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# Sleep Duration and Myocardial Infarction

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## Abstract

**Background:** Observational studies suggest associations between extremes of sleep duration and myocardial infarction (MI), but the causal contribution of sleep to MI and its potential to mitigate genetic predisposition to coronary disease is unclear.

**Objectives:** To investigate associations between sleep duration and incident myocardial infarction (MI), accounting for joint effects with other sleep traits and genetic risk of coronary artery disease (CAD), and to assess causality using Mendelian randomization (MR).

**Methods:** In 461,347 UK Biobank (UKB) participants free of relevant cardiovascular disease, we estimated multivariable adjusted hazard ratios (HR) for MI (5,128 incident cases) across habitual self-reported short (<6h) and long (>9h) sleep duration, and examined joint effects with sleep disturbance traits and a CAD genetic risk score. We conducted two-sample MR for short (27

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**Tweet:** Observational findings and Mendelian randomization support short sleep duration as a potentially causal risk factor for heart attack. Healthy sleep may mitigate inherited risk for coronary disease.

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SNPs) and continuous (78 SNPs) sleep duration with MI (n=43,676 cases / 128,199 controls), and replicated results in UKB (n=12,111/325,421).

**Results:** Compared to sleeping 6-9 hours/night, short sleepers had a 20% higher multivariable-adjusted risk of incident MI (HR=1.20, 95% confidence interval 1.07-1.33), and long sleepers had a 34% higher risk (1.34, 1.13-1.58); associations were independent of other sleep dimensions. Healthy sleep duration mitigated MI risk even amongst individuals with high genetic liability (0.82, 0.68-0.998). MR was consistent with a causal effect of short sleep duration on MI in CARDIoGRAMplusC4D (1.19, 1.09-1.29) and UKB (1.21, 1.08-1.37).

**Conclusions:** Prospective observational and MR analyses support short sleep duration as a potentially causal risk factor for MI. Investigation of sleep extension to prevent MI may be warranted.

## Condensed abstract:

Although short and long sleep duration are associated with myocardial infarction (MI), it is unclear whether this relationship is causal. The present study triangulated observational and Mendelian randomization (MR) analyses to address this question. Short and long sleep duration were independently associated with incident myocardial infarction (MI), and healthy sleep duration mitigated MI risk even amongst individuals at high genetic risk. In MR, short sleep duration was associated with higher risk for MI. Our results support short sleep duration as a potentially causal risk factor for MI and warrant investigation of interventions to promote healthy sleep duration.

### Keywords

Sleep duration; myocardial infarction; coronary artery disease; genetic risk score; Mendelian randomization; UK Biobank

## Introduction

Insufficient sleep has been identified as a public health epidemic (1), emphazing the need to understand risks associated with unfavorable sleep habits. Both short (<7h) and long sleep duration (>8h) are associated with greater risk of myocardial infarction (MI) (2-4). Potential mediators of this association include cardiometabolic risk factors (5,6), unhealthy lifestyle behaviors (7), inflammation (8), and endothelial dysfunction (9). Given the global burden of heart disease, it is critical to understand the impact of modifiable risk factors such as sleep duration.

Previous studies have predominantly focused on sleep duration as an isolated risk factor for cardiovascular disease (2). However, sleep is multidimensional (10), such that studies of both the independent and joint effects of sleep duration with other sleep traits such as sleep quality (11), sleep timing (12) , insomnia (13), and daytime napping (14) on cardiovascular outcomes are warranted. Furthermore, although a healthy lifestyle appears to reduce coronary artery disease (CAD) risk across strata of genetic liability (15), no work has investigated this finding with regards to sleep health.

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Observational studies are susceptible to reverse causality and residual confounding, which limit causal inference. These limitations may be overcome by use of genetic variants (or single nucleotide polymorphisms, SNPs) as proxies for lifetime exposure to longer or shorter sleep in Mendelian randomization (MR). MR leverages the random assignment of genetic variants at gametogenesis, independently of environmental confounders, to obtain causal estimates of exposure risks that are substantially less confounded and not susceptible to reverse causality (16). Genome-wide association studies (GWAS) have identified suitable genetic variants as proxies for sleep duration, allowing for a test for the hypothesis that sleep duration is a causal risk factor for MI. Establishing causality between sleep duration and coronary disease could have important implications for sleep targeted interventions to reduce cardiovascular risk.

We tested whether short and long sleep durations are associated with higher MI risk in the UK Biobank (UKB). We investigated whether sleep traits (insomnia symptoms, difficulty getting up, napping, or late sleep timing) or genetic predisposition for CAD modified the association between sleep duration and MI. MR analysis utilizing genetic data from UKB and from the largest, publically-available CAD genome-wide association study (GWAS) (17) was used to assess evidence for causality.

## Methods

### Population

The UKB is an ongoing prospective population-based cohort study that enrolled over 500,000 volunteers aged 40-69 from 2006-2010 (18). Participants were recruited from across the UK and enrolled at one of several assessment centers. Of the 9 million individuals invited to participate, 5.5% were ultimately enrolled. At baseline recruitment, each participant completed a standardized questionnaire, a standardized interview with a study nurse, and had anthropometric and physiological measurements taken (18). Blood, saliva, and urine were collected from each participant.

### Ascertainment of Exposure

Sleep duration was self-reported with a standardized question “About how many hours sleep do you get in every 24 hours? (please include naps)”, with responses in hourly increments. We excluded individuals with missing sleep duration and sleep durations <4 or >11 hours (to minimize implausible sleep durations and possible confounding by poor health). Questions to assess other sleep traits are listed in the Online Appendix.

### Ascertainment of Outcomes and Covariates

Incident MI was the primary outcome for observational analyses, comprising fatal and non-fatal ST-segment elevation and non-ST-segment elevation MIs. Cases were ascertained through a UKB algorithm combining data from linked hospital admissions and death registries (Online Appendix), with all other participants presumed to be free of myocardial infarction. The last recorded MI was on 02/21/16, which was used as the censoring date for other participants if no death or outcome had been recorded. This resulted in a median follow-up of 7.04 years. Individuals with baseline self-reported coronary revascularization,

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ischemic stroke, MI, lung cancer, breast cancer, prostate cancer, and colorectal cancer were excluded; stroke and MI exclusions were supplemented by EHR data gathered as part of the UKB outcomes adjudication Secondary analyses included incident coronary revascularization as an outcome (based on hospital episode database codes K40-46,K49-50, and K75) (19). Unless otherwise specified, all 32 covariates used in multivariable models were ascertained at baseline through self-report or nurse interview (Online Appendix).

## Phenotypic analyses

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for incident MI across hours of habitual sleep duration with 7-8 hours initially serving as a referent group (additional details in Online Appendix Supplementary methods 4). We report models that are i) unadjusted, ii) adjusted for age and sex, iii) additionally adjusted for BMI and waist-hip ratio, and iv) fully adjusted, including all covariates with a p-value <0.10 in the multivariable models. Statistical significance of sleep duration after multivariable adjustment guided creation of bins of habitual sleep duration that aggregated individuals with similar risk attributed to sleep duration (<6, 6-9 and >9 hours). These bins were used in subsequent models with multivariable adjustment and are the primary reported results. To estimate the independent effect of sleep duration, the main model adjusted for insomnia symptoms. We then adjusted for difficulty getting up, sleep timing, and napping to evaluate whether the association of sleep duration with MI is independent of other dimensions of sleep. Covariate modeling and missing data handling is detailed in the supplement (Online Appendix, Online Appendix Section 3).

Analyses involving interactions of sleep duration with the CAD genetic risk score (GRS) were restricted to unrelated participants of White British ancestry (n=310,917) who passed genomic quality control procedures (see Genetic Analysis section). The CAD GRS included 68 SNPs achieving genome-wide significance in prior CAD GWAS excluding the UKB (Online Appendix Online Table 11) (20). Each UKB participant's GRS was calculated as described below for one-sample MR analyses. We first tested multivariable-adjusted interactions of the GRS with sleep duration. We then stratified participant groups by genetic risk and unfavorable sleep duration (<6h or >9h, to maximize power), and tested associations with incident MI; we report estimates for favorable sleep duration within each stratum of genetic CAD risk ($1^{st}$ quartile for low risk; $2^{nd}$ and $3^{rd}$ quartile for medium risk; $4^{th}$ quartile for high risk). To assess reverse causality of coronary disease on sleep duration, we regressed the CAD GRS on long and short sleep duration in logistic regressions adjusted for sex, age, genotyping array, and 10 principal components (PCs) of ancestry. In addition to genetic interaction analyses, we assessed interactions with sex, insomnia symptoms, difficulty getting up, sleep timing, napping, depression, obesity (using ethinicity-specific cut-offs (21)), hypertension, and type 2 diabetes (Online Appendix Section 4).

Secondary analyses added incident coronary revascularization to the MI outcome (19). We additionally adjusted for the following diseases self-reported at baseline: hypo- and hyperthyroidism, migraines, rheumatoid arthritis, osteoarthritis, deep vein thrombosis, and chronic obstructive pulmonary disease. To determine whether undiagnosed sleep apnea may be a confounder, we also created and adjusted for a modified STOP-BANG (22) risk scale

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for sleep apnea (missing the question 'Has anyone observed you stop breathing during sleep?', and replacing neck circumference with waist circumference dichotomized to the threshold for metabolic syndrome (23)). In sensitivity analyses, we excluded participants with baseline CAD risk factors (hypertension, diabetes, high cholesterol, use of aspirin, angina, and smoking) and excluded the first year of follow-up to address concerns of reverse causality (11). We estimated associations without removing participants with extreme (<4 or >11h) sleep durations. Finally, we used Fine-Gray models to assess whether accounting for the competing risk of death influenced results (24).

## Genetic analysis

**Generation of genetic instruments for sleep duration—**Genotyping, quality control, and imputation procedures in the UKB are described elsewhere (25). GWAS in individuals of European ancestry in the UKB have identified 78 SNPs associated with continuous sleep duration (n=446,118), 27 SNPs associated with short sleep duration (<7 hours; n=106,192 cases/305,742 controls), and 8 SNPs associated with long sleep duration (>8 hours; n=34,184 cases/305,742 controls) (Online Appendix Online Tables 13 and 14) (26). We refer to a set of SNPs that proxy sleep duration as 'genetic instruments.' These genetic instruments are strongly associated with objectively measured, 7-day accelerometry (n = 85,499) sleep duration estimates in UKB (26).

To minimize bias in effect estimates induced by correlation between SNPs, we restricted our genetic instrument to independent SNPs not in linkage disequlibrium ($R^2 < 0.1$). Analogous to our observational analysis, we started with broad definitions of short (<7h) and long sleep duration (>8h). We did not test long sleep in MR given the limited number of SNPs.

## Mendelian randomization analyses

This Mendelian randomization (MR) study can be conceptualized as a natural experiment whereby, at gametogenesis, study participants are randomly allocated genetic variants that either increase or decrease lifelong exposure to longer or shorter sleep duration. We combine these genetic variants into a multi-SNP genetic instrument that robustly and reliably associates with sleep duration. We then regress the SNP-sleep associations against the SNP-MI associations, and meta-analyze across all SNPs in the genetic instrument. For valid causal estimates, MR makes three assumptions: i) the genetic instrument is strongly associated with the exposure of interest (in this case sleep duration); ii) the genetic instrument does not share common causes with the outcome of interest (e.g. the SNP-sleep estimates being confounded by hypercholesterolemia), and iii) the genetic instrument influences the outcome only through the exposure of interest (no horizontal pleiotropy, e.g., variants influencing the outcome through higher blood pressure) (26). A clinically-oriented summary of MR is available elsewhere (27).

Our primary MR analysis utilized a two-sample design, where exposures and outcomes are measured in non-overlapping datasets, which minimizes the false positive rate (27). We used beta-weighted sleep duration genetic instruments as exposures, and outcome data from a MI GWAS with no participant overlap with UKB (CARDioGRAMplusC4D; n=43,676 cases / 128,199 controls; Online Appendix Supplementary methods 5) (17). Participants in the

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GWAS were predominantly of European ancestry. To harmonize effects with observational analyses, MI was the primary outcome in MR. We also estimated two-sample MR associations of sleep duration with CAD in CARDioGRAMplusC4D (n=60,801 cases/ 123,504 controls), which included the following outcomes: myocardial infarction, acute coronary syndrome, chronic stable angina, and coronary stenosis >50%. Fixed-effects inverse-variance weighted (IVW) was our main MR approach. Estimates for the continuous sleep duration trait were scaled to hours by multiplying per-minute betas and confidence intervals by 60. Estimates for the short sleep duration trait were scaled to the increase in odds of MI per doubling in the odds of short sleep duration by multiplying log-odds ratios by 0.693 as previously described (28).

For replication, we used individual-level data of unrelated UKB participants of White British ancestry in one-sample MR. Here, MI included self-reported heart attack and ICD codes for MI (as used in the phenotypic analyses for incident MI, Online Appendix Supplementary methods 2), and CAD included MI and/or revascularization as reported in a previous UKB GWAS (29) (Online Appendix Supplementary methods 6). We used this combined incident and prevalent GWAS definition of MI and CAD in MR as, unlike in observational studies, there is no concern for disease occurrence influencing the exposure. MR thus represents an opportunity to use genetic instruments independently of the timing of the outcome and baseline assessment. The sum of sleep duration risk alleles multiplied by GWAS effect sizes was regressed against the MI and CAD outcomes, adjusting for the top 10 PCs of ancestry, genotyping array, age, and sex. Effect estimates were scaled as stated above.

### Sensitivity analyses for pleiotropy, outliers, and confounding

We undertook several analyses to test the second MR assumption that the genetic instrument is not influenced by confounding. First, we tested the association of the genetic instrument with key coronary risk factors (Online Appendix Online Table 11). We then created genetic instruments from GWAS (26) adjusted for either BMI, insomnia, or a composite of clinically relevant variables (BMI, naps, Townsend deprivation index, smoking status, alcohol consumption, menopause status, employment status, and sleep apnea). We also used SNP estimates from GWAS that excluded participants participating in shift work or who reported a range of baseline prevalent disease (including coronary disease and ischemic stroke; detailed in Online Appendix Online Table 12).

We undertook several analyses to test the third MR assumption that the genetic instrument influences the outcome only through sleep duration rather than through pleiotropic pathways. In two-sample MR, we used random-effects IVW, weighted median (30), MR Egger (31), MR-PRESSO (32), MR-RAPS (Zhao, arXiv 2018), and manual pruning of pleiotropic SNPs associated with cardiometabolic risk factors as sensitivity analyses for genetic confounding through pleiotropy (Online Appendix Section 5). Given the reduced power in these MR sensitivity analyses, in cases where the MR sensitivity analysis results differed between the MI and CAD outcomes, we deferred to the results from the CAD GWAS, as it included ˜17,000 more cases than the MI GWAS (Online Appendix Section 5). We examined leave-one-out plots to identify outlier SNPs. For one-sample MR sensitivity

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analyses, we used an unweighted GRS and the control function estimator (Online Appendix Section 5).

A 2-tailed significance threshold of 0.05/2=0.025 was used for all analyses except interaction analyses; for these, we used a Bonferroni-adjusted alpha of 0.05/11=0.0045 to account for multiple comparisons. Analyses were conducted in R version 3.3, and the TwoSampleMR package was used for MR analyses (33).

## Results

### Sleep duration and incident MI

The analytic sample for the prospective cohort analysis consisted of 461,347 participants, with 5,218 incident MIs over a median follow-up of 7.04 years [IQR 1.41 years] (Figure 1). Baseline characteristics across hours of sleep duration are shown in Online Appendix Online Table 2. Participants regularly sleeping 7-8h were more likely to be employed and report excellent self-reported health, and were less likely to report a history of smoking, depression, high cholesterol, or hypertension.

In age and sex-adjusted analyses, participants sleeping <7h or >8h had a significantly higher risk of incident MI, and effect sizes across strata of sleep duration were consistent with a dose-dependent association (Table 1). After multivariable adjustment sleep durations of 4, 5, 10, and 11h remained independently associated with incident MI (Table 1). We thus binned 6, 7, 8, and 9h into the referent group for subsequent observational analyses. Short and long sleep were consistently associated with incident MI after full adjustment ($MVHR_{<6h}$=1.20, 1.07-1.33, p=0.001; $MVHR_{>}$9h=1.34, 1.13-1.58, p=0.0006; Table 2). We found no evidence for effect modification of the association of sleep duration with MI (Online Appendix Online Table 4). Results were robust in sensitivity and secondary analyses (Table 2), were similar when including coronary revascularization in the outcome ($MVHR_{<6h}$=1.12, 1.03-1.23; $MVHRM_{>9h}$=1.25, 1.08-1.44; Online Appendix Online Table 5), and were unchanged in Fine-Gray models treating death as a competing risk. The sleep duration effects persisted with control for other sleep traits and disturbances, and were not influenced by control for a modified STOP-BANG risk scale for sleep apnea (Online Appendix Online Table 6). Compared to individuals without insomnia sleeping 6-9h, concomitant short sleep duration and frequent insomnia symptoms were associated with a 30% higher risk of incident MI (MVHR=1.30, 1.15-1.47). Relative to those with favorable (6-9h) sleep duration and the least difficulty getting up, those with unfavorable sleep duration (<6h or >9h) and who reported getting up to be ‘not at all easy’ had an 81% higher risk of incident MI (MVHR=1.81, 1.42-2.31).

### Interplay between genetic risk of CAD and sleep duration on risk of incident MI

The CAD GRS was associated with increased risk of incident MI (n=310,917, cases=3,513; adjusted HR for 1 standard deviation (SD) increase=1.31, 1.27-1.35; HR Q4 *vs.* Q1=1.91, 1.74-2.10). There was no evidence of interaction between short or long habitual sleep duration with the GRS, suggesting independent contributions of genetic predisposition and sleep duration to MI risk (p=0.13 and 0.14, respectively). Compared to those with 6-9h of

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sleep and low genetic risk (lowest 25% genetic risk), having unfavorable sleep duration (<6 or >9h) and high genetic risk (top 25% genetic risk) was associated with a 130% higher risk of MI (MVHR=2.30, 1.88-2.82; Figure 2). Point estimates were consistent with a cardioprotective association of favorable sleep duration at high genetic CAD risk ($MVHR_{favorable\ sleep\ duration}$=0.82, 0.68-0.998, p=0.048; Online Appendix Online Table 9). There was no association between the CAD GRS and short (p=0.21) or long (p=0.95) sleep duration.

## Mendelian randomization of sleep duration against prevalant CAD

IVW estimates in two-sample MR were consistent with a causal effect of short sleep duration on MI ($OR_{per\ additional\ h\ of\ sleep}$= 0.80, 0.67-0.95, p=0.013; $OR_{short\ sleep}$ = 1.19, 1.09-1.29, p=4.2e-04; Figure 3). Similar results were seen with CAD in two-sample MR ($OR_{per\ additional\ h\ of\ sleep}$=0.79, 0.68-0.92, p=3.20e-03; $OR_{short\ sleep}$=1.24, 1.11-1.38, p=1.79e-06; ).

One-sample MR analyses were restricted to 337,532 unrelated UKB participants of White British ancestry (n=17,157 cases/320,375 controls). We observed similar causal effects for shorter sleep duration on MI ($OR_{per\ additional\ h\ of\ sleep}$=0.86, 0.70-1.06, p=0.17; $OR_{short\ sleep}$=1.21, 1.08-1.37, p=1.47e-03; Figure 3). The overlap of the confidence intervals for the continuous sleep duration genetic instrument estimates in UKB was likely driven by low power, as the estimates for CAD (sample size n=17,157 cases/320,375 controls) did not overlap with the null (0.81, 0.68-0.97; Online Appendix Supplementary figure 1). Results from unweighted analyses and the control function estimator ($OR_{per\ additional\ h\ of\ sleep}$=0.84, 0.67-1.04) were similar.

## Mendelian randomization sensitivity analyses

The genetic instrument was associated with BMI (Online Appendix Online Table 11), consistent with either a confounding or mediating role for BMI. Using a genetic instrument adjusted for BMI in two-sample MR did not influence results ($OR_{per\ additional\ h\ of\ sleep}$=0.81, 0.65-0.99; Online Appendix Online Table 12). Similar results were obtained using an instrument controlling for insomnia and a range of lifestyle traits (Online Appendix Online Table 12). To further address confounding of SNP-sleep associations by occupation or prevalent disease, we used a genetic instrument from GWAS excluding shiftworkers or participants with a range of prevalent disease, including stroke and coronary disease; this also yielded similar effect estimates (Online Appendix Online Table 12).

Sensitivity analyses testing violations of the third MR assumption were consistent with the primary analysis, indicating that pleiotropy was likely not driving results (Online Appendix Online Table 9). The MR egger intercept test for horizontal pleiotropy was not significant ($p_{continuous\ sleep}$ = 0.23; $p_{short\ sleep}$ = 0.22). A single variant considerably distorted the weighted median and MR Egger estimates, and effects were more concordant with IVW estimates when this outlier was pruned (Online Appendix Online Table 10). Leave-one-out-analyis did not reveal outlier SNPs driving IVW associations (Online Appendix Online Figures 2-5).

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## Discussion

In this first MR analysis of sleep duration and coronary disease, we identified a potentially causal effect of short sleep duration on MI. Prospective observational analysis identified a dose-dependent contribution of short and long habitual sleep duration to the risk of incident MI independent of numerous confounders and sleep traits. Concomitant insomnia symptoms and difficulty getting up exacerbated this risk. Favorable sleep duration protected against MI independently of individual genetic predisposition to coronary disease. Altogether, our results highlight sleep as a modifiable and potentially causal risk factor for MI regardless of inherited risk and other sleep traits.

### Mendelian Randomization

MR analyses were consistent with a causal link between shorter sleep duration and MI, and were robust to numerous sensitivity analyses for confounding, horizontal pleiotropy, and reverse causality. Given that MR is a priori less susceptible to confounding and reverse causality, these results provide high-quality evidence supporting sleep duration as a potentially causal risk factor for MI. These findings, triangulated (34) with our robust prospective observational findings, are supported by a strong mechanistic basis, with pathways including metabolic disease (5), deranged sympathetic function (5), and impaired endothelial function (9). Direct comparison of genetic with observational estimates is limited given that inherited genetic variation influences exposures over the lifecourse, whereas observational associations capture phenotypes at one point in life. This potentially explains why MR demonstrated an effect for <7h sleep duration per night, whereas observational analyses showed an association for <6h per night. This causal evidence is timely, as recent work has demonstrated that sleep extension for short sleepers is a feasible intervention (35). However, randomized trials of sleep extension will be the most rigorous test of causality.

### Epidemiologic analyses

The second key contribution is the finding that a healthy sleep duration mitigates risk of MI even among those with high genetic liability. This is in line with previous work showing that a healthy lifestyle may mitigate inherited risk for CAD (15), with our results extending this finding to sleep health. Finally, we showed that the association of sleep duration with MI was independent of all other sleep traits and additively increased risk when comorbid with sleep disturbances. There was no evidence of interaction between sleep traits, implying that effects of individual sleep traits on coronary risk are unchanged by the presence or absence of other sleep traits. This is overall consistent with prior work (13), however we did not replicate a previously reported interaction between sleep quality and sleep duration (11).

### Limitations

We acknowledge limitations to our study. Residual confounding and reverse causality potentially explain observational associations, but have a smaller effect on MR analyses. For instance, while sleep apnea is a risk factor for CAD, its prevalence in the UKB is lower than in previous studies and is likely incompletely assessed (36). However, adjusting for a modified STOP-BANG sleep apnea risk scale did not influence results. As evidence against reverse causality, the CAD GRS was not associated with sleep duration, and results from

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lag-time analyses were largely unchanged. Results from MR sensitivity analyses utilizing sleep duration GWAS with exclusions for baseline comorbidities also indicated that our causal estimates were unlikely to be biased by confounding or reverse causality. Other limitations include the use of self-reported rather than objective sleep duration assessment (37), and selection of relatively healthy participants into UKB, which might induce collider bias (38). We did not have information on whether participants were lost to follow-up (e.g. emigration), which may have led to misclassification of cases as controls. If non-differential, this measurement error would likely bias results towards the null. Finally, generalizability of genetic analyses is limited to individuals of European ancestry.

## Conclusions

Altogether, triangulation of Mendelian randomization and observational analyses support short sleep duration as a potentially causal risk factor for MI, and a healthy sleep duration may mitigate MI risk among those at high genetic risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
|---|---|
| **MI** | myocardial infarction |
| **CAD** | coronary artery disease |
| **SNP** | single nucleotide polymorphism |
| **MR** | mendelian randomization |
| **GWAS** | genome-wide association study |
| **UKB** | UK Biobank |
| **GRS** | genetic risk score |
| **MVHR** | multivariable adjusted hazard ratio |

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## CLINICAL PERSPECTIVES

*Competency in Medical Knowledge:* Short duration of sleep increases the risk of developing acute myocardial infarction, and healthy sleep duration may be cardioprotective for people with a genetic predisposition to coronary disease.

*Translational Outlook:* Future research should investigate whether lengthening sleep can help prevent coronary events in short sleepers with cardiac risk factors.

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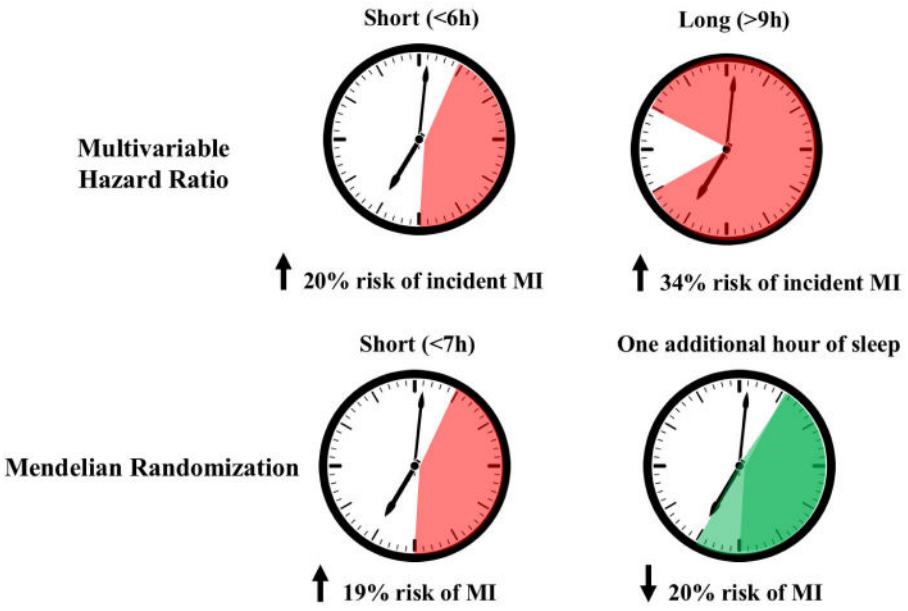


**Central illustration. Associations of sleep duration with coronary disease: Observational and 2-sample mendelian randomization.**

Magnitude of effects observed for effects of phenotypic and genetically varying sleep duration. Note, that while the clocks show variable sleep timing for short and long sleep, the observed effects are independent of self-reported sleep timing preference.

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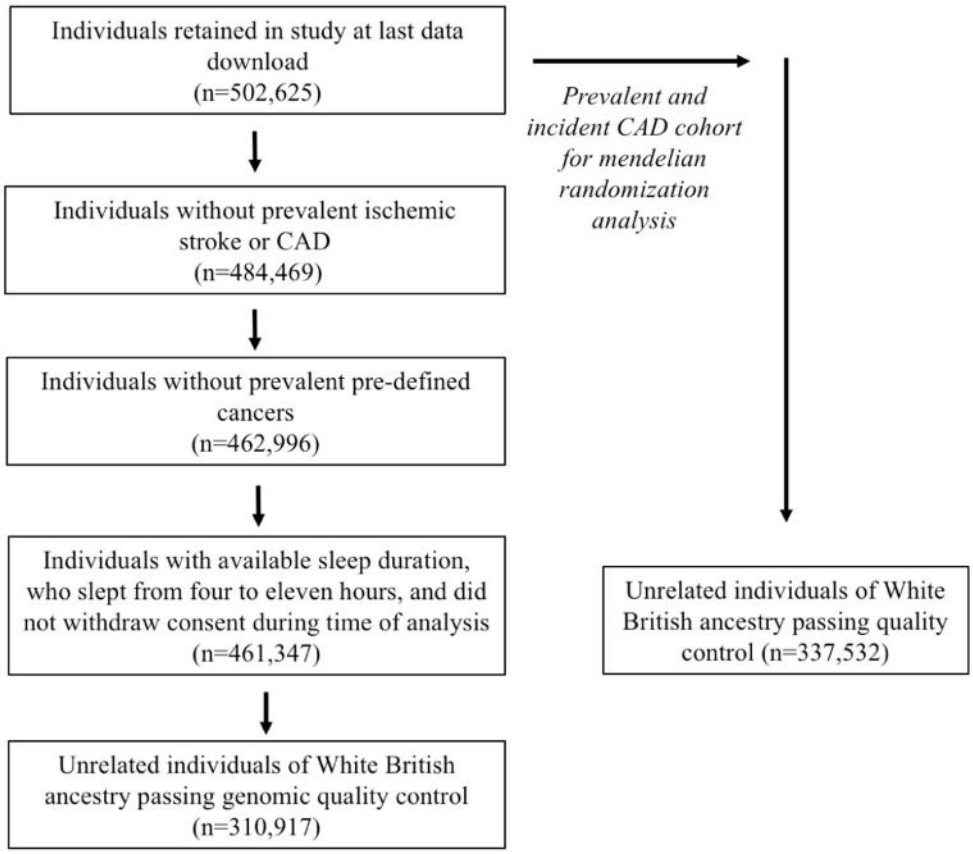


**Figure 1. Study sample flow diagram.**

Exclusions undertaken for creation of an incident MI (for epidemiologic analyses) and a combined prevalent/incident CAD cohort (for MR analyses). CAD: coronary artery disease; MI: myocardial infarction; MR: mendelian randomization.

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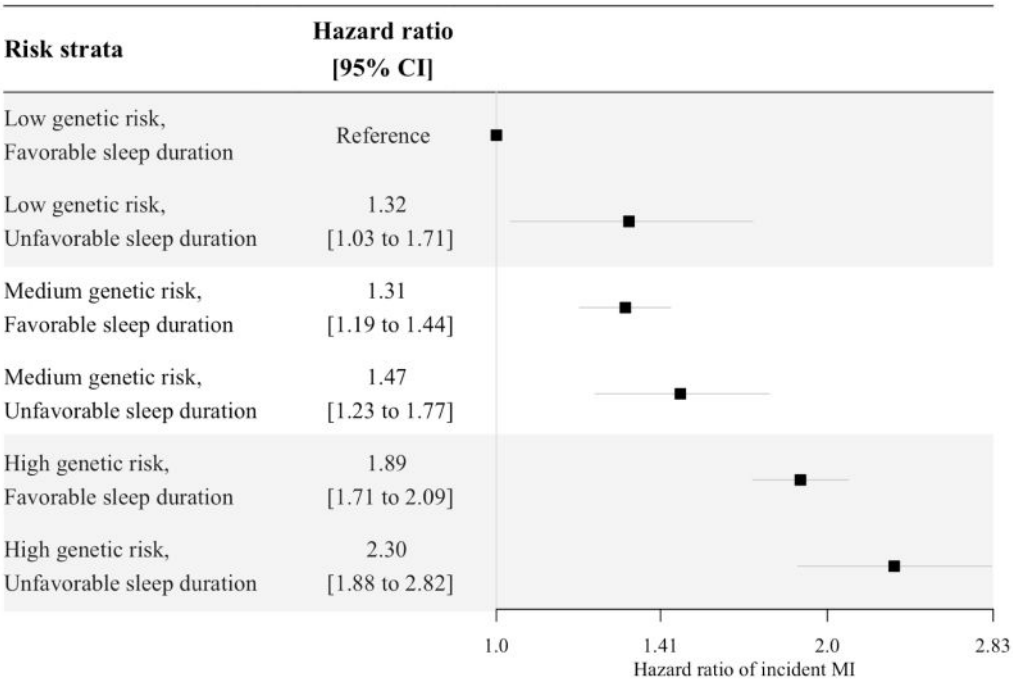


**Figure 2. Concomitant associations of sleep duration and CAD GRS with risk of incident MI (n=310,917).**

The comparator group is low genetic risk and favorable sleep duration. To maximize power, sleep durations of <6 or >9 hours per night were combined into 'unfavorable sleep,' and six to nine hours of habitual sleep duration was defined as 'favorable sleep.' Sleep and genetic liability additively increase risk, but do not have statistical interaction. Bars represent 95% CI. Low genetic risk: 1$^{st}$ quartile of CAD GRS; Medium genetic risk: 2$^{nd}$ and 3rd quartile of CAD GRS; High genetic risk: 4$^{th}$ quartile of CAD GRS; Favorable sleep duration: 6-9h; Unfavorable sleep duration: <6h or >9h. CAD: coronary artery disease; CI: confidence interval; GRS: genetic risk score; MI: myocardial infarction.

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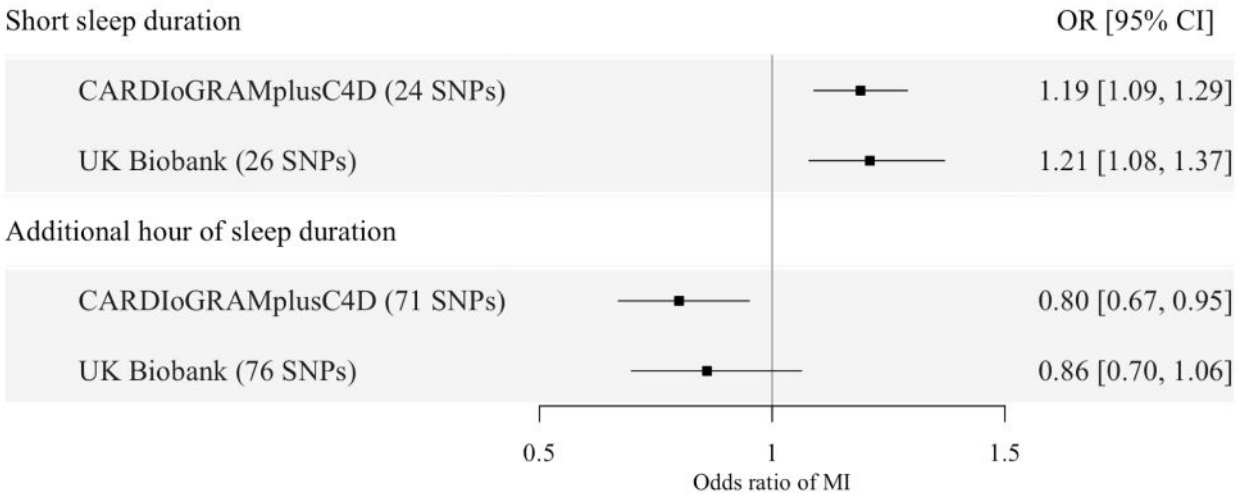


**Figure 3. MR estimates of short and continuous sleep duration against MI in CARDIoGRAMPlusC4D (n=43,676 cases / 128,199 controls) and in UKB (n=12,111 cases / 325,421 controls).**

Two-sample MR results reflect fixed-effects inverse variance weighted associations with MI risk. One-sample MR results reflect association of the weighted sleep genetic instrument with MI risk using individual-level data from UKB. Short sleep duration associations reflect the increase in MI risk concomitant with a doubling in the odds of short sleep duration. Continuous sleep duration associations reflect the effect of increasing sleep duration by 1 hour. CI: confidence interval; MI: myocardial infarction; OR: odds ratio; SNP: single nucleotide polymorphism.

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**Table 1**

Association of habitual sleep duration (in hours) with incident myocardial infarction in the UK Biobank (n=461,347).

| | Habitual sleep duration (hours) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **4** | **5** | **6** | **7-8** | **9** | **10** | **11** |
| Cases/person-years | 82/28,496 | 310/138,902 | 1,058/621,416 | 3,248/2,205,231 | 375/182,263 | 129/42,441 | 16/3,948 |
| Incidence rates per 1,000 person-years | 2.88 | 2.23 | 1.70 | 1.47 | 2.06 | 3.04 | 4.05 |
| Sample size | 4,120 | 20,023 | 89,189 | 315,055 | 26,217 | 6,166 | 577 |
| Unadjusted model: HR (95% CI) | **1.96** (1.57-2.43) | **1.52** (1.35, 1.70) | **1.16** (1.08, 1.24) | **1.00** (ref) | **1.40** (1.26, 1.56) | **2.07** (1.73, 2.46) | **2.78** (1.59, 4.51) |
| Model 1: Age-and sex-adjusted HR (95% CI) | **2.12** (1.70-2.64) | **1.58** (1.40-1.77) | **1.18** (1.10-1.26) | **1.00** (ref) | **1.24** (1.10-1.37) | **1.87** (1.57-2.24) | **2.79** (1.71-4.56) |
| Model 2: Model 1 + BMI and WHR HR (95% CI) | **1.93** (1.55-2.41) | **1.48** (1.32-1.66) | **1.14** (1.06-1.22) | **1.00** (ref) | **1.18** (1.06-1.32) | **1.69** (1.42-2.02) | **2.45** (1.50-4.00) |
| Model 3: MV adjusted * (95% CI) | **1.34** (1.07-1.68) | **1.19** (1.06-1.35) | **1.05** (0.98-1.13) | **1.00** (ref) | **1.07** (0.96-1.19) | **1.32** (1.11-1.58) | **1.87** (1.14-3.06) |

MV: multivariable, HR: hazard ratio, BMI: body mass index, WHR: waist-hip ratio

*Variables used for adjustment were age, sex, ethnicity, smoking status, frequency of alcohol consumption, history of heart disease in family, marital status, education, income, Townsend deprivation index, employment status, physical activity (MET/h-week), television watching, grip strength, BMI, waist-hip ratio (WHR), history of seeing provider for mental health, snoring, use of sleep medications, self-reported or medical record derived sleep apnea, and self-reported insomnia, probable type 2 diabetes, hypertension, use of blood pressure lowering medication, history of high cholesterol, use of cholesterol lowering medication, and use of aspirin.

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**Table 2.**

Association of habitual sleep duration with incident myocardial infarction by category of sleep duration (n=461,347).

| | Habitual sleep duration (hours) | | |
|---|---|---|---|
| | **<6** | **6-9** | **>9** |
| Total cases/person-years | 392/167,398 | 4,681/3,008,910 | 145/46,389 |
| Incidence rates per 1,000 person-years | 2.34 | 1.56 | 3.13 |
| Total sample size | 24,143 | 430,461 | 6,743 |
| ***Primary analyses*** | | | |
| Unadjusted model: HR (95% CI) | **1.51** (1.36, 1.67) | **1.00** (ref) | **2.01** (1.71, 2.37) |
| Model 1: Age- and sex-adjusted HR (95% CI) | **1.58** (1.43-1.76) | **1.00** (ref) | **1.85** (1.56-2.18) |
| Model 2: Model 1 + BMI and waist-hip ratio HR (95% CI) | **1.49** (1.34-1.65) | **1.00** (ref) | **1.68** (1.42-1.98) |
| Model 3: MV-adjusted HR [*](95% CI) | **1.20** (1.07-1.33) | **1.00** (ref) | **1.34** (1.13-1.58) |
| ***Secondary analyses*** | | | |
| Modelling continuous covariates using linear and quadratic terms [†] | **1.19** (1.07-1.33) | **1.00** (ref) | **1.34** (1.13-1.58) |
| Controlling for additional baseline comorbidities [‡] | **1.18** (1.06-1.32) | **1.00** (ref) | **1.32** (1.12-1.57) |
| ***Low-risk cohort (n=266,455)*** [§] | | | |
| Total cases/person-years | 103/80,650 | 1,506/1,770,536 | 35/19,765 |
| Total sample size | 11,551 | 252,054 | 2,850 |
| MV-adjusted HR (95% CI) | **1.37** (1.12-1.67) | **1.00** (ref) | **1.62** (1.15-2.27) |
| ***Lag-time analysis (n=460,232)*** [/] | | | |
| Total cases/person-years | 353/167,354 | 4,208/ 3,008,364 | 128/46,369 |
| Total sample size | 24,062 | 429,466 | 6,704 |
| MV-adjusted HR (95% CI) | **1.19** (1.06-1.33) | **1.00** (ref) | **1.31** (1.10-1.57) |

MV: multivariable; CI: confidence interval

[*]Variables used for adjustment were age, sex, ethnicity, smoking status, frequency of alcohol consumption, family history of heart disease, marital status, education, income, Townsend deprivation index, employment status, physical activity (MET/h-week), television watching, grip strength, BMI, waist-hip ratio, history of seeing provider for mental health, snoring, self-reported/medical record derived sleep apnea, self-reported insomnia, probable type 2 DM, hypertension, history of high cholesterol, and use of: antihypertensive, cholesterol medication, aspirin, or sleep medication.

[†]Model 3 with quintiles replaced with of linear and quadratic terms for continuous covariates.

[‡]Additional chronic conditions: hypothyroidism, hyperthyroidism, migraines, rheumatoid arthritis, osteoarthritis, deep vein thrombosis, and chronic obstructive pulmonary disease.

[§]Excluded participants with baseline hypertension, high cholesterol, probable type 2 DM, self-reported angina, current smokers, or use of antihypertensives, cholesterol medication, or aspirin.

[/]Follow-up was started one year after enrollment, with exclusion of deaths or myocardial infarctions taking place during the first year.