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Sleep traits causally affect epigenetic age acceleration: a Mendelian randomization study

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Sleep disorders (SDs) are a common issue in the elderly. Epigenetic clocks based on DNA methylation (DNAm) are now considered highly accurate predictors of the aging process and are associated with age-related diseases. This study aimed to investigate the causal relationship between sleep traits and the epigenetic clock using Mendelian randomization (MR) analysis. The genome-wide association study (GWAS) statistics for epigenetic clocks (HannumAge, intrinsic epigenetic age acceleration [IEAA], PhenoAge, and GrimAge) and sleep traits were obtained from the UK Biobank (UKB), 23andMe and Finngen. Moreover, crucial instrumental variables (IVs) were evaluated. Inverse variance weighted (IVW), MR-Egger, weighted median (WM), weighted mode, and simple mode methods were employed to assess the causal relationship between them. Multiple analyses were performed for quality control evaluation. Our study showed that self-reported insomnia may speed up the aging process by GrimAge clock, while GrimAge acceleration could faintly reduce self-reported insomnia. Epigenetic clocks mainly influence sleep traits by PhenoAge and GrimAge with weak effects. This may indicate that early interventions of SDs could be a breaking point for aging and age-related diseases. Further studies are required to elucidate the potential mechanisms involved.

Keywords Sleep disorders, Aging, Epigenetic age acceleration, Mendelian randomization

Abbreviations

CpG	Cytosine-phospho-Guanine
DNAm	DNA methylation
EAA	Epigenetic age acceleration
GDF15	Growth differentiation factor 15
GWAS	Genome-wide association study
HDL	High-density lipoprotein
ICD	The International Classification of Diseases
IEAA	Intrinsic epigenetic age acceleration
IVs	Instrumental variables
IVW	Inverse variance weighted
L5 timing	Least active 5-h timing
LD	Linkage disequilibrium
MR	Mendelian randomization
NF-kB	Nuclear factor kappa B
No. sleep episodes	Number of nocturnal sleep episodes
OR	Odds ratio
OSA	Obstructive sleep apnea
PACKYRS	Smoking pack-years
PRS	Polygenic risk score
SD	Standard deviation
SDs	Sleep disorders

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SNP	Single nucleotide polymorphism
UKB	UK Biobank
WM	Weighted median

Sleep is a neurochemical process regulated by sleep-promoting and arousal centers in the brain. It serves as a vital process that can be energizing and mentally focused, as well as providing opportunities for cellular repair[1]. There are large individual differences in sleep quality, duration, depth, efficiency, and recovery value[2,3]. It has been found that sleep significantly changes as individuals age, both in terms of sleep at the macro level (which includes sleep stages and duration) and sleep at the micro level (which includes the quality of sleep oscillations and number)[4]. A notable decrease in deep sleep with aging was observed, and about half of the elderly (generally considered to be those aged 65 years and above) reported sleep disturbances[5,6]. With the prevalence of unhealthy modern lifestyles and the growing aging population, sleep disorders (SDs) are becoming a common complaint. According to the International Classification of Sleep Disorders, SDs mainly include insomnia, sleep-related breathing disorders, circadian rhythm sleep–wake disorders, central disorders of hypersomnolence, and sleep-related movement disorders. There are numerous studies highlighting the critical role of SDs in a group of age-related conditions such as hypertension, type 2 diabetes, and coronary atherosclerosis[7–9]. As the study develops in depth, researchers not only identified SDs as a risk factor for these diseases but also as a contributing factor in aging.

People born on the same day with the same chronological age may have different biological ages under the influence of different lifestyles, environmental factors, diseases, and so on[10,11]. Given that, previous studies have indicated that biological age is a more accurate indicator of the aging process and how well a person is functioning than their chronological age[12,13]. Epigenetic clocks predict human age accurately based on DNA methylation (DNAm) analysis at particular Cytosine-phospho-Guanine (CpG) sites and are generally regarded as the most promising biomarker for biological aging[14,15].

Epigenetic age acceleration (EAA) was used to describe individuals with greater epigenetic-clock-estimated age than their true chronological age, indicating worse health outcomes[16]. By Hannum et al. and Horvath et al., respectively, the first representative epigenetic clocks (HannumAge and HorvathAge) were constructed. The HannumAge was constructed using CPG markers of whole blood cells, while the HorvathAge was based on 51 human tissues and cell types[17,18]. In addition, the Intrinsic Epigenetic Age Acceleration (IEAA) was also developed from the Horvath Clock and was intended to mitigate the effects of different blood components[19]. The second-generation epigenetic clocks (PhenoAge and GrimAge) tailored to predict biological age and death based on biomarkers, can more accurately link epigenetic alterations with outcomes related to aging[13]. Previous studies elucidate that SDs were a contributing factor for EAA, mitochondrial dysfunction, and inflammation[1,20]. Of particular interest is that biological aging also alters the structure and function of the brain regions that regulate sleep[4]. Since considerable evidence arises from cross-sectional studies, it is still unclear whether SDs modulate the aging process or co-occur with aging. A bidirectional interaction between aging and SDs is also hypothesized.

Mendelian randomization (MR) is a method of used in genetic epidemiology. This method has been used extensively to assess causality and is more effective at controlling for confounding and reverse causality in genome-wide association study (GWAS) data[21]. By using published summary estimates from large and diverse GWAS, MR has greater statistical power to identify causal effects between "exposure" and "outcome"[22,23].

In our study, we carried out a rigorous and detailed analysis to investigate the causal relationship between EAAs and multiple sleep traits, including self-reported phenotypes and objectively measured phenotypes. Our findings may help unravel the relationship between sleep traits and aging, and examine whether the intervention for SDs is a promising prevention for aging.

Materials and methods

Study design

This study conducted a two-sample MR analysis to explore the possible relationship between sleep-related phenotypes and biological aging. As this study was based on existing publications and public databases, there was no need for ethical approval. Figure 1 presents a comprehensive overview of this study's basic principles, design, and procedures.

Study population

All participants in our study were from Europe, and no overlap exists between exposure and outcome GWAS. The characteristics of GWAS employed for this analysis were delineated in Table 1.

Data sources for sleep traits

The GWAS for 13 sleep-related traits was obtained by searching PubMed[24–31]. There were a total of 9 self-reported traits, including sleep duration, long sleep duration, short sleep duration, chronotype, napping, daytime sleepiness, snoring, insomnia, and obstructive sleep apnea (OSA). Except for data for OSA, the summary-level data for 12 sleep traits are acquired from questionnaires and accelerometer estimates. Of note, insomnia is diagnosed as sleep continuity disturbance related to sleepiness, fatigue, and somatic symptoms in the daytime, while sleep continuity disturbance involves sleep latency, total sleep time, wake after sleep onset, number of awakenings, and sleep efficiency. The GWAS for self-reported insomnia (n = 13,31,010), obtained from a questionnaire conducted by UK Biobank (UKB) and 23andMe, mainly reflects on sleep latency and wake after sleep onset of the participant. The summary-level data for other self-reported traits are from UKB, with samples ranging from 408,317 to 452,663[32]. The GWAS data for OSA (n = 217,955) was derived from the

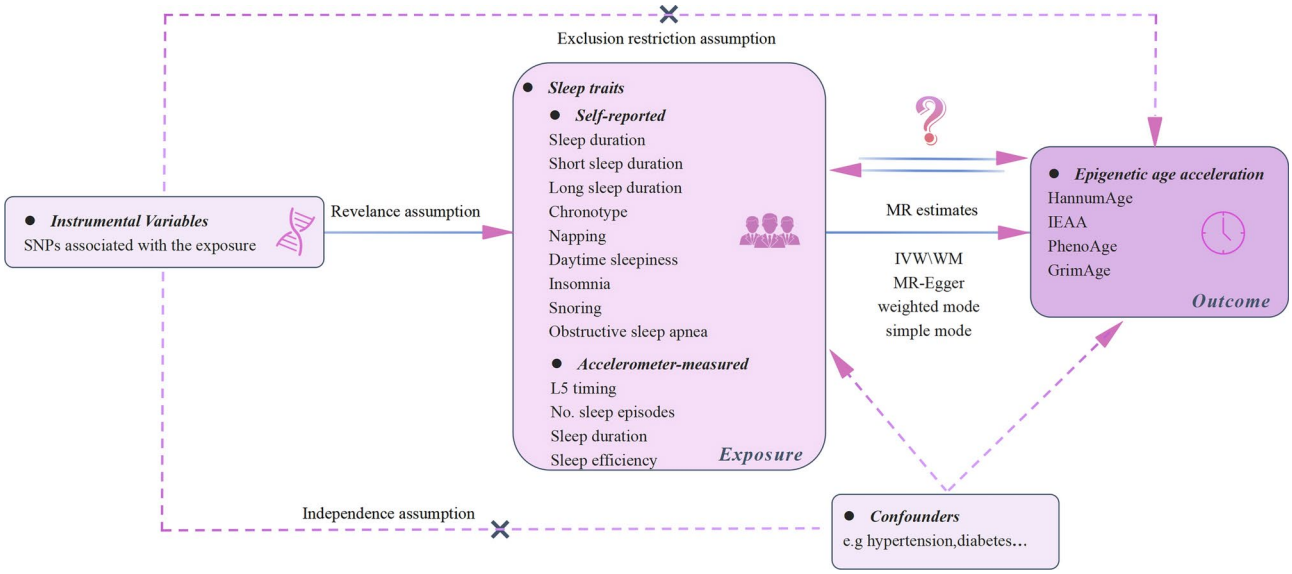

Fig. 1. The overall design of MR analysis in this study. The objective of this two-sample bidirectional MR analysis is to investigate the causality between sleep traits and EAAs. The GWAS meta-analysis utilized in this study is from mixed-sex European cohorts.

FinnGen project, a large-scale nationwide biobank, and the diagnosis was established using the International Classification of Diseases (ICD) 10th edition and 9th edition[30].

Considering the subjectivity of self-reported phenotypes, data on objective sleep characteristics such as accelerometer estimates were also extracted and analyzed, including least active 5-h timing (L5 timing), number of nocturnal sleep episodes (No. sleep episodes), sleep duration, and sleep efficiency. In the accelerometer study conducted by UKB, a triaxial accelerometer (Axivity AX3) was used to collect seven days of continuous data from 103,711 participants, and 47 signals from 8 sleep parameters were used for a more objective investigation of sleep duration, timing, quality, and number of sleep nights[33]. 85,670 UKB participants were available for analysis after quality control[31]. All genomic analyses were adjusted for aspects such as sex, age, and study-specific variables.

Data sources for EAAs

To estimate EAA, a mathematical algorithm is applied, which converts the level of methylation of the selected CPGs into years[34]. Four epigenetic age measures in this study were derived from a relevant GWAS meta-analysis based on 29 cohorts comprising 34,710 participants of European ancestry, namely HannumAge, IEAA, PhenoAge, and GrimAge[19].

Genetic instrumentation

The selected instrumental variables (IVs) must satisfy three core assumptions of MR analysis. Firstly, genetic variation should be largely related to exposure. Secondly, genetic variation should be independent of potential confounders. Finally, genetic variation should only affect the outcome through exposure, thus revealing that genetic pleiotropy is excluded[35]. Following are the quality control steps implemented to ensure high-quality gene IVs.

1) A threshold for statistical significance ($p < 5E{-}08$) was employed to obtain genetic variations related to exposure.
2) To ensure the mutual independence of genetic variations, linkage disequilibrium (LD) tests ($r2 < 0.001$, LD distance > 10,000 kb) were conducted.
3) For all exposures, an F-statistic of > 10 was employed to decrease the impact of weak instrument bias ($F = R2(N - 2)/(1 - R2)$[36].
4) Palindromic single nucleotide polymorphisms (SNPs) were removed to avoid distortions in strand orientation or allele coding.
5) In the NHGRI-EBI GWAS database (https://www.ebi.ac.uk/gwas/downloads/summary-statistics), potential related genetic traits of SNPs were documented based on numerous previous studies. To avoid possible confounding factors, SNPs relating to confounding factors, such as body mass index (BMI), diabetes mellitus, hypertension, obesity, and smoking, were excluded from the analysis.

Statistical analysis

MR analysis

In our study, a range of MR computational models was employed, including inverse variance weighting (IVW), MR-Egger, weighted median (WM), weighted mode, and simple mode, to investigate the potential causal

Traits	PMID	Phenotype definition (units)	Data adjustment	Sample size	Cohort/consortium	Population
Self-report						
Sleep duration Short sleep duration Long sleep duration	30,846,698	Participants were asked: About how many hours sleep do you get in every 24 h? (please include naps), with responses in hour increments. Sleep duration < 7 h was defined as short sleep duration, w hile sleep duration ≥ 9 h was defined as long sleep duration, and 7 h ≤ sleep duration < 9 h was defined as normal sleep duration. Extreme responses of less than 3 h or more than 18 h were excluded and Do not know or Prefer not to answer responses were set to missing.	Age, sex, 10 principal components of ancestry, genotyping array (UK BiLEVE and UK Biobank Axiom), and genetic correlation matrix with a maximum per SNP missingness of 10% and per sample missingness of 40%.	446,118 411,934 (106,192/305,742) 339,926 (34,184/305,742)	UKB	European
Chronotype	30,696,823	Participants were asked: Do you consider yourself to be?" with six possible responses: "Definitely a 'morning' person," "More a 'morning' than 'evening' person," "More of an 'evening' than a 'morning' person," "Definitely an 'evening' person," "Do not know," and "Prefer not to answer."	Age, sex, study center and a derived variable representing genotyping release.	449,734	UKB and 23andMe	European
Napping	33,568,662	Participants were asked: Do you have a nap during the day?" with four possible responses: "Never/rarely," "Sometimes," "Usually," and "Prefer not to answer."	Age, sex, 10 principal components of ancestry, genotyping array (UK BiLEVE and UK Biobank Axiom) and genetic correlation matrix with a maximum per SNP missingness of 10% and per sample missingness of 40%.	452,633 (255,746/172,897/23,990)	UKB	European
Daytime sleepiness	31,409,809	Participants were asked, "How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g., when working, reading, or driving)" with five possible responses: "Never/rarely," "Sometimes," "Often," "Prefer not to answer," and "Do not know."	Age, sex, genotyping array (UK BiLEVE and UK Biobank Axiom), ten principal components of ancestry and genetic relatedness matrix.	452,071 (347,285/92,794/11,963/29)	UKB	European
Insomnia	30,804,566	Participants were asked, "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" with four possible responses: "Never/rarely," "Sometimes," "Usually," and "Prefer not to answer."	Age, sex, ten principal components of ancestry, and genotyping array (UK BiLEVE and UKB Axiom).	13,31,010	UKB and 23andMe	European
Snoring	32,060,260	Participants were asked, "Does your partner or a close relative or friend complain about your snoring?" with four possible responses: "Yes," "No," "Do not know," and "Prefer not to answer."	Age, sex, genotyping array (the Illumina Infinium Global Screening Array platform) and the first 20 genetic principal components as fixed effects.	408,317(151,077/257,240)	UKB	European
OSA	33,243,845	The diagnosis of OSA was established using the International Classification of Diseases, 10th edition (ICD-10), and 9th edition (ICD-9) codes (ICD-10: G47.3, ICD-9: 347.2A). This diagnosis relied on a combination of subjective symptoms, clinical examination, and sleep registration applying apnea–hypopnea-index (AHI) ≥ 5/hour or respiratory event index (REI) ≥ 5/hour (binary variable of yes/no).	sex, age and the 10 first principal components.	217,955 (16,761/201,194)	UKB and FinnGen	European
Accelerometer-measured						
Continued						

Traits	PMID	Phenotype definition (units)	Data adjustment	Sample size	Cohort/consortium	Population
L5 timing Sleep duration No. sleep episodes Sleep efficiency	30,952,852	The midpoint of the least active 5-h (L5) of each day (continuous variable of the number of hours elapsed since previous midnight; provides an indication of phase of most restful hours with later times indexing greater tendency towards 'eveningness'). Average duration of sleeping in 24 h, including naps (continuous variable, hours). The number of sleep episodes separated by at least 5 min of wakefulness per night (continuous variable, number of episodes) Sleep duration divided by the time between the start and end of the first and last nocturnal inactivity period, respectively (continuous variable, ratio).	Age at accelerometry, sex, study center, season when activity-monitor worn and genotyping array (UK Bileve and UKB Axiom).	85,670	UKB	European
Epigenetic age acceleration						
HannumAge IEAA GrimAge PhenoAge	34,187,551		Adjustments for each cohort were available in the supplementary of original article.	34,710	29 studies from UK (n = 9), USA (n = 8), Netherlands (n = 3), Finland (n = 2), and Australia (n = 1), Denmark (n = 1), Estonia (n = 1), Germany (n = 1), Italy (n = 1), Sweden (n = 1) and Switzerland (n = 1).	European

Table 1. Description of GWAS statistic included in present study.

relationship between sleep traits and EAAs. The IVW method was employed as the primary method[37]. The IVW method assessed the overall estimates of association using a meta-analysis that assumed all selected IVs were valid, thus generating a possibility for horizontal pleiotropy. This necessitates a robust method to detect horizontal pleiotropy. The auxiliary methods, including MR-Egger, WM, simple mode, and weighted mode, are less efficient than IVW. MR-Egger conducted a weighted linear regression to screen out bias in meta-analysis. The MR-Egger could provide consistent estimates of causal effects, even though all selected IVs are invalid. But the results from MR-Egger may be imprecise if selected IVs have a similar effect on exposure. The WM method can prevent invalid tools, and it can provide reliable estimates of causal effects When the weight of valid IVs is more than 50%. The weighted mode method is less effective at detecting causal effects but also has fewer biases[38]. Simple mode is a model-based assessment approach that offers pleiotropy robustness[39]. Consistent effect estimates from different methods support the robustness of the effect estimates. Only results received support of consistent direction from five methods pass the examination (all $\beta > 0$ or all $\beta < 0$). During the analysis of MR, we inferred the causal impact between the sleep traits and EAAs by presenting the odds ratio (OR). For example, our forward MR analyses quantify the alteration in the EAAs acceleration with each standard deviation (SD) rise in the level of sleep traits. 95%CI of OR was calculated using a formula: In ($\beta \pm 1.96$*SD).

Sensitivity assessment

The introduction of pleiotropic IVs may result in a biased outcome for the IVW method. The introduction of pleiotropic IVs may result in a biased outcome for the IVW method. The MR-Egger method takes into account the presence of an intercept term and was employed to address the issue of pleiotropy[38,40]. We also generated funnel plots to determine the extent of pleiotropy. Moreover, Cochran's Q statistic was applied to detect the heterogeneity among different genetic variants in the IVW method[40]. As part of the analysis, the "leave-one-out" analysis was applied to screen out the SNP that independently drove the direction of estimation[41]. A similar set of results was obtained when palindromic SNPs were excluded, demonstrating that the results were reliable even after excluding palindromic SNPs[42].

The statistical analysis was undertaken using the packages "TwoSampleMR" and "MRPRESSO" in R version 4.2.2 (2021-02-15).

Results

Genetic instruments selection

The SNPs were selected from the pooled GWAS data. The numbers of SNPs in each process were shown in Fig. 2. The F-statistics for the SNPs appeared to be greater than 10 suggesting that the power of selected IVs was strong. Detailed information on IVs was presented in Tables S2 and S3.

Estimation of effects based on MR analysis

As shown in Fig. 3, self-reported insomnia was strongly positively associated with GrimAge acceleration (OR 1.17; 95% CI 1.04 to 1.31; P = 0.007). Due to horizontal pleiotropy, the correlation between daytime sleepiness and IEAA was discarded. Besides, the objective data measured by the accelerometer is mainly related to the first-generation clock. Accelerometer-measured sleep efficiency and number of sleep episodes were positively associated with HannumAge (OR 3.65; 95% CI 1.03 to 12.91; p = 0.044) and IEAA (OR 1.59; 95% CI 1.01 to 2.48; p = 0.044), respectively.

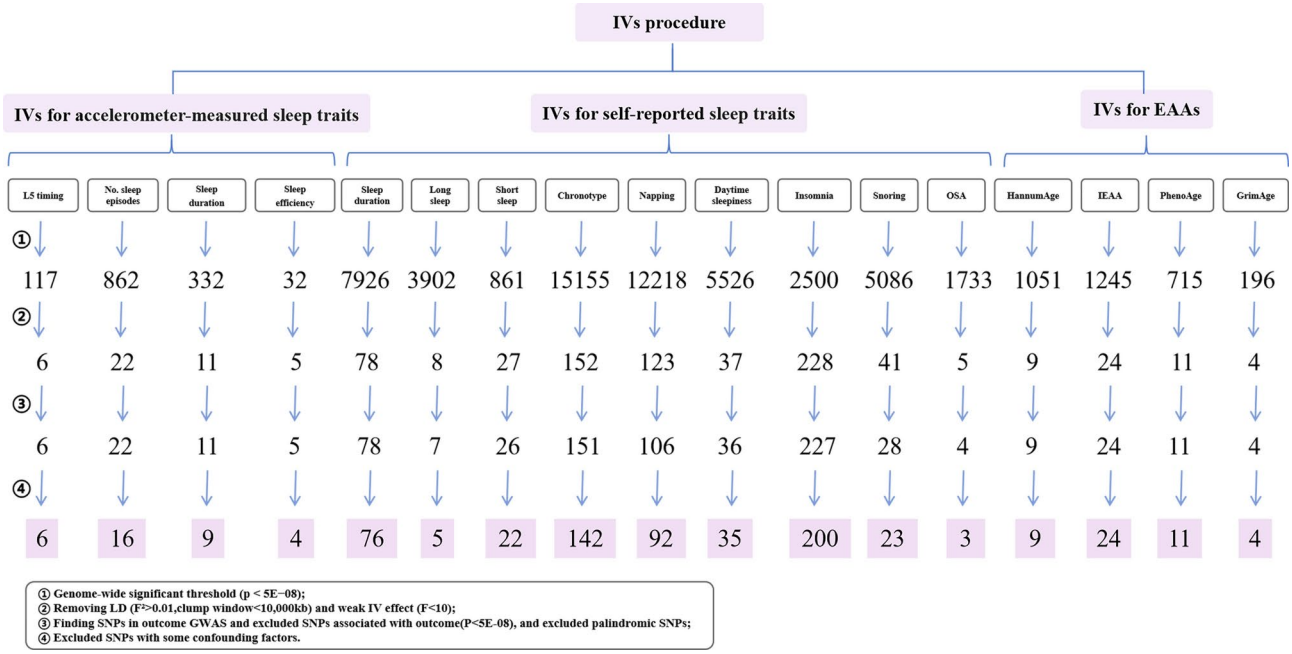

Fig. 2. Procedure of IVs selection.

Next, we performed a reverse MR analysis with EAAs as exposure to explore the potential causality of EAAs on sleep traits. The results were presented in Fig. 4. In this analysis, weak effects of EAAs on sleep traits were found.

The acceleration of GrimAge was found to cause daytime sleepiness (OR 1.01; 95% CI 1.00 to 1.01; P = 0.047), while the acceleration of PhenoAge clock could faintly reduce daytime napping (OR 1.00; 95% CI 0.99 to 1.00; P = 0.013) and daytime sleepiness (OR 0.997; 95% CI 0.995 to 0.999; P = 0.015). The acceleration PhenoAge clock could also faintly alter short sleep duration (OR 1.002; 95% CI 1.000 to 1.004; P = 0.033). The IEAA only had a weak effect on accelerometer-measured L5 timing (OR 1.01; 95% CI 1.00 to 1.02; P = 0.040).

It is noteworthy that we found a bidirectional association between GrimAge and insomnia. The GrimAge was found to alleviate self-reported insomnia (OR 0.99; 95% CI 0.98 to 1.00; P = 0.040), while self-reported insomnia was found to accelerate GrimAge.

Sensitivity

According to Cochran's Q test, heterogeneity was found in two groups (sleep efficiency on HannumAge and IEAA on L5 timing). If heterogeneity was found, then the random-effects model of the IVW method was adopted. Although daytime sleepiness was suggested to be possibly associated with the IEAA clock in the forward analyses, we discarded this association due to the presence of horizontal pleiotropy in the MR-Egger intercept test. Aside from this, no evidence of horizontal pleiotropy was examined in this study. Further details can be found in Tables S7 and S8.

Discussion

This study represented the first to explore the two-way causal relationship between sleep traits and EAAs. As a result of our findings, some traits are causally associated with particular epigenetic changes at the genetic level. Specifically, we observed that self-reported insomnia may speed up the aging process by GrimAge clock, while GrimAge acceleration could faintly reduce self-reported insomnia. Additionally, sleep efficiency and No. sleep episodes based on accelerometer measurements were positively correlated with HannumAge and IEAA, respectively. Furthermore, EAAs mainly influence sleep traits by PhenoAge and GrimAge with weak effects. These findings may highlight the early interventions of SDs as a breaking point for aging and age-related diseases. More attention should be paid to SDs in clinical practice.

Our research found that insomnia was a significant driver of GrimAge acceleration, while GrimAge acceleration may faintly alleviate insomnia. Previous studies demonstrated that GrimAge can better predict all-cause and cause-specific mortality than other DNAm-based age estimates. Two-step approaches were taken in the construction of GrimAge to estimate the mortality risk. First are seven plasma proteins: adrenomedullin, beta-2 microglobulin, cystatin C, growth differentiation factor 15 (GDF15), plasminogen activation inhibitor 1 (PAI-1), leptin, and tissue inhibitor metalloproteinase 1. Then the smoking pack-years (PACKYRS) based on DNAm indicators was employed[43] The GrimAge was a better predictor of morbidity or mortality and was highly reliable in predicting health and cognitive decline with aging[44,45]. The results based on GrimAge were more feasible than others.

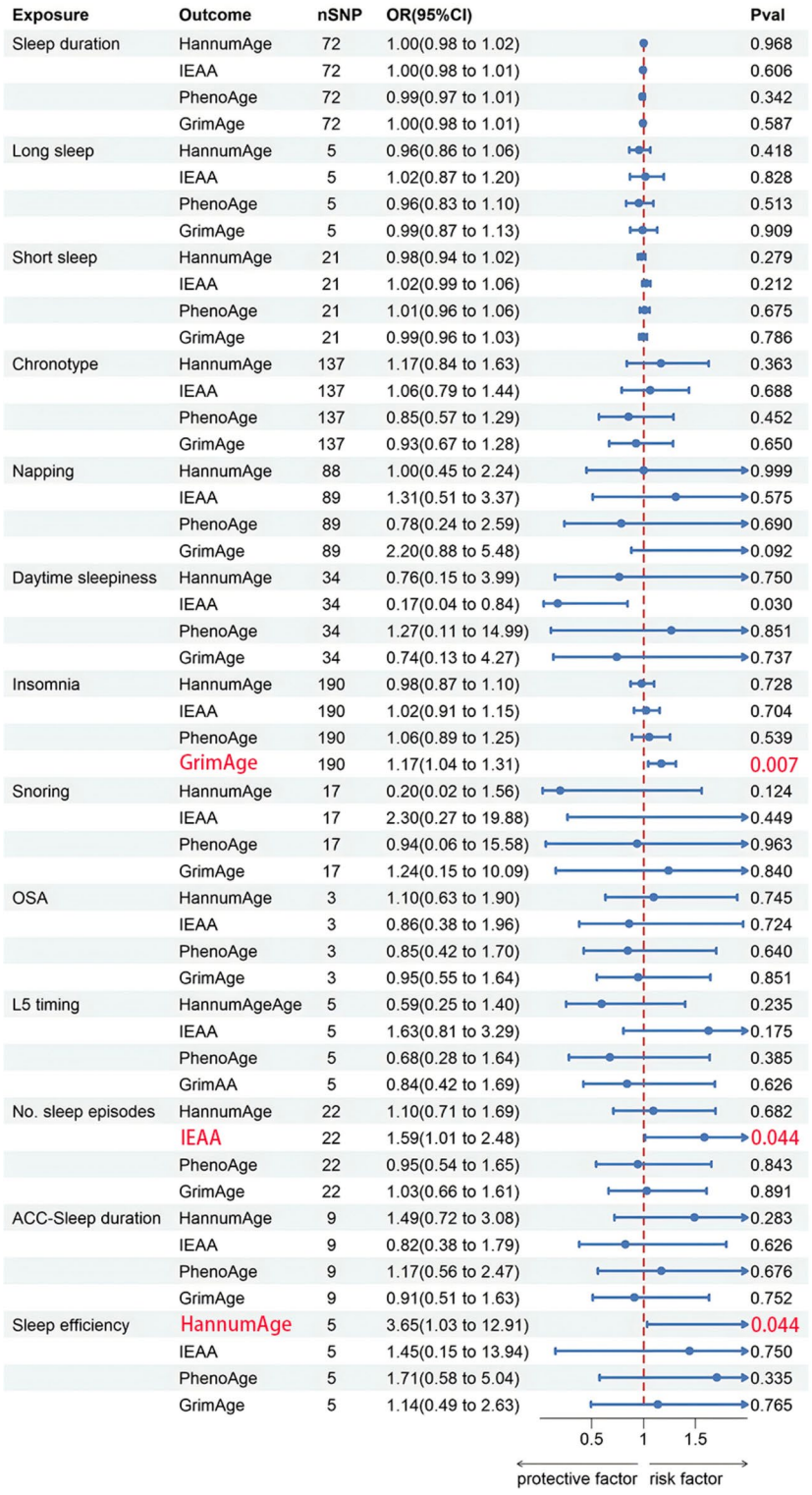

Fig. 3. MR analyses of sleep traits on EAAs.

Inflammatory mechanisms may be a key pathway between insomnia and GrimAge. A range of evidence underlined that sleep disturbance could be a risk factor in developing chronic inflammatory diseases and a higher mortality rate[46]. It has been proved that SDs can influence the activation of β-adrenergic signaling, which contrarily induces nuclear factor kappa B (NF-kB), inflammatory gene expression, pro-inflammatory cytokine production, and the increase of systemic inflammation markers[47]. In addition to being a sleep continuity disorder, insomnia also encompasses a range of symptoms and disorders during the daytime. These include sleepiness, fatigue, somatic symptoms, mood disorders, and cognitive or occupational disorders resulting from

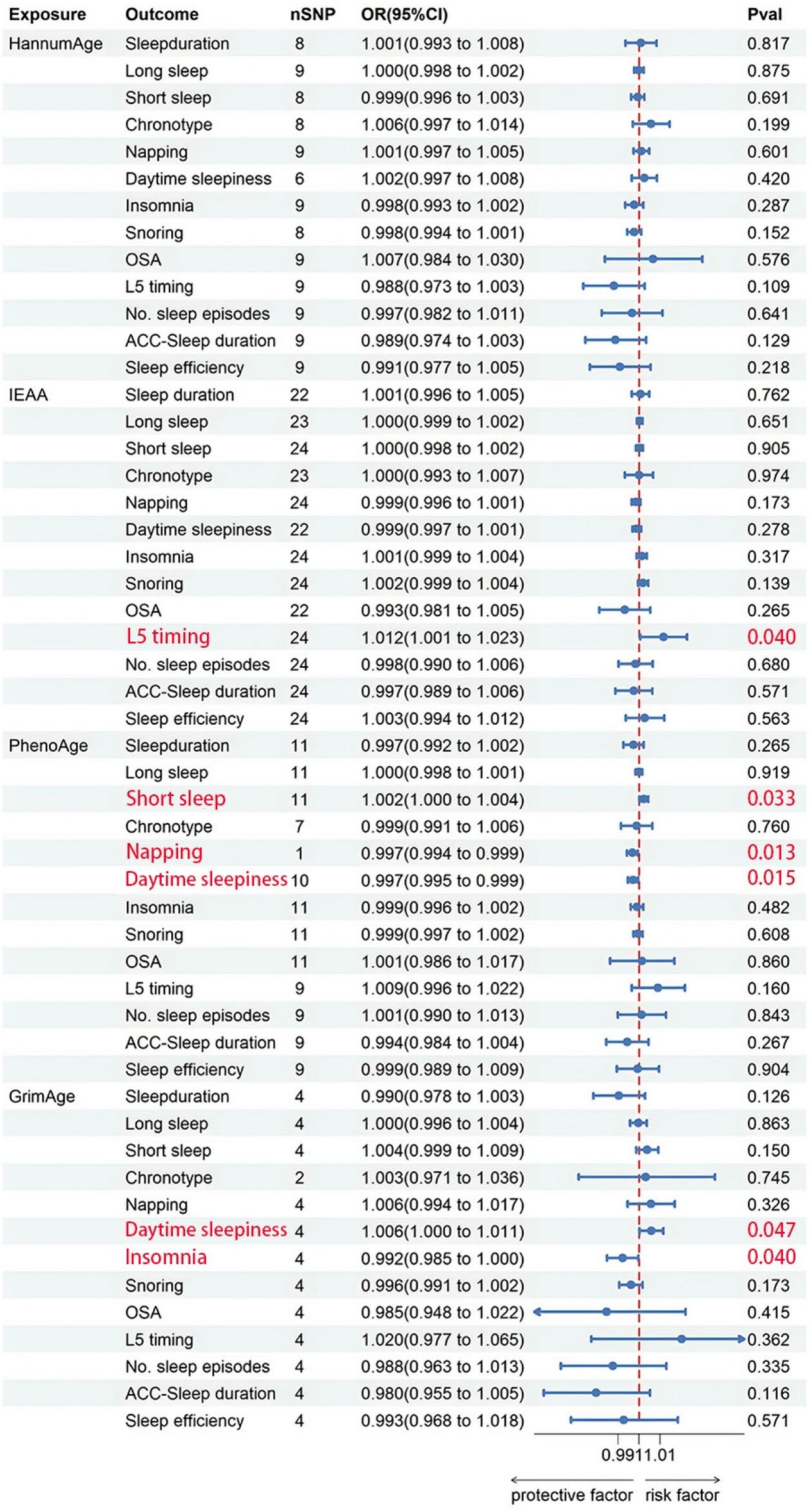

Fig. 4. MR analyses of EAAs on sleep traits.

dissatisfaction with sleep[48]. Based on the National Health and Veterans Resilience Study, Amanda J. F. Tamman et al. found that the polygenic risk score (PRS) for three inflammatory markers: apolipoprotein B, high-density lipoprotein (HDL), and gamma-glutamyl transferase, was negatively associated with GrimAge acceleration. Furthermore, greater sleep quality could reinforce the proactive effect of HDL PRS on GrimAge[49].

Insomnia symptoms may speed up biological senescence through immunological factors. In a study conducted by Judith E. Carroll and her colleagues, individuals with symptoms of insomnia reported a higher prevalence of late-differentiated T cells in a state of near-senescence[50]. The loss of CD28, a cell surface marker

on CD8$^+$ T cells and an indicator of T cell senescence/exhaustion, was positively correlated with GrimAge[51]. Another study also revealed that worsening sleep quality is related to accelerated GrimAge, and GrimAge acceleration increases the risk of metabolic syndrome which is a kind of age-related disease in turn[52]. Evidence from a cohort study supported that the Mediterranean diet could improve sleep quality accompanied by a reduction in GDF-15 levels. GDF-15, as mentioned above, is one of the plasma proteins in GrimAge[53]. Hyon-Seung Yi et al., found that T-cell aging in prediabetes promotes ATF5-driven GDF15 production in the liver[54]. Proinflammatory cytokines (e.g., interleukin-1b, interleukin-6, and interleukin-17) as well as the serum acute phase protein C-reactive protein increased following sleep restriction[55]. Sleep restriction could activate the expression of the NF-kB signaling pathway and the interleukin-8 generating pathway[56]. There were associations between insomnia symptoms and the following GrimAge components: PACKYRS and PAI-1[57]. The results of the reverse analyses were unexpected, with accelerated GrimAge predicting a reduction in insomnia. However, we must interpret this result cautiously, as it may be influenced by other variables, or reflect some aspect of the relationship between GrimAge and insomnia.

It was unexpected that sleep duration, both self-reported and accelerometer-measured sleep duration, did not correlate with these clocks in our results. However, a growing number of studies have demonstrated that both excessive and insufficient sleep are detrimental to health. As far as sleep duration is concerned, it has been the subject of the most extensive research, and it has been linked to cardiovascular disease, obesity, and mortality[58]. In a large East Asian population-based cohort, Svensson et al. found that seven hours of sleep per night was the lowest point involved with a decreased risk of mortality from all causes, risk of cardiovascular disease, and risk of death from other causes. Sleep duration of less than seven hours or more is associated with an increased risk of death from all causes[59]. According to a study by You et al., the relationship between sleep duration and age acceleration was inverted U-shaped in 48,762 American adults[60]. In a comparable study, Mei Wang et al. discovered a curvilinear relationship between sleep duration and PhenoAge acceleration risk[61]. Even though our MR study did not demonstrate a U-shaped relationship, perhaps due to differences in statistical methods, sleep duration plays a role in the apparent acceleration of aging. Moreover, we found only very weak relationships between sleep traits with the first-generation clock, for example, No. sleep episodes on IEAA ($p = 0.044$) and sleep efficiency on HannumAge ($p = 0.044$).

The results of the reverse MR analyses are all relatively weak, yet the potential role of EAA in the prediction and inference of sleep-related disease cannot be discounted. Efforts are needed to improve the construction of the EAA model. The CompositeAge-DNAmAge composite methylation clock, based on multimodal age training and more suitable for Chinese individuals, demonstrated great efficacy in predicting both age and health status. By comparing age-accelerated and age-decelerated individuals, the researchers elucidated that this clock could assess the negative impact of unhealthy lifestyles (e.g., sleep deprivation and unhealthy dietary habits) on the aging process. They suggested that individuals suffering from chronic diseases, such as hypertension, have a faster aging rate[62].

We rigorously draw conclusions with attention to methodology, and the current study possesses several advantages. Firstly, the data volume of this analysis is larger than that of previous studies, and the integrated relationship between 13 sleep traits and 4 epigenetic clocks is discussed. Secondly, data on sleep traits was no longer limited to self-reported and subjective perceptions. Data based on accelerometer measurements was introduced and analyzed, greatly enhancing the reliability of the results. Thirdly, to avoid potential population stratification bias, this study only used GWAS data from European ancestry. Finally, EAAs provide a comprehensive insight into the influence of genetic and environmental factors on the process of aging, thus representing an invaluable resource for studying aging and its related diseases[63]. Our study hopes that interventions of SDs accepted by the public as an epigenetic rejuvenation strategy. Compared with drug interventions, it is non-invasive, low-cost, and easy to access[13].

It should be noted that the present study is also subject to several limitations. It is important to note that four EAAs didn't consistently associate with any sleep traits in our study. This discrepancy may be attributed to their diversity in construction, which is trained according to varying tissue and clinical outcomes[63]. Secondly, This has implications for the general applicability of the findings. Thirdly, the observed rate of sleep loss in the results was low and should be interpreted with caution. Moreover, epigenetic aging is an intrinsic consequence of environmental exposure, rather than a genetic phenomenon. This underscores the constraints of MR in this context[64].

Conclusions

In conclusion, the present study employed a comprehensive two-sample analysis to elucidate the evidence for the potential causal impacts of sleep traits and EAAs. It is more likely to observe the effects of reduced sleep quality on both GrimAge and HannumAge. However, it cannot be denied that sleep duration also affects aging. In light of the modest discrepancies in sleep phenotypes attributable to genetic variability, it is imperative to corroborate the findings of this study through additional replication studies utilizing independent samples in the future.

Data availability

The summary statistics analyzed in the study are included in the article/Supplementary Material. Sleep-related traits summary statistics are available at the following links: [http://sleepdisordergenetics.org/] and [https://fingen.gitbook.io/documentation/]. EAA-related GWAS datasets are available at the Edinburgh Data Commons at the following link: https://datashare.ed.ac.uk/handle/10283/3645. Further inquiries can be directed to the corresponding author to make it accurate.

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Author contributions

Wen Zhao and Jingbo Sun guided the manuscript writing, with Wen conducting the analysis and drafting the initial version. Shiyao Yu, Yan Xu, and Ting Lu created and proofread graphs, while Daiyi Chen and Huijuan Liao assisted in the draft. Jianhiu Liu, Zhixuan Ren, and Lijuan Ge offered suggestions and revisions to refine the final product.

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Competing interests

The authors declare no competing interests.

Additional information

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