
Supplementary information

Sleep chart of biological ageing clocks in middle and late life

In the format provided by the
authors and unedited

Supplementary Note 1: U-shaped patterns between sleep duration and imaging-derived phenotypes, plasma proteins, and metabolites

Imaging-derived phenotypes from 8 organ systems and tissues show U-shaped relationships with sleep duration

Using *in vivo* imaging-derived phenotypes (IDPs) derived from MRI data of 8 organs and tissues, we provided a granular understanding of how sleep duration impacts specific structural and functional aspects of various organs (**Extended Data Figure 1** and **Method 4**).

We identified a total of 162 statistically significant associations ($P < 0.05/720$) between sleep duration and IDPs (**Extended Data Figure 1a**). Among the 27 brain IDPs derived from T1-weighted MRI (i.e., brain-GM) and diffusion MRI (i.e., brain-WM), nonlinear relationships with sleep duration were observed across brain regions (**Extended Data Figure 1b**), including the frontal, temporal, and parietal lobes, as well as subcortical structures, with the left hippocampus showing pronounced association ($\text{EDF}=1.96$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$, $P_3=1$; **Extended Data Figure 1d**). Among the 10 diffusion MRI-derived IDPs (i.e., brain-WM; **Extended Data Figure 1c** for fractional anisotropy), exemplified by the right superior cerebellar peduncle ($\text{EDF}=1.97$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3 < 1 \times 10^{-20}$; **Extended Data Figure 1e**). Among the 54 resting-state fMRI-derived imaging phenotypes, the 189th functional connectivity measure (FullCorr_189) between two brain networks exhibited a U-shaped association with sleep duration ($\text{EDF}=3.48$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3=1$; **Extended Data Figure 1f**).

Beyond the brain, we observed 51 significant associations, exemplified by the INL-ELM thickness of the central subfield in the left eye ($\text{EDF}=3.42$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3=0.18$; **Extended Data Figure 1g**). Among the 10 significant heart IDPs, the largest volume of the right atrium of the heart showed a significant U-shaped pattern with sleep duration ($\text{EDF}=1.97$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3=0.93$; **Extended Data Figure 1h**). For the rest of the abdominal IDPs, U-shaped patterns were observed in abdominal fat ratio ($\text{EDF}=3.30$; $P_1=3.0 \times 10^{-5}$, $P_2 < 1 \times 10^{-20}$; $P_3=0.03$; **Extended Data Figure 1i**) and corrected T1 (cT1) of the liver ($\text{EDF}=1.96$; $P_1 < 1 \times 10^{-20}$, $P_2=3.94 \times 10^{-3}$; $P_3=0.97$; **Extended Data Figure 1j**). Detailed statistics, including the P value, optimal family distribution, and EDF, are presented in **Supplementary File 2**.

We found widespread nonlinear associations between sleep duration and structural and functional imaging phenotypes across 8 organs. These organ-level changes point to systemic effects of abnormal sleep duration, leading us to examine corresponding molecular signatures in proteomic and metabolomic profiles.

Sleep duration and plasma proteomics show a U-shaped relationship

We analyzed associations between sleep duration and 2923 plasma proteins using the same GAM model. When considering only the 342 organ-enriched proteins (i.e., at least four-fold higher mRNA level in brain compared to any other tissues) defined by our previous study¹, we identified 77 significant proteins ($P < 0.05/2923$) (**Method 5**).

We identified 29, 14, 9, and 8 significant organ-enriched proteins corresponding to the hepatic, immune system, endocrine system, and brain, respectively (**Extended Data Figure 2a**). For instance, the brain-enriched protein FGFR2 demonstrated a U-shaped relationship with sleep duration (EDF=3.64; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3 = 0.03$; **Extended Data Figure 2b**). We performed protein-protein interaction (PPI) analysis using STRING (v12.0: <https://string-db.org/>) on the significant organ-enriched proteins to explore functional relationships among the 14 immune-enriched and 29 hepatic-enriched proteins. For the immune protein set, we found a cluster of immune-enriched proteins that likely reflects a coordinated immune response involving cell surface receptors, leukocyte activation, and inflammatory signaling (CD27, FCER2, ITGAM, NCR1, PLAUR, PRTN3, RETN; **Extended Data Figure 2c**). For the hepatic protein set, k-means clustering of the PPI network revealed a prominent cluster consisting of 19 proteins involved in innate immune defense and blood coagulation, particularly complement components (e.g., C3, C4A, CFB) and coagulation factors (e.g., FGA, FGB, FGG), highlighting the role of complement and coagulation cascades (**Extended Data Figure 2d**).

Our protein set enrichment analysis (PSEA), based on Gene Ontology (GO) biological process terms for the significant immune- and hepatic-enriched proteins, identified a coherent set of pathways that align with well-established hypotheses connecting sleep duration to systemic physiological regulation and disease susceptibility. Notably, a substantial proportion of enriched pathways mapped to immune activation and inflammation, including "defense response" (GO:0006952), "innate immune response" (GO:0045087), "complement activation" (GO:0006956), and "neutrophil chemotaxis" (GO:0030593), supporting prior evidence that sleep disruption can modulate both innate and adaptive immune pathways. Additionally, we observed enrichment in metabolic regulation and protein processing, including "regulation of catalytic activity" (GO:0050790), "enzyme inhibitor activity" (GO:0004857), extracellular signaling and vesicle transport (e.g., "extracellular exosome" (GO:0070062), "blood microparticle" (GO:0072562)), and cell surface and receptor signaling, reflecting the role of sleep in coordinating cellular communication, metabolic homeostasis, and systemic signaling. Enrichment in generalized response to stimulus and stress-related pathways further underscores the broad physiological perturbations linked to altered sleep duration. Collectively, these findings provide mechanistic support for the hypothesis that sleep impacts multi-organ health through diverse but interconnected biological systems. Detailed statistics, including the P value, optimal family distribution, and EDF, are presented in **Supplementary File 3**.

Sleep duration and plasma metabolomics show a U-shaped relationship

We further investigated the relationship between sleep duration and 327 NMR-derived metabolomic measures, which included 107 raw small-molecule metabolites and lipid subclasses, along with additional composite metrics derived from these metabolites. Among the 107 organ-associated metabolites identified in our previous study², we observed 21 significant associations after Bonferroni correction ($P < 0.05/327$) (**Method 6**).

We identified 14 significant organ-associated metabolites linked to the hepatic system, 4 to the digestive system, and 2 to the endocrine system (**Extended Data Figure 3a**). For instance, the average number of double bonds in fatty acid chains within lipid molecules ('Unsaturation') demonstrated a U-shaped relationship with sleep duration ($\text{EDF}=3.75$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3=0.003$; **Extended Data Figure 3b**). Similarly, the U-shaped relationship was also observed in acetoacetate ($\text{EDF}=1.98$; $P_1 < 1 \times 10^{-20}$, $P_2=1$; $P_3=0.46$), docosahexaenoic acid (DHA) ($\text{EDF}=3.23$; $P_1 < 1 \times 10^{-20}$, $P_2=1$, $P_3 < 1 \times 10^{-20}$), and acetate ($\text{EDF}=1.97$; $P_1 < 1 \times 10^{-20}$, $P_2 < 1 \times 10^{-20}$; $P_3=0.69$) (**Extended Data Figure 3c-e**).

Our metabolite set enrichment analysis (MSEA) using the MetaboAnalyst (v6.0: <https://www.metaboanalyst.ca/MetaboAnalyst/ModuleView.xhtml>), including only the small-molecule metabolites that were mapped to the platform (e.g., HMDB and PubChem ID). This resulted in acetic acid, acetoacetic acid, creatinine, dehydroepiandrosterone, glycine, L-Tyrosine, L-Valine, and sphingomyelins. We identified a coherent grouping of pathways that support potential hypotheses linking sleep duration to systemic physiology (**Extended Data Figure 3f**). Pathways within the "Transport Axis" cluster highlight the involvement of solute carrier (SLC) transporters, which regulate the movement of amino acids, neurotransmitters, and ions across cellular membranes. This cluster includes both generic and disorder-specific pathways, such as SLC-mediated transmembrane transport, amino acid transport across the plasma membrane, and Na/Cl-dependent neurotransmitter transporters, underscoring a possible role for sleep in modulating nutrient and neurotransmitter bioavailability across tissue barriers. The "Neurochemical Plasticity" cluster reflects the role of sleep in maintaining neural homeostasis through amino acid metabolism and synaptic remodeling. Enriched pathways such as tyrosine catabolism, creatine metabolism, and various tRNA aminoacylation processes suggest that sleep duration may influence neurotransmitter synthesis, protein translation fidelity, and post-translational modifications critical for brain function. Finally, the "Liver-Sleep Axis" cluster includes pathways like synthesis of ketone bodies and cyclosporin A-induced metabolic pathways, pointing toward the hepatic regulation of energy metabolism and detoxification as potential downstream targets of sleep-driven metabolic adaptation. Together, these findings further support a multi-system view of sleep biology involving molecular transport, neurochemical processing, and liver-mediated metabolic control. Detailed statistics, including the P value, optimal family distribution, and EDF, are presented in **Supplementary File 4**.

Supplementary Note 2: The definition of genomic loci, independent significant SNP, lead SNP, candidate SNP

FUMA defined the significant independent SNPs, lead SNPs, candidate SNPs, and genomic risk loci as follows (<https://fuma.ctglab.nl/tutorial#snp2gene>):

Independent significant SNPs

They are defined as SNPs with $P \leq 5 \times 10^{-8}$ that are independent of each other at the user-defined r^2 (set to 0.6 in the current study). We further describe *candidate SNPs* as those in linkage disequilibrium (LD) with independent significant SNPs. FUMA then queries each candidate SNP in the GWAS Catalog to check whether any clinical traits have been reported to be associated with previous GWAS studies.

Lead SNPs

Lead SNPs are defined as independent significant SNPs that are also independent of each other at $r^2 < 0.1$. If multiple independent significant SNPs are correlated at $r^2 \geq 0.1$, then the one with the lowest individual P -value becomes the lead SNP. If r^2 threshold is set to 0.1 for the independent significant SNPs, then they would constitute the identical set as the lead SNPs. FUMA thus advises setting r^2 to be 0.6 or higher.

Genomic risk loci

FUMA defines genomic risk loci to include all independent signals physically close or overlapping in a single locus. First, independent significant SNPs dependent on each other at $r^2 \geq 0.1$ are assigned to the same genomic risk locus. Then, independent significant SNPs with less than the user-defined distance (250 kilobases by default) away from one another are merged into the same genomic risk locus – the distance between two LD blocks of two independent significant SNPs is the distance between the closest points from each LD block. Each locus is represented by the SNP within the locus with the lowest P -value.

Supplementary Note 3: Comparisons between our sleep trait GWAS and genetic correlation results with previous literature

We re-ran GWAS for short and long sleep duration in the UK Biobank for both practical and methodological reasons. Practically, this allowed us to apply a unified quality-control pipeline and to obtain harmonized information on allele frequencies and linkage disequilibrium, which are not always fully available in previously published summary statistics. Methodologically, our design choices, defining short, normal, and long sleep using specific bins (short <6 h, normal 6–8 h, long >8 h), restricting the analysis to individuals reporting 4–10 h of sleep to reduce the influence of extreme outliers, and treating sleep duration consistently as a categorical phenotype in downstream models, were aligned with the aims and structure of our multi-organ analyses.

These choices differ from those in Dashti et al.³, who primarily modeled sleep duration as a continuous trait and used different categorical thresholds for short vs. normal and long vs. normal sleep duration (≤ 6 h, 7–8 h, ≥ 9 h), and from Austin-Zimmerman et al.⁴, who combined UK Biobank with the MVP cohort and used alternate cutoffs (≤ 5 h, 7–8 h, ≥ 10 h). Dashti et al. excluded extreme responses of less than 3 h or more than 18 h, which is much less strict than ours. Consequently, their studies achieved larger effective sample sizes and identified more genome-wide significant loci.

To directly compare these efforts, we downloaded GWAS summary statistics from Dashti et al. and Austin-Zimmerman et al. and estimated pairwise genetic correlations between their GWAS and our own short vs. normal and long vs. normal sleep GWAS using LDSC. We observed very high genetic correlations ($0.83 < r_g < 0.98$; $P\text{-value} < 1 \times 10^{-5}$; **Supplementary Figure 19**), indicating that the underlying genetic architecture is highly similar and that differences in the number of genome-wide significant loci are largely attributable to differences in sample size, power, and operational definitions of short, normal, and long sleep duration rather than to fundamentally different biology.

Genetic correlations between sleep traits and other complex traits have been reported in multiple previous studies^{3,4,5,6,7}. However, these prior analyses generally follow a candidate or hypothesis-driven strategy, focusing on selected domains (such as psychiatric or cardiometabolic traits) and typically pairing each trait with the single most highly powered GWAS available. In contrast, our work leverages large biobank-scale resources (in particular for FinnGen) in a non-selective, data-driven manner and is explicitly organized around a multi-organ perspective, linking short and long sleep duration to disease endpoints across primary organ systems (brain, heart, lung, metabolic organs, etc.). We provided additional analyses by re-performing genetic correlation between the FinnGen DEs with the GWAS summary statistics from Dashti et al.³ and Austin-Zimmerman et al.⁴ (**Supplementary Figure 20–21**), re-confirming the multi-organ dysfunction relationship with both short and long sleep duration. Overall, the DE–sleep genetic associations identified in our GWAS showed strong concordance with those from the two previous studies. However, the latter generally detected a larger number of significant genetic correlation signals, likely reflecting their larger sample sizes and differing definitions of short, normal, and long sleep duration. Thus, our re-analysis of sleep GWAS and the accompanying LDSC framework are not intended to supersede prior sleep GWAS per se, but to provide a harmonized, biobank-based foundation for systematically mapping how sleep disturbances are genetically connected to diseases spanning the whole body.

Supplementary Note 4: Sleep-DE signals identified in the UK Biobank in the TriNetX database

Data: We used EHR data from the TriNetX database to validate the survival analysis of the 153 significant disease endpoints (DEs) associated with short and long sleep durations identified in the UK Biobank (UKBB). Since sleep duration is not directly available in TriNetX, we used diagnoses of insomnia and hypersomnia as proxy measures. Baseline characteristics were compared with chi-square tests for categorical variables and independent-sample t-tests for continuous variables (**Supplementary Table 6**). This active comparator cohort study used data from commercially insured adults (aged ≥ 18 years), with insomnia or hypersomnia diagnoses and controls without insomnia or hypersomnia, respectively, between January 1st, 2010, and August 31st, 2017. Patients were included if they had undergone a healthcare visit within one year before their cohort entry. Patients were excluded if they had any DE diagnosis at any time before cohort entry. This analysis was conducted on 6th May 2025 on the TriNetX Analytics Platform.

Method: The TriNetX platform was used to run 1:1 propensity score matching using logistic regression. Once it yields scores that range between 0 and 1, the platform utilizes a greedy, nearest neighbour matching with a calliper of 0.1 pooled standard deviations once propensity scores have been calculated for each patient. Kaplan–Meier analysis was used to estimate the probability of outcome at daily time intervals with censoring applied. When the last fact (outcomes of interest or other medical encounters) in the patient’s record was in the time window for analysis, the patient was censored on the day after the last fact in their record. We adjusted for the following covariates: age, sex, ethnicity, race, cerebrovascular diseases, infectious diseases, neoplasms, outpatient visits, hospital inpatient visits, beta blockers, ace inhibitors, calcium channel blockers, angiotensin blockers, metformin, glucagon-like peptide 1 agonist, body mass index, total cholesterol, LDL-C, HDL-C, and HbA1c. We defined participants with insomnia at baseline who were diagnosed later for the DE of interest (e.g., I10 for essential (primary) as cases, and participants without insomnia at baseline who were diagnosed later for the DE as controls. The Cox proportional hazards model was employed to derive the adjusted hazard ratios (HRs). HRs and 95% confidence intervals (CIs) were used to describe the relative hazard of the outcomes based on a comparison of time-to-event rates. The proportional hazards assumption was tested using the generalized Schoenfeld approach on the TriNetX platform, with adjusted HRs recalculated for specific time intervals if the assumptions were violated.

Compared to UKBB: In the TriNetX database, after propensity score matching, there were 110,374 participants with insomnia, and 16,371 participants with hypersomnia. We identified 109 overlapping DEs, along with data on all-cause mortality and an additional disease category encompassing all types of dementia. Using a Bonferroni correction threshold (0.05/111), we found that 110 signals were replicated for insomnia, and 97 for hypersomnia (**Extended Data Figure 5 and Supplementary File 7**).

Insomnia: In TriNetX, our replication of the UKBB results for insomnia yielded consistent hazard ratios (all > 1), reinforcing the robustness of the associations with short sleep duration noted in UKBB. Key endpoints such as hypertension (I10), hypercholesterolemia (E780), diverticular disease (K573), diaphragmatic hernia (K449), asthma (J459), gastroesophageal reflux disease (K219), type 2 diabetes (E119), circulatory conditions (Z867), and osteoarthritis (M179) all demonstrated hazard ratios in the range of ~ 6 –17 in TriNetX, well above the ~ 1.5 –2.8 range observed in UKBB. It may be noted here that these HRs across datasets are not directly comparable

due to different reference populations. This pattern held across numerous endpoints, including COPD, obesity, depressive episodes, and musculoskeletal disorders, with especially high replication signals (e.g., gastritis [K297 HR ~15.6] and anemia [D649 HR ~11.5]). Importantly, we also confirmed replication for all-cause mortality (HR ~1.49) and, available in TriNetX, all-types of dementia, which showed a strong association (HR ~7.2), further validating the link between sleep disturbance and neurodegeneration. Overall, the TriNetX evidence not only supports the UKBB findings but also amplifies the magnitude of risk, particularly for neurological and chronic conditions, highlighting the profound health impact of insomnia-associated DEs.

Hypersomnia: The TriNetX replication analysis of hypersomnia ($P < 0.05/111$) identified significant associations with 97 DEs, mortality, and all-type dementia, demonstrating remarkably consistent directionality with the UKBB's long sleep duration findings despite different methodologies. The strongest replicated associations included metabolic disorders (obesity: HR=16.96), psychiatric conditions (depression: HR=11.8; anxiety: HR=10.46), and gastrointestinal diseases (GERD: HR=9.52), with particularly robust effects for sleep apnea (HR=45.59). Notably, effect sizes in TriNetX were substantially larger than UK Biobank (e.g., 3.9-fold higher HR for obesity), likely reflecting the more extreme phenotype of clinically diagnosed hypersomnia versus self-reported long sleep. Both datasets converged on elevated risks for cardiometabolic, neuropsychiatric, and digestive disorders, though TriNetX revealed stronger associations with acute conditions (e.g., pulmonary fibrosis: HR=13.26) and medical interventions (chemotherapy: HR=7.20), potentially due to its electronic health record-based population with greater disease severity. The risk of dementia (HR=8.35) and replication of mortality (HR=1.15) across cohorts underscores the clinical significance of prolonged sleep phenotypes.

Supplementary Note 5: Association of binary traits of sleep duration as outcome variables in Mendelian randomization analyses with 525 disease endpoints in FinnGen and PGC

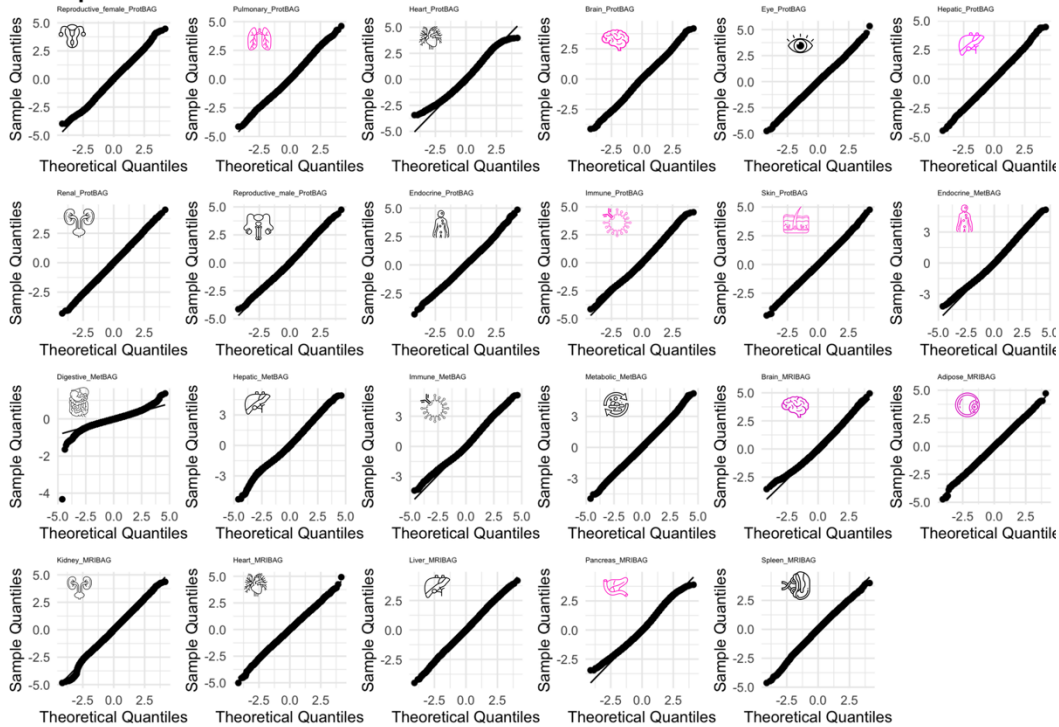
In our previous study⁸, two-sample Mendelian randomization suggested that sleep duration may arise as a consequence (outcome) of brain aging (exposure). Importantly, that analysis was based on a sleep duration GWAS using a linear model (via Plink), which did not account for the nonlinear associations identified in the current work. Given the relatively underpowered GWAS for the LLD subtypes, we could not directly test the inverse causality from the 2 LLD subtypes to the 2 sleep duration binary traits.

To further explore the possibility of reverse causality, specifically, whether sleep duration patterns may reflect consequences of underlying disease burden, we performed additional two-sample Mendelian randomization analyses using the binary sleep duration traits (short vs. normal and long vs. normal) as outcome variables, and 525 disease endpoints (DEs) from FinnGen and PGC as exposure variables (**Supplementary File 9**). Among the 179 DEs with sufficient instrumental variables (>7 IVs), we found no widespread evidence of causal effects on sleep duration. The only association that remained statistically significant after Bonferroni correction was from obesity (FinnGen code: E4_OBESITYCAL) to long sleep duration, with a P-value of 3.00×10^{-6} and an odds ratio of 0.80 (95% CI: 0.74–0.88) based on 10 SNPs. This suggests a potential inverse relationship, where genetic liability to obesity is associated with a lower likelihood of long sleep duration.

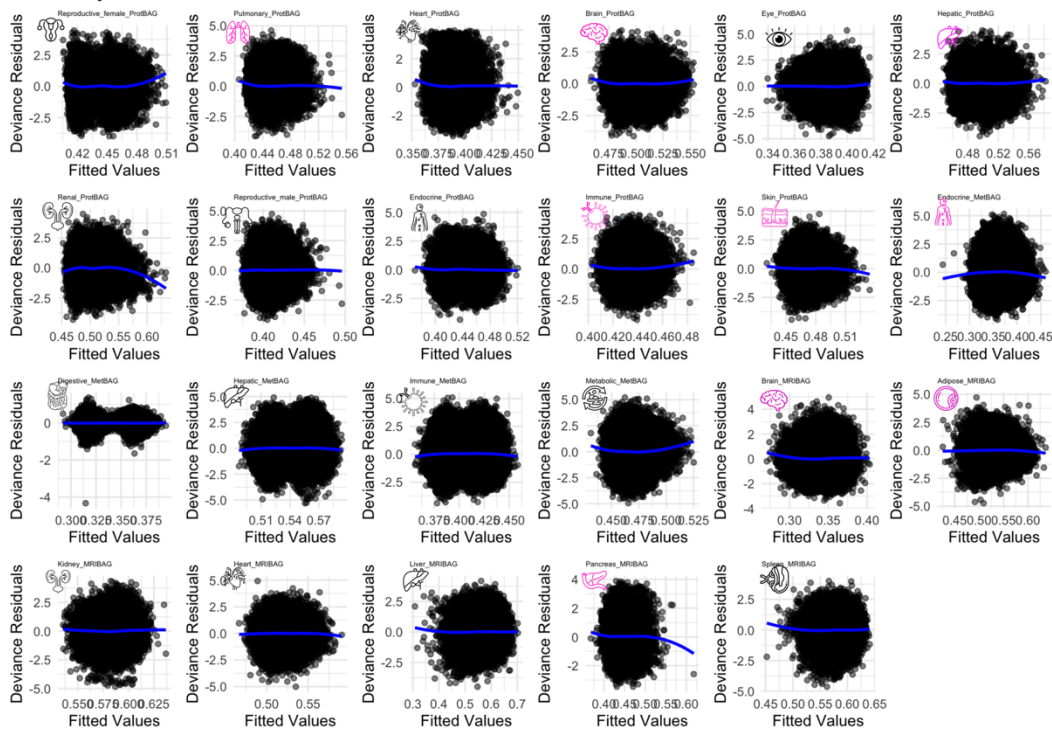
Furthermore, our sequential equation modeling results support a mediating role of organ-specific BAGs in linking sleep patterns to neuropsychiatric outcomes, suggesting a directional pathway (not strictly causal) where sleep may influence systemic aging processes that in turn modulate disease risk. Taken together, although we cannot fully rule out the possibility of reverse causality, especially for certain traits such as obesity, our current multi-modal evidence, integrating GWAS, MR, genetic correlation, and SEM, leans toward the interpretation that sleep duration is more likely a modifiable factor rather than a downstream consequence of disease burden. This perspective reinforces the potential of sleep-targeted interventions in disease prevention and aging modification strategies.

Supplementary Figure 1: Quantile-quantile (QQ) plots and residual vs. fitted value (RVF) plots for the 23 BAGs

QQ plot



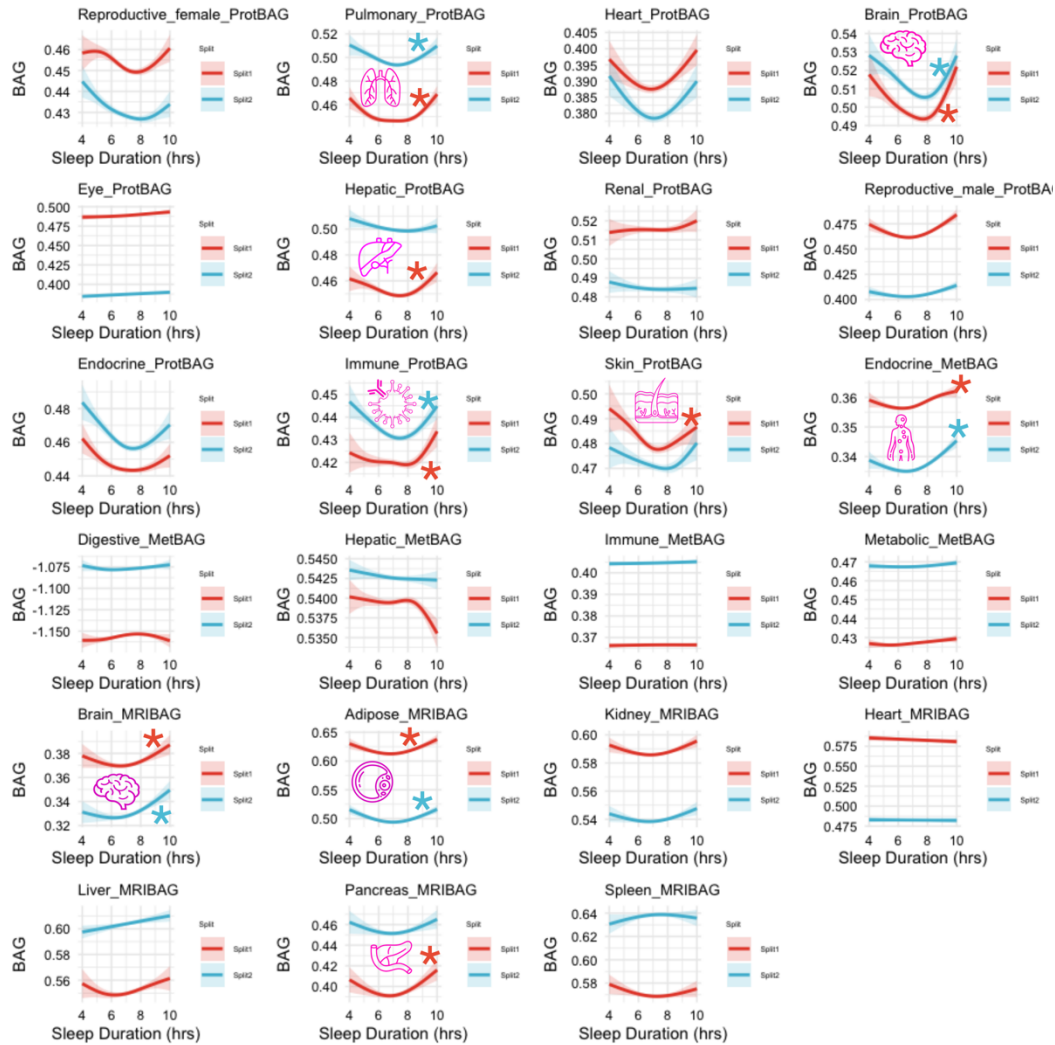
RVF plot



For the optimal model, defined by the selected smoothing parameter k and appropriate distribution family, we present the QQ plots and residual vs. fitted value (RVF) plots for each

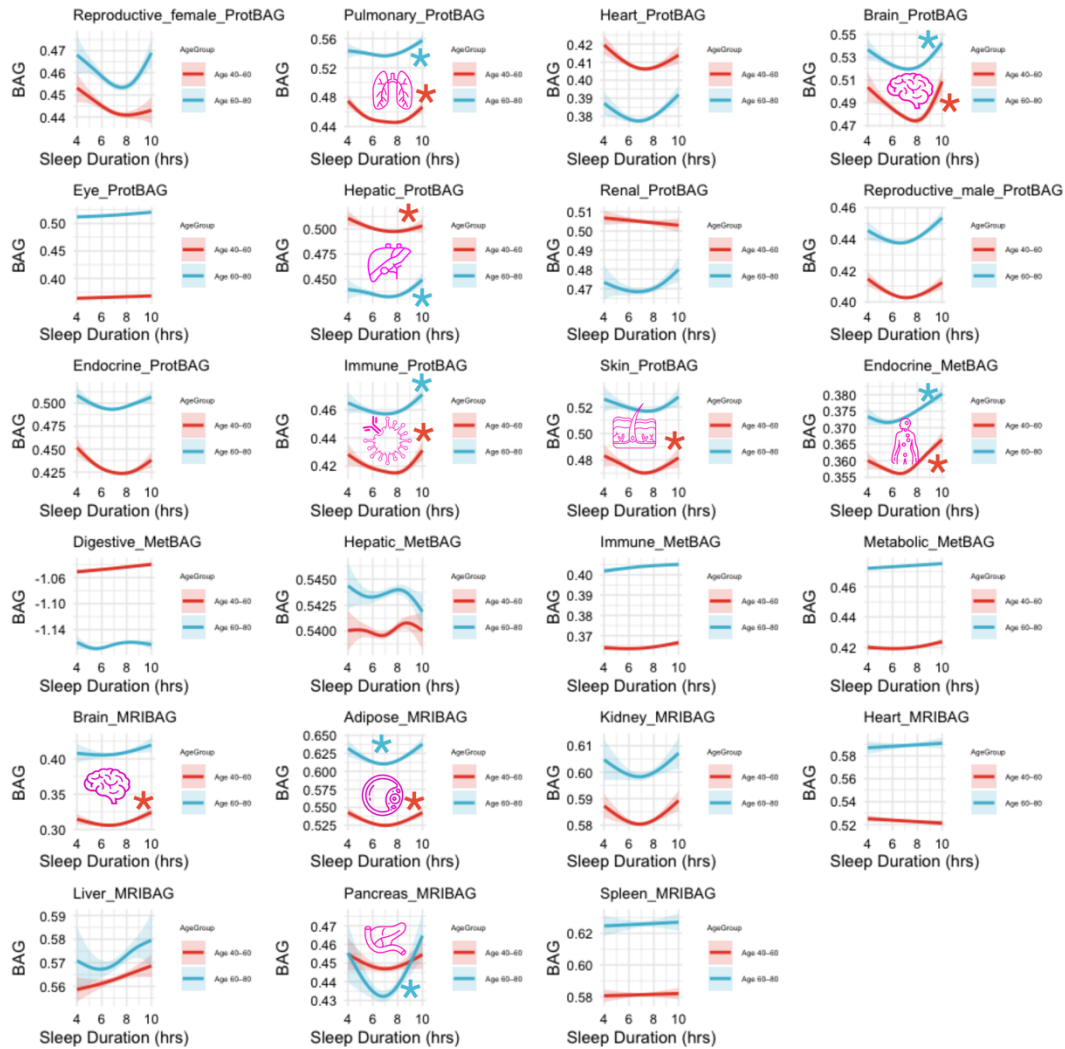
BAG. The QQ plots demonstrated that the residuals from these significant models generally followed the theoretical normal distribution, with only minor deviations in the tails. Similarly, the residual-vs-fitted (RVF) plots for the significant associations exhibited no major heteroscedasticity, with residuals evenly scattered around zero and smooth loess lines remaining largely flat. These patterns indicate stable variance, and a good model fit across the range of predicted values. Importantly, the significant associations did not display stronger deviations or assumption violations compared to non-significant models. Together, these diagnostics support that the reported significant sleep–BAG associations are unlikely to be artifacts of model misspecification or assumption violations.

Supplementary Figure 2: Split-sample analysis of the 23 BAGs



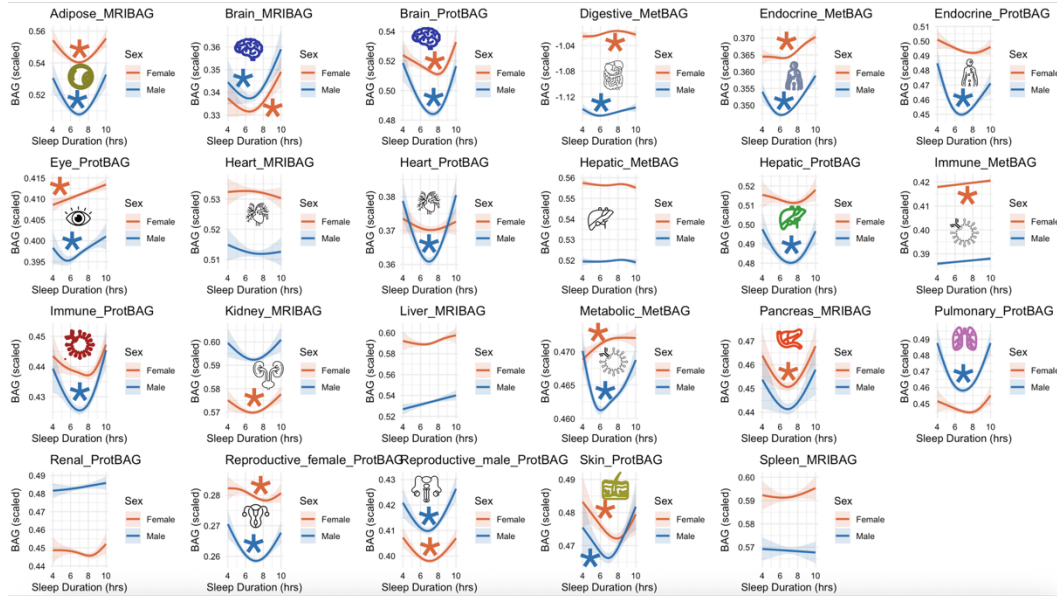
We randomly divided the entire population into split1 and split2 populations, then refitted the same GAM model (i.e., the optimal k and family distribution) to evaluate the consistency of the detected U-shaped patterns. Due to reduced sample size, we defined the P-value threshold here as $P < 0.05/9$; we used the star symbol (*) to indicate significant signals. Overall, we found a robust U-shaped pattern across random splits. Reduced statistical power may explain the lack of significant findings in some BAGs. We showed the modeling results for all 23 BAGs for transparency. Detailed statistics are presented in **Supplementary Table 3**.

297 **Supplementary Figure 3: Age-stratified analysis of the 23 BAGs**



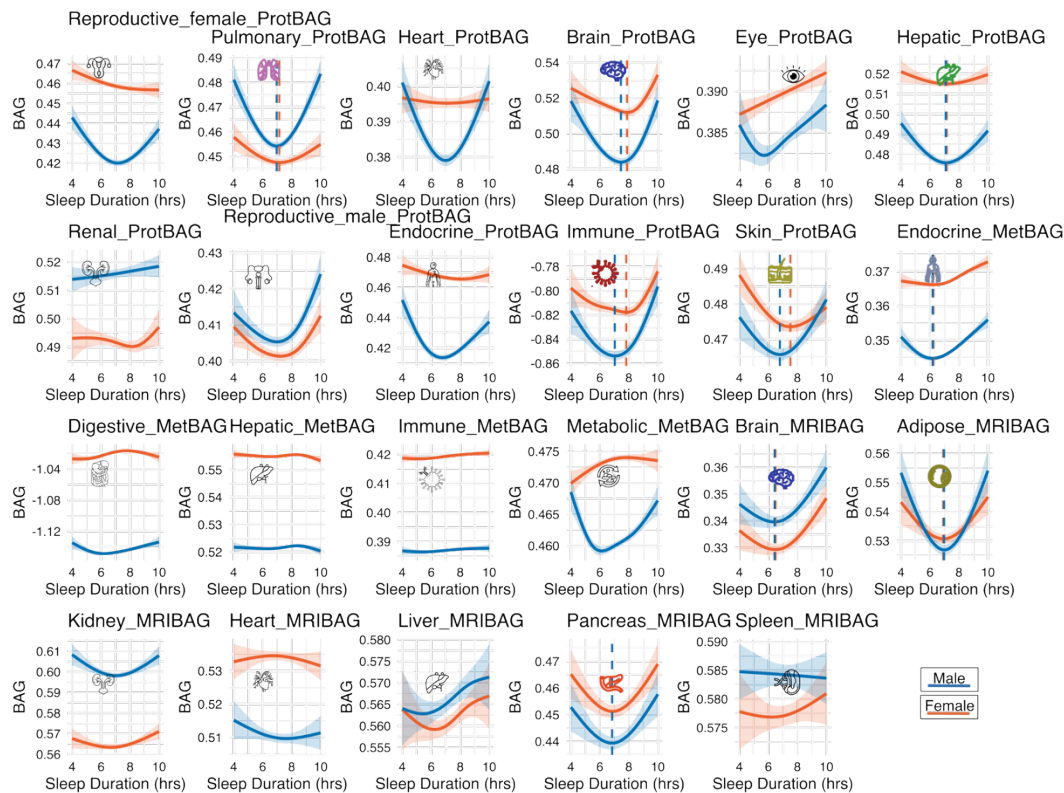
298 We stratified the entire population into [40-60] years old and [60-80] years old bins to evaluate
 299 the robustness of the U-shaped patterns. Due to reduced sample size, we defined the P-value
 300 threshold here as $P < 0.05/9$; we used the star symbol (*) to indicate significant signals. Overall,
 301 we found a robust U-shaped pattern across age strata. Age-stratified analyses largely reproduced
 302 the main associations, with only non-significant effects observed in the 60–80-year group for
 303 skin ProtBAG and brain MRIBAG, and in the 40-60-year group for pancreas MRIBAG.
 304 Reduced statistical power and a narrower age range within strata may explain the lack of
 305 significant findings in these age groups. We showed the modeling results for all 23 BAGs for
 306 transparency. Detailed statistics are presented in **Supplementary Table 3**.
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Supplementary Figure 4: Sex-stratified analysis of 23 BAGs



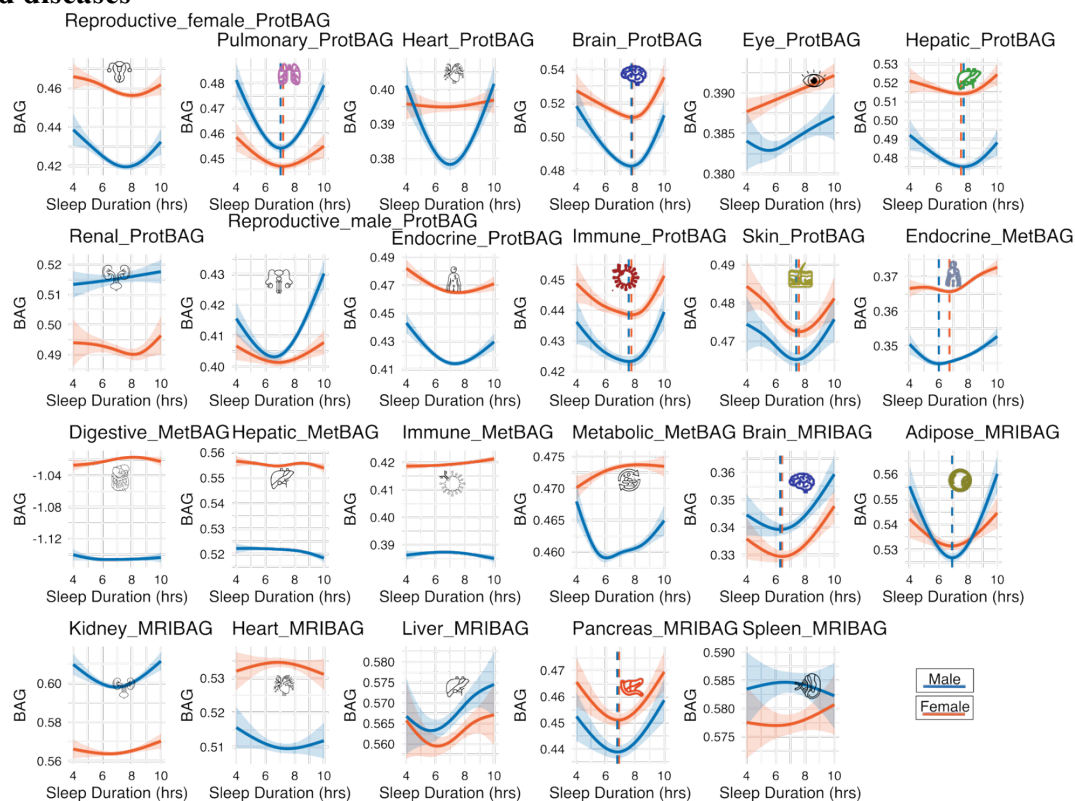
We split the cohort into females and males and re-fit the same GAM specification selected in the main analysis (fixed optimal k and family), testing the sleep term within each sex. Significance was assessed with Bonferroni correction ($\alpha = 0.05/23$); significant panels are marked with icons and asterisks. Overall, U-shaped associations were broadly reproducible across sexes, with some BAGs showing stronger effects in males (e.g., the endocrine ProtBAG) and others in females (e.g., pancreas and kidney MRIBAG). These sex differences may reflect biology, such as hormone milieu (estrogen/androgen signaling), sex-specific sleep architecture and circadian regulation, organ-specific metabolic and inflammatory pathways, and life-stage effects (e.g., menopause), in addition to possible sample-size or residual confounding differences between strata. Colored icons represent the 9 significant sleep-BAG signals identified in **Fig. 1**. Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 5: Sensitivity check analysis by including age-sex interaction as an additional term



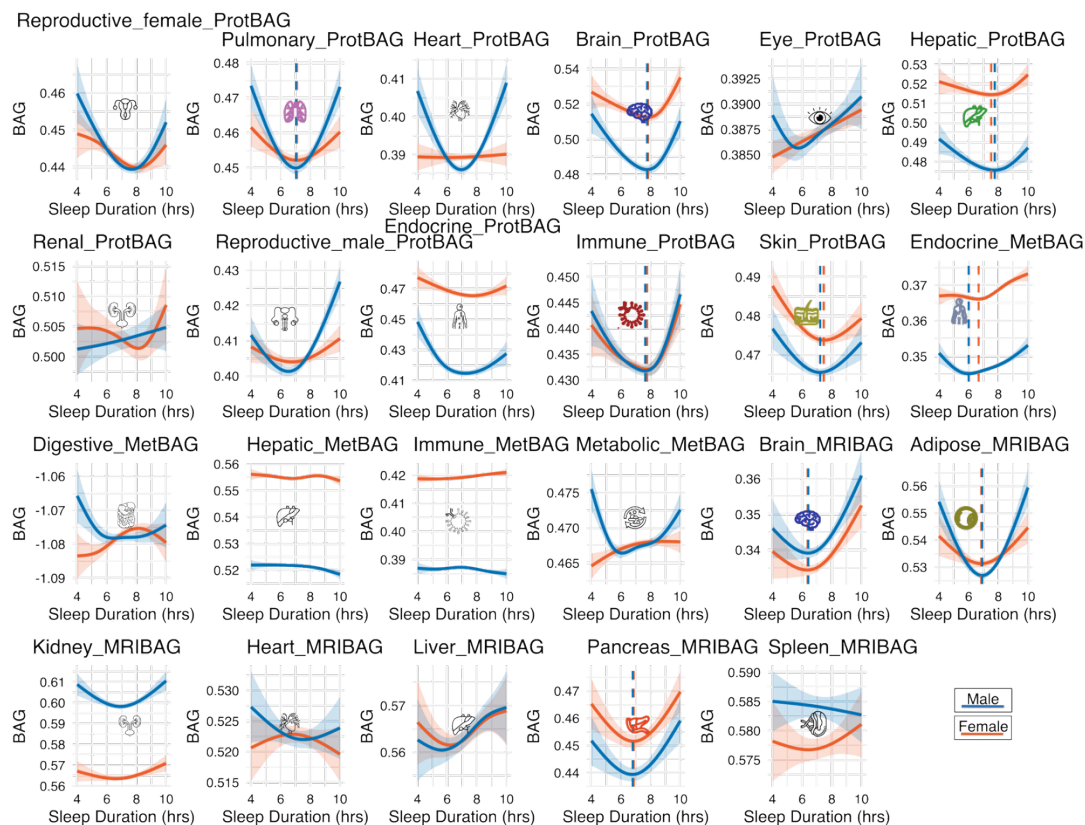
Generalized additive models were fit in the UK Biobank after adding the age-sex interaction term in the original GAM model. Dashed vertical lines indicate the sex-specific sleep duration corresponding to the minimum predicted BAG (“optimal” sleep). Colored icons correspond to the 9 significant BAGs identified in **Fig. 1**. The age-sex interaction term was significant for several BAGs, consistent with the age-stratified results shown in **Supplementary Fig. 4**, where the estimated “optimal” sleep duration differs between the two age groups. Nevertheless, the overall U-shaped association remains, with only minor shifts in the curves. Sex differences in the sleep-BAG associations may also be influenced by sex-specific reporting/measurement differences in self-reported sleep duration, as well as by other sleep exposures with marked sex disparities, such as higher prevalence of insomnia/restless legs syndrome in females and sleep apnea in males, which could confound or modify the observed relationships. Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 6: Sensitivity check analysis by excluding participants with 3 sleep-related diseases



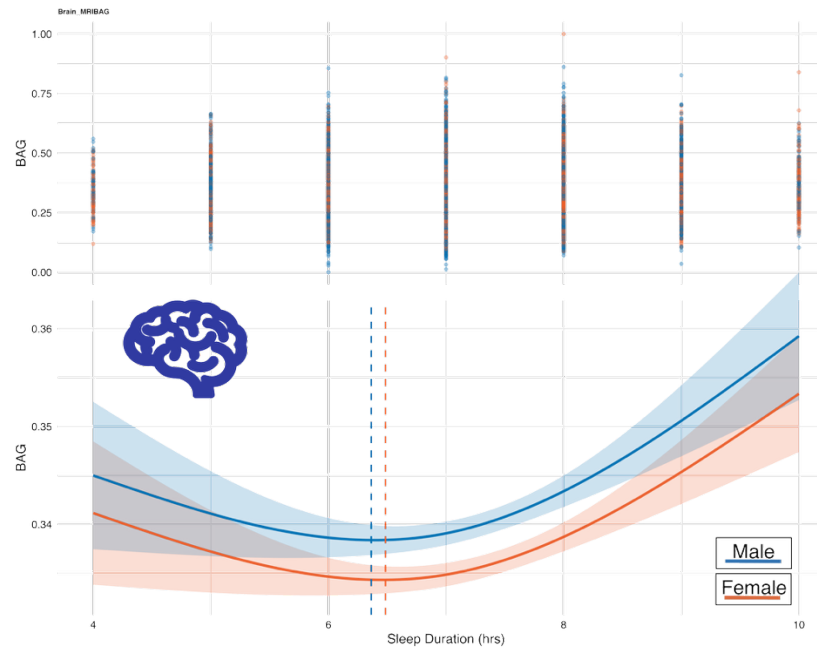
Generalized additive models were fit in the UK Biobank after removing individuals with any of the following sleep-related diagnoses (sleep apnea, insomnia, or restless legs syndrome). For each organ-specific BAG, we refit the same model as in **Fig. 1**. Dashed vertical lines indicate the sex-specific sleep duration corresponding to the minimum predicted BAG (“optimal” sleep). Colored icons correspond to the 9 significant BAGs identified in **Fig. 1**. After excluding participants with three types of sleep disorders, the U-shaped pattern persisted, although the estimated curve and the “optimal” sleep duration changed slightly. Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 7: Sensitivity check analysis by including smoking status as an additional covariate



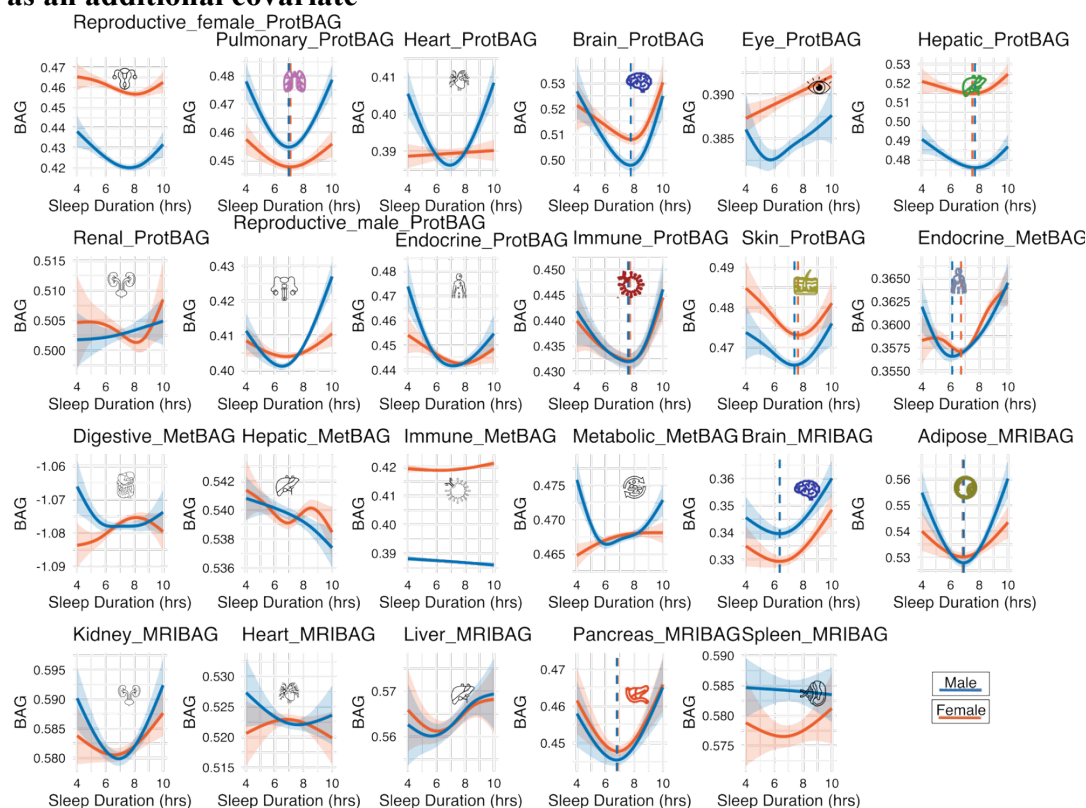
Generalized additive models were fit in the UK Biobank after adding smoking status (Field ID: 20116) as an additional covariate in the original GAM model. Dashed vertical lines indicate the sex-specific sleep duration corresponding to the minimum predicted BAG (“optimal” sleep). Colored icons correspond to the 9 significant BAGs identified in **Fig. 1**. After accounting for smoking status in the GAM, the U-shaped relationship pattern between sleep and BAG was robust, although the curve and the “optimal” sleep duration showed slight variations. Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 8: Sensitivity check analysis by including alcohol consumption status as an additional covariate



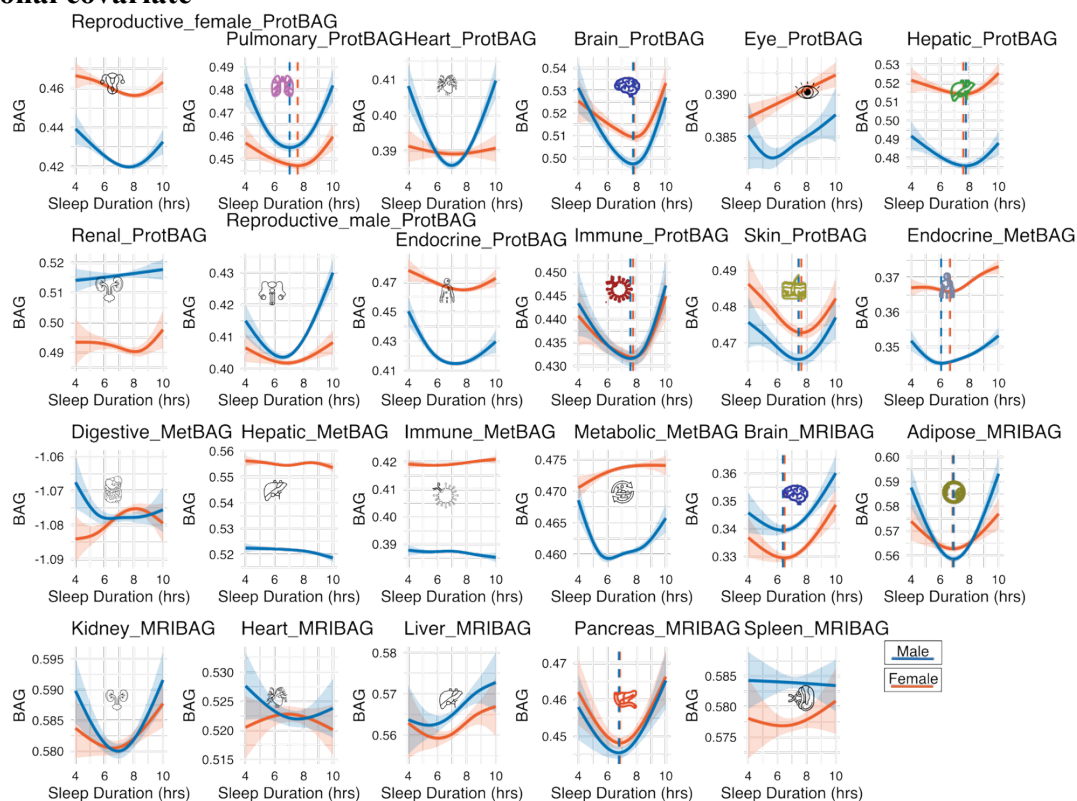
Generalized additive models were fit in the UK Biobank after adding alcohol consumption status (Field ID: 20117) as an additional covariate in the original GAM model for the brain MRIBAG (our data only covers the MRIBAG population for this variable). Dashed vertical lines indicate the sex-specific sleep duration corresponding to the minimum predicted BAG (“optimal” sleep). Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 9: Sensitivity check analysis by including Townsend deprivation index as an additional covariate



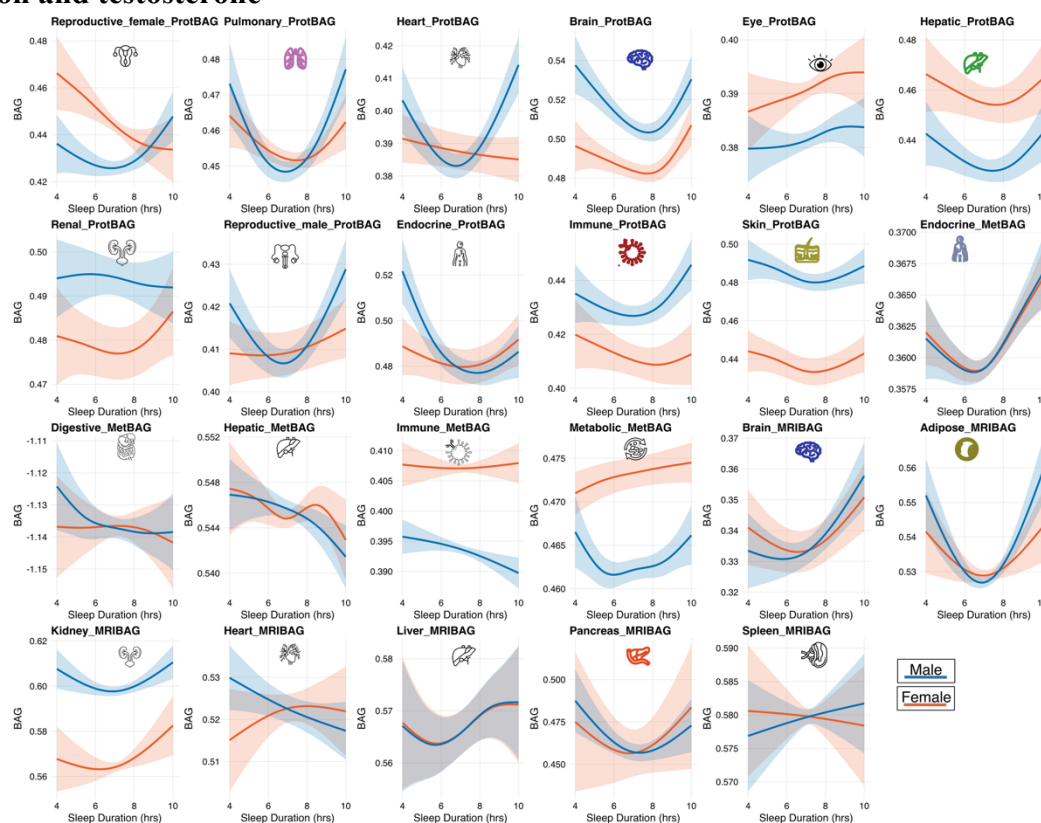
Generalized additive models were fit in the UK Biobank after adding the Townsend deprivation index (TDI; Field ID: 22189) as an additional covariate in the original GAM model. Dashed vertical lines indicate the sex-specific sleep duration corresponding to the minimum predicted BAG (“optimal” sleep). Colored icons correspond to the 9 significant BAGs identified in **Fig. 1**. After accounting for TDI in the GAM, the U-shaped relationship pattern between sleep and BAG was robust, although the curve and the “optimal” sleep duration showed slight variations (e.g., endocrine MetBAG). Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 10: Sensitivity check analysis by including computer use time as an additional covariate



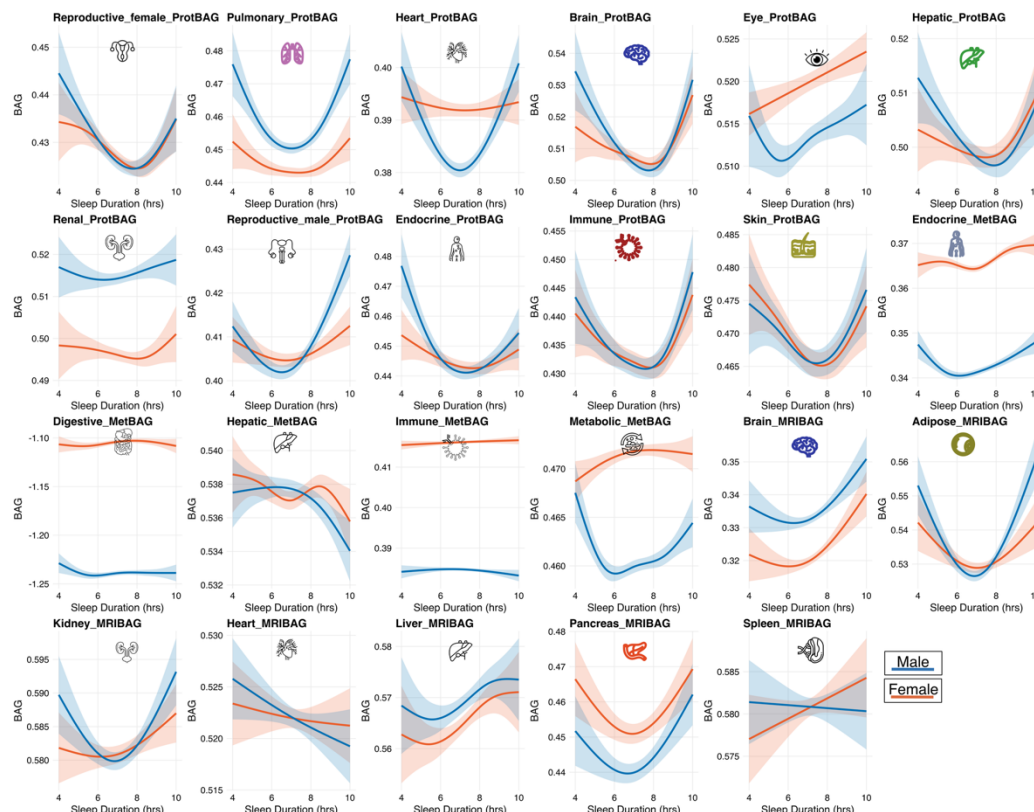
Generalized additive models were fit in the UK Biobank after adding the computer use time (Field ID: 1080) as an additional covariate in the original GAM model. Dashed vertical lines indicate the sex-specific sleep duration corresponding to the minimum predicted BAG (“optimal” sleep). Colored icons correspond to the 9 significant BAGs identified in **Fig. 1**. After accounting for computer use time in the GAM, the U-shaped relationship pattern between sleep and BAG was robust, although the curve and the “optimal” sleep duration showed slight variations. Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 11: Sensitivity check analysis by testing the interaction of sleep duration and testosterone



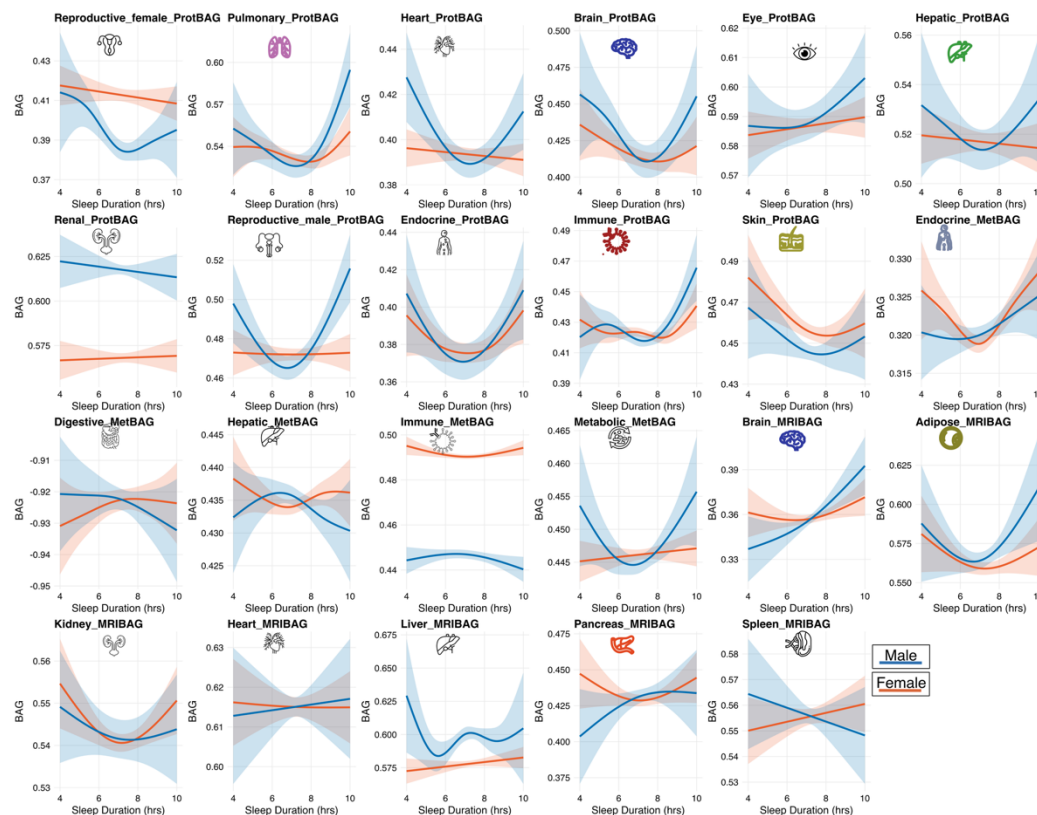
We refit the GAMs to include testosterone as a covariate and an interaction term with sleep duration (sleep duration $\times$ testosterone). None of the interaction effects reached significance (all $P > 0.05$), and while the 9 U-shaped associations remained, based on the results from **Fig. 1** in the main text, their curvature or inflection points shifted slightly in a few BAGs. Of note, the sample sizes reduced slightly compared to **Fig. 1**, because not all the full UKBB samples have data available for testosterone (i.e., UKBB only covers 426,570 participants out of the 500k population before merging with the BAG populations: <https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=30850>). Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 12: Sensitivity check analysis by testing the interaction of sleep duration and SHBG



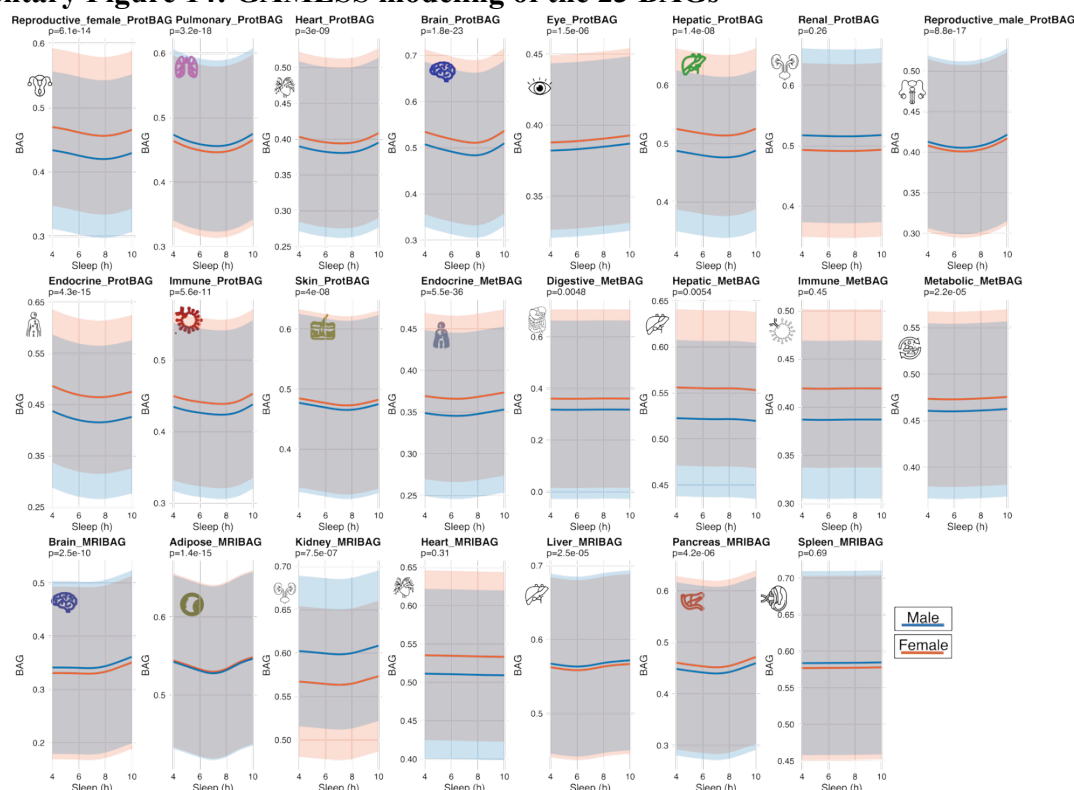
We refit the GAMs to include SHBG as a covariate and an interaction term with sleep duration (sleep duration $\times$ SHBG). None of the interaction effects reached significance (all $P > 0.05$), and while the 9 U-shaped associations remained, based on the results from **Fig. 1** in the main text, their curvature or inflection points shifted slightly in a few BAGs. Of note, the sample sizes reduced slightly compared to **Fig. 1**, because not all the full UKBB samples have data available for SHBG (i.e., UKBB only covers 427,697 participants out of the 500k population before merging with the BAG populations: <https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=30830>). Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 13: Sensitivity check analysis by testing the interaction of sleep duration and estradiol



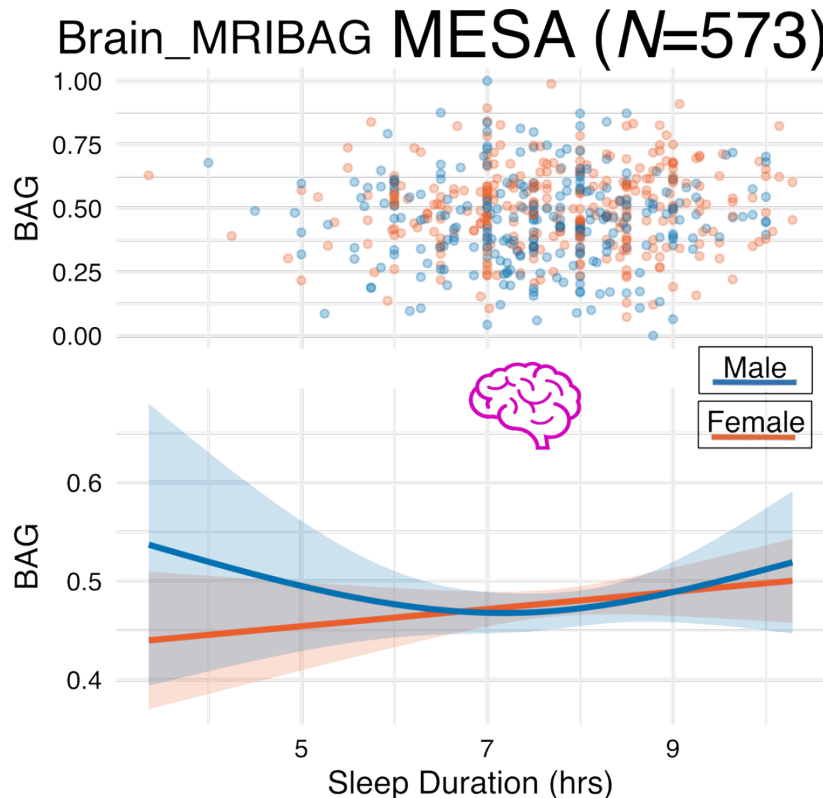
We refit the GAMs to include estradiol as a covariate and an interaction term with sleep duration (sleep duration $\times$ estradiol). Adding estradiol altered the fitted curves and, for the hepatic ProtBAG, the sleep $\times$ estradiol interaction was nominally significant ($P=0.0196$). That means the association between sleep duration and hepatic BAG appears to depend on estradiol level, e.g., the U-shape's curvature/inflection may differ at low vs. high estradiol. Of note, the sample sizes reduced dramatically compared to **Fig. 1**, because not all the full UKBB samples have data available for estradiol (i.e., UKBB only covers 77,594 participants out of the 500k population before merging with the BAG populations: <https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=30800>). Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 14: GAMLSS modeling of the 23 BAGs



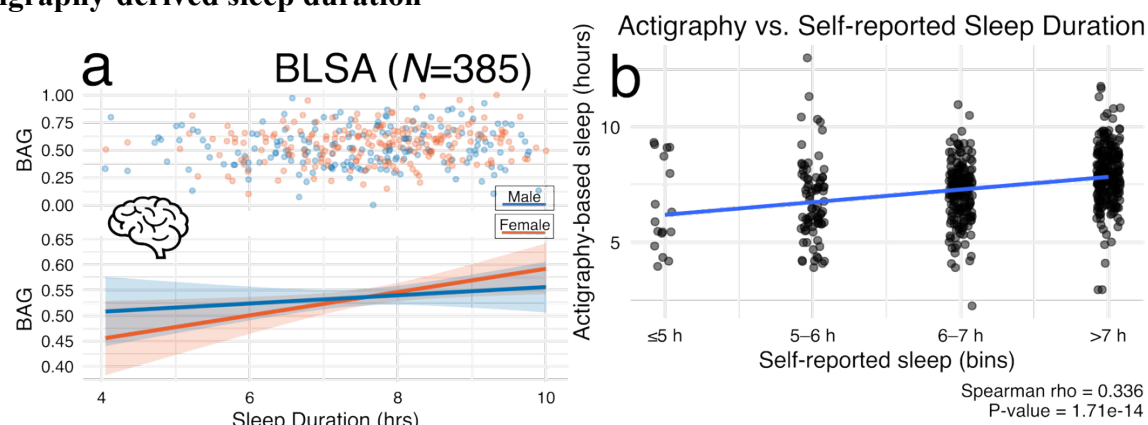
All 23 sleep–BAG associations were modelled using the `gamlss::gamlss()` model, with consistent U-shaped patterns observed across the 9 significant signals identified in Fig. 1, although minor differences exist due to different modelling assumptions. This likely reflects the more conservative nature of the `gamlss` framework, which not only models the mean but also incorporates variance and shape parameters, often smoothing over subtle group-specific interactions. In contrast, `mgcv::gam()` flexibly fits group-specific splines (e.g., $s(\text{sleep_duration}, \text{by} = \text{sex})$), which can accentuate interaction effects. Despite harmonizing settings such as the smoothing method, number of knots, and family distribution, the underlying assumptions and modeling focus differ: `mgcv` emphasizes flexibility in mean structure. At the same time, `GAMLSS` prioritizes stable distributional fitting, potentially underestimating sex–sleep interactions in the presence of noisy predictors like self-reported sleep duration. These results highlight that the associations are robust across distinct statistical frameworks, despite differences in how they handle complexity and interaction. Detailed statistics are presented in **Supplementary Table 3**.

Supplementary Figure 15: External validation of the U-shaped patterns using MESA self-reported sleep duration



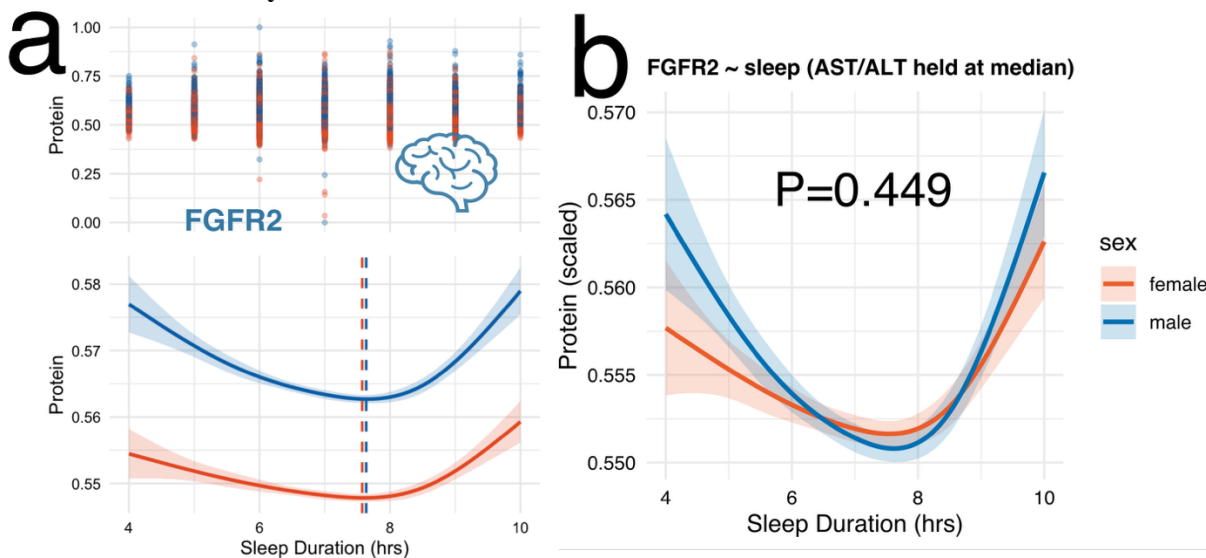
Using data from 573 MESA participants, we applied the same GAM model to examine the association between brain MRIBAG and self-reported sleep duration, calculated as the average of weekday and weekend sleep durations measured separately. In the MESA cohort, we observed a weak U-shaped relationship between sleep duration and brain MRIBAG, particularly among males, although this pattern did not reach statistical significance ($P_1=0.47$). Several factors may contribute to the attenuated signal in MESA compared to the UK Biobank. First, the sample size in MESA was substantially smaller ($N=573$), limiting statistical power to detect subtle non-linear associations. Second, the MESA population is older on average (mean age of 72.06 years), which may reduce variability in sleep duration and increase the influence of age-related comorbidities and neurodegenerative changes, thereby masking the effect of sleep. Sex differences may also play a role, as the U-shaped pattern was visually evident only in males, suggesting potential biological or behavioral differences in sleep-brain aging dynamics.

Supplementary Figure 16: External validation of the U-shaped patterns based on BLSA actigraphy-derived sleep duration



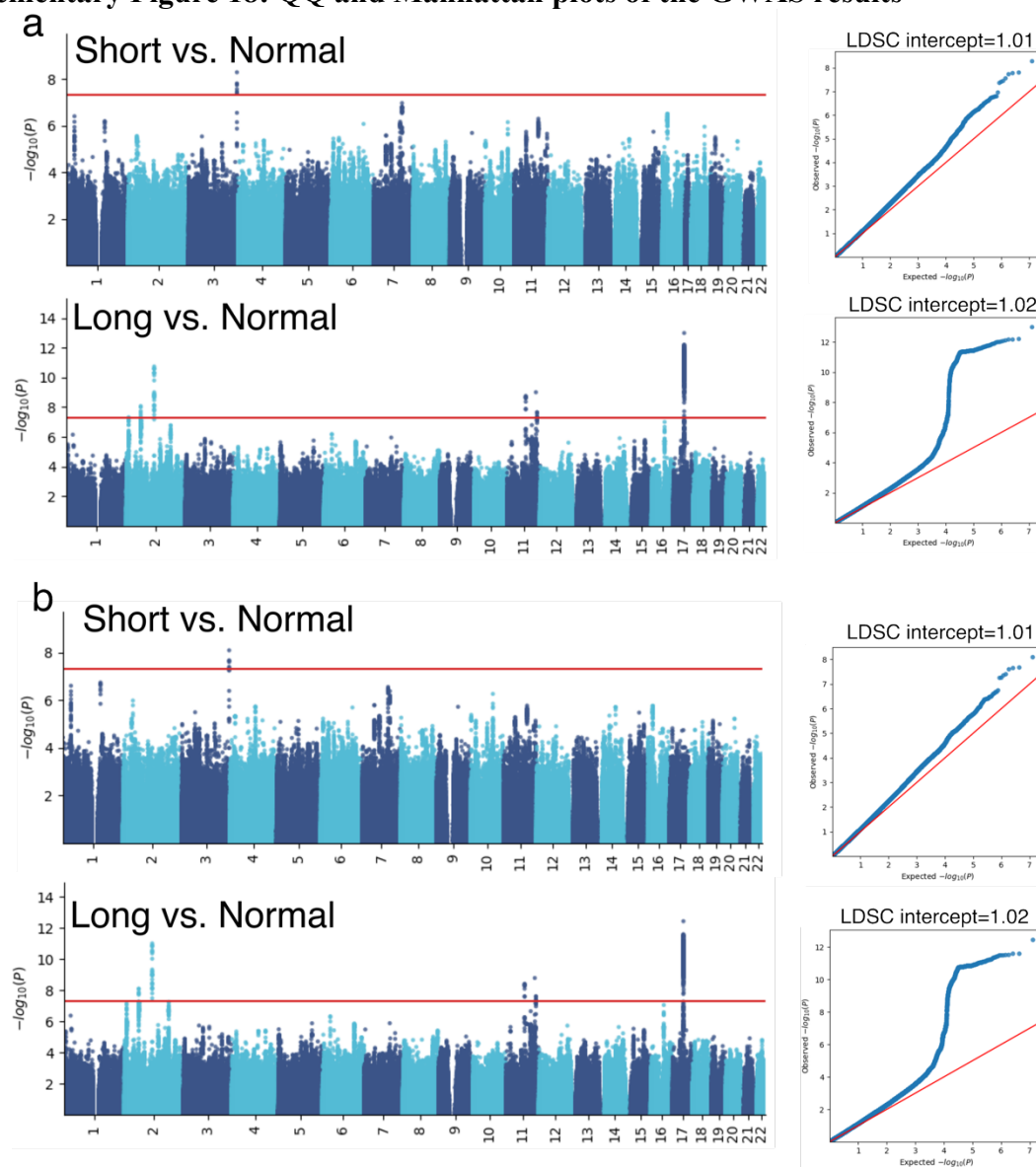
a) Actigraphy-derived sleep duration (hours) is not linked to the brain MRIBAG among BLSA participants ($N=385$; $P_1=0.40$). Lines represent sex-specific with shaded 95% confidence intervals. No significant associations were observed, likely due to the limited statistical power from the small sample size and the relatively healthy, older BLSA cohort (predominantly >70 years), which may exhibit a narrower range of both sleep and brain aging phenotypes. The absence of a U-shaped pattern often observed in younger or more heterogeneous populations could reflect physiological adaptation in late life, where sleep variability may exert weaker effects on brain aging due to homeostatic and circadian adjustments associated with aging. **b)** Correlation between actigraphy-based and self-reported sleep duration, indicating only a modest concordance between objective and subjective measures, echoing previous studies^{9,10}. The U-shaped association between sleep duration and biological age gap observed with self-reported sleep likely reflects perceived sleep adequacy and long-term behavioral patterns, which integrate both physiological and psychosocial dimensions of sleep health. In contrast, actigraphy-based sleep provides a more objective, momentary measure of sleep–wake activity, capturing nightly variability but less influenced by subjective factors such as fatigue, sleep satisfaction, or chronic insomnia symptoms. Self-reports tend to overestimate sleep duration and incorporate cognitive and emotional perceptions of restfulness, which are closely tied to overall well-being and biological aging processes. Conversely, actigraphy may detect shorter but fragmented sleep periods that do not necessarily correspond to self-perceived sleep deficiency. As a result, self-reported sleep duration may better reflect long-term sleep behaviors and their cumulative physiological impact, whereas actigraphy captures short-term sleep patterns that might not yet manifest as measurable biological aging differences.

Supplementary Figure 17: Sensitivity check of the ProWAS for protein FGFR2 of sleep duration mediated by the AST/ALT ratio



a) Original ProWAS results for FGFR2. **b)** Results after including AST/ALT as an additional covariate and its interaction with sleep duration. The interaction term was not statistically significant ($P\text{-value} > 0.05$), although the U-shaped association pattern showed a slight change.

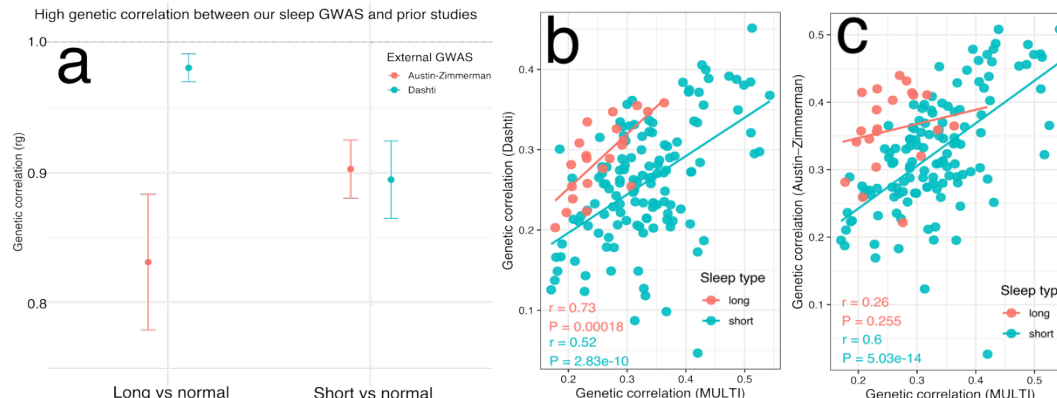
517 **Supplementary Figure 18: QQ and Manhattan plots of the GWAS results**



518 **a)** We present Manhattan and QQ plots for the two GWAS results: short vs. normal sleep
 519 duration and long versus normal sleep duration. The LDSC intercepts were close to 1, suggesting
 520 minimal bias from population structure. **b)** Manhattan and QQ plots for the two GWASs by
 521 adding additional covariates, including smoke status, Townsend deprivation index, and computer
 522 use time, in the original GWASs.

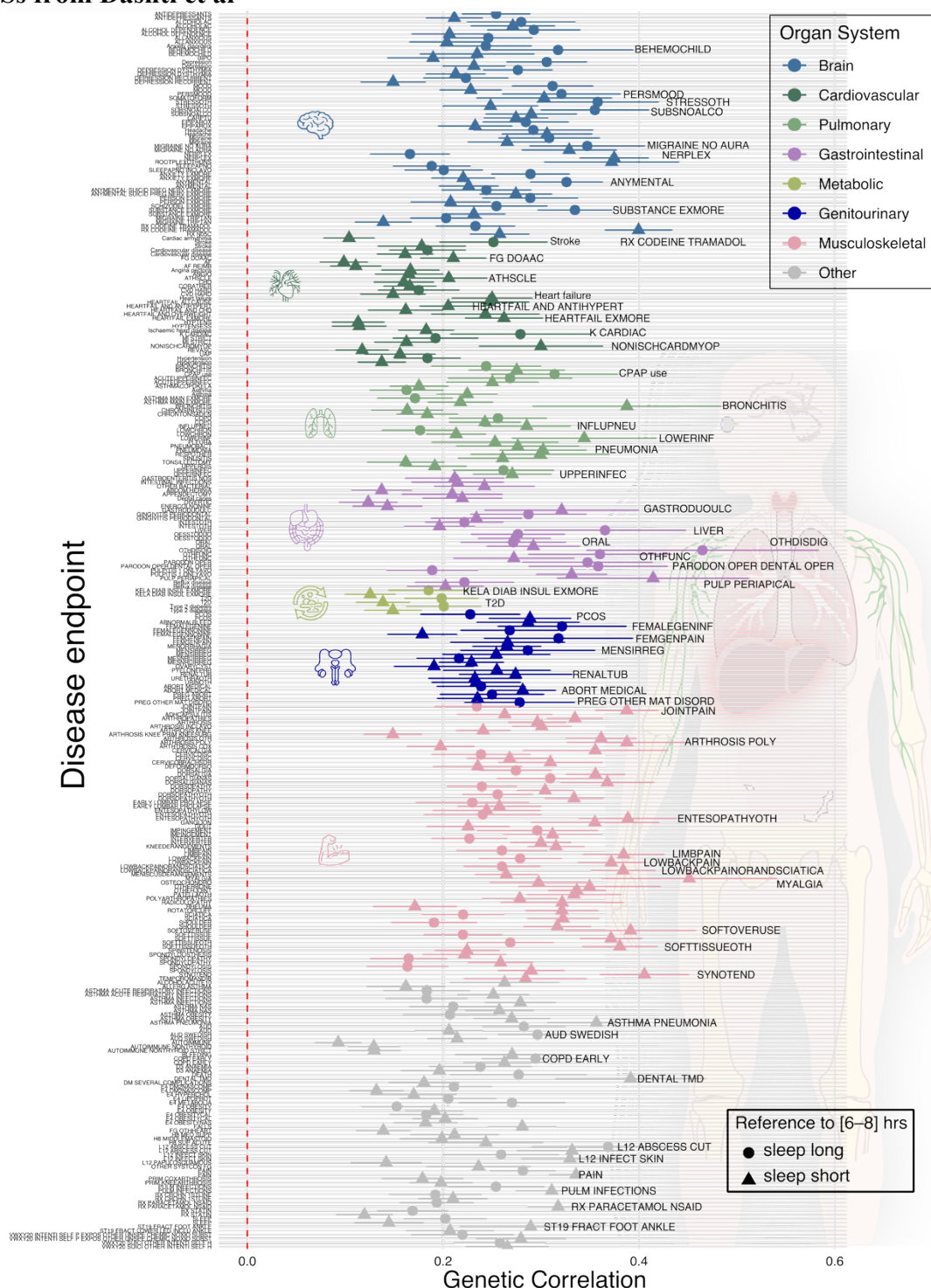
524

Supplementary Figure 19: Genetic correlation between our binary sleep GWAS with two previous GWASs from Dashti et al and Austin-Zimmerman et al



a) We downloaded GWAS summary statistics from Dashti et al. and Austin-Zimmerman et al. and used LDSC to estimate pairwise genetic correlations between our GWAS and each of these studies for short vs. normal and long vs. normal sleep. We observed consistently high genetic correlations, indicating that differences in the number of genomic loci across studies are largely driven by differences in sample size and in the operational definitions of short, normal, and long sleep duration. **b)** Using FinnGen, we demonstrate that the significant DE-sleep signals we found in our GWAS correlate with signals in the sleep GWAS summary statistics of Dashti et al. **c)** Using FinnGen, we demonstrate that the significant DE-sleep signals we found in our GWAS correlate with signals in the sleep GWAS summary statistics of Austin-Zimmerman et al.

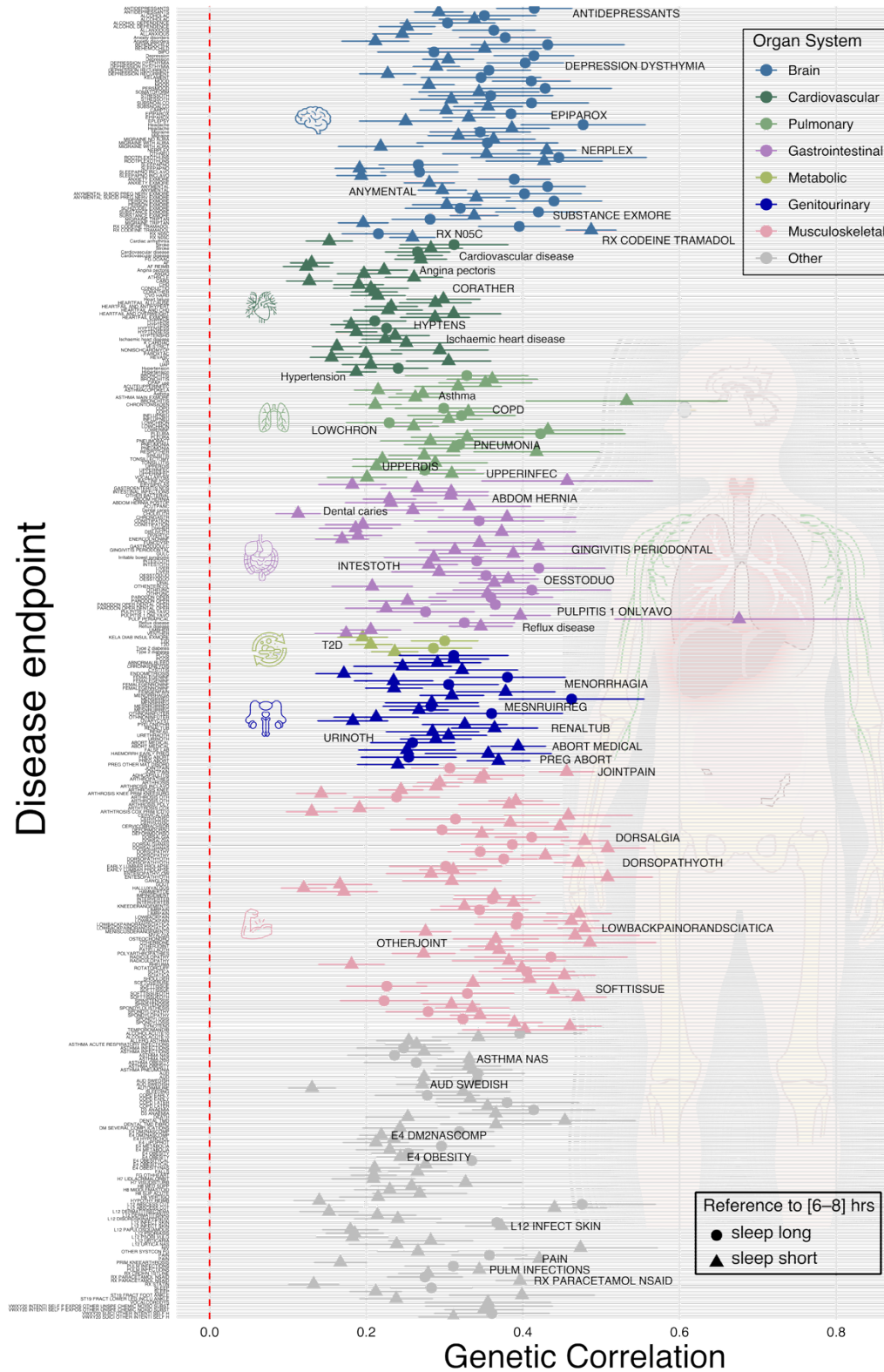
Supplementary Figure 20: Genetic correlation between FinnGen DEs and previous sleep GWASs from Dashti et al



Genetic correlations (LDSC; mean $\pm$ s.e.) were shown between short sleep vs. normal sleep (triangles) and long sleep vs. normal sleep (circles) and 309 disease endpoints (DEs) from FinnGen (P-value $< 0.05/527$). Points are colored by organ system and ordered on the y-axis from the brain (top) to other (bottom) to reflect approximate human anatomy. Horizontal error bars

denote ± 1 s.e., and the dashed red-vertical line indicates zero genetic correlation. For interpretability, the disease names shown as text annotations correspond to the top 10 representative DEs within each organ category (ranked by the smallest available p-value for the sleep–DE genetic correlation; otherwise by the largest absolute genetic correlation). **Supplementary File 5b** presents detailed statistics for our genetic correlation analysis.

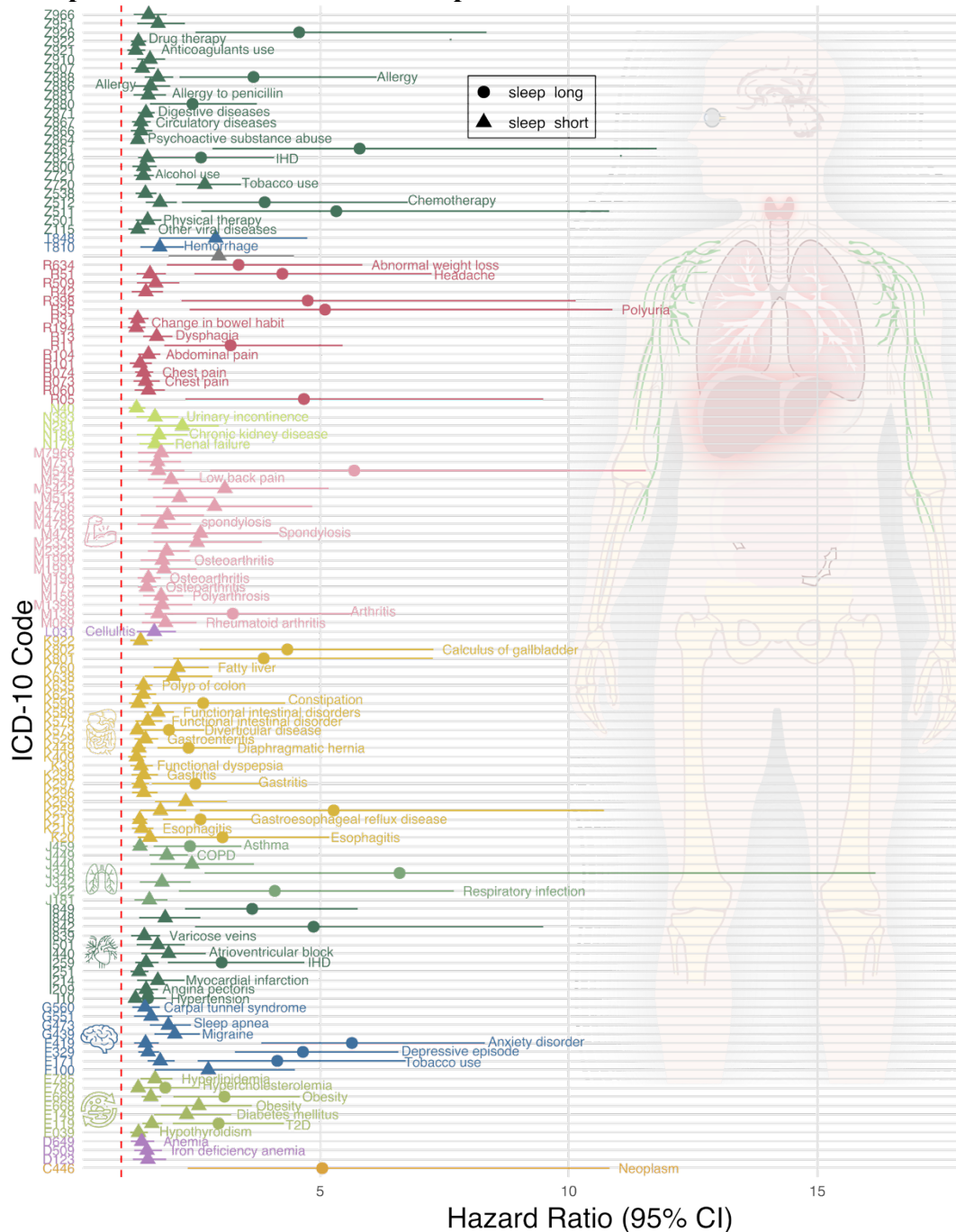
552 **Supplementary Figure 21: Genetic correlation between FinnGen DEs and previous sleep**
 553 **GWASs from Austin-Zimmerman et al**



554 Genetic correlations (LDSC; mean $\pm$ s.e.) were shown between short sleep vs. normal sleep
 555 (triangles) and long sleep vs. normal sleep (circles) and 361 disease endpoints (DEs) from
 556

FinnGen (P-value<0.05/527). Points are colored by organ system and ordered on the y-axis from the brain (top) to other (bottom) to reflect approximate human anatomy. Horizontal error bars denote ± 1 s.e., and the dashed red-vertical line indicates zero genetic correlation. For interpretability, the disease names shown as text annotations correspond to the top 10 representative DEs within each organ category (ranked by the smallest available p-value for the sleep–DE genetic correlation; otherwise by the largest absolute genetic correlation). **Supplementary File 5c** presents detailed statistics for our genetic correlation analysis.

Supplementary Figure 22: Sensitivity analysis using 7-9 hours as the reference category for normal sleep duration in disease incidence prediction



We re-ran the survival analysis using 7-9 hours as the reference for normal sleep duration and confirmed replication of the main sleep-DE associations observed in the primary analysis.

Supplementary Table 1: The characteristics of participants consolidated via the MULTI study

Data type	BAG/Omics	Study	N	Age	Sex (female)
Individual	7 MRIBAG	UKBB	43,135	64.15±7.53	19,744/53%
	11 ProtBAG		50,316	64.16±8.04	28,581/54%
	5 MetBAG		274,247	56.56±8.08	147,994/54%
	Genetics		342,341	56.80±7.91	181,440/53%
	Sleep duration (self-report)		494,951	56.53±8.09	268,970/54%
	Disease endpoints	TriNetX ^a	162,253,371	47.00±25.00	84,372,753/52%
	Sleep duration ^c (self-report & actigraphy) & Brain MRIBAG	BLSA	385	70.07±13.45	206/53%
	Sleep duration (self-report) & Brain MRIBAG	MESA	573	72.06±6.63	315/55%
Summary	Genetics	FinnGen	521	NA ^b	NA ^b
		PGC	6	NA ^b	NA ^b

^aA detailed table for TriNetX is presented in **Table 8**.

^bFinnGen and PGC only provide summary-level GWAS statistics; individual-level age and sex information are unavailable.

^cIn BLSA, sleep duration was assessed through both actigraphy and self-reported questionnaires. For the questionnaire-based measure, participants were asked: ‘On average, in the past month, how many hours of sleep did you get each night?’ with the following response options: ‘More than 7 hours,’ ‘More than 6, up to 7 hours,’ ‘More than 5, up to 6 hours,’ ‘5 hours or fewer,’ ‘Didn’t know,’ and ‘Refuse to answer’. This categorical format differs from the -UK Biobank, which recorded sleep duration as rounded hourly values.

Supplementary Table 2: Statistics of the GAM analysis between sleep duration and the 23 multi-organ, multi-omics biological aging clocks

For each BAG, we fitted a generalized additive model (GAM) with cubic regression splines to assess the nonlinear association between sleep duration and BAG, stratified by sex and sex-sleep interaction term. Model selection was performed by evaluating combinations of smoothing dimensions ($k=1, 3, 5, 10, 15, 20$) and GAM families (i.e., Gaussian, t-distribution, and gamma distribution), with the optimal model chosen based on the lowest Akaike information criterion. We tested *i*) the main effect (sleep duration; P_1), *ii*) sex difference in population mean (P_2), and *iii*) sex-sleep interaction terms (P_3) on each BAG, including relevant covariates. Using bold text, we denote the significant signals ($P\text{-value}<0.05/23$). Of note, EDF reflects the complexity of the smoothing term, serving as an indicator of non-linearity in the modeled relationship rather than the model's overall effect size and fit to the outcome (BAG). The full stats for the covariates are included in **Supplementary File 1**. We used bold-text to highlight the 9 significant sleep-BAG signals identified in **Fig. 1**.

BAG	Famil y	EDF	P_1	$P_2\text{-coeff}$	P_2	P_3	Optimal (F)	Optimal (M)	N
Reproductive_fe male_ProtBAG	tdist	3.1241788 5	0.003024 09	-0.036085	0	0.04204 807	8.06060606	7.63636364	39450
Pulmonary_Pro tBAG	tdist	3.2086425 7	0.000109 19	0	NA	8.16E- 05	7.63636364	7.03030303	39450
Heart_ProtBAG	tdist	1.3686169 6	0.785444 72	- 0.013175 2	2.58E- 30	0	7.03030303	6.96969697	39450
Brain_ProtBAG	tdist	3.6070063 9	0	0.027077 2	0	0.06225 086	7.81818182	7.6969697	39450
Eye_ProtBAG	tdist	1.0135989 1	0.227725 88	- 0.005701 5	1.11E- 23	0.14519 924	4	5.63636364	39450
Hepatic_ProtBA G	tdist	3.1288468 4	0.001367 37	- 0.037458 9	1.5E- 207	0.12538 411	7.51515152	7.6969697	39450
Renal_ProtBAG	tdist	1.0002315 2	0.698060 26	0	NA	0.70418 125	8.12121212	4	39450
Reproductive_ma le_ProtBAG	tdist	1.8988802 8	0.011256 16	0.004706 86	1.26E- 06	7.6986E -07	6.84848485	6.54545455	39450
Endocrine_ProtB AG	tdist	2.8868634 9	0.002361 83	- 0.049079 5	0	0.02173 371	7.75757576	7.27272727	39450
Immune_ProtB AG	tdist	3.4725053	1.7753E- 05	0	NA	0.34395 093	7.75757576	7.57575758	39450
Skin_ProtBAG	tdist	3.2109813 8	3.1166E- 06	- 0.007554 8	0	0.99394 745	7.6969697	7.39393939	39450

Endocrine_Met BAG	tdist	1.0387028	3.968E- 05	- 0.020496 1	0	5.71E- 07	6.66666667	6.36867576	237781
Digestive_MetB AG	gamma	1.9915983 8	0.109232 83	0	NA	0.06909 867	4	6.3030303	244056
Hepatic_MetBA G	tdist	2.6392064	0.005182 85	0	1	0.99924 933	10	10	242727
Immune_MetBA G	tdist	1.0143236 5	0.003567 03	0	NA	0.00632 848	4.84848485	10	247310
Metabolic_MetB AG	tdist	1.0303559 6	0.130406 43	0	NA	0	4	6.12121212	227395
Brain_MRIBA G	tdist	1.9429943 2	3.85E-07	0.010529 19	0	0.84315 248	6.48484848	6.42424242	33051
Adipose_MRIB AG	tdist	1.9339929 9	0.000283 66	- 0.001870 2	0	0.00058 391	6.90909091	6.90909091	22214
Kidney_MRIBA G	tdist	1.8592987 4	0.047362 54	0	NA	0.03085 264	6.60606061	6.90909091	31584
Heart_MRIBAG	tdist	1.0014530 4	0.767595 41	- 0.024022 2	0	0.23399 526	10	7.57575758	32624
Liver_MRIBAG	tdist	2.5686849 2	0.051687 32	0.004880 97	0.0010 4338	0.48552 144	6.12121212	5.57575758	22250
Pancreas_MRIB AG	tdist	1.9540234 2	9.9544E- 06	- 0.011899 4	1.018E -09	0.71800 183	6.84848485	6.78787879	25481
Spleen_MRIBA G	tdist	1.0134026 1	0.595099 68	0.006748 66	4.1389 E-06	0.80134 742	6.42424242	10	24411

Supplementary Table 3: Sensitivity check analyses between sleep duration and the 23 BAGs

We used bold-text to highlight the 9 significant sleep-BAG signals identified in **Fig. 1**. We present *i*) the main effect (sleep duration; P_1), *ii*) sex difference in population mean (P_2), and *iii*) sex-sleep interaction terms (P_3) on each BAG.

a) Split-sample analysis

BAG	Family	Optimal k	EDF	P_1	Split
Reproductive_female_ProtBAG	tdist	5	3.40990517	4.32E-07	Split1
Pulmonary_ProtBAG	tdist	5	3.60464839	0	Split1
Heart_ProtBAG	tdist	3	1.94577602	4.49E-05	Split1
Brain_ProtBAG	tdist	5	3.54561137	0	Split1
Eye_ProtBAG	tdist	5	1.68030972	0.00130492	Split1
Hepatic_ProtBAG	tdist	5	3.25321596	1.52E-06	Split1
Renal_ProtBAG	tdist	5	2.25456061	0.46852205	Split1
Reproductive_male_ProtBAG	tdist	3	1.97650719	0	Split1
Endocrine_ProtBAG	tdist	5	3.10868703	0.00014551	Split1
Immune_ProtBAG	tdist	5	3.32770689	0.00417126	Split1
Skin_ProtBAG	tdist	5	3.06500098	2.22E-05	Split1
Endocrine_MetBAG	tdist	5	3.31403875	0	Split1
Digestive_MetBAG	gamma	5	2.86811232	0.00749071	Split1
Hepatic_MetBAG	tdist	5	3.42593569	0.00172921	Split1
Immune_MetBAG	tdist	3	1.17866086	0.83085718	Split1
Metabolic_MetBAG	tdist	5	2.50322362	0.00078332	Split1
Brain_MRIBAG	tdist	3	1.89567361	0.00100219	Split1
Adipose_MRIBAG	tdist	3	1.96445018	0	Split1
Kidney_MRIBAG	tdist	3	1.92878969	0.0003637	Split1
Heart_MRIBAG	tdist	3	1.00697631	0.18228465	Split1
Liver_MRIBAG	tdist	5	2.6642057	0.00176361	Split1
Pancreas_MRIBAG	tdist	3	1.9331389	9.03E-05	Split1
Spleen_MRIBAG	tdist	3	1.84051695	0.06429083	Split1
Reproductive_female_ProtBAG	tdist	5	3.07378452	2.40E-06	Split2
Pulmonary_ProtBAG	tdist	5	3.21715252	3.41E-07	Split2
Heart_ProtBAG	tdist	3	1.9537369	3.49E-05	Split2
Brain_ProtBAG	tdist	5	3.46777297	0	Split2
Eye_ProtBAG	tdist	5	1.04558127	0.00034558	Split2
Hepatic_ProtBAG	tdist	5	2.46189641	0.01697513	Split2
Renal_ProtBAG	tdist	5	1.65843831	0.49527592	Split2
Reproductive_male_ProtBAG	tdist	3	1.93289922	9.83E-06	Split2
Endocrine_ProtBAG	tdist	5	3.2131639	0	Split2
Immune_ProtBAG	tdist	5	3.29984535	0	Split2
Skin_ProtBAG	tdist	5	2.99831599	0.00950557	Split2
Endocrine_MetBAG	tdist	5	3.3599701	0	Split2
Digestive_MetBAG	gamma	5	2.49705697	0.11742895	Split2
Hepatic_MetBAG	tdist	5	1.55641378	0.25311001	Split2
Immune_MetBAG	tdist	3	1.1798613	0.28855037	Split2
Metabolic_MetBAG	tdist	5	2.12113067	0.04992084	Split2
Brain_MRIBAG	tdist	3	1.91007336	1.05E-08	Split2
Adipose_MRIBAG	tdist	3	1.97245593	0	Split2
Kidney_MRIBAG	tdist	3	1.89660316	0.00242667	Split2
Heart_MRIBAG	tdist	3	1.00691438	0.83872591	Split2
Liver_MRIBAG	tdist	5	1.01535176	0.00531592	Split2
Pancreas_MRIBAG	tdist	3	1.86852578	0.02436188	Split2
Spleen_MRIBAG	tdist	3	1.70219838	0.21934225	Split2

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b) Age-stratified analysis

BAG	Age Group (yrs)	Family	Optimal k	EDF	P ₁
Reproductive_female_ProtBAG	[40-60]	tdist	5	2.47929624	0.00010859
Reproductive_female_ProtBAG	[60-80]	tdist	5	3.28924924	9.98E-08
Pulmonary_ProtBAG	[40-60]	tdist	5	3.68528492	0
Pulmonary_ProtBAG	[60-80]	tdist	5	3.07717932	4.35E-07
Heart_ProtBAG	[40-60]	tdist	3	1.94462295	5.79E-05
Heart_ProtBAG	[60-80]	tdist	3	1.9508635	2.83E-06
Brain_ProtBAG	[40-60]	tdist	5	3.62099293	0
Brain_ProtBAG	[60-80]	tdist	5	3.37986947	0
Eye_ProtBAG	[40-60]	tdist	5	1.00940526	0.00623431
Eye_ProtBAG	[60-80]	tdist	5	1.59300727	5.66E-06
Hepatic_ProtBAG	[40-60]	tdist	5	2.70418844	0.00092072
Hepatic_ProtBAG	[60-80]	tdist	5	3.06908616	0.00010663
Renal_ProtBAG	[40-60]	tdist	5	1.01691156	0.26518242
Renal_ProtBAG	[60-80]	tdist	5	2.50885389	0.01038931
Reproductive_male_ProtBAG	[40-60]	tdist	3	1.96209676	2.29E-06
Reproductive_male_ProtBAG	[60-80]	tdist	3	1.95599299	0
Endocrine_ProtBAG	[40-60]	tdist	5	3.34820355	0
Endocrine_ProtBAG	[60-80]	tdist	5	3.02443553	3.63E-05
Immune_ProtBAG	[40-60]	tdist	5	3.43257411	4.42E-06
Immune_ProtBAG	[60-80]	tdist	5	2.99060222	5.42E-05
Skin_ProtBAG	[40-60]	tdist	5	2.98678363	0.00014909
Skin_ProtBAG	[60-80]	tdist	5	2.74687839	0.01336974
Endocrine_MetBAG	[40-60]	tdist	5	3.57871596	0
Endocrine_MetBAG	[60-80]	tdist	5	3.06890784	0
Digestive_MetBAG	[40-60]	gamma	5	1.15932782	0.00014016
Digestive_MetBAG	[60-80]	gamma	5	3.44468294	2.34E-05
Hepatic_MetBAG	[40-60]	tdist	5	3.24040023	0.04218487
Hepatic_MetBAG	[60-80]	tdist	5	3.03710161	0.09495551
Immune_MetBAG	[40-60]	tdist	3	1.83095236	0.00065235
Immune_MetBAG	[60-80]	tdist	3	1.54177702	0.00050281
Metabolic_MetBAG	[40-60]	tdist	5	2.6207173	4.41E-05
Metabolic_MetBAG	[60-80]	tdist	5	1.00667415	0.0008325
Brain_MRIBAG	[40-60]	tdist	3	1.93961673	4.11E-06
Brain_MRIBAG	[60-80]	tdist	3	1.66287313	0.05840601
Adipose_MRIBAG	[40-60]	tdist	3	1.97104816	0
Adipose_MRIBAG	[60-80]	tdist	3	1.96251605	3.39E-07
Kidney_MRIBAG	[40-60]	tdist	3	1.93981775	0.00015496
Kidney_MRIBAG	[60-80]	tdist	3	1.85182348	0.02694113
Heart_MRIBAG	[40-60]	tdist	3	1.00713063	0.15132763
Heart_MRIBAG	[60-80]	tdist	3	1.00868926	0.42449593
Liver_MRIBAG	[40-60]	tdist	5	1.30033668	0.01175562
Liver_MRIBAG	[60-80]	tdist	5	2.1660193	0.02186497
Pancreas_MRIBAG	[40-60]	tdist	3	1.80016153	0.13829659
Pancreas_MRIBAG	[60-80]	tdist	3	1.9447499	1.45E-05
Spleen_MRIBAG	[40-60]	tdist	3	1.0200997	0.72290745
Spleen_MRIBAG	[60-80]	tdist	3	1.00722982	0.68151139

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c) Sex-stratified analysis

BAG	Sex	Family	Optimal k	EDF	P ₁
Reproductive_female_ProtBAG	Female	tdist	5	2.88048221	0.00056244
Reproductive_female_ProtBAG	Male	tdist	5	3.36851646	0
Pulmonary_ProtBAG	Female	tdist	5	3.01162763	0.00351465

Pulmonary_ProtBAG	Male	tdist	5	3.62453121	0
Heart_ProtBAG	Female	tdist	3	1.69323001	0.33620365
Heart_ProtBAG	Male	tdist	3	1.98176342	0
Brain_ProtBAG	Female	tdist	5	3.50572566	6.65E-07
Brain_ProtBAG	Male	tdist	5	3.5298186	0
Eye_ProtBAG	Female	tdist	5	1.0336401	0.00040973
Eye_ProtBAG	Male	tdist	5	3.06303629	2.53E-05
Hepatic_ProtBAG	Female	tdist	5	2.55688216	0.09725832
Hepatic_ProtBAG	Male	tdist	5	3.24561795	7.53E-07
Renal_ProtBAG	Female	tdist	5	2.9050947	0.10148904
Renal_ProtBAG	Male	tdist	5	1.20101925	0.21590821
Reproductive_male_ProtBAG	Female	tdist	3	1.96230451	2.19E-06
Reproductive_male_ProtBAG	Male	tdist	3	1.96535989	0
Endocrine_ProtBAG	Female	tdist	5	2.55659993	0.00508666
Endocrine_ProtBAG	Male	tdist	5	3.63940804	0
Immune_ProtBAG	Female	tdist	5	3.1698081	0.0091142
Immune_ProtBAG	Male	tdist	5	3.34800558	0
Skin_ProtBAG	Female	tdist	5	2.82703424	0.00103676
Skin_ProtBAG	Male	tdist	5	2.97219816	2.94E-05
Endocrine_MetBAG	Female	tdist	5	3.20835097	0
Endocrine_MetBAG	Male	tdist	5	3.66051872	0
Digestive_MetBAG	Female	gamma	5	3.14616228	1.60E-05
Digestive_MetBAG	Male	gamma	5	3.19365559	7.61E-06
Hepatic_MetBAG	Female	tdist	5	3.12204622	0.17469654
Hepatic_MetBAG	Male	tdist	5	2.85656673	0.1138149
Immune_MetBAG	Female	tdist	3	1.02242724	0.0005673
Immune_MetBAG	Male	tdist	3	1.02028543	0.00754742
Metabolic_MetBAG	Female	tdist	5	2.2384226	0.00185076
Metabolic_MetBAG	Male	tdist	5	3.77371641	0
Brain_MRIBAG	Female	tdist	3	1.90713689	2.06E-05
Brain_MRIBAG	Male	tdist	3	1.90690714	3.10E-05
Adipose_MRIBAG	Female	tdist	3	1.96388916	9.31E-07
Adipose_MRIBAG	Male	tdist	3	1.97042448	0
Kidney_MRIBAG	Female	tdist	3	1.92169393	0.00039019
Kidney_MRIBAG	Male	tdist	3	1.89530592	0.01012402
Heart_MRIBAG	Female	tdist	3	1.36932306	0.51730877
Heart_MRIBAG	Male	tdist	3	1.41461327	0.60453837
Liver_MRIBAG	Female	tdist	5	2.41880644	0.00600284
Liver_MRIBAG	Male	tdist	5	1.01205988	0.00568765
Pancreas_MRIBAG	Female	tdist	3	1.92706747	0.000531
Pancreas_MRIBAG	Male	tdist	3	1.87493757	0.01912217
Spleen_MRIBAG	Female	tdist	3	1.50248213	0.3868693
Spleen_MRIBAG	Male	tdist	3	1.00816804	0.75391225

d) Age-sex interaction as an additional term

BAG	Family	Optimal k	EDF	P ₁	Age-sex coef	Age-sex P-value
Reproductive_female_ProtBAG	tdist	3	1.68718 855	0.00224312	-0.0019905	2.72E-112
Pulmonary_ProtBAG	tdist	3	1.92699 698	0.00104244	-0.0010592	1.20E-29
Heart_ProtBAG	tdist	3	1.00408 756	0.63188287	0.00035741	9.05E-05
Brain_ProtBAG	tdist	5	3.51963 313	1.15E-05	-0.0021568	9.55E-70

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Eye_ProtBAG	tdist	5	1.01885 855	0.00031284	-0.000359	1.55E-15
Hepatic_ProtBAG	tdist	3	1.83386 282	0.00189172	-0.0019799	2.22E-94
Renal_ProtBAG	tdist	5	1.00067 997	0.6212926	-0.0002332	0.02001364
Reproductive_male_ProtBAG	tdist	5	3.28783 379	2.58E-05	0.00261804	1.88E-261
Endocrine_ProtBAG	tdist	5	2.35731 362	0.01982627	-0.0035014	1.40E-265
Immune_ProtBAG	gamma	5	3.35238 495	0.00724521	-0.0040787	3.53E-87
Skin_ProtBAG	tdist	3	1.94319 598	0.00013296	-0.0024061	5.52E-126
Endocrine_MetBAG	tdist	5	3.14329 301	0	-0.001135	0
Digestive_MetBAG	gamma	5	1.99008 831	0.5609586	-0.0038222	0
Hepatic_MetBAG	tdist	5	3.50857 49	0.00590508	-0.0011115	0
Immune_MetBAG	tdist	5	2.60771 981	0.00492697	-0.0010527	0
Metabolic_MetBAG	tdist	5	1.15110 441	0.02825922	-0.0006325	4.30E-116
Brain_MRIBAG	tdist	3	1.95036 718	6.63E-07	0.00016203	0.22194206
Adipose_MRIBAG	tdist	3	1.94656 684	0.00014905	0.00157058	3.09E-43
Kidney_MRIBAG	tdist	3	1.89000 532	0.01594308	0.00076695	3.40E-23
Heart_MRIBAG	tdist	3	1.00838 371	0.18279153	5.95E-05	0.51846454
Liver_MRIBAG	tdist	5	2.34729 655	0.03189794	0.00043212	0.00061975
Pancreas_MRIBAG	tdist	3	1.95271 412	1.99E-05	0.00086172	1.72E-07
Spleen_MRIBAG	tdist	3	1.00439 983	0.80203926	-0.0004056	0.00105952

e) Exclude participants with the 3 sleep-related disorders

BAG	Family	Optimal k	EDF	P ₁
Reproductive_female_ProtBAG	tdist	5	3.06199438	0.00068348
Pulmonary_ProtBAG	tdist	3	1.93343141	0.00041776
Heart_ProtBAG	tdist	3	1.43630571	0.6698409
Brain_ProtBAG	tdist	5	3.59501735	0
Eye_ProtBAG	tdist	5	1.00920811	0.00163023
Hepatic_ProtBAG	tdist	5	3.07745069	0.00298033
Renal_ProtBAG	tdist	5	1.00054027	0.93706198
Reproductive_male_ProtBAG	tdist	3	1.89460705	0.00935819

Endocrine_ProtBAG	tdist	3	1.94760656	0
Immune_ProtBAG	tdist	5	3.48830349	5.00E-06
Skin_ProtBAG	tdist	5	3.20537479	6.31E-06
Endocrine_MetBAG	tdist	5	1.11848162	0.12476373
Digestive_MetBAG	gamma	5	1.41633043	0.81268972
Hepatic_MetBAG	tdist	5	2.74813197	0.00516592
Immune_MetBAG	tdist	3	1.01636922	0.00278415
Metabolic_MetBAG	tdist	5	1.05526167	0.03866805
Brain_MRIBAG	tdist	3	1.94357569	5.77E-08
Adipose_MRIBAG	tdist	3	1.93006499	0.00122662
Kidney_MRIBAG	tdist	3	1.81667525	0.04390236
Heart_MRIBAG	tdist	3	1.00811013	0.20544092
Liver_MRIBAG	tdist	5	2.74229668	0.02682607
Pancreas_MRIBAG	tdist	3	1.95448438	9.85E-06
Spleen_MRIBAG	tdist	3	1.00329122	0.49425251

f) Smoking status as an additional covariate

BAG	Family	Optimal k	EDF	P ₁	Smoking P- value
Reproductive_female_ProtBAG	tdist	5	3.07647389	0.00020392	1.38E-06
Pulmonary_ProtBAG	tdist	3	1.92565438	0.00156381	3.15E-157
Heart_ProtBAG	tdist	3	1.16350055	0.88334803	8.29E-15
Brain_ProtBAG	tdist	5	3.58453521	0	5.26E-51
Eye_ProtBAG	tdist	5	1.0182443	0.08746729	7.75E-17
Hepatic_ProtBAG	tdist	5	3.09768189	5.72E-05	2.58E-09
Renal_ProtBAG	tdist	5	1.00054783	0.71742104	0.00581246
Reproductive_male_ProtBAG	tdist	3	1.88355152	0	8.94E-43
Endocrine_ProtBAG	tdist	5	2.79259193	0.00522227	5.78E-45
Immune_ProtBAG	tdist	5	3.46806149	1.47E-05	3.89E-27
Skin_ProtBAG	tdist	3	1.95637863	3.24E-06	7.62E-61
Endocrine_MetBAG	tdist	5	1.12400433	0.08133393	2.11E-80
Digestive_MetBAG	gamma	5	1.87037714	0.11885018	1.09E-27
Hepatic_MetBAG	tdist	5	2.65050042	0.03504743	8.62E-20
Immune_MetBAG	tdist	5	1.14129896	0.0106696	2.09E-112
Metabolic_MetBAG	tdist	5	1.03560927	0.0318311	1.11E-13
Brain_MRIBAG	tdist	3	1.92414741	6.58E-06	1.05E-31
Adipose_MRIBAG	tdist	3	1.92935164	0.00042851	2.83E-18
Kidney_MRIBAG	tdist	3	1.86974092	0.02318972	1.88E-07
Heart_MRIBAG	tdist	3	1.00598814	0.25169447	2.43E-05
Liver_MRIBAG	tdist	5	2.54371042	0.06699496	1.23E-16
Pancreas_MRIBAG	tdist	3	1.95314256	1.27E-05	0.02078851
Spleen_MRIBAG	tdist	3	1.01337469	0.60022369	0.68429839

g) Drinking status as an additional covariate

BAG	Family	Optimal k	EDF	P ₁	Drinking P- value
Brain_MRIBAG	tdist	3	1.94357937	6.78E-07	0.9794196

h) Townsend deprivation index as an additional covariate

BAG	Family	Optimal k	EDF	P ₁	TDI P-value
Reproductive_female_Prot					
BAG	tdist	5	3.03173739	0.00176373	1.13E-21
Pulmonary_ProtBAG	tdist	3	1.92909154	0.0014534	3.12E-46
Heart_ProtBAG	tdist	3	1.00450041	0.64082859	5.25E-30
Brain_ProtBAG	tdist	5	3.57445827	6.16E-08	4.40E-42
Eye_ProtBAG	tdist	5	1.00866595	0.03456436	7.96E-05
Hepatic_ProtBAG	tdist	5	3.08802828	0.00231753	1.73E-11
Renal_ProtBAG	tdist	5	1.02227627	0.7559679	0.00592547
Reproductive_male_ProtB					
AG	tdist	3	1.88206974	0	1.87E-12
Endocrine_ProtBAG	gaussia	5	2.62155036	0.00025258	4.60E-18
Immune_ProtBAG	tdist	5	3.43097426	1.43E-05	4.82E-28
Skin_ProtBAG	tdist	5	3.13677944	3.55E-05	6.64E-12
Endocrine_MetBAG	tdist	5	1.05443513	0.07202273	0.0008329
Digestive_MetBAG	gamma	5	1.29447643	0.13015654	6.64E-07
Hepatic_MetBAG	tdist	5	1.82609884	0.00137251	1.23E-42
Immune_MetBAG	tdist	3	1.00542948	0.00381486	1.90E-57
Metabolic_MetBAG	tdist	5	1.03798729	0.026891	0.02246045
Brain_MRIBAG	tdist	3	1.9369181	7.63E-07	8.12E-09
Adipose_MRIBAG	tdist	3	1.92548561	0.00058181	0.02314232
Kidney_MRIBAG	tdist	3	1.8572008	0.04731968	0.59550499
Heart_MRIBAG	tdist	3	1.00113383	0.86635344	0.23855493
Liver_MRIBAG	tdist	5	2.63688227	0.03493911	0.00014025
Pancreas_MRIBAG	tdist	3	1.95213973	1.62E-05	0.11460292
Spleen_MRIBAG	tdist	3	1.00480559	0.7863594	0.41165241

i) Computer use time as an additional covariate

BAG	Family	Optimal k	EDF	P ₁	Computer P- value
Reproductive_female_Prot					
BAG	tdist	5	3.18944764	0.00067925	0.74821762
Pulmonary_ProtBAG	tdist	5	3.22474103	0.00019265	0.00544064
Heart_ProtBAG	tdist	3	1.50862194	0.62910784	0.09686478
Brain_ProtBAG	tdist	5	3.61909242	0	0.01987495
Eye_ProtBAG	tdist	5	1.00911381	0.02520375	0.5545165
Hepatic_ProtBAG	tdist	5	3.18615336	0.00061533	0.88429267
Renal_ProtBAG	tdist	5	1.00054743	0.65898516	0.49449189
Reproductive_male_ProtB					
AG	tdist	3	1.88764293	0	0.71022606
Endocrine_ProtBAG	tdist	5	2.84427693	0	0.79565575
Immune_ProtBAG	tdist	5	3.46868396	1.62E-05	0.85143241
Skin_ProtBAG	tdist	5	3.24114512	0	0.03997704
Endocrine_MetBAG	tdist	5	1.20433165	0.22905252	6.30E-05
Digestive_MetBAG	gamma	5	1.94910956	0.53611163	0.00018247
Hepatic_MetBAG	tdist	5	2.56076449	0.04778857	6.40E-07
Immune_MetBAG	tdist	5	1.32332746	0.09150513	0.07623785
Metabolic_MetBAG	tdist	5	1.03429731	0.00107858	1.09E-22

Brain_MRIBAG	tdist	3	1.95218679	5.26E-07	0.43210818
Adipose_MRIBAG	tdist	3	1.93069926	0.00040982	0.00149075
Kidney_MRIBAG	tdist	3	1.86228808	0.04389015	0.00020942
Heart_MRIBAG	tdist	3	1.00153078	0.18121213	0.00096716
Liver_MRIBAG	tdist	5	2.43983282	0.05015158	4.23E-05
Pancreas_MRIBAG	tdist	3	1.95303053	2.20E-05	0.01033234
Spleen_MRIBAG	tdist	3	1.00459786	0.84805194	0.0025427

j) Testosterone as an additional covariate

BAG	Family	Optimal k	EDF	P ₁	Testosterone- sex P-value
Reproductive_female_Prot					
BAG	tdist	5	2.84226889	0.00046516	0.02277355
Pulmonary_ProtBAG	tdist	5	3.0433898	0.00113916	0.56362198
Heart_ProtBAG	tdist	3	1.01709612	0.12902099	0.08104452
Brain_ProtBAG	tdist	5	3.53915248	6.28E-07	0.69955614
Eye_ProtBAG	tdist	5	1.01560282	0.48292884	0.20427132
Hepatic_ProtBAG	tdist	5	3.08174128	0.0008631	0.60014667
Renal_ProtBAG	tdist	5	1.00153944	0.7516835	0.0252769
Reproductive_male_ProtB					
AG	tdist	3	1.65681854	0.10800177	0.21850358
Endocrine_ProtBAG	tdist	5	2.80241613	1.49E-06	0.03290308
Immune_ProtBAG	tdist	5	2.78996734	0.03230766	0.4342481
Skin_ProtBAG	tdist	5	3.18241734	1.82E-05	0.31569186
Endocrine_MetBAG	tdist	5	3.52594116	0	0.17216201
Digestive_MetBAG	gamma	5	1.20767056	0.67224535	0.37888247
Hepatic_MetBAG	tdist	5	2.62979272	0.12726215	0.61544352
Immune_MetBAG	tdist	3	1.02801117	0.30731306	0.01430927
Metabolic_MetBAG	tdist	5	1.05727051	0.1803341	0.07914344
Brain_MRIBAG	tdist	3	1.94272223	3.55E-06	0.42789179
Adipose_MRIBAG	tdist	3	1.92812902	0.00104041	0.94711766
Kidney_MRIBAG	tdist	3	1.94279662	0.00041159	0.36445145
Heart_MRIBAG	tdist	3	1.00557206	0.39871486	0.25835639
Liver_MRIBAG	tdist	5	2.75106161	0.08235739	0.94124085
Pancreas_MRIBAG	tdist	3	1.9475421	0.00012862	0.06519536
Spleen_MRIBAG	tdist	3	1.00197394	0.54937148	0.51936839

k) SHBG use time as an additional covariate

BAG	Family	Optimal k	EDF	P ₁	SHBG-sex P- value
Reproductive_female_Prot					
BAG	tdist	5	3.01870211	0.03401377	0.05484021
Pulmonary_ProtBAG	tdist	5	3.08981744	0.01059715	0.1126294
Heart_ProtBAG	tdist	3	1.49161172	0.61211574	0.77058205
Brain_ProtBAG	tdist	5	3.49913133	0	0.5581973
Eye_ProtBAG	tdist	5	1.0103298	0.00059469	0.6029346
Hepatic_ProtBAG	tdist	5	3.11971439	0.00147547	0.20173444
Renal_ProtBAG	tdist	5	1.09991854	0.7397906	0.68639925
Reproductive_male_ProtB					
AG	tdist	3	1.89352713	5.81E-07	0.45821297
Endocrine_ProtBAG	tdist	5	2.75622067	0.00687666	0.05384894
Immune_ProtBAG	tdist	5	3.43253247	7.45E-05	0.05227508
Skin_ProtBAG	tdist	5	3.18867577	2.38E-06	0.45275612
Endocrine_MetBAG	tdist	5	1.04511838	0.44538986	0.22282905
Digestive_MetBAG	gamma	5	2.75642165	0.2497407	0.16843459

Hepatic_MetBAG	tdist	5	2.09930704	0.25170464	0.35219559
Immune_MetBAG	tdist	3	1.00954793	0.1021914	0.00714115
Metabolic_MetBAG	tdist	5	1.08186155	0.06099562	0.59147502
Brain_MRIBAG	tdist	3	1.93187785	1.59E-06	0.76742474
Adipose_MRIBAG	tdist	3	1.93135174	0.00065938	0.45277903
Kidney_MRIBAG	tdist	3	1.74368015	0.06400277	0.74039525
Heart_MRIBAG	tdist	3	1.00579189	0.054327	0.64550715
Liver_MRIBAG	tdist	5	2.69601661	0.02442577	0.12881184
Pancreas_MRIBAG	tdist	3	1.95187447	3.67E-06	0.85898724
Spleen_MRIBAG	tdist	3	1.00217496	0.13323092	0.7381724

l) Estradiol use time as an additional covariate

Of note, the sample sizes reduced dramatically compared to Fig. 1, because not all the full UKBB samples have data available for estradiol (i.e., UKBB only covers 77,594 participants out of the 500k population before merging with the BAG populations:

<https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=30800>).

BAG	Family	Optimal k	EDF	P ₁	Estradiol-sex P-value
Reproductive_female_Prot					
BAG	tdist	5	1.00087574	0.52593908	0.33062635
Pulmonary_ProtBAG	tdist	5	2.97862243	0.02639053	0.27371533
Heart_ProtBAG	tdist	3	1.00042744	0.0850369	0.85407943
Brain_ProtBAG	tdist	5	2.3158273	0.18105885	0.0911572
Eye_ProtBAG	tdist	5	1.00134332	0.75437986	0.27806343
Hepatic_ProtBAG	tdist	5	1.00067089	0.1629343	0.01958318
Renal_ProtBAG	tdist	5	1.0013687	0.81846298	0.04770111
Reproductive_male_ProtB					
AG	tdist	3	1.41017194	0.69433227	0.39839317
Endocrine_ProtBAG	tdist	5	2.74968973	0.04483631	0.23368963
Immune_ProtBAG	tdist	5	1.82752125	0.89679547	0.40191012
Skin_ProtBAG	tdist	5	2.33726922	0.07899631	0.06714145
Endocrine_MetBAG	tdist	5	1.91030582	0.37967898	0.43184208
Digestive_MetBAG	gamma	5	1.95075084	0.25088444	0.39171171
Hepatic_MetBAG	tdist	5	1.00426347	0.64147517	0.62064032
Immune_MetBAG	tdist	3	1.00663804	0.70033281	0.91679333
Metabolic_MetBAG	tdist	5	1.00846985	0.78364727	0.48745155
Brain_MRIBAG	tdist	3	1.7138767	0.25726918	0.94053148
Adipose_MRIBAG	tdist	3	1.8343143	0.08377288	0.21982963
Kidney_MRIBAG	tdist	3	1.52938374	0.56890008	0.94408945
Heart_MRIBAG	tdist	3	1.00089616	0.79391252	0.44827056
Liver_MRIBAG	tdist	5	1.00032981	0.17315766	0.79358438
Pancreas_MRIBAG	tdist	3	1.00134533	0.01147831	0.96429587
Spleen_MRIBAG	tdist	3	1.00027543	0.4406184	0.9974435

m) GAMLSS analysis for the 9 significant sleep-BAG relationships

BAG	Family	P ₁	P ₂	P ₃
Reproductive_female_ProtBAG	TF	6.10E-14	0	1
Pulmonary_ProtBAG	TF	3.22E-18	0	1
Heart_ProtBAG	TF	3.01E-09	0	1
Brain_ProtBAG	TF	1.77E-23	0	1
Eye_ProtBAG	TF	1.48E-06	0	0.30910717
Hepatic_ProtBAG	TF	1.35E-08	0	1
Renal_ProtBAG	TF	0.25631225	0	1
Reproductive_male_ProtBAG	TF	8.83E-17	2.58E-11	1

Endocrine_ProtBAG	TF	4.29E-15	0	1
Immune_ProtBAG	TF	5.60E-11	0	1
Skin_ProtBAG	TF	4.00E-08	2.81E-11	1
Endocrine_MetBAG	TF	5.47E-36	0	1
Digestive_MetBAG	gamma	0.00484392	0	1
Hepatic_MetBAG	TF	0.00536906	0	1
Immune_MetBAG	TF	0.45163538	0	0.52623149
Metabolic_MetBAG	TF	2.18E-05	0	1
Brain_MRIBAG	TF	2.50E-10	2.46E-13	1
Adipose_MRIBAG	TF	1.40E-15	0.06256714	1
Kidney_MRIBAG	TF	7.49E-07	0	1
Heart_MRIBAG	TF	0.30835973	0	0.16592368
Liver_MRIBAG	TF	2.48E-05	2.11E-05	1
Pancreas_MRIBAG	TF	4.17E-06	8.24E-12	1
Spleen_MRIBAG	TF	0.69124192	4.31E-09	0.13406013

Supplementary Table 4: Genomic loci identified in our GWAS of the abnormal sleep duration patterns

Using sleep durations as a binary trait for Short vs. Normal sleep duration and Long vs. Normal sleep duration, we identified genomics loci linked to these patterns using REGENIE. Genome-wide P-value threshold was used ($P < 5 \times 10^{-8}$).

Top Lead SNP	Chromosome	Position	P-value	Phenotype	Cytogenetic region
rs34382732	3	193108140	5.23E-09	short_vs_normal	3q29
rs62118577	2	9266185	4.80E-08	long_vs_normal	2p25.1
rs74889896	2	58933235	8.40E-09	long_vs_normal	2p16.1
rs62158206	2	114084596	1.81E-11	long_vs_normal	2q13
11:76414249_GT_G	11	76414249	1.75E-09	long_vs_normal	11q13.5
rs75458655	11	118115331	9.85E-10	long_vs_normal	11q23.3
rs1057703	11	122830251	2.21E-08	long_vs_normal	11q24.1
rs62061734	17	44018488	1.01E-13	long_vs_normal	17q21.31

Supplementary Table 5: Genetic correlation between short/long sleep duration and 23 BAGs

Using sleep durations as a binary trait for short/long vs. normal sleep duration, we identified significant signals (bold text; P-value<0.05/23). NC indicated the LDSC model did not converge.

Sleep type	BAG	BAG_type	gc_mean	gc_std	Z	P
short_vs_normal	Reproductive_female	ProtBAG	0.1131	0.128	0.883	0.3772
short_vs_normal	Pulmonary	ProtBAG	0.013	0.0602	0.2162	0.8288
short_vs_normal	Heart	ProtBAG	0.0094	0.0883	0.1061	0.9155
short_vs_normal	Brain	ProtBAG	0.0186	0.0763	0.2443	0.807
short_vs_normal	Eye	ProtBAG	NC	NC	NC	NC
short_vs_normal	Hepatic	ProtBAG	0.1863	0.0764	2.439	0.0147
short_vs_normal	Renal	ProtBAG	-0.0007	0.0585	-0.0112	0.9911
short_vs_normal	Reproductive_male	ProtBAG	0.0776	0.0613	1.2653	0.2058
short_vs_normal	Endocrine	ProtBAG	0.0111	0.0802	0.1383	0.89
short_vs_normal	Immune	ProtBAG	0.0344	0.0546	0.6295	0.529
short_vs_normal	Skin	ProtBAG	0.017	0.0579	0.294	0.7688
short_vs_normal	Endocrine	MetBAG	0.1442	0.0394	3.6582	0.0003
short_vs_normal	Digestive	MetBAG	-0.0826	0.048	-1.7224	0.085
short_vs_normal	Hepatic	MetBAG	0.0841	0.0427	1.9725	0.0485
short_vs_normal	Immune	MetBAG	0.0099	0.0447	0.2213	0.8249
short_vs_normal	Metabolic	MetBAG	0.0121	0.0494	0.2445	0.8068
short_vs_normal	brain	MRIBAG	0.0239	0.0542	0.4404	0.6596
short_vs_normal	adipose	MRIBAG	0.1948	0.0759	2.5673	0.0102
short_vs_normal	heart	MRIBAG	0.107	0.1	1.0693	0.2849
short_vs_normal	kidney	MRIBAG	0.0944	0.0654	1.4447	0.1486
short_vs_normal	liver	MRIBAG	0.0508	0.075	0.6767	0.4986
short_vs_normal	pancreas	MRIBAG	-0.0365	0.0668	-0.5459	0.5851
short_vs_normal	spleen	MRIBAG	-0.1161	0.094	-1.2348	0.2169
long_vs_normal	Reproductive_female	ProtBAG	0.138	0.1121	1.2307	0.2184
long_vs_normal	Pulmonary	ProtBAG	0.0081	0.0611	0.132	0.895
long_vs_normal	Heart	ProtBAG	0.1566	0.0852	1.8389	0.0659
long_vs_normal	Brain	ProtBAG	-0.0886	0.074	-1.1974	0.2311
long_vs_normal	Eye	ProtBAG	NC	NC	NC	NC
long_vs_normal	Hepatic	ProtBAG	0.0183	0.0771	0.2371	0.8126
long_vs_normal	Renal	ProtBAG	0.1303	0.0592	2.2001	0.0278
long_vs_normal	Reproductive_male	ProtBAG	0.0822	0.0672	1.2231	0.2213
long_vs_normal	Endocrine	ProtBAG	0.1031	0.0765	1.3475	0.1778
long_vs_normal	Immune	ProtBAG	0.0468	0.0531	0.8822	0.3777
long_vs_normal	Skin	ProtBAG	-0.0762	0.0573	-1.3294	0.1837
long_vs_normal	Endocrine	MetBAG	0.0391	0.039	1.0038	0.3155
long_vs_normal	Digestive	MetBAG	-0.0563	0.0493	-1.1415	0.2537
long_vs_normal	Hepatic	MetBAG	-0.0165	0.0396	-0.4173	0.6765
long_vs_normal	Immune	MetBAG	0.0102	0.048	0.2134	0.831
long_vs_normal	Metabolic	MetBAG	-0.1108	0.0507	-2.1847	0.0289
long_vs_normal	brain	MRIBAG	0.0723	0.0574	1.2594	0.2079
long_vs_normal	adipose	MRIBAG	0.1803	0.076	2.3739	0.0176
long_vs_normal	heart	MRIBAG	0.0024	0.0739	0.0322	0.9743
long_vs_normal	kidney	MRIBAG	0.1227	0.0575	2.1317	0.033
long_vs_normal	liver	MRIBAG	0.079	0.0753	1.0503	0.2936
long_vs_normal	pancreas	MRIBAG	0.2079	0.0663	3.1372	0.0017
long_vs_normal	spleen	MRIBAG	0.0634	0.0817	0.7763	0.4376

Supplementary Table 6: Sensitivity analysis for our mediation analysis using brain MRI as the mediator

In the mediation analysis framework, $a1$ and $c1$ represent the indirect pathways' coefficients, capturing the exposure's effect on the outcome that operates through intermediate variables (mediators). In contrast, $c2$ denotes the coefficient of the direct pathway, quantifying the portion of the exposure's effect on the outcome that is not mediated. The variable $prop_mediated$ reflects the proportion of the total effect that is explained by the indirect pathways, offering insight into how much of the exposure's influence on the outcome is transmitted through mediators rather than occurring directly.

a) The results of the forward mediational analysis: sleep $\rightarrow$ brain MRIBAG $\rightarrow$ LLD1/2.

Outcome	Exposure	Mediator	label	EST	SE	Pvalue	CI.lower	CI.upper
LLD_1	short	Brain_MRIBAG	c1	-0.1159724	0.00374705	0	-0.1234494	-0.1087631
LLD_1	short	Brain_MRIBAG	c2	-0.2929474	0.06010315	1.09E-06	-0.4121581	-0.1781465
LLD_1	short	Brain_MRIBAG	a1	0.07285311	0.10015028	0.46695777	-0.1288059	0.27273862
LLD_1	short	Brain_MRIBAG	indirect	-0.0084489	NA	NA	NA	NA
LLD_1	short	Brain_MRIBAG	total	-0.3013963	NA	NA	NA	NA
LLD_1	short	Brain_MRIBAG	prop_mediated	0.02803268	NA	NA	NA	NA
LLD_1	long	Brain_MRIBAG	c1	-0.1133255	0.00362608	0	-0.1203902	-0.1059577
LLD_1	long	Brain_MRIBAG	c2	-0.0166764	0.05004374	0.73895606	-0.1127656	0.0847863
LLD_1	long	Brain_MRIBAG	a1	0.54340736	0.07821339	3.71E-12	0.38809163	0.69511799
LLD_1	long	Brain_MRIBAG	indirect	-0.0615819	NA	NA	NA	NA
LLD_1	long	Brain_MRIBAG	total	-0.0782583	NA	NA	NA	NA
LLD_1	long	Brain_MRIBAG	prop_mediated	0.78690595	NA	NA	NA	NA
LLD_2	short	Brain_MRIBAG	c1	0.10853972	0.00278399	0	0.1027339	0.11385597
LLD_2	short	Brain_MRIBAG	c2	0.23816434	0.04826107	8.02E-07	0.14301172	0.33321658
LLD_2	short	Brain_MRIBAG	a1	0.07285311	0.1005749	0.46884064	-0.1308664	0.27253572
LLD_2	short	Brain_MRIBAG	indirect	0.00790746	NA	NA	NA	NA
LLD_2	short	Brain_MRIBAG	total	0.2460718	NA	NA	NA	NA
LLD_2	short	Brain_MRIBAG	prop_mediated	0.03213475	NA	NA	NA	NA
LLD_2	long	Brain_MRIBAG	c1	0.10719328	0.00274408	0	0.10184037	0.11248424
LLD_2	long	Brain_MRIBAG	c2	0.03422376	0.03930302	0.38388161	-0.0418017	0.10925456
LLD_2	long	Brain_MRIBAG	a1	0.54340736	0.07861616	4.77E-12	0.38747366	0.69499392
LLD_2	long	Brain_MRIBAG	indirect	0.05824962	NA	NA	NA	NA
LLD_2	long	Brain_MRIBAG	total	0.09247337	NA	NA	NA	NA
LLD_2	long	Brain_MRIBAG	prop_mediated	0.6299069	NA	NA	NA	NA

b) The results of the forward mediational analysis: sleep $\rightarrow$ LLD1/2 $\rightarrow$ brain MRIBAG.

Unreasonable $prop_mediated$ value > 1 is highlighted to support the potential violation of the timing-order underlying the data presented in this analysis.

Mediator	Outcome	Exposure	Label	EST	SE	Pvalue	CI.lower	CI.upper
LLD_1	Brain_MRIBAG	short	c1	-0.2649692	0.00852904	0	-0.2813043	-0.2485956
LLD_1	Brain_MRIBAG	short	c2	-0.0070076	0.09757933	0.94274941	-0.1956114	0.18025664
LLD_1	Brain_MRIBAG	short	a1	-0.3013963	0.06307823	1.77E-06	-0.4288353	-0.1800933
LLD_1	Brain_MRIBAG	short	indirect	0.07986073	NA	NA	NA	NA
LLD_1	Brain_MRIBAG	short	total	0.07285311	NA	NA	NA	NA
LLD_1	Brain_MRIBAG	short	prop_mediated	1.09618843	NA	NA	NA	NA
LLD_1	Brain_MRIBAG	long	c1	-0.260579	0.00844469	0	-0.27672	-0.2433674
LLD_1	Brain_MRIBAG	long	c2	0.52301489	0.08037933	7.68E-11	0.36693716	0.68122753
LLD_1	Brain_MRIBAG	long	a1	-0.0782583	0.05124766	0.12674575	-0.1770108	0.01915737
LLD_1	Brain_MRIBAG	long	indirect	0.02039247	NA	NA	NA	NA
LLD_1	Brain_MRIBAG	long	total	0.54340736	NA	NA	NA	NA
LLD_1	Brain_MRIBAG	long	prop_mediated	0.03752705	NA	NA	NA	NA
LLD_2	Brain_MRIBAG	short	c1	0.42961069	0.01064015	0	0.4085734	0.45158347
LLD_2	Brain_MRIBAG	short	c2	-0.032862	0.09725948	0.73545411	-0.2268089	0.15327048
LLD_2	Brain_MRIBAG	short	a1	0.2460718	0.05076844	1.25E-06	0.14794822	0.34476181
LLD_2	Brain_MRIBAG	short	indirect	0.10571508	NA	NA	NA	NA
LLD_2	Brain_MRIBAG	short	total	0.07285311	NA	NA	NA	NA
LLD_2	Brain_MRIBAG	short	prop_mediated	1.45107162	NA	NA	NA	NA
LLD_2	Brain_MRIBAG	long	c1	0.42576711	0.01061222	0	0.40287709	0.44528729
LLD_2	Brain_MRIBAG	long	c2	0.50403524	0.07977	2.64E-10	0.34946602	0.65886541
LLD_2	Brain_MRIBAG	long	a1	0.09247337	0.03889352	0.01742556	0.01569276	0.16699961
LLD_2	Brain_MRIBAG	long	indirect	0.03937212	NA	NA	NA	NA
LLD_2	Brain_MRIBAG	long	total	0.54340736	NA	NA	NA	NA

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LLD 2	Brain MRIBAG	long	prop mediated	0.07245415	NA	NA	NA	NA
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Supplementary Table 7: 521 FinnGen and 6 PGC GWAS summary statistics

We used summary statistics from 6 PGC GWAS in all genetic correlation analyses, two of which lacked allele frequency information and were therefore excluded from the Mendelian randomization analysis.

PGC:

Author	DE	Download URL	PMID	Build #	Ancestry
Ditte Demontis	ADHD	https://figshare.com/articles/dataset/adhd2022/22564390	36702997	GRCh37	European
Douglas P. Wightman	AD	https://ctg.cnr.nl/software/summary_statistics	34493870	GRCh37	European
Jakob Grove	ASD	https://figshare.com/articles/dataset/asd2019/14671989	30804558	GRCh37	European
Niamh Mullins	BIP	https://figshare.com/articles/dataset/PGC3_bipolar_disorder_GWAS_summary_statistics/14102594	34002096	GRCh37	European
OCGAS	OCD	https://figshare.com/articles/dataset/ocd2018/14672103	28761083	GRCh37	European
Vassily Trubetskoy	SCZ	https://figshare.com/articles/dataset/scz2022/19426775	35396580	GRCh37	European

FinnGen:

DE	Full disease name	Category	N-cases	N-controls
RX_PARAC ETAMOL_N SAID	Paracetamol of NSAID medication	Drug purchase endpoints	314977	62300
RX_ANTIH YP	Antihypertensive medication - note that there are other indications	Drug purchase endpoints	199546	177731
FG_CVD	Cardiovascular diseases (excluding rheumatic etc)	Cardiometabolic endpoints	185353	191924
PAIN	Pain (limb, back, neck, head abdominally)	Miscellaneous, not yet classified endpoints	171922	204598
K11_CARIE S_1_ONLY AVO	Dental caries 1, only avohilmo	XI Diseases of the digestive system (K11_)	161113	216164
M13_ARTH ROPATHIE S	Arthropathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	136415	240862
RX_STATI N	Statin medication	IX Diseases of the circulatory system (I9_)	127169	250108
K11_ORAL	Diseases of oral cavity, salivary glands and jaws	XI Diseases of the digestive system (K11_)	118043	259234
PULM_INF ECTIONS	COPD/asthma/ILD related infections	Interstitial lung disease endpoints	117312	259965
I9_HYPTE NS	Hypertension	IX Diseases of the circulatory system (I9_)	111581	265626
ANTIDEPR ESSANTS	Depression medications	Comorbidities of Neurological endpoints	106785	88536
O15_DELIV _SPONT	Single spontaneous delivery	XV Pregnancy, childbirth and the puerperium (O15_)	106627	92306
M13_DORS OPATHY	Dorsopathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	106313	270964
N14_FEMA LEGENNO NINF	Noninflammatory disorders of female genital tract	XIV Diseases of the genitourinary system (N14_)	103306	107564
M13_SOFT TISSUE	Soft tissue disorders	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	102065	275212
KRA_PSY ANYMENT AL	Any mental disorder	Psychiatric endpoints from Katri R $\sqrt{\text{§ikk}\sqrt{\partial\text{nen}}$	99751	277526
M13_ARTH ROSIS_INC LAVO	Artrosis, including avohilmo	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	96500	280777
AUTOIMM UNE	Autoimmune diseases	Diseases marked as autoimmune origin	96150	281127
J10_UPPER DIS	Other diseases of upper respiratory tract	X Diseases of the respiratory system (J10_)	93935	283342
FALLS	Falls/tendency to fall	Miscellaneous, not yet classified endpoints	92857	284420

I9_HYPTE N SESS	Hypertension, essential	IX Diseases of the circulatory system (I9_)	92462	265626
G6_EPIPAR OX	Episodal and paroxysmal disorders	VI Diseases of the nervous system (G6_)	89440	287837
K11_GINGI VITIS PERI ODONTAL	Gingivitis and periodontal diseases	XI Diseases of the digestive system (K11_)	87497	259234
K11_PULPI TIS_1 ONL YAVO	Dental pulpitis 1, only avohilmo	XI Diseases of the digestive system (K11_)	81713	295564
M13_OTHE RJOINT	Other joint disorders	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	81676	240862
M13_DORS OPATHYOT H	Other dorsopathies, not elsewhere classified	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	79212	270964
FG_OTHHE ART	Other heart diseases	Cardiometabolic endpoints	77711	191924
RX_CROHN 1STLINE	First line medication for Crohn's disease	Drug purchase endpoints	77497	299780
C3_CANCE R_EXALLC	Malignant neoplasm (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	77325	287137
K11_INTES TOTH	Other diseases of intestines	XI Diseases of the digestive system (K11_)	75346	301931
M13_ARTH ROSIS	Arthrosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	73710	240862
J10_UPPERI NFEC	Acute upper respiratory infections	X Diseases of the respiratory system (J10_)	69111	308166
CARDIAC ARRHYTM	Cardiac arrhythmias	Comorbidities of COPD	67035	220224
J10_LOW C HRON	Chronic lower respiratory diseases	X Diseases of the respiratory system (J10_)	65991	311286
RX_N05C	Use of hypnotics and sedatives	V Mental and behavioural disorders (F5_)	65814	311463
I9_IHD	Ischaemic heart disease, wide definition	IX Diseases of the circulatory system (I9_)	63744	313533
J10_INFLUP NEU	Influenza and pneumonia	X Diseases of the respiratory system (J10_)	62604	314673
O15_PREG ABORT	Pregnancy with abortive outcome	XV Pregnancy, childbirth and the puerperium (O15_)	61248	149622
I9_CVD_HA RD	Hard cardiovascular diseases	Cardiometabolic endpoints	61240	316037
H7_CATAR ACTSENIL E	Senile cataract	VII Diseases of the eye and adnexa (H7_)	59522	312864
M13_DORS ALGIA	Dorsalgia	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	59438	270964
J10_PNEUM ONIA	All pneumoniae	X Diseases of the respiratory system (J10_)	58174	319103
RX_CODEI NE_TRAM ADOL	Codeine or tramadol medication	Drug purchase endpoints	57823	319454
T2D	Type 2 diabetes, definitions combined	Diabetes endpoints	57698	308252
K11_OESST ODUO	Diseases of oesophagus, stomach and duodenum	XI Diseases of the digestive system (K11_)	56890	320387
E4_THYROI D	Disorders of the thyroid gland	IV Endocrine, nutritional and metabolic diseases (E4_)	56574	320703
BRONCHIT IS	Bronchitis	Asthma and related endpoints	55222	322055
K11_HERNI A	Hernia	XI Diseases of the digestive system (K11_)	54691	322586
KELA_DIA B_INSUL_E XMORE	Diabetes, insulin treatment (Kela reimbursement) (more control exclusions)	Diabetes endpoints	53892	308249
AUTOIMM UNE_NONT HYROID	Autoimmune diseases excluding thyroid diseases	Diseases marked as autoimmune origin	53213	280251

I9_DISVEIN LYMPH	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	IX Diseases of the circulatory system (I9_)	53156	324121
E4_METAB OLIA	Metabolic disorders	IV Endocrine, nutritional and metabolic diseases (E4_)	53127	324150
AUTOIMM UNE_NONT HYROID_S TRICT	Autoimmune diseases excluding thyroid diseases, strict definition	Diseases marked as autoimmune origin	51863	275890
N14_URINO TH	Other diseases of urinary system	XIV Diseases of the genitourinary system (N14_)	49276	328001
F5_DEPRES SION_DYS THYMIA	Depression or dysthymia	V Mental and behavioural disorders (F5_)	48847	225483
O15_COMP LIC_LAB_D ELIV	Complications of labour and delivery	XV Pregnancy, childbirth and the puerperium (O15_)	48093	162777
F5_MOOD	Mood [affective] disorders	V Mental and behavioural disorders (F5_)	48085	329192
I9_CORAT HER	Coronary atherosclerosis	IX Diseases of the circulatory system (I9_)	47550	313400
N14_MALE GEN	Diseases of male genital organs	XIV Diseases of the genitourinary system (N14_)	47110	119297
G6_NERPL EX	Nerve, nerve root and plexus disorders	VI Diseases of the nervous system (G6_)	46900	330377
E4_DM2NA SCOMP	Type 2 diabetes with other specified/multiple/unspecified complications	IV Endocrine, nutritional and metabolic diseases (E4_)	46373	308280
I9_AF	Atrial fibrillation and flutter	IX Diseases of the circulatory system (I9_)	45766	191924
H8_OTHER EAR	Other disorders of ear	VIII Diseases of the ear and mastoid process (H8_)	45541	331736
AB1_OTHE R_BACTER IAL	Other bacterial diseases	I Certain infectious and parasitic diseases (AB1_)	44934	332343
M13_ARTH ROSIS_KNE E	Gonarthrosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	44688	240862
SLEEP	Sleep disorders (combined)	Neurological endpoints	44299	329251
I9_CHD	Major coronary heart disease event	IX Diseases of the circulatory system (I9_)	43518	333759
J10_CHRON TONSADEN	Chronic diseases of tonsils and adenoids	X Diseases of the respiratory system (J10_)	43325	283342
F5_DEPRES SIO	Depression	V Mental and behavioural disorders (F5_)	43280	329192
M13_SOFT TISSUEOT H	Other soft tissue disorders, not elsewhere classified	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	43190	275212
J10_ASTHM A_EXMOR E	Asthma (more control exclusions)	X Diseases of the respiratory system (J10_)	42163	202399
O15_MATE RN_CARE	Maternal care related to the fetus and amniotic cavity and possible delivery problems	XV Pregnancy, childbirth and the puerperium (O15_)	41941	168929
M13_LOWB ACKPAINO RANDSCIA TICA	Lower back pain or/and sciatica	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	41815	335462
G6_SLEEPA PNO_INCL AVO	Sleep apnoea, including avohilmo	VI Diseases of the nervous system (G6_)	41704	335573
J10_ASTHM ACOPDKEL A	Asthma/COPD (KELA code 203)	X Diseases of the respiratory system (J10_)	41495	311286
E4_HYTHY _AI_STRIC T	Hypothyroidism, strict autoimmune	IV Endocrine, nutritional and metabolic diseases (E4_)	40926	274069
AB1_INTES TINAL_INF ECTIONS	Intestinal infectious diseases	I Certain infectious and parasitic diseases (AB1_)	40881	336396

L12_DERMA ATITISECZ EMA	Dermatitis and eczema	XII Diseases of the skin and subcutaneous tissue (L12_)	40688	336589
DEATH	Any death	Common endpoint	40455	336822
KRA_PSY_ ANXIETY_ EXMORE	Anxiety disorders (more control exclusions)	Psychiatric endpoints from Katri R $\sqrt{\text{§ikk}\sqrt{\text{önen}}$	40191	277526
C_STROKE	STROKE	Comorbidities of Diabetes	39818	271817
MIGRAINE_ TRIPTAN	Migraine, single triptan purchase ok & required. ICD- code if available is included	Neurological endpoints	39387	337890
G6_SLEEPA PNO	Sleep apnoea	VI Diseases of the nervous system (G6_)	38998	336659
T2D_WIDE	Type 2 diabetes, wide definition	Diabetes endpoints	38657	310131
N14_RENA LTUB	Renal tubulo-interstitial diseases	XIV Diseases of the genitourinary system (N14_)	38335	338942
M13_SPON DYLOPATH Y	Spondylopathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	38276	270964
E4_LIPOPR OT	Disorders of lipoprotein metabolism and other lipidaemias	IV Endocrine, nutritional and metabolic diseases (E4_)	37742	324150
M13_INTER VERTEB	Other intervertebral disc disorders	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	37636	270964
K11_CHOL ELITH	Cholelithiasis	XI Diseases of the digestive system (K11_)	37041	330903
N14_MESN RUIRREG	Excessive, frequent and irregular menstruation	XIV Diseases of the genitourinary system (N14_)	36824	107564
J10_ACUTE UPPERINFE C	Acute upper respiratory infections of multiple and unspecified sites	X Diseases of the respiratory system (J10_)	36445	308166
O15_ABOR T_MEDICA L	Medical abortion	XV Pregnancy, childbirth and the puerperium (O15_)	36232	149622
K11_CONS TIPATION	Constipation	XI Diseases of the digestive system (K11_)	36022	341255
BLEEDING	Bleeding	Miscellaneous, not yet classified endpoints	35917	341360
M13_KNEE DERANGE MENTS	Internal derangement of knee	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	35511	240862
M13_SHOU LDER	Shoulder lesions	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	34594	275212
I9_ANGINA	Angina pectoris	IX Diseases of the circulatory system (I9_)	34456	313400
J10_ASTHM A_MAIN_E XMORE	Asthma (only as main- diagnosis) (more control exclusions)	X Diseases of the respiratory system (J10_)	34343	202399
N14_URET HRAOTH	Other disorders of urethra and urinary system	XIV Diseases of the genitourinary system (N14_)	32905	328001
H7_CHORO IDRETINA	Disorders of choroid and retina	VII Diseases of the eye and adnexa (H7_)	32708	344569
H7_LIDLAC RIMALORB IT	Disorders of eyelid, lacrimal system and orbit	VII Diseases of the eye and adnexa (H7_)	32593	344684
H8_HL_SE N_NAS	Sensorineural hearing loss	VIII Diseases of the ear and mastoid process (H8_)	32487	331736
K11_HERIN G	Inguinal hernia	XI Diseases of the digestive system (K11_)	32335	322586
M13_POLY ARTHROPA THIES	Polyarthropathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	32199	240862
CD2_BENI GN_LEIOM YOMA_UT ERI	Leiomyoma of uterus	II Neoplasms from hospital discharges (CD2_)	31661	179209

E4_PCOS_C ONCORTIU M	Polycystic ovarian syndrome, consortium definition	IV Endocrine, nutritional and metabolic diseases (E4_)	31548	179322
O15_PREG_ OTHER_M AT_DISOR D	Other maternal disorders predominantly related to pregnancy	XV Pregnancy, childbirth and the puerperium (O15_)	30971	179899
K11_DIVER TIC	Diverticular disease of intestine	XI Diseases of the digestive system (K11_)	30649	301931
M13_LIMB PAIN	Pain in limb	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	30485	275212
K11_PARO DON_OPER	Parodontitis or operation codes	XI Diseases of the digestive system (K11_)	30377	346900
N14_PROST HYPERPLA	Hyperplasia of prostate	XIV Diseases of the genitourinary system (N14_)	30066	119297
I9_VARICV E	Varicose veins	IX Diseases of the circulatory system (I9_)	29539	324121
AB1_GAST ROENTERI TIS_NOS	Diarrhoea and gastroenteritis of presumed infectious origin	I Certain infectious and parasitic diseases (AB1_)	29401	336396
M13_LOWB ACKPAIN	Low back pain	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	29329	270964
H7_CONJU NCTIVITIS	Conjunctivitis	VII Diseases of the eye and adnexa (H7_)	28895	345122
K11_APPEN DACUT	Acute appendicitis	XI Diseases of the digestive system (K11_)	28745	346283
I9_OTHAR R	Other arrhythmias	IX Diseases of the circulatory system (I9_)	28079	286109
K11_PARO DON_OPER _DENTAL_ OPER	Parodontitis or/and operation codes	XI Diseases of the digestive system (K11_)	27833	349444
JOINTPAIN	Pain in joint	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	27688	205355
J10_TONSI LLECTOM Y	Tonsillectomy	X Diseases of the respiratory system (J10_)	27449	349828
D3_ANAEM IA	Anaemias	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	27371	88536
I9_HEARTF AIL	Heart failure,strict	IX Diseases of the circulatory system (I9_)	27304	349973
I9_HEARTF AIL_EXMO RE	Heart failure,strict (more control exclusions)	IX Diseases of the circulatory system (I9_)	27304	328105
G6_OTHNE U	Other neurological diseases	VI Diseases of the nervous system (G6_)	27026	350251
I9_HEARTF AIL_ALLC AUSE	All-cause Heart Failure	IX Diseases of the circulatory system (I9_)	26872	349361
K11_CHOL ECYSTECT OMY	Cholecystectomy	XI Diseases of the digestive system (K11_)	26778	350499
K11_REFLU X	Gastro-oesophageal reflux disease	Interstitial lung disease endpoints	26184	320387
K11_APPEN DECTOMY	Appendectomy	XI Diseases of the digestive system (K11_)	26013	351264
E4_HYPER CHOL	Pure hypercholesterolaemia	IV Endocrine, nutritional and metabolic diseases (E4_)	25928	324150
I9_HEARTF AIL_AND_ ANTIHYPE RT	Heart failure and antihypertensive medication	Cardiometabolic endpoints	25827	177731
I9_STR	Stroke, excluding SAH	IX Diseases of the circulatory system (I9_)	25398	339920

K11_CARIE S_2	Dental caries 2	XI Diseases of the digestive system (K11_)	25095	352182
H8_MIDDL EMASTOID	Diseases of middle ear and mastoid	VIII Diseases of the ear and mastoid process (H8_)	24706	352571
F5_ALLAN XIOUS	All anxiety disorders	V Mental and behavioural disorders (F5_)	24662	337577
L12_OTHE RSKINSUB CUTIS	Other disorders of skin and subcutaneous tissue	XII Diseases of the skin and subcutaneous tissue (L12_)	24189	353088
I9_MI_STRI CT	Myocardial infarction, strict	IX Diseases of the circulatory system (I9_)	24185	313400
M13_MENI SCUÐDERA NGEMENT S	Meniscus derangement	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	24158	240862
M13_ROTA TORCUFF	Rotator cuff syndrome	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	24061	275212
N14_PYEL ONEPHR	Acute tubulo-interstitial nephritis	XIV Diseases of the genitourinary system (N14_)	23912	338942
H7_RETINA LDISOTH	Other retinal disorders	VII Diseases of the eye and adnexa (H7_)	23610	344569
KRA_PSY_ SUBSTANC E_EXMORE	Substance abuse (more control exclusions)	Psychiatric endpoints from Katri R $\sqrt{\text{§ikk}\sqrt{\text{ðnen}}$	23194	277526
I9_REVASC	Coronary revascularization (ANGIO or CABG)	IX Diseases of the circulatory system (I9_)	23139	313400
N14_FEMA LEGENINF	Inflammatory diseases of female pelvic organs	XIV Diseases of the genitourinary system (N14_)	22575	188295
G6_CARPT U	Carpal tunnel syndrome	VI Diseases of the nervous system (G6_)	22426	330377
M13_ARTH TROSIS_CO X	Coxarthrosis,	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	22254	240862
FG_DOAAC	Diseases of arteries, arterioles and capillaries (FINNGEN)	IX Diseases of the circulatory system (I9_)	22224	191924
APPENDAC UT_NOCO MPLIC	Acute appendicitis, no complications	XI Diseases of the digestive system (K11_)	21998	346283
AUD_SWE DISH	Alcohol use disorder, Swedish definition	Alcohol related diseases	21996	355281
L12_DERM ATITISNAS ASTHMA_I NFECTION S	Other and unspecified dermatitis	XII Diseases of the skin and subcutaneous tissue (L12_)	21951	336589
I9_AF_REI MB	Asthma-related infections	Asthma and related endpoints	21927	335114
N14_MENO RRHAGIA	Atrial fibrillation and flutter with reimbursement	IX Diseases of the circulatory system (I9_)	21700	191924
ASTHMA_ NAS	Menorrhagia	XIV Diseases of the genitourinary system (N14_)	21496	107564
E4_OBESIT Y	Asthma, unspecified (mode)	Asthma and related endpoints	21392	210122
L12_INFEC T_SKIN	Obesity	IV Endocrine, nutritional and metabolic diseases (E4_)	21375	355786
H7_ALLER GICCONJU NCTIVITIS	Infections of the skin and subcutaneous tissue	XII Diseases of the skin and subcutaneous tissue (L12_)	21308	355969
C3_SKIN_E XALLC	Allergic conjunctivitis	VII Diseases of the eye and adnexa (H7_)	20958	356319
M13_ARTH ROSIS_OTH	Malignant neoplasm of skin (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	20951	287137
I9_VHD	Other arthrosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	20949	240862
J10_LOWE RINF	Valvular heart disease excluding rheumatic fever	IX Diseases of the circulatory system (I9_)	20929	286109
I9_NONRH EVALV	Other acute lower respiratory infections	X Diseases of the respiratory system (J10_)	20873	356404
	Non-rheumatic valve diseases	IX Diseases of the circulatory system (I9_)	20772	286109

N14_OVAR YCYST	Ovarian cyst	XIV Diseases of the genitourinary system (N14_)	20750	107564
K11_REIMB _202	KELA_REIMBURSEMENT_ 202	Gastrointestinal endpoints	20730	356547
J10_SINUSI TIS	Acute sinusitis	X Diseases of the respiratory system (J10_)	20520	308166
M13_SYNO TEND	Disorders of synovium and tendon	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	20492	275212
AB1_ERYSI PELAS	Erysipelas	I Certain infectious and parasitic diseases (AB1_)	20470	332343
RX_CROHN _2NDLINE	Second line medication for Crohn's disease	Drug purchase endpoints	20353	356924
CD2_BENI GN_COLOR ECANI	Benign neoplasm of colon, rectum, anus and anal canal	II Neoplasms from hospital discharges (CD2_)	20336	356941
M13_ARTH TROSIS_CO X_PRIM_IC D10	Coxarthrosis, primary	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	20056	357221
ST19_FRAC T_LOWER_ LEG_INCL U_ANKLE	Fracture of lower leg, including ankle	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	19994	323307
M13_SPON DYLOSIS	Spondylosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	19892	270964
ST19_FRAC T_FOREA	Fracture of forearm	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	19577	351196
J10_VOCAL LARYNX	Diseases of vocal cords and larynx+other diseases of upper respiratory tract, no elsewhere classified	X Diseases of the respiratory system (J10_)	19530	283342
C3_BASAL _CELL_CA RCINOMA_ INCLAVO_ EXALLC	Basal cell carcinoma, including avohilmo (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	19522	286768
H7_SCLER ACORNEA	Disorders of sclera, cornea, iris and ciliary body	VII Diseases of the eye and adnexa (H7_)	19463	357814
I9_VTE	Venous thromboembolism	IX Diseases of the circulatory system (I9_)	19372	357905
I9_K_CARD IAC	Death due to cardiac causes	IX Diseases of the circulatory system (I9_)	19295	357982
M13_OSTE OCHONDR O	Osteopathies and chondropathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	19263	358014
M13_ARTH ROSIS_KNE E_PRIM_K NEESURG	Gonarthrosis, primary, with knee surgery	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	19126	337196
M13_SPINS TENOSIS	Spinal stenosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	18989	270964
C3_BASAL _CELL_CA RCINOMA_ EXALLC	Basal cell carcinoma (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	18982	287137
H7_GLAUC OMA	Glaucoma	VII Diseases of the eye and adnexa (H7_)	18902	358375
AB1_BACTI NF_NOS	Bacterial infection, other or unspecified	I Certain infectious and parasitic diseases (AB1_)	18576	332343
M13_SCIAT ICA	Sciatica+with lumbago	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	18569	270964
G6_MIGRAI NE	Migraine	VI Diseases of the nervous system (G6_)	18477	287837
I9_TIA	Transient ischemic attack	IX Diseases of the circulatory system (I9_)	18398	342294

RX_GLUCO SAMINE	Glucosamine medication	Drug purchase endpoints	18341	358936
J10_COPD	COPD	X Diseases of the respiratory system (J10_)	18266	311286
N14_CYSTI TIS	Cystitis	XIV Diseases of the genitourinary system (N14_)	18080	328001
C3_OTHER _SKIN_EXA LLC	Other malignant neoplasms of skin (=non-melanoma skin cancer) (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	17958	287137
F5_DEMEN TIA_INCLA VO	Dementia, including avohilmo	V Mental and behavioural disorders (F5_)	17901	359376
H7_CATAR ACTOTHER	Other cataract	VII Diseases of the eye and adnexa (H7_)	17699	312864
K11_ENER COLNONIN F	Noninfective enteritis and colitis	XI Diseases of the digestive system (K11_)	17350	359927
N14_MENSI RREG	Irregular menses	XIV Diseases of the genitourinary system (N14_)	17228	179322
F5_DEPRES SION_REC URRENT	Recurrent or chronic depression	V Mental and behavioural disorders (F5_)	17227	228647
N14_FEMG ENPROL PRIM_KNE EARTHROS IS	Female genital prolapse	XIV Diseases of the genitourinary system (N14_)	17150	107564
O15_ABOR T_SPONTA N	Primary gonarthrosis, bilateral	Rheuma endpoints	17009	332589
N14_BREA ST	Spontaneous abortion	XV Pregnancy, childbirth and the puerperium (O15_)	16906	149622
F5_ANXIET Y	Disorders of breast	XIV Diseases of the genitourinary system (N14_)	16897	193973
I9_HEARTF AIL_AND_ OVERWEIG HT	Other anxiety disorders	V Mental and behavioural disorders (F5_)	16887	337577
F5_DEMEN TIA	Heart failure and bmi 25plus	Cardiometabolic endpoints	16707	154410
CD2_BENI GN_COLON	Dementia	V Mental and behavioural disorders (F5_)	16499	356660
J10_CHRON SINUSITIS	Benign neoplasm: Colon	II Neoplasms from hospital discharges (CD2_)	16445	360832
DM_SEVER AL_COMPL ICATIONS	Chronic sinusitis	X Diseases of the respiratory system (J10_)	16395	283342
K11_OTHF UNC	Diabetes, several complications	Diabetes endpoints	16320	271817
J10_PNEUM OBACT	Other functional intestinal disorders	XI Diseases of the digestive system (K11_)	16311	301931
K11_OTHDI G	Bacterial pneumoniae	X Diseases of the respiratory system (J10_)	16244	314673
L12_DISOR DSKINAPP ENDIX	Other diseases of the digestive system	XI Diseases of the digestive system (K11_)	16222	361055
H7_OCUM USCLE	Disorders of skin appendages	XII Diseases of the skin and subcutaneous tissue (L12_)	16137	361140
ASTHMA_ ACUTE_RE SPIRATOR Y_INFECTI ONS	Disorders of ocular muscles, binocular movement, accommodation and refraction	VII Diseases of the eye and adnexa (H7_)	16040	361237
G6_HEADA CHE	Asthma-related acute respiratory infections	Asthma and related endpoints	16018	335114
AUD	Other headache syndromes	VI Diseases of the nervous system (G6_)	15851	287837
	Alcohol use disorder, ICD-based	V Mental and behavioural disorders (F5_)	15715	361562

H7_VISUDI STURB	Visual disturbances	VII Diseases of the eye and adnexa (H7_)	15707	360091
C3_BREAS T_EXALLC	Malignant neoplasm of breast (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	15680	167189
F5_KELAM ENT	Kela-code for severe mental illness	V Mental and behavioural disorders (F5_)	15451	360114
J10_PLEUR A	Other diseases of pleura	X Diseases of the respiratory system (J10_)	15441	361836
J10_BRONC HITIS	Acute bronchitis	X Diseases of the respiratory system (J10_)	15393	356404
ABDOM_H ERNIA	Hernia of abdominal wall	XI Diseases of the digestive system (K11_)	15338	361939
E4_ENDOG LAND	Disorders of other endocrine glands	IV Endocrine, nutritional and metabolic diseases (E4_)	15289	361988
H7_VITRB ODYGLOB E	Disorders of vitreous body	VII Diseases of the eye and adnexa (H7_)	15177	361552
H7_MACUL ADEGEN	Degeneration of macula and posterior pole	VII Diseases of the eye and adnexa (H7_)	15137	344569
N14_ENDO METRIOSIS	Endometriosis	XIV Diseases of the genitourinary system (N14_)	15088	107564
E4_OBESIT YCAL	Obesity due to excess calories	IV Endocrine, nutritional and metabolic diseases (E4_)	15045	355902
I9_ATHSCL E	Atherosclerosis, excluding cerebral, coronary and PAD	IX Diseases of the circulatory system (I9_)	15002	349539
M13_ARTH TROSIS_CO X_PRIM_HI PSURG	Coxarthrosis, primary, with hip surgery	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	14990	357221
H8_VERTIG O	Disorders of vestibular function (Vertigo)	VIII Diseases of the ear and mastoid process (H8_)	14918	359094
O15_HYPT ENSPREG	Pregnancy hypertension	XV Pregnancy, childbirth and the puerperium (O15_)	14727	196143
M13_HALL UXVALGU S	Hallux valgus (acquired)	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	14726	240862
I9_ANGIO	Coronary angioplasty	IX Diseases of the circulatory system (I9_)	14723	313400
H8_MED_S UPP	Suppurative and unspecified otitis media	VIII Diseases of the ear and mastoid process (H8_)	14406	352571
KRA_PSY_ DEMENTIA EXMORE	Any dementia (more control exclusions)	Psychiatric endpoints from Katri R $\sqrt{\text{§ikk}\sqrt{\text{önen}}$	14367	277526
H7_EYELID DIS	Other disorders of eyelid	VII Diseases of the eye and adnexa (H7_)	14347	344684
N14_POLYP FEMGEN	Polyp of the female genital tract	XIV Diseases of the genitourinary system (N14_)	14324	107564
O15_FALSE LAB	False labour	XV Pregnancy, childbirth and the puerperium (O15_)	14282	168929
AB1_VIRA L_SKIN_M UCOUS_ME MBRANE	Viral infections characterized by skin and mucous membrane lesions	I Certain infectious and parasitic diseases (AB1_)	14280	362997
N14_RENF AIL	Renal failure	XIV Diseases of the genitourinary system (N14_)	14100	363177
M13_DORS ALGIANAS	Other/unspecified dorsalgia	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	14075	270964
F5_STRESS OTH	Other reaction to severe stress, and adjustment disorders	V Mental and behavioural disorders (F5_)	13913	337577
D3_ANAEM IA_IRONDE F	Iron deficiency anaemia	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	13689	360528
D3_ANAEM IANAS	Other and unspecified anaemias	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	13600	362319
L12_ATOPI C	Atopic dermatitis	XII Diseases of the skin and subcutaneous tissue (L12_)	13473	336589

M13_CERVI CDISC	Cervical disc disorders	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	13394	270964
G6_AD_WI DE	Alzheimer, Åôs disease, wide definition	VI Diseases of the nervous system (G6_)	13393	363884
H7_LACRI MALSYSTE M	Disorders of lacrimal system	VII Diseases of the eye and adnexa (H7_)	13326	344684
I9_UAP	Unstable angina pectoris	IX Diseases of the circulatory system (I9_)	13304	333375
TEMPORO MANDIB_I NCLAVO	Temporomandibular joint disorders, including avohilmo	XI Diseases of the digestive system (K11_)	13282	363995
C3_PROST ATE_EXAL LC	Malignant neoplasm of prostate (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	13216	119948
L12_PAPUL OSQUAMO US	Papulosquamous disorders	XII Diseases of the skin and subcutaneous tissue (L12_)	13206	364071
J10_TONSI LLITIS	Other and unspecified tonsillitis	X Diseases of the respiratory system (J10_)	13190	308166
N14_FEMA LEINFERT	Female infertility	XIV Diseases of the genitourinary system (N14_)	13142	107564
NEURODE GOTH	Other degenerative diseases of the nervous system	Comorbidities of Gastrointestinal endpoints	13086	212179
KRA_PSY_ SCHIZODE	Schizophrenia or delusion (more control exclusions)	Psychiatric endpoints from Katri R√§ikk√°nen	13061	277526
L_EXMORE GEST_DIA BETES	Gestational diabetes (for exclusion)	Diabetes endpoints	13039	197831
I9_HEARTF AIL_AND_ CHD	Heart failure and coronary heart disease	Cardiometabolic endpoints	12872	333759
I9_VEINSO TH	Other disorders of veins	IX Diseases of the circulatory system (I9_)	12630	324121
O15_DELIV _CAESAR	Single delivery by caesarean section	XV Pregnancy, childbirth and the puerperium (O15_)	12596	92306
M13_RHEU MA	Rheumatoid arthritis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	12555	240862
CD2_BENI GN_SKIN	Other benign neoplasms of skin	II Neoplasms from hospital discharges (CD2_)	12341	364936
E4_HYPER LIPNAS	Hyperlipidaemia, other/unspecified	IV Endocrine, nutritional and metabolic diseases (E4_)	12304	324150
AB1_OTHE R_SEPSIS	Other septicaemia	I Certain infectious and parasitic diseases (AB1_)	12301	332343
O15_OTHE R_MATERN _DIS_ELSE _WHERE	Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium	XV Pregnancy, childbirth and the puerperium (O15_)	12297	198180
K11_PULP_ PERIAPICA L	Diseases of pulp and periapical tissues	XI Diseases of the digestive system (K11_)	12078	259234
ASTHMA_P NEUMONI A	Asthma-related pneumonia	Asthma and related endpoints	12044	335114
HYPOTHY_ REIMB	Hypothyroidism, drug reimbursement	IV Endocrine, nutritional and metabolic diseases (E4_)	12040	88531
H7_VITROT H	Other and unspecified disorders of vitreous body	VII Diseases of the eye and adnexa (H7_)	12004	361552
K11_DIAHE R	Diaphragmatic hernia	XI Diseases of the digestive system (K11_)	11757	322586
ST19_FRAC T_SHOUL UPPER_AR M	Fracture of shoulder and upper arm	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	11750	345173
M13_SYST CONNECT	Systemic connective tissue disorders	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	11744	365533

G6_EPLEPSY	Epilepsy	VI Diseases of the nervous system (G6_)	11740	287837
O15_CONCEPT_ARM	Other abnormal products of conception	XV Pregnancy, childbirth and the puerperium (O15_)	11716	149622
J10_SEPTD_EV	Deviated nasal septum	X Diseases of the respiratory system (J10_)	11680	283342
Z21_PROCREATIVE_MANAG	Procreative management	XXI Factors influencing health status and contact with health services (Z21_)	11666	300151
R18_RETENURINE	Retention of urine	XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R18_)	11657	343006
H7_KERATITIS	Keratitis	VII Diseases of the eye and adnexa (H7_)	11611	357814
N14_POSTMENBLEED	Postmenopausal bleeding	XIV Diseases of the genitourinary system (N14_)	11582	107564
I9_SEQUELAE	Sequelae of cerebrovascular disease	IX Diseases of the circulatory system (I9_)	11408	342673
ST19_FRAC_T_WRIST_HAND_LEVE	Fracture at wrist and hand level	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	11394	336418
N14_FIOTHNAS	Female infertility, cervigal, vaginal, other or unspecified origin	XIV Diseases of the genitourinary system (N14_)	11348	107564
H7_RETINALDETACH	Retinal detachments and breaks	VII Diseases of the eye and adnexa (H7_)	11230	344569
L12_ACTINIKERA	Actinic keratosis	XII Diseases of the skin and subcutaneous tissue (L12_)	11081	364831
RHEU_ARTHRITIS_OTHER	Other arthritis (FG)	Rheuma endpoints	11033	285035
E4_OBESITY_NAS	Obesity, other/unspecified	IV Endocrine, nutritional and metabolic diseases (E4_)	11025	355902
ALLERG_RHINITIS	Allergic rhinitis	Comorbidities of Asthma	11009	359149
I9_CABG	Coronary artery bypass grafting	IX Diseases of the circulatory system (I9_)	10938	313400
AB1_SEXUAL_TRANSMISSION	Infections with a predominantly sexual mode of transmission	I Certain infectious and parasitic diseases (AB1_)	10937	366340
J10_CHRONRHINITIS	Chronic rhinitis, nasopharyngitis and pharyngitis	X Diseases of the respiratory system (J10_)	10868	283342
K11_LIVER	Diseases of liver	XI Diseases of the digestive system (K11_)	10827	366450
KRA_PSY_ANYMENTAL_SUICIDAL_PREG_NERV_EXMORE	Any mental disorder, or suicide (or attempt), or psychic disorders complicating pregnancy, partum or puerperium or nerve system disorders (more control exclusions)	Psychiatric endpoints from Katri R√§ikk√©nen	10811	276857
H7_GLAUCUSUSP	Glaucoma suspect	VII Diseases of the eye and adnexa (H7_)	10758	358375
K11_OTHDI_SDIG	Other diseases of the digestive system	XI Diseases of the digestive system (K11_)	10589	361055
M13_ENTESOPATHYOTH	Other enthesopathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	10581	275212
DM_RETINOPATHY_EXMORE	Diabetic retinopathy (more control exclusions)	Diabetes endpoints	10413	308633
COPD_LATER	Later onset COPD	COPD and related endpoints	10404	161813
F5_BEHAVIOURAL	Behavioural syndromes associated with physiological	V Mental and behavioural disorders (F5_)	10401	366876

	disturbances and physical factors			
N14_ABNO RMALBLEE D	Other abnormal uterine and caginal bleeding	XIV Diseases of the genitourinary system (N14_)	10319	107564
ASTHMA_ OBESITY_ DENTAL_T MD	Obesity related asthma TMD related pain	Comorbidities of Asthma Dental endpoints	10306 10303	335114 366974
O15_PREEC _OR_FETG RO	Pre-eclampsia or poor fetal growth	XV Pregnancy, childbirth and the puerperium (O15_)	10297	200573
H8_EXTER NAL	Diseases of external ear	VIII Diseases of the ear and mastoid process (H8_)	10272	367005
D3_ANAEM IA_IRONDE F_NAS	Other and unspecified iron deficiency	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	10208	360528
L12_URTIC ARIA	Urticaria	XII Diseases of the skin and subcutaneous tissue (L12_)	10175	364583
KRA_PSY_ PERSON_E XMORE	Personality disorders (more control exclusions)	Psychiatric endpoints from Katri R√§ikk√§nen	10012	277522
I9_CONDU CTIO	Conduction disorders	IX Diseases of the circulatory system (I9_)	9949	286109
K11_OTHA NRECT	Other diseases of anus and rectum	XI Diseases of the digestive system (K11_)	9932	301931
I9_NONISC HCARDMY OP	Non-ischemic cardiomyopathy	IX Diseases of the circulatory system (I9_)	9926	303607
F5_ALCOH OL_DEPEN DENCE	Alcohol dependence	V Mental and behavioural disorders (F5_)	9876	353355
K11_DENT OFACIAL_ ANOMALIE S	Dentofacial anomalies [including malocclusion]	XI Diseases of the digestive system (K11_)	9866	259234
H8_SUP_A CUTE	Acute suppurative otitis media	VIII Diseases of the ear and mastoid process (H8_)	9850	352571
G6_XTRAP YR	Extrapyramidal and movement disorders	VI Diseases of the nervous system (G6_)	9833	367444
AB1_OTHE R_VIRAL	Other viral diseases	I Certain infectious and parasitic diseases (AB1_)	9805	367472
O15_MATE RN_CARE_ OTHER	Maternal care for other known or suspected fetal problems	XV Pregnancy, childbirth and the puerperium (O15_)	9783	168929
N14_CALC UKIDUR	Calculus of kidney and ureter	XIV Diseases of the genitourinary system (N14_)	9713	366693
C3_BREAS T_ERPLUS_ EXALLC	Malignant neoplasm of breast, HER-positive (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	9698	167017
E4_FLUIDE LECTRO	Other disorders of fluid, electrolyte and acid-base balance	IV Endocrine, nutritional and metabolic diseases (E4_)	9694	324150
M13_DEFO RMDORSO	Deforming dorsopathies	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	9672	270964
ALLERG_A STHMA	Allergic asthma (mode)	Asthma and related endpoints	9631	210122
I9_PAROXT AC	Paroxysmal tachycardia	IX Diseases of the circulatory system (I9_)	9604	191924
K11_CHRO NGASTR	Chronic gastritis	XI Diseases of the digestive system (K11_)	9570	320387
DM_RETIN A_PROLIF	Proliferative diabetic retinopathy	Diabetes endpoints	9511	362581
E4_NONTO XIC_THYR OID	Nontoxic goitre/thyroid nodule	IV Endocrine, nutritional and metabolic diseases (E4_)	9485	367792

O15_HAEM ORRH_EAR LY_PREG CD2_BENI GN_LIPOM ATOUS	Haemorrhage in early pregnancy	XV Pregnancy, childbirth and the puerperium (O15_)	9433	179899
K11_IBS	Irritable bowel syndrome	II Neoplasms from hospital discharges (CD2_)	9431	367846
G6_ALZHEI MER	Alzheimer disease	XI Diseases of the digestive system (K11_)	9323	301931
L12_PSORI ASIS	Psoriasis	VI Diseases of the nervous system (G6_)	9301	367976
I9_PULME MB	Pulmonary embolism	XII Diseases of the skin and subcutaneous tissue (L12_)	9267	364071
RHEUMA_S EROPOS_W IDE	Seropositive rheumatoid arthritis, wide	IX Diseases of the circulatory system (I9_)	9243	367108
N14_FEMA LE_GENIT AL_DYSPL ASIA_ALL K11_GAST RODUOUL C	All dysplastic lesions of the cervix uteri, vagina or vulva	Rheuma endpoints	9243	368029
I9_CAVS_O PERATED O15_MATE RN_CARE PELVIC_AB NORM	Calcific aortic valvular stenosis, operated	XIV Diseases of the genitourinary system (N14_)	9227	201643
RHEUMA_S EROPOS_O TH	Other/unspecified seropositive rheumatoid arthritis	XI Diseases of the digestive system (K11_)	9216	320387
I9_PHLETH ROMBDVT LOW	DVT of lower extremities	IX Diseases of the circulatory system (I9_)	9153	368124
ST19_FRAC T_RIBS_ST ERNUM_T HORACIC_ SPINE	Fracture of rib(s), sternum and thoracic spine	XV Pregnancy, childbirth and the puerperium (O15_)	9149	168929
N14_CHRO NKIDNEYD IS	Chronic kidney disease	Rheuma endpoints	9139	368029
DENTAL_T MD_FIBRO VWXY20_S UICI_OTHE R_INTENTI _SELF_H	TMD muscular pain linked with fibromyalgia	IX Diseases of the circulatory system (I9_)	9109	324121
T1D_WIDE	Type 1 diabetes, wide definition	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	9094	362260
F5_ALCOH OLAC	Acute alcohol intoxication	XIV Diseases of the genitourinary system (N14_)	9073	363177
H7_AMD	Age-related macular degeneration (whether dry or wet)	Dental endpoints	8995	368282
H7_CONJU NCTIVITIS ACUNONA TOPIC	Conjunctivitis (acute, non atopic)	Psychiatric endpoints from Katri R√§ikk√°nen	8978	368299
CD2_BENI GN_MELA NOCYTIC K11_FISTU LA	Melanocytic naevi	Diabetes endpoints	8967	308373
K11_FUNC DYSP	Colonic or urogenital fistula	V Mental and behavioural disorders (F5_)	8957	353355
	Functional dyspepsia	VII Diseases of the eye and adnexa (H7_)	8913	348936
		VII Diseases of the eye and adnexa (H7_)	8907	345122
		II Neoplasms from hospital discharges (CD2_)	8900	368377
		XI Diseases of the digestive system (K11_)	8879	368398
		XI Diseases of the digestive system (K11_)	8875	320387

H8_OTHHE ARINGLOS S	Other hearing loss	VIII Diseases of the ear and mastoid process (H8_)	8833	331736
ST19_FRAC T_FEMUR	Fracture of femur	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	8766	360928
N14_OTHN ONINFUTE R	Other noninflammatory disorders of uterus, except cervix	XIV Diseases of the genitourinary system (N14_)	8752	107564
OTHER_SY STCON_FG	Other systemic involvement of connective tissue (FG)	Rheuma endpoints	8695	285035
M13_IMP GEMENT	Impingement syndrome of shoulder	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	8676	275212
K11_ILEUS	Paralytic ileus and intestinal obstruction	XI Diseases of the digestive system (K11_)	8660	301931
O15_COMP LIC_PUERP PRIM_COX ARTHROSIS	Complications predominantly related to the puerperium	XV Pregnancy, childbirth and the puerperium (O15_)	8603	202267
K11_HAEM ORR	Primary coxarthrosis, bilateral	Rheuma endpoints	8597	355023
J10_INFLU ENZA	Haemorrhoids and perianal venous thrombosis	XI Diseases of the digestive system (K11_)	8583	301931
H7_BLEPH AROCHAL ASIS	All influenza	X Diseases of the respiratory system (J10_)	8555	314673
K11_UMBH ER	Blepharochalasis	VII Diseases of the eye and adnexa (H7_)	8547	344684
O15_PRETE RM	Umbilical hernia	XI Diseases of the digestive system (K11_)	8510	322586
O15_GEST AT_HYPER T	Preterm labour and delivery	XV Pregnancy, childbirth and the puerperium (O15_)	8507	162777
M13_GOUT	Gestational [pregnancy- induced] hypertension	XV Pregnancy, childbirth and the puerperium (O15_)	8502	194266
I9_HYPTEN SHD	Gout	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	8489	240862
M13_EARL Y_LUMBA R_PROLAP SE	Hypertensive Heart Disease	IX Diseases of the circulatory system (I9_)	8387	265626
O15_LABO UR_FETAL STRESS	Early lumbar disc prolapse, operated	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	8351	368926
H8_NONSU PPNAS	Labour and delivery complicated by fetal stress [distress]	XV Pregnancy, childbirth and the puerperium (O15_)	8324	162777
H8_BPV	Nonsuppurative otitis media	VIII Diseases of the ear and mastoid process (H8_)	8315	352571
O15_POSTP ART_HEA MORRH	Benign paroxysmal vertigo	VIII Diseases of the ear and mastoid process (H8_)	8280	359094
O15_POSTP ART_HEA MORRH_A LLW	Postpartum haemorrhage	XV Pregnancy, childbirth and the puerperium (O15_)	8249	162777
O15_POSTP ART_HEA MORRH_L B	Postpartum haemorrhage	XV Pregnancy, childbirth and the puerperium (O15_)	8249	202621
M13_SOFT OVERUSE	Postpartum haemorrhage	XV Pregnancy, childbirth and the puerperium (O15_)	8249	146016
AB1_MYCO SES	Soft tissue disorders related to use, overuse and pressure	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	8236	275212
THYROTO XICOSIS	Mycoses	I Certain infectious and parasitic diseases (AB1_)	8179	369098
	Thyrotoxicosis	Comorbidities of Gastrointestinal endpoints	8173	367407

L12_ABSCESS_CUT	Cutaneous abscess, furuncle and carbuncle	XII Diseases of the skin and subcutaneous tissue (L12_)	8157	355969
K11_EMBIMPACT_TEETH_INCL_AVO	Embedded and impacted teeth , including avohilmo	XI Diseases of the digestive system (K11_)	8139	369138
N14_CERVICAL_DYSPLASIA_ALL	All dysplastic lesions of the cervix uteri	XIV Diseases of the genitourinary system (N14_)	8025	202845
K11_OTHER_NTERCOL	Other noninfective gastroenteritis and colitis	XI Diseases of the digestive system (K11_)	7988	359927
M13_FIBROBLASTIC	Fibroblastic disorders	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	7952	275212
G6_MIGRAINE_WITH_AURA	Migraine with aura	VI Diseases of the nervous system (G6_)	7917	287837
O15_LABOUR_LONG	Long labour	XV Pregnancy, childbirth and the puerperium (O15_)	7866	162777
DM_KETOACIDOSIS	Diabetic ketoacidosis	Diabetes endpoints	7841	271817
H7_GLAUCOMA_POAG	Primary open-angle glaucoma, strict	VII Diseases of the eye and adnexa (H7_)	7756	358375
H7_REFRACTION_ACCOMMODATION_DIS	Disorders of refraction and accommodation	VII Diseases of the eye and adnexa (H7_)	7737	361237
K11_CARIES_DENTIN	Dental caries	XI Diseases of the digestive system (K11_)	7680	259234
O15_DELIVERY_FORCEPS_VACUUM_EXTRACTOR	Single delivery by forceps and vacuum extractor	XV Pregnancy, childbirth and the puerperium (O15_)	7630	92306
K11_VENTRAL_HERNIA	Ventral hernia	XI Diseases of the digestive system (K11_)	7628	322586
K11_IBD_STRICT	Inflammatory bowel disease, strict (require KELA)	XI Diseases of the digestive system (K11_)	7625	369652
K11_KELAI_BD	IBD patients in KELA-register	XI Diseases of the digestive system (K11_)	7625	359927
AB1_VIRAL_OTHER_INTENTIONAL_INFECTIONS	Viral and other specified intestinal infections	I Certain infectious and parasitic diseases (AB1_)	7613	336396
ST19_FRACTURE_OF_FOOT_OR_ANKLE	Fracture of foot, except ankle	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	7593	351392
N14_ENDOMETRIOSIS_ASRM_STAGES_3_4	Endometriosis ASRM stages 3,4	XIV Diseases of the genitourinary system (N14_)	7574	203296
CD2_PRIMARY_LYMPHOID_HEMATOPOIETIC_NEOPLASMS_EXCLUDING_ALL_CANCERS	Primary lymphoid and hematopoietic malignant neoplasms (controls excluding all cancers)	II Neoplasms from hospital discharges (CD2_)	7519	299952
K11_OTHER_GASTRITIS_OR_DUODENITIS	Other gastritis (incl. Duodenitis)	XI Diseases of the digestive system (K11_)	7514	320387
J10_PERITONSILLAR_ABSCESS	Peritonsillar abscess	X Diseases of the respiratory system (J10_)	7510	283342
F5_OTHER_NONORGANIC_PSYCHOTIC_DISORDERS	Other and unspecified nonorganic psychotic disorders	V Mental and behavioural disorders (F5_)	7508	364160
E4_DMNADIS	Unspecified diabetes	IV Endocrine, nutritional and metabolic diseases (E4_)	7455	308280
O15_LABOUR_MALPOSITION_OR_MALPRESENTATION_OF_FETUS	Obstructed labour due to malposition and malpresentation of fetus	XV Pregnancy, childbirth and the puerperium (O15_)	7414	162777
I9_AORTIC_ANEURYSM	Aortic aneurysm	IX Diseases of the circulatory system (I9_)	7395	349539
M13_CERVICOBRACHIAL_SYNDROME	Cervicobrachial syndrome	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	7353	270964

DM_HYPO GLYC	Diabetic hypoglycemia	Diabetes endpoints	7332	271817
H7_VISUDI STURBSUB	Subjective visual disturbances	VII Diseases of the eye and adnexa (H7_)	7313	360091
H7_IRIDOC YCLITIS	Iridocyclitis	VII Diseases of the eye and adnexa (H7_)	7306	357814
M13_OSTE OPOROSIS	Osteoporosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	7300	358014
M13_GANG LION	Ganglion	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	7270	275212
CPAP	Continuous positive airway pressure	Interstitial lung disease endpoints	7247	164315
O15_PRE_O R_ECLAMP SIA	Pre-eclampsia or eclampsia	XV Pregnancy, childbirth and the puerperium (O15_)	7212	194266
H7_STRAB OTH	Other strabismus	VII Diseases of the eye and adnexa (H7_)	7179	361237
H8_TINNIT US	Tinnitus	VIII Diseases of the ear and mastoid process (H8_)	7175	331736
O15_MEMB R_PREMAT RUPT	Premature rupture of membranes	XV Pregnancy, childbirth and the puerperium (O15_)	7147	168929
NONALLER G_ASTHM A_EXMOR E	Non-allergic asthma (mode) (more control exclusions)	Asthma and related endpoints	7143	202399
M13_ENTE SOPATHYL OW	Enthesopathies of lower limb, excluding foot	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	7125	270964
COPD_EAR LY	Early onset COPD	COPD and related endpoints	7079	359794
I9_PHLETH ROM	Phlebitis and thrombophlebitis (not including DVT)	IX Diseases of the circulatory system (I9_)	7037	324121
M13_MYAL GIA	Myalgia	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	7024	275212
CD2_BENI GN_COLON _NOS	Benign neoplasm: Colon, unspecified	II Neoplasms from hospital discharges (CD2_)	7013	370264
F5_BIPO	Bipolar affective disorders	V Mental and behavioural disorders (F5_)	7006	329192
N14_FEMG ENPAIN	Pain and other conditions associated with female genital organs and menstrual cycle	XIV Diseases of the genitourinary system (N14_)	6976	107564
ST19_FRAC T_SKULL_F ACIAL_BO NES	Fracture of skull and facial bones	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	6907	329318
D3_BLOOD OTHER	Other diseases of blood and blood-forming organs	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	6877	370400
N14_PHIM OSIS	Redundant prepuce, phimosis and paraphimosis	XIV Diseases of the genitourinary system (N14_)	6859	119297
K11_DISOR D_TEETH	Other disorders of teeth and supporting structures	XI Diseases of the digestive system (K11_)	6850	259234
O15_PREG_ MATERN_C ARE	Maternal care for other conditions predominantly related to pregnancy	XV Pregnancy, childbirth and the puerperium (O15_)	6845	179899
FE	Focal epilepsy	VI Diseases of the nervous system (G6_)	6842	365537
H7_RETINO PATHYDIA B	Diabetic retinopathy	VII Diseases of the eye and adnexa (H7_)	6818	344569
F5_PERSM OOD	Persistent mood disorders	V Mental and behavioural disorders (F5_)	6756	329192

APPENDAC UT_COMPL IC	Acute appendicitis, with complications	XI Diseases of the digestive system (K11_)	6747	346283
G6_MIGRAI NE_NO_AU RA	Migraine without aura	VI Diseases of the nervous system (G6_)	6730	287837
TRAUMBR AIN_NONC ONCUS	severe traumatic brain injury, does not include concussion	Neurological endpoints	6687	370590
M13_CERVI CALGIA	Cervicalgia	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	6684	270964
L12_CELLU LITIS	Cellulitis	XII Diseases of the skin and subcutaneous tissue (L12_)	6683	355969
O15_PREEC LAMPS	Pre-eclampsia	XV Pregnancy, childbirth and the puerperium (O15_)	6663	194266
F5_SUBSN OALCO	Substance use, excluding alcohol	V Mental and behavioural disorders (F5_)	6605	353355
M13_OTHE RBONE	Other disorders of bone	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	6568	358014
H8_EXTOTI TIS	Otitis externa	VIII Diseases of the ear and mastoid process (H8_)	6547	367005
H7_IRIDOC YC_ANTER	Anterior Iridocyclitis	VII Diseases of the eye and adnexa (H7_)	6536	370741
I9_INTRAC RA	Nontraumatic intracranial haemorrhage	IX Diseases of the circulatory system (I9_)	6530	342673
F5_SCHZPH R	Schizophrenia	V Mental and behavioural disorders (F5_)	6515	364160
C3_COLOR ECTAL_EX ALLC	Colorectal cancer (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	6509	287137
AD_LO_EX MORE	Alzheimer, Åôs disease (Late onset) (more control exclusions)	Neurological endpoints	6489	170429
K11_PARO DON_PERI APIC_CHR ONIC	Chronic periapical parodontitis	XI Diseases of the digestive system (K11_)	6466	259234
RX_INFERT ILITY	Medical treatment for female infertility	Drug purchase endpoints	6446	204424
J10_RESPO THER	Other diseases of the respiratory system	X Diseases of the respiratory system (J10_)	6381	370896
L12_URTIC A_NAS	Other and unspecified urticaria	XII Diseases of the skin and subcutaneous tissue (L12_)	6381	364583
E4_PARAT HYRO	Disorders of parathyroid gland	IV Endocrine, nutritional and metabolic diseases (E4_)	6362	361988
M13_PATE LLAOTH	Other disorders of patella	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	6333	240862
SPONDYLO ARTHRITIS NIV	Spondyloarthritis	Comorbidities of Interstitial lung disease endpoints	6333	341455
ALCOHOL ACUTE10	Non-invasive ventilation	Interstitial lung disease endpoints	6315	164315
K11_SALIV ARY	Acute alcohol intoxication	Alcohol related diseases	6289	369838
K11_ANOM ALI_DENT AL_ARCH RELATION S1_INCLAV O	Diseases of salivary glands	XI Diseases of the digestive system (K11_)	6269	259234
J10_NASAL POLYP	Anomalies of dental arch relationship, including avohilmo	XI Diseases of the digestive system (K11_)	6260	371017
E4_DM1NA SCOMP	Nasal polyp	X Diseases of the respiratory system (J10_)	6255	283342
K11_ACUT PANC	Type 1 diabetes with other specified/multiple/unspecified complications	IV Endocrine, nutritional and metabolic diseases (E4_)	6234	308280
	Acute pancreatitis	XI Diseases of the digestive system (K11_)	6223	330903

FE_STRICT	Focal epilepsy, strict definition	VI Diseases of the nervous system (G6_)	6213	365534
ST19_FRAC T_LUMBAR _SPINE_PE _LVIS	Fracture of lumbar spine and pelvis	XIX Injury, poisoning and certain other consequences of external causes (ST19_)	6209	364504
M13_ARTH ROSIS_POL Y	Polyarthrosis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	6185	240862
H7_IRIDOA CUTE	Acute and subacute iridocyclitis	VII Diseases of the eye and adnexa (H7_)	6166	357814
F5_BEHEM OCHILD	Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	V Mental and behavioural disorders (F5_)	6160	371117
RHEUMA_ OTHER_WI DE	Other (seronegative) rheumatoid arthritis, wide	Rheuma endpoints	6153	371124
E4_GOITRE MULTINOD POLLENAL LERG	Nontoxic multinodular goitre	IV Endocrine, nutritional and metabolic diseases (E4_)	6149	320703
N14_HYPE RTROPHYB REAST_BO TH	Pollen allergy	Comorbidities of Asthma	6118	368409
	Hypertrophy of breast in women and men	XIV Diseases of the genitourinary system (N14_)	6105	359487
DRY_AMD	Dry age-related macular degeneration (includes geographic atrophy)	VII Diseases of the eye and adnexa (H7_)	6065	251042
D3_IMMUN EMECHANIS M	Certain disorders involving the immune mechanism	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	6022	371255
N14_FEMA LE_GENIT AL_HSIL	HSIL lesion of the cervix uteri, vagina or vulva	XIV Diseases of the genitourinary system (N14_)	5996	204874
C3_BREAS T_ERNEG_ EXALLC	Malignant neoplasm of breast, HER-negative (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	5965	167017
O15_MAT_ CARE_MAL PRESENT	Maternal care for known or suspected malpresentation of fetus	XV Pregnancy, childbirth and the puerperium (O15_)	5957	168929
K11_GULC	Gastric ulcer	XI Diseases of the digestive system (K11_)	5935	320387
K11_OTHIL EUS	Other or unspecified ileus, impaction or obstruction	XI Diseases of the digestive system (K11_)	5925	301931
N14_ACUT ERENFAIL	Acute renal failure	XIV Diseases of the genitourinary system (N14_)	5908	363177
I9_CARDM YO	Cardiomyopathy	IX Diseases of the circulatory system (I9_)	5874	286109
N14_ENDO METRIOSIS _OVARY	Endometriosis of ovary	XIV Diseases of the genitourinary system (N14_)	5867	107564
ASTHMA_C HILD_EXM ORE	Childhood asthma (age<16) (more control exclusions)	Asthma and related endpoints	5865	202399
AB1_VIRA L_NOS	Other viral diseases, not elsewhere classified	I Certain infectious and parasitic diseases (AB1_)	5864	367472
C3_BRONC HUS_LUNG _EXALLC	Malignant neoplasm of bronchus and lung (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	5842	287137
L12_SEBOR RKERAT	Seborrhoeic keratosis	XII Diseases of the skin and subcutaneous tissue (L12_)	5835	353088
VWXY20_I NTENTI_SE LF_P_EXPO S_OTHER_ UNSPCH EMIC_NOX IO_SUBST	Intentional self-poisoning by and exposure to other and unspecified chemicals and noxious substances	XX External causes of morbidity and mortality (VWXY20_)	5811	371466

K11_ORAL _LICHEN_P LANUS_WI DE	Oral lichen ruber planus, wide definition	XI Diseases of the digestive system (K11_)	5791	371486
ABDOM_H ERNIA_POS TOP	Hernia of abdominal wall, postoperative	XI Diseases of the digestive system (K11_)	5775	210314
D3_COAGD EF_PURPU R_HAEMO RRHAGIC N14_ENDO METRIOSIS _ASRM_ST AGE1_2	Coagulation defects, purpura and other haemorrhagic conditions	III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D3_)	5773	371504
N14_SALPH OOPH	Endometriosis ASRM stages 1,2	XIV Diseases of the genitourinary system (N14_)	5769	205101
M13_SPON DYLOLIST HESIS	Salpingitis and oophoritis	XIV Diseases of the genitourinary system (N14_)	5768	188295
L12_PSORI _VULG	Spondylolisthesis/Spondylolysis	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	5766	270964
AB1_SEXU AL_TRANS MISSION_N OS	Psoriasis vulgaris	XII Diseases of the skin and subcutaneous tissue (L12_)	5759	364071
TEMPORO MANDIB O15_PREG_ ECTOP	Other predominantly sexually transmitted diseases, not elsewhere classified	I Certain infectious and parasitic diseases (AB1_)	5753	366340
N14_GLOM ERULAR	Temporomandibular joint disorders	XI Diseases of the digestive system (K11_)	5668	205355
AB1_BACT _INTEST_O TH	Ectopic pregnancy	XV Pregnancy, childbirth and the puerperium (O15_)	5648	149622
N14_ENDO METRIOSIS _PELVICPE RITONEUM	Glomerular diseases	XIV Diseases of the genitourinary system (N14_)	5642	371635
M13_HAM MERTOIE	Other bacterial intestinal infections	I Certain infectious and parasitic diseases (AB1_)	5631	336396
CD2_BENI GN_RECTU M_ANAL E4_HYPER PARA	Endometriosis of pelvic peritoneum	XIV Diseases of the genitourinary system (N14_)	5628	107564
G6_POLYO THUNS	Other hammer toe(s) (acquired)	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	5625	240862
M13_RADI CULOPATH Y	Benign neoplasm: Rectum, anus and anal canal	II Neoplasms from hospital discharges (CD2_)	5613	371664
M13_ADHC APSULITIS	Hyperparathyroidism	IV Endocrine, nutritional and metabolic diseases (E4_)	5590	361988
I9_AVBLO CK	Other and unspecified polyneuropathies, also in other diseases	VI Diseases of the nervous system (G6_)	5553	370790
K11_EROSI ON_INCLA VO	Radiculopathy	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	5550	270964
H7_CORNU LCER	Adhesive capsulitis of shoulder	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	5538	275212
L12_FOLLI CULARCYS T	AV-block	IX Diseases of the circulatory system (I9_)	5536	286109
N14_CERVI CAL_HSIL	Erosion of teeth, including avohilmo	XI Diseases of the digestive system (K11_)	5521	371756
K11_IMPAC TED TEET	Corneal ulcer	VII Diseases of the eye and adnexa (H7_)	5476	357814
	Follicular cysts of skin and subcutaneous tissue	XII Diseases of the skin and subcutaneous tissue (L12_)	5459	361140
	HSIL lesion of the cervix uteri	XIV Diseases of the genitourinary system (N14_)	5459	205411
	Impacted teeth , including avohilmo	XI Diseases of the digestive system (K11_)	5435	371842

H_INCLAV O				
F5_ALZHD EMENT	Dementia in Alzheimer disease	V Mental and behavioural disorders (F5_)	5422	356660
C3_COLOR ECTAL_AD ENO_EXAL LC	Colorectal adenocarcinoma (controls excluding all cancers)	II Neoplasms, from cancer register (ICD-O-3)	5378	287137
I9_SAHANE UR	Aneurysms, operations, SAH	IX Diseases of the circulatory system (I9_)	5342	342673
CHILDHOOD D_ALLERGY	Childhood allergy (age < 16)	Asthma and related endpoints	5337	371940
CD2_BENI GN_OVAR Y	Benign neoplasm of ovary	II Neoplasms from hospital discharges (CD2_)	5308	205562
G6_ROOTP LEXOTHU NS	Other and unspecified nerve root and plexus disorders, also in other diseases	VI Diseases of the nervous system (G6_)	5294	330377
GOUT_NOS KRA_PSY	Gout, unspecified	Rheuma endpoints	5292	368788
SLEEP_NO NORG_EX MORE	Nonorganic sleeping disorders (more control exclusions)	Psychiatric endpoints from Katri R $\sqrt{\text{§ikk}\sqrt{\text{önnen}}$	5254	277526
N14_HYDR OCELE	Hydrocele	XIV Diseases of the genitourinary system (N14_)	5221	119297
N14_HYPE RTROPHYB REAST	Hypertrophy of breast	XIV Diseases of the genitourinary system (N14_)	5212	193973
E4_DM1OP TH	Type 1 diabetes with ophthalmic complications	IV Endocrine, nutritional and metabolic diseases (E4_)	5202	308280
F5_SOMAT OFORM	Somatoform disorder	V Mental and behavioural disorders (F5_)	5164	337577
E4_HYPOO SMNAT	Hypo-osmolality and hyponatraemia	IV Endocrine, nutritional and metabolic diseases (E4_)	5137	324150
INFLUENZ A	All influenza (not pneumonia)	Asthma and related endpoints	5136	314673
M13_DUPU TRYEN	Palmar fascial fibromatosis [Dupuytren]	XIII Diseases of the musculoskeletal system and connective tissue (M13_)	5128	275212
N14_OTHF EMPELINF	Other female pelvic inflammatory diseases	XIV Diseases of the genitourinary system (N14_)	5117	188295
VOCALCO RDDYS	Vocal cord dysfunction	COPD and related endpoints	5087	139795
CD2_BENI GN_OTHER DIGESTIVE	Benign neoplasm of other and ill-defined parts of digestive system	II Neoplasms from hospital discharges (CD2_)	5062	372215
K11_DISLI VOTH	Other diseases of liver	XI Diseases of the digestive system (K11_)	5052	366450
K11_UC_ST RICT2	Ulcerative colitis (strict definition, require KELA, min 2 HDR)	XI Diseases of the digestive system (K11_)	5034	371530
L12_LICHE NPLANUS_ INCLAVO	Lichen planus, including avohilmo	XII Diseases of the skin and subcutaneous tissue (L12_)	5015	372262

665 **Supplementary Table 8: Baseline characteristics of the TriNetX database**

After propensity-score matching						
	Hypersomnia	Controls	Standardized mean difference	Insomnia	Controls	SMD
Total, n	16,371	16,371		110,374	110,374	
Age, Mean $\pm$ SD	41.5 $\pm$ 18.9	42 $\pm$ 19.5	0.0226	45.6 $\pm$ 19.1	45.9 $\pm$ 19.7	0.0135
Sex (%)						
Male	50.2	50.5	0.007	37.9	39.1	0.024
Female	48.3	48.7	0.007	59.3	59.3	0.0004
Ethnicity (%)						
Hispanic/Latino	6.0	5.9	0.008	6.9	6.5	0.015
Not Hispanic/Latino	71.9	72.3	0.01	70.1	70.7	0.009
Unknown	22.1	21.8	0.006	22.5	22.8	0.007
Race (%)						
White	71.5	71.4	0.002	74.3	74.7	0.014
Black	12.5	12.6	0.003	9.8	9.5	0.01
Asian	2.5	2.5	0.004	2.7	2.7	0.002
Other risk/conditions (%)						
Cerebrovascular diseases	0.9	0.9	0.002	0.6	0.8	0.017
Neoplasms	4.1	4.1	0.0003	6.1	6.5	0.018
Certain infectious and parasitic diseases	3.5	3.4	0.002	4.7	4.4	0.016
Pre-existing medical procedures (%)						
Office or other outpatient services	25.3	25.3	0.002	23.2	24.8	0.037
Hospital inpatient and observation care services	0.9	1.1	0.02	1.4	1.5	0.006

Medication prescriptions (%)						
Beta-blockers	3.3	3.3	<0.0001	4.1	4.6	0.029
ACE inhibitors	1.9	2.1	0.014	2.5	2.7	0.014
Angiotensin II inhibitor	1.9	2.1	0.014	1.4	1.3	0.013
Calcium channel blockers	1.6	1.6	<0.0001	2.0	2.0	0.001
Metformin	1.1	0.9	0.02	1.1	1.0	0.009
Glucagon-like Peptide 1 Agonist	0.1	0.1	0.019	0.1	0.0	0.02
Laboratory values						
Hemoglobin A1C/Hemoglobin total in blood [%]	6.07 ± 1.55	6.95 ± 1.61	0.557	6.11 ± 1.66	6.8 ± 1.63	0.420
Cholesterol in serum or plasma [mg/dL]	182 ± 46.4	178 ± 43.4	0.094	182 ± 48.7	178 ± 45.5	0.081
Cholesterol in LDL in serum or plasma [mg/dL]	109 ± 34.9	105 ± 34.4	0.109	106 ± 35.5	105 ± 33.2	0.047
Cholesterol in HDL in serum or plasma [mg/dL]	47.7 ± 17.6	49.6 ± 15.8	0.115	53.4 ± 19.9	51.5 ± 16.7	0.104
Body Mass Index	30.2 ± 8.06	26.8 ± 6.28	0.469	27.2 ± 6.59	27 ± 6.4	0.03

References

1. Wen, J. Refining the generation, interpretation, and application of multi-organ, multi-omics biological aging clocks. *Nature Aging* 2025.02.06.25321803 (2025) doi:10.1038/s43587-025-00928-9.
2. The MULTI Consortium *et al.* Multi-organ metabolome biological age implicates cardiometabolic conditions and mortality risk. *Nat Commun* **16**, 4871 (2025).
3. Dashti, H. S. *et al.* Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun* **10**, 1100 (2019).
4. Austin-Zimmerman, I. *et al.* Genome-wide association studies and cross-population meta-analyses investigating short and long sleep duration. *Nat Commun* **14**, 6059 (2023).
5. Wu, Y. *et al.* Shared genetic architecture and causal relationship between sleep behaviors and lifespan. *Transl Psychiatry* **14**, 108 (2024).
6. O'Connell, K. S. *et al.* Characterizing the Genetic Overlap Between Psychiatric Disorders and Sleep-Related Phenotypes. *Biol Psychiatry* **90**, 621–631 (2021).
7. Goodman, M. O. *et al.* Genome-wide association analysis of composite sleep health scores in 413,904 individuals. *Commun Biol* **8**, 115 (2025).
8. Wen, J. *et al.* The genetic architecture of biological age in nine human organ systems. *Nat Aging* 1–18 (2024) doi:10.1038/s43587-024-00662-8.
9. Cespedes, E. M. *et al.* Comparison of Self-Reported Sleep Duration With Actigraphy: Results From the Hispanic Community Health Study/Study of Latinos Sueño Ancillary Study. *Am J Epidemiol* **183**, 561–573 (2016).

- 689 10. Matthews, K. A. *et al.* Similarities and Differences in Estimates of Sleep Duration by
690 Polysomnography, Actigraphy, Diary, and Self-reported Habitual Sleep in a Community
691 Sample. *Sleep Health* **4**, 96–103 (2018).

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