Genetic studies of accelerometer-based sleep measures in 85,670 individuals yield new insights into human sleep behaviour

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ABSTRACT

Sleep is an essential human function but its regulation is poorly understood. Identifying genetic variants associated with quality, quantity and timing of sleep will provide biological insights into the regulation of sleep and potential links with disease. Using accelerometer data from 85,670 individuals in the UK Biobank, we performed a genome-wide association study of 8 accelerometer-derived sleep traits. We identified 47 genetic associations across the sleep traits ($P<5x10^{-8}$) and replicated our findings in 5,819 individuals from 3 independent studies. These included 10 novel associations for sleep duration and 26 for sleep quality. Most newly identified variants were associated with a single sleep trait, but variants previously associated with restless legs syndrome were observed to be associated with multiple sleep traits. As a group, sleep quality loci were enriched for serotonin processing genes and all sleep traits were enriched for cerebellar-expressed genes. These findings provide new biological insights into sleep characteristics.

INTRODUCTION

Sleep is an essential human function, but many aspects of its regulation remain poorly understood. Adequate sleep is important for health and wellbeing, and variation in sleep quality, quantity and timing are strongly associated with several human diseases and psychiatric disorders[1-5]. Identifying genetic variants influencing sleep traits will provide new insights into the molecular regulation of sleep in humans and help clarify the genetic contribution to causal links with disease.

Previous large-scale genetic studies have used self-report estimates of sleep to identify genetic variants associated with sleep traits. For example, using questionnaire data from 47,180 individuals, the CHARGE consortium identified the first common genetic variant, near *PAX8*, robustly associated with sleep duration[6]. Subsequent studies using up to 128,286 individuals in the first phase of the UK Biobank identified two additional sleep duration loci[7,8] and a parallel analysis of the full UK Biobank release of 446,118 individuals identified a total of 78 associated loci (Dashti *et al*., BioRxiv, 2018). Genetic associations have also been identified for other self-reported traits including chronotype[8-10], insomnia, and daytime sleepiness[7,11,12] (Jansen *et al.* BioRxiv, 2018, https://doi.org/10.1101/214973).

Although the reported associations revealed potentially relevant pathways related to mechanisms underlying sleep regulation, self-report measures are typically based on a limited number of questions and subject to bias related to an individual's perception and recall of sleeping patterns. These measures can often reflect well-being rather than specific aspects of sleep. These limitations may reduce the biological relevance of findings and provide inaccurate insights into links with disease. Polysomnography (PSG) is regarded as the "gold standard" method of quantifying nocturnal sleep traits, but it is impractical to perform in large cohorts. Additionally, PSG is burdensome for the participant making it unsuitable for measuring sleep over multiple nights and capturing inter-daily variability. Research-grade activity monitors (accelerometers), also known as actigraphy devices, provide cost-effective estimates of sleep behaviours using validated algorithms[13,14]. However, accelerometer-based studies have often involved much smaller sample sizes than those required for genome-wide association studies (GWAS) and have generally not focussed on night-time activity[15,16]. The UK Biobank study is a unique resource collecting vast amounts of clinical, biomarker, and questionnaire data on 500,000 UK residents. Of these, 103,000 participants wore activity monitors continuously for up to 7 days. This study provides an unprecedented

opportunity to derive accelerometer-based estimates of sleep quality, quantity and timing and to use these data to study the genetics of sleep traits. We have previously developed a method, validated against PSG using an independent dataset, to extract a range of sleep estimates from the UK Biobank accelerometer data[17] (Van Hees *et al*. BioRxiv 2018, https://doi.org/10.1101/257972).

In this study, we aimed to identify genetic variants associated with 8 main accelerometer-based measures of sleep quality (sleep efficiency and the number of nocturnal sleep episodes), quantity (nocturnal sleep duration and variability, and diurnal inactivity) and timing (sleep-midpoint, timing of the least active 5 hours (L5), and timing of the most active 10 hours (M10)) by performing a GWAS in 85,670 UK Biobank participants.

RESULTS

Measures of sleep quality and quantity are not correlated with sleep timing

Summary statistics for, and correlations between, the eight accelerometer-derived phenotypes are shown in **Supplementary Tables 1** and **2**. We observed little correlation between measures of sleep timing and duration (L5 timing r_s = -0.02; sleep-midpoint r_s = -0.04) and sleep quality estimates (L5 timing r_s < 0.04; sleep-midpoint r_s < 0.12). These negligible or limited correlations between timing and duration are consistent with data from self-report measures (r_s = 0.005). We also observed limited correlation between sleep duration and sleep quality as represented by the number of nocturnal sleep episodes (r_s = 0.14) but observed a modest correlation with sleep efficiency (r_s = 0.57). We observed modest correlation between self-report sleep duration and accelerometer-derived sleep duration (r_s = 0.19) and between self-report chronotype ('morningness') and L5 timing (r_s = 0.29) in the same individuals.

Accelerometer-derived estimates of sleep patterns are heritable

We used BOLT-REML to estimate SNP-based heritability (h_{SNP}^2) of the eight-estimated sleep traits (**Table 1**). h_{SNP}^2 estimates ranged from 2.8% (95% CI 2.0%, 3.6%) for variation in sleep duration (defined as the standard deviation of accelerometer-derived sleep duration across all nights), to 22.3% (95% CI 21.5%, 23.1%) for number of nocturnal sleep episodes. For sleep duration, we observed higher heritability using the accelerometer-derived measure (h_{SNP}^2 = 19.0%, 95% CI 18.2%, 19.8%) in comparison to self-report sleep duration (h_{SNP}^2 = 8.8%, 95% CI 8.6%, 9.0%).

Forty-seven genetic associations identified across the accelerometer-derived sleep traits

We performed a genome-wide association of 11,977,111 variants in up to 85,670 individuals for the 8 accelerometer-derived sleep traits. We identified 47 genetic associations across 7 of the phenotypes at the standard GWAS threshold $P<5x10^{-8}$ and among which 28 reached $P<5x10^{-9}$, a threshold that we estimate reflects a better 5% type 1 error rate (Jones *et al*. BioRxiv, 2018) (**Table 2** and **Supplementary Figs 1-2**). These associations included 21 variants (13 at $P<5x10^{-9}$) associated with number of nocturnal sleep episodes, 11 (7) associated with sleep duration, 6 (4) associated with L5 timing, 5 (2) associated with sleep efficiency, 2 (1) associated with diurnal inactivity, 1 (0) associated with midpoint-sleep, and 1 (1) associated with M10 timing. Of these 47 associations, 31 (14) were not previously reported in studies based on self-report measures (**Table 2**).

Replication of 47 genetic associations in 5,819 individuals

We attempted to replicate the 47 associations in up to 5,819 adults from the Whitehall (N=2,144), CoLaus (N=2,257), and Rotterdam Study (subsample from RS-I, RS-II and RS-III, N=1,418) who had worn similar wrist-worn accelerometer devices for a comparable duration as the UK Biobank participants. Individual study and meta-analysis results for the three replication studies are presented in **Supplementary Table 3**. Of the 47 signals, 35 were directionally consistent in the replication cohort meta-analysis ($P_{binomial}$ = 0.001). For traits with more than one SNP associated at $P<5\times10^{-8}$ in the UK Biobank, we combined the effects of each SNP and tested them in the replication data. We observed overall associations for sleep duration (P=0.008), sleep efficiency ($P=3\times10^{-4}$), number of nocturnal sleep episodes ($P=2\times10^{-6}$), and sleep timing (P=0.034) in the same directions (**Supplementary Tables 3** and **4**).

Ten novel sleep duration loci identified from accelerometer-derived sleep duration GWAS

We identified 11 loci associated with accelerometer-derived sleep duration, including ten not previously reported to be associated with self-report sleep duration, despite the sample size available for a parallel self-report sleep duration GWAS study being five times that of the accelerometer study (Dashti *et al.* BioRxiv, 2018; **Figure 1** and **Supplementary Table 5**). The lead variants representing the ten new sleep duration loci all had larger effects in the accelerometer data compared to self-report data, with effect sizes ranging from 1.3 to 5.9 minutes compared to 0.1 to 0.8 minutes, with the

MEIS1 locus having the strongest effect. Two of the ten new sleep duration signals (rs113851554 in *MEIS1* and rs9369062 in *BTBD9*) have previously been associated with restless legs syndrome. The one variant previously detected based on self-report sleep duration, near *PAX8,* was the first variant to be identified as associated with sleep duration through GWAS[6]. The minor *PAX8* allele effect size was consistent across accelerometer-derived measures of sleep duration (2.7mins per allele, 95% CI: 2.1 to 3.3, $P=3x10^{-21}$) and self-report sleep duration (2.4mins per allele, 95% CI: 2.1 to 2.8, $P=7x10^{-49}$). We observed similar effect sizes in a subset of 72,510 unrelated Europeans from the UK Biobank when removing individuals on depression medication and adjusting for BMI and lifestyle factors. To confirm that associations were not influenced by age related differences in sleep, we confirmed that there was also no difference in effect sizes between the youngest and oldest 50% of individuals (above and below the age of 63.7 years) (**Supplementary Table 6**).

Variants associated with sleep quality include known restless legs syndrome, sleep duration, and cognitive decline associated variants

Of the 5 variants associated with sleep efficiency, one is the *PAX8* sleep duration signal and one the restless legs syndrome associated signal (*MEIS1*). Of the 20 loci associated with number of nocturnal sleep episodes, one is represented by the *APOE* variant (rs429358) that is strongly associated with risk for late-onset Alzheimer's disease and cognitive decline before disease diagnosis[18]. This variant is a proxy for the *APOE ε4* risk allele and shows that the *ε4* allele is associated with a reduced number of nocturnal sleep episodes (-0.13 sleep episodes; 95% CI: -0.16, -0.11; $P=4x10^{-8}$). This finding strengthened by additional analyses of the *ε2, ε3* and *ε4 APOE* Alzheimer's disease risk alleles, with an overall reduction in the number of nocturnal sleep episodes observed with higher risk haplotypes ($F(5, 72578)=5.36$, $P=0.001$) (**Supplementary Table 7**). This finding is inconsistent with the observational association between cognitive decline in older age and poorer sleep quality[19-22]. We also noted that the APOE *ε4* risk allele was nominally associated ($P<0.05$) with sleep timing (L5, -1.8 minutes per allele, $P=4x10^{-6}$; sleep-midpoint (-0.6 minutes per allele; $P=0.002$), sleep duration (-1.1 minutes per allele, $P=7x10^{-4}$), and diurnal inactivity (-1.0 minutes per allele, $P=2x10^{-5}$). Apart from the *APOE* variant, there were minimal differences in effect sizes in a range of sensitivity analyses, including removing individuals on sleep or depression medication, adjustments for BMI and lifestyle factors, and splitting the cohort by median age (**Supplementary Table 6** and **Supplementary Methods**).

Six association signals identified for accelerometer-derived measures of sleep timing

We identified 6 loci associated with L5 timing, of which 3 have not previously been associated with self-report chronotype but have been associated with restless legs syndrome[23]. The index variants at these 3 loci are in strong to modest LD with the previously reported variants associated with restless legs syndrome (rs113851554, *MEIS1*, LD r^2 = 1.00; rs12991815, *C1D*, LD r^2 = 0.96; rs9369062, *BTBD9,* LD r^2 = 0.49). The three variants that reside in loci previously associated with self-report chronotype are in strong to modest linkage disequilibrium with those previously reported[8-10] (rs1144566, *RSG16*, LD r^2 > 0.91; rs12927162 *TOX3,* LD r^2 = 1.00; rs4882315, *ALG10B*, LD r^2 = 0.58). The *RSG16* gene is a known circadian rhythm gene and which contains the SNP most strongly associated with self-report chronotype. There were minimal differences in effect sizes when we performed a range of sensitivity analyses, including removing individuals on depression medication, adjustments for BMI and lifestyle factors and splitting the cohort by median age (**Supplementary Table 6** and **Supplementary Methods**).

Associated loci are enriched for genes expressed in the cerebellum and the serotonin metabolic process related genes

We used MAGMA[24] to assess tissue enrichment of genes at associated loci across the sleep traits. All traits showed an enrichment of genes in the cerebellum (**Supplementary Figures 3 and 4**). As a group, the loci associated with number of nocturnal sleep episodes were enriched for genes involved in the serotonin metabolic process pathway ($P_{Bonferroni}$=0.0003) (**Supplementary Table 8**).

Multiple sleep traits have genetic variants previously associated with restless legs syndrome

We observed most variants to influence either sleep duration, quality, or timing, but not combinations of these sleep characteristics. However, the variant rs113851554 at the *MEIS1* locus was associated with sleep duration, quality (sleep efficiency), and timing (L5). In addition, the variant rs9369062 at the *BTBD9* locus was associated with both sleep duration and L5 timing. Both variants have previously been reported as associated with restless legs syndrome (**Figure 2**). To follow up this observation, we performed Mendelian Randomisation using 20 variants associated with restless legs syndrome in the discovery stage of the most recent and largest genome-wide association study[23]. We tested these 20 variants against all 8 activity-monitor derived

sleep traits and showed a clear causative association of restless legs syndrome with all sleep traits. We also observed a causative association of restless legs syndrome with self-report sleep duration and chronotype, suggesting that variants associated with restless legs syndrome were not artefacts of the accelerometer-derived measures of sleep (**Supplementary Table 9**).

Accelerometer-derived estimates of the effects of sleep trait associated variants correlate well with self-report estimates

We compared effects of variants associated with self-reported sleep duration and chronotype identified in parallel GWAS analyses. Overall, we observed directional consistency with the accelerometer-derived measures. In a parallel GWAS of sleep duration in 446,118 individuals from the UK Biobank, we identified 78 associated loci at $P<5x10^{-8}$ (Dashti *et al.* BioRxiv, 2018). Sixty-seven of these SNPs were directionally consistent between the self-report and activity monitor derived sleep duration GWAS ($P_{binomial} = 6x10^{-11}$; **Figure 3** and Dashti *et al.* BioRxiv, 2018). Furthermore, in a parallel report (Jones *et al.* BioRxiv 2018) we have shown that of the 341 lead variants at self-reported chronotype loci, 310 had a consistent direction of effect for accelerometer-derived midpoint-sleep ($P_{binomial} = 5x10^{-59}$), 316 with L5 timing ($P_{binomial} = 3x10^{-65}$) and 310 with M10 timing ($P_{binomial} = 5x10^{-59}$; Jones *et al.* BioRxiv, 2018). **Figure 4** shows a scatter plot of self-reported associated chronotype effects against L5 timing effects.

DISCUSSION

Our analysis presents the first large-scale GWAS of multiple sleep traits estimated from accelerometer data using our validated activity-monitor sleep algorithm[17] (Van Hees *et al*. BioRxiv 2018, https://doi.org/10.1101/257972). We have identified 47 genetic associations at $P<5\times10^{-8}$ across 7 traits representing sleep duration, quality and timing. These loci included 10 novel variants for sleep duration and 26 for sleep quality not detected in larger studies of self-report sleep traits.

The observed associations included variants in loci previously associated with self-report sleep traits, including *PAX8*, and loci previously associated with diagnosed sleep disorders, including *MEIS1* and *BTBD9*. Variants with novel sleep-related associations included rs2660302, which occurs near the genes *DPYD* and *MIR137*. This variant represents the lead signal (LD r^2 = 0.91) for a previously reported schizophrenia and autism spectrum disorder locus[25]. In addition, the variant associated with sleep-duration at the *PDE11A* locus (rs17400325) is a low frequency (minor allele

frequency (MAF) = 4.2%) coding variant (p.Tyr727Cys) and has previously been associated with migraine and near-sightedness[26].

Our analysis identified variants in loci that were enriched for genes involved in the serotonin processing pathway - the strongest pathway associated with sleep quality. Serotonin plays a role in sleep cycles[27,28]. High levels of serotonin are associated with wakefulness and lower levels with sleep. Furthermore, serotonin is synthesized by the pineal gland as a processing step for melatonin production, a key hormone in circadian rhythm regulation and sleep timing. Melatonin is frequently taken as a dietary supplement in the United States with its use more than doubling between 2007 and 2012[29], although clinical trial results for sleep and circadian rhythm disorders are mixed[30]. In addition, excess melatonin levels can also lead to disturbed sleeping and other health issues and the American Academy of Sleep Medicine has previously recommended that melatonin not be used for chronic insomnia[31].

A subset of variants previously associated with restless legs syndrome were associated with sleep duration, quality and timing measures. It is unlikely to be just a feature of artefact (e.g. due to moving limbs during sleep) because the same variants are associated with self-report measures of sleep, chronotype and insomnia. Therefore, it is likely that we are picking up the sleep consequences of restless legs syndrome and provides evidence that restless leg syndrome is one cause of poor sleep. In the UK Biobank, restless legs syndrome was only identified through the Hospital Episodes Statistics (HES) data using the ICD-10 code “G25.8” (“Other specified extrapyramidal and movement disorders”), the parent category of the more specific “G25.81” code (“Restless legs syndrome”). Under the assumption that all individuals reporting “G25.8” had restless legs, we observed 38 individuals within our accelerometer subset. Removing these individuals did not change our conclusions.

Our data provide strong evidence that some accelerometer derived measures of sleep provide more precision than self-report measures, whilst for others there is little gain and questionnaire data is just as effective. For example, of the 11 accelerometer-based sleep duration loci we identified, only one (the *PAX8* variant) had been previously identified in self-reported sleep duration GWAS despite these studies having much larger sample sizes. Variants with nominal evidence of association with self-reported sleep duration had weaker effects. This difference may be due to reporting biases and due to the UK Biobank questionnaire asking participants to include nap time in their response. In contrast the accelerometer derived estimates of

L5 timing, the least active 5 hours of the day, correlated well with self-report estimates. These data suggest that the answer to the very simple question "are you a morning or evening person" provides similar power as wearing accelerometers for 7 days and nights. In a parallel GWAS analysis, the *PAX8* variant was also associated with self-report insomnia. In addition, five of the loci were nominally associated ($P<0.05$) with either self-report sleep-duration or insomnia. At least two of the sleep duration signals have been previously associated with mental health disorders including schizophrenia and migraine[25,26].

The Alzheimer's disease risk allele at the *APOE* locus was seen to have apparently paradoxical associations with sleep related traits. Given the well-established association between the *ε*4 allele and greater risk of Alzheimer's disease, we would not expect associations between this allele and higher quality of sleep, given previously observed associations of sleeping patterns with cognitive decline and Alzheimer's disease[4]. A similar paradoxical association was also reported recently in a previous study of over 2,300 men aged over 65 with overnight PSG data that showed the total time in stage N3 sleep was higher for individuals carrying two copies of *ε4* compared with those carrying one or zero copies[32]. Furthermore, a recent genetic study of physical activity also identified a paradoxical association between the *ε*4 allele and increased levels of physical activity (Klimentidis *et al,* BioRxiv 2017, https://doi.org/10.1101/179317). The more likely explanations for these associations we suggest are ascertainment and survival bias. The UK Biobank participants ranged from 44 to 79 years of age when wearing the accelerometer devices. Individuals participating in the UK Biobank who are older, with the highest risk of cognitive decline with an *ε4/ε4* haplotype and agreeing to an accelerometer-based experiment are more likely to be protected from cognitive decline based on other factors[33]. Consistent with this potential bias, the *ε4* allele association with reduced numbers of nocturnal sleep periods is stronger with increasing age. For example, when splitting individuals by median age, the per allele effect on number of sleep periods was twice that of the older versus younger group.

There are some limitations to this study. First, a sleep diary was not collected by the UK Biobank, a traditional tool to guide the start and end timing of nocturnal sleep episodes, commonly used in accelerometer studies. However, we have developed and used a method to overcome the lack of a sleep diary that has been validated against polysomnography[17] (Van Hees *et al*. BioRxiv 2018, https://doi.org/10.1101/257972) to

estimate sleep onset. However, as no sleep diary data exists it is hard to define bedtime prior to sleep, resulting in the inability to characterise phenotypes such as sleep onset latency (the time between going to bed and falling asleep), for example. Second, the activity monitors were worn up to 10 years from when baseline data was collected. Despite this, the correlation between self-report and activity measures of sleep duration was consistent with previous studies, and the correlation did not differ based on time between baseline (self-report time) and accelerometer wear when splitting by time-difference deciles (r = -0.03, P = 0.94). Finally, the UK Biobank was not a representative cohort of the UK population, as participants had a higher socio-economic status overall and were healthier, on average, given the prevalence of diseases amongst the participants[33,34]. This was particularly true of the participants who took part in the activity monitor study.

In conclusion, we have performed the first large-scale GWAS of objective sleep measures. We demonstrate that self-report measures are good proxies for objective sleep measures, but identify additional loci not identified by previous self-report GWAS studies.

METHODS

UK Biobank participants

The study population was drawn from the UK Biobank study – a longitudinal population-based study of individuals living in the UK[34]. Analyses were based on individuals estimated to be of European ancestry. European ancestry was defined through the projection of UK Biobank individuals into the principal component space of the 1000 Genomes Project samples[35] and subsequent clustering based on a *K*-means approach, centering on the means of the first 4 principal components.

Genetic Data

Imputed genetic data was downloaded from the UK Biobank (Bycroft, *et al.* BioRxiv, 2017, https://doi.org/10.1101/166298). We limited our analysis to 11,977,111 genetic variants imputed using the Haplotype Reference Consortium imputation reference panel with a minimum minor allele frequency (MAF) > 0.1% and imputation quality score (INFO) > 0.3.

Activity-monitor Devices

A triaxial accelerometer device (Axivity AX3) was worn between 2.8 and 9.7 years after study baseline by 103,711 individuals from the UK Biobank for a continuous period of up to 7 days. Details of data collection and processing have been previously described[36]. Of these 103,711 individuals, we excluded 11,067 individuals based on activity-monitor data quality. This included individuals flagged by UK Biobank as having data problems (field 90002), poor wear time (field 90015), poor calibration (field 90016), or unable to calibrate activity data on the device worn itself requiring the use of other data (field 90017). Individuals were also excluded if number of data recording errors (field 90182), interrupted recording periods (field 90180), or duration of interrupted recoding periods (field 90181) was greater than the respective variable's 3rd quartile + 1.5×IQR. Phenotypes determined using the SPT-window (all phenotypes except L5 and M10 timing) had additional exclusions based on short (<3 hours) and long (>12 hours) mean sleep duration and too low (<5) or too high (>30) mean number of sleep episodes per night (see below). These additional exclusions were to ensure that individuals with extreme (outlying), and likely incorrect, sleep characteristics were not included in any subsequent analyses. A maximum of 85,670 individuals remained for our analyses.

Accelerometer data processing and sleep measure derivations

We derived 8 measures of sleep quality, quantity and timing. All measures were derived by processing raw accelerometer data (.cwa). We first converted the .cwa files available from the UK Biobank to .wav files using "omconvert" for signal calibration to gravitational acceleration[36,37] and interpolation[36]. The .wav files were processed with the R package GGIR (van Hees *et al*. BioRxiv 2018, https://doi.org/10.1101/257972; http://doi.org/10.5281/zenodo.1175883 (Version v1.5-17)) to infer accelerometer non-wear time[38], and extract the z-angle across 5-second epochs from the time-series data for subsequent use in estimating the sleep period time window (van Hees *et al*. BioRxiv 2018, https://doi.org/10.1101/257972) and sleep episodes within it[17].

Sleep period time window (SPT-window). The SPT-window was estimated using a validated algorithm previously described (van Hees *et al*. BioRxiv 2018, https://doi.org/10.1101/257972) and implemented in the GGIR R package. Briefly, for each individual, median values of the absolute change in estimated z-angle (representing the dorsal-ventral direction when the wrist is in the anatomical position) across 5-minute rolling windows were calculated across a 24-hour period, chosen to make the algorithm insensitive to accelerometer orientation. The 10th percentile was incorporated into the threshold distinguishing movement from non-movement. Bouts of inactivity lasting ≥30 minutes are recorded as inactivity bouts. Inactivity bouts that are <60 minutes apart are combined to form inactivity blocks. The start and end of the longest block defined the start and end of the SPT-window.

Sleep duration and variability. Sleep episodes within the SPT-window were defined as periods of at least 5 minutes with no change larger than 5° associated with the z-axis of the activity-monitor, as motivated and described in van Hees *et al.* (2015). The summed duration of all sleep episodes was used as indicator of sleep duration within the SPT-window. The total duration over the activity-monitor wear-time was averaged. Individuals with an average sleep duration <3 hours or >12 hours were excluded from all analyses. In addition, the standard deviation of sleep duration was also calculated and put forward for statistical analysis for individuals with 7 days of accelerometer wear.

Sleep efficiency. This was calculated as sleep duration (defined above) divided by the time elapsed between the start of the first inactivity bout and the end of the last inactivity bout (which equals the SPT-window duration).

Number of nocturnal sleep episodes within the SPT-window.

This was defined as the number of sleep episodes within the SPT-window. Individuals with an average number of nocturnal sleep episodes ≤5 or ≥30 were excluded from all analyses.

Least active 5 hours (L5) timing. The mid-point of the least-active 5 hours (L5) of each day were defined as the 5-hour period with the minimum average acceleration. These periods were estimated using a rolling 5-hour time window. The midpoint was defined as the number of hours elapsed since the previous midnight (for example, 7pm = 19 and 2am = 26). Days with <16 hours of valid-wear time (as estimated by GGIR) were excluded from L5 estimates.

Most-active 10 hours (M10) timing. The mid-point of the most-active 10 hours (M10) of each day were defined as the 10-hour period with the maximum average acceleration. These periods were estimated using a rolling 10-hour time window. The midpoint was defined as the number of hours elapsed since the previous midnight. Days with <16 hours of valid-wear time (as estimated by GGIR) were excluded from M10 estimates.

Sleep-midpoint timing. Sleep midpoint was calculated for each sleep period as the midpoint between the start of the first detected sleep episode and the end of the last sleep episode used to define the overall SPT-window (above). This variable is represented as the number of hours from the previous midnight.

Diurnal inactivity. Diurnal inactivity was estimated by the duration of estimated bouts of inactivity that fell outside of the SPT-window.

Comparison against self-reported sleep measures

We performed analyses of self-reported measures of sleep. Self-reported measures analysed included a) the number of hours spent sleeping over a 24-hour period (including naps); b) insomnia; c) chronotype – where "definitely a 'morning' person", "more a 'morning' than 'evening' person", "more an 'evening' than a 'morning' person", "definitely an 'evening' person" and "do not know", were coded as 2, 1, -1, -2 and 0 respectively, in our continuous variable.

Statistical Analysis

Genome-wide association analyses. We performed all association tests in the UK Biobank using BOLT-LMM v2.3[39], which applies a linear mixed model (LMM) to adjust

for the effects of population structure and individual relatedness and enables the inclusion of all related individuals in our white European subset, boosting our power to detect associations. This meant a sample size of up to 85,670 individuals, as opposed to a maximal set of 72,696 unrelated individuals. Prior to association testing, phenotypes were first adjusted for age at accelerometry, sex, study centre, and season when activity monitor worn (categorical). All phenotypes except sleep duration variation were also adjusted for the number of measurements used to calculate each participant's measure (number of L5/M10 measures for L5/M10 timing and number of nights for all other phenotypes). At runtime, association tests included genotyping array (categorical; UKBileve array, UKB Axiom array interim release and UKB Axiom array full release) as a covariate.

SNP-based heritability analysis. We estimated the pseudo-heritability of the eight derived accelerometer traits using BOLT-REML (version 2.3.1)[39]. We used 524,307 high-quality genotyped single nucleotide polymorphisms (SNPs) (bi-allelic; MAF ≥1%; HWE $P>1x10^{-6}$; non-missing in all genotype batches, total missingness <1.5% and not in a region of long-range LD[40]) to build the relatedness model and thus to estimate heritability. For LD structure information, we used the default 1000 Genomes 'LD-Score' table provided with the BOLT-REML software.

Gene-set, tissue expression enrichment, and overlap with GWAS-catalog analyses. Gene-set analyses and tissue expression analyses were performed using MAGMA[24] as implemented in the online Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) tool[41]. Analysis of differentially expressed genes was based on data from GTEx v6 RNA-seq data[42]. Enrichment analyses of the overlap with associations previously reported through GWAS was also implemented through FUMA. Enrichment P-values for the proportion of overlapping genes present was based on the NIH GWAS catalog[43].

Replication of findings. Associations reaching $P<5x10^{-8}$ were followed up in the CoLaus, Whitehall and Rotterdam studies. The GENEActiv accelerometer was used by the CoLaus and Whitehall studies and worn on the wrist by the participants. In the CoLaus study, 2,967 individuals wore the accelerometer for up to 14 days. Of these, 10 were excluded because of insufficient data, 234 excluded as non-European, and a further 148 were excluded due to an average sleep duration of less than 3 hours or more than 12 hours. A total of 2,575 individuals remained for analysis of which 2,257 had genetic data. In the Whitehall study, 2,144 were

available for analysis, with the GENEActiv accelerometer worn for up to 7 days having performed the same exclusions. The Rotterdam studies used the Actiwatch AW4 accelerometer device (Cambridge Technology Ltd.). Genetic association analysis was based on imputed data (where available) and performed using standard multiple linear regression. Overall summary statistics were obtained through inverse-variance based meta-analysis implemented in METAL[44]. Combined variant effects on respective traits were subsequently calculated using the 'metan' function in STATA using the betas and standard errors obtained through the primary meta-analysis of the three replication studies.

Sensitivity Analysis. To assess whether stratification was responsible for any of the individual variant associations in a subset of the cohort, we performed multiple sensitivity analyses in unrelated European subsets of the UK Biobank using STATA. The sensitivity analyses carried out were: 1) males only, 2) females only 3) individuals younger than the median age (at start of the activity monitor wear period), 4) individuals older than the median age, 5) adjustment for body mass index (BMI) (UK Biobank data field 21001), 6) adjusting for BMI and lifestyle factors and 7) excluding individuals working shifts, taking medication for sleep or psychiatric disorders, self-reporting a mental health or sleep disorder, or diagnosed with depression, schizophrenia, bipolar disorder, anxiety disorders or mood disorder in the HES data (see **Supplementary Methods**). The sensitivity analyses were performed by regressing the phenotype against the variant dosage, adjusting for the same covariates as described for the BOLT-LMM GWAS and additionally adjusting for the first 5 principal components to account for population structure. All exclusions and adjustments were made using baseline records (taken at the assessment centre).

Mendelian Randomisation (MR). We used the inverse variance weighted approach[45] as our main analysis method, and MR-Egger[45], weighted median estimation[46] and penalised weighted median estimation[46] as sensitivity analyses in the event of unidentified pleiotropy of our genetic instruments. MR results may be biased by horizontal pleiotropy, i.e. where the genetic variants that are robustly related to the exposure of interest independently influence the outcome, through association with another risk factor for the outcome. IVW assumes that there is either no horizontal pleiotropy (under a fixed effect model) or, if implemented under a random effects model after detecting heterogeneity amongst the causal estimates, that (i) the strength of association of the genetic instruments with the risk factor is not correlated with the magnitude of the pleiotropic effects, and (ii) the pleiotropic effects have an average

value of zero. MR-Egger provides unbiased causal estimates if just the first condition above holds, by estimating and adjusting for non-zero mean pleiotropy. The weighted median approach is valid if less than 50% of the weight in the analysis stems from variants that are pleiotropic (i.e. no single SNP that contributes 50% of the weight or a number of SNPs that together contribute 50% should be invalid because of horizontal pleiotropy). Given these different assumptions, if all methods are broadly consistent this strengthens our causal inference.

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AUTHOR CONTRIBUTIONS

The study was designed by T.M.F., P.G., V.T.v.H., S.E.J., D.R.M., M.N.W. and A.R.W. Participation in acquisition, analysis and/or interpretation of data was performed by N.A., R.N.B., H.S.D., J.E., T.M.F., R.M.F., J.W.H., V.T.v.H., Y.J., S.E.J., D.K., M.Z., Z.K., A.I.L., D.R.M., A.M., K.S.R., S.Sabia, R.S., S.Sharp, A.v.d.S., H.T., M.A.T., J.T., P.M.V., M.N.W., A.R.W. and H.Y. Main writing group comprised of H.S.D. T.M.F., P.G., V.T.v.H, S.E.J., D.K., J.M.L., A.I.L. D.R.M., S.Sabia, H.T., M.K.T., P.M.V., M.N.W. and A.R.W. All authors reviewed this manuscript. A.R.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING FINANCIAL INTERESTS

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Tables and Figures

Table 1. Pseudo-heritability estimates of derived sleep variables from BOLT-REML

Sleep variable	h_2	95% CI
Sleep duration	0.190	0.182 – 0.198
Sleep duration variability (SD)	0.028	0.020 – 0.036
Number of nocturnal sleep episodes	0.223	0.215 – 0.231
Sleep efficiency	0.130	0.122 – 0.138
L5 timing	0.117	0.109 – 0.125
M10 timing	0.087	0.079 – 0.095
Sleep midpoint timing	0.101	0.093 – 0.109
Diurnal Inactivity	0.148	0.134 – 0.161

Table 2. Summary statistics for 47 genetic associations identified in the UK Biobank reaching $P<5\times10^{-8}$

TRAIT	SNP	Chr	BP (hg19)	E/O Allele	EA Freq	BETA	SE	P	Gene Region	Previous associations
L5 timing	rs1144566	1	182,569,626	C/T	0.970	0.096	0.014	8E-12	*RGS16/RNASEL*	3
L5 timing	rs113851554	2	66,750,564	T/G	0.057	0.133	0.011	2E-35	*MEIS1*	2,3,4
L5 timing	rs12991815	2	68,071,990	C/G	0.424	0.029	0.005	2E-09	*C1D*	2,4
L5 timing	rs9369062	6	38,437,303	A/C	0.708	0.039	0.005	9E-14	*BTBD9*	2,4
L5 timing	rs4882315	12	38,458,906	T/C	0.507	0.027	0.005	2E-08	*CPNE8/ALG10B*	3
L5 timing	rs12927162	16	52,684,916	G/A	0.277	0.029	0.005	3E-08	*TOX3*	3
M10 timing	rs1973293	12	38,679,575	C/T	0.481	0.029	0.005	1E-09	*CPNE8/ALG10B*	3
Sleep duration	rs2660302	1	98,520,219	A/T	0.811	0.041	0.006	9E-12	*DPYD*	
Sleep duration	rs113851554	2	66,750,564	G/T	0.943	0.110	0.011	2E-25	*MEIS1*	2,3,4
Sleep duration	rs62158170	2	114,082,175	G/A	0.217	0.054	0.006	3E-21	*PAX8*	1,2
Sleep duration	rs17400325	2	178,565,913	T/C	0.958	0.066	0.012	2E-08	*PDE11A*	
Sleep duration	rs72828540	6	19,102,286	T/C	0.752	0.041	0.005	1E-13	*LOC101928519*	3
Sleep duration	rs9369062	6	38,437,303	C/A	0.292	0.033	0.005	2E-10	*BTBD9*	2, 4
Sleep duration	rs2975734	8	10,090,097	C/G	0.561	0.027	0.005	1E-08	*MSRA*	
Sleep duration	rs13282541	8	41,723,550	C/T	0.739	0.032	0.005	4E-09	*ANK1*	
Sleep duration	rs2880370	8	105,987,057	A/T	0.670	0.028	0.005	2E-08	-	
Sleep duration	rs800165	12	67,645,219	C/T	0.343	0.028	0.005	3E-08	*CAND1*	
Sleep duration	rs10138240	14	63,353,479	G/C	0.514	0.029	0.005	7E-10	*KCNH5*	
Sleep midpoint	rs11892220	2	231,691,067	T/A	0.339	0.029	0.005	3E-08	*CAB39*	
Sleep efficiency	rs113851554	2	66,750,564	G/T	0.943	0.101	0.011	5E-22	*MEIS1*	2,3,4
Sleep efficiency	rs62158169	2	114,081,827	T/C	0.216	0.032	0.006	2E-08	*PAX8*	1,2
Sleep efficiency	rs17400325	2	178,565,913	T/C	0.958	0.074	0.012	2E-10	*PDE11A*	
Sleep efficiency	rs13094687	3	52,450,043	G/A	0.315	0.029	0.005	1E-08	*PHF7*	
Sleep efficiency	rs13080973	3	138,596,050	G/A	0.202	0.032	0.006	3E-08	*FOXL2*	
No. sleep episodes	rs12714404	2	282,462	T/G	0.283	0.037	0.005	1E-12	*ACP1/SH3YL1*	
No. sleep episodes	rs310727	3	4,336,589	T/C	0.475	0.026	0.005	3E-08	*SUMF1/SETMAR*	
No. sleep episodes	rs55754932	3	87,847,754	C/A	0.284	0.037	0.005	2E-12	*HTR1F*	
No. sleep episodes	rs9864672	3	137,076,353	T/C	0.522	0.029	0.005	2E-10	-	1
No. sleep episodes	rs4974697	4	2,473,092	T/A	0.390	0.026	0.005	5E-08	*RNF4*	
No. sleep episodes	rs7377083	4	102,708,997	A/C	0.430	0.029	0.005	2E-09	*BANK1*	
No. sleep episodes	rs749100	5	63,307,862	A/G	0.582	0.033	0.005	9E-12	*HTR1A/RNF180*	
No. sleep episodes	rs9341399	6	73,773,644	C/T	0.936	0.066	0.010	6E-12	*KCNQ5*	
No. sleep episodes	rs1889978	6	124,771,233	C/T	0.485	0.027	0.005	5E-09	*NKAIN2*	
No. sleep episodes	rs2141277	7	39,099,178	A/G	0.478	0.026	0.005	1E-08	*POU6F2*	
No. sleep episodes	rs10233848	7	103,122,645	G/A	0.293	0.035	0.005	2E-11	*RELN*	3
No. sleep episodes	rs1124116	10	99,371,147	A/G	0.730	0.031	0.005	2E-09	*HOGA1/MORN4*	
No. sleep episodes	rs4755731	11	43,685,168	G/A	0.431	0.028	0.005	3E-09	*HSD17B12*	1
No. sleep episodes	rs3751837	16	3,583,173	C/T	0.781	0.033	0.006	4E-09	*CLUAP1*	
No. sleep episodes	rs8045740	16	20,262,776	G/T	0.868	0.052	0.007	6E-14	*GPR139*	
No. sleep episodes	rs11078917	17	37,746,359	A/C	0.279	0.029	0.005	3E-08	*NEUROD2*	
No. sleep episodes	rs11082030	18	35,501,739	T/C	0.725	0.030	0.005	8E-09	-	
No. sleep episodes	rs8098424	18	52,458,218	G/A	0.619	0.027	0.005	1E-08	*RAB27B*	
No. sleep episodes	rs76753486	19	42,684,264	T/C	0.084	0.047	0.008	2E-08	*DEDD2/ZNF526*	
No. sleep episodes	rs429358	19	45,411,941	T/C	0.848	0.036	0.007	4E-08	*APOE*	
No. sleep episodes	rs12479469	20	61,145,196	A/G	0.342	0.031	0.005	4E-10	*MIR133A2*	
Diurnal inactivity	rs17805200	9	13,764,434	C/T	0.272	0.031	0.005	5E-09	-	
Diurnal inactivity	rs7155227	14	63,365,094	T/G	0.523	0.033	0.005	2E-12	*KCNH5*	

CHR=chromosome; BP=base-pair position (GRCh37/hg19); EA/OA=effect allele/other allele, EA Freq=effect allele frequency; SE=standard error; L5 timing=midpoint of least active 5 hours; M10 timing=midpoint of most active 10 hours; No. sleep episodes=number of nocturnal sleep episodes; Previous associations=previous associations with sleep-related traits: 1=sleep duration (self-report) (Dashti *et al.* BiorXiv, 2018), 2=insomnia (self-report) (Lane *et al*. BioRxiv 2018, https://doi.org/10.1101/257956), 3=chronotype (self-report) (Jones *et al*. BioRxiv 2018), 4=Restless Legs Syndrome[23].

FIGURES

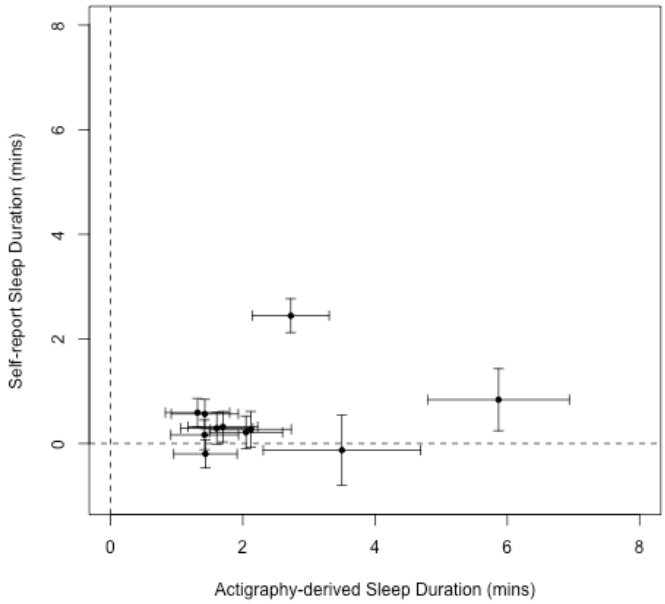

Figure 1. Comparisons of betas for 11 genetic variants associated with accelerometer-derived sleep duration against betas from a parallel GWAS of self-report sleep duration.

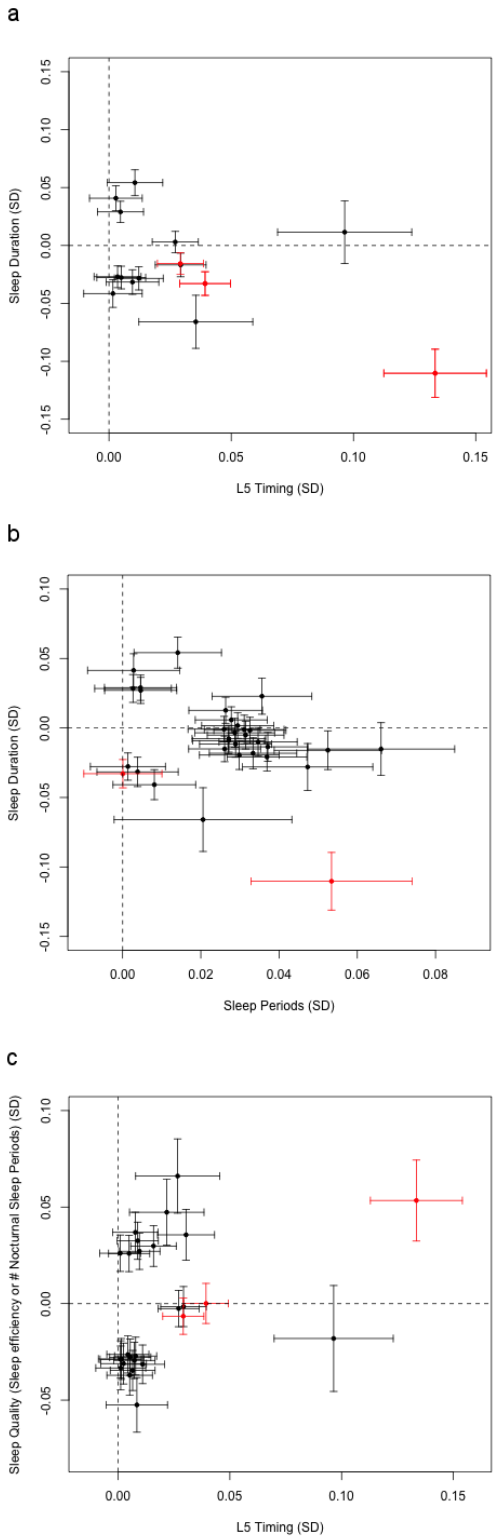

Figure 2. Comparison of betas for genetic variants associated with **a)** either L5 timing or sleep duration, **b)** either sleep duration or the number of nocturnal sleep episodes, and **c)** either L5 timing or sleep quality (number of nocturnal sleep episodes or sleep efficiency). Variants previously associated with restless legs syndrome are highlighted in red. Betas represent standard deviations of the inverse-normal distribution of each trait.

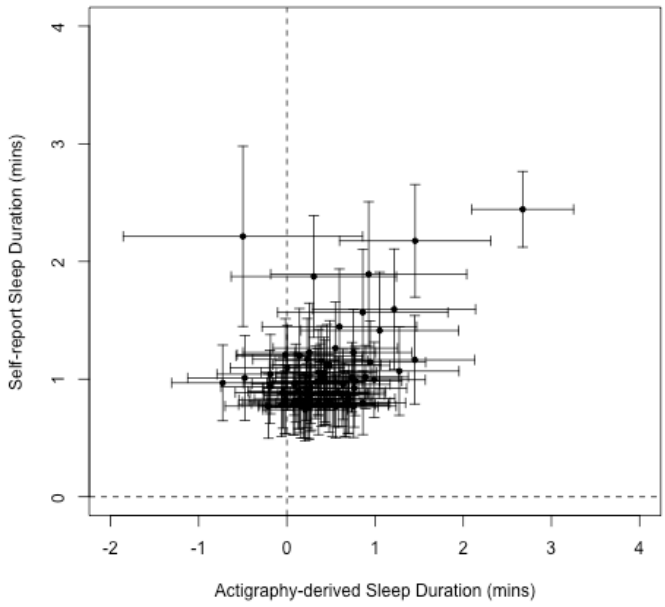

Figure 3. Comparisons of betas for 78 genetic variants associated with self-report sleep duration in a parallel GWAS effort (Dashti *et al,* BioRvix, 2018).

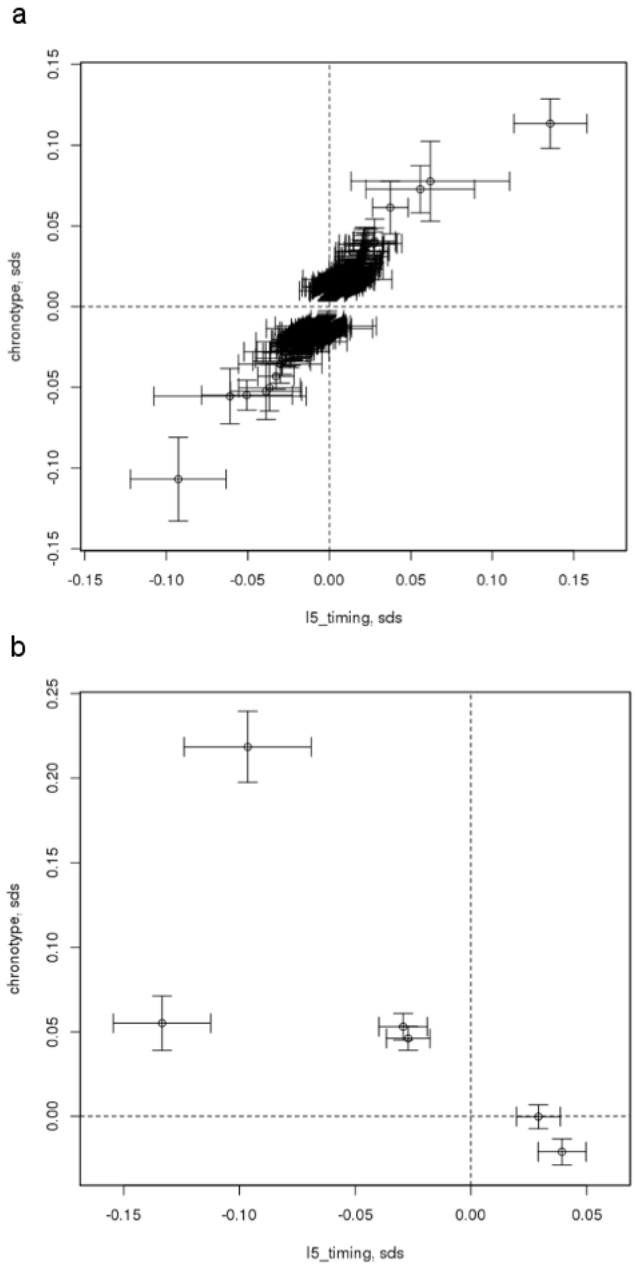

Figure 4. Correlations of genetic effect estimates based on self-report chronotype meta-analysis versus activity monitor midpoint sleep estimated from L5 timing for **a**) 351 variants identified from self-report chronotype GWAS and **b**) 6 variants identified for L5 timing from accelerometer derived estimates

Supplementary Tables

Supplementary table 1. Basic summary statistics of the filtered but raw sleep and activity measures. Units for L5 timing, M10 timing, sleep duration (mean and SD), sleep midpoint and diurnal inactivity are in hours. Sleep efficiency is a ratio and number of sleep episodes is a count.

Supplementary Table 2: Spearman's rank correlation statistics for activity monitor derived sleep traits and self-report hours slept and self report chronotype (coded for increased morningness).

Supplementary Table 3. Association statistics for the 47 signals discovered in UKB Biobank in the Whitehall and COLAUS and ROTTERDAM I, II, and III replication cohorts. Meta-analysis of the results across the studies are also provided.

Supplementary Table 4. Analysis of the combined genetic effects from Supplementary Table 3 within the Whitehall, COLAUS and Rotterdam replication studies.

Supplementary Table 5. Association result cross-tabulation against other traits for the 47 SNPs representing genetic associations reaching $P<5\times10^{-8}$ in UK Biobank. Cross-tabulation also includes results based on the latest self-report chronotype meta-analyses (Jones *et al.*, BioRxiv, 2018), self-report Insomnia GWAS (Lane et al., BioRxiv 2018, https://doi.org/10.1101/257956) and sleep duration GWAS in UK Biobank are also provided

Supplementary Table 6. Results from sensitivity analyses performed for the 47 signals reaching $P<5\text{x}10^{-8}$ in the UK Biobank.

Supplementary Table 7. Averages of the mean sleep periods detected within individuals in the UK Biobank split by APOE Alzheimer's disease risk haplotypes and lower/upper age groups.

Supplementary Table 8. MAGMA Gene-Set Analysis for SNPs associated with disturbed sleep based on number of sleeping periods reaching Bonferroni significance.

Supplementary Table 9. Results from Mendelian Randomization (MR) analyses of Restless Legs Syndrome exposure against multiple outcomes using 4 methods: 1) using Inverse-variance (IV) weighted MR, 2) Egger MR, 3) Weighted Median (WM) MR. 4) Penalised-weighted mean (PWM).