Longer sleep duration may negatively affect renal function

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Abstract

Background Observational studies evaluating the link between sleep duration and kidney function reported controversial results. In the present study, Mendelian randomization analysis was applied to obtain unconfounded estimates of the casual association of genetically determined sleep duration with estimated glomerular filtration rate and the risk of chronic kidney disease.

Methods Data from the largest genome-wide association studies on self-reported and accelerometer-derived sleep duration, estimated glomerular filtration rate and chronic kidney disease were analysed in total, as well as separately in diabetic and non-diabetic individuals. Inverse variance weighted (IVW) method, weighted median-based method, MR-Egger and MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) were applied, as well as the leave-one-out method to rule out the impact of single single-nucleotide polymorphism.

Results Individuals with genetically longer self-reported sleep duration had a higher chronic kidney disease risk (IVW: \( \beta = 0.358, p = 0.047 \)). Furthermore, in non-diabetics, longer self-reported sleep duration was negatively associated with estimated glomerular filtration rate (IVW: \( \beta = -0.024, p = 0.020 \)). Similarly, accelerometer-derived sleep duration was negatively related to estimated glomerular filtration rate in the total population (IVW: \( \beta = -0.019, p = 0.047 \)) and then on-diabetic individuals. No significant association was found between self-reported sleep duration and estimated glomerular filtration rate in the whole population and type-2 diabetes mellitus patients. None of the estimated associations was subjected to a significant level of heterogeneity. MR-PRESSO analysis did not show any chance of outliers for all estimates. The pleiotropy test also indicated low chance of pleiotropy. The leave-one-out method demonstrated that the links were not driven by single-nucleotide polymorphisms.

Conclusions For the first time, the present study shed a light on the potential harmful effects of longer sleep duration (measured both objectively and subjectively) on kidney function. This finding was observed in the total population and in non-diabetic individuals, but not in those with diabetes. Further research is needed to elucidate the links between sleep duration, estimated glomerular filtration rate and the risk of chronic kidney disease.

Keywords Mendelian randomization · Sleep duration · Chronic kidney disease · Estimated glomerular filtration rate

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Introduction

Adequate sleep is crucial for the regulation of body metabolism and various physiological functions [1]. Observational studies have previously reported that sleeping patterns are closely linked to morbidity and mortality [2, 3], as well as with chronic metabolic disorders, including type 2 diabetes mellitus (T2DM), respiratory diseases, hypertension and obesity [4–8]. Considering the harmful effects of short sleep duration on glucose and insulin homeostasis, it has been suggested that sleep duration may also influence renal function [9–15]. Furthermore, animal studies showed that the majority of kidney physiological mechanisms (such as the regulation of the renin–angiotensin system, sodium reabsorption, renal blood flow, glomerular filtration, and filtration fraction) are related to the diurnal rhythm [16].

Although the effects of sleep duration on several diseases have been studied, its association with chronic kidney disease (CKD) has not been widely evaluated and the available results are still controversial [9–15]. In this context, a higher risk of CKD has been reported mainly for individuals with shorter sleep duration [9]. In a prospective cohort of 4238 participants from the Nurse Health Study over an 11-year period, shorter sleep duration was associated with a rapid decline in estimated glomerular filtration rate (eGFR) [11]. Moreover, in another prospective study of 6834 Japanese individuals, short sleep duration (≤ 6 h per night) was a predictor of proteinuria [12]. On the other hand, a population-based study of Malay and Indian adults with diabetes showed that long sleep duration (> 8 h per night) was linked to lower eGFR [13]. In the same study, both long (> 8 h) and very short (< 5 h) duration of sleep were associated with albuminuria [13]. Of note, a previous meta-analysis found a direct association of short sleep duration with proteinuria (but not with the risk of CKD) [10]. In another study, a significant association between short sleep duration and higher risk for diabetic nephropathy has been reported [15].

Methods

Study design

A two-sample MR study design was used. Summary statistics were obtained from the largest genome wide association studies (GWAS) on sleep duration and interested outcomes. We applied methods to estimate the unbiased effect of sleep duration on eGFR and the risk of CKD (defined as eGFR < 60 ml/min/1.73 m²).

Genetic instruments for sleep duration

Genotyping, quality control, and imputation procedures in the UK Biobank (UKB) are described elsewhere [19]. From the largest GWAS, 78 SNPs were identified to be associated with sleep duration (self-reported) among individuals of European ancestry (n = 446,118) (Table 1). More information can be found elsewhere [20].

The GWAS performed in the UK Biobank for the accelerometer-driven sleep duration data (an hour increase of nocturnal sleep duration) to be compared with causal estimates obtained using genetic variants associated with self-reported sleep duration. Further details on this process can be found elsewhere [21]. If a single-nucleotide polymorphism (SNP) was unavailable for the outcome GWAS summary statistics, we identified proxy SNPs with a minimum linkage disequilibrium (LD) $r^2 = 0.8$. To minimize bias in effect estimates induced by correlation between SNPs, we restricted our genetic instrument to independent SNPs not in linkage disequilibrium ($p = 0.0001$). We refer to a set of SNPs that proxy sleep duration as “genetic instruments.”

Association of genetic instruments with outcome

Genetic associations with renal function were obtained from the largest available extensively genotyped study based on a meta-analysis (n = 133,413 individuals with replication in up to 42,166 individuals) [22]. eGFR was estimated using the four-variable modification of diet in renal disease (MDRD) Study equation [22]. CKD was defined as eGFR < 60 ml/min/1.73 m². T2DM was defined as fasting glucose ≥ 126 mg/dl, antidiabetic drug treatment or by self-reports. Kidney function and T2DM were assessed simultaneously.

For GWAS analysis, a centralized analysis plan was applied with each study regressing sex- and age-adjusted residuals of the logarithm of eGFR on SNP dosage levels. Furthermore, logistic regression of CKD was performed on SNP dosage levels adjusting for sex and age. For all traits, adjustment for appropriate study-specific features, such as study site and genetic principal components, was included.
We combined the effect of five instruments using inverse
variance weighted (IVW) method as implemented in the
two sample MR package running under R [version 3.4.2 R
Core Team (2017)]. We assessed the heterogeneity using
Q value for IVW. To address potential effect of pleiotropic
variants on the final effect estimate, we performed a sen-
sitivity analysis including weighted median (WM) and
MR-Egger. Sensitivity analysis was conducted using the
leave-one-out method to identify instruments that might
drive the MR results. The WM estimate provides correct
estimates as long as SNPs accounting for ≥ 50% of the
weight are valid instruments. Inverse variance is used to
weight the variants and bootstrapping is applied to esti-
mate the confidence intervals (CIs) [23]. MR-Egger has an
ability to make estimates even under the assumption that
all SNPs are invalid instruments, as long as the assump-
tion of instrument strength independent of direct effect
(InSIDE) is satisfied [23]. However, the InSIDE assump-
tion cannot be easily verified. Average directional plei-
otropy across genetic variants was assessed from the p
value of the intercept term from MR-Egger [23]. Causal

### Table 1

| SNP | GX | GX SE | EA | OA | EAF |
|-----|----|-------|----|----|-----|
| rs3095508 | 0.015352 | 0.002304 | C | A | 0.593529 |
| rs11643715 | −0.0139 | 0.002497 | C | G | 0.709058 |
| rs9940646 | 0.016946 | 0.002291 | C | G | 0.577569 |
| rs7503199 | 0.014745 | 0.002564 | C | T | 0.734267 |
| rs1991556 | 0.016566 | 0.002724 | G | A | 0.773765 |
| rs12607679 | 0.020139 | 0.002593 | T | C | 0.737717 |
| rs10421649 | −0.0133 | 0.002295 | T | A | 0.44303 |
| rs2072727 | 0.013243 | 0.002285 | T | C | 0.43617 |

**EA** effect allele, **OA** other allele, **EAF** effect allele frequency, **GX** the per-allele effect on standard deviation units of the telomere length, **GX SE** standard error of **GX**

in the regression and family studies appropriately
counted for relatedness.

**MR analysis**

We combined the effect of five instruments using inverse
variance weighted (IVW) method as implemented in the
two sample MR package running under R [version 3.4.2 R
Core Team (2017)]. We assessed the heterogeneity using
Q value for IVW. To address potential effect of pleiotropic
variants on the final effect estimate, we performed a sen-
sitivity analysis including weighted median (WM) and
MR-Egger. Sensitivity analysis was conducted using the
leave-one-out method to identify instruments that might
drive the MR results. The WM estimate provides correct
estimates as long as SNPs accounting for ≥ 50% of the
weight are valid instruments. Inverse variance is used to
weight the variants and bootstrapping is applied to esti-
mate the confidence intervals (CIs) [23]. MR-Egger has an
ability to make estimates even under the assumption that
all SNPs are invalid instruments, as long as the assumption
of instrument strength independent of direct effect
(InSIDE) is satisfied [23]. However, the InSIDE assump-
tion cannot be easily verified. Average directional plei-
otropy across genetic variants was assessed from the p
value of the intercept term from MR-Egger [23]. Causal
estimates in MR-Egger are less precise than those obtained by IVW MR [24]. Analysis using MR-Egger has a lower false-positive rate but a higher false-negative rate than IVW, i.e. it has a lower statistical power [25].

To assess heterogeneity between individual genetic variant estimates, we performed the Q’ heterogeneity statistic [26] and the MR pleiotropy residual sum and outlier (MR-PRESSO) test [26]. The Q’ statistic uses modified second-order weights that are a derivation of a Taylor series expansion and consider the uncertainty in both numerator and denominator of the instrumental variable ratio [26]. The MR-PRESSO framework detects effect estimates that are outliers and removes them from the analysis. This is done by regressing the variant-outcome associations on variant-exposure associations. A global heterogeneity test is then implemented, comparing the observed distance between residual sums of squares of all variants to the regression line with the distance expected under the null hypothesis of no pleiotropy [27]. Furthermore, we applied on MR-Robust Adjusted Profile Score (RAPS); this method is able to correct for pleiotropy using robust adjusted profile scores. RAPS can provide an unbiased causal estimate in the presence of weak instruments. We consider as results causal estimates that agreed in direction and magnitude across MR methods, passed nominal significance in IVW MR and did not show any evidence of bias from horizontal pleiotropy using heterogeneity tests. To assess the instrumental variable analysis “exclusion-restriction” assumption, we used Ensembl release (https://useast.ensembl.org/index.html) that contains a base of SNP phenotypes.

**Ethics**

This investigation uses published or publicly available summary data with no further involvement of participants. No original data were collected for this study. Ethical approval for each of the studies included in the analyses can be found in the original publications (including informed consent from each participant). The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

**Results**

**Mendelian randomization (MR) analysis**

The list of all instruments’ associations for sleep duration (subjective and objective) is shown in Table 1. The results, expressed as \( \beta \)-coefficient for sleep duration per 1 standard deviation (SD) increase in outcomes, are presented in Table 2 (for self-reported sleep duration) and Table 3 (for accelerometer-derived sleep duration). With regard to the self-reported sleep duration, individuals with longer sleep duration had a greater risk of CKD (IVW: \( \beta = 0.358 \), \( p = 0.047 \)) in the total population. A significant link between longer self-reported sleep duration and lower eGFR was also observed but only

### Table 2 Results of the Mendelian randomization (MR) analysis for all exposures (for self-reported sleep duration)

| Exposures | MR | Method | Beta | SE  | \( p \) | Heterogeneity | Method | \( Q \) | \( p \) value | Pleiotropy | Intercept | SE | \( p \) |
|-----------|----|--------|------|-----|------|--------------|--------|------|-----------|------------|-----------|----|-----|
| CKD       |     | MR-Egger | 0.9034 | 0.6866 | 0.1966 | MR-Egger | 45.34 | 0.1368 | -0.0093 | 0.011 | 0.415 |
| WM        |     | 0.4764 | 0.2685 | 0.07603 | | | | | | | |
| IVW       |     | 0.3583 | 0.1856 | 0.047 | | | | | | | |
| RAPS      |     | 0.4413 | 0.1941 | 0.02299 | | | | | | | |
| eGFR      |     | MR-Egger | -0.0409 | 0.03856 | 0.2959 | MR-Egger | 45.05 | 0.1434 | 0.00038 | 0.00064 | 0.562 |
| Total     |     |     |     |     |     |     | | | | | |
| Non-DM    |     | MR-Egger | -0.06524 | 0.04006 | 0.1121 | MR-Egger | 42.11 | 0.2235 | 0.000069 | 0.00066 | 0.302 |
| WM        |     | -0.03157 | 0.01585 | 0.04633 | | | | | | | |
| IVW       |     | -0.02476 | 0.01066 | 0.02016 | | | | | | | |
| RAPS      |     | -0.02577 | 0.01084 | 0.01744 | | | | | | | |
| DM        |     | MR-Egger | 0.04857 | 0.1499 | 0.7478 | MR-Egger | 37.96 | 0.3801 | -0.00035 | 0.0025 | 0.888 |
| WM        |     | 0.02369 | 0.06189 | 0.7019 | | | | | | | |
| IVW       |     | 0.02804 | 0.04007 | 0.4841 | | | | | | | |
| RAPS      |     | 0.02957 | 0.04148 | 0.4759 | | | | | | | |

WM weighted median, IVW inverse variance weighted, SE standard error, \( \beta \) beta-coefficients, MR Mendelian randomization, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, T2DM type 2 diabetes mellitus
Table 3 Results of the mendelian randomization (MR) analysis for all exposures (for accelerometer derived sleep duration)

| Exposures | MR | Heterogeneity | Pleiotropy |
|-----------|----|---------------|------------|
|           | Method | Beta | SE  | p    | Method | Q  | p value | Intercept | SE  | p     |
| CKD       | MR-Egger | 1.557 | 0.7086 | 0.07938 | MR-Egger | 2.765 | 0.7362 | −0.066 | 0.028 | 0.0665 |
|           | WM   | 0.1731 | 0.2271 | 0.4459 |           |     |        |        |      |       |
|           | IVW  | −0.04924 | 0.204 | 0.8093 |           |     |        |        |      |       |
|           | RAPS | −0.01708 | 0.2092 | 0.9349 |           |     |        |        |      |       |
| eGFR Total| MR-Egger | −0.03524 | 0.04022 | 0.421 | MR-Egger | 1.4 | 0.9243 | 0.00065 | 0.0016 | 0.706 |
|           | WM   | −0.01553 | 0.01165 | 0.1824 |           |     |        |        |      |       |
|           | IVW  | −0.01969 | 0.01 | 0.04702 |           |     |        |        |      |       |
|           | RAPS | −0.01978 | 0.01038 | 0.05679 |           |     |        |        |      |       |
| eGFR Non-DM| MR-Egger | −0.03565 | 0.04178 | 0.4325 | MR-Egger | 2.015 | 0.847 | 0.00043 | 0.0017 | 0.808 |
|           | WM   | −0.02424 | 0.01263 | 0.055 |           |     |        |        |      |       |
|           | IVW  | −0.02527 | 0.01038 | 0.01486 |           |     |        |        |      |       |
|           | RAPS | −0.02541 | 0.01082 | 0.01891 |           |     |        |        |      |       |
| eGFR DM   | MR-Egger | −0.2975 | 0.1684 | 0.1377 | MR-Egger | 4.758 | 0.4461 | 0.011 | 0.0068 | 0.153 |
|           | WM   | −0.01371 | 0.05743 | 0.8113 |           |     |        |        |      |       |
|           | IVW  | −0.02287 | 0.04688 | 0.6256 |           |     |        |        |      |       |
|           | RAPS | −0.02561 | 0.04763 | 0.5908 |           |     |        |        |      |       |

WM weighted median, IVW inverse variance weighted, SE standard error, beta beta-coefficients, MR mendelian randomization, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, DM diabetes

Among non-diabetics (IVW: $\beta = -0.024, p=0.020$). No significant association was found between self-reported sleep duration and eGFR in the whole population (IVW: $\beta = -0.019, p=0.072$) and T2DM patients (IVW: $\beta = 0.028, p=0.484$).

With regard to the accelerometer-derived sleep duration, individuals with longer sleep duration had a lower eGFR both in the total population (IVW: $\beta = -0.019, p=0.047$) and the non-diabetics (IVW: $\beta = -0.022, p=0.014$), but not among T2DM patients (IVW: $\beta = -0.022, p=0.625$). Furthermore, there was no significant link between sleep duration and the risk for CKD in the total population, the non-diabetics and the T2DM group.

None of the IWV estimates showed heterogeneity. MR-PRESSO analysis did not show any possibility of outlier for all of the estimates. The pleiotropy test, with very negligible intercept and insignificant p value, also indicated low chance of the pleiotropy for all of our estimations (all $p > 0.539$). The results of the MR-RAPS were identical with the IVW estimates, highlighting again a low likelihood of pleiotropy. The results of the leave-one-out method demonstrated that the links were not driven by single SNPs.

Discussion

In the present study, we performed a MR analysis to evaluate the impact of sleep duration on the risk of CKD and renal function indexes in a casual mode. Potential harmful effects of longer sleep duration (measured both objectively and subjectively) on kidney function were found. This finding was observed in the total population and in non-diabetic individuals, but not in those with T2DM, with low level of the heterogeneity and chance of pleiotropic.

There are several plausible mechanisms regarding the association of sleep duration with renal function that need to be further elucidated. Most renal physiological processes follow a circadian rhythm, including the regulation of sodium excretion, renin–angiotensin system and blood pressure [28]. Therefore, disruption in sleeping patterns (short or long sleep duration) may negatively affect this chronobiological process and lead to renal dysfunction. In this context, disruption in cyclic behavioural patterns in animal models was associated with proteinuria, glomerulosclerosis, tubular hyperplasia, and renal fibrosis [29]. Furthermore, sleeping 5 h or fewer per night was more related to the development of hypertension and T2DM during a 10-year follow-up period compared with sleeping 7 h per night [5, 30]. In short term studies, lasting 3–6 weeks, sleep duration was a modifiable predictor of insulin resistance and blood pressure [31, 32]. Short sleep duration was associated with a rapid decline in renal function independently of established CKD risk factors such as blood pressure and insulin resistance [11]. Moreover, sleep duration may affect the levels of pro-inflammatory markers such as interleukin-6 and C-reactive protein [33, 34] that play an important role in CKD pathogenesis [35]. Obstructive sleep apnea (OSA)
has been linked to the risk of CKD [36, 37] via enhanced sympathetic activation, oxidative and nitrosative stress, and impaired microvascular and endothelial function in T2DM patients, leading to renal dysfunction [38, 39]. Taking into consideration the association between sleep duration and OSA [40], sleep duration may also affect the risk for CKD development via this pathway.

A few studies investigated the relationship between sleep duration and CKD with controversial results. Cross-sectional studies have previously reported that advanced CKD can lead to a higher prevalence of several sleep disorders, including reversal of day–night sleep patterns, increased sleep latency, and fragmented sleep related to sleep apnea or restless leg syndrome [9]. In this context, shorter sleep duration (i.e. < 5 h) measured by actigraphy was significantly more prevalent in non-dialysis dependent CKD and end-stage renal disease (ESRD) patients compared with individuals with normal kidney function [41]. Ohkuma et al. [14] reported that both short and long sleep duration were associated with higher UACR (urinary albumin-to-creatinine ratio) and albuminuria. Moreover, consistent with our observations, lower eGFR correlated with long sleep duration independently of potential confounders [14]. In a population-based cross-sectional study of 1258 T2DM patients (aged 40–80 years), long sleep duration (> 8 h) was associated with renal insufficiency compared with normal sleep duration (7–8 h) [13]. In the same study, both long and very short duration of sleep (< 5 h) were linked with albuminuria; after adjusting for potential confounders, only long sleep duration remained significantly related to 2.3-fold higher odds of low eGFR [13]. Another study of 6834 Japanese adults (aged 20–65 years) reported that proteinuria was more frequently developed in individuals who slept 6 or fewer hours than those who slept for 7–8 h per night; however, eGFR did not differ between these individuals [12]. Similarly, sleep parameters were not associated with a 5-year change in eGFR in a prospective study of 463 adults (aged 32–51 years) [42]. However, each 1 h decrease in sleep duration was significantly related to a 1.5 ml/min/1.73 m² higher eGFR [42].

In contrast to our results, a systematic review and meta-analysis of 6 observational studies with 252,075 individuals and 3 observational studies with 37,197 participants reported a positive significant association between short sleep duration and proteinuria, but no association between short sleep duration and CKD [10]. In another study, short (but not long) sleep duration was related to diabetic CKD (DKD), defined as the presence of albuminuria and eGFR < 60 ml/min/1.73 m² [15]. Furthermore, a prospective cohort study of 4238 individuals from the Nurse Health Study over an 11-year period reported that shorter sleep duration was associated with a rapid reduction in eGFR [11]. Of note, women who slept 5 h or less per night experienced the quickest decline in renal function, whereas the slowest rate of decline was observed in those who reported sleeping 7–8 h per night [11]. Moreover, albuminuria was twice as prevalent among those who slept 5 or fewer hours per night compared with those who reported 7–8 h of sleep per night [11]. However, some limitations should be considered for this study. First of all, sleep duration was collected 3 years prior to initial eGFR measurement. Second, the U-shaped association between sleep duration and rapid decline in renal function was not assessed due to the limited number of individuals reporting sleep duration of 9 h or more [11]. Third, the study population was limited to women, and most individuals were white. Therefore, findings cannot be applied to men and other racial groups.

The present study has several strengths, e.g. the possibility of reverse causation was minimized, genotypes were assumed to be randomly distributed with respect to confounders, the ability to perform an array of sensitivity analyses was enhanced by the use of pleiotropy-robust methods. There are also certain limitations, including the inability to thoroughly evaluate individual-level confounding factors and horizontal pleiotropy.

In conclusion, potential harmful effects of longer sleep duration (measured both objectively and subjectively) on kidney function was observed in a casual mode in the present MR analysis. This finding was observed both in total population and non-diabetic individuals, but not in those with T2DM. Further research is needed in this field to elucidate the associations between sleep duration and renal function.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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