Evaluating the nonlinear effects of sleep duration on biological aging across phenotypic, genomic, and epigenomic data

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ABSTRACT

Short and long sleep durations have been inconsistently linked to aging and health outcomes, potentially due to underexplored nonlinear associations. Using phenotypic and genomic data from the UK Biobank (n=442,664), we applied multivariable linear regression, restricted cubic splines, and Mendelian randomization (MR) to analyze nonlinear relationships between self-reported sleep duration and biomarkers of accelerated aging: PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length (LTL). Functional annotation analyses were performed to assess potential shared biological pathways using epigenomic profiles. Observational analyses supported U-shaped phenotypic associations between sleep duration and PhenoAgeAccel/BioAgeAccel, with optimal sleep around 7 h/d. For LTL, linear models suggested a U-shape, while spline models indicated an inverted reverse J-pattern. MR analyses corroborated the deleterious impacts of insufficient, but not excessive, sleep, by revealing a threshold nonlinear relationship between increasing genetically-predicted sleep duration up to 7 h/d and lower PhenoAgeAccel/BioAgeAccel, and a linear relationship with longer LTL. Cell-type enrichment analyses connected short sleep to BioAgeAccel/LTL through pathways related to muscle maintenance and immune function. These findings suggest that extending sleep may mitigate accelerated aging, though further research is needed to clarify the underlying biological mechanisms and whether excessive sleep also contributes causally to biological aging.

INTRODUCTION

Aging affects individuals both personally and societally [1]. Recognizing that relying solely on chronological age is insufficient to comprehend the internal physiological states nor the inter-individual variation in the rate and manner of aging [2], extensive efforts have been made to develop measures to capture the underlying aging processes at the biological level, also termed biological age [3]. These measures involve the use of individual or composite biomarkers that demonstrate associations with typically chronological age or mortality [4]. Of particular interest, clinical-parameter biological-age algorithms (i.e., PhenoAge [5] and BioAge [6]) and telomere length have been validated as among the most reliable predictors of aging outcomes and hold promise for routine application in large populations [7–9].

While the determinants of the rate of aging are intricate, it is possible to moderate the aging process through lifestyle interventions that influence metabolic processes. As one of these potentials, sleep assumes a significant role in daily life and functions as a restorative process facilitating both physical and mental recovery [10]. Accumulating evidence suggests that deviations from normal sleep duration may contribute to the premature development and progression of age-related conditions [11, 12]. However, the specific impact of insufficient or excessive sleep on accelerated biological aging remains uncertain [10, 13, 14]. Previous observational studies, often limited in scale and focused on linear effects, have yielded conflicting findings within specific populations [15–22]. Notably, existing studies have predominantly relied on binary categorizations of "short" and "long" sleep, rather than exploring the potentially diverse patterns across the entire duration continuum. A comprehensive investigation for potential non-linear dose-response relationships may elucidate the need for tailored interventions or recommendations across different ranges of sleep duration to extend a healthy lifespan and mitigate the risks of age-related health outcomes.

The lack of consensus in the existing evidence can be attributed, at least in part, to the vulnerability of conventional observational studies to residual confounding and reverse causality. While these limitations can be tackled by implementing an experimental study, it is unethical to conduct experiment of long-term sleep deprivation to confirm its causal effect in accelerating aging. In such case, Mendelian randomization (MR) provides an alternative means of uncovering the causal nature underlying a phenotypic association by using genetic variants (randomly distributed at conception) as proxies for life-long exposure risks [23]. Recent methodological advancements have introduced the doubly ranked method, a novel nonlinear MR approach that provides more robust stratum-specific estimates compared to conventional approaches [24]. Despite these developments, few nonlinear MR studies have been conducted in the realm of sleep duration and biological aging [25, 26].

Therefore, the present study aimed to provide a parametric visualization of the relationship between sleep duration and three key markers of biological aging status - PhenoAge acceleration, BioAge acceleration, and telomere length, utilizing extensive phenotypic and genotyping data from the UK Biobank. Multivariable regressions and restricted cubic spline analyses were first performed to examine phenotypic associations and whether phenotypic data support nonlinear effects. Linear and non-linear MR were then applied to delineate the shape of the causal relationships of genetically-predicted sleep duration with biological age measurements. Integrating genome-wide association study (GWAS) summary statistics and cell-type-specific annotations, functional annotation analyses were finally undertaken to interrogate potential genetic mechanisms relating sleep duration to the aging process. A graphical abstract is provided in Figure 1.

MATERIALS AND METHODS

The flowchart of participant selection and overall study design is outlined in Figure 2. In general, observational and MR analyses were conducted based on individual participant data from the UK Biobank, while functional annotation analyses were conducted using summary statistics from the hitherto largest GWAS of each phenotype. All analyses were performed in R (version 4.1.0) unless otherwise specified, with a two-sided P-value of 0.05 used as the threshold for statistical significance.

Study participants

Participants were drawn from the UK Biobank, a large population-based prospective cohort study which recruited more than 500,000 individuals aged 40-69 years between 2006 and 2010. The study protocol is available online (www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf) and more details are published elsewhere [27]. At the initial visit, participants completed online questionnaire and physical measurements, and their biological samples were collected for genotyping and biochemistry tests. In our study, we used information on habitual sleep duration, biological traits for PhenoAge and BioAge construction, telomere length measurements, relevant confounding factors, and genetic variants. UK Biobank
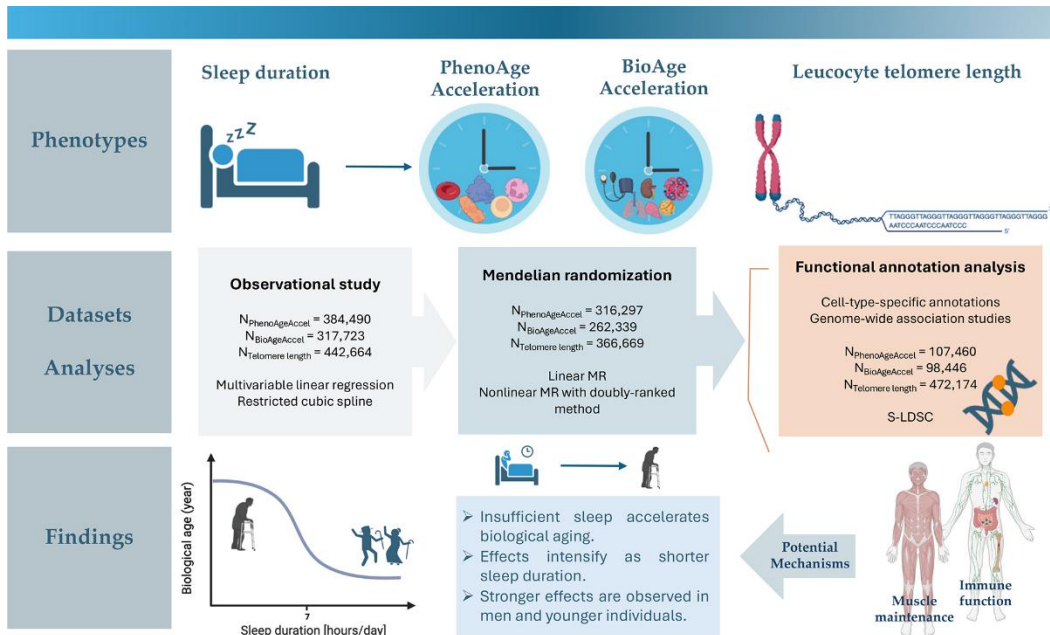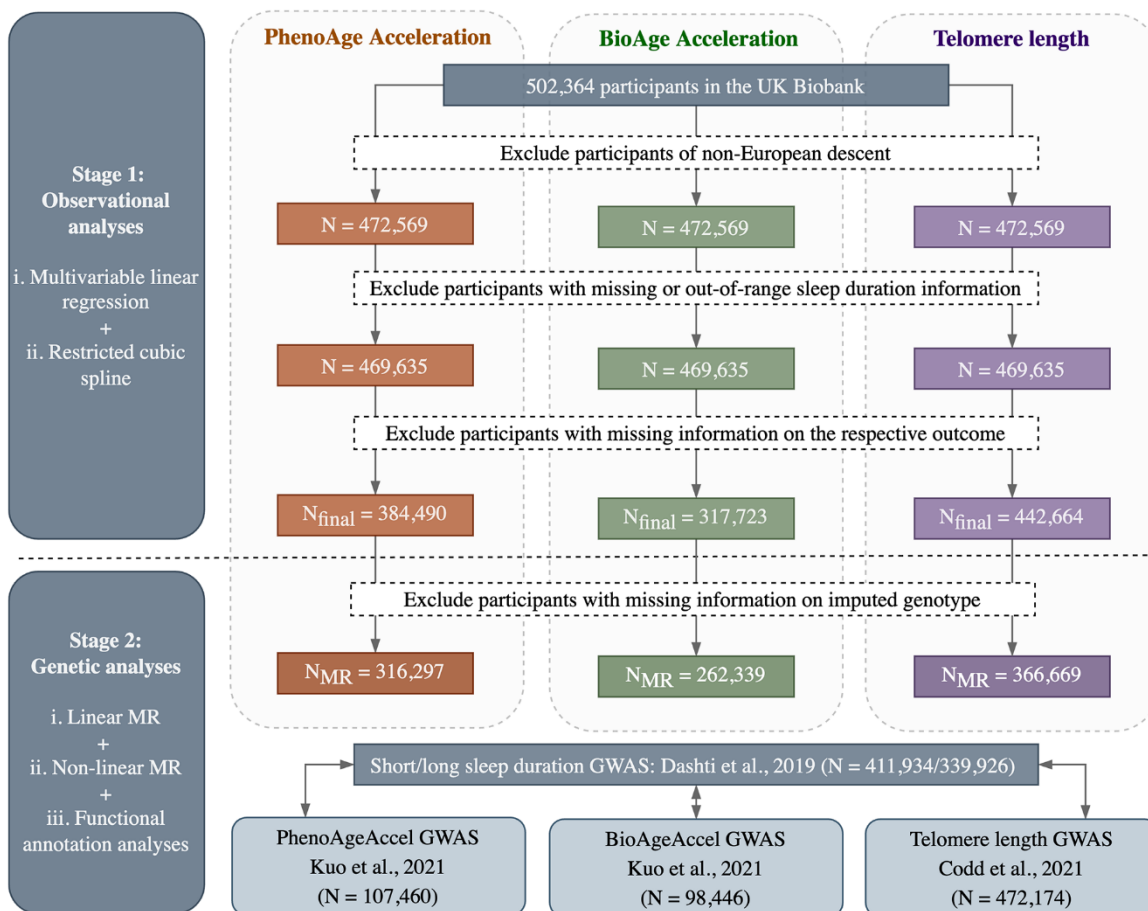
Figure 1. Graphical abstract.

Figure 2. Flowchart of participant selection and overall study design.

received ethical approval from the North West Multi-centre Research Ethics Committee and obtained written informed consent from all participants. Our study was performed under application number 99713.

Self-reported habitual sleep duration

In the UK Biobank, participants' habitual sleep duration was assessed at the baseline assessment via a standardized question: "About how many hours sleep do you get in every 24 hours? (please include naps)", with responses in hour increment. Following the methods of previous studies [28, 29], participants with sleep durations below 2 hours or above 12 hours (extreme responses) were treated similarly to those who did not respond to the question. These participants along with those who responded with "Do not know" or "Prefer not to answer" were excluded from our analysis.

PhenoAge, BioAge, and age accelerations

We computed two validated biological age predictors, PhenoAge [5] and BioAge [6], using two sets of nine clinical-based biomarkers involving a total of 12 blood chemistry and blood count traits as well as assessments of lung function and blood pressure. Details of the included biomarkers can be found in Supplementary Table 1. Both PhenoAge and BioAge were initially trained using data from the third National Health and Nutrition Examination Survey (NHANES III), but with different objectives. While PhenoAge was derived from an algorithm based on multivariate analysis of mortality hazards in the reference population to provide an estimate of the risk of death, BioAge was computed using an algorithm that involved a series of regressions of individual biomarkers on chronological age in the reference population, aiming to quantify the decline in overall system integrity. We applied the previously trained algorithms to the UK Biobank biomarker data to calculate PhenoAge and BioAge for each participant, using the R package "BioAge" [30]. To better quantify the differences between participants in biological aging, we utilized linear regression models to estimate the residual of the computed PhenoAge or BioAge after subtracting the effect of chronological age. These residuals were referred to as PhenoAge acceleration (PhenoAgeAccel) and BioAge acceleration (BioAgeAccel), respectively, and served as the primary outcomes in our analysis. Any observations with missing biomarkers values were excluded.

Leukocyte telomere length

Telomeres are nucleoprotein complexes located at the ends of chromosomes that undergo shortening with each cell division. The length of telomere has been proposed as a biological measure of aging, reflecting the degree of cellular senescence and oxidative stress [31]. In this study, we focused on telomere length measured in leukocyte (LTL), a practical measure correlating well with telomere length across different tissues within individuals. In the UK Biobank, LTL measurements were ascertained on DNA from peripheral blood leukocytes collected at baseline assessment using a well-validated multiplex qPCR assay [32]. Measurements were reported as a ratio of telomere repeat copy number relative to that of a single copy gene (T/S ratios), which were then log-transformed to obtain a normal distribution ($\log_e$LTL). Multiple quality checks were applied to control and adjust for technical factors, as described elsewhere [32]. To allow direct comparison to other studies, we used z-standardized $\log_e$LTL as our primary outcome. Participants with missing LTL measurements were excluded.

Genetic risk score of self-reported sleep duration

Genetic variants used in MR analyses were extracted genotypes from the UKB imputation dataset (n = 487,150 at the time of our study). Detailed information on genotyping, imputation, and quality control in the UK Biobank has been described previously [33]. We took 85 independent single-nucleotide polymorphisms (SNPs) robustly associated with continuous sleep duration (P-value $< 5\times10^{-8}$), obtained by applying PLINK's clumping function [34] (parameters: -clump-r2 0.001 --clump-kb 1000) to results from the largest published GWAS of self-reported habitual sleep duration (n = 446,118) [35], as our genetic instruments. Details of the included SNPs are shown in Supplementary Table 2. Following SNP quality control [36], two palindromic SNPs (rs17732997 and rs4333549) were detected and subsequently excluded. To avoid one-sample bias towards confounded observational associations, we calculated an unweighted genetic risk score (GRS) by directly summing the number of sleep duration-increasing alleles across the 83 SNPs. Collectively, the unweighted GRS explained 6.22% of the genome-wide SNP-based heritability of sleep duration, as determined by comparing residual variance in linear regression models of sleep duration on GRS (F-statistic = 2,239).

GWAS data sources

The largest published GWAS of self-reported habitual sleep duration also conducted separate GWAS for short (< 7 h/d; n = 106,192 cases) and long (> 8 h/d; n = 34,184 cases) sleep relative to 7–8 h/d sleep duration (n = 305,742 controls) [35]. We retrieved the full sets of summary statistics for the three sleep duration phenotypes for further functional annotation analyses. We also obtained the largest available GWAS of PhenoAgeAccel (n = 107,460) [37], BioAgeAccel (n =

98,446) [37], and LTL (n = 472,174) [32]. All original GWAS analyses were performed using imputed genotype data from the UK Biobank, involving only participants of European descent.

Statistical analyses

Observational analyses

Participants of European ancestry (to mirror the genetic analyses) with complete (and within range) exposure and outcome data were included. Separate multivariable linear regression models were employed to assess the relationships of continuous sleep duration with PhenoAgeAccel, BioAgeAccel, and LTL. In addition to the top five genetic principal components (PCs), factors previously described as associated with biological age measurements were included as covariates, including age, sex, educational qualifications (degree, no degree), body mass index, smoking history (current, former, or never), drinking history (current, former, or never), physical activity status (low, moderate, high), histories of cardiovascular disease (angina, heart attack, or stroke), hypertension, diabetes mellitus, and leucocyte count (for LTL as an outcome).

To assess the potential for nonlinear associations, we entered the levels of self-reported sleep duration as indicator variables, and obtained estimates comparing each of < 5 h/d, 5 h/d, 6 h/d, 8 h/d, 9 h/d, and > 9 h/d to our chosen reference category of 7 h/d. Restricted cubic spline regressions were further employed to model the non-linear relationships between continuous sleep duration and biological age measurements with four knots (located at the 5th, 35th, 65th, and 95th percentiles) after adjustments.

Considering the previously observed sex differences in biological aging [32, 38] and the age-dependent variations in sleep duration [39], all analyses were additionally stratified by sex and age (using the median age of 58 years as the cutoff point).

Mendelian randomization analyses

Participants of European ancestry (to avoid population stratification) with complete data on sleep duration, aging outcomes, and genotypes were further included in the MR analyses. We first applied a two-stage method to estimate the average causal effect of sleep duration on the outcomes. This conventional MR approach tests for the presence of a causal relationship, yielding effect estimates under a linear modeling framework. In the first-stage analysis, we regressed the exposure (sleep duration) on the unweighted GRS. In the second stage, we regressed the outcomes on the fitted values of the exposure from the first stage. The regression models in both stages were adjusted with age at baseline, sex, age-squared, age-by-sex, age-squared-by-sex, the top five PCs of ancestry, and genotyping array.

While linear MR was conducted in the overall population to estimate averaged causal effects, nonlinear MR involves generating strata within the study sample and undertaking MR analyses within each stratum [40]. We applied the fractional polynomial method to examine nonlinearity and used the recently developed doubly-ranked stratification approach [24] to construct five equal-sized strata of the population. Compared to the conventional residual-based method [40], the doubly-ranked approach offers increased reliability when the genetic effects on the exposure vary across the population, or when the exposure measurement is coarsened (e.g., self-reported sleep duration measured in hourly units) [24]. We first stratified all participants into preliminary strata (each containing 50 participants) according to the levels of the GRS, and then stratified them into final strata based on the levels of observed sleep duration within each pre-stratum. This ensures that the constructed strata are uncorrelated with the GRS, while also guaranteeing that the average exposure level increases monotonically across the strata.

For each final stratum, we calculated a linear MR estimate of the causal effect of increasing sleep duration using the two-stage method described above. To stabilize estimates, we performed a bootstrap averaging approach. We randomly removed a small number of participants (n = 12) from the analysis and performed the doubly-ranked approach using this dataset. We repeated this procedure 100 times and then combined the estimates using Rubin's rules. To evaluate the presence of a trend in the stratum-specific estimates, we performed a meta-regression of these estimates on the mean value of observed sleep duration in each stratum [40, 41], considering a P-value < 0.05 as evidence supporting nonlinearity. Sex- and age-stratified MR analyses were also performed.

Two sensitivity analyses were performed. First, we incorporated all additional confounding factors included in the multivariable regression models into the two-stage MR analyses to address potential residual confounding. Second, to assess the MR assumption that genetic variants influence biological aging solely through sleep duration, we recalculated the unweighted GRS after disregarding six potential pleiotropic SNPs that demonstrated associations (P-value < 5×10^{-8}) with phenotypes other than sleep duration, as indicated by the GWAS catalog [42], and repeated MR analyses. The potential pleiotropic SNPs and their corresponding related phenotypes are shown in Supplementary Table 2. Given the methods for exploring horizontal pleiotropy in one-sample MR can be underpowered in each stratum,

we compared the effect estimates derived from sensitivity analyses with those obtained from the primary analyses to assess the consistency of patterns. All MR analyses were performed using the R packages "ivreg" and "SUMnlmr".

Functional annotation analyses

To elucidate the potential shared biological mechanisms underlying the observed relationships between sleep duration and biological aging, we conducted functional annotation analyses by partitioning the SNP-heritability of each phenotype based on cell-type-specific annotations and examining their clustering patterns. A total of 396 annotations from the Roadmap Epigenomics project encompassing six histone marks (DNase, H3K27ac, H3K36me3, H3K4me1, H3K4me3, and H3K9ac) across 88 primary cell types or tissues [43] were utilized. These annotations were further categorized into nine broad groups, including adipose, central nervous system (CNS), digestive system, cardiovascular, musculoskeletal and connective tissue, immune and blood, liver, pancreas, and other. For each phenotype, annotation-specific enrichment values were calculated using stratified-LDSC [44], which were then transformed into a color scale and visualized through hierarchical clustering. FDR-adjusted *P*-value was applied based on the specific numbers of comparisons made in each analysis.

Data availability

The data underlying the results presented in the study are available to researchers upon application to UK Biobank (https://www.ukbiobank.ac.uk/).

Consent to participate

The participants in the UK Biobank study provided written informed consent for their data to be used in health-related research. As this study analyzes aggregated GWAS summary statistics that do not contain any personally identifiable information, no additional consent for publication is required.

Consent to publish

The participants in the UK Biobank study provided written informed consent for their data to be used in publications.

RESULTS

Study population

Table 1 summarizes the baseline characteristics of study participants included in the observational analyses of PhenoAgeAccel (n = 384,490), BioAgeAccel (n =

317,723), and LTL (n = 442,664). The mean age of participants ranged from 56.6 to 56.8 years, and 53.7% to 54.2% of participants were women. More detailed characteristics of the three partially overlapping groups of participants according to self-reported sleep duration are presented in Supplementary Tables 3–5.

Linear and nonlinear phenotypic associations

Linear observational analyses revealed significantly positive associations between continuous sleep duration with both PhenoAgeAccel (β = 0.08 years per additional hour of sleep duration, 95%CI = 0.07 to 0.09) and BioAgeAccel (β = 0.02 years per additional hour of sleep duration, 95%CI = 0.01 to 0.03), but not with LTL (β = 0.0003 SD change per additional hour of sleep duration, 95%CI = –0.0024 to 0.0029) (Supplementary Table 6). Compared to participants reporting 7 hours of sleep per day, those reporting shorter (< 7 h/d) or longer (> 7 h/d) sleep durations showed significantly higher PhenoAgeAccel and BioAgeAccel, as well as significantly shorter LTL (Figure 3). Restricted cubic spline regressions also demonstrated U-shaped nonlinear associations of sleep duration with PhenoAgeAccel and BioAgeAccel, while suggested an inverted reverse J-shaped association of sleep duration with LTL (Supplementary Figure 1). All spline analyses yielded a *P*-value for nonlinearity below 0.001.

Sex- and age-stratified observational analyses demonstrated similar patterns of nonlinear associations, despite slightly larger statistical uncertainties (Supplementary Table 6 and Supplementary Figure 1). Notably, the magnitude of associations was consistently higher in men than in women across all outcomes. Insufficient sleep exhibited seemingly stronger associations with both PhenoAgeAccel and BioAgeAccel in younger (< 58 years) compared to older participants (≥ 58 years).

Linear and nonlinear mendelian randomization

Utilizing 83 SNPs to instrument self-reported sleep duration, linear MR within the overall UK Biobank population found significant causal associations between genetically-predicted sleep duration and PhenoAgeAccel (β = –0.31 years per 1 hour increase in genetically-predicted sleep duration, 95%CI = –0.50 to –0.12), BioAgeAccel (β = –0.38 years per 1 hour increase in genetically-predicted sleep duration, 95%CI = –0.53 to –0.24), and LTL (β = 0.07 SD change per 1 hour increase in genetically-predicted sleep duration, 95%CI = 0.03 to 0.11) (Figure 4).

Stratifying the overall study sample into five strata, nonlinear MR demonstrated threshold nonlinear

Table 1. Baseline characteristics of UK Biobank participants included in observational analyses.

Characteristics	Analysis of PhenoAgeAccel	Analysis of BioAgeAccel	Analysis of LTL
No. of participants	384490	317723	442664
Sleep duration, h/d	7.16 (1.08)	7.16 (1.06)	7.16 (1.08)
Age at recruitment, y	56.8 (8.02)	56.6 (8.04)	56.8 (8.03)
Sex (women), n (%)	206642 (53.7%)	171835 (54.1%)	239936 (54.2%)
Education			
Degree, n (%)	315151 (82.7%)	263167 (83.5%)	363075 (82.7%)
No degree, n (%)	66008 (17.3%)	51954 (16.5%)	75785 (17.3%)
Body mass index, kg/m^2	27.4 (4.75)	27.3 (4.67)	27.4 (4.76)
Smoking status			
Never, n (%)	206510 (53.9%)	172605 (54.5%)	237954 (53.9%)
Previous, n (%)	136638 (35.7%)	112269 (35.5%)	157078 (35.6%)
Current, n (%)	40062 (10.5%)	31820 (10.0%)	46137 (10.5%)
Drinking status			
Never, n (%)	12340 (3.21%)	10002 (3.15%)	14243 (3.22%)
Previous, n (%)	13271 (3.45%)	10414 (3.28%)	15299 (3.46%)
Current, n (%)	358575 (93.3%)	297067 (93.6%)	412778 (93.3%)
IPAQ activity group			
High, n (%)	126921 (40.5%)	106018 (40.9%)	146179 (40.5%)
Moderate, n (%)	127813 (40.8%)	105833 (40.8%)	147130 (40.8%)
Low, n (%)	58433 (18.7%)	47654 (18.4%)	67260 (18.7%)
Leukocyte count, 10^9 cells/Litre	/	/	6.90 (2.04)
Major diseases			
Cardiovascular disease, n (%)	22051 (5.74%)	16096 (5.07%)	25440 (5.76%)
Hypertension, n (%)	103404 (26.9%)	82698 (26.1%)	118845 (26.9%)
Diabetes mellitus, n (%)	18386 (4.79%)	14409 (4.54%)	21267 (4.81%)
Components of biological ages			
Lymphocyte (%)	28.7 (7.34)	/	/
Mean cell volume (fL)	82.9 (5.25)	/	/
Serum glucose (mmol/L)	5.11 (1.21)	/	/
Red cell distribution width (%)	13.5 (0.95)	/	/
White blood cell count (1000 cells/uL)	6.89 (1.93)	/	/
Albumin (g/L)	45.2 (2.61)	45.3 (2.59)	/
Creatinine (umol/L)	72.2 (16.2)	72.2 (17.1)	/
C-reactive protein (mg/dL)	0.26 (0.44)	0.25 (0.41)	/
Alkaline phosphatase (U/L)	83.5 (26.1)	83.0 (25.9)	/
FEV$_1$ (L)	/	2.85 (0.80)	/
SBP (mm Hg)	/	138 (18.5)	/
Total Cholesterol (mg/dL)	/	221 (43.9)	/
Glycated hemoglobin (%)	/	3.58 (0.63)	/
Blood urea nitrogen (mg/dL)	/	15.2 (3.82)	/
Biological ages, y			
PhenoAge	50.8 (9.42)	/	/
PhenoAge acceleration	0.00 (4.66)	/	/
BioAge	/	53.9 (8.67)	/
BioAge acceleration	/	0.00 (3.31)	/
Z-standardized leucocyte telomere length	/	/	-0.01 (0.99)

Characteristics were presented as mean values (standard deviation) for continuous variables and n (%) for categorical variables. PhenoAgeAccel, PhenoAge acceleration; BioAgeAccel, BioAge acceleration; LTL, leucocyte telomere length.

relationships for sleep duration with both PhenoAgeAccel and BioAgeAccel. We observed a strong inverse causal association of increasing genetically-predicted sleep duration with PhenoAgeAccel in the lowest strata ($\beta = -1.00$ years per 1 hour increase in genetically-predicted sleep duration, 95%CI = -1.48 to -0.51), an inverse but slightly weaker association in the second lowest stratum ($\beta = -0.68$, 95%CI = -1.07 to -0.30), whereas no significant association in the other three strata with mean observed durations > 7.1 h/d. Similarly, the strongest inverse causal association of increasing genetically-predicted sleep duration with BioAgeAccel was found in the lowest stratum ($\beta = -0.81$ years per 1 hour increase in genetically-predicted sleep duration, 95%CI = -1.17 to -0.45), followed by the second lowest stratum ($\beta = -0.56$, 95%CI = -0.88 to -0.24). The trends in estimates were significant, as evidenced by the significant P-values for nonlinearity for both PhenoAgeAccel ($P = 3.75 \times 10^{-5}$) and BioAgeAccel ($P = 3.45 \times 10^{-3}$) (Figure 4).

Nonlinear MR demonstrated a significant positive causal association of increasing genetically-predicted sleep duration with LTL in the second highest stratum ($\beta = 0.08$ SD change per 1 hour increase in genetically-predicted sleep duration, 95%CI = 0.01 to 0.16). No significant association was observed in the other duration groups, likely due to lower power arising from reduced sample size, nor a significant trend across stratum estimates ($P = 0.97$) (Figure 4).

We found largely consistent results in the sex-stratified nonlinear MR analyses of each biological age measurement, although some confidence intervals included the null (particularly in analyses of LTL) due to reduced statistical power. Notably, compared to women-specific analyses, men-specific nonlinear MR yielded higher effect magnitudes of extremely insufficient sleep duration on PhenoAgeAccel ($\beta = -0.92$ vs. $\beta = -0.90$) and BioAgeAccel ($\beta = -1.44$ vs. $\beta = -0.71$) (Supplementary Tables 7, 8). Additionally, insufficient sleep duration demonstrated stronger effects in younger participants compared to older participants for PhenoAgeAccel ($\beta = -0.86$ vs. $\beta = -0.65$), BioAgeAccel ($\beta = -0.96$ vs. $\beta = -0.72$), and LTL ($\beta = 0.15$ vs. $\beta = 0.12$) (Supplementary Tables 9, 10).
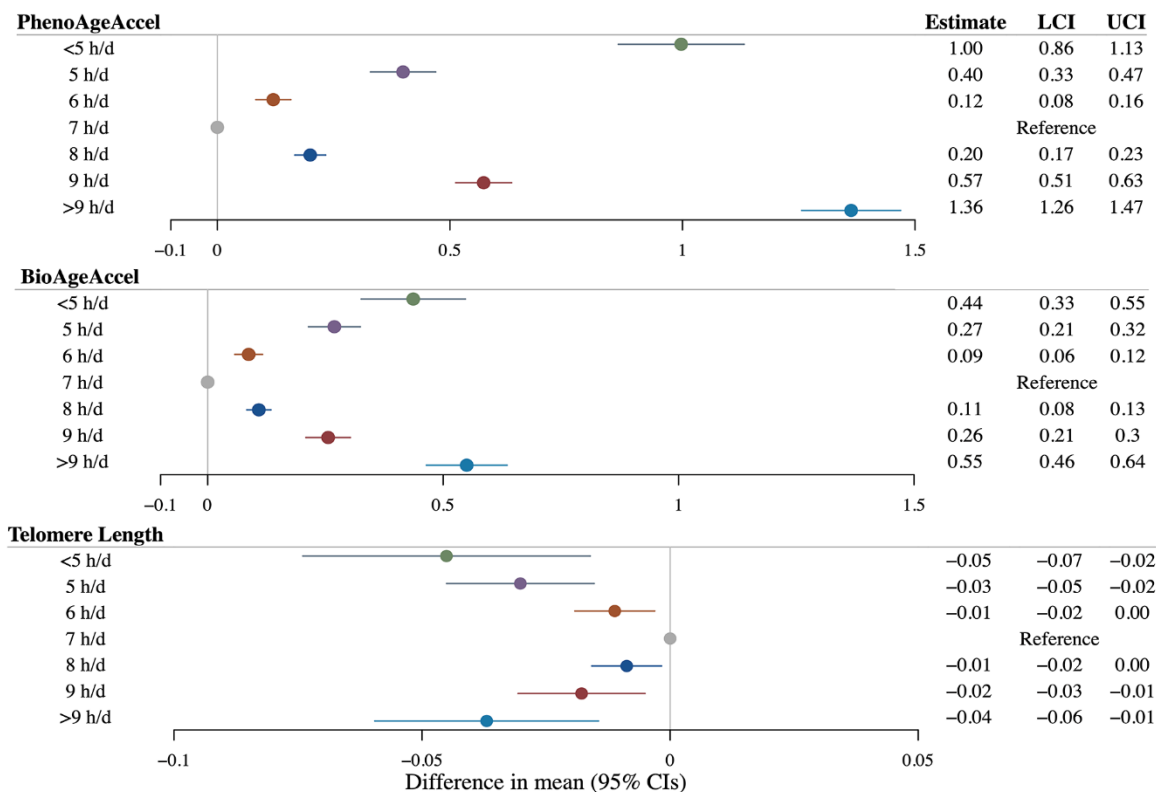
Figure 3. Results of multivariable linear regressions of PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length on sleep duration. Circles denote point estimates. Error bars denote 95% confidence intervals. Regression models adjusted for: age at baseline, sex, the top five genetic principal components, educational qualifications, body mass index, smoking history, drinking history, physical activity status, leucocyte count (for telomere length as an outcome), and histories of cardiovascular diseases, hypertension, and diabetes mellitus.

Sensitivity analyses incorporating additional confounders or utilizing a reconstructed GRS largely recapitulated the primary results (Supplementary Tables 11, 12).

Cell-type-specific heritability enrichments

Functional annotation analyses further revealed extensively distributed heritability enrichments for sleep duration phenotypes, predominantly in cell types of the CNS, as well as in other components related to blood/immune, pancreas, and musculoskeletal/connective tissues. Comparing the heritability enrichments between sleep duration and biological age measurements, we found that both short sleep (< 7 h/d) and LTL were significantly enriched in the fetal thymus annotation, a component of the blood/immune system. Additionally, short sleep showed significant enrichment in the fetal muscle leg annotation, while BioAgeAccel displayed enrichment in the foreskin fibroblast primary cells annotation, both representing components of the musculoskeletal/connective system. In contrast, no common significant enrichment was identified between long sleep (> 8 h/d) and any of the biological aging outcomes (Supplementary Figure 2).

DISCUSSION

To the best of our knowledge, this is the first phenotypic and genetic analysis that systematically interrogates a nonlinear relationship between sleep duration and accelerated biological aging. Our observational study suggests U-shaped phenotypic associations of sleep duration with PhenoAgeAccel and BioAgeAccel and an inverted reverse J-shaped phenotypic association of sleep duration with LTL, with approximately 7 h/d as the optimal sleep duration. A comprehensive GRS-based MR study further confirmed the detrimental roles of insufficient sleep across all outcomes (in a dose-response manner for PhenoAgeAccel and BioAgeAccel), while finding no evidence to support deleterious impacts of excessive sleep on any of the biological aging measurements.

PhenoAgeAccel

	Estimate	LCI	UCI	P for nonlinearity
Overall population	−0.31	−0.5	−0.12	
Mean duration in each stratum				
5.7 h/d	−1.00	−1.48	−0.51	
6.7 h/d	−0.68	−1.07	−0.30	
7.1 h/d	−0.26	−0.91	0.39	3.75×10^{-5}
7.8 h/d	−0.04	−0.40	0.33	
8.5 h/d	0.27	−0.27	0.81	

BioAgeAccel

	Estimate	LCI	UCI	P for nonlinearity
Overall population	−0.38	−0.53	−0.24	
Mean duration in each stratum				
5.8 h/d	−0.81	−1.17	−0.45	
6.8 h/d	−0.56	−0.88	−0.24	
7.1 h/d	−0.21	−0.74	0.33	3.45×10^{-3}
7.8 h/d	−0.08	−0.37	0.21	
8.5 h/d	−0.26	−0.66	0.15	

Telomere length

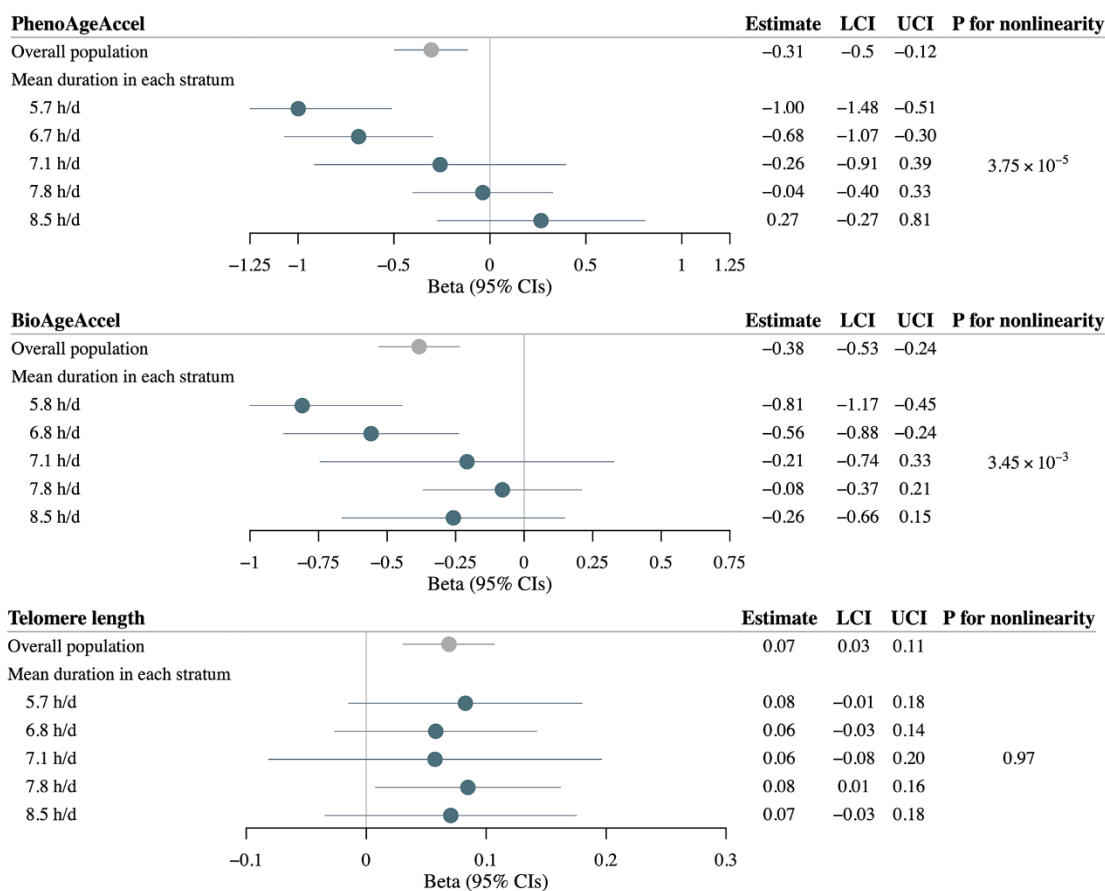|	Estimate	LCI	UCI	P for nonlinearity
Overall population	0.07	0.03	0.11	
Mean duration in each stratum				
5.7 h/d	0.08	−0.01	0.18	
6.8 h/d	0.06	−0.03	0.14	
7.1 h/d	0.06	−0.08	0.20	0.97
7.8 h/d	0.08	0.01	0.16	
8.5 h/d	0.07	−0.03	0.18	

Figure 4. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration. Grey circles denote overall estimates, and blue circles denote stratum estimates. Error bars denote 95% confidence intervals. Models adjusted for: age at baseline, sex, the top five genetic principal components, and genotyping array.

In utilizing various analytical approaches that designed specifically for linear relationships, we found that the direction of the effect estimates for sleep duration on biological age measurements largely differs when comparing the results of linear MR and multivariable linear regressions. Such disparity suggests that evaluating continuous sleep duration as a whole may lead to unreliable findings underscoring the need to consider potential nonlinear effects when studying its health impact.

PhenoAgeAccel and BioAgeAccel, recognized as the best validated measures for biological aging that could also be implemented with data available in the UK Biobank [6, 9, 45], were designed based on different assumptions to capture distinct aspects of the aging process. BioAge models biological age as the average physiology of an individual with the same age as the research subjects [6], while PhenoAge estimates biological age as the average physiology of an individual with the same risk of death as the research subjects [5]. Therefore, the U-shaped relationship between sleep duration and PhenoAgeAccel observed in our observational study aligns with previous findings that a sleep duration of 7 hours represents the optimal duration associated with lowest all-cause and other-cause mortality [46, 47]. However, leveraging robust genetic instruments, our nonlinear MR analyses failed to confirm a causative role of long sleep duration in increasing PhenoAgeAccel, indicating that the observed associations are likely due to residual confounding or/and reverse causation. Indeed, given long sleep itself can be a consequence of underlying health conditions or comorbidities, and that accelerated aging may cause fatigue or other symptoms that lead to increased sleep duration [39], the association between excessive sleep and accelerated biological aging may be more susceptible to these common limitations inherent in conventional observational studies. Notably, such disagreement between observational and MR findings was consistently observed for PhenoAgeAccel and BioAgeAccel, providing reassurance that the associations reflect genuine biological aging rather than artifacts specific to a particular method of biological age measurement.

Previous observational studies have demonstrated a detrimental role of both insufficient and excessive sleep in PhenoAgeAccel/BioAgeAccel. For example, a study involving 615 participants from the Baltimore Longitudinal Study of Aging reported significantly lower DNA methylation-based PhenoAge among individuals sleeping ≤ 6 h/d compared to those sleeping > 7 h/d [17]. Another study involving 29,309 participants from the Korean NHANES V-VI found significantly higher metabolism diagnostic parameters-

based BioAgeAccel among individuals who sleep > 8 h/d compared to those sleeping between 6 to 8 h/d [15]. It is important to note that these previous studies, like many others investigating sleep duration, employed a block classification of "short" and "long" sleep duration that imposed a linear relationship between aging and more or less sleep around a chosen cut-off (e.g., 6, 7, or 8 h/d). This approach, coupled with relatively small sample sizes, limited their ability to detect the impact of different duration patterns or the magnitude of effects associated with more extreme sleep durations. Building upon previous findings, our work based on triangulated evidence supporting that an insufficient sleep duration (defined as < 7 h/d) may exert increasingly pronounced detrimental effects on accelerated biological aging as sleep insufficiency becomes more severe.

While PhenoAge and BioAge aim to capture integrated multi-system dysregulation during aging, LTL and its natural shortening primarily reflect cellular proliferative capacity [31]. To date, epidemiological evidence regarding the relationship of sleep duration and telomere length has remained highly inconclusive. As one of the pioneering studies in this field, an investigation involving 4,117 female participants from the Nurses' Health Study reported a positive association between sleep duration (9 h/d compared to ≤ 6 h/d) and LTL [18]. However, a separate study with 245 women reported no significant association [19]. Similar mixed results have further been reported in samples of both men and women [13, 14], particularly regarding long sleep duration, which has been linked to both significantly longer [20] and shorter telomere length [21]. A previous exploratory study involving 154 participants indicated a U-shaped association between sleep duration and telomere length [22], which was recapitulated by our large-scale multivariable linear regressions. Nonetheless, stratified MR findings again indicate no causative role of excessive sleep in shortening LTL. Unlike the nonlinear relationships identified for the composite biological age measurements, the stratum estimates for LTL were more consistent across strata and centered around the population-averaged estimate, suggesting a linear effect. While such discrepancy may support the notion that these measurements capture different hallmarks of aging [48], additional investigations are warranted to corroborate our findings and provide deeper insights into the reasons behind the distinct associations observed.

Through the integration of genomics and epigenomics data, our study reveals genetic similarities between short sleep and BioAgeAccel in the musculoskeletal system, as well as between short sleep and LTL in the immune system, providing additional evidence for

potential shared genetic mechanisms that contribute to these causal links. Sleep plays a crucial role in connective tissue repair and muscle growth [49], and inadequate sleep has been associated with increased risks of muscle mass reduction and functional decline commonly observed during aging [50]. Moreover, laboratory studies have demonstrated that both acute and chronic sleep loss can have an impact on a wide range of immune function [51]. The immune system is intricately connected to telomere shortening, as its proper functioning relies on the renewal and clonal expansion of T- and B-cell populations [52]. Emerging evidence suggests that immune dysfunctions also contribute to telomere and telomerase deficiency [52]. Taken together, our findings, along with the previous research, support the hypothesis that insufficient sleep adversely affects the musculoskeletal system and immune function, consequently accelerating biological aging. To gain a deeper understanding of these hypothesized mechanisms, future in-depth experimental studies are needed.

A notable strength of our study lies in the comprehensive interrogation of potential sex-heterogeneous effects of sleep duration on biological aging, revealing that short sleep duration accelerates aging more prominently in men than women. This finding aligns with prior research indicating that men are more susceptible to immunosenescence, inflammaging, and higher mortality risk at comparable frailty levels [38]. Importantly, while prior work reported sex-specific association between sleep duration and LTL in men [53], our findings extend this by demonstrating that sufficient sleep slows biological aging in both sexes. Similarly, our age-stratified analyses indicate that insufficient sleep accelerates biological aging in both younger (< 58 years) and older (≥58 years) adults, with a seemingly more pronounced effect observed in the younger group. This is consistent with evidence that younger individuals typically require longer sleep durations and demonstrate reduced resilience to acute sleep deprivation compared to their older counterparts [54]. Overall, these findings emphasize the importance of adequate sleep duration for healthy aging across the population, with particular attention to the needs of men and younger adults. Nevertheless, validation in larger, independent cohorts is necessary before these subgroup findings can inform clinical recommendations.

Several limitations need to be acknowledged. Our sample only comprises individuals of White European ethnic background, necessitating future investigations to ensure the generalizability of findings across diverse racial or ethnic groups. Additionally, the potential presence of a healthy volunteer bias within the UK Biobank may introduce a null bias, given the anticipated lower age

accelerations relative to the general UK population. Sleep duration was assessed using a single self-administrated question in the UK Biobank. However, the potential for misclassification error is unlikely to influence our MR estimates as sleep duration is measured in 1-hour increments [55]. Future studies with objective sleep measures are essential to validate our findings. Our study specifically examined telomere length measurements in leukocytes, and further research is needed to determine how well these measurements reflect telomere length in other organ tissues. Finally, it is important to recognize the cross-sectional design of our observational study and approach the interpretation of causality between sleep duration and aging with caution. While MR offers some potential for causal inference, it relies on several assumptions [23] that we have tried to scrutinize, albeit residual uncertainty inevitably remains. For example, it remains possible that some genetic instruments exert direct effects on biological aging, which would violate the exclusion restriction assumption.

CONCLUSIONS

Taken together, our study, utilizing extensive phenotypic, genomic, and epigenomic data, consistently demonstrates a significant association between insufficient sleep duration and increased acceleration of biological aging, as indicated by PhenoAgeAccel, BioAgeAccel, and LTL measurements. Further investigation is needed to determine if long sleep is a causal risk factor for accelerating biological aging. Findings suggest that interventions aimed at addressing insufficient sleep may serve as a pathway towards alleviating the burden of aging.

AUTHOR CONTRIBUTIONS

X.W and X.J. conceptualized the study. X.W. and X.Z. performed the primary analyses with the assistance of S.B., A.G., Z.H., C.H., Y.H., J.X., and M.F. X.W. wrote the manuscript with significant input and comments from X.J., S.B., X.Z., A.G., Z.H., C.H., Y.H., M.F., J.X., and J.L. X.J., J.L., and S.B. supervised the study. All authors contributed to interpreting the findings and critically revising the manuscript.

CONFLICTS OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

ETHICAL STATEMENT AND CONSENT

UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382). The original GWAS studies used in this research

obtained ethical approval from relevant ethics review committees. The written informed consent was obtained from all participants. This study utilizes GWAS summary statistics, which are aggregated data and do not contain any personal information.

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Supplementary Figures
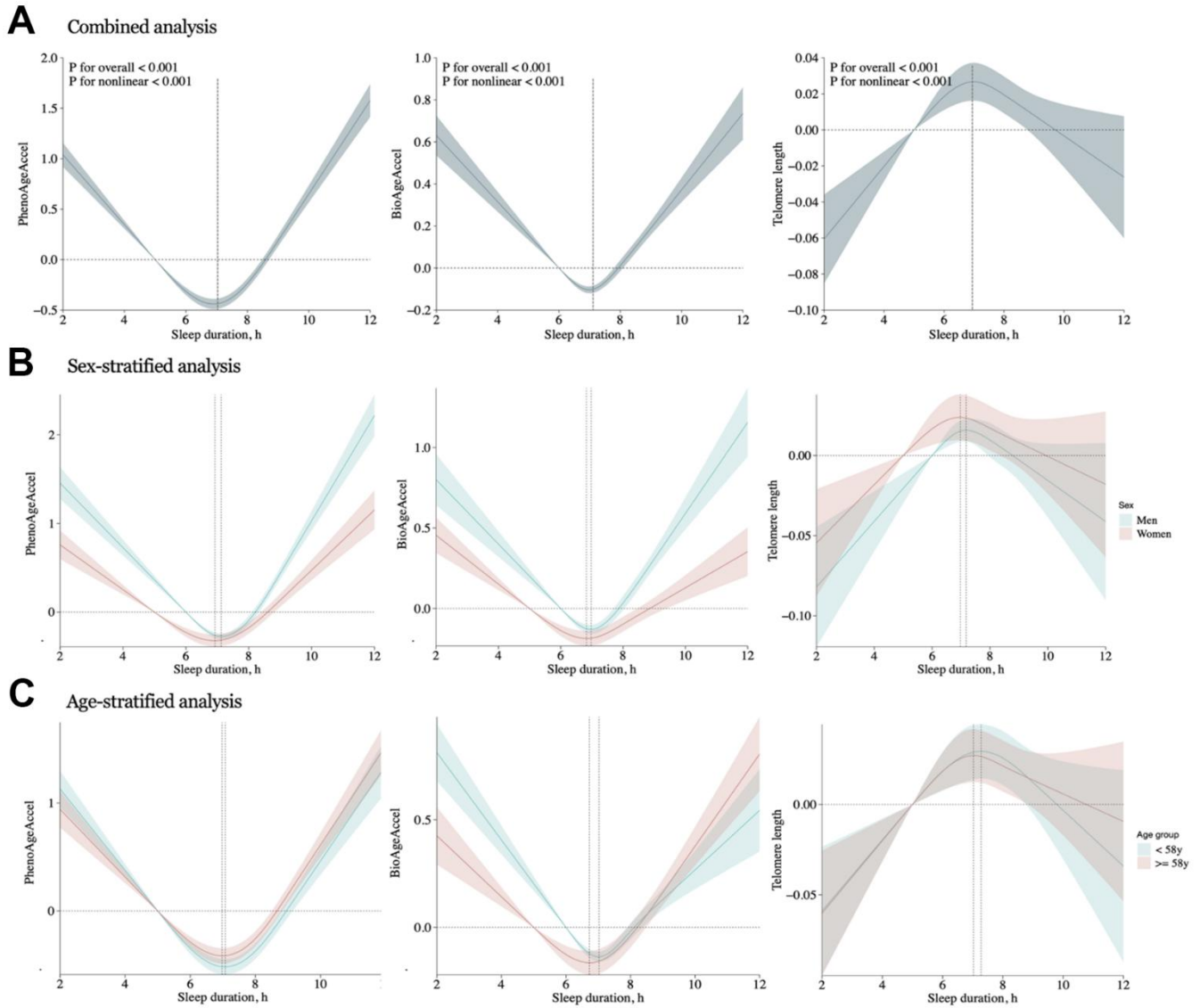
Supplementary Figure 1. Results of restricted cubic spline regressions of PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length on sleep duration. Models adjusted for, where appropriate, age at baseline, sex, the top five genetic principal components, educational qualifications, body mass index, smoking history, drinking history, physical activity status, leucocyte count (for telomere length as an outcome), and histories of cardiovascular diseases, hypertension, and diabetes mellitus. (**A**) Combined analysis, (**B**) Sex-stratified analysis, (**C**) Age-combined analysis.

A DNase

B H3K27ac

C H3K36me3

D H3K4me1

E H3K4me3
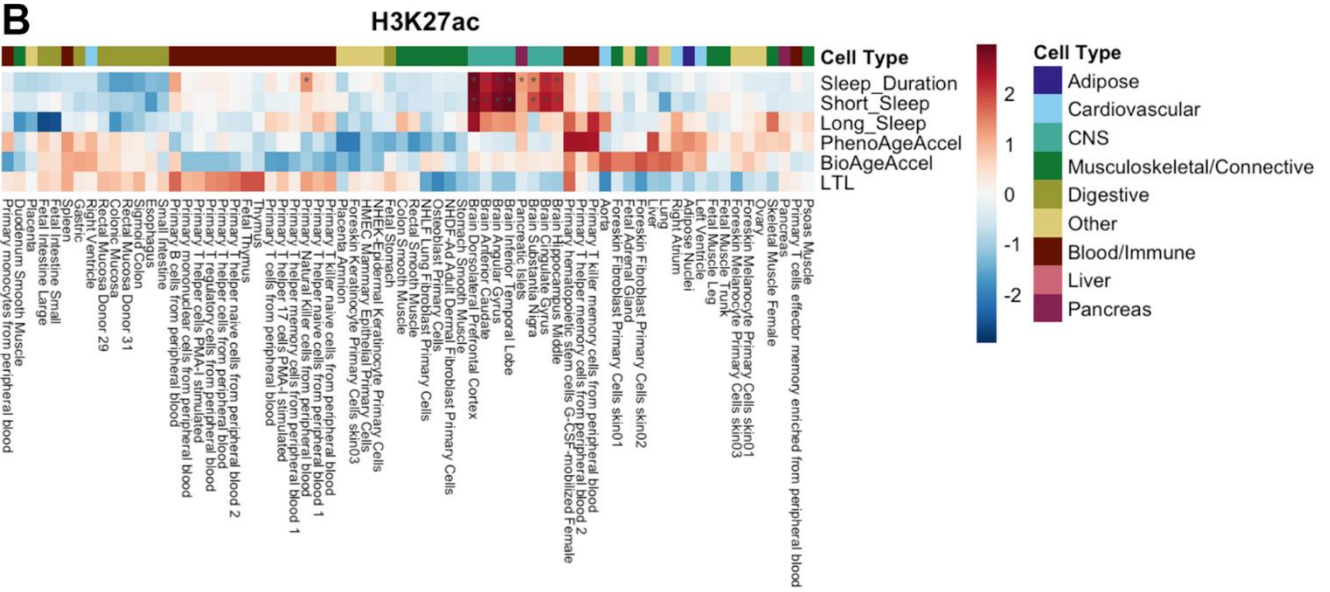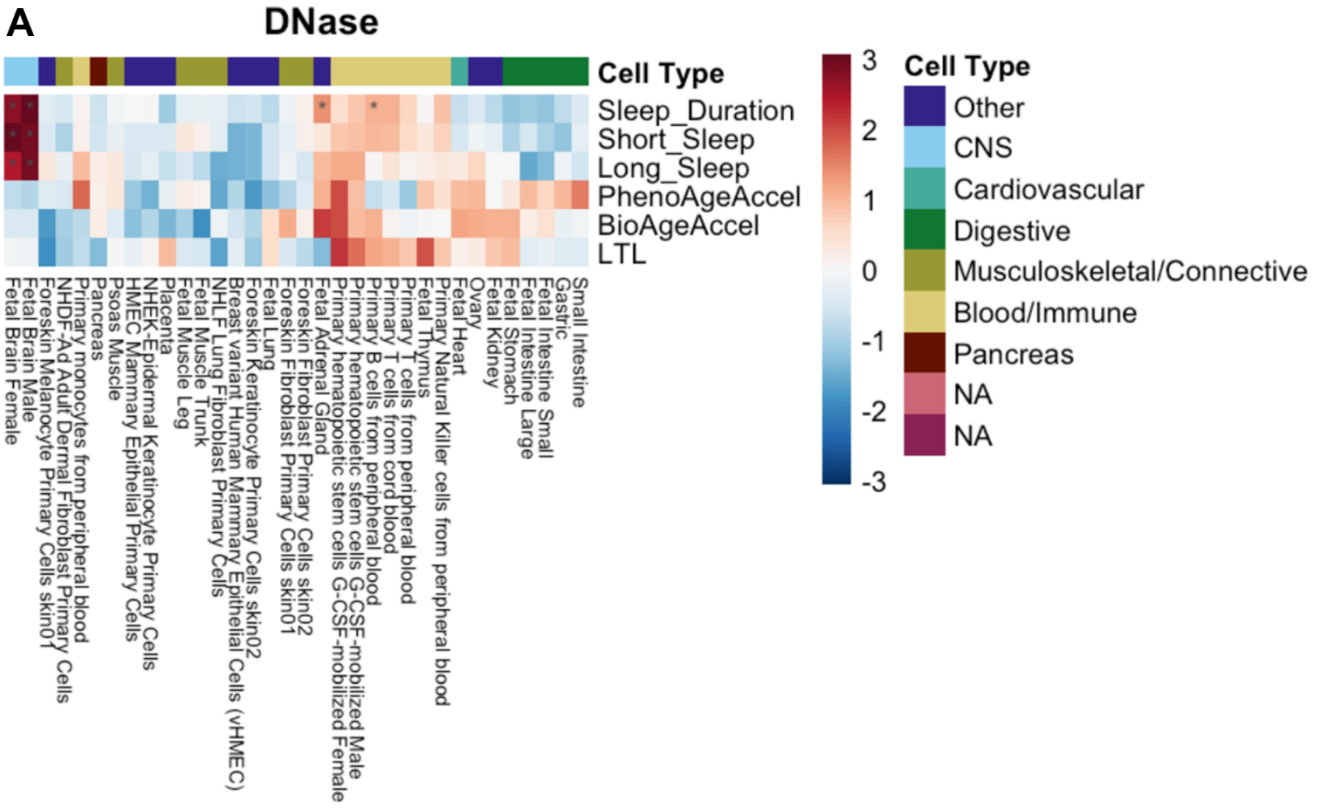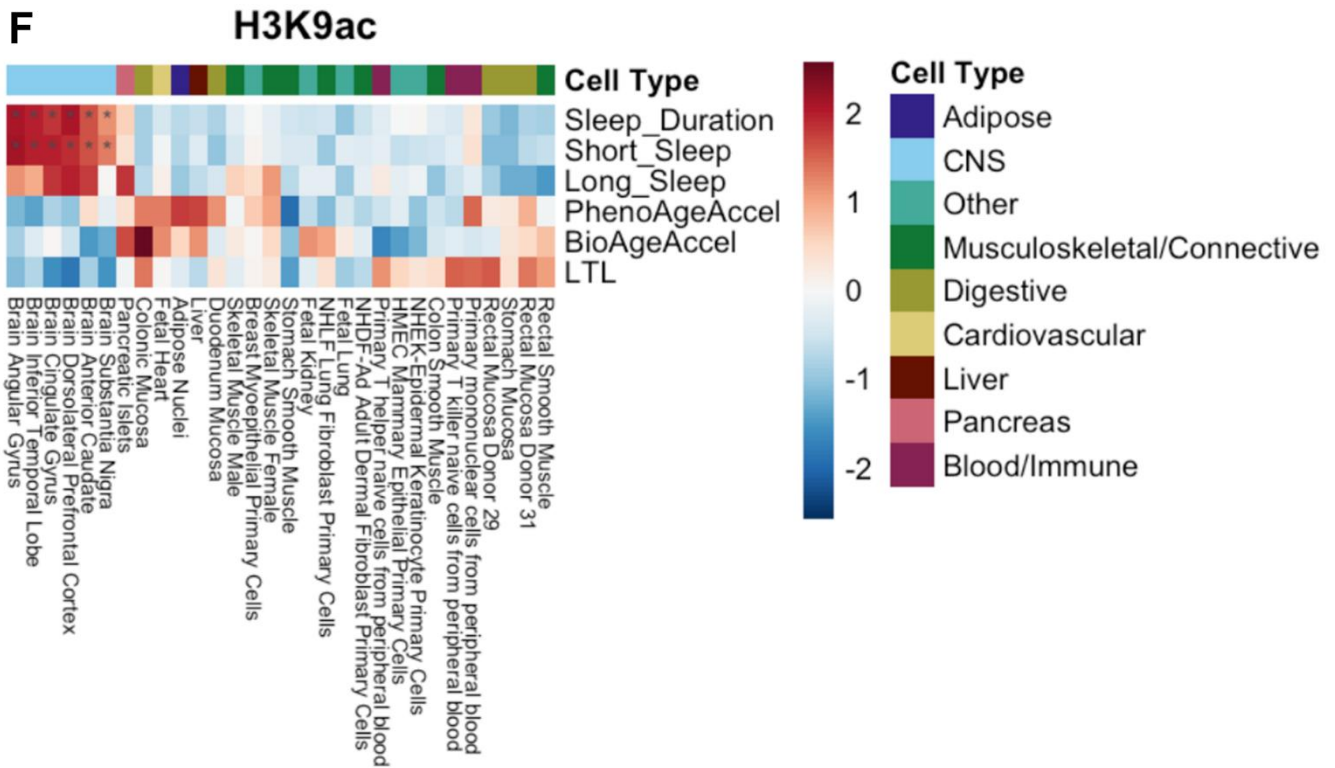
Supplementary Figure 2. Clustering of cell-type-specific annotation for sleep duration phenotypes and biological age measurements over histone marks. Each colored square reflects the z-score, scaled by traits. Red indicates enrichment, blue indicates depletion. Deeper color represents stronger magnitude of effects. Asterisks represent statistical significance withstanding correction (FDR-adjusted *P*-value < 0.05). (**A**). DNase, (**B**). H3K27ac, (**C**). H3K36me3, (**D**). H3K4me1, (**E**). H3K4me3, and (**F**). H3K9ac. PhenoAgeAccel: PhenoAge acceleration; BioAgeAccel: BioAge acceleration; LTL: leucocyte telomere length.

Supplementary Tables

Please browse Full Text version to see the data of Supplementary Tables 6 to 12.

Supplementary Table 1. Full names and field IDs of variables included in the current study.

Phenotypes	Labels in the current study	Full name in UK Biobank data dictionary	UK Biobank Field ID
Sleep duration	Sleep duration (h/d)	Sleep duration	1160
Components of biological ages	FEV$_1$ (L)	Forced expiratory volume in 1-second (FEV$_1$) (litres)	3063
	SBP (mm Hg)	Systolic blood pressure, automated reading (mm Hg)	4080
	Total Cholesterol (mg/dL)	Cholesterol (mmol/L)	30690
	Glycated hemoglobin (%)	Glycated haemoglobin (HbA1c) (mmol/mol)	30750
	Blood urea nitrogen (mg/dL)	Urea (mmol/L)	30670
	Lymphocyte (%)	Lymphocyte percentage (%)	30180
	Mean cell volume (fL)	Mean sphered cell volume (femtolitres)	30270
	Serum glucose (mmol/L)	Glucose (mmol/L)	30740
	Red cell distribution width (%)	Red blood cell (erythrocyte) distribution width (%)	30070
	White blood cell count (1000 cells/uL)	White blood cell (leukocyte) count (10^9 cells/Litre)	30000
	Albumin (g/L)	Albumin (g/L)	30600
	Creatinine (umol/L)	Creatinine (umol/L)	30700
	C-reactive protein (mg/dL)	C-reactive protein (mg/L)	30710
	Alkaline phosphatase (U/L)	Alkaline phosphatase (U/L)	30610
Leucocyte telomere length	Leucocyte telomere length	Z-standardized leucocyte telomere length values (LTL)	22192

Supplementary Table 2. Characteristics on genetic variants used for construction of polygenic risk score of self-reported sleep duration.

SNP	Chromosome	Base pair	Effect Allele	Reference Allele	BETA	EAF	Pleiotropic phenotypes
rs915416	1	34731984	C	G	0.0192587	0.289947	
rs269054	1	57864304	T	A	-0.0136431	0.577924	
rs61796569	1	66476437	C	T	-0.0154442	0.730417	
rs12567114	1	98527951	G	A	-0.0148307	0.724198	
rs62120041	2	9185564	T	C	0.0261113	0.933902	
rs374153	2	40382712	C	T	0.0176119	0.158085	
rs2717076	2	58061127	C	T	-0.0184107	0.372584	
rs75539574	2	58871658	A	C	-0.0362482	0.914208	
rs72804080	2	59358659	A	G	-0.0177935	0.850072	
rs7556815	2	114085785	G	A	-0.0407248	0.780856	
rs12611523	2	139195328	A	G	0.0126347	0.545244	
rs35662245	2	147583187	T	A	-0.0145968	0.661256	Schizophrenia
rs4538155	2	157040773	C	T	-0.0129753	0.352574	
rs11885663	2	166944004	C	T	-0.0162176	0.752191	
rs10173260	2	210377845	T	C	-0.0128368	0.393765	
rs112230981	3	55879269	A	G	0.0315275	0.94984	
rs17732997	3	70470834	C	G	0.0129345	0.569098	
rs7644809	3	107564459	T	C	0.0130621	0.421606	
rs13088093	3	135838598	T	G	-0.0162722	0.663683	
rs7616632	3	137031237	T	G	0.0132035	0.522135	Intelligence
rs2192528	4	18327896	A	G	0.0133687	0.480065	
rs17427571	4	82254908	A	G	0.0138255	0.684313	
rs35531607	4	92533225	T	C	-0.0128402	0.525917	
rs13109404	4	102896591	T	G	0.0312035	0.928024	
rs365663	5	1428883	A	G	0.0146291	0.545963	
rs460692	5	3126584	C	T	0.0210557	0.137484	
rs56372231	5	102321905	C	T	-0.0169439	0.665907	
rs180769	5	135615615	T	C	0.0127243	0.424698	
rs11567976	5	137654218	C	T	-0.0128042	0.429092	
rs151014368	5	176751059	G	A	-0.0160924	0.793742	
rs72838268	6	27021173	A	G	0.0167192	0.77265	
rs34556183	6	28584775	A	G	0.0169228	0.719606	
rs1633005	6	29764472	C	T	0.0174716	0.791845	Sarcoidosis
rs80193650	6	33464363	A	G	-0.0168389	0.837534	
rs113113059	6	43160375	T	C	0.0161406	0.78	
rs9382445	6	54937974	T	C	0.014536	0.62305	
rs2231265	6	89790201	A	G	-0.014955	0.227711	
rs9345234	6	93162639	A	C	-0.0130117	0.421984	
rs34731055	7	2106928	C	T	-0.0194603	0.81911	
rs2079070	7	114126432	C	G	0.0175475	0.264613	
rs7806045	7	132610266	T	C	0.0147916	0.754703	
rs330088	8	9149746	T	C	-0.0144687	0.452988	
rs4333549	8	10979561	C	G	0.0139369	0.47293	
rs73219758	8	14279446	G	A	0.0164012	0.708064	
rs10973207	9	37100525	G	T	-0.0204339	0.842323	
rs1776776	9	140497072	T	C	0.019963	0.873832	
rs12246842	10	21830580	A	G	0.0133949	0.459815	
rs10761674	10	64618340	C	T	0.0123329	0.477334	
rs11190970	10	103128332	G	A	0.015379	0.798661	
rs7915425	10	125016501	T	C	0.0190638	0.174682	Neutropenia, response to gemcitabine, pancreatic carcinoma
rs1517572	11	28829882	A	C	-0.0146443	0.419464	
rs4592416	11	43800474	A	G	-0.0146828	0.535593	
rs11039544	11	48173412	G	A	0.018389	0.837779	
rs174560	11	61581764	T	C	-0.0135751	0.685785	Chronic kidney disease, serum metabolite measurement
rs12791153	11	80685181	A	T	-0.0235481	0.918911	
rs1553132	11	88297740	A	G	-0.0145068	0.741567	

rs1939455	11	101520886	G	T	0.0204253	0.879446	
rs1079727	11	113289182	T	C	-0.0182922	0.842182	
rs7115462	11	113408517	G	A	-0.0265639	0.92647	
rs1263056	11	116576415	A	G	0.0127992	0.519099	
rs7951019	11	118358027	T	G	-0.0368792	0.967773	
rs3751046	11	122828342	A	G	-0.0194129	0.853507	
rs34354917	12	38764559	C	A	0.0137464	0.710472	
rs11614986	12	110007939	A	G	0.016379	0.820952	
rs4767550	12	117951150	A	G	-0.0143001	0.585862	
rs6575005	14	26954078	T	C	0.0155637	0.757854	
rs10483350	14	29816155	A	G	-0.017369	0.804582	
rs61985058	14	60233841	C	T	-0.0185938	0.856824	
rs55658675	14	65554638	C	T	0.0131415	0.644938	
rs11621908	14	78495761	C	T	0.0240951	0.917141	
rs8038326	15	47989799	A	G	0.0159204	0.72691	
rs3095508	16	6550400	C	A	0.0153518	0.593529	
rs11643715	16	23909538	C	G	-0.013895	0.709058	
rs9937053	16	53799507	G	A	0.0169348	0.576695	
rs8050478	16	56120461	G	A	0.0160009	0.500253	
rs7503199	17	8134275	C	T	0.0147449	0.734267	
rs205024	17	11227352	C	T	-0.0138261	0.616265	
rs8072993	17	21335627	T	G	-0.0174776	0.363492	
rs147114641	17	43581015	C	A	0.0159801	0.773722	
rs2696429	17	44335274	G	A	0.0168884	0.773626	
rs9895274	17	45539117	C	T	0.0133426	0.510408	
rs9903973	17	50571227	C	T	0.0127747	0.46702	
rs12607679	18	53059748	T	C	0.0201387	0.737717	
rs10421649	19	9942262	T	A	-0.0132975	0.44303	
rs2072727	20	43538733	T	C	0.0132425	0.43617	Chronotype measurement

Supplementary Table 3. Descriptive statistics for UK Biobank participants of European ancestry (N = 317,723) included in the main analyses of sleep duration and PhenoAge acceleration, according to self-reported sleep duration.

Characteristics	All	Short sleep, <6 h/d	Intermediate sleep, 6-8 h/d	Long sleep, >8 h/d
No. of participants	384,490	19,928	335,202	29,360
Sleep duration, h/d	7.16 (1.08)	4.76 (0.52)	7.12 (0.73)	9.30 (0.64)
Age at recruitment, y	56.8 (8.02)	57.2 (7.70)	56.6 (8.03)	58.8 (7.90)
Sex (women), n (%)	206642 (53.7%)	11162 (56.0%)	179092 (53.4%)	16388 (55.8%)
Education				
Degree, n (%)	315151 (82.7%)	13978 (71.2%)	279810 (84.2%)	21363 (73.6%)
No degree, n (%)	66008 (17.3%)	5651 (28.8%)	52683 (15.8%)	7674 (26.4%)
Body mass index, kg/m2	27.4 (4.75)	28.5 (5.45)	27.3 (4.66)	28.1 (5.09)
Smoking status				
Never, n (%)	206510 (53.9%)	9732 (49.1%)	182171 (54.5%)	14607 (50.0%)
Previous, n (%)	136638 (35.7%)	6996 (35.3%)	118480 (35.5%)	11162 (38.2%)
Current, n (%)	40062 (10.5%)	3094 (15.6%)	33501 (10.0%)	3467 (11.9%)
Drinking status				
Never, n (%)	12340 (3.21%)	1036 (5.21%)	10017 (2.99%)	1287 (4.39%)
Previous, n (%)	13271 (3.45%)	1290 (6.49%)	10479 (3.13%)	1502 (5.12%)
Current, n (%)	358575 (93.3%)	17560 (88.3%)	314470 (93.9%)	26545 (90.5%)
IPAQ activity group				
High, n (%)	126921 (40.5%)	6218 (41.0%)	111974 (40.8%)	8729 (37.2%)
Moderate, n (%)	127813 (40.8%)	5507 (36.3%)	112751 (41.1%)	9555 (40.8%)
Low, n (%)	58433 (18.7%)	3429 (22.6%)	49854 (18.2%)	5150 (22.0%)
Major diseases				
Cardiovascular disease, n (%)	22051 (5.74%)	1879 (9.45%)	17307 (5.17%)	2865 (9.78%)
Hypertension, n (%)	103404 (26.9%)	6797 (34.2%)	86839 (25.9%)	9768 (33.3%)
Diabetes mellitus, n (%)	18386 (4.79%)	1420 (7.16%)	14568 (4.35%)	2398 (8.19%)
Component of biological age				
Lymphocyte (%)	28.7 (7.34)	28.3 (7.54)	28.7 (7.31)	28.2 (7.56)
Mean cell volume (fL)	82.9 (5.25)	83.0 (5.52)	82.8 (5.20)	83.2 (5.59)
Serum glucose (mmol/L)	5.11 (1.21)	5.21 (1.42)	5.10 (1.16)	5.26 (1.51)
Red cell distribution width (%)	13.5 (0.95)	13.6 (1.08)	13.5 (0.93)	13.6 (1.04)
White blood cell count (1000 cells/uL)	6.89 (1.93)	7.14 (1.99)	6.85 (1.91)	7.13 (2.11)
Albumin (g/L)	45.2 (2.61)	45.1 (2.69)	45.3 (2.59)	45.0 (2.67)
Creatinine (umol/L)	72.2 (16.2)	71.7 (18.3)	72.2 (15.8)	73.3 (19.4)
C-reactive protein (mg/dL)	0.26 (0.44)	0.32 (0.50)	0.25 (0.42)	0.32 (0.51)
Alkaline phosphatase (U/L)	83.5 (26.1)	88.2 (30.1)	82.9 (25.6)	86.7 (28.8)
Biological ages, y				
PhenoAge	50.8 (9.42)	**52.0 (9.30)**	50.4 (9.34)	**53.7 (9.82)**
PhenoAge acceleration	0.00 (4.66)	**0.80 (5.39)**	-0.12 (4.53)	**0.87 (5.39)**

Baseline characteristics of UK Biobank participants were presented as mean values (standard deviation) for continuous variables and n (%) for categorical variables.

Supplementary Table 4. Descriptive statistics for UK Biobank participants of European ancestry (N = 317,723) included in the main analyses of sleep duration and BioAge acceleration, according to self-reported sleep duration.

Characteristics	All	Short sleep, <6 h/d	Intermediate sleep, 6-8 h/d	Long sleep, >8 h/d
No. of participants	317,723	15,821	278,440	23,462
Sleep duration, h/d	7.16 (1.06)	4.78 (0.51)	7.12 (0.73)	9.28 (0.62)
Age at recruitment, y	56.6 (8.04)	57.0 (7.76)	56.4 (8.04)	58.7 (7.97)
Sex (women), n (%)	171835 (54.1%)	8961 (56.6%)	149596 (53.7%)	13278 (56.6%)
Education				
Degree, n (%)	263167 (83.5%)	11368 (72.8%)	234480 (84.9%)	17319 (74.6%)
No degree, n (%)	51954 (16.5%)	4238 (27.2%)	41827 (15.1%)	5889 (25.4%)
Body mass index, kg/m2	27.3 (4.67)	28.4 (5.29)	27.2 (4.59)	27.9 (5.00)
Smoking status				
Never, n (%)	172605 (54.5%)	7923 (50.4%)	152827 (55.1%)	11855 (50.7%)
Previous, n (%)	112269 (35.5%)	5575 (35.4%)	97811 (35.2%)	8883 (38.0%)
Current, n (%)	31820 (10.0%)	2236 (14.2%)	26954 (9.71%)	2630 (11.3%)
Drinking status				
Never, n (%)	10002 (3.15%)	788 (4.99%)	8216 (2.95%)	998 (4.26%)
Previous, n (%)	10414 (3.28%)	956 (6.06%)	8336 (3.00%)	1122 (4.79%)
Current, n (%)	297067 (93.6%)	14040 (89.0%)	261702 (94.1%)	21325 (91.0%)
IPAQ activity group				
High, n (%)	106018 (40.9%)	5080 (41.9%)	93744 (41.0%)	7194 (38.3%)
Moderate, n (%)	105833 (40.8%)	4414 (36.4%)	93756 (41.0%)	7663 (40.8%)
Low, n (%)	47654 (18.4%)	2623 (21.6%)	41091 (18.0%)	3940 (21.0%)
Major diseases				
Cardiovascular disease, n (%)	16096 (5.07%)	1260 (7.98%)	12804 (4.60%)	2032 (8.68%)
Hypertension, n (%)	82698 (26.1%)	5178 (32.8%)	69991 (25.2%)	7529 (32.2%)
Diabetes mellitus, n (%)	14409 (4.54%)	1044 (6.63%)	11570 (4.16%)	1795 (7.67%)
Component of biological age				
FEV_1 (L)	2.85 (0.80)	2.71 (0.81)	2.87 (0.80)	2.68 (0.75)
SBP (mm Hg)	138 (18.5)	138 (18.3)	138 (18.4)	139 (19.0)
Total Cholesterol (mg/dL)	221 (43.9)	222 (45.5)	221 (43.5)	220 (47.1)
Glycated hemoglobin (%)	3.58 (0.63)	3.67 (0.72)	3.57 (0.61)	3.67 (0.76)
Blood urea nitrogen (mg/dL)	15.2 (3.82)	15.2 (4.10)	15.1 (3.76)	15.5 (4.27)
Albumin (g/L)	45.3 (2.59)	45.2 (2.66)	45.3 (2.58)	45.1 (2.65)
Creatinine (umol/L)	72.2 (17.1)	71.5 (18.8)	72.2 (16.4)	73.3 (23.7)
C-reactive protein (mg/dL)	0.25 (0.41)	0.30 (0.46)	0.24 (0.40)	0.30 (0.48)
Alkaline phosphatase (U/L)	83.0 (25.9)	87.4 (29.5)	82.5 (25.4)	85.9 (28.3)
Biological ages, y				
BioAge	53.9 (8.67)	**54.9 (8.36)**	**53.7 (8.65)**	**56.5 (8.59)**
BioAge acceleration	0.00 (3.31)	**0.61 (3.47)**	**-0.08 (3.28)**	**0.49 (3.49)**

Baseline characteristics of UK Biobank participants were presented as mean values (standard deviation) for continuous variables and n (%) for categorical variables.

Supplementary Table 5. Descriptive statistics for UK Biobank participants of European ancestry (N = 442,664) included in the main analyses of sleep duration and telomere length, according to self-reported sleep duration.

Characteristics	All	Short sleep, <6 h/d	Intermediate sleep, 6-8 h/d	Long sleep, >8 h/d
No. of participants	442,664	23,030	385,786	33,848
Sleep duration, h/d	7.16 (1.08)	4.76 (0.52)	7.12 (0.73)	9.30 (0.64)
Age at recruitment, y	56.8 (8.03)	57.2 (7.71)	56.6 (8.03)	58.8 (7.90)
Sex (women), n (%)	239936 (54.2%)	12977 (56.3%)	207921 (53.9%)	19038 (56.2%)
Education				
Degree, n (%)	363075 (82.7%)	16186 (71.3%)	322253 (84.2%)	24636 (73.6%)
No degree, n (%)	75785 (17.3%)	6501 (28.7%)	60436 (15.8%)	8848 (26.4%)
Body mass index, kg/m2	27.4 (4.76)	28.5 (5.47)	27.3 (4.67)	28.1 (5.13)
Smoking status				
Never, n (%)	237954 (53.9%)	11218 (49.0%)	209880 (54.6%)	16856 (50.0%)
Previous, n (%)	157078 (35.6%)	8075 (35.3%)	136152 (35.4%)	12851 (38.1%)
Current, n (%)	46137 (10.5%)	3611 (15.8%)	38519 (10.0%)	4007 (11.9%)
Drinking status				
Never, n (%)	14243 (3.22%)	1204 (5.24%)	11541 (2.99%)	1498 (4.43%)
Previous, n (%)	15299 (3.46%)	1496 (6.51%)	12062 (3.13%)	1741 (5.15%)
Current, n (%)	412778 (93.3%)	20280 (88.3%)	361920 (93.9%)	30578 (90.4%)
IPAQ activity group				
High, n (%)	146179 (40.5%)	7155 (40.9%)	128972 (40.8%)	10052 (37.3%)
Moderate, n (%)	147130 (40.8%)	6340 (36.3%)	129825 (41.1%)	10965 (40.7%)
Low, n (%)	67260 (18.7%)	3989 (22.8%)	57324 (18.1%)	5947 (22.1%)
Major diseases				
Cardiovascular disease, n (%)	25440 (5.76%)	2207 (9.61%)	19903 (5.17%)	3330 (9.86%)
Hypertension, n (%)	118845 (26.9%)	7889 (34.3%)	99691 (25.9%)	11265 (33.4%)
Diabetes mellitus, n (%)	21267 (4.81%)	1667 (7.27%)	16815 (4.37%)	2785 (8.25%)
White blood cell (leukocyte) count, 10^9 cells/Litre	6.90 (2.04)	7.15 (1.98)	6.86 (2.03)	7.14 (2.21)
Z-standardized leucocyte telomere length values	-0.01 (0.99)	-0.07 (0.98)	-0.01 (0.99)	-0.09 (1.01)

Baseline characteristics of UK Biobank participants were presented as mean values (standard deviation) for continuous variables and n (%) for categorical variables.

Supplementary Table 6. Results of multivariable linear regressions of PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length on sleep duration.

Supplementary Table 7. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration among UK biobank men participants.

Supplementary Table 8. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration among UK biobank women participants.

Supplementary Table 9. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration among younger (age < 58 years) UK biobank participants.

Supplementary Table 10. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration among older (age >= 58 years) UK Biobank participants.

Supplementary Table 11. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration after adjusting for additional confounders.

Supplementary Table 12. Mendelian randomization estimates for PhenoAge acceleration (PhenoAgeAccel), BioAge acceleration (BioAgeAccel), and leukocyte telomere length in overall population and strata of population defined by residual sleep duration after excluding potential pleiotropic variants from the genetic risk score.