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Original Article

Association of bedtime with mortality and major cardiovascular events: an analysis of 112,198 individuals from 21 countries in the PURE study

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ABSTRACT

Objectives: This study aimed to examine the association of bedtime with mortality and major cardiovascular events.
Methods: Bedtime was recorded based on self-reported habitual time of going to bed in 112,198 participants from 21 countries in the Prospective Urban Rural Epidemiology (PURE) study. Participants were prospectively followed for 9.2 years. We examined the association between bedtime and the composite outcome of all-cause mortality, non-fatal myocardial infarction, stroke and heart failure. Participants with a usual bedtime earlier than 10PM were categorized as 'earlier' sleepers and those who reported a

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bedtime after midnight as 'later' sleepers. Cox frailty models were applied with random intercepts to account for the clustering within centers.
Results: A total of 5633 deaths and 5346 major cardiovascular events were reported. A U-shaped association was observed between bedtime and the composite outcome. Using those going to bed between 10PM and midnight as the reference group, after adjustment for age and sex, both earlier and later sleepers had a higher risk of the composite outcome (HR of 1.29 [1.22, 1.35] and 1.11 [1.03, 1.20], respectively). In the fully adjusted model where demographic factors, lifestyle behaviors (including total sleep duration) and history of diseases were included, results were greatly attenuated, but the estimates indicated modestly higher risks in both earlier (HR of 1.09 [1.03–1.16]) and later sleepers (HR of 1.10 [1.02–1.20]).
Conclusion: Early (10 PM or earlier) or late (Midnight or later) bedtimes may be an indicator or risk factor of adverse health outcomes.

1. Introduction

Sleep is a vital part of human life, with about one third of an individual's lifetime spent sleeping. Like other lifestyle factors, sleep behaviors (eg sleep duration) have been considered as important contributors to health [1,2]. Prior numerous studies have shown that shorter and longer sleep are associated with greater risks of cardiovascular (CV) outcomes and deaths [3–5]. Sleep deprivation could negatively affect energy metabolism (intake/expenditure balance) and lead to adverse metabolic outcomes (eg obesity and diabetes). Prolonged sleep may be a sign of underlying conditions but not yet showing clinical manifestations.

In addition to sleep duration, sleep timing, especially bedtime, may affect health by disrupting circadian rhythms and certain metabolic processes. However, the association between bedtime and health is comparatively less examined and current evidence lacks consistency. Some studies have shown that later bedtime is linked to higher insulin resistance, higher prevalence of diabetes and elevated blood pressure [6–8]. While other reports indicate contradictory results [9]. Moreover, these previous studies [6–9] are mostly cross-sectional designs and relatively small in size, and mainly focused on cardiometabolic related conditions (eg obesity and diabetes) instead of hard endpoints. Whether bedtime relates to the occurrence of CV events or deaths is still unclear. In this analysis, we aimed to investigate the association of bedtime with mortality and CV events in adults aged 35–70 based on a large prospective multi-national cohort study of about 120,000 people.

2. Methods

2.1. Study design and participants

The detailed study design and population selection of the Prospective Urban Rural Epidemiology (PURE) study have been described in previous publications [10,11]. Briefly, it is a cohort study which enrolled individuals aged 35–70 years at baseline during 2003–2009 (the first phase) from 21 countries in seven geographic regions (North America and Europe, South America, the Middle East, South Asia, Southeast Asia, China, and Africa). It includes 4 high-income countries (Canada, Sweden, Saudi Arabia and United Arab Emirates), 12 middle-income countries (Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestine, Philippines, Poland, South Africa, and Turkey) and 5 low-income countries (Bangladesh, India, Pakistan, Tanzania and Zimbabwe) according to the World Bank classification at the time of enrollment of participants. The study protocol was approved by institutional research ethics boards at all sites and informed consent was obtained from all participants.

Baseline data were collected using standardized questionnaires, which were translated into local languages where appropriate by trained research staff. As it is not feasible to precisely measure times of sleep onset and offset using complex methods (eg polysomnography) in large studies, bedtime (ie time of going to bed) and waketime (ie time of waking up) were based on self-reports using questions ("during your longest or nocturnal sleep period, what time do you normally go to bed and wake up"). Using median of bedtime (10:00 PM) and midnight (00:00AM) as cutoffs, participants were categorized into 3 groups: bedtime 10 PM or earlier (earlier sleepers), 10 PM to midnight, midnight or later (later sleepers). Nighttime sleep duration was estimated as the period between bedtime and wake time. Total sleep duration per day was defined as the sum of estimated nocturnal sleep time and self-reported nap duration, which was obtained by asking "do you usually take naps/siestas and if yes, how long (min) the nap duration is". Information on smoking, alcohol intake, physical activity (using the International Physical Activity Questionnaire [12]) and diet (using country- or region-specific validated food frequency questionnaires [13,14]) was also recorded. Participants were contacted at least every 3 years after the baseline survey by local research teams. Standardized case report forms were used to document the occurrence of events. Additional information from interviews, medical records, death certificates, or verbal autopsies was used to classify the cause of deaths. All deaths and major CV events were adjudicated using pre-specified definitions (Appendix) by trained physicians in each participating country.

A total of 164,084 participants were followed up at least once until July 2019 in our study, among which 21,475 individuals from India were enrolled prior to incorporating questions on sleep. Of the remaining participants, 141,142 (99.0%) provided complete information on sleep timing. Similar to our previous study [2], individuals (n = 132,656) who reported plausible durations of nocturnal sleep (4–12 h/night) and daytime nap (0–3h/day) were included in the analysis. Further, participants with prior CV diseases, cancers, human immunodeficiency virus infection or acquired immune deficiency syndrome (HIV/AIDS) (n = 12,298), or missing information on age, sex or last-known date (n = 1171) were excluded. In the primary analyses, we also excluded 6989 night shift workers (defined as waketime before 4:00 AM or after 12:00 PM, or bedtime between 4:00 AM and 6:00 PM). A total of 112,198 participants were included in the final analyses (Fig. 1).

2.2. Outcomes

The primary outcome of interest is time to the composite of all-cause deaths, non-fatal myocardial infarction (MI), stroke and heart failure (HF). Time to all-cause deaths and major CV events (defined

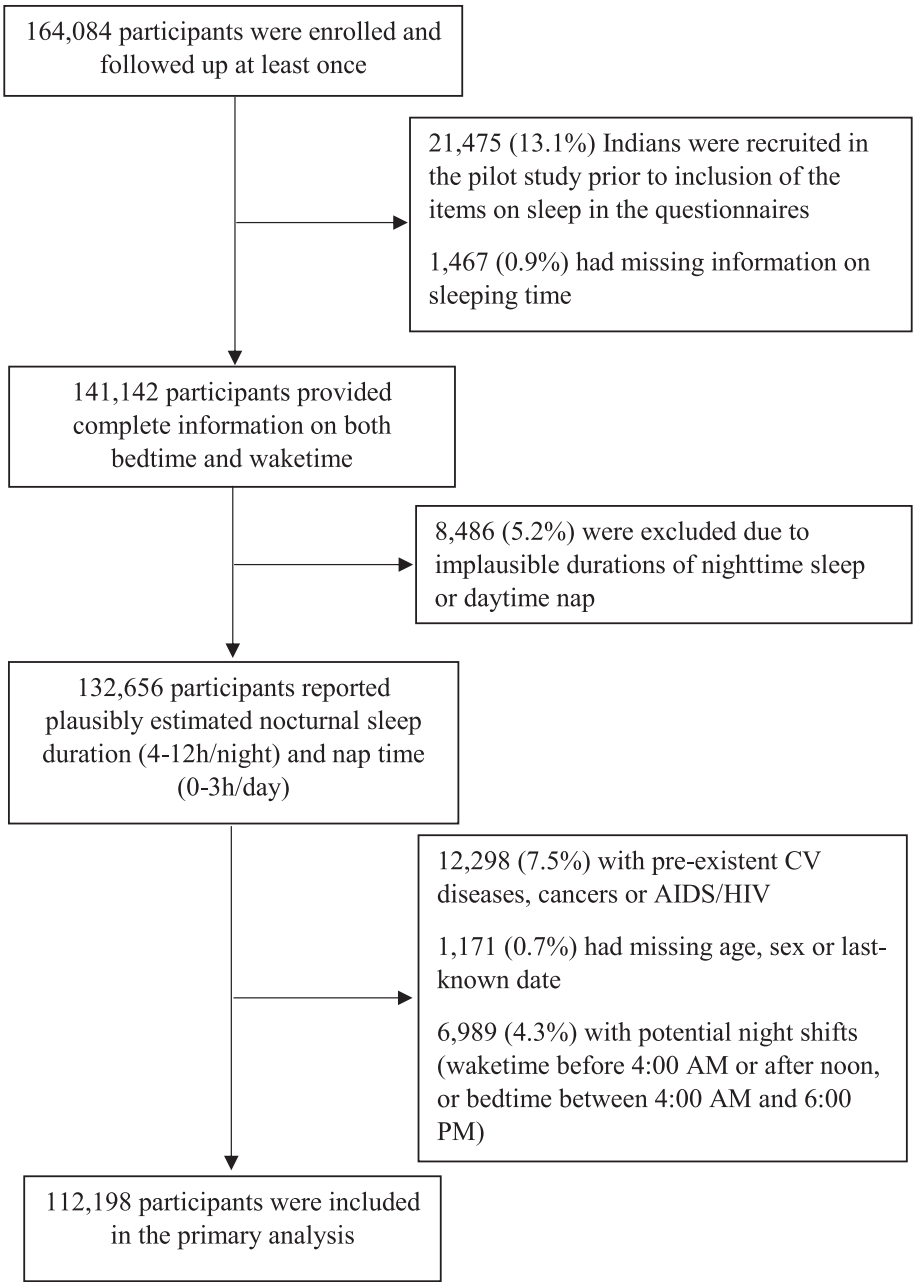

Fig. 1. Participants Enrollment Flow Chart. CV: cardiovascular; HIV/AIDS: human immunodeficiency virus infection/acquired immune deficiency syndrome.

as CV deaths, non-fatal MI, stroke and HF) are also examined separately as secondary outcomes.

2.3. Statistical analysis

Sleep parameters and other baseline characteristics of participants were presented by bedtime categories. Crude incidences of events were reported using percentage and person years for different groups of sleepers. To explore the associations between bedtime and health outcomes, we utilized Cox frailty models with random intercepts for center to account for the clustering within centers. Adjusted hazard ratios (HRs) and corresponding confidence intervals (CIs) were computed. Age, sex and center (as random effects) were included as covariates in minimally adjusted models. In fully adjusted models, further adjustments for education level, tobacco and alcohol intake (ever or current versus never), daily total sleep duration ($\leq$6 h, 6–8 h, 8–9 h, 9–10 h or >10 h), body mass index (<18.5, 18.5–24.9, 25.0–29.9 or $\geq$30.0 kg/m^2 [BMI]), place of residence (urban or rural), history of diabetes (self-reported or taking medications for diabetes), hypertension (systolic blood pressure>140 mmHg, diastolic blood pressure>90 mmHg, self-reported or taking medications for hypertension), chronic obstructive pulmonary disease (COPD) and depression, as well as family history of CV diseases (coronary heart disease or stroke) were done.

Considering that rural residents were more likely to sleep early due to work activities (eg farming), subgroup analysis of urban versus rural residence was conducted. Likewise, as the sleep schedule might be earlier with older age, associations by subgroups of age based on the median (50-year-old) were also presented.

Additionally, sensitivity analysis by exclusion of those having events within the first two years of follow-up was performed to address the concerns of reverse causality (ie illnesses affecting sleep patterns). Moreover, given that sleep disorders could affect sleep behaviors, we removed participants who were likely to have sleep disorders (defined as taking sleeping pills, BMI≥40 kg/m^2 or feeling depressed for ≥2 weeks with at least 5 symptoms in the previous year). As later bedtime may lead to increased calories intake, physical activity and total energy intake were further adjusted on the basis of fully adjusted models. Additional adjustment for country economic status and wealth index (reflecting economic status of participants) was also performed to rule out their potential influence on bedtime. All statistical analyses were performed using SAS 9.4 (Cary, NC, USA).

3. Results

During a median follow-up of 9.2 years (interquartile range, IQR 7.1–10.3), a total of 9024 events of interest were documented. Specifically, 5633 participants died, and 5346 participants had major CV events. Using those going to bed between 10 PM and midnight as the reference group, earlier sleepers were slightly older, less educated, more likely to be females and live in rural areas; slept more, smoked and drank less, consumed less energy and had a lower BMI; were more hypertensive but less diabetic and depressive (Table 1). In contrast, later sleepers showed the opposite. Participants from low- and middle-income countries (eg China) were more likely to be earlier sleepers. By contrast, more people from high-income countries/regions (eg North America and Middle East) had a late bedtime.

The association of bedtime with events was illustrated in Fig. 2. Using the participants going to bed between 10PM and midnight as the reference group, after adjusting for age, sex and center (as random effect), a U-shaped association was observed between bedtime and risks of events. With a further adjustment for lifestyle behaviors (including total sleep duration) and health status, the estimates were substantially attenuated but showed similar directional results. Both earlier and later bedtime were associated with higher risks of the composite of all-cause deaths and major CV events. A slightly more striking association was observed for mortality. As for major CV events, going earlier to bed indicated a modest increased risk while later bedtime showed a non-significant trend of excess risks.

The pattern of results was consistent in various subgroups defined by residency and age (Table 2). In addition, analysis by excluding individuals who had events in the first 2 years of follow-up showed consistent association of bedtime with risks of events (Table 3). Additional sensitivity analysis by exclusion of those likely

Table 1
Participant characteristics by bedtime.

	Bedtime		
	(6PM,10PM] (n = 57,365)	(10PM, Midnight) (n = 38,699)	[Midnight,4AM) (n = 16,134)
Demographics			
Age (years), mean (SD)	50.7 (9.9)	50.2 (9.6)	49.0 (9.1)
Female (%)	34,683 (60.5)	22,069 (57.0)	8816 (54.6)
Urban resident (%)	23,147 (40.4)	26,405 (68.2)	12,116 (75.1)
Body mass index (kg/m^2), mean (SD)	25.3 (4.8)	26.4 (5.0)	28.2 (5.7)
Education (%)			
None, Primary, or Unknown	27,086 (47.3)	11,832 (30.6)	5768 (35.8)
Secondary/High/Higher secondary	23,015 (40.2)	14,941 (38.7)	6015 (37.3)
Trade or College/University	7149 (12.5)	11,877 (30.7)	4339 (26.9)
Country economic status (%)			
High-income countries	3874 (27.2)	7745 (54.4)	2630 (18.5)
Middle-income countries	46,169 (54.0)	26,532 (31.0)	12,781 (15.0)
Low-income countries	7322 (58.7)	4422 (35.5)	723 (5.8)
Geographic regions (%)			
South Asia	5274 (51.4)	4286 (41.8)	705 (6.9)
China	28,737 (69.4)	11,077 (26.8)	1573 (3.8)
Southeast Asia	3470 (33.8)	4230 (41.2)	2558 (24.9)
Africa	4921 (92.6)	335 (6.3)	61 (1.1)
North America/Europe	4801 (28.5)	9143 (54.2)	2915 (17.3)
Middle East	1995 (24.0)	2946 (35.5)	3367 (40.5)
South America	8167 (41.2)	6682 (33.7)	4955 (25.0)
Lifestyle behaviors			
Total sleep duration median (q1-q3), hours	9.0 (8.0–9.5)	8.0 (7.0–8.5)	7.0 (6.0–8.0)
Total sleep duration (%)			
≤6 h	0 (0.0)	2382 (6.2)	5208 (32.3)
6–8 h	17,270 (30.1)	23,624 (61.0)	7823 (48.5)
>8 h	40,095 (69.9)	12,693 (32.8)	3103 (19.2)
Taking naps (%)	22,552 (39.3)	14,921 (38.6)	6182 (38.3)
Smokers (former and current, %)	16,706 (29.4)	12,637 (32.8)	6755 (42.0)
Drinkers (former and current, %)	16,332 (28.8)	14,230 (37.1)	5309 (33.6)
Physical activity, MET × min/week			
Low (<600)	8658 (16.2)	6143 (16.5)	3670 (23.5)
Moderate (600–3000)	19,914 (37.2)	14,250 (38.3)	5857 (37.5)
High (>3000)	24,912 (46.6)	16,834 (45.2)	6090 (39.0)
Total energy intake (Kcal), mean (SD)	2132 (938)	2229 (940)	2397 (1025)
Medical history			
Hypertension (%)	23,484 (41.0)	14,865 (38.4)	5880 (36.4)
Diabetes (%)	3077 (5.4)	2714 (7.0)	1506 (9.3)
Chronic obstructive pulmonary diseases (%)	327 (0.6)	254 (0.7)	149 (0.9)
Depression (%)	7780 (13.6)	6517 (16.9)	3806 (23.6)

MET, metabolic equivalent of task; SD, standard deviation.

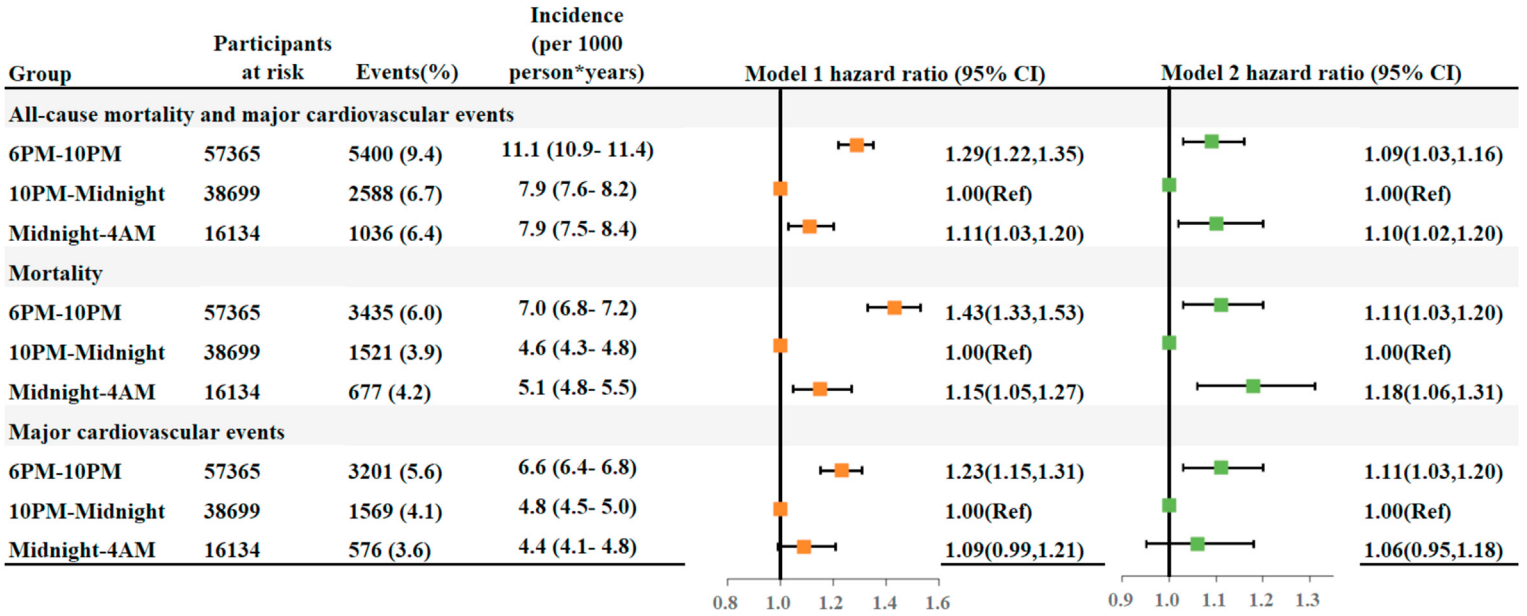

Fig. 2. Association of bedtime with all-cause deaths and major cardiovascular events. Model 1: adjusted for age, sex and center (random effects); Model 2: adjusted for age, sex, education attainment, smoking status (current/former versus never), drinking status (current/former versus never), body mass index, residency (urban versus rural), family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, depression, and sleep duration (as categorical variable: ≤6 h,6–8 h,8–9 h,9–10 h and >10 h) and center (random effects).

to have sleep disorders did not alter the results. The estimates remained robust when further adjusted for physical activity and total energy intake, or country economic status and wealth index.

4. Discussion

In this large-scale cohort study, compared with those who went to bed between 10 PM and midnight, we observed that both those who went to bed earlier and later experienced a modestly higher risks of mortality and major CV events. It showed a U-shaped association between bedtime and events, suggesting that 'extreme' bedtimes may be detrimental to health.

Our findings of potential detrimental effects of delayed bedtime were consistent with prior reports that delayed bedtime was associated with elevated blood pressure and higher prevalence of diabetes [6,8], which are important risk factors of CV events and deaths. Individuals going to bed later tend to have poorer diet habits (eg consumption of more energy-dense but nutrient-poor foods and less fruit and vegetables), less physical activity, higher waist circumferences, greater severity of overweight [15,16], contributing to greater risks of CV events. The association did not change by further adjusting for physical activity and total energy intake. It is possible that delayed bedtime disrupts the circadian rhythms of metabolic function and impacts the metabolism. Prior evidence has shown that those with later sleep timing had abnormal metabolic measures such as higher insulin resistance and higher fasting glucose [7], which could elevate the risks of obesity and diabetes and lead to adverse outcomes.

We also found that going to bed earlier was associated with greater risks of CV events and mortality. However, there is much less evidence on the significant association between earlier bedtime and adverse health outcomes. A prior cohort study [8] has shown that adolescents with earlier bedtime had higher risks of developing high blood pressure. Additionally, Chang et al. [17] has reported that earlier bedtime was linked to poorer cardiac vagal function among older adults and might indicate a declined health status. We performed stratified analysis by age but found consistent results in each subgroup without significant interaction. Although sensitivity analyses by excluding those who had events within the first 2 years of follow-up, or by exclusion of those who were likely to have sleep disorders showed similar results, one possible explanation is that early bedtime may serve as a marker of underlying health problems. Therefore, an early bedtime may simply be a sign of a poorer health status that itself elevates the risks of deaths or CV events. The mechanisms underlying the observed positive association of earlier bedtime with adverse events are not fully understood yet, which require further research.

Table 3
Sensitivity analyses of associations of bedtime with the composite of mortality and major cardiovascular events.

	Bedtime		
	(6PM,10PM]	(10PM, Midnight)	[Midnight,4AM)
SA1: Exclusion of participants having events occurred in the first 2 years of follow-up (n=110,884)			
Hazard ratio (95% CI)	1.10 (1.03,1.17)	**1.00 (Ref)**	1.12 (1.02,1.22)
SA2: Exclusion of participants who were likely to have sleep disorders (defined as taking sleeping pills, BMI≥40 kg/m2 or feeling depressed for ≥2 weeks with at least 5 symptoms in the previous year, n=101,188)			
Hazard ratio (95% CI)	1.10 (1.03,1.17)	**1.00 (Ref)**	1.09 (0.99,1.19)
SA3: Further adjusting for physical activity and total energy intake (n=112,198)			
Hazard ratio (95% CI)	1.11 (1.05,1.18)	**1.00 (Ref)**	1.10 (1.01,1.20)
SA4: Further adjusting for country economic status and wealth index (n=112,198)			
Hazard ratio (95% CI)	1.08 (1.02,1.15)	**1.00 (Ref)**	1.11 (1.02,1.21)

BMI, body mass index.
SA1: adjusted for age, sex, education attainment, smoking status (current/former vs never), drinking status (current/former vs never), BMI, residency (urban vs rural), family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, depression, sleep duration (as categorical variable: ≤6 h, 6–8 h, 8–9 h, 9–10 h and >10 h) and center (RE).
SA2: adjusted for age, sex, education attainment, smoking status (current/former vs never), drinking status (current/former vs never), BMI, residency (urban vs rural), family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, sleep duration (as categorical variable: ≤6 h, 6–8 h, 8–9 h, 9–10 h and >10 h) and center (RE).
SA3: adjusted for age, sex, education attainment, smoking status (current/former vs never), drinking status (current/former vs never), BMI, residency (urban vs rural), family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, depression, sleep duration (as categorical variable: ≤6 h, 6–8 h, 8–9 h, 9–10 h and >10 h), physical activity, total energy intake, and center (RE).
SA4: adjusted for age, sex, education attainment, smoking status (current/former vs never), drinking status (current/former vs never), BMI, residency (urban vs rural), family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, depression, sleep duration (as categorical variable: ≤6 h, 6–8 h, 8–9 h, 9–10 h and >10 h), country economic status (high, middle and low), wealth index, and center (RE).

Table 2
Subgroup analyses of associations of bedtime with the composite of mortality and major cardiovascular events.

	Bedtime			P for interaction
	(6PM,10PM]	(10PM, Midnight)	[Midnight,4AM)	
	Residency[a]			
	Urban residents (n = 61,668)			
Incidence (per 1000 person*years)	9.6 (9.2–10.1)	7.3 (6.9–7.6)	7.0 (6.5–7.5)	**0.4770**
Hazard ratio (95% CI)	1.09 (1.00,1.18)	**1.00 (Ref)**	1.06 (0.95,1.17)	
	Rural residents (n = 50,530)			
Incidence (per 1000 person*years)	12.1 (11.7–12.5)	9.2 (8.6–9.8)	11.0 (9.9–12.2)	
Hazard ratio (95% CI)	1.10 (1.01,1.20)	**1.00 (Ref)**	1.17 (1.02,1.35)	
	Age[b]			
	<50 years old (n = 54,582)			
Incidence (per 1000 person*years)	5.5 (5.2–5.8)	3.6 (3.4–3.9)	3.9 (3.4–4.4)	**0.0775**
Hazard ratio (95% CI)	1.13 (1.00,1.27)	**1.00 (Ref)**	1.13 (0.95,1.33)	
	≥50 years old (n = 57,616)			
Incidence (per 1000 person*years)	16.2 (15.7–16.7)	12.0 (11.5–12.5)	12.9 (12.0–13.8)	
Hazard ratio (95% CI)	1.10 (1.03,1.17)	**1.00 (Ref)**	1.06 (0.96,1.17)	

[a] Adjusted for age, sex, education attainment, smoking status (current/former vs never), drinking status (current/former vs never), body mass index, family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, depression, total sleep duration (categorical variable) and center (RE).
[b] Adjusted for sex, education attainment, smoking status (current/former vs never), drinking status (current/former vs never), body mass index, residency (urban vs rural), family history of cardiovascular diseases, diabetes, hypertension, chronic obstructive pulmonary diseases, depression, total sleep duration (categorical variable) and center (RE).

The estimates were attenuated markedly among early sleepers with further adjustment, while the U-shaped association between bedtime and the composite outcome was unchanged. The substantial proportion (69.9%) of longer sleepers (>8 h/day), who have been reported to be associated with higher risks of adverse health [2], may contribute to such changes. Despite the correlation between bedtime and sleep duration (earlier sleepers tend to sleep more), these two sleep parameters indicate different aspects of sleep patterns. The time of going to sleep somewhat reflects an individual's circadian rhythm but is an integrated result of internal and external factors. By contrast, sleep duration is a quantitative measurement of sleep. And we have reported the association between sleep duration and health outcomes in details elsewhere [2]. Our current analyses showed that bedtime was associated with health outcomes independent of sleep duration, suggesting sleep patterns may affect health through multiple manners. Moreover, the modest effect sizes of extreme bedtimes observed may be of clinical significance. Going to bed earlier than midnight may help keep in line with internal biological rhythms and reduce the risks of potential CV events and premature deaths. Alternatively, earlier bedtimes might be early signs of impaired health without clinical manifestation.

4.1. Limitations

Our study has some potential limitations. First, we estimated bedtime by self-reported timing of going to bed, rather than measurements using objective approaches like actigraphy or polysomnography. It may cause potential misclassifications. However, the use of such measurements is not feasible in large epidemiological studies involving the general population from several countries. Moreover, such occurrence of misclassifications is likely to dilute the strength of association that we have observed. Application of more convenient but precise approaches in such large studies are highly needed in future research. Second, we did not collect information on sleep separately for weekdays or weekends, and the estimated sleep times reported was an assessment of overall habitual sleep behaviors. The possible discrepancy between sleep times on workdays and on free days might impact health outcomes [18]. Third, sleep quality (eg sleep disorders) is a potential confounder. We did not have detailed information on sleep disorders but we performed sensitivity analysis by excluding those who were likely to have sleep disorders with consistent results [19,20]. Last, although we adjusted for a considerable number of covariates, as with other observational studies, we cannot completely rule out the possibility of residual confounding from unmeasured factors.

5. Conclusion

We observed a U-shaped association between bedtime and the composite of mortality and major CV events. Those going to bed between 10PM and midnight experienced the lowest risks of events, while early or late bedtimes were associated with a modest detrimental effect on health, suggesting that early or late bedtimes could be an indicator or risk factor of adverse health outcomes.

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Conflict of interest

None.

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Abbreviations

Body Mass Index BMI
Cardiovascular CV
Chronic Obstructive Pulmonary Disease COPD
Confidence Interval CI
Hazard Ratio HR
Heart Failure HF
Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome HIV/AIDS
Interquartile Range IQR
Myocardial Infarction MI
Prospective Urban Rural Epidemiology PURE

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.01.057.

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