phenotype in patients with the co-morbid alcohol use and bipolar disorders. Alcohol Alcohol 2008;43:564–8.
[37] Roenneberg Pilz, Zerbini Winnebeck. Chronotype and social jetlag: a (self-) critical review. Biology 2019;8:54. https://doi.org/10.3390/biology8030054.
[38] Hu Y, Shmygelska A, Tran D, et al. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. Nat Commun 2016;7:10448. https://doi.org/10.1038/ncomms10448.
[39] Jones SE, Lane JM, Wood AR, et al. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun 2019;10:343. https://doi.org/10.1038/s41467-018-08259-7.
[40] Lane JM, Vlasac I, Anderson SG, et al. Genome-wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. Nat Commun 2016;7:10889. https://doi.org/10.1038/ncomms10889.
[41] Ioannidis JPA, Thomas G, Daly MJ. Validating, augmenting and refining genome-wide association signals. Nat Rev Genet 2009;10:318–29. https://doi.org/10.1038/nrg2544.
[42] Dudbridge F. Power and predictive accuracy of polygenic risk scores. PLoS Genet 2013;9:e1003348. https://doi.org/10.1371/journal.pgen.1003348.
[43] Merikanto I, Lahti J, Kuula L, et al. Circadian preference and sleep timing from childhood to adolescence in relation to genetic variants from a genome-wide association study. Sleep Med 2018;50:36–41. https://doi.org/10.1016/j.sleep.2018.04.015.
[44] Jones SE, Tyrrell J, Wood AR, et al. Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. PLoS Genet 2016;12:e1006125. https://doi.org/10.1371/journal.pgen.1006125.

[45] FinnGen. FinnGen 2020.
[46] Loh P-R, Danecek P, Palamara PF, et al. Reference-based phasing using the haplotype reference consortium panel. Nat Genet 2016;48:1443.
[47] Browning BL, Browning SR. Genotype imputation with millions of reference samples. Am J Hum Genet 2016;98:116–26. https://doi.org/10.1016/j.ajhg.2015.11.020.
[48] Euesden J, Lewis CM, O'Reilly PF. PRSice: polygenic risk score software. Bioinformatics 2015;31:1466–8. https://doi.org/10.1093/bioinformatics/btu848.
[49] Sulkava S, Ollila HM, Alasaari J, et al. Common genetic variation near melatonin receptor 1A gene linked to job-related exhaustion in shift workers. Sleep 2017;40. https://doi.org/10.1093/sleep/zsw011.
[50] Viitasalo K, Hemiö K, Puttonen S, et al. Prevention of diabetes and cardiovascular diseases in occupational health care: feasibility and effectiveness. Primary Care Diabetes 2015;9:96–104. https://doi.org/10.1016/j.pcd.2014.07.008.
[51] Merikanto I, Kronholm E, Peltonen M, et al. Relation of chronotype to sleep complaints in the general **Finnish population**. Chronobiol Int 2012;29:311–7. https://doi.org/10.3109/07420528.2012.655870.
[52] Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. Sleep Med Rev 2007;11:429–38.
[53] Kääriäinen H, Muilu J, Perola M, et al. Genetics in an isolated population like Finland: a different basis for genomic medicine? J Community Genet 2017;8:319–26. https://doi.org/10.1007/s12687-017-0318-4.
[54] Tam V, Patel N, Turcotte M, et al. Benefits and limitations of genome-wide association studies. Nat Rev Genet 2019;20:467–84. https://doi.org/10.1038/s41576-019-0127-1.
[55] Cox KH, Takahashi JS. Circadian clock genes and the transcriptional architecture of the clock mechanism. J Mol Endocrinol 2019;63:R93–102. https://doi.org/10.1530/JME-19-0153.
[56] Vitaterna MH, Shimomura K, Jiang P. Genetics of circadian rhythms. Neurol Clin 2019;37:487–504. https://doi.org/10.1016/j.ncl.2019.05.002.
[57] Nguyen C, Murray G, Anderson S, et al. In vivo molecular chronotyping, circadian misalignment, and high rates of depression in young adults. J Affect Disord 2019;250:425–31. https://doi.org/10.1016/j.jad.2019.03.050.
[58] Duffy JF, Cain SW, Chang A-M, et al. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. Proc Natl Acad Sci Unit States Am 2011;108:15602–8. https://doi.org/10.1073/pnas.1010666108.