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SCIENTIFIC INVESTIGATIONS

The association between sleep characteristics and the risk of all-cause mortality among individuals with cardiometabolic multimorbidity: a prospective study of UK Biobank

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Study Objectives: To investigate the implications of both sleep factors and sleep patterns on the prognosis of cardiometabolic multimorbidity.

Methods: From UK Biobank, individuals with cardiometabolic multimorbidity , defined as the coincidence of at least 2 cardiometabolic diseases (hypertension, diabetes mellitus, coronary heart disease, and stroke) were included in this study. Four low-risk sleep factors, including early chronotype, sleep 7–8 h/d, free of insomnia, and no frequent excessive daytime sleepiness, were used to generate a healthy sleep score ranging from 0 to 4. Participants with a score of 0–1, 2, 3–4 were clustered into groups with poor, intermediate, and healthy sleep pattern, respectively. We assessed the adjusted hazard ratios and 95% confidence intervals for all-cause mortality using the Cox proportional hazards model.

Results: Among included 35,757 participants, the mean age (standard deviation)) was 61.82 (6.3) years. After full adjustment, early chronotype, sleep 7–8 h/d, no frequent excessive daytime sleepiness, and free of insomnia were independently associated with 8%, 12%, 11%, and 8% lower risk of all-cause mortality among all persons with cardiometabolic multimorbidity. We found the fully adjusted hazard ratio (95% confidence interval) for all-cause mortality was 0.90 (0.88–0.92) for a 1-point increase in the healthy sleep score. Compared with the reference group, participants with the intermediate and healthy sleep pattern had 9% and 23% lower risk of all-cause death, respectively, in the fully adjusted model.

Conclusions: A healthy sleep pattern combining 4 low-risk sleep factors could be regarded as a healthy lifestyle for individuals with cardiometabolic multimorbidity to lower the risk of all-cause mortality.

Keywords: cardiometabolic multimorbidity, sleep pattern, mortality, UK Biobank

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The high prevalence and poor prognosis of cardiometabolic multimorbidity has been rising as a global issue of public health. The implication of sleep behaviors, including sleep factors and sleep patterns, on the prognosis of cardiometabolic multimorbidity is not clear yet.

Study Impact: Our results indicated that 4 low-risk sleep factors and a healthy sleep pattern were associated with lower risks of all-cause mortality among patients with cardiometabolic multimorbidity. These findings emphasized the importance of healthy sleep again and suggested that a healthy sleep pattern combining the 4 low-risk sleep factors could be regarded as a healthy lifestyle for individuals with cardiometabolic multimorbidity to lower the risk of all-cause mortality.

INTRODUCTION

The prevalence of cardiometabolic multimorbidity (CMM), co-occurrences of ≥ 2 cardiometabolic diseases (CMDs) (including hypertension, diabetes mellitus [DM], and coronary heart disease [CHD] in our study), has been rising rapidly.[1–3] Evidence suggests that CMM is associated with a poor prognosis of coronavirus disease 2019 (COVID-19).[4] In addition, several large-scale cohort studies found that CMM cumulatively increased the risk of all-cause mortality.[2,5–7] However, despite the increasing prevalence and poor prognosis of CMM, interventions to improve outcomes is limited. Only a few studies have explored the association of common factors, including social status, lifestyles, and clinical profiles, with the risk of mortality among patients with CMM, as most studies have focused on single-disease–related outcomes.[8,9] Potential effects of other modifiable and important factors, including sleep, on the prognosis of CMM remain unclear.

The importance of healthy sleep behaviors to physical and mental health has been gradually recognized. Several studies have demonstrated that some sleep factors, including short or long sleep duration,[10–13] insomnia,[14,15] late chronotype,[16] and excessive daytime sleepiness,[17] are related to the higher mortality risk in the general population or patients with single CMD. However, the role of these high-risk sleep factors in the prognosis of CMM remains to be examined. Furthermore, it is inappropriate to directly assume the same implications of these sleep factors in the condition of CMM, since evidence has suggested that clinical profiles, lifestyle, and socioeconomic factors exhibit distinct effects on different processes, from healthy status to the first CMDs, CMM, and mortality.[8,9] In addition, sleep is a multidimensional

concept, and a sleep pattern combining various sleep behaviors collectively would better reflect the whole sleep condition.[18] In the literature, the protective roles of proper sleep duration, no insomnia, early chronotype, and no frequent excessive daytime sleepiness on all-cause mortality among the general population have been determined and accepted, as mentioned above. Whether a composite healthy sleep pattern generated by these 4 common low-risk sleep characteristics has the same implications for the prognosis of CMM also needs to be further investigated.

Therefore, based on the UK Biobank study, we explored the associations of 4 sleep factors and sleep patterns with the risk of all-cause mortality among individuals with CMM.

METHODS

Data and participants

UK Biobank is an open-access database, which is globally accessible to approved researchers. Detailed information about UK Biobank has been provided in previous studies.[19] Briefly, UK Biobank recruited > 500,000 people across the United Kingdom from 2006 to 2010. Detailed information on demographics, lifestyles, anthropometry, clinical profiles, and biological samples of participants were collected and thereafter linked to their medical records with written informed consents. UK Biobank was approved by the National Health Service and National Research Ethics Service. Our research was conducted using the UK Biobank Resource under project number 76118. Data from 502,414 participants was accessible to our study.

At baseline, we included participants with CMM (n = 41,578), which was defined as the coexistence of at least 2 CMDs, including hypertension, DM, CHD, and stroke. Participants with missing data on sleep duration, insomnia, chronotype, and daytime sleepiness (n = 5,821) were excluded. Finally, a total of 35,757 participants with CMM remained in our study for the main analyses. For the specific CMM patterns, there were 11 different combinations of the 4 CMDs, which are summarized in **Table S1** in the supplemental material. After excluding specific CMM patterns reported by < 3,000 participants, we categorized participants into 4 patterns: (1) hypertension + DM, (2) hypertension + CHD, (3) hypertension + stroke, and (4) hypertension + DM + CHD.

Measures

Ascertainment of CMDs

The occurrences of these diseases were ascertained based on self-reported information (diagnoses by physicians, medication history, and operation history) and medical records (inpatient diagnoses coded by the *International Classification of Diseases, Ninth Revision* [ICD-9], ICD-10, and operations coded by the Office of Population Censuses and Surveys Classification of Interventions and Procedures, Version 4 [OPCS-4]). Detailed definitions of CMDs, including hypertension, DM, CHD, and stroke, are provided in **Table S2**. For an individual with a specific CMD, if the earliest available date of diagnosis was before the date of recruitment, they were considered to have this disease at baseline.

Assessment of exposure

This study included 4 self-reports of sleep behaviors recorded via touchscreen questionnaires: chronotype, sleep duration, sleeplessness/insomnia, and daytime sleepiness. For chronotype, participants were asked, "Do you consider yourself to be: (1) definitely a 'morning' person; (2) more a 'morning' person than 'evening' person; (3) more an 'evening' person than a 'morning' person; (4) definitely an 'evening' person". For sleep duration, participants were asked how many hours of sleep, including naps, do you get every 24 hours?". For sleeplessness/insomnia, participants were asked, "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" with several choices provided: (1) never or rarely; (2) sometimes; (3) usually. For excessive daytime sleepiness, participants were asked, "How likely are you to doze off or fall asleep during the daytime when you do not mean to? (eg, when working, reading, or driving)", with multiple choices provided: (1) never or rarely; (2) sometimes; (3) often; (4) all of the time.

Early chronotype (definitely a "morning" person or "morning" than "evening" person), sleep 7–8 h/d, free of insomnia ("never/rarely"), and no frequent excessive daytime sleepiness ("never/rarely" or "sometimes") were defined as low-risk sleep factors. These 4 low-risk sleep factors were used to generate a healthy sleep score ranging from 0 to 4 (1 point was given for each low-risk sleep factor). Then, participants were clustered into the groups poor, intermediate, and healthy sleep pattern corresponding to the healthy sleep score of 0–1, 2, 3–4, respectively.

Ascertainment of outcomes

The primary outcome of this study was all-cause mortality. Information on death dates was derived via linkages to the National Health Service (NHS) Information Centre in England, Wales, and the NHS Central Register in Scotland.

Assessment of covariates

Covariates including sociodemographic characteristics, lifestyle factors, and clinical profiles were documented using touchscreen questionnaires, verbal interview records, and physical measures at recruitment. Sociodemographic characteristics included age, sex (male/female), race (White/non-White), and Townsend Deprivation Index (TDI), a composite measure of deprivation based on unemployment, non–car ownership, non–home ownership, and household overcrowding. A positive value of TDI indicates low socioeconomic status.[20] Lifestyle factors included smoking status (current/past or never), alcohol consumption, physical activity, and diet. Based on responses to questions regarding alcohol intake frequency over the last year, participants were classified as never, special occasions only, once or twice a week, 3 or 4 times a week, and daily or almost daily. Further, we categorized the participants as never or occasionally drinkers (never, special occasions only, and once or twice a week) vs usually drinkers (3 or 4 times a week and daily or almost daily). For physical activity, participants were dichotomized according to whether they met the 2019 UK Physical Activity Guidelines (150 minutes of walking or moderate activity per week or 75 min of vigorous activity).[21] For those who responded that their weekly frequency of walking/moderate/vigorous physical activity was 10+ minutes,

we conservatively substituted the corresponding duration with 10 minutes to partly offset the exclusion of participants with missing data in the physical activity questionnaires. We used the American Heart Association Guidelines to assess each participant's diet condition at baseline (see **Table S3**). A healthy diet was considered if ≥ 2 healthy food items were consumed.[22] Clinical profiles included body mass index (BMI) and use of antihypertensives, cholesterol-lowering drugs, aspirin, and mental/sleep medication. BMI (kg/m^2) was calculated as body weight in kilograms divided by height in meters squared. Detailed information on mental/sleep medication use is provided in **Table S4**.

Statistical analysis

Percentages of missing values of covariates were less than 5%. We did multiple imputation for all missing values. Baseline characteristics are expressed as mean (standard deviation [SD]) or number (percentage) in each category of the 3 groups. We used the Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI). Follow-up time was used as the timescale, calculated from the recruitment date to the date of death or June 1, 2021, whichever came first. We examined the proportional hazards assumption using Kaplan-Meier survival curves and found no evidence suggesting deviation from this assumption. Three models were used to assess the association between specific exposure and all-cause mortality. Model 1 was adjusted for age and sex. Model 2 was further adjusted for race, TDI, smoking status, alcohol consumption, diet, and physical activity. Model 3 was additionally adjusted for BMI. Analyses of the association between sleep characteristics and the outcome were performed in 2 steps. First, we estimated the associations of the 4 low-risk sleep factors with all-cause mortality among all participants with CMM in the 3 models. When analyzing the individual sleep factor, the models included 4 low-risk sleep factors simultaneously, and the Spearman rank correlation coefficients (Rs) among these 4 sleep factors were determined to be < 0.10 (see **Table S5**). The dose-dependent association of the healthy sleep score with all-cause mortality among all persons with CMM or individuals with specific CMM patterns, including hypertension + CHD, hypertension + DM, hypertension + stroke, and hypertension + DM + CHD, was analyzed by setting the healthy sleep score as a continuous variable. Using the poor sleep pattern as the reference group, we further examined the association of sleep patterns and all-cause mortality.

We conducted 4 sensitivity analyses to examine the robustness of our findings. In sensitivity analysis 1, we excluded participants who died within the first year of the follow-up. In sensitivity analysis 2, we additionally adjusted for the use of antihypertensives, cholesterol-lowering drugs, aspirin, insulin, and mental/sleep medicine. In sensitivity analysis 3, we only used ICD-10 records to define hypertension, DM, CHD, and stroke. In sensitivity analysis 4, we created a weighted healthy sleep score ranging from 0 to 4, which was calculated by the equation: weighted healthy sleep score = ($\beta1 \times$ sleep 1 + $\beta2 \times$ sleep 2 + … + $\beta4 \times$ sleep 4) × (4/sum of the β coefficients). According to the weighted healthy sleep score, all included participants were also classified into three groups: poor sleep pattern (0–1), intermediate sleep pattern (2), and healthy sleep pattern (3–4). We further analyzed the association of the sleep pattern generated by the weighted healthy sleep score with all-cause mortality.

Furthermore, to assess whether the association between sleep patterns and all-cause mortality differed across subpopulations, we examined potential effect modification by age (< 60 or ≥ 60 years), sex (male or female), smoking status (current smoking or previously/never smoking), alcohol consumption (never/occasional drinking or usual drinking), healthy diet (yes or no), proper physical activity (yes or no), BMI (≥ 30 or < 30 kg/m^2), and the number of CMDs (2 or ≥ 3) at baseline. We tested homogeneity across stratum-specific HRs using the interaction between the sleep patterns and each potential modifier.

All analyses were performed using R version 4.1.1. All *P*-values for the tests were 2-sided, and a *P*-value < .05 was considered statistically significant.

RESULTS

The baseline characteristics of all patients with CMM are presented in **Table 1**. Of the 35,757 participants, the mean age (SD) was 61.82 (6.3) years, and 22,957 (64.2%) were male. The number of participants in the poor, intermediate, and healthy sleep patterns was 10,490 (29.3%), 13,437 (37.6%), and 11,830 (33.1%), respectively. Participants with a healthy sleep pattern were less likely to be younger, females, or current smokers. They tended to drink usually and had a negative TDI, healthy diet, proper physical activity, and lower BMI.

During a median of 12.0 years of follow-up, 6,652 all-cause deaths were recorded. The Kaplan-Meier survival curves of the relationships of chronotype (early chronotype vs later chronotype), sleep duration (7–8 h/d vs < 7 h/d or > 8 h/d), daytime sleepiness (excessive daytime sleepiness vs no frequent excessive daytime sleepiness), and insomnia (yes vs no) with all-cause mortality among all persons with CMM are presented in **Figure S1** in the supplemental material, indicating that 4 low-risk sleep factors including early chronotype, 7–8 h/d, no frequent excessive daytime sleepiness, and no insomnia were inversely associated with all-cause mortality. These inverse associations remained significant even after adjustment for multiple covariates (**Table 2**). **Table 2** shows that early chronotype, 7–8 h/d, no frequent excessive daytime sleepiness, and no insomnia were independently related to all-cause mortality, with 8%, 12%, 11%, and 8% lower risks, respectively, after full adjustment for demographic characteristics, lifestyle factors, and BMI.

When the 4 sleep factors were combined jointly, we observed that a healthier sleep pattern was related to a higher survival probability among all persons with CMM (**Figure 1**). The healthy sleep score was inversely associated with all-cause mortality (*P* < .001 for 3 models). After full-adjustment, the HR (95% CI) for all-cause mortality was 0.90 (0.88–0.92) for a 1-point increase in the healthy sleep score. Compared with participants with a poor sleep pattern, those with intermediate and healthy sleep patterns were associated with 17% and 33% lower risks of all-cause mortality (HR = 0.83, 95% CI 0.78–0.88; HR = 0.67, 95% CI 0.63–0.71), respectively, after adjusting for age

Table 1—Baseline characteristic of 35,757 participants with CMM.

Variable	Groups of Sleep Pattern			Total Sample
	Poor Sleep	Intermediate Sleep	Healthy Sleep	
Participants, n (%)	10,490 (29.3)	13,437 (37.6)	11,830 (33.1)	35,757 (100.0)
Age, years, mean (SD)	61.57 (6.50)	61.89 (6.3)	61.95 (6.2)	61.82 (6.3)
Sex, n (%)				
Male	6,392 (60.9)	8,438 (62.8)	8,127 (68.7)	22,957 (64.2)
Female	4,098 (39.1)	4,999 (37.2)	3,703 (31.3)	12,800 (35.8)
White, n (%)	9,460 (90.2)	12,463 (92.8)	11,063 (93.5)	32,863 (92.3)
Townsend Deprivation Index, mean (SD)	0.07 (3.6)	−0.67 (3.3)	−1.10 (3.2)	−0.60 (3.4)
Current smoker, n (%)	1,552 (14.8)	1,549 (11.5)	1,085 (9.2)	4,186 (11.7)
Alcohol consumption, n (%)				
Never or occasionally drinking	7,293 (69.5)	8,534 (63.5)	7,036 (59.5)	22,863 (63.9)
Drinking usually	3,197 (30.5)	4,903 (36.5)	4,794 (40.5)	12,894 (36.1)
Healthy diet, n (%)	5,625 (53.6)	7,559 (56.3)	7,073 (59.8)	20,257 (56.7)
Proper physical activity, n (%)	6,960 (66.3)	9,731 (72.4)	9,144 (77.3)	25,835 (72.3)
BMI, kg/m^2, mean (SD)	31.35 (6.0)	30.42 (5.5)	29.90 (5.2)	30.52 (5.6)
Hypertension, n (%)	10,199 (97.2)	13,114 (97.6)	11,555 (97.7)	34,868 (97.5)
DM, n (%)	5,496 (52.4)	6,560 (48.8)	5,528 (46.7)	17,584 (49.2)
CHD, n (%)	5,719 (54.5)	7,167 (53.3)	6,119 (51.7)	19,005 (53.2)
Stroke, n (%)	1,969 (18.8)	2,428 (18.1)	2,099 (17.7)	6,496 (18.2)
Low risk sleep factors, n (%)				
Early chronotype	3,245 (30.9)	8,497 (63.2)	10,564 (89.3)	22,306 (62.4)
Sleep 7–8 h/d	2,133 (20.3)	7,905 (58.8)	10,926 (92.4)	20,964 (58.6)
No frequent excessive daytime sleepiness	2,664 (25.4)	9,001 (67.0)	11,001 (93.0)	22,666 (63.4)
Never/rarely insomnia	296 (2.8)	1,471 (10.9)	5,206 (44.0)	6,973 (19.5)

BMI = body mass index, CHD = coronary heart disease, CMM = cardiometabolic multimorbidity, DM = diabetes mellitus, SD = standard deviation.

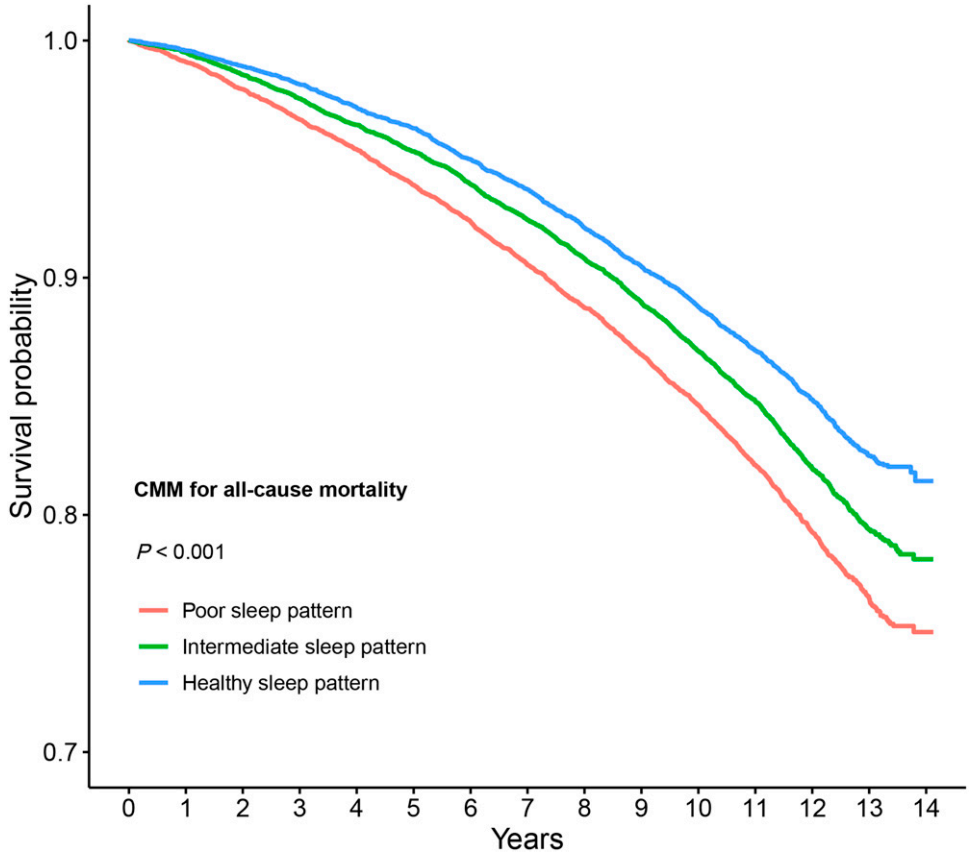
and sex (**Table 3**). With further adjustment for race, TDI, lifestyle behaviors, and BMI, the decreased risks of all-cause mortality were 9% and 23% among individuals with the intermediate sleep pattern and the healthy sleep pattern (HR = 0.91, 95% CI 0.86–0.96; HR = 0.77, 95% CI 0.73–0.82) than those with a poor sleep pattern (**Table 3**). The associations of the healthy sleep score and sleep patterns with all-cause mortality showed a similar trend among participants with different CMM patterns (see **Figure S2**). For individuals with hypertension + DM, hypertension + CHD, hypertension + stroke, and hypertension + DM + CHD, the healthy sleep pattern was associated with 23%, 13%, 24%, and 24% fully adjusted lower risks of all-cause mortality, respectively, compared with those with a poor sleep pattern (**Table S6**).

Table 2—HRs (95% CIs) for all-cause mortality by 4 low-risk sleep factors among all individuals with CMM.

Low-Risk Sleep Factors	Model 1*		Model 2†		Model 3‡	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Early chronotype	0.86 (0.82–0.90)	< .001	0.91 (0.87–0.96)	< .001	0.92 (0.87–0.96)	< .001
Sleep 7–8 h/d	0.81 (0.77–0.85)	< .001	0.87 (0.83–0.92)	< .001	0.88 (0.83–0.92)	< .001
No frequent excessive daytime sleepiness	0.85 (0.81–0.89)	< .001	0.88 (0.84–0.93)	< .001	0.89 (0.85–0.94)	< .001
Free of insomnia	0.89 (0.84–0.95)	< .001	0.92 (0.87–0.98)	.014	0.92 (0.87–0.99)	.015

*Model 1: adjusted for age, sex, and other 3 individual dimensions of sleep. †Model 2: adjusted for variables in model 1 plus race, Townsend Deprivation Index, smoking statue, alcohol consumption, diet, and physical activity. ‡Model 3: additionally adjusted for body mass index. CI = confidence interval, HR = hazard ratio.

Figure 1—Survival probability according to sleep patterns among all participants with CMM.



CMM = cardiometabolic multimorbidity.

The association of a healthy sleep score and sleep pattern with a lower risk of all-cause mortality in a series of sensitivity analyses remained consistent (see **Table S7**). In addition, stratified analyses were performed to identify potentially vulnerable subpopulations (**Figure 2**). The associations between sleep patterns and all-cause mortality were not significantly modified by factors including sex, age, smoking status, physical activity, diet, BMI, and the number of CMDs (all *P* for interaction > .05), except for alcohol consumption (*P* for interaction = .029).

DISCUSSION

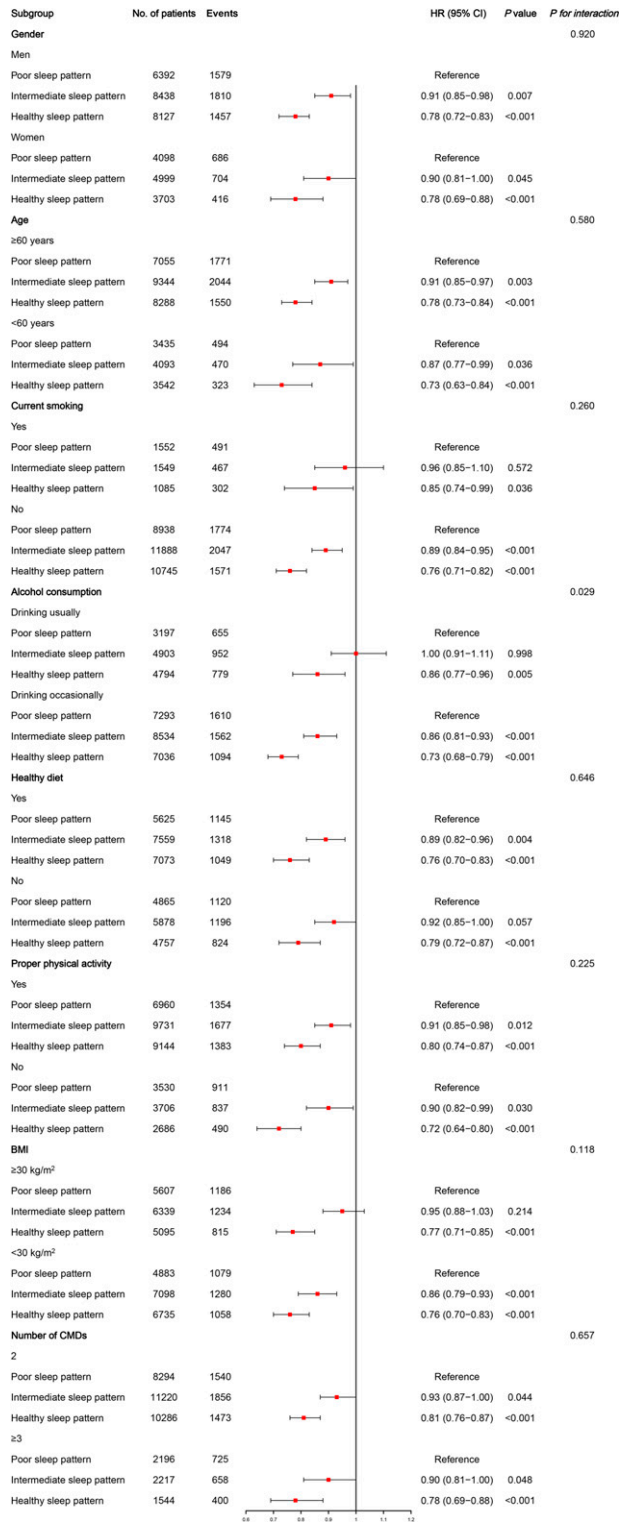
In this large-scale prospective study involving 35,757 participants with CMM at baseline from UK Biobank, we found that 4 sleep factors, including early chronotype, sleep 7–8 h/d, no insomnia, and no frequent excessive daytime sleepiness, were associated with lower risks of all-cause mortality, and demonstrated significant inverse associations of a healthy sleep score

Table 3—HRs (95% CIs) for all-cause mortality by healthy sleep score and sleep patterns among all participants with CMM.

	Model 1*		Model 2†		Model 3‡	
Main Exposure	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Healthy sleep score	0.85 (0.83–0.87)	< .001	0.89 (0.87–0.92)	< .001	0.90 (0.88–0.92)	< .001
Poor sleep	Ref	…	Ref	…	Ref	…
Intermediate sleep	0.83 (0.78–0.88)	< .001	0.90 (0.85–0.95)	< .001	0.91 (0.86–0.96)	< .001
Healthy sleep	0.67 (0.63–0.71)	< .001	0.77 (0.72–0.82)	< .001	0.77 (0.73–0.82)	< .001

*Model 1: adjusted for age, sex, and race. †Model 2: adjusted for variables in model 1 plus Townsend Deprivation Index, smoking statue, alcohol consumption, diet, and physical activity. ‡Model 3: additionally adjusted for body mass index. CI = confidence interval, CMM = cardiometabolic multimorbidity, Ref = reference, HR = hazard ratio.

Figure 2—Subgroup analysis.



CI = confidence interval, CMDs = cardiometabolic diseases, BMI = body mass index, HR = hazard ratio.

and sleep pattern with the risk of all-cause mortality. For all persons with CMM, a healthy sleep score was related to a 10% lower risk of all-cause mortality, and participants with a healthy sleep pattern had a 23% lower risk of all-cause mortality than those with a poor sleep pattern. The association of a healthier sleep pattern with a lower risk of all-cause mortality among all participants with CMM was not modified by age, sex, smoking status, physical activity, diet, BMI, and number of CMDs, except for alcohol consumption.

To our knowledge, no existing studies have assessed the role of either a single sleep factor or combined sleep patterns in the prognosis of CMM. Considering the high prevalence and mortality associated with CMM and the intimate relationship between sleep and health outcomes, we first demonstrated the protective role of 4 low-risk sleep factors and a healthy sleep pattern on the risk of all-cause mortality among individuals with CMM. In our study, we observed that early chronotype, sleep 7–8 h/d, no frequent excessive daytime sleepiness, and free of insomnia were independently associated with 8%, 12%, 11%, and 8% lower risks of all-cause mortality, respectively, among all patients with CMM in the fully adjusted model. These results are consistent with those of previous studies reporting that late chronotype,[16] short or long sleep duration,[12,23,24] excessive daytime sleepiness,[25,26] and insomnia[27] were each related to a higher risk of all-cause mortality in the general population or patients with individual CMDs.

Taking the complexity of sleep and internal correlations of various sleep characteristics into account, we further constructed a comprehensive sleep pattern combining these 4 common sleep factors and found an inverse relationship between a healthier sleep pattern and all-cause mortality. Similar to our research, a sleep pattern combining 5 sleep factors, including sleep duration, chronotype, insomnia, snoring, and excessive daytime sleepiness, was used to examine its association with all-cause mortality among the general population and patients with DM in 2 large-scale cohort studies. The results showed that a favorable sleep pattern was related to 24% and 21% decreased risks of all-cause mortality in the general population and diabetic patients, respectively.[28,29] Our study also observed that a healthy sleep pattern was associated with 23%, 23%, 13%, 24%, and 24% lower risks of all-cause mortality among all participants with CMM and individuals with several specific CMM patterns: hypertension + DM, hypertension + CHD, hypertension + stroke, and hypertension + DM + CHD, respectively. However, there was a slight difference in the detailed definitions of the healthy sleep pattern between these 2 studies and ours. In the present study, we did not use nonsnoring to generate a healthy sleep pattern, as the role of snoring in the risk of death is controversial.[29–31] Additionally, our results were consistent with prior studies that investigated the relationship between other particular sleep patterns combining at least 2 sleep factors and the risk of death in the general population or patients with CMDs.[32–34] For example, a recent study showed that individuals with a sleep pattern combining at least 4 of 7 extreme sleep characteristics, including short or long sleep duration, early or late sleep midpoint, sleepiness (Epworth Sleepiness Scale score > 10), sleep discontinuity, irregularity, poor rhythmicity, and poor sleep quality, had a 57% increased risk of all-cause mortality, compared with participants with the sleep pattern consisting of zero extreme sleep characteristics.[35] Although those findings suggested that sleep health was associated with a lower risk of death in the general population or patients with CMDs, it is necessary to examine

whether sleep health plays the same role in the prognosis of CMM, as evidence has suggested that the importance of clinical, lifestyle, and socioeconomic profiles in disease progression, from disease-free state to first cardiometabolic disease, CMM, and death, varies depending on the disease stage.[9] Our results addressed the gap in the impact of sleep characteristics on the progression from CMM to death. In general, they indicate that healthy sleep characteristics, including low-risk sleep factors and the combined healthy sleep pattern, might play protective roles in all-cause mortality not only in the general population and patients with CMDs but also among individuals with CMM.

The potential mechanisms of the protective role of healthy sleep behaviors in lowering the risk of all-cause mortality might be complex. On the one hand, several studies have found that short or long sleep duration and insomnia are associated with endocrine or metabolic disruption, increased inflammatory responses, and oxidative stress.[36–38] Late chronotype was related to disrupted circadian rhythm and poor metabolic and cardiovascular health.[39–41] Excessive daytime sleepiness was reported to be related to increased risks of disability and motor-vehicle accidents.[42,43] Additionally, the fact that excessive daytime sleepiness is one of the common symptoms of obstructive sleep apnea syndrome, which was demonstrated to be associated with a higher risk of mortality, might be another explanation.[44] On the other hand, previous studies found that the poor sleep pattern was associated with higher risks of cardiovascular diseases, arrhythmia, and heart failure.[45,46] Collectively, a healthy sleep pattern may lower the risk of mortality through various mechanisms, contributing to a lower risk of all-cause mortality among individuals with CMM.

Strengths and limitations

This study has several strengths. First, UK Biobank was a large-scale population-based prospective cohort study. Based on this, the present study had adequate statistical power. Second, we explored the role of sleep characteristics in the prognosis of CMM, which is steadily becoming an important topic. Third, we comprehensively combined 4 common and important sleep factors to generate a sleep pattern that would reflect the entire sleep condition to some extent.

However, our study had several limitations. First, the results of this observational study cannot be directly interpreted as describing causal relationships. Second, as the information on sleep behaviors was self-reported, misclassification of exposures was inevitable. Third, the exposures and covariables collected at recruitment were assumed to be relatively constant during the follow-up. Future studies investigating the changes in sleep characteristics over time will further elucidate their implications for the prognosis of CMM. Finally, other important sleep characteristics, including sleep apnea syndrome, reported to be associated with mortality in the general population, were not considered in this sleep pattern, as its information was not acquired in UK Biobank.[47,48]

CONCLUSIONS

In this cohort study, we first explored the role of sleep characteristics in the prognosis of CMM, and results suggested that a healthy sleep pattern combining the 4 low-risk sleep factors could be regarded as a healthy lifestyle for individuals with CMM that may lower the risk of all-cause mortality. However, the potential protective role of other uninvolved low-risk sleep factors in reducing the risk of all-cause mortality among patients with CMM remains to be assessed in the future studies.

ABBREVIATIONS

BMI, body mass index
CHD, coronary heart disease
CMD, cardiometabolic disease
CMM, cardiometabolic multimorbidity
DM, diabetes mellitus
HR, hazard ratio
ICD, *International Classification of Diseases*
TDI, Townsend Deprivation Index

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