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

Samuel E. Jones,[a,i] Fahrisa I. Maisha,[b,e,f,i] Satu J. Strausz,[a,c] Vilma Lammi,[a] Brian E. Cade,[d,e] Anniina Tervi,[a] Viola Helaakoski,[a] Martin E. Broberg,[a] FinnGen, Jacqueline M. Lane,[d,e,f] Susan Redline,[d,g] Richa Saxena,[e,f,h] and Hanna M. Ollila[a,e,f,h,*]

[a]Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland
[b]Department of Neurology, School of Medicine, Yale University, New Haven, CT, USA
[c]Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA
[d]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[e]Broad Institute of MIT and Harvard, Cambridge, MA, USA
[f]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
[g]Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA
[h]Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

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Summary

Background Poor sleep is associated with an increased risk of infections and all-cause mortality but the causal direction between poor sleep and respiratory infections has remained unclear. We examined if poor sleep contributes as a causal risk factor to respiratory infections.

Methods We used data on insomnia, influenza and upper respiratory infections (URIs) from primary care and hospital records in the UK Biobank (N ≈ 231,000) and FinnGen (N ≈ 392,000). We computed logistic regression to assess association between poor sleep and infections, disease free survival hazard ratios, and performed Mendelian randomization analyses to assess causality.

Findings Utilizing 23 years of registry data and follow-up, we discovered that insomnia diagnosis associated with increased risk for infections (FinnGen influenza Cox's proportional hazard (CPH) HR = 4.34 [3.90, 4.83], $P = 4.16 \times 10^{-159}$, UK Biobank influenza CPH HR = 1.54 [1.37, 1.73], $P = 2.49 \times 10^{-13}$). Mendelian randomization indicated that insomnia causally predisposed to influenza (inverse-variance weighted (IVW) OR = 1.65, $P = 5.86 \times 10^{-7}$), URI (IVW OR = 1.94, $P = 8.14 \times 10^{-31}$), COVID-19 infection (IVW OR = 1.08, P = 0.037) and risk of hospitalization from COVID-19 (IVW OR = 1.47, $P = 4.96 \times 10^{-5}$).

Interpretation Our findings indicate that chronic poor sleep is a causal risk factor for contracting respiratory infections, and in addition contributes to the severity of respiratory infections. These findings highlight the role of sleep in maintaining sufficient immune response against pathogens.

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Keywords: Insomnia; COVID-19; Respiratory infections; Mendelian randomization; Sleep; Severe infection

Introduction

Insomnia is a condition characterized as the "persistent difficulty with sleep initiation, duration, consolidation or quality."[1] Between 9 and 25% of the population suffer from insomnia at any given time.[2–4] In the USA, this has led to the recognition of insomnia as a critical public health concern (https://www.cdc.gov/sleep/about_us.html) and as an important intervention target in future clinical studies and public health policy.[5]

Earlier intervention studies have indicated that acute sleep loss and sleep disruption are associated with inflammation[6] and a greater risk of viral infection.[7,8] Additionally, a systematic review and meta-analysis of 72 studies demonstrated that acute sleep disruption was

*Corresponding author. Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland.
E-mail address: hanna.m.ollila@helsinki.fi (H.M. Ollila).
[i]Equal contribution.

Research in context

Evidence before this study

Epidemiological and sleep deprivation studies suggest that acute sleep loss and sleep disruption are associated with an increase in circulating inflammatory cytokines, an increased risk of viral infection and a poorer vaccine response. Chronic (long-term) sleep loss is linked to higher rates of all-cause mortality and infection risk. Several studies have shown the association between COVID-19 and poor sleep including insomnia and sleep apnea. Despite the known observational associations linking poor sleep to infection risk, cause and effect is still not well understood.

Added value of this study

Here we examine the connection between chronic insomnia and influenza, upper respiratory infections and COVID-19 in a population setting. This study provides evidence for the causal role of insomnia as a risk factor for respiratory infections.

Implications of all the available evidence

Our findings have two major implications. First, our findings are in line with earlier experimental sleep deprivation studies suggesting that poor sleep has a role in infection risk, but we go on to demonstrate that poor sleep is a causal risk factor for respiratory infections. Our findings indicate that insomnia may contribute to public health through affecting susceptibility to infections. Second, our findings suggest that safe interventions such as sleep management and treating individuals with insomnia may have public health impact if promoted, as they may reduce infections and save lives.

associated with increase in common indicators for inflammation–IL-6 and C-reactive protein (CRP). Acute sleep loss may dampen or delay the development of vaccination response,[9–11] which indicates that a lack of sleep may have concrete effects on the immune system and consequently on our ability to fight off infections. However, the acute effects may be transient, especially if environmentally driven, and may not reflect the effects of long-term sleep disruption.

In contrast, large cohort studies have shown that chronic sleep loss and insomnia are associated with increase in all-cause mortality[12,13] and viral infections.[14] More recently, a review of nine small-scale studies that assessed the effect of chronic short and long sleep on risk of developing respiratory infections,[15] found that short sleep was associated with an increased overall risk of respiratory infections (logistic regression OR = 1.30 [1.19, 1.42], $P < 1 \times 10^{-5}$). Evidence collected from a number of cross-sectional studies also points to insomnia being associated with an increased prevalence of respiratory infections.[16] However, insomnia has not yet been ascribed a causal role in respiratory infection risk due, in part, to the complex bidirectional relationship between sleep and immune function.

The ongoing COVID-19 pandemic has had a documented effect on sleep with a subset of individuals suffering from poor sleep, nightmares and changes in circadian rhythms.[17–19] Sleep disruption is also a common sequela of SARS-CoV-2 infection. A recent meta-analysis of 66 studies reported that sleep disturbances including post-viral insomnia were common and COVID-19 severity was a predictor for sleep disruption.[20] What is less clear, however, is the effect of pre-infection sleep disruption on the risk of developing COVID-19 and subsequent severity of the infection.

Motivated, in part, by the ongoing SARS-CoV-2 pandemic, our aim was to assess if chronic insomnia causally increases the risk for respiratory infections including upper respiratory tract infections and the known severe pathogens influenza and SARS-CoV-2. We tested the hypothesis that insomnia is a risk factor for influenza, upper respiratory infections and COVID-19 using longitudinal data from over 558,000 study participants across two cohorts. We employed methods from genetic epidemiology to infer the one-directional causal associations of sleep disruption on influenza, upper respiratory tract infections and COVID-19 susceptibility, severity, and hospitalization.

Methods

Cohorts

FinnGen (www.finngen.fi/en) is a study of a population-based cohort of Finnish residents, from newborn to 104 years old 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. The data (R9) contains health and genetic data on up to 392,396 participants. When a study participant is recruited, their entire medical record is linked into the FinnGen database 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.[21] 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.[22]

Phenotype/endpoint definitions

For insomnia, upper respiratory infection (URI), and influenza endpoints we used the pre-existing FinnGen endpoint definitions, which utilize secondary care

(hospital inpatient and outpatient, and death records) to determine endpoint cases and controls. To complement these data, we also included diagnoses from primary care (health center/doctor visits). 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 and 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).

For each endpoint, we excluded participants if they had diagnoses of other sleep conditions, non-acute upper airway infections and pneumonia for insomnia, URI and influenza respectively: a list of these codes is provided in the Supplementary Methods. Of 392,396 FinnGen R9 participants, there were 17,489, 90,447 and 12,057 with insomnia, URI and influenza endpoints respectively (Supplementary Table S1), of which approximately 83%, 77%, and 30% (respectively) were from primary care records (Supplementary Table S2).

To define equivalent endpoints in the UK Biobank, we used diagnostic information from the EHR 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. 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)

The same diagnosis-based sample exclusions were made as with FinnGen (see Supplementary Methods). The 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 (Supplementary Table S1).

COVID-19 diagnoses

Diagnoses of SARS-CoV-2 infection (COVID-19) in Finland are recorded in the 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 derived using linked data collected by Public Health England (PHE), Public Health Scotland (PHS) and SAIL Databank for England, Scotland and Wales, respectively. We used diagnosis data with a cut off of 2020/10/02 and had data on 1713 unique samples with a positive COVID-19 diagnosis, of which 733 had both HES and GP data available. All samples 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 these phenotypes 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. 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[23] v2.2.4 and in the model-building step (step 1) were adjusted for sex, genotyping batch, the first 10 genetic principal components and age at follow-up end (2021/10/11) or death, as the FinnGen endpoint diagnosis data extends beyond the initial recruitment visit.

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 performed this analysis using the Python module "lifelines" (v0.26.0)[24] 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 Supplementary Table S2 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 body mass index (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 Supplementary Table S2).

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 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).

Logistic regression

Logistic regression was 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

where "prior_endpoint" and "outcome_endpoint" were binary variables representing their case-control status for these endpoints. We imposed a follow-up end date, as the registries contained within both FinnGen and UK Biobank were right-censored at different dates with imposed cut-offs of 2020/12/31 and 2019/08/18 for FinnGen and UKB, respectively, except for COVID-19 diagnosis (2021/05/27 and 2020/10/02, respectively). In these models, age at end of follow-up was measured in years and BMI was untransformed.

Mendelian randomization

Single-exposure two-sample Mendelian randomization was performed in R (v3.6.3) using the package *TwoSampleMR*[25,26] (v0.5.6) and multivariable MR (MVMR) was performed using the package MendelianRandomization[27] (v0.5.0). For our exposures, we used summary statistics from the most recent genome-wide association meta-analysis (GWAMA) of insomnia in over 2.3 million 23andMe and UK Biobank individuals[28] (593,724 insomnia cases vs. 1,771,286 controls), from earlier GWAS of frequent insomnia symptoms in UK Biobank[4] (237,627 participants; 129,270 cases vs. 108,357 controls) and from the largest GWAS of habitual short sleep in 411,934 UK Biobank participants[29] (106,192 cases vs. 305,742 controls). 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 and we identified the lead variants by using PLINK[30] v1.90b6.21 to first LD-clump the results before selecting the most significant variant at each locus (Supplementary Methods). The smoking exposure was represented by the "lifetime smoking behaviour" measure from a recent GWAS in 462,690 European-ancestry UK Biobank participants,[31] which captures a combination of smoking duration, heaviness and cessation. We used the published lead variants for lifetime smoking behaviour, which were selected through LD-clumping with the *TwoSampleMR* package with $P \leq 5 \times 10^{-8}$, LD r^2 threshold of 0.001 and a distance of 10 Mb. To avoid sample overlap in our two-sample design, we used GWAS summary statistics from FinnGen (release 9) for the influenza and URI outcomes. With the COVID-19 outcomes, we obtained publicly available summary statistics from freeze 6 of the GWAS

meta-analyses[32] 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 to avoid sample overlap.

For all exposures, we selected all reported independent lead variants (with association $P \leq 5 \times 10^{-8}$) in the discovery GWAS as instruments (see Supplementary Methods) and used the same study for both instrument selection and effect size determination (Supplementary Table S3). To help harmonize the exposures with the outcomes, we lifted the COVID HGI and FinnGen summary statistics from genome build 38 to build 37 and then constructed a unique variant ID using the chromosome, position and alleles (lowest alphabetical allele first).

In both the univariate and multivariate MR analyses, we used the random effects inverse-variance weighted (IVW)[33,34] MR estimate as the primary causal estimate and weighted median (WM)[35] MR and MR Egger[36] 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 $P \leq 0.05/15 = 3.3 \times 10^{-3}$ 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.

Ethics

FinnGen

All FinnGen participants provided informed consent for biobank research based on the Finnish Biobank Act (FBA). Prior to the FBA coming into effect (September 2013), participants recruited into the individual research cohorts provided study-specific consent for research. These consent permissions were transferred to the Finnish biobanks, at the conception of FinnGen in August 2017, after approval by Fimea (the Finnish Medicines Agency), the National Supervisory Authority for Welfare and Health. The recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) statement number for the FinnGen study is Nr HUS/990/2017.

The FinnGen study is approved by the Finnish Institute for Health and Welfare (THL) under permit numbers THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019, THL/1524/5.05.00/2020, and THL/2364/14.02/2020, by the Digital and Population Data Service Agency (DVV) under permits VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3, the Social Insurance Institution (KELA) under permits KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020, the Finnish Social and Health Data Permit Authority (Findata) under permit THL/2364/14.02/2020 and by Statistics Finland (Tilastokeskus) under permits TK-53-1041-17 and TK/143/07.03.00/2020 (formerly TK-53-90-20).

For freeze (release) 7 of the FinnGen study, the biobank access decisions include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154 and amendment #1 (August 17 2020), Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018 and amendment 22 § /2020, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 & 06.10.2020), Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001.

UK Biobank

The UK Biobank has received approval as a Research Tissue Bank from the North West Multi-centre Research Ethics Committee (MREC) under MREC permits 11/NW/0382 (2011–2016), 16/NW/0274 (2016–2021) and 21/NW/0157 (2021–2026). Researchers with approved applications are covered by these permits and are not required to seek additional approval, except in specific cases (see section B7 of the UK Biobank Access Procedures document: https://www.ukbiobank.ac.uk/media/omtl1ie4/access-procedures-2011-1.pdf). All participants of the UK Biobank study provided consent, at the baseline visit, for their personal data and biological samples to be collected and stored for research purposes. Participants are given the option to withdraw their consent at any time; any samples that have withdrawn their consent at the time of analysis were excluded from this study. A print version of the electronic consent form is stored as UK Biobank Resource 100252.

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The funders had no role in the design of this study, data collection and analysis, interpretation of results, writing of this manuscript or any other aspects relating to this publication. No authors were paid to write this article by a pharmaceutical company or other agency.

Results

Survival analysis in population cohorts

To understand whether there is a discernible impact of poor sleep on subsequent risk of respiratory infections, we performed survival analysis by testing the associations between insomnia and respiratory infections and computing multivariable adjusted hazard ratios in over 392,000 individuals from FinnGen free of relevant

respiratory infectious diseases (Table 1 and Supplementary Table S4). We found that a prior diagnosis of insomnia increased the risk of a later URI diagnosis (Cox proportional hazard (CPH) HR = 5.80 [5.51, 6.12], $P < 1 \times 10^{-300}$) and subsequent influenza diagnosis (CPH HR = 4.34 [3.90, 4.83], $P = 4.16 \times 10^{-159}$). COVID-19 data was examined from February 2020 to May 2021, but as the pandemic occurred after the end of available records for other diagnoses, we instead performed a logistic regression to test whether those with prior diagnoses of insomnia were over-represented in COVID-19 patients (Table 1 and Supplementary Table S5). Our analyses indicated no significant change in risk of COVID-19 infection for those previously diagnosed with insomnia (logistic regression (LR) P > 0.99).

To replicate these results, we assessed the same endpoints in approximately 231,000 UK Biobank participants using hospital and primary care records collected between March 2002 and August 2019. In concordance with observations in FinnGen, survival analyses suggested that a prior diagnosis of insomnia increased the risk of URI by 52% (CPH HR = 1.52 [1.43, 1.61], $P = 1.72 \times 10^{-45}$) and increased the risk of influenza by 54% (CPH HR = 1.54 [1.37, 1.73], $P = 2.49 \times 10^{-13}$) (Table 2 and Supplementary Table S4). As with FinnGen, the period in which both primary care and hospital records were available in the UK Biobank did not overlap with the COVID-19 diagnosis interval. Logistic regression did not identify significant enrichment of diagnosed insomnia sufferers within COVID-positive patients (LR OR = 1.21 [0.82, 1.70], P = 0.311) (Table 2 and Supplementary Table S5).

Mendelian randomization analysis

We then estimated the causal impact of insomnia on COVID-19, URI and influenza (Table 3) using genetic instruments identified for insomnia in a recent large-scale GWAS meta-analysis.[28] We identified that insomnia was causally associated with an increased risk of severe COVID-19 symptoms (inverse-variance weighted (IVW) OR = 1.64 [1.22, 2.21], $P = 1.00 \times 10^{-3}$), greater risk of hospitalization from COVID-19 (IVW OR = 1.47 [1.22, 1.77], $P = 4.96 \times 10^{-5}$) and with increased risk of influenza infection (IVW OR = 1.66 [1.36, 2.02], $P = 5.86 \times 10^{-7}$ and URI (IVW OR = 1.94 [1.73, 2.17], $P = 8.14 \times 10^{-31}$). In the MR sensitivity analyses, in which we apply methods that are robust to pleiotropy but statistically less powerful, there was potential evidence of directional pleiotropy in insomnia's effect on both COVID-19 severity and hospitalization risk, with the MR Egger intercept (an estimate of the total pleiotropic effect) being non-zero (MR Egger intercept P = 0.013 and 0.019 for severe symptoms and hospitalization risk, respectively). This suggests that some of the insomnia instruments may not be affecting COVID-19 severity and hospitalization risk directly through insomnia but via other, as yet, unknown pathways. We did not, however, see strong evidence of pleiotropy for COVID susceptibility, URI or influenza (Supplementary Table S6). Consequently, we tested potential modifying factors including body mass index (BMI) and smoking in a multivariate mendelian randomization analysis together with insomnia. We demonstrated a causal effect from insomnia to URI, influenza and to COVID-19 infection and hospitalization when accounting for BMI and lifetime smoking behaviour (Supplementary Table S7) suggesting that the potential pleiotropic factors that contribute to COVID-19 infection and COVID-19 hospitalization are more complex than traditional association with BMI or smoking.

To understand whether loss of sleep is an important factor in insomnia's causal associations, we tested the effect of genetically instrumented short sleep, using 27 variants associated with short sleep.[29] We found suggestive evidence that habitually short sleeping increased the risk of COVID-19 infection (IVW P = 0.03), but no strong evidence that risk of hospitalization with COVID-19 was affected (IVW P = 0.09). We also found evidence that habitual short sleep leads to an elevated risk of infection for influenza and URI (IVW P = 0.019 and 1.21×10^{-3}, respectively). As with all statistical tests, a negative finding in MR analyses could be indicative of either no true association or lack of statistical power to detect causal effects. We therefore calculated the available power to detect the causal effects we identified (Table 3) and found generally sufficient power to estimate causality across all tested exposure traits (Supplementary Table S8).

To demonstrate the robustness of the insomnia findings, we performed sensitivity analysis using 45 genetic variants robustly associated with insomnia in the UK Biobank cohort.[4] Despite the smaller number of available instruments, we were still able to see the impact of insomnia on both COVID-19 hospitalization

Outcome	Disease free survival analysis (up to 23 years of follow-up)			Logistic regression		
	Hazard Ratio (HR)	HR 95% CI	P	OR	OR 95% CI	P
Influenza	4.34	[3.90,4.83]	4.16×10^{-159}	1.65	[1.53, 1.77]	2.65×10^{-43}
Upper respiratory infection (URI)	5.80	[5.51, 6.12]	$<1 \times 10^{-300}$	2.29	[2.22, 2.36]	$<1 \times 10^{-300}$
COVID-19				1.00	[0.96, 1.04]	0.996

Table 1: **FinnGen endpoint-to-endpoint survival and logistic regression analyses results for insomnia exposure.**

Outcome	Disease free survival analysis (up to 17 years of follow-up)			Logistic regression		
	Hazard Ratio (HR)	HR 95% CI	P	OR	OR 95% CI	P
Influenza	1.54	[1.37, 1.73]	2.49×10^{-13}	2.12	[1.98, 2.27]	3.84×10^{-98}
Upper respiratory infection (URI)	1.52	[1.43, 1.61]	1.72×10^{-45}	2.13	[2.04, 2.23]	9.13×10^{-247}
COVID-19				1.21	[0.82, 1.70]	0.311

Table 2: **UK Biobank endpoint-to-endpoint survival and logistic regression analyses results for Insomnia exposure.**

(IVW OR = 1.13 [1.03, 1.24], P = 0.011) and URI (IVW OR = 1.10 [1.05, 1.16], P = 1.62×10^{-4}) and saw no strong evidence of pleiotropy (MR Egger intercept P > 0.05). The effect sizes were much attenuated in comparison to the larger set of insomnia instruments (Supplementary Table S3). No significant association was seen for COVID severity or influenza susceptibility (IVW P > 0.05).

Discussion

Here we provide compelling evidence that insomnia causally impacts the risk of developing respiratory infections including influenza and severe COVID-19. Leveraging the complex longitudinal health data from two large independent cohorts, the UK Biobank and FinnGen, we assessed whether a prior diagnosis of insomnia led to an increased risk of either influenza or URI. Results from up to 23 years of follow-up diagnoses in both cohorts suggested an increase in URI and influenza infection risk for insomnia sufferers.

We used a framework from genetic epidemiology called Mendelian randomization through which we demonstrated that insomnia is causally associated with an increased risk of URI, influenza, COVID-19 hospitalization and COVID-19 severity, and to a lesser extent, with an increased risk of SARS-CoV-2 infection. These findings are in line with earlier literature and together demonstrate the impact that sleep has on immune function, which then likely has a downstream effect on the ability to fight off infections.

Interestingly, we saw a stronger association with COVID-19 severity than with COVID-19 infection, despite having greater statistical power to detect association with COVID-19 infection than severity. We conjecture that this may be due to three factors. Firstly, insomnia may act on the severity of the respiratory infections more strongly than on the risk of initial infection, as seen with other risk factors like BMI,[37–39] obstructive sleep apnea,[40–42] fasting blood glucose,[43] and high blood pressure.[44,45] This would be in line with evidence that those with severe COVID-19 have

Exposure	Outcome	Nvar	IVW			Power
			logOR	SE	P	
Insomnia (Watanabe et al., 2022)	**Severe COVID**	**464**	**0.496**	**0.151**	**0.001**	**0.61**
	Hospitalized COVID	**489**	**0.387**	**0.095**	**4.96×10^{-5}**	**0.74**
	COVID infection	*452*	*0.075*	*0.036*	*0.037*	*0.14*
	URI	**472**	**0.662**	**0.057**	**8.14×10^{-31}**	**1**
	Influenza	**472**	**0.505**	**0.101**	**5.86×10^{-7}**	**0.75**
Short sleep	Severe COVID	24	0.208	0.131	0.113	0.75
	Hospitalized COVID	24	0.154	0.091	0.090	0.981
	COVID infection	*25*	*0.078*	*0.036*	*0.032*	*1*
	URI	**24**	**0.152**	**0.047**	**1.21×10^{-3}**	**1**
	Influenza	*24*	*0.277*	*0.118*	*0.019*	*0.99*
No. of sleep episodes	Severe COVID	21	0.065	0.174	0.708	1
	Hospitalized COVID	21	0.045	0.111	0.688	1
	COVID infection	21	−0.022	0.034	0.525	1
	URI	*19*	*0.134*	*0.061*	*0.029*	*1*
	Influenza	19	0.136	0.108	0.206	1

Rows with results in bold font are statistically significant after Bonferroni correction and those in italics are significant (IVW P ≤ 0.05) at the single test level but not after Bonferroni correction (15 tests; IVW P ≤ 0.05/15 = 3.3×10^{-3}). NVar = number of exposure genetic instruments used.

Table 3: **Causal analysis results of insomnia, short sleep and a measure of sleep fragmentation of COVID severity, susceptibility and hospitalization risk, upper respiratory infection and influenza.**

elevated levels of IL-6 and CRP when compared to non-severe COVID-19 patients,[46] given the relationship between chronic sleep disruption and higher levels of circulating inflammatory markers, but remains to be seen for other respiratory infections.

Secondly, both insomnia and COVID-19 infection and severity are correlated with demographic measures and therefore not distributed uniformly in the population. For example, socioeconomic factors, occupation, age, sex and ethnicity are all associated with increased rates of insomnia and COVID-19 susceptibility and severity.[2,47] While we estimate some of the multifactorial causal associations through multivariate Mendelian randomization where we corrected for BMI and lifetime smoking behaviour, these uncaptured confounders are likely to affect the estimates from longitudinal analyses and, for inherited unmeasured factors, may result in pleiotropy in the causal estimates, more so as GWAS sample sizes increase.[48] For the insomnia exposure that used instruments from the most recent GWAS meta-analysis, there was some evidence of pleiotropy in the causal estimate on COVID-19 severity and hospitalization outcomes (Supplementary Table S6), though the sensitivity analyses using a more restricted set of instruments found no evidence of pleiotropy, albeit with more moderate causal effects on COVID-19 severity and hospitalization.

Thirdly, we recognize that insomnia itself is a multifactorial disorder with a variety of potential causes and presentations, each of which may confer differing levels of risk for susceptibility to or severity of respiratory infections. It is possible that different symptoms of insomnia have different downstream biological effects which, when considered separately, would show heterogeneous effects on susceptibility, but more homogenous effects on respiratory infection severity.

We note the following limitations. Firstly, while we ensured that the FinnGen endpoints were identified using both hospital and primary care records, around 30% of influenza, 75% of URI and 83% of insomnia diagnoses were from primary care. Comparatively, in the UK Biobank, about 90% of influenza, 99% of URI and 98% of insomnia diagnoses were captured through primary care records. Consequently, FinnGen cases may contain a higher proportion of severe diagnoses. It is therefore possible that the differences in hazard ratio we see between the two cohorts represent a) greater statistical power due to more severe insomnia diagnosis, b) a real difference in effect of insomnia on more severe (FinnGen) and less severe (UK Biobank) respiratory infections, c) differences between the cohort demographics or d) a combination of these factors.

Secondly, while MR is a powerful tool to estimate causality, there were some noticeable limitations to its use in this study. We could not produce easily interpretable causal estimate effect sizes due to both exposure and outcomes being binary phenotypes. We selected our insomnia instruments from the largest GWAS meta-analysis, to date, of self-report insomnia in order to maximize statistical power and there was some evidence of horizontal pleiotropy in these variants as evidenced by the non-zero MR-Egger intercept (Supplementary Table S6). It is possible that, due to the large sample size of the meta-analysis and thus the high power to detect genetic associations, that a proportion of the selected instruments may be secondary associations for insomnia, being associated with a phenotype that itself influences insomnia risk.

Thirdly, we were unable to provide longitudinal estimates for COVID-19 infection and severity in the context of a prior insomnia diagnosis, which would have better contextualized the MR findings. In both cohorts, the available health records did not overlap the pandemic period (beginning March 2020) and so there was no contemporaneous non COVID-19 diagnosis data, meaning that survival analyses were not appropriate.

Finally, the survival analyses and the GWA analyses used in the MR were performed in entirely (FinnGen, UK Biobank and 23andMe) or predominantly (COVID-19 HGI) European-ancestry individuals. The lack of diverse ancestral representation in large biomedical cohorts and publicly available GWAS data remains one of the greatest limitations of the field and therefore we cannot comment on applicability of our findings to other ancestries. However, the findings should be generalizable across other exposure levels and timings.

Contributors

Designed the study and both analyzed and verified the underlying data: SEJ, FIM, SJS, and HMO. Provided mentorship and intellectual contributions: HMO, RS, SR, JML, VL, MEB, AT, VH, and BEC. Wrote the manuscript: HMO, SJS, and SEJ. Revised the manuscript: HMO, SJS, SEJ, RS, SR, JML, VL, VH, MEB, AT, and BEC. All contributing authors have read and approved the final version of this manuscript.

Data sharing statement

Individual-level data can be accessed on successful application to FinnGen and the UK Biobank cohorts. For FinnGen, applications for individual-level data can be made through the Finnish Biobanks' "FinBB" portal (https://finbb.fi/) and summary GWA data, including for the influenza and URI phenotypes, can be accessed through the FinnGen website (https://www.finngen.fi/en/access_results). For the UK Biobank, applications for individual-level data can be made through the UK Biobank portal at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access. The FinnGen R9 GWA summary statistics for influenza and URI are available to researchers at https://r9.finngen.fi/. The scripts used to perform the logistic regression, survival and MR analyses are available at https://github.com/samuelejones/manuscript_repository/. The variant-exposure associations for the MR analyses can be found in Supplementary Table S3 (single-exposure) and Supplementary Table S9 (multi-exposure).

Declaration of interests

SR reports receiving consultancy fees from Jazz Pharmaceuticals and Eli Lilly, participates on an advisory board for Apnimed and has received equipment from Philips Respironics and Nox Medical, all of which are unrelated to this study and so do not represent conflicts of interest. BC is an executive committee member for the American Thoracic Society. All other authors made no declaration.

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The COVID-19 Human Genetics Initiative (HGI) (https://www.covid19hg.org/) is an ongoing international effort to identify the genetic factors that predispose people to a greater risk of COVID-19 (SARS-CoV-2 infection), severe COVID-19 and hospitalization from COVID-19. We would like to thank the COVID-19 HGI for publicly sharing their results ahead of publication, allowing us to investigate the causal effects of poor sleep on COVID-19.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104630.

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