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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data collection was not performed by any software.
Data analysis	• SleepChart-R: https://github.com/anbai106/SleepChart, customized R code for linking sleep duration and 23 BAGs • MLNI (v0.1.2): https://github.com/anbai106/mlni, BAG generation; • MGCV (v1.9.1) with R v4.2.2: https://cran.r-project.org/web/packages/mgcv/index.html, core package for the GAM implementation. • GAMLSS (v5.4.22) with R v4.2.2: https://www.gamlss.com/; replicate the 9 sleep-BAG signals identified by the GAM modeling. • Lifelines (v0.27.8): https://lifelines.readthedocs.io/en/latest/, survival analysis; • Lavaan (v0.6.19): https://lavaan.ugent.be/, mediation analysis; • String (v12.0): https://string-db.org/, protein set enrichment analyses and network analysis; • MetaboAnalyst (v6.0): https://www.metaboanalyst.ca/, metabolite enrichment analysis and network analysis; • REGENIE (v4.1): https://rgcgithub.github.io/regenie/, binary sleep GWASs (v4.1); FinnGen used v2.4.4 for their disease endpoints GWASs; • LDSC (git version aa33296): https://github.com/bulik/ldsc, genetic correlation • FUMA (v1.8.0): https://fuma.ctglab.nl/, Gene mapping, genomic locus annotation • KING (v.2.2.7): https://www.kingrelatedness.com/, Kinship-based inference for GWAS

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The GWAS summary statistics for long and short sleep duration are publicly available via the Sleep Chart portal (https://labs-laboratory.com/sleepchart). The GWAS summary statistics for the 23 multi-organ BAGs are publicly accessible via the MEDICINE portal (https://labs-laboratory.com/medicine/). All GWAS summary statistics are also available at Synapse (https://www.synapse.org/Synapse:syn64923248/wiki/630992105 and https://www.synapse.org/Synapse:syn68602065/wiki/633329106). Our study used data generated by the Human Protein Atlas (https://www.proteinatlas.org) and MetaboAnalyst (https://www.metaboanalyst.ca/MetaboAnalyst/ModuleView.xhtml). GWAS summary data for the DEs were downloaded from the official websites of FinnGen (R9: https://www.finngen.fi/en/access_results) and PGC (https://pgc.unc.edu/for-researchers/download-results/). Individual data from UKBB can be requested with proper registration at https://www.ukbiobank.ac.uk/. The data used to link insomnia/hypersomnia with disease endpoints are from TriNetX (https://trinetx.com/), which requires a valid registration and request. Data from the BLSA study (https://www.blsa.nih.gov/) and the MESA study (https://mesa-nhlbi.org/) can be requested with proper registration, respectively. We also shared the original PDF for the 4 main figures at: https://zenodo.org/records/17409426.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Throughout the manuscript, we consistently employed the variable of sex, incorporating both self-reported sex and genetic sex as covariates and quality-check criteria.
Reporting on race, ethnicity, or other socially relevant groupings	Whenever appropriate, we report ethnic groups. All GWAS were conducted in people of European ancestry.
Population characteristics	Study population is detailed in Method 1 and Supplementary Table 1
Recruitment	UK Biobank details the recruitment criteria at: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf
Ethics oversight	The protocols of this study were approved by the Columbia University institutional review board

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No formal statistical methods were used to predetermine sample size. Instead, we included all available UK Biobank participants who passed standard quality control and had the required data to derive the 23 biological age gaps (BAGs), encompassing the relevant imaging, proteomics, and metabolomics inputs. For the sleep-duration analyses, we limited the analytic range to 4–10 hours/day because observations at the extremes were sparse and can lead to unstable or biased smoothing in GAM models, thereby improving the robustness of model fitting. We did not perform an a priori power analysis, as the resulting cohort size is large and provides adequate statistical power for the associations tested.
Data exclusions	Data exclusions were applied as part of pre-specified quality control and analytic filtering. Specifically, for the sleep-duration analyses, we restricted sleep duration to 4-10 hours/day because observations at the extremes are sparse and can lead to unstable or biased smoothing in GAM models. This range restriction excluded 6,529 participants, leaving 494,978 participants for the sleep-duration analyses.
Replication	We performed replication analyses in two independent external cohorts, the Baltimore Longitudinal Study of Aging (BLSA) and the Multi-Ethnic Study of Atherosclerosis (MESA), to evaluate the sleep duration vs. brain MRI-derived biological age gap (MRIBAG) relationship. In both BLSA and MESA, we observed a consistent U-shaped pattern. However, these associations did not reach statistical significance in either cohort, likely due to substantially smaller sample sizes than the UK Biobank. The sleep-disease endpoint survival analysis in the UK Biobank was tentatively replicated in TrinetX, although insomnia and hypersomnia cannot be treated equally as short and long sleep duration.
Randomization	Randomization was not used in this observational study. For the primary sleep–BAG association analyses, sleep duration was modeled as a

Randomization	continuous exposure and potential confounding was addressed by including disease status and other relevant covariates in the GAM framework. For downstream analyses that required discrete group definitions (e.g., GWAS and survival/time-to-incident disease models), we additionally derived categorical sleep variables based on established thresholds, classifying sleep duration as short (<6 hours), normal (6–8 hours), and long (>8 hours). We also performed a sensitivity analysis for incident disease prediction using 7-9 hours as the normal sleep duration (Supplementary Fig. 22), consistent with National Sleep Foundation guidance for young and older adults.
Blinding	Blinding was not performed because this was an observational study using pre-existing UK Biobank data, with no experimental allocation or intervention. The derivation of biological age gaps and the statistical analyses were conducted using standardized, largely automated pipelines and pre-specified criteria, minimizing subjective decision-making that could be influenced by knowledge of sleep duration category or disease status. For downstream analyses requiring categorical sleep definitions (e.g., GWAS and survival analyses), categories were defined using fixed thresholds applied uniformly to all participants.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging