Polygenic Predisposition, Sleep Duration, and Depression: Evidence from a Prospective Population-Based Cohort

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Abstract

Background.

Suboptimal sleep durations and depression frequently cooccur. Short-sleep and long-sleep are commonly thought of as symptoms of depression, but a growing literature suggest that they may be prodromal. While each represents a process of mutual influence, directionality between them remains unclear. Using polygenetic scores (PGS), we investigate the prospective direction involved in suboptimal sleep durations and depression symptoms.

Methods.

Participants aged ≥ 50 were recruited from the English Longitudinal Study of Ageing (ELSA). PGS for sleep duration, short-sleep, and long-sleep were calculated using summary statistics data from the UK Biobank cohort. Sleep duration, categorised into short-sleep (“≤5hrs”), optimal-sleep (“>5-<9hrs”), and long-sleep (“≥9hrs”), was measured at baseline and across an average 8-year follow-up. Severe depression symptoms (measured with Centre for Epidemiological Studies Depression Scale) were also ascertained at baseline and across an average 8-year follow-up.

Results.

One standard deviation increase in PGS for short-sleep was associated with 14% higher odds of severe depression symptoms onset (95%CI = 1.03–1.25, $p = 0.008$). However, PGS for sleep duration (OR = 0.92, 95%CI = 0.84-1.00, p = 0.053) and long-sleep (OR = 0.97, 95%CI = 0.89–1.06, p = 0.544) were not associated with severe depression symptoms onset during follow-up. During the same period, PGS for depression was not associated with overall sleep duration, short-sleep, or long-sleep.

Conclusion.

Polygenetic predisposition to short-sleep was associated with severe depression symptoms onset over the average 8-year period. However, polygenic predisposition to depression was not associated with overall sleep duration, short-sleep or long-sleep, suggesting that different mechanisms underlie the relationship between depression and the subsequent onset of suboptimal sleep durations in older adults.

Introduction

Short-sleep (typically less than 5–6 hours per night)[1–3] and long-sleep (typically more than 8–10 hours per night)[1–3] are suboptimal sleep durations that, along with depression, are major contributors to public health burden among community-dwelling older adults. Depression prevalence increases with age but

plateaus in adults aged 55-74.[4] Older adults also tend to experience a downward trajectory of optimal sleep duration as they age.[5] Given the worldwide phenomenon of population ageing, an emergent need has arisen for a better understanding of the mechanism driving the nexus of suboptimal sleep durations and depression onset in older adults.

Clinical and epidemiological evidence have demonstrated the comorbid nature of suboptimal sleep durations and depression,[6] with longitudinal associations shown in both directions.[1,7] Specifically, some evidence suggests that short-sleep[8] and long-sleep[9] precedes the onset of depression, whereas others have suggested that depression leads to the onset of suboptimal sleep durations.[1] Inconsistencies observed between results may be due to methodological constraints, such as the use of different measures for sleep and depression,[1,9] cross-sectional designs,[10,11] relatively small sample sizes, and participant pools with a diverse range of characteristics, including military personnel[7] and adolescents,[12] across clinical and sub-clinical populations.[7,13] One compelling study on bidirectionality revealed that sleep disorders predict depression more consistently than depression predicts sleep disorders over a 20-year period.[13] However, the absence of genetic information may be an important factor that contributes to the uncertainty of directionality between suboptimal sleep durations and depression in adults.

Although environmental factors contribute substantially to suboptimal sleep durations and depression onset, these traits are highly heritable.[14] A twin study showed that genetic differences account for ~ 40% of the variance in sleep duration, with no evidence of a decline in genetic predisposition with age.[15] For depression, twin-based heritability approximates to 35%,[16] which has been notably consistent across samples and methods.[17] More recently, polygenetic scores (PGS) are thought to be key in beginning to understand the nature of sleep duration[18] and depression.[19] PGSs are indices of individuals' genetic propensity for a trait, derived as the sum of the total number of trait-associated alleles, otherwise known as polymorphisms, across the genome and weighted by their respective association effect size estimated through genome-wide association analysis.[20] PGS-derived hereditability estimates, therefore, differ from those documented in twin studies. Dashti, Jones et al. (2019),[10] for example, found that sleep duration heritability was 9.8%, although short-sleep was 7.9%, and long-sleep was 4.7%. PGSs can detect whether a common genetic basis exists between related traits or diseases, and can provide prediction of an individuals' genetic risk for a particular disease or outcome.[21] This approach, therefore, can be used to investigate whether suboptimal sleep durations and depression possess underlying shared genetic aetiology.

Using a large, phenotypically well-defined sample of UK population-representative older adults we employed PGSs across an average course of 8 years. First, we wished to ascertain the role of polygenic predisposition to overall sleep duration, short-sleep, and long-sleep in the development of severe depression symptoms. Second, we tested the role of polygenic predisposition to depression in overall sleep duration, and the onset of short-sleep and long-sleep. Despite substantial variation in thresholds defining short-sleep and long-sleep in the literature, a meta-analysis of prospective studies supported a

curvilinear risk of short-sleep (< 5-7hrs) and long-sleep (> 8-9hrs) sleep on depression that did not differ substantially by age.[6] The extremes of these durations informed the sleep thresholds used in the present study. As sleep disorders have been found to be stronger and more persistent longitudinal predictors of future depression than the inverse,[13] we hypothesised a significant, unidirectional association between polygenic predisposition to overall sleep duration, short-sleep, and long-sleep duration in the onset of severe depression symptoms during an average 8-year period.

Methods

Participants and procedures

Data were derived from the English Longitudinal Study of Aging (ELSA), which is a multi-disciplinary prospective cohort study of nationally representative men and women aged 50 years and older in England.[22] The study began in 2002 with reassessments biennially since then. Data from combined waves 2 and 4 (2004–2008) were used as baseline as genetic data were first introduced across this period. Data for outcomes on sleep duration and depression symptoms were derived from combined waves 6 and 8 (2012–2016) given that symptoms of depression and sleep duration may fluctuate within subjects over time. Data were collected in participants' homes, through nurse visits and computer-assisted personal interviews (CAPI). The sample of 7146 was reduced by 625 (8.8%) participants who experienced severe depression symptoms and 1076 (15.1%) who experienced short-sleep or long-sleep at baseline were excluded from analyses, leaving two analytic samples of 6521 and 6070, respectively (Fig. 1). Participants provided written informed consent and ethical approval was granted by the National Research Ethics Service (London Multicentre Research Ethics Committee).

Study variables

Sleep duration. Sleep duration was measured with an open-ended question, asking participants about the length of their sleep on an average weeknight. Following literature,[7,23] sleep duration was also categorised into "≤5hrs" (short-sleep), ">5-<9hrs" (optimal-sleep), and "≥9hrs" (long-sleep).

Depressive Symptoms. The eight-item Centre for Epidemiologic Studies Depression Scale[24] (CES-D) was used to assess self-reported depression symptoms over the past week. The psychometric properties are excellent in validity and reliability to the original 20-item scale.[25] The scale was reduced by a single item (i.e., "*whether their sleep was restless during the past week*"), as this item iterated sleep estimations. The reduced seven-item scale included whether, *during past week,* participants felt "*…depressed much of the time*"; "*…everything was an effort*"; "*…happy much of the time*"; "*…felt sad much of the time*"; "*…lonely much of the time*"; "*…enjoyed life much of the time*"; and "*…could not get going much of the time*". The items were scored on a binary response scale (anchored at 1='*yes*'; 0='*no*'). Positively worded items were reversed scored. Higher scores indicated greater depression symptoms. Scores were summed to generate a total continuous score, ranging 0 ('*no depression symptoms*') to 7 ('*severe depression symptoms*'). The

Cronbach's alpha in this sample was 0.80. To indicate severe depression symptoms, scores were dichotomised by ≥4; a well-recognised clinically significant indicator of depression.[25]

Covariates. Covariates included age (≥50); age squared (age^2) to account for nonlinearity; sex (male/female); and genetic ancestry to account for ancestry differences in genetic structures that could bias results (as measured by principal components [described below]).

Genetic data

The genome-wide genotyping was performed at University College London (UCL) Genomics in 2013-2014 with the funding the Economic and Social Research Council (ESRC) using the Illumina HumanOmni2.5 BeadChips (HumanOmni2.5-4v1, HumanOmni2.5-8v1.3), which measures ~2.5 million markers that capture the genomic variation down to 2.5% minor allele frequency.

Quality Control. Single-nucleotide polymorphisms (SNPs) were excluded if they were non-autosomal, minor allele frequency was <1%, if more than 2% of genotype data were missing and if the Hardy-Weinberg Equilibrium *p*-value was $<10^{-4}$. Samples were removed based on call rate (<0.99), sex difference, heterozygosity, and relatedness. To improve genome coverage, we imputed untyped quality-controlled genotypes to the Haplotype Reference Consortium[26] using the University of Michigan Imputation Server.[27] Post-imputation, we kept variants that were genotyped or imputed at INFO>0.80, in low linkage disequilibrium (R^2<0.1) and with Hardy-Weinberg Equilibrium *p*-value>10^{-5}. After the sample quality control 7179780 variants were retained for further analyses. To account for potentially biasing ancestry differences in genetic structures, a principal components (PCs) analysis was conducted, retaining the top 10 PCs,[28] which were subsequently used to adjust for possible population stratification in the association analyses.[28,29]

Polygenic risk scores (PGS). PGS for sleep duration, short-sleep, and long-sleep were calculated using summary statistics from genome-wide association studies (GWAS) from the UK Biobank.[10,30] To calculate PGS for depression, summary statistics from GWAS of major depressive disorders (MDD) was conducted by the Psychiatric GWAS Consortium (PGC) encompassing *n*=1331010 participnats.[19] All PGSs were calculated using a six p-value threshold (P_T; i.e., 0.001, 0.01, 0.05, 0.1, 0.3, and 1) using PRSice (Supplementary [S] Table 1).[31] Using information on sample size (*n*), total number of independent markers in genotyping panel (*m*) and lower and upper *P*-values to select markers into polygenic score, we estimated the predictive accuracy (R^2), and estimated a predictive power of each P_T using Avenge me package implemented in R.[32,33] Our results showed that the ultimate P_T was 0.001 for the PGSs for sleep duration (*m*=39476, R^2=0.003, P=2.12×10^{-5}), short-sleep (*m*=52197, R^2=0.004, P=6.52×10^{-08}), and depression (*m*=63824, R^2=0.001, P=0.003). Whereas the optimal P_T for the PGS for long-sleep was 0.01 (*m*=127099, R^2=0.003, P=5.79×10^{-06}). The estimated predictive accuracy for PGSs can be found in Table S1. To aid interpretability of the results, all PGSs were standardised by subtracting the mean and multiplying by their corresponding standard deviations; this scaling led to a unit increase, doubling the

risk of the corresponding outcome. The correlations between PGSs and phenotypic data ranged $^{-}$-0.057-$^{+}$0.048 (Table S2).

Statistical Analyses

Imputation of missing values. Missingness in the main and sensitivity analyses ranged from 0.0-17.0% (Table S3). Given the possibility of bias in the complete case analysis,[34,35] missing values were imputed using missForest based on Random Forests, an iterative imputation method, in RStudio v.4.0.3. In ELSA, socioeconomic variables are the main drivers of attrition,[22] so the assumption that missingness was not dependent on unobserved values, and was, thus, missing at random (MAR), was likely to be met. It has previously been shown that in the presence of nonlinearity and interactions, missForest outperformed prominent imputation methods, such as multivariate imputation by chained equations and *k*-nearest neighbours.[36] The imputation of the missing values yielded a minimal error for continuous (Normalized Root Mean Squared Error=0.09%) and categorical (proportion of falsely classified=0.14%) variables. A comparison of imputed and observed data indicates homogeneity between samples (Table S4).

Association analyses. Logistic regressions, reported as odds ratios (OR) with 95% confidence intervals (95%CI), were used to test whether PGSs for sleep duration, short-sleep, and long-sleep were associated with the onset of severe depression symptoms during an average 8-year follow-up period. Using multilinear and multinomial regressions, associations were investigated between PGS for depression and overall sleep duration, and onset of short-sleep and long-sleep during follow-up. Here, standardised regression coefficients (β) and relative risk ratios (RRR), respectively, with standard errors (SE) and 95%CI, denote the unit increase in overall sleep duration and the relative risk of short-sleep and long-sleep, as compared to optimal-sleep (the reference category). Sleep duration was modelled continuously with quadratic (squared) terms to account for nonlinearity. When significant linear and quadratic effects were detected, the linear effect took lower-order and was subsumed under the quadratic effect. Models were fitted to understand the role of covariates on associations: Model 1 was unadjusted; Model 2 controlled for baseline age, age^2, sex and 10 PCs. All association analyses were conducted in Stata 17.1 (STATA CorpLP, USA).

Sensitivity analyses. Three sets of sensitivity were performed to measure the robustness of the main results. First, we tested whether associations were dependent on the categorisation of depression, so analyses were repeated using continuous scores. Second, phenotypic associations, using self-reported sleep duration, short-sleep, long-sleep, and depression symptoms, were tested to assess consistency with the genetic findings. Finally, to ensure consistency with results from imputed data, analyses were repeated using complete cases. No corrections for multiple comparisons were made as exploratory studies do not strictly require multiplicity adjustment.[37]

Results

Sample characteristics

The details of the sample at baseline are given in **Table 1**. There were no notable differences in participant characteristics between the analytic samples when the exposures were overall sleep duration, short-sleep, and long-sleep (n = 6521) versus severe depression symptoms (n = 6070). Participants, with an average age of 65 years (SD = 9), were followed up to 12 years (mean = 8; range = 4–12). At baseline, mean sleep duration was 6.97 hours a night (SD = 1.24); 10.47% (n = 755) of participants reported ≤ 5 hours a night, and 4.49% (n = 321) reported sleeping ≥ 9 hours a night, whereas 15.27% (n = 625) of all older adults reported the presence of severe depressive symptoms. At the end of the follow-up period, mean sleep duration was 6.92 (SD = 1.14); 15.27% (n = 1091) of participants reported sleeping ≤ 5 hours a night, and 4.76% (n = 340) reported sleeping ≥ 9 hours a night, while 11.47% (n = 820) of all older adults reported presence of severe depressive symptoms.

PGSs for sleep duration, short-sleep, and long-sleep in severe depression symptoms onset

Relationships between PGSs for sleep duration, short-sleep, and long-sleep in onset of severe depression symptoms during the average 8-year follow-up are presented in **Table 2**. One standard deviation increase in PGS for short-sleep was associated with an average increase of 14% in odds of developing severe depression symptoms during the follow-up period in the fully adjusted model (95%CI=1.03-1.25, p=0.008). However, there was no significant association of the PGS for sleep duration (Model 2: OR=0.92, 95%CI=0.84-1.00, p=0.053) and long-sleep (Model 2: OR=0.97, 95%CI=0.89=-1.06, p=0.544) and the onset of severe depression symptoms during the same follow-up period.

PGS for depression in overall sleep duration, and short-sleep and long-sleep onset

Relationships between PGS for depression in overall sleep duration, and onset of short-sleep and long-sleep during a 8-year follow-up are presented in **Table 3**. In the fully adjusted model, no significant associations were observed between PGS for depression and future overall sleep duration (β=-0.02; 95%CI=-0.04-0.00, p=0.061), or short-sleep (RRR=1.05, 95%CI=0.97-1.15, p=0.212), and long-sleep (RRR=0.97, 95%CI=0.85-1.10, p=0.607) by the end of the follow-up period.

Sensitivity analyses

The results from the first set of sensitivity analyses that used continuous scores for depression followed the same pattern as those found in the main analyses, therefore, the categorisation of depression did not bias results (Table S5). The second set of sensitivity analyses between phenotypic associations (Tables S6-S7) showed that overall sleep duration was associated with lower odds of severe depression symptoms onset (Model 2: OR=0.79, 95%CI=0.74-0.84, p<0.001). However, short-sleep (Model 2: OR=2.58, 95%CI=2.05-3.26, p<0.001) and long-sleep (Model 2: OR=1.58, 95%CI=1.07-2.33, p=0.022) were associated with higher odds of severe depression symptoms onset. Severe depression symptoms were associated with overall sleep duration (Model 2: β=-0.02, 95%CI=-0.03- -0.00, p=0.012) and short-sleep onset (Model 2: RRR=1.31, 95%CI=0.98-1.75, p=0.050), but not long-sleep onset (Model 2: RRR=1.02, 95%CI=0.62-1.66, p=0.944). A conceptual diagram of established associations between PGSs and phenotypic outcomes can be found in Figure S1. The final set of sensitivity analyses that used complete

cases (i.e., non-imputed data) followed the same pattern as those in the main analyses (Table S8-S9; Figure S2).

Discussion

To our knowledge, this is the first study to use polygenic predisposition to prospectively investigate directionality between suboptimal sleep durations and severe depression symptoms, in a large population-representative sample of older adults. Our results show that genetic predisposition to short-sleep was strongly associated with onset of severe depression symptoms over the average 8-year period, but genetic predisposition to overall sleep duration and long-sleep was not. During the same follow-up period, polygenic predisposition to depression was not associated with overall sleep duration, short-sleep, or long-sleep among older adults, suggesting that different mechanisms underlie the relationship between depression and the subsequent onset of suboptimal sleep durations in older adults. Our findings were, by and large, upheld in a comprehensive set of sensitivity analyses highlighting their robustness.

Results showed that suboptimal sleep durations were experienced by 15% or less of an otherwise healthy, non-clinical sample of English older adults. While there was no change to the average sleep time of seven hours per night, the 43% increase in percentage incidence of short-sleep echoes earlier evidence[1]. While this within-person change may reflect age-related changes in sleep patterns,[5] it is inconsistent with reviews that have cast doubt on the proliferation of suboptimal sleep durations among the general population.[38,39] It is conceivable that an increased awareness of poor sleep, along with the emergence of sleep medicine, have led to observed rises in self-reported sleep problems and clinical sleep disorder diagnoses.

Corresponding to earlier evidence,[1,37] levels of severe depression symptoms also increased over the average follow-up period of 8 years. In line with hypotheses, our results showed that polygenic predisposition to short-sleep was related to between-person variation in depression. These results are consistent with twin studies,[12] and findings highlighting a positive genetic correlation between short-sleep and depressive symptoms in adults aged 40-69.[10] Several mechanisms have been theorised to translate short-sleep to severe depression symptoms, including electroencephalogram abnormalities (e.g., prolonged time spent in rapid eye movement sleep), abnormal circadian rhythms,[40] and hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, which is closely linked to impaired sleep continuity and reduction of slow-wave sleep.[41] We extend this evidence by demonstrating that common genetic markers for short-sleep also play an important role the incidence of depression in older adults.

In agreement with meta-analytic results that combined data on 23663 participants from seven prospective studies,[6] table six in the supplementary shows that phenotypic self-reported long-sleep was a risk factor for the onset of severe depression symptoms during the average 8-year follow-up in older adults. In addition, overall phenotypic sleep duration was negatively associated with severe depression symptoms, which aligns with earlier work.[8] However, contrary to hypotheses, these relationships were not

replicated in the genetic analyses. Specifically, no significant relationships were found of polygenic predisposition for sleep duration and long-sleep with onset of severe depression symptoms. Congruently, no associations were observed between polygenic predisposition to depression in onset of long-sleep during the same follow-up period. Together, these results suggest that other underlying factors drive the nexus of overall sleep duration, long-sleep, and depression in older adults. Inflammation and metabolic abnormalities are two such potential factors that could account for increases in long-sleep[42] and depression symptoms.[43,44]

Overall, findings from our data support a growing view that short-sleep is more salient to symptoms of depression than long-sleep, and that this is true across lifespan.[8,45] Different molecular mechanisms are said to underlie associations at either end of the sleep duration distribution.[18,46] Indeed, Garfield (2021)[18] found that of the two novel SNPs at the PAX8 signal, the one associated with short-sleep was near the activator of transcription and developmental regulator (AUTS2) gene, but the one associated with long-sleep was near the mitogen-activated protein kinase associated protein 1 (MAPKAP1) gene. Mutations at each gene have been implicated in different disorders, so this variation in gene expression could underlie the differences observed in the present study between polygenic short-sleep and long-sleep in severe depression symptoms. Though robustly replicated common variants of sleep duration are at the Vaccinia Related Kinase 2 (VRK2) and Paired Box 8 (PAX8) genes[18], there may be unidentified markers of large effects that drive the risk for long-sleep. Important also is that the genic basis of sleep duration is known to be pleiotropic, with the presence of the same SNPs but different risk alleles reacting in a multiplicity of ways.[47] This could additionally explain differences seen in the present study between polygenic risk for short-sleep and long-sleep in onset of severe depression symptoms.

Polygenic predisposition to depression was not associated with overall sleep duration, nor short-sleep or long-sleep onset. But on the same basis in phenotypic data, we echo earlier assertions[48,49] that severe depression symptoms are risk factors for the expression of short-sleep, and are negatively associated with overall sleep duration. However, in line with the genetic findings, severe depression symptoms did not precede long-sleep. This contrasts observational evidence put forward that depression has a curvilinear association with sleep duration, so is salient to both short-sleep and long-sleep.[7,23]

Strengths And Limitations

There are several strengths to the present study. Data were drawn from a large, nationally representative sample of older adults in the UK. The prospective cohort study design allowed for an investigation of the directional, prospective relationships between overall sleep duration, short-sleep, and long-sleep with severe depression symptoms using polygenic and phenotypic data. All associations were tested in a sizeable sample, the PGSs were constructed using the results from most recent and largest GWAS meta-analyses, so analyses were not constrained by our sample size.

Notwithstanding, our study should be interpreted with respect to some limitations. First, there are many aspects sleep, so assessments of sleep duration offer only one indication of risk. Second, incidence for

outcomes is low, particularly for long-sleep, so power is limited. Third, owing to the non-random nature of the study we cannot claim to show prevalence. Fourth, in line with the phenotypic data that is derived from a pool of respondents who are 99% Caucasian, our genetic analyses were conducted in individuals of European ancestry only; as has been common in genetic studies. A broader ethnic representation would have improved generalisability. Finally, our assessment of several associations may raise some concerns over multiple statistical testing, but our sample size was large enough to withstand multiple testing without increasing risk for false positive results, plus adjusting for multiple statistical testing has significant disadvantages.[47]

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Conclusion

Here, we lay important groundwork for future investigations on the intersection of genetics, sleep, and depression. Polygenic predisposition to short-sleep was associated with onset of severe depression symptoms, but polygenic predisposition to sleep duration and long-sleep were not. Polygenic predisposition to depression was also not associated with overall sleep duration, short-sleep, or long-sleep onset. We provide evidence of pathophysiological mechanisms involved, with an indication of the direction of effects, independent of a robust selection of confounders. Future research should focus on the clinical utility of these results, with genetic-medical integration used to improve the quality of care.

Declarations

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Tables 1-3

Tables 1-3 are available in the Supplementary Files section.

Figures

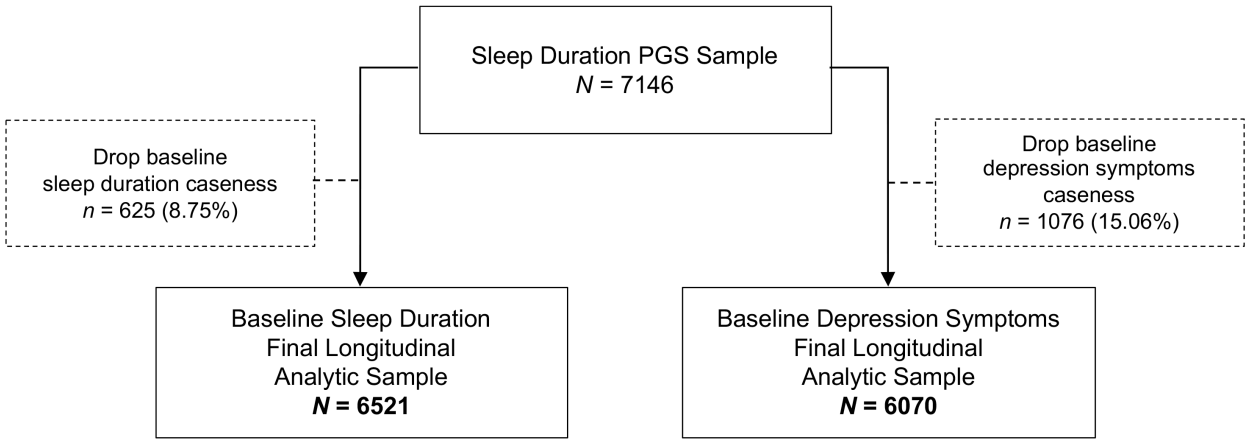

Figure 1

Flow chart of the analytic sample for imputed data

Supplementary Files

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- PolygenicPredispositionSleepDurationDepressionTables.pdf
- PolygenicPredispositionSleepDurationDepressionSupplementaryMaterial.pdf