**Supplementary Materials**

**Title: Assessing the causal role of sleep traits on glycated haemoglobin: a Mendelian randomization study**

**Author list:**

Junxi Liu, PhD*Ω[1, 2], Rebecca C Richmond, PhD*[1, 2], Jack Bowden, PhD[3, 1], Ciarrah Barry, BSc[1, 2], Hassan S Dashti, PhD[4, 5, 6], Iyas Daghlas, MD candidate[4, 5, 6], Jacqueline M Lane, PhD[4, 5, 6], Samuel E Jones, PhD[7], Andrew R Wood, PhD[8], Timothy M Frayling, PhD[8], Alison K Wright, PhD[9], Matthew J Carr, PhD[10, 11, 12], Simon G Anderson, PhD[13, 14], Richard A Emsley, PhD[15], David W Ray, PhD[16, 17], Michael N Weedon, PhD[8], Richa Saxena, PhD[4, 5, 6, 18], Deborah A Lawlor, PhD[1, 2, 19], Martin K Rutter, MD[†9, 20]

* = Joint first authors, with equal contributions; [†] = Joint senior authors, with equal contributions; Ω Corresponding author

**Affiliations:**

1. MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK

2. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

3. College of Medicine and Health, the University of Exeter, Exeter, UK

4. Centre for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

5. Broad Institute of MIT and Harvard, Cambridge, MA, USA

6. Department of Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA

7. Institute for Molecular Medicine Finland, University of Helsinki, Uusimaa, Finland

8. Genetics of Complex Traits, University of Exeter Medical School, Exeter, UK

9. Division of Diabetes, Endocrinology and Gastroenterology, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

10. Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

11. Manchester Academic Health Science Centre, University of Manchester, Manchester, UK

12. National Institute for Health Research (NIHR) Greater Manchester Patient Safety Translational Research Centre, University of Manchester, UK

13. George Alleyne Chronic Disease Research Centre, Caribbean Institute of Health Research, University of the West Indies, Kingston, Jamaica

14. Division of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK

15. Department of Biostatistics and Health Informatics, King's College London, London, UK

16. National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford UK

17. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford UK

18. Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

19. National Institute for Health Research (NIHR) Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and the University of Bristol, Bristol, UK

20. Diabetes, Endocrinology and Metabolism Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, Manchester, UK

Ω Corresponding author:

Dr. Junxi Liu

MRC Integrative Epidemiology Unit, Bristol Medical School, University of Bristol

Oakfield House, Oakfield Grove, Clifton, Bristol, BS8 2BN

Email: ieu_james.liu@bristol.ac.uk

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**UK Biobank**

*The UK Biobank participants*

Between 2006 and 2010, UK Biobank (UKB) recruited 503,317 participants aged 40-69 years, from 9.2 million adults who were invited to take part (5.5% response rate).(1; 2) All participants provided informed consent. Baseline data on self-reported sleep traits and other lifestyle and socio-demographic characteristics were obtained using a touchscreen questionnaire. At the same time, anthropometric measures and non-fasting venous blood samples were taken. These samples were used for glycated haemoglobin (HbA1c), non-fasting glucose, and chip-based genome-wide analyses; the latter providing single-nucleotide polymorphism (SNP) data. HbA1c (mmol/mol) was measured in red blood cells by HPLC on a Bio-Rad VARIANT II Turbo analyzer and non-fasting glucose (mmol/l) was assayed in serum by hexokinase analysis on a Beckman Coulter AU5800.(3)

UKB included 488,377 successfully genotyped participants: 49,979 using the UK BiLEVE chip and 438,398 using the UKB axiom chip. Pre-imputation quality control, phasing and imputation of the UKB genetic data have been described.(4) Of the 488,377 successfully genotyped participants, 488,288 were with available phenotypic data, among which, 409,629 were self-reported as "White British". Of these 409,629, 72,617 were excluded, after accounting for duplication, based on sex mismatch (n=312), sex chromosome aneuploidy (n=556), outliers in heterozygosity and missing rates (n=731), and relatedness based on estimated kinship coefficients (n=71,274).(5) Additionally, 13 participants who had withdrawn consent prior to our

analyses were removed (by 04 February 2020). Thus, 336,999 participants were included in the final analysis (**Supplementary Figure 1**).

*Details of self-reported sleep traits – exposures*

To assess the frequency of insomnia symptoms, participants were asked: "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" with responses "Never/rarely", "Sometimes", "Usually", "Prefer not to answer", and "Do not know". Those who responded "Prefer not to answer" or "Do not know" were set into missing. We derived a binary variable for the frequency of insomnia symptoms where "Usually" was coded as 1 and "Never/rarely" or "Sometimes" were coded as 0.

24-hour sleep duration was assessed by asking: "How many hours sleep do you get in every 24 hours? (Please include naps)". The answer could only contain integer values. Binary variables for short sleep duration (≤6 hours *vs* 7-8 hours) and long sleep duration (≥9 hours *vs* 7-8 hours) were also derived.

Self-reported daytime sleepiness was ascertained using the question "How likely are you to dose off or fall asleep during the daytime when you don't mean to? (e.g., when working, reading or driving)" with the response options of "Never/rarely", "Sometimes", "Usually", "All of the time", "Prefer not to answer", and "Do not know". Participants reporting "Prefer not to answer" or "Do not know" were set into missing. Other responses were coded as 1 to 4 corresponding to the severity of daytime sleepiness.

To assess daytime napping, participants were asked: "Do you have a nap during the day?" with responses "Never/rarely", "Sometimes", "Usually", "Prefer not to answer", and "Do not know". Those who responded "Prefer not to answer" or "Do not know" were set into missing. We derived a three-levels ordinal variable for napping frequency where "Never/rarely," "Sometimes," and "Usually" were coded as 1, 2, and 3, respectively.

Chronotype was assessed in the question "Do you consider yourself to be?" with the following answers: "Definitely a 'morning' person", "More a 'morning' than an 'evening' person", "Do not know", "More an 'evening' than a 'morning' person", "Definitely an 'evening person", and "Prefer not to answer" which were coded from 1 to 5 and missing respectively.

**Multivariable-adjusted regression model**

We considered the following potential confounders in multivariable-adjusted regression (MVR) model: baseline age, sex, smoking, alcohol intake, Townsend residential area deprivation score, education vigorous physical activity levels, diagnosed sleep apnoea, and body mass index (BMI). The covariates were determined to be potential confounders based on being known or plausible cause of both variation in sleep characteristics and glycaemic levels.(6-18) Data on the confounders in the multivariable-adjusted regression (MVR) were taken from baseline questionnaire responses with the exceptions of sleep apnoea, BMI and deprivation scores. Of the lifestyle and environment questions, participants were asked their smoking status (categorised into 'never', 'former' or 'current') and their alcohol intake frequency (categorised into 'never', 'occasionally', '1-3 times a month' 'once or twice a week', '3-4 times a week' or 'daily').

Participants were also asked how many days in a typical week that they would do 10 or more minutes of vigorous physical activity ("activities that make you sweat or breathe hard such as fast cycling, aerobic exercise and heavy lifting"). Participants were asked which qualifications they had. A categorial variable was generated for education in the UKB corresponding to 5 International Standard Classification of Education (ISCED) codes based on the years of education in UK Biobank (5: College or university degree / NVQ or HND or HNC or equivalent; 4: Other prof.equal. eg: nursing, teaching; 3: A levels / AS levels or equivalent; 2: O levels / GCSEs or equivalent / CSEs or equivalent; 1: None of the above). Townsend deprivation index(19) was calculated based on the preceding national census output areas, where each participant was assigned a continuous score corresponding to the output area in which their postcode was located. A higher index indicates a greater level of deprivation. At the initial Assessment Centre visit, height (cm) was measured using a Seca 202 device in all participants in the UKB along with sitting height while weight (kg) was measured by a variety of means, which was amalgamated into a single weight variable. Diagnosed sleep apnoea (ICD-10) was obtained from the Hospital Episode Statistics (HES) data (code G47.33) in the UKB. We ensured that the diagnosis occurred before the baseline UKB assessment using dates of diagnosis and UKB assessment. BMI was calculated from height and weight in kg/m$^2$, which were measured at UKB assessment centres (fieldworker assessed weight and height at baseline. Standing height (cm) was measured using a Seca 202 device following a protocol and training. Weight (kg) was measured by a variety of means during the initial Assessment Centre visit. This field amalgamates these values into a single item).

**One-sample Mendelian randomization**

Biallelic and autosomal SNPs identified in genome-wide association study (GWAS) of self-reported sleep traits were used in the UKB:(2) 245 SNPs for insomnia symptoms,(20) 77 SNPs for sleep duration,(21) 27 SNPs for short sleep (≤ 6hours *vs* 7-8 hours),(21) 7 SNPs for long sleep (≥ 9hours *vs* 7-8 hours),(21) 37 SNPs for excessive daytime sleepiness,(22) 114 SNPs for napping,(23) and 341 SNPs for chronotype(24) (specific SNPs can be checked in **Supplementary Table 7**). After the identification of genetic variants from the discovery GWAS, we recoded the SNPs in the UKB to ensure they were aligning with the discovery GWAS, in the direction of specific sleep traits' increasing allele. To be noticed, the chronotype increasing allele was coded for morning preference (categories were ordered from more 'eveningness' to more 'morningness') in the discovery GWAS of chronotype.(24) We have flipped the evening preference alleles for chronotype for a better interpretation (where 'definitely a morning person' is the reference category). Accordingly, the unweighted allele scores of each sleep traits were generated by summing the number of effect alleles harboured by each individual.

For one-sample Mendelian randomization (1SMR), the genetic variants were extracted from the UKB Haplotype Reference Consortium reference panel dataset. These data have undergone extensive quality control checks including removal of related participants (third degree or closer) and non-White British participants based on questionnaire and PCA.(25) Unweighted allele scores were generated as the total number of adverse sleep trait increasing alleles present for each participant (evening preference alleles for chronotype). Two-stage least squares (2SLS) instrumental variable analyses were performed with adjustment for assessment centre and 40 genetic principal components to minimize confounding by population stratification,(26) as well

as baseline age, sex and genotyping chip to account for known confounders and to reduce random variation.

**Two-sample Mendelian randomization**

We conducted two-sample Mendelian randomization (2SMR) analyses of sleep traits with glycaemic measures using the summary associations between the genetic instruments and sleep traits identified in the respective GWAS(20-23) (sample 1) (**Supplementary Table 1**) and estimates of the associations between the genetic instruments and glycaemic measures (HbA1c and fasting glucose)(27; 28) from Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) (sample 2). Analyses were conducted using the "TwoSampleMR" package in R (version MRCIEU/TwoSampleMR@0.4.26).(29) If a SNP was unavailable in the outcome GWAS summary statistics, we identified a proxy in strong linkage disequilibrium (LD) with the missing SNP ($r^2>0.8$) (proxy SNPs were shown in **Supplementary Table 9**). All SNPs used to instrument the sleep traits were found to be conditionally independent in the GWAS studies, as such we did not apply LD clumping function, which might reduce the number of SNPs. The effect allele frequency of the outcome summary data was misinterpreted in the "TwoSampleMR" package (by the time of the analyses was conducted). Therefore, we manually corrected the effect allele frequency of all the merged palindromic SNPs according to the data (i.e., minor allele frequency) downloaded from the MAGIC and the information of minor allele obtained from the Ensembl (EUR population) (https://www.ensembl.org/index.html). We then performed harmonization of the direction of effects between SNPs in the exposure and outcome GWAS. Palindromic SNPs were harmonized if they were aligned and the minor allele frequency

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was <0.3, otherwise they were excluded. In the primary analysis, we used the inverse-variance weighted (IVW) regression under a multiplicative random-effects model(30) (weights are equal to the inverse of variance of SNP-outcome associations) to obtain causal effects of sleep traits on HbA1c and fasting glucose.

To enable the comparison of the 2SMR estimates to the MVR and 1SMR results, we converted the results of the SNP-binary sleep traits (i.e., insomnia symptoms, short sleep, and long sleep) from the multiplicative log odds scale to a difference in risk scale by $\beta = \log OR * \mu * (1 - \mu)$, $se = se_{\log OR} * \mu * (1 - \mu)$, with $\mu = n_{case}/(n_{case} + n_{control})$.(31)

**Sensitivity analyses**

*Collider-correction*

The method of Barry et al, termed `collider-correction', enables weak instrument and pleiotropy robust 2SMR methods to be applied to one-sample data to obtain causal estimates.(32) It is based on a generalization of the algorithm described in Dudridge et al , to adjust for collider bias in genetic association studies of disease progression.(33) This method artificially induces and then corrects for collider bias, with an additional simulation extrapolation (SiMEX) correction(34) step to cope with weak instrument bias. Further methodological details are provided in the link publication (https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1009703), but we provide a brief description below.

The association among SNP (G), exposure (X), and outcome (Y) for subject $i$ is assumed to obey the following data generating process:

$$X_i \mid G_i, U_i = \sum_{j=1}^{k} \beta_{XGj} G_{ij} + \beta_{UX} U_i + \varepsilon_{Xi} \qquad (1)$$

$$Y_i \mid X_i, G_i, U_i = \beta X_i + \sum_{j=1}^{k} \alpha_j G_{ij} + \beta_{UY} U_i + \varepsilon_{Yi} \qquad (2)$$

where U is the unmeasured confounding predicting X and Y, $\varepsilon$ is the independent residual error term.

In order to obtain the unbiased causal effect $\beta$ using 2SLS which assuming there is no pleiotropy ($\alpha_j = 0$), we would firstly regress the exposure (X) on all $k$ genetic variant under model (1) to derive the predicted exposure $\widehat{X}_i = \sum_{j=1}^{k} \beta_{XGj} G_{ij}$. Subsequently, we would regress the outcome (Y) on $\widehat{X}_i$ to obtain the causal estimate $\hat{\beta}$. However, in a one-sample setting, the unmeasured confounder U is common to both X and Y, therefore the respectively residual error $\varepsilon_{Xi}$ and $\varepsilon_{Yi}$ are correlated, which might bias the estimate toward the observational estimate as long as the instruments are weak (F-statistics <10).(35; 36)

Artificially, we introduce collider bias into the SNP-outcome associations by fitting model (3):

$$Y_i \mid X_i, G_i = \beta^* X_i + \sum_{j=1}^{k} \alpha_j^* G_{ij} + \varepsilon_i' \qquad (3)$$

where $\beta^*$ and $\alpha_j^*$ are collider biased estimates distinct from $\beta$ and $\alpha_j$, when confounding exists between the exposure and outcome exists. The parameters $\alpha_j^*$, $\alpha_j$, $\beta^*$, and $\beta$ are linked via:

$$\alpha_j^* = \alpha_j + (\beta - \beta^*)\,\beta_{XGj} \qquad (4)$$

To estimate $\beta$ we therefore fit a linear model to obtain an estimate $(\widehat{\beta - \beta^*})$:

$$\widehat{\alpha_j^*} = \alpha_0 + (\beta - \beta^*)\,\widehat{\beta_{XGj}} + \varepsilon_i \qquad (5)$$

As such, the causal effect is then estimated as

$$\widehat{\beta} = \widehat{\beta^*} + (\widehat{\beta - \beta^*}) \qquad (6)$$

To additionally adjust for weak instrument bias we fit linear model (5) using SiMEX(34) or another classical measurement error correction method. This method can be used because the collider correction algorithm removes the correlation in the uncertainties of $\widehat{\beta_{XGj}}$ and the $\widehat{\alpha_j^*}$ .

In this study, the summary statistics for collider-correction (i.e., $\beta_{XG}$, se$\beta_{XG}$, $\beta_{YG}$, se$\beta_{YG}$, $\beta^*$, se$\beta^*$, $\alpha^*$, se$\alpha^*$) were obtained from the linear regression adjusted for age, sex, chip, assessment centre, and 40 principal components. This collider correction can be implemented to different 2SMR methods regarding different assumptions of pleiotropy. The following methods were named 1SMRsensitivity1, 1SMRsensitivity2, and 1SMRsensitivity3 respectively in the manuscript, tables, and figures.

When implementing into IVW, we assume the mean pleiotropy is zero and the Instrument Strength Independent of Direct Effect (InSIDE) assumption. Thus, in regression (5) we can set $\alpha_0 = 0$ and fit using least squares. (1SMRsensitivity1)

To account for potential pleiotropy with a non-zero mean we repeat the above procedure but allow the intercept to be estimated in (5), This is equal to performing MR-Egger regression.[37] (1SMRsensitivity2)

To account for 'majority valid' pleiotropy that is nevertheless potentially in violation of the InSIDE assumption, we fit model (5) with no intercept using least-absolute deviation (LAD) regression, This is close in spirit to the weighted median (WM) approach.[38] (1SMRsensitivity3)

Applying the combination of collider correction and 2SMR methods as a sensitivity analysis, it provides an alternative to account for both pleiotropy and weak instrument bias in a 1SMR setting, which is a less biased but more precise causal estimate comparing with the application of standard 2SMR methods.

*Winner's curse correction*

To address this, we identified subsets of genome-wide significance SNPs (p-value$<5\times10^{-8}$) of some sleep traits in other independent GWAS that did not include UKB. For insomnia symptoms: a subset of 108 SNPs were identified in Jansen et al GWAS,[20] when analyses were run in the 23andMe separately; for excessive daytime sleepiness: a subset of 19 SNPs were identified in Wang H et al GWAS,[22] when analyses were ran in 337,539 unrelated individuals of European Ancestries separately; for napping: a subset of 17 SNPs were identified in Dashti HS et al GWAS,[23] when analyses were ran in the 23andMe separately; for chronotype: a

subset of 72 SNPs were identified in Jones et al GWAS,(24) when analyses were ran in the 23andMe separately. These SNPs could be accessed in the supplementary of the specific discovery GWAS studies.(20; 22-24)

We did not identify a study (other than UKB) that had undertaken genome-wide analyses of sleep duration. Replication of the 78 genome-wide significant SNPs predicting sleep duration in the UKB were conducted in the CHARGE (adult, n=47,180) and the EAGLE (childhood/adolescent, n=10,554) cohorts respectively, as well as, meta-analysis of these two cohorts with the UKB (n =446,118) were presented in the discovery GWAS.(21) Despite, the summary statistics were driven by the UKB considering to the larger sample size of UKB. Besides, no summary statistics of meta-analysis of these two independent cohorts were given in the discovery GWAS.(21) Although we have conducted a meta-analysis to obtain the summary statistics from the CHARGE and the EAGLE, no genome-wide significance SNP was identified. As such, no winner's curse robust sensitivity analysis was conducted.

Additional analyses

*Assessing associations of HbA1c with insomnia*

1SMR and 2SMR were conducted to assess the association of HbA1c with insomnia to rule out the possibility of reverse causality that HbA1c levels could influence sleep perhaps through mechanisms including neuropathic pain and nocturia.

For 1SMR, 11 genome-wide significance (p-value<$5×10^{-8}$) SNPs predicting HbA1c were identified in Soranzo N et al GWAS (n=46,368, aged 53 years-old (52% female), from 23 GWAS)(27) from MAGIC. We generated the unweighted allele score as the total number of HbA1c increasing alleles present for each participant in the UKB. 2SLS instrumental variable analyses were performed with adjustment for assessment centre and 40 genetic principal components to minimize confounding by population stratification, as well as baseline age, sex, and genotyping chip to account for known confounders and to reduce random variation.

2SMR analyses of HbA1c with insomnia symptoms were conducted using the summary associations between the genetic instruments and HbA1c identified in the in Soranzo N et al' s GWAS(27) (exposure, sample 1) and estimates the associations between the genetic instruments and insomnia symptoms(20) (downloaded from https://ctg.cncr.nl/software/summary_statistics) (outcome, sample 2). Analyses were conducted using the "TwoSampleMR" package in R.(29) All the 11 (non-palindromic) SNPs identified in the exposure GWAS can be merged in the outcome summary statistics. IVW regression under a multiplicative random-effects model(30) was used as the primary 2SMR analysis, meanwhile, WM and MR-Egger were also applied as sensitivity analyses.

*Multivariable Mendelian randomization assessing the direct effect of insomnia symptoms on HbA1c independent of BMI*

97 genome-wide significance SNPs predicting BMI were extracted from Locke et al GWAS.(39) Among which, 96 SNPs were identified and were used to generate the unweighted allele scores

as the total number of BMI increasing alleles present for each participant in the UKB. We conducted a multivariable Mendelian randomization(40) (MVMR) to assess the direct effect of insomnia symptoms on HbA1c independent of BMI in the UKB. The Sanderson-Windmeijer F statistics(40) of insomnia symptoms unweighted allele score and BMI unweighted allele score were 1,596 and 3,970 respectively. For comparison, unique variable Mendelian randomization (UVMR) for the effect of BMI on HbA1c was also conducted separately in the UKB. Both MVMR and UVMR were performed with adjustment for age at recruitment, sex, assessment centre, 40 genetic principal components, and genotyping chip.

**Assessing associations of sleep traits with glucose**

Glucose was measured in the same unit of mmol/l in UKB (non-fasting glucose, n = 293,838) and in MAGIC (fasting glucose, n = 46,186, mean (SD) age = 52 years (56% female) from 21 GWAS).(28) In the UKB, non-fasting glucose was right skewed, therefore, we natural log-transformed it and converted it into SD units (1 SD = 0.17 log mmol/l). In 2SMR, we also presented results in SD units of the summary data from MAGIC (1SD was equal to an fasting glucose value of 0.73 mmol/l). Thus, for all analyses (MVR, 1SMR, and 2SMR) we estimated the mean difference in glucose SD per 1 unit or category increase in the sleep traits (i.e., 24-hour sleep duration, daytime sleepiness, daytime napping, and chronotype) except for insomnia symptoms, short sleep (≤6 hours *vs* 7-8 hours), and long sleep (≥9 hours *vs* 7-8 hours). For these binary exposures, in MVR and 1SMR we estimated the average difference in glucose under the counterfactual assumption which provides an estimate of the difference between everyone (in the population of interest) experiencing the exposure (i.e. assuming exposure prevalence is 100%)

compared to no-one experiencing the exposure (assuming exposure prevalence: 0%).(41) To enable the comparison of the 2SMR estimates to the MVR and 1SMR results, we converted the results of the SNP-binary sleep trait from the multiplicative log odds scale to a difference in risk scale by $\beta = \log OR * \mu * (1 - \mu), \ se = \ se_{\log OR} * \mu * (1 - \mu)$, with $\mu = n_{case}/(n_{case} + n_{control})$.(31)

In UKB, glucose was measured without fasting, because participants were not advised to fast before attending. However, participants were asked to record the last time they ate or drank anything before attending the clinic and those answers were used as 'fasting time'. As such, we repeated MV and 1SMR main analyses with additional adjustment for fasting time (hours) and dilution factor. During routine quality control checks, the UKB laboratory team observed that some assay results were lower than expected for samples acquired during certain time periods. This affected biochemical results for ~ 8% of the samples and a dilution correction factor has been provided for the relevant measures.(42; 43) As such, the dilution factor was adjusted for. While the assessment of sleep traits on glucose levels was secondary to our primary aim, it should be highlighted that both MVR and 1SMR were conducted on non-fasting glucose in UKB. Analyses were adjusted for fasting time, but even with this adjustment differences between the 1SMR and 2SMR may be because the latter was based on fasting glucose.

**Testing Mendelian randomization assumptions**

In 1SMR, the variation in sleep traits explained by the allele scores varied from 2.14% (F-statistic 7359) for chronotype to 0.07% (F-statistic 181) for long sleep duration (**Supplementary**

**Table 1**). For collider-correction, the mean F-statistics of individual SNPs (mean ($F_i$ = BetaXGi^2 / seBetaXGi^2) (BetaXGi and seBetaXGi were obtained from UKB)) for each of the sleep traits calculated in UKB were ≥ 23, except for insomnia symptoms for which it was 8 (**Supplementary Table 7**). In 2SMR, the variance explained by the combined SNPs was also highest for chronotype (2.09%, mean F-statistic 60) and lowest for long sleep duration (0.06%, mean F-statistic 41) (**Supplementary Table 1**). Details of any proxy SNPs used in the 2SMR are described in **Supplementary Table 9**.

After accounting for multiple testing ($p < 0.05/7 = 0.007$, 7 risk factors), the allele score for insomnia symptoms was associated with six potential risk factors for variation in glycaemic traits that might result in directional pleiotropy (smoking, alcohol, Townsend residential deprivation index, BMI, education, physical activity except sleep apnoea). To differing degrees, the allele scores of short sleep duration, daytime sleepiness, daytime napping, and chronotype also associated with one or more of these risk factors, whereas allele scores of total sleep duration and long sleep duration were not substantively associated with these risk factors (**Supplementary Table 8**).

In 1SMR, the Sargan test indicated heterogeneity ($p < 0.05$) of the SNP estimates for all sleep traits with HbA1c and glucose, which could suggest horizontal pleiotropy. However, MR-Egger intercepts did not provide evidence of any meaningful bias due to directional pleiotropy (**Supplementary Table 3** and **Supplementary Table 5**).

**Quantifying the population-level impact of a hypothetical insomnia intervention on the prevalence of diabetes in the UK**

Here we describe our methods for obtaining a population-level estimate of the effect of a hypothetical insomnia intervention on the UK prevalence of type 2 diabetes. We base the size of the treatment effect on the 1SMR causal estimate in UKB participants. This causal estimate indicates if we were able to successfully intervene in all of those who "usually" experience insomnia so that the frequency of their symptoms becomes "sometimes" or "rarely/never" then this intervention would be predicted to lead to a 0.52 SD, (0.42 to 0.63) reduction in their HbA1c levels, which is equivalent to 1.08 (1.07 to 1.10) mmol/mol (1SD = 0.15 log mmol/mol in the UKB). We defined diabetic status as the level of HbA1c $\geq$ 48 mmol/mol. As such:

The proportion of diabetes in the UKB (before insomnia treatment, regardless of insomnia status):

$$p_0 = n_{HbA1c\ \geq 48} / n_{total} \text{ (before insomnia treatment)}$$

Among 28% participants in the UKB with "usually" insomnia frequency, we lower their HbA1c level by 1.08 mmol/mol. Then we re-calculated the proportion of people who have diabetes in the UKB:

$$p_1 = n_{HbA1c\ \geq 48} / n_{total} \text{ (after insomnia treatment)}$$

As such, the difference between $p_0$ and $p_1$ is the reduction in the proportion of people with diabetes as a consequence of insomnia treatment. We then used a parametric bootstrap (1,000

times) to obtain the corresponding 95% confidence interval, which is 0.109%, (0.107 to 0.110) reduction.

Lastly, we applied this proportional effect to the expected number of people in the UK between the ages of 40 and 70 years in 2018,(44) which was the age range at baseline in UKB participants when insomnia symptoms were assessed. Approximately 38% of the UK population (i.e., 25 million out of 66 million in total) are in this age range.(44) Therefore, ~27,300 (95%CI 26,800 to 27,500) people with frequent insomnia symptoms would be free from having diabetes (HbA1c ≥ 48 mmol/mol) in the UK, if an effective intervention was delivered to the 25 million adults between 40 and 70 years of age.(44) This estimate is based on the 28% of the population "usually" experiencing insomnia symptoms in the UKB cohort, which is similar to the recorded national surveys of adult population in the UK that range from 5% to 38%.(45)These values could be uncertain. On one hand, the percentage of insomnia symptoms in the UKB cohort might be higher than that in the general population given UKB participants are older (mean age ~56). Thus, the estimate may be exaggerated in terms of what we would expect of a population including all ages. However, the UKB cohort is healthier than the age equivalent UK population,(46) which could underestimate risk. The quantification of the impact of a hypothetical insomnia intervention could also be an overestimate as current (largely behavioural) interventions would be challenging to implement in all people who usually experience insomnia symptoms and the intervention is unlikely to be effective in all participants.(47; 48)

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