Supplementary Information

The public health impact of poor sleep on severe COVID-19, influenza and upper respiratory infections
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Supplementary Methods

Cohorts

FinnGen is a study of a population-based cohort of Finnish residents, from newborn to age 104 at baseline recruitment, that have consented to participate in regional biobanks in Finland. The study combines genetic data with electronic health record data derived from primary care registers, hospital in- and out-patient visits and prescription information and aims to understand the genetic etiology of, and drive the development of drugs to treat, a wide variety of diseases and disorders. The current release (R9) contains health and genetic data on up to 392,396 participants, primarily of Finnish ancestry. Diagnosis data extraction from the public healthcare records is ongoing with this data being released on a regular basis and all participants continue to be followed up unless they die (follow-up ends at death), or they withdraw their consent from the study (their data is removed entirely and is not used in analyses). When a study participant is recruited, their entire medical record is linked into the FinnGen database and not just subsequent healthcare provider visits, allowing a detailed understanding of their medical history.

The UK Biobank is a prospective study of over 500,000 participants, aged between 37 and 73 at recruitment, from the mainland UK population[1]. Participants were invited to undertake a baseline interview between 2006 and 2010 where data was collected on a variety of health and lifestyle measures, and where blood and urine samples were also taken for genetic and biochemistry analysis. Electronic health records, consisting of Hospital Episode Statistics in-patient (HES; max. N=440,512) and primary care (GP; max. N=231,364) were later linked up to provide longitudinal data on disease diagnosis, operations, medications, and deaths. Recent diagnoses are frequently added to the records and, as with FinnGen, the participants' entire medical history is made available, and they continue to be followed-up unless they die or withdraw their consent. While the UK Biobank participants are drawn from the general UK population, the study suffers from recruitment bias and as such participants are on average healthier, more educated and less deprived than the average UK resident[2].

Phenotype/endpoint definitions

Diagnosis data in the FinnGen study is compiled from multiple sources, some of which are disease-specific, such as the cancer, visual impairment, kidney disease, and infectious disease registries, whilst others cover more general health events such as visits to health centers ("Avohilmo"), hospital inpatient and outpatient visits ("Hilmo") and from the Finnish Social Insurance Institution (KELA) drug purchases. Inpatient and outpatient diagnoses and death records were available from 1969, whereas hospital outpatient procedures were available from 1998. For the purpose of classifying diagnoses as originating from primary and secondary healthcare events, we considered health center visits ("Avohilmo") as primary healthcare and all other sources (i.e., hospital and specialist visits, and death register) as secondary healthcare. FinnGen defines endpoint cases and controls using only secondary healthcare records; in the logistic regression and survival analyses, we defined our insomnia, influenza and URI endpoints using the same codes (see below), but also included diagnoses from primary care. Study participants were classed as endpoint cases if they had at least one record with a relevant ICD-8, ICD-9, or three-digit ICD-10 code assigned to it. The relevant codes were:

- insomnia: "F51.0", "G47.0" (ICD-10)
- upper respiratory infection (URI): "J06", "J06.0", "J06.9" (ICD-10) or "465" (ICD-9 & ICD-8)
- influenza: "J09", "J10", "J10.0", "J10.1", "J10.2", "J10.8", "J11", "J11.0", "J11.1", "J11.2", "J11.8" (ICD-10) or "487" (ICD-9) or "470", "471", "472", "473", "474" (ICD-8).

Exclusions were made in the control group for insomnia, influenza and URI, based on the presence of the following ICD-8, ICD-9, or three-digit ICD-10 codes:

- insomnia: "F51.1", "F51.3", "F51.4", "F51.5", "F51.8", "F51.9" (ICD-10) or "3074" (ICD-9) or "3064" (ICD-8)
- influenza: "J12", "J13", "J14", "J15", "J16", "J17", "J18" (ICD-10)
- URI: "J00", "J01", "J02", "J03", "J04", "J05" (ICD-10)

If the ICD codes listed above contained subcodes, then these were included in the endpoint diagnosis definition. For instance, including ICD-9 code "465" in the URI endpoint meant that we included the subcodes "465.0", "465.8" and "465.9" in addition to the original "465" code. For the purposes of the survival analysis in which diagnosis date is used, the date of diagnosis was the first date at which the participant was diagnosed with any of the included codes. Control groups were created separately for each endpoint and were defined as those with no relevant diagnosis for the specific endpoint. Of 392,396 FinnGen participants, there were 17,489, 90,447 and 12,057 with insomnia, URI and influenza endpoints respectively (Supp Table 1), of which approximately 83%, 77% and 30% (respectively) were from primary care records (Supp Table 2).

The UK Biobank cohort has both self-report and EHR-based disease definitions. To define equivalent endpoints in the UK Biobank, we used only diagnostic information from the EHR data. Electronic health data from multiple sources has been linked to the UK Biobank. Currently, these include death, cancer, hospital inpatient, primary care (GP) diagnosis, primary care prescription and primary care registration records. To define insomnia and respiratory infection endpoints in the UK Biobank, we used only the hospital inpatient (HES; field 41234) and primary care diagnosis records (field 42040). In the hospital inpatient data, we included individuals as a case for the endpoint if they had at least one of the same ICD-10 or ICD-9 diagnosis codes used for FinnGen (see above) and, as with FinnGen, included participants with subcodes in the endpoint. In the primary care data, diagnoses were coded using the NHS-specific Read v2 or CTV3 codes. We used the following Read codes to define the respective endpoints:

- insomnia: “1B1B0”, “1B1B1”, “1B1B2”, “E2742”, “Eu510”, “Fy00.”, “R0052”, “X007s”, “X007u”, “X76AF”, “X76AG”, “Xa7wV”, “XaIv5”, “XE1Yg”, “XE2Pv” (Read CVT3) or “Eu510”, “Fy00.”, “R0051”, “R0052” (Read v2)
- URI: “H0...”, “H050.”, “H05z.”, “H0z..”, “X1003”, “Xa1sb”, “XaDcC”, “XE0Xq” (Read CVT3) or “H0...”, “H050.”, “H05z.”, “H0z..”, “X1003” (Read v2)
- influenza: “H2...”, “H27..”, “H270.”, “H2700”, “H270z”, “H271.”, “H2710”, “H2711”, “H271z”, “H27y.”, “H27y1”, “H27z.”, “H2y..”, “H2z..”, “XaQQp”, “XE0YK”, “XM0rz” (Read CVT3) or “H2...”, “H27..”, “H270.”, “H2700”, “H270z”, “H271.”, “H2710”, “H2711”, “H271z”, “H27y.”, “H27y1”, “H27z.” (Read v2)

From each endpoint’s control group, in the UK Biobank, we excluded individuals if they had at least one diagnosis of the ICD-10 or ICD-9 codes listed above (for FinnGen control group exclusions), or at least one of the following Read CTV3 or Read v2 codes:

- insomnia: “A3By4”, “H20..”, “H200.”, “H201.”, “H202.”, “H20y.”, “H20z.”, “H22..”, “H220.”, “H221.”, “H223.”, “H2230”, “H224.”, “H22y.”, “H22y0”, “H22y1”, “H22yz”, “H22z.”, “H23..”, “H232.”, “H23z.”, “Hyu08”, “Hyu09”, “Hyu0A”, “Hyu0B”, “X100E”, “X100H”, “X100N”, “X100R”, “XE0YG”, “XM0rv”, “Xa0lY”, “Xa7nL”, “Xa7nM”, “Xa7nN”, “Xa7nP”, “Xa7nT”, “Xa7nU”, “XaBfJ”, “XaYYu”, “XaZ1k”, “XaZ1l”, “XaeVO” (Read CTV3) or “H20..”, “H200.”, “H201.”, “H202.”, “H203.”, “H20y.”, “H20z.”, “H22..”, “H220.”, “H221.”, “H223.”, “H2230”, “H224.”, “H22y.”, “H22y0”, “H22y1”, “H22y3”, “H22yX”, “H22yz”, “H22z.”, “H23..”, “H230.”, “H231.”, “H232.”, “H233.”, “H23z.”, “Hyu08”, “Hyu09”, “Hyu0A”, “Hyu0B” (Read v2)
- URI: “1C9Z.”, “2DB6.”, “2DC3.”, “A34..”, “A340.”, “A3400”, “A3401”, “A3402”, “A3403”, “A340z”, “A341.”, “A34z.”, “G33..”, “H01..”, “H010.”, “H011.”, “H012.”, “H013.”, “H01y.”, “H01y0”, “H01yz”, “H01z.”, “H02..”, “H020.”, “H021.”, “H022.”, “H023.”, “H0230”, “H0231”, “H023z”, “H024.”, “H025.”, “H02z.”, “H030.”, “H031.”, “H032.”, “H033.”, “H034.”, “H035.”, “H0350”, “H0351”, “H035z”, “H036.”, “H037.”, “H03z.”, “H040.”, “H0400”, “H0401”, “H0402”, “H0403”, “H0404”, “H0405”, “H0406”, “H040w”, “H040x”, “H040z”, “H041.”, “H0410”,

"H0411", "H041z", "H042.", "H0420", "H0421", "H042z", "H043.", "H0430", "H0431", "H043z", "H04z.", "H134.", "H13y1", "H14y6", "Hyu00", "Hyu01", "Hyu02", "X00hi", "X00m3", "X00m4", "X00m9", "X00mG", "X00mN", "X00mr", "X00n1", "X00n4", "X00n5", "X00n7", "X00n8", "X00n9", "X1002", "X104U", "X70Id", "XA03t", "XE0Xl", "XE0Xm", "XE0Xn", "XE0Xo", "XE0Xp", "XE0sE", "XE2aC", "XM1Md", "XM1QH", "XM1QI", "XM1QJ", "XM1QS", "Xa05b", "Xa1sc", "Xa1sd", "Xa7I0", "Xa7tY", "Xa86D", "Xa87h", "Xa9Bt", "Xa9Bu", "Xa9zW", "XaDuG", "XaDuH", "XaKyZ", "XaNkV" (Read CTV3) or "A340.", "A3400", "A3401", "A3402", "A3403", "A340z", "A34z.", "H01..", "H010.", "H011.", "H012.", "H013.", "H014.", "H01y.", "H01y0", "H01yz", "H01z.", "H02..", "H020.", "H021.", "H022.", "H023z", "H024.", "H025.", "H02z.", "H03..", "H030.", "H031.", "H032.", "H033.", "H034.", "H035z", "H036.", "H037.", "H03z.", "H04..", "H040.", "H0400", "H0401", "H0402", "H0403", "H0406", "H040w", "H040x", "H040z", "H041.", "H0410", "H0411", "H041z", "H042.", "H0420", "H0421", "H042z", "H043.", "H0430", "H0431", "H0432", "H043z", "H044.", "H04z.", "H14y6", "Hyu00", "Hyu01", "Hyu02" (Read v2)

- influenza: "A3By4", "H20..", "H200.", "H201.", "H202.", "H20y.", "H20z.", "H22..", "H220.", "H221.", "H223.", "H2230", "H224.", "H22y.", "H22y0", "H22y1", "H22yz", "H22z.", "H23..", "H232.", "H23z.", "Hyu08", "Hyu09", "Hyu0A", "Hyu0B", "X100E", "X100H", "X100N", "X100R", "XE0YG", "XM0rv", "Xa0lY", "Xa7nL", "Xa7nM", "Xa7nN", "Xa7nP", "Xa7nT", "Xa7nU", "XaBfJ", "XaYYu", "XaZ1k", "XaZ1l", "XaeVO" (Read CTV3) or "H20..", "H200.", "H201.", "H202.", "H203.", "H20y.", "H20z.", "H22..", "H220.", "H221.", "H223.", "H2230", "H224.", "H22y.", "H22y0", "H22y1", "H22y3", "H22yX", "H22yz", "H22z.", "H23..", "H230.", "H231.", "H232.", "H233.", "H23z.", "Hyu08", "Hyu09", "Hyu0A", "Hyu0B" (Read v2)

As with FinnGen, date of diagnosis for an endpoint was taken as the date of the first identified visit with any of the included ICD-9, ICD-10, Read v2 or Read CTV3 codes and thus the first diagnosis could be either a hospital inpatient or primary care visit. As primary care data is only available in a subset of participants, unlike hospital inpatient data, we limited endpoint definition and therefore subsequent analyses to those with both hospital inpatient and primary care data. Of 231,364 participants with both HES and GP records available, there were 8,693, 55,250 and 12,948 with diagnoses of insomnia, URI and influenza, respectively, in the UK Biobank (Supp Table 1).

COVID-19 diagnoses

Diagnoses of SARS-CoV-2 infection (COVID-19) in Finland are recorded in the THL (Finnish Institute for Health and Welfare) Infectious Disease Register, from which the COVID-19 diagnoses have been extracted and linked to FinnGen participants. In release 9 of FinnGen, diagnoses were available until 2022/05/22, at which point there were 57,333 unique individuals with a positive lab-confirmed COVID-19 diagnosis. Laboratory testing was primarily done using PCR (N=56,394), with a small

proportion of samples tested through antigen testing (N=730) or antibody testing (N=7), and 202 samples with a missing test type.

In the UK Biobank, COVID-19 diagnosis data was obtained from data field 40100. This field is derived using linked data collected by Public Health England (PHE), Public Health Scotland (PHS) and SAIL for England, Scotland and Wales, respectively. We used diagnosis data with a cut off of 2020/10/02 and had data on 1,713 unique samples with a positive COVID-19 diagnosis, of which 733 had both HES and GP data available. All samples included in UKB data field 40100 were diagnosed through PCR testing (https://biobank.ndph.ox.ac.uk/ukb/exinfo.cgi?src=COVID19).

Genetic Data and Analyses

To undertake the Mendelian randomization analyses for the influenza and URI outcomes, we performed genome-wide association analyses of influenza and URI in FinnGen release 9 (R9). Cases were those participants with at least one of the above (case-inclusion) diagnosis codes and controls were those who were not cases and had no records of the respective (control-exclusion) diagnosis codes listed above. Diagnoses were captured from both primary and secondary healthcare records. Samples were genotyped using Illumina and Affymetrix chip arrays (Illumina Inc., San Diego, and Thermo Fisher Scientific, Santa Clara, CA, USA) and imputed to GRCh38/hg38 using Beagle v4.1[3] with the SISu v4.0 reference panel, consisting of 8,554 high-coverage (25x) whole genome-sequenced Finnish individuals[4] (see https://dx.doi.org/10.17504/protocols.io.nmndc5e for the complete imputation and QC protocol). A total of 20,175,454 imputed genotypes were available in 392,651 participants. In the GWAS of influenza, there were 12,091 cases and 310,746 controls whereas for the URI GWAS there were 102,100 cases and 240,562 controls. These GWA analyses were performed using REGENIE[5] v2.2.4 and in the model-building step (step 1) were adjusted for age at follow-up end (2021/10/11) or death, sex, genotyping batch and the first 10 genetic principal components. Age at follow-up end was used instead of age at recruitment to reflect the fact that endpoints were defined using diagnoses from the participant's entire medical history, including the intervening time since they were recruited into the study. Step 1 was performed using leave-one-chromosome-out (LOCO) prediction with 55,139 well-imputed (imputation INFO > 0.95 in all batches) common (MAF > 1%) genetic variants with <3% missingness that had been LD pruned using a 1Mb window and r^2 threshold of 0.1.

Survival Analyses

We performed endpoint-to-endpoint survival analyses, which compare the risk of developing an outcome endpoint if subject to diagnosis of a prior endpoint and accounting for the time taken to be

diagnosed with the outcome. We followed a near-identical approach to the FinnGen Risteys pipeline (see "Survival analyses between endpoints" at https://risteys.finngen.fi/documentation), only considering the date of first diagnosis for each endpoint. Unlike in the Risteys pipeline we did not follow a case-cohort design, which involves selecting all cases and a fixed number of controls through random sampling; in both the FinnGen and UK Biobank survival analyses, we used all available controls. We performed this analysis using the Python module "lifelines" (v0.26.0)[6] with Python (v3.8.11 for FinnGen, v3.7.11 for UK Biobank) applying a Cox Proportional Hazards model.

Briefly, study start and end dates were chosen in each study based on the availability of records for the majority of participants (see below). Participants who were prevalent cases of the outcome endpoint (those with an outcome diagnosis before the study start date) were removed (see Supp Table 2 for sample exclusion counts). Prior endpoint cases whose first diagnosis occurred before the study start were given a diagnosis date of the study start date. Prior endpoint cases whose first diagnosis occurred after the study start date were separated into two entries corresponding to their time as controls (from date of study entry to diagnosis date) and as cases (from diagnosis date to date of study exit). These individuals are each treated as two separate participants, the control who "leaves" the study on the diagnosis date and the case who "enters" the study on the diagnosis date.

The survival model used in this analysis can be written as:

```
Surv(time_in_study,outcome_endpoint) ~
                                prior_endpoint + birth_year + sex
```

where "prior_endpoint" and "outcome_endpoint" were binary variables representing their case-control status and "time_in_study" was calculated (in years) from date of study entry to date of study exit. For sensitivity analyses, untransformed BMI was added as an extra term in the additive model and those without a BMI measurement were excluded in these analyses (exclusion counts provided in Supp Table 2). Date of study entry was taken as the study start date unless the participant was born later than this date (i.e., study entry is date of birth - this occurred only in FinnGen) or was diagnosed with the prior endpoint (their post-diagnosis or "case" record has study entry date as the date of diagnosis). Participants in both studies remain in the study and continue to accumulate diagnosis data unless they either withdraw their consent (and so are removed from the study entirely) or die. Therefore, for all included participants in FinnGen and the UK Biobank, the date of leaving the study was the specified study end date, unless the participant died before this date (study exit is the date of death) or was diagnosed with the prior endpoint (their pre-diagnosis or "control" record has study exit date as the date of diagnosis). For FinnGen (release 9), study start and end dates were set as 1998/01/01 and 2020/12/31, respectively, as the dates from which inpatient, outpatient

and death records were available from and to for all participants. In the UK Biobank, the GP data is maintained in four distinct databases by three providers (see https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf). To minimize the bias in UK Biobank-based analyses, we calculated a median primary care registration date (field 42038) in each database and selected a follow-up start date of 2002/03/01, the latest of these four median dates, ensuring that the majority of participants were already registered in each of the four databases. The study end date was identified as 2019/08/18 for the UK Biobank, the date of the latest available record from the primary care data (at the time of analysis). Diagnosis events in the UK Biobank hospital records that occurred later than this date were ignored. In the UK Biobank, some individuals had valid endpoint diagnoses but no valid date of diagnosis. For each prior and outcome endpoint pair, if either or both the endpoint diagnosis dates were invalid, the participant was removed from the analysis.

Logistic Regression

These analyses were used to test whether insomnia diagnoses were enriched in participants with each of the outcome endpoints (URI, influenza, and COVID-19), regardless of which occurred first. The model we applied can be formulated as:

```
outcome_endpoint ~ prior_endpoint + age_end_followup + sex + BMI
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where “prior_endpoint” and “outcome_endpoint” were binary variables representing their case-control status for these endpoints. Unlike the survival analyses, we did not impose a follow-up start time and thus made no sample exclusions based on the date of outcome endpoint diagnosis (including those with no valid diagnosis date). It was still necessary to impose a follow-up end date, as the different registries contained within both FinnGen and UK Biobank were right-censored at different dates. Therefore, as with the survival analysis, for all endpoints except COVID-19 infection we imposed cut-off dates of 2020/12/31 and 2019/08/18 for FinnGen and UKB, respectively. Study participants with their first non-COVID endpoint diagnoses occurring after these dates were treated as controls for those endpoints. The COVID-19 diagnosis information was obtained from additional linked datasets for both cohorts and because all COVID-19 diagnoses occurred after the follow-up cut-off dates, we did not right-censor this outcome endpoint. In all logistic regression analyses, except with the COVID-19 outcome, the “age_end_followup” was defined as the participant’s age in years at the study’s respective cut-off date or their age at death if they died before this date. With the COVID-19 outcome, all participants who died before reaching the study’s cut-off date were excluded and so the “age_end_followup” simply represented each participant’s age in years at the cut-off date for all included samples. In performing this logistic regression analysis with the COVID-

19 outcome, we did not consider death records after each study's follow-up cut-off date and therefore made the assumption that study participants who survived until the study cut-off date also survived to the end of the COVID-19 diagnosis records (2021/05/27 in FinnGen and 2020/10/02 in the UK Biobank) or that cases and controls for the insomnia prior died at an equal rate after the follow-up cut-off date. BMI was included as an untransformed measure in these analyses.

Mendelian randomization

Mendelian randomization (MR) is an analysis method by which genetic variants robustly associated with an exposure (through GWAS) can be used to infer the one-directional causal impact of the exposure on an outcome by looking at the effect of the exposure's variants on the outcome[7]. The causal effect is estimated from the gradient of the best-fit regression line of the variants' effects on the outcome against their effect on the exposure. Evidence of a causal effect is assumed if the regression slope is significantly different from 0 (representing complete independence between the effects on the exposure and the outcome). Multiple methods exist for performing this regression, each with their own strengths and weaknesses[8] and with different methods allowing for various degrees of violation of the three core MR assumptions[9], these being:

- Relevance – the selected genetic instruments need to be robustly associated with the exposure.
- Independence – there are no common confounders of both the genetic instruments and the outcome.
- Exclusion-restriction – genetic instruments influence the outcome only through the exposure (i.e., there is no independent pathway from the instruments to the outcome).

Single-exposure two-sample Mendelian randomization was performed in R (v3.6.3) using the package *TwoSampleMR*[10,11] (v0.5.6) and multivariable MR was performed using the package MendelianRandomization[12] (v0.5.0). For our primary insomnia exposure, we used summary statistics from the most recent GWA meta-analysis (GWAMA) of insomnia in over 2.3 million individuals[13] (593,724 insomnia cases vs. 1,771,286 controls). In this study, a GWAS in unrelated UK Biobank European participants (analysed with PLINK[14] and corrected for age, sex, genotyping array and the first 10 genetic principal components (PCs)) was meta-analysed with results from a GWAS in European-ancestry individuals from 23andMe (corrected for age, sex, genotyping array, and the first 5 genetic PCs). Lead variants in this GWAMA were identified using FUMA (https://fuma.ctglab.nl)[15], first by clumping variants with $P<5x10^{-8}$ and LD $r^2=0.6$ and defining independent significant variants using a threshold of $P<1x10^{-5}$, then by further clumping with $r^2=0.1$ and genomic distance of 250kb to define the loci, for which the variant with lowest P-value was considered the lead variant. For our secondary insomnia exposure and our short sleep exposure, we used summary statistics from a UK

Biobank-only GWAS of frequent insomnia symptoms in 237,627 European-ancestry participants[16] (129,270 cases vs. 108,357 controls) and a UK Biobank-only GWAS of habitual short sleep in 411,934 European-ancestry samples[17] (106,192 cases vs. 305,742 controls). Both GWAS (frequent insomnia and short sleep) were analyzed using BOLT-LMM[18] and corrected for age, sex, the first 10 genetic PCs and genotyping array. As with the insomnia GWAMA, independent loci for frequent insomnia and short sleep were mapped through FUMA by clumping variants with $P<5x10^{-8}$ and LD $r^2=0.6$ and then lead variants identified by selecting the most significant variant in each locus. For our "number of sleep episodes" exposure, we obtained summary statistics from a GWAS of 85,502 UK Biobank participants for accelerometer-derived measures[19], where the phenotype represents the number of distinct segments of sleep, separated by significant movement during sleep, as a function of time in bed. The accelerometer-measure GWAS were performed using BOLT-LMM v2.3, adjusting for age at accelerometer wear, sex, recruitment centre, season of accelerometer wear and genotyping array. In our MVMR sensitivity analysis, we included two additional exposures: BMI and smoking. We accessed BMI GWAS summary statistics published online by the Neale lab (http://www.nealelab.is/uk-biobank/). The BMI GWAS was performed on ~337,000 unrelated white British participants of the UK Biobank on the inverse-normalized BMI measure collected at the UK Biobank baseline visit, using the covariates age, age^2, inferred sex, age × inferred sex, age^2 × inferred sex, and genetic PCs 1-20. We identified the lead variants by using PLINK v1.90b6.21 to first LD-clump the results before selecting the most significant variant (with $P\leq5x10^{-8}$) at each locus. To do this, we used the following PLINK flags "--clump-p1 5E-8", "--clump-r2 0.001" and "--clump-kb 10000", and "best guess" unrelated European genotypes created from v3 of the UK Biobank imputed data (using PLINK v2.00a3LM with all default options) as the LD reference. For the smoking exposure, we used lead variants from a UK Biobank GWAS in 462,690 Europeans of "lifetime smoking index"[20], with the phenotype being a composite of smoking duration, heaviness and cessation and being described previously[21]. This lifetime smoking GWAS was performed using BOLT-LMM with genotyping array and sex included as covariates. Lead variants for the smoking GWAS were identified through clumping loci with the TwoSampleMR package (P-value threshold of $5x10^{-8}$, LD r^2 threshold of 0.001 and a distance of 10,000kb) and selecting the most significant variant in each independent locus. To avoid sample overlap in our two-sample design, we used GWAS summary statistics from FinnGen (release 9) for the influenza and URI outcomes. As the FinnGen analyses were performed in only Finnish-ancestry samples and the 23andMe research cohort does not include Finnish 23andMe customers, we anticipate negligible overlap between exposure and outcome cohorts. Similarly, with the COVID-19 outcomes, we obtained summary statistics from freeze 6 of the COVID-19 Host Genetics Initiative (HGI) GWAS meta-analyses[22] that excluded both UK Biobank and 23andMe for the A2 ("very severe" COVID-19 vs. population controls), B2 ("hospitalized" COVID-19 vs. population controls) and C2 (COVID-19 infection vs. population controls) phenotypes. Studies that contributed summary statistics for the COVID-19 HGI were

instructed to perform their analyses in SAIGE[23], though some used other software, and to include age, age^2, sex, age × sex and the first 20 genetic PCs as covariates, in addition to necessary study-specific covariates. The total sample sizes in these COVID-19 HGI meta-analyses that excluded both 23andMe and UK Biobank was 1,010,654 (8,779 cases vs. 1,001,875 controls), 1,649,760 (20,980 cases vs. 1,628,780 controls) and 2,145,360 (97,991 cases vs. 2,047,369 controls) for A2, B2 and C2 respectively.

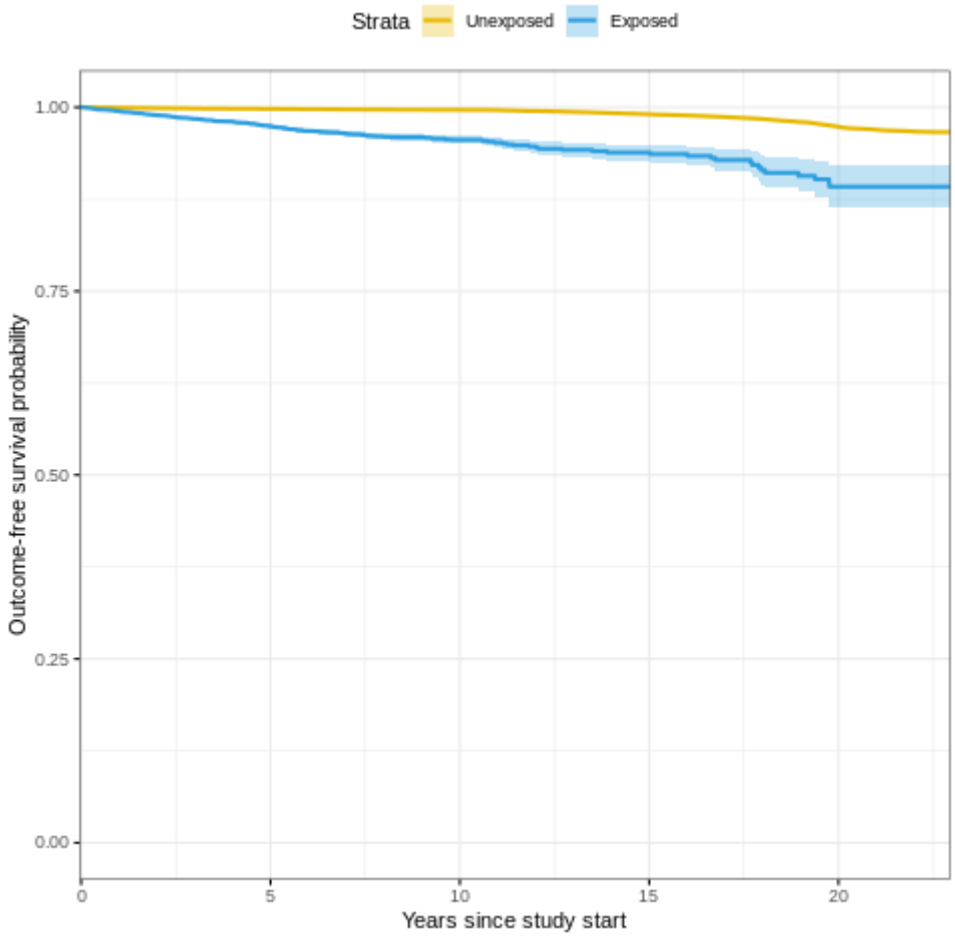
As exposure instruments, we selected all variants identified as independent lead variants (described above) with association $P \leq 5x10^{-8}$ in the respective discovery GWAS and used the same study for both instrument selection and effect size determination (see Supp Table 3 for univariate and Supp Table 9 for multivariate MR). Ideally, we would have performed the MR in a three-sample setting[24] by determining effect sizes from an GWAS in an independent cohort to that of the exposure discovery GWAS, as two-sample MR settings suffer from winner's curse bias, which can bias the causal estimate towards the null[25]. Independent (non-overlapping) cohorts of comparable size with both genetic data and either insomnia or habitual sleep duration are simply not available, making a three-sample setting unfeasible for this study.

For summary statistics that were in genome build 38 (COVID HGI and FinnGen URI and Influenza), we first used Picard[26] to lift them over to genome build 37. To ensure that we harmonized the maximum number of variants, we then matched them across the exposure and outcomes based on chromosome, position and alleles, checking whether the reference and alternative alleles were assigned the opposite way round. If they were, we flipped the alleles and corrected the beta to correspond to the other allele so that the effect allele was consistent between datasets. For the single-exposure MR analyses, variants without available association statistics in either the exposure or outcome were not included in the analysis for that exposure-outcome pair. In the multivariable MR, variants were not included if they were missing association statistics in either the outcome or any one of the exposures.

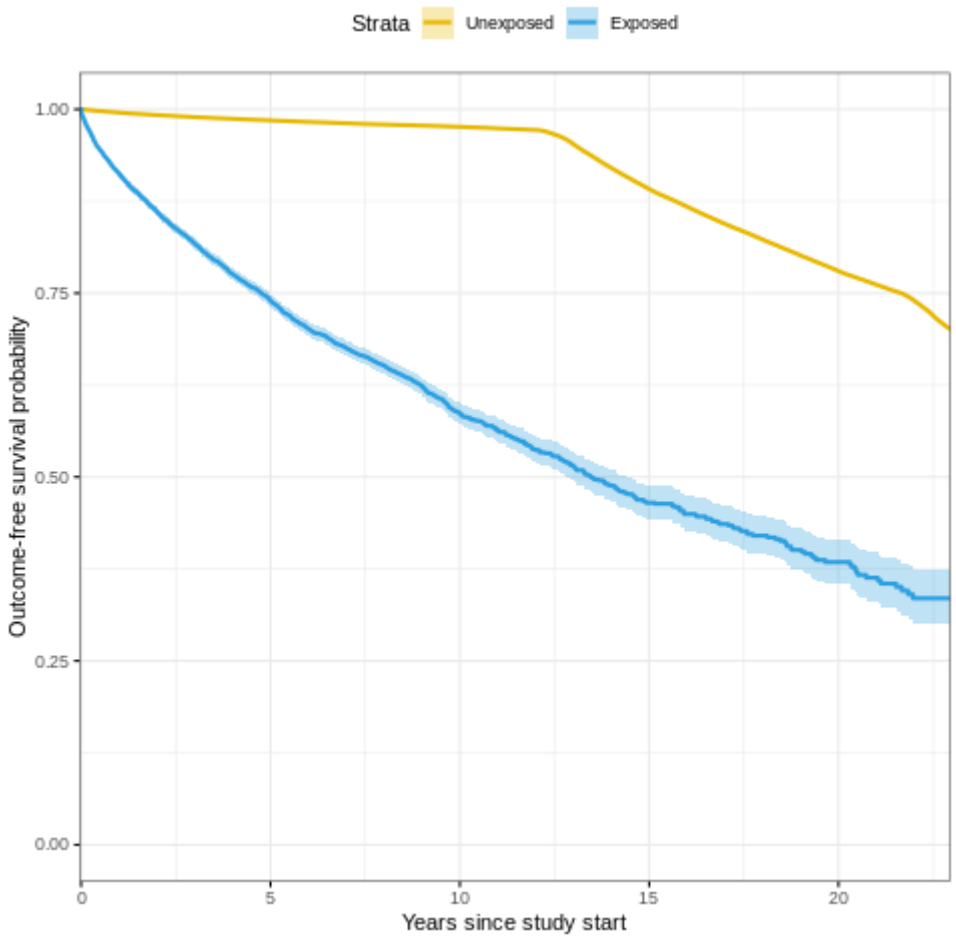
In both the univariate and multivariate MR analyses, we used the random effects inverse-variance weighted (IVW)[27,28] MR estimate as the primary causal estimate and weighted median (WM)[29] MR and MR Egger[30] as sensitivity analyses. We considered there to be evidence of a causal association if the IVW estimate was significant at a Bonferroni-adjusted threshold of $P \leq 0.05/15 = 3.3x10^{-3}$ and if the less well-powered, but pleiotropy-robust, WM and MR Egger estimates were directionally consistent with the IVW estimate. A statistically significant MR Egger intercept term ($P<0.05$) was considered as evidence of directional pleiotropy.

We performed MR power calculations for the single-exposure analyses using the web-based tool *mRnd*[31], available at https://shiny.cnsgenomics.com/mRnd/, and selected the option "Binary outcome", where we input the known variables: sample size, case proportion and exposure variance explained by the instruments. We set the alpha to 0.05 and input the causal MR odds ratios that we wished to calculate the power level for. The estimated power for a range of odds ratios, along with the parameters used for each exposure-outcome pair, are provided in Supp Table 8. To calculate the variance explained in the exposure by each instrument, we used a piece of code from another MR study of Alzheimer's Disease[32] where they estimated the variance explained to calculate instrument strength (via the F-statistic) and which is available as the second supplementary file of that paper. We provide estimates of each variant's exposure R^2 (pseudo-R^2 for binary exposures) in Supp Table 3 for the univariate MR and Supp Table 9 for the multivariate MR, as well as the estimated total exposure R^2 (pseudo-R^2 for binary exposures) of the included variants for each outcome in Supp Table 6 (univariate) and Supp Table 7 (multivariate). The total (pseudo-)R^2 of exposure variants analysed for each outcome was used as the variance explained in the univariate MR power calculations (Supp Table 8).

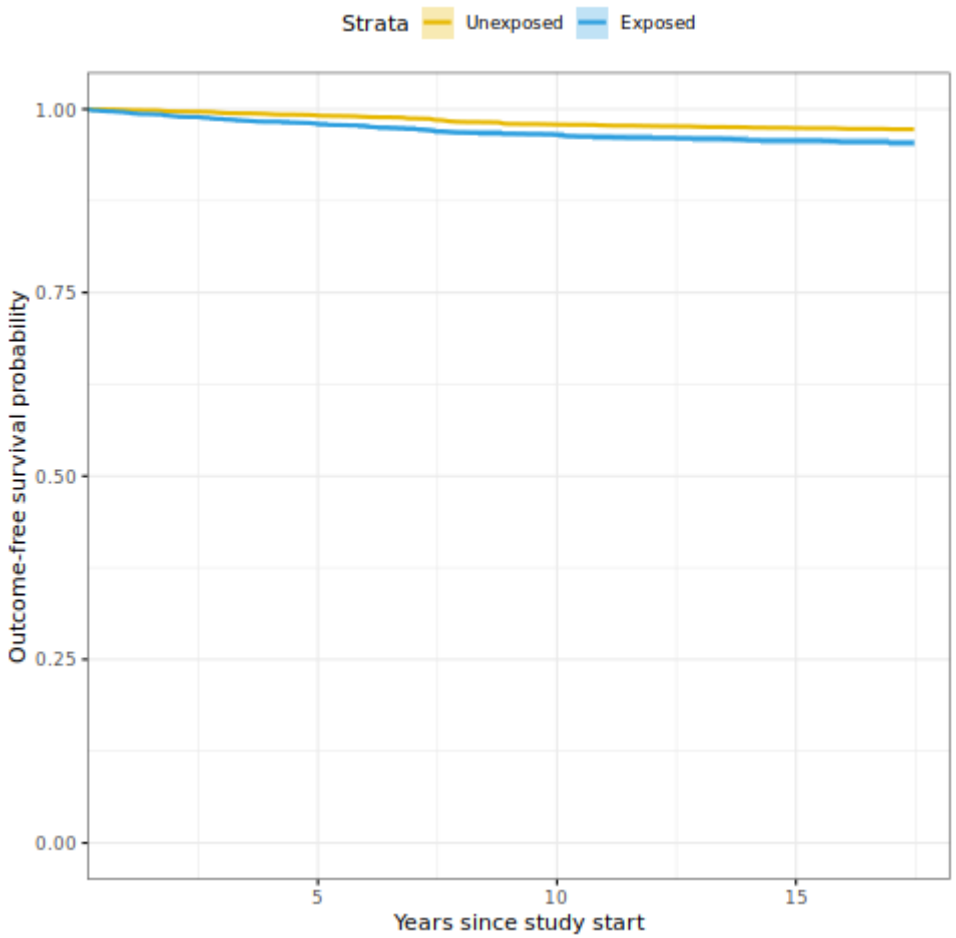
Supplementary Figures



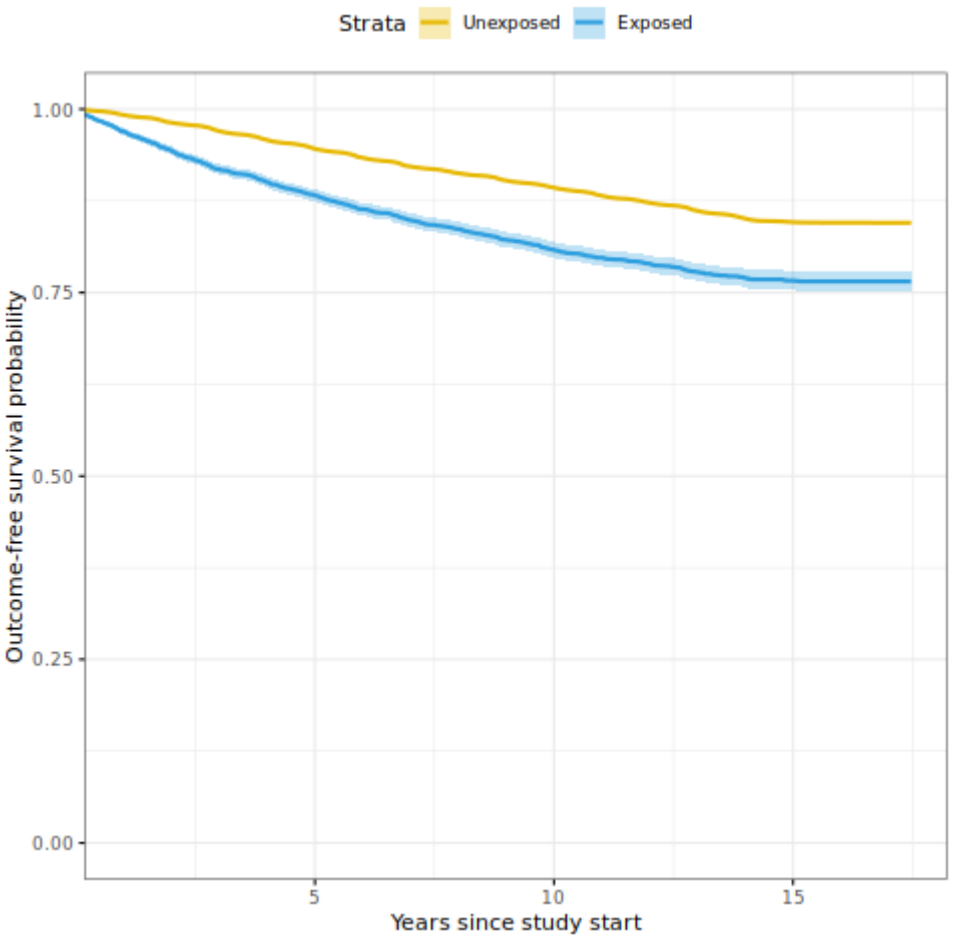
Supplementary Figure 1. Kaplan-Meier survival curves for the FinnGen R9 endpoint-to-endpoint survival analysis, with insomnia exposure and influenza outcome. The strata represent those with (“Exposed”) and without (“Unexposed”) a diagnosis for insomnia. The x-axis represents the number in years since samples either entered the study or since diagnosis with the exposure (for “Exposed” samples).



Supplementary Figure 2. Kaplan-Meier survival curves for the FinnGen R9 endpoint-to-endpoint survival analysis, with insomnia exposure and URI outcome. The strata represent those with (“Exposed”) and without (“Unexposed”) a diagnosis for insomnia. The x-axis represents the number in years since samples either entered the study or since diagnosis with the exposure (for “Exposed” samples).



Supplementary Figure 3. Kaplan-Meier survival curves for the UK Biobank endpoint-to-endpoint survival analysis, with insomnia exposure and influenza outcome. The strata represent those with ("Exposed") and without ("Unexposed") a diagnosis for insomnia. The x-axis represents the number in years since samples either entered the study or since diagnosis with the exposure (for "Exposed" samples).



Supplementary Figure 4. Kaplan-Meier survival curves for the UK Biobank endpoint-to-endpoint survival analysis, with insomnia exposure and URI outcome. The strata represent those with ("Exposed") and without ("Unexposed") a diagnosis for insomnia. The x-axis represents the number in years since samples either entered the study or since diagnosis with the exposure (for "Exposed" samples).

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