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FULL RESEARCH PAPER
Physical activity

Joint association of physical activity and sleep duration with risk of all-cause and cause-specific mortality: a population-based cohort study using accelerometry

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Aims To investigate the joint association of accelerometer-measured physical activity (PA) and sleep duration with mortality risk.

Methods and results A 7-day accelerometer recording was performed on 92 221 participants (age 62.4 ± 7.8 years; 56.4% women) from the UK Biobank between February 2013 and December 2015. We divided sleep duration into three groups (short, normal, and long), total volume of PA into three levels according to tertiles (high, intermediate, low), and moderate-to-vigorous PA (MVPA) into two groups based on the World Health Organization guidelines. The mortality outcomes were prospectively collected through the death registry. Over a median follow-up of 7.0 years, 3080 adults died, of which 1074 died from cardiovascular disease (CVD) and 1871 from cancer. The associations of PA and sleep duration with mortality risk were all in a curvilinear dose–response pattern ($P_{nonlinearity}$ <0.001). PA and sleep duration had additive and multiplicative interactions on mortality risk ($P_{interaction}$ <0.05). Compared with the participants with guideline-recommended MVPA and normal sleep duration, those without recommended MVPA but having short or long sleep duration were at a higher risk for all-cause mortality [short sleep: hazard ratio (HR) = 1.88; 95% confidence interval (CI), 1.61–2.20; long sleep: HR = 1.69; 95% CI, 1.49–1.90]. A higher volume of PA or recommended MVPA attenuated the detrimental effects of short or long sleep duration on all-cause and CVD mortality risks.

Conclusion MVPA meeting recommendations or a higher volume of PA at any intensity potentially diminished the adverse effects on all-cause and cause-specific mortality associated with short and long sleep duration.

Lay summary All-cause and cause-specific mortality risks associated with accelerometer-measured short or long sleep duration were attenuated by physical activity (PA).

- Both accelerometer-measured short and long sleep duration were associated with higher risk for all-cause and CVD mortality.
- Either a higher volume of PA or moderate-to-vigorous PA reaching the WHO-recommended level, as was also measured with accelerometer, attenuated the excessive mortality risks associated with short or long sleep duration.

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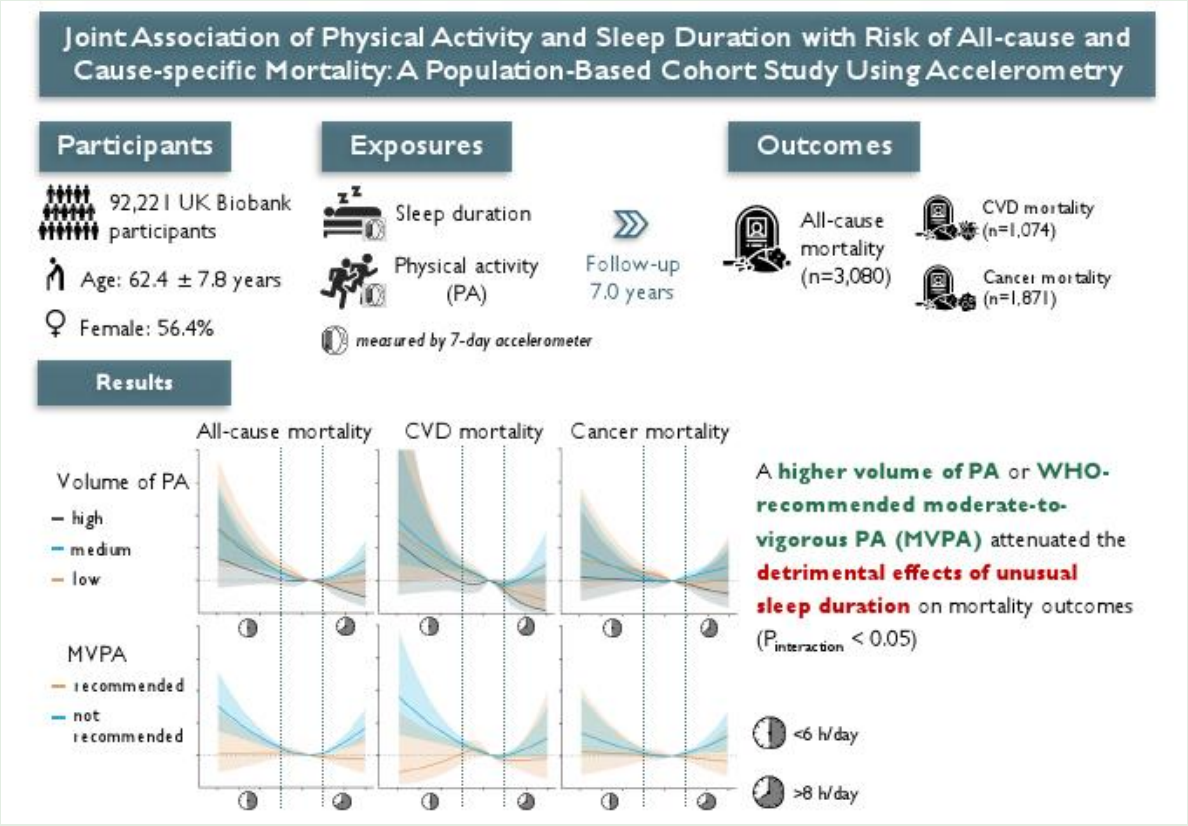
Graphical Abstract



Keywords Sleep duration • Physical activity • Accelerometer • Mortality • UK Biobank

Introduction

Physical activity (PA) and sleep are two core lifestyle components occupying the 24-h life cycle.[1] Adherence to sufficient PA and healthy sleep is essential for prolonging life expectancy. PA is well recognized as a beneficial factor that can reduce up to 70% risk for premature mortality.[2] On the other hand, mounting evidence has suggested that short or long sleep duration significantly increases mortality risk in a U- or J-shaped pattern.[3,4] Time spent in PA and sleep is co-dependent.[5] PA is also suggested to exert short-term effects on sleep duration.[6] However, it is unclear how PA may interact with sleep duration in promoting health. Therefore, the joint association of PA and short or long sleep duration with mortality has recently attracted increasing attention beyond the individual associations.

Evidence on the combined effects of PA and sleep duration on mortality risk has been inconclusive.[7,8,9,10] For instance, a higher level of PA was reported to modify mortality risks associated with either only short sleep duration,[8] only long sleep duration,[7] or both.[10] Despite the controversial findings, these studies have implied that sufficient PA attenuates the mortality risk related to unhealthy sleep. Potential sources of the inconsistency across studies may include differences concerning sample characteristics, type of PA studied, and classifications of PA and sleep duration. Notably, the key limitation of all these studies is self-reported PA and sleep measures, commonly subject to recall and response bias.[11,12] The subjective measures likely underestimate the total amount of PA,[13] which may be attributed to the lack of consideration of light-intensity PA with an unstructured nature and dispersion during the day.[14] Subjective sleep duration may be biased by the current mental or physical health status.[12] In contrast to subjective measures, the accelerometer provides reliable and objective estimates of PA and sleep duration across consecutive days. To the best of our knowledge, no study till date has examined the joint effects of PA and sleep duration on mortality risk using accelerometry.

Therefore, the present study using accelerometry data aimed to examine the association of the joint effects of PA levels [total PA volume and time spent in moderate-to-vigorous PA (MVPA)] and sleep duration with all-cause, cardiovascular disease (CVD), and cancer mortality among middle-aged and older participants of the UK Biobank cohort. We hypothesized that the mortality risk associated with short or long sleep duration is attenuated by a high volume of PA or eliminated by meeting guideline recommendations for MVPA.

Methods

Study population

The UK Biobank, a population-based prospective cohort, recruited over 500 000 community-dwelling adults aged 40–73 years across 22 assessment centres in the UK between 2006 and 2010. Details of the UK Biobank are described elsewhere.[15] From February 2013 to December 2015, 236 519 participants from the UK Biobank were invited to wear a wrist-worn Axivity AX3 accelerometer device (Axivity, Newcastle upon Tyne, UK) for one week. A total of 106 053 participants agreed to participate, and 103 712 datasets were received. The UK Biobank accelerometer working

group processed the raw data and provided the data quality metrics. Finally, 92 221 participants with valid data were included in this study. A detailed flowchart of inclusion and exclusion of participants in the current study is provided in Supplementary material online, *eFigure S1*. The North West Multi-centre Research Ethical Committee Study approved the UK Biobank study. All included participants provided written informed consent. The current research was conducted using the UK Biobank Resource under Application Number 58 082.

Accelerometer-measured physical activity and sleep duration

Details on accelerometry data processing and analyses have been described previously.[16] The total volume of PA was measured as the weekly average vector magnitude in milligravity (mg) units (field ID 90012), which is a well-validated surrogate for global PA.[17,18] Moderate intensity PA (MPA) was defined as 5-min bouts where over 80% of the 5-s epochs having a mean acceleration between 100 and 400 mg.[19] Vigorous intensity PA (VPA) was defined as the 5-s epochs where mean acceleration was above 400 mg.[20] The minutes of MPA and VPA throughout 1 week was summed to form the total volume of PA, which was categorized by tertiles as low (≤24.0 mg), intermediate (24.0–30.4 mg), or high (≥30.4 mg). We also divided MVPA into two groups (recommended, not recommended) according to whether MVPA levels met WHO standard recommendations (≥150 min of MPA, or ≥75 min of VPA, or equivalent combinations of both throughout the week).[21]

We used the returned sleep duration data from the published study by Jones *et al.* for further analysis.[22] In brief, all sleep episodes in a given sleep period time (SPT) window were added to estimate sleep duration. The average and variability of sleep quantity were measured using the mean and standard deviation of sleep duration of all valid SPT windows. Sleep duration was further divided into three groups: short (<6 h/day), normal (6–8 h/day), and long sleep duration (>8 h/day).[23]

Outcomes

The primary endpoint was all-cause mortality. The secondary endpoints were CVD and cancer mortality. The date and underlying cause of death were obtained from the death datasets from the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register, Scotland (Scotland). We ascertained the cause-specific mortality using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, with the following codes: I00–I99 (for CVD) and C00–C97 (for cancer). We censored the Cox analyses at the date of death or date of mortality data available (12 November 2021), whichever came first.

Covariates

The potential covariates included age, sex, ethnicity, recruitment centre, educational attainment, the season in which accelerometer was worn, socioeconomic deprivation [Townsend deprivation index (TDI)], body mass index (BMI) categories, diet-related factors, smoking status, frequency of alcohol intake, work shift history, and prevalent illness (CVD, cancer, or diabetes) (see Supplementary material online, *eText S1*).

Statistical analyses

Descriptive characteristics by sleep duration and PA categories are presented as frequencies and percentages for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for quantitative variables as appropriate. Missing data of covariates (missing rate <5%, Supplementary material online, *eTable S3*) were inputted with multiple imputations by chained equations to minimize the potential inferential.

The independent associations of sleep duration and PA as categorical variables with all-cause, CVD, and cancer mortality were studied with multivariable Cox proportional hazards regression models, including the minimally adjusted model (adjusted for age and sex) and the fully adjusted model (additionally adjusted for ethnicity, recruitment centre, educational attainment, season in which accelerometer was worn, TDI, BMI, diet-related factors, smoking status, frequency of alcohol intake, work shift history, and sleep duration/PA when appropriate). In addition, as continuous variables, the linear or non-linear associations of PA and sleep duration with outcomes were examined with penalized cubic splines fitted in the additional adjusted Cox models.

Three types of analyses were performed using multivariate Cox models to examine the combined effects of sleep duration and PA on mortality. First, we analysed both the additive and multiplicative interactions between the PA and sleep duration with mortality.[9] Second, in stratified analyses, restricted cubic splines of changes in sleep duration according to the categories of the total volume of PA or MVPA were applied to graphically estimate the association of the joint effects. Furthermore, the associations of sleep duration (normal sleep duration as reference) with mortality were investigated within each level of total PA or MVPA. Third, the joint association was subsequently investigated using additional adjusted Cox models. Thereafter, the overall sample was stratified into nine mutually exclusive groups based on total PA volume and sleep duration (with the group with higher PA volume and normal sleep duration as the reference). Similarly, joint analyses with six mutually exclusive groups based on MVPA and sleep duration categories were also completed.

To enhance the robustness of our findings, we conducted several sensitivity analyses. We repeated the analyses in the sample with complete data of all covariates and that including only participants who wore the accelerometer for seven whole days. In addition, to minimize the likelihood of reverse causality, we first reanalysed using Cox models additionally adjusted for prevalent illnesses at baseline and subsequently, by restricting the sample to those without major chronic diseases at baseline. We also performed time lag analyses by excluding deaths occurring within the first two years of enrollment. Finally, to minimize the potential bias caused by the COVID-19 pandemic, we reperformed the primary analyses after censoring the data up to 31 December 2019.

The proportional hazards assumption was confirmed with Schoenfeld residuals for all Cox models. The statistical analyses were performed with R software version 4.1.2 (R Development Core Team, Vienna, Austria). A two-sided *P* value of <0.05 was considered to indicate statistical significance. The *P* values and 95% confidence intervals (CIs) were further adjusted using a false discovery rate (FDR) method in the main analyses to address the multiple testing issues.

Results

Baseline characteristics

The baseline characteristics of the study participants across sleep duration categories are listed in *Table 1*. Among the 92 221 participants included, the mean (SD) age was 62.4 (7.8) years, and 52 018 (56.4%) were women. The majority (73.2%) of the participants had a normal sleep duration, followed by a long sleep duration (19.7%) and a short sleep duration (7.1%). Over one-third of the participants were physically inactive (33.4% had a low volume of PA, and 39.1% did not meet MVPA recommended targets). Relative to the normal sleep duration group, younger age, a higher proportion of obesity and prevalent CVD and cancer, taking shifts at work, and insufficient MVPA were found among the short sleep duration group. In contrast, the long sleep duration group were older and more likely to be women and obese and had more comorbidities but less amount of PA.

Independent associations of accelerometer-measured physical activity and sleep duration with mortality

A total of 3080 all-cause death events occurred during a median follow-up period of 7.0 years (IQR, 6.5–7.5), of which 1074 (1.16%) participants died of CVD and 1871 (2.03%) died of cancer. Sleep duration was associated with all-cause and CVD mortality in U- and L-shaped patterns, respectively, in the non-linear analyses (both $P_{nonlinearity}$ <0.001) (*Figure 1A and B*). However, sleep duration was not significantly associated with cancer mortality (*Figure 1C*). As a categorized variable, compared with normal sleep duration, only short sleep duration dramatically increased the risk of all-cause [hazard ratio (HR), 1.34; 95%

Table 1 Baseline characteristics of the study participants by categories of accelerometer-measured sleep duration

Characteristics	Sleep duration			
	Total ($n = 92\,221$)	Short sleep duration (<6 h/day) ($n = 6545$)	Normal sleep duration (6–8 h/day) ($n = 67\,519$)	Long sleep duration (>8 h/day) ($n = 18\,157$)
Age at accelerometry (years) (mean ± SD)	62.4 ± 7.8	61.5 ± 8.0	62.1 ± 7.9	63.5 ± 7.6
Female [*n* (%)]	52 018 (56.4)	2662 (40.7)	38 250 (56.7)	11 106 (61.2)
White ethnicity [*n* (%)]	89 380 (96.9)	6005 (91.7)	65 484 (97.0)	17 891 (98.5)
Townsend deprivation index,[a] median (IQR)	−2.44 [3.64]	−1.90 [4.45]	−2.44 [3.63]	−2.62 [3.32]
Recruitment centre [*n* (%)]				
England	82 785 (89.8)	5929 (90.6)	60 651 (89.8)	16 205 (89.2)
Wales	3450 (3.7)	259 (4.0)	2486 (3.7)	705 (3.9)
Scotland	5986 (6.5)	357 (5.5)	4382 (6.5)	1247 (6.9)
Education level [*n* (%)]				
Degree or above	40 346 (43.7)	2969 (45.4)	30 342 (44.9)	7035 (38.7)
Any other qualification	44 154 (47.9)	3085 (47.1)	31 840 (47.2)	9229 (50.8)
No qualification	7721 (8.4)	491 (7.5)	5337 (7.9)	1893 (10.4)
Season of accelerometer wear (*n* (%))				
Spring	20 816 (22.6)	1461 (22.3)	15 172 (22.5)	4183 (23.0)
Summer	24 082 (26.1)	1944 (29.7)	18 170 (26.9)	3968 (21.9)
Autumn	27 605 (29.9)	1943 (29.7)	20 049 (29.7)	5613 (30.9)
Winter	19 718 (21.4)	1197 (18.3)	14 128 (20.9)	4393 (24.2)
Body mass index [*n* (%)]				
Normal/underweight (<25 kg/m^2)	36 476 (39.6)	1946 (29.7)	26 905 (39.8)	7625 (42.0)
Overweight (25–30 kg/m2)	37 758 (40.9)	2747 (42.0)	27 718 (41.1)	7293 (40.2)
Obese (≥30 kg/m2)	17 987 (19.5)	1852 (28.3)	12 896 (19.1)	3239 (17.8)
Healthy diet score (mean ± SD)	2.7 ± 1.2	2.6 ± 1.2	2.7 ± 1.2	2.7 ± 1.2
Smoking status [*n* (%)]				
Never	52 972 (57.4)	3453 (52.8)	38 742 (57.4)	10 777 (59.4)
Previous	33 397 (36.2)	2470 (37.7)	24 510 (36.3)	6417 (35.3)
Current	5852 (6.3)	622 (9.5)	4267 (6.3)	963 (5.3)
Alcohol consumption [*n* (%)]				
Not current	5539 (6.0)	517 (7.9)	3926 (5.8)	1096 (6.0)
Two or less times a week	42 732 (46.3)	3014 (46.1)	30 870 (45.7)	8848 (48.7)
Three or more times a week	43 950 (47.7)	3014 (46.1)	32 723 (48.5)	8213 (45.2)
Shift work history [*n* (%)]	20 529 (22.3)	1698 (25.9)	14 977 (22.2)	3854 (21.2)
Health status [*n* (%)]				
CVD history	22 677 (24.6)	1791 (27.4)	16 100 (23.8)	4786 (26.4)
Cancer history	13 426 (14.6)	793 (12.1)	9577 (14.2)	3056 (16.8)
Diabetes history	4462 (4.8%)	506 (7.7%)	3117 (4.6%)	839 (4.6%)
Total volume of PA (milligravity) (mean ± SD)	28.0 ± 8.2	29.8 ± 9.1	28.6 ± 8.1	25.2 ± 7.5
Low	30 797 (33.4)	1789 (27.3)	20 390 (30.2)	8618 (47.5)
Moderate	30 706 (33.3)	1998 (30.5)	22 940 (34.0)	5768 (31.8)
High	30 718 (33.3)	2758 (42.1)	24 189 (35.8)	3771 (20.8)
MVPA (min/week) (mean ± SD)	156.5 ± 149.3	158.5 ± 169.0	160.1 ± 149.3	142.1 ± 140.3
Recommended MVPA [*n* (%)]	36 031 (39.1)	2468 (37.7)	27 157 (40.2)	6406 (35.3)
Not recommended MVPA [*n* (%)]	56 190 (60.9)	4077 (62.3)	40 362 (59.8)	11 751 (64.7)

Abbreviations: CVD, cardiovascular disease; IQR, interquartile range; MVPA, moderate-to-vigorous physical activity; PA, physical activity; SD, standard deviation.
[a]Lower income was defined as average total household income before tax less than £1800.

CI, 1.18–1.51] and CVD (HR, 1.56; 95% CI, 1.29–1.89) mortality in the additional adjusted multivariate Cox models (see Supplementary material online, *Model S2*, Supplementary material online, *eTable S6*). Non-linear dose–response patterns were observed in the associations of a higher amount of total PA or MVPA with a reduced risk of all-cause, CVD, and cancer mortality (all $P_{overall}$ <0.001; all $P_{nonlinearity}$ <0.001) (*Figure 1*). A higher volume of PA, compared with a low volume of PA, achieved a dramatic benefit of almost 50% reduced all-cause, CVD, and cancer mortality risks (see Supplementary material online, *eTable S7*). MVPA exceeding the WHO standard recommendation

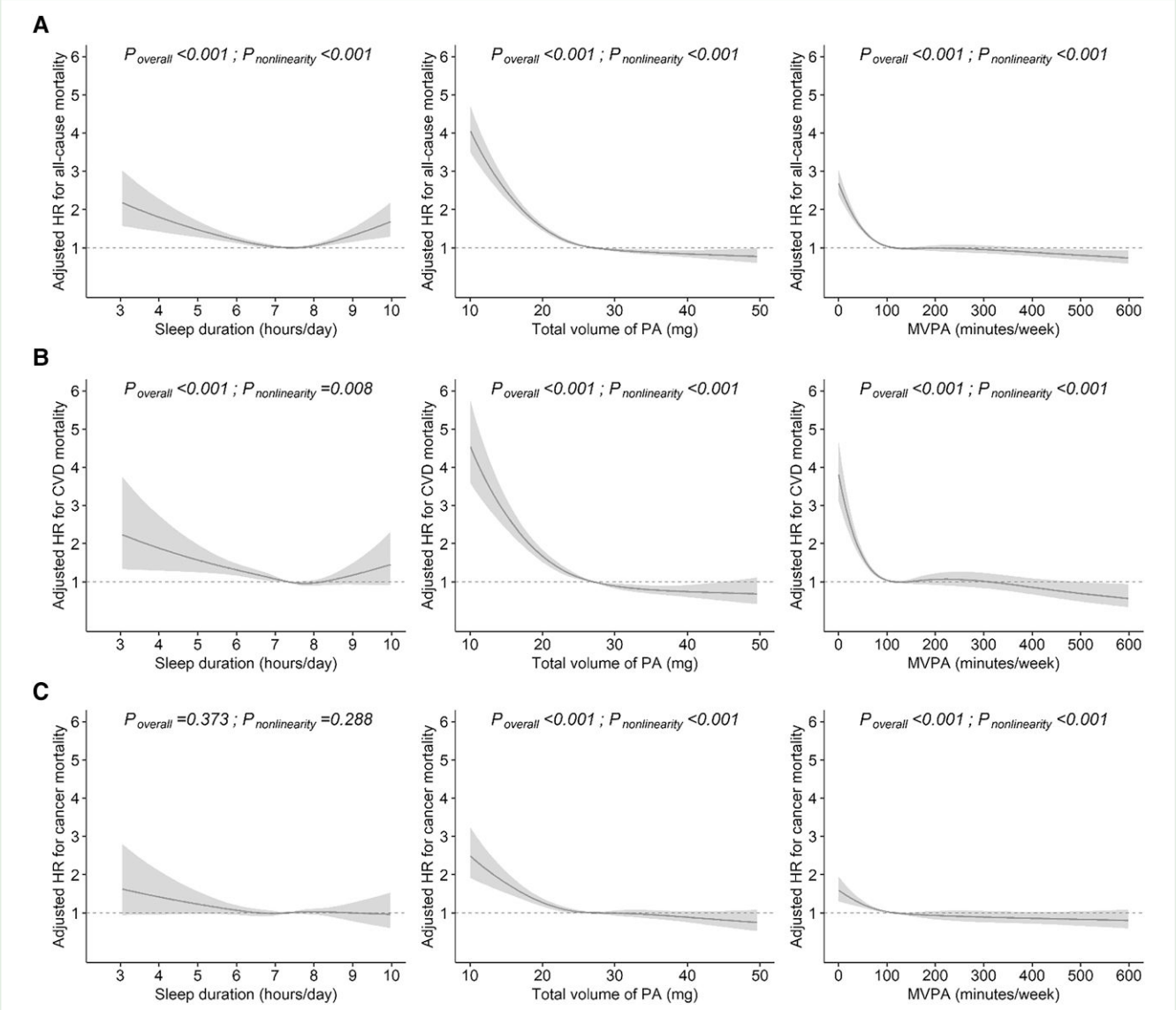


Figure 1 Dose–response associations between accelerometer-measured sleep duration, the total volume of physical activity, moderate-to-vigorous physical activity with all-cause (*A*), cardiovascular disease (*B*), and cancer mortality (*C*) restricted cubic splines were constructed with five knots located at the 5th, 35th, 65th, and 95th percentiles of each exposure. Adjusted hazard ratios (95% CI) were calculated with adjustment for age, sex, ethnicity, Townsend deprivation index, recruitment centre, education level, season of accelerometer wear, body mass index, healthy diet score, smoking status, alcohol intake, and shift work history.

also substantially decreased all-cause (HR, 0.67; 95% CI, 0.48–0.59), CVD (HR, 0.61; 95% CI, 0.52–0.71), and cancer (HR, 0.73; 95% CI, 0.65–0.81) mortality risks (see Supplementary material online, *eTable S7*). The independent associations remained significant after multiple testing correction using the FDR method (all FDR-adjusted $P < 0.05$).

Joint associations of accelerometer-measured physical activity and sleep duration with mortality

Figure 2 and *Table 2* show the associations of sleep duration with all-cause, CVD, and cancer mortality stratified by categories of the total volume of PA and MVPA. When stratified by categories of the total volume of PA, a decreasing trend of mortality risk associated with both short and long sleep duration was observed following a higher volume of PA. Engagement of MVPA above the recommended target (150 min/week), compared with below the target, showed a trend of completely reducing the excess risks of all-cause, CVD, and cancer mortality associated with short and long sleep duration.

The results of joint analyses of sleep duration and PA with mortality are displayed in *Figure 3*. When categorized by the total volume of PA, the lowest risk of death occurred in the group with normal sleep duration and a high volume of PA (reference group) (*Figure 3A*). The combinations of a low volume of PA with short (HR, 2.51; 95% CI, 2.07–3.05) and long sleep duration (HR, 2.06; 95% CI, 1.80–2.36) were associated with the highest risk of all-cause mortality, followed by the

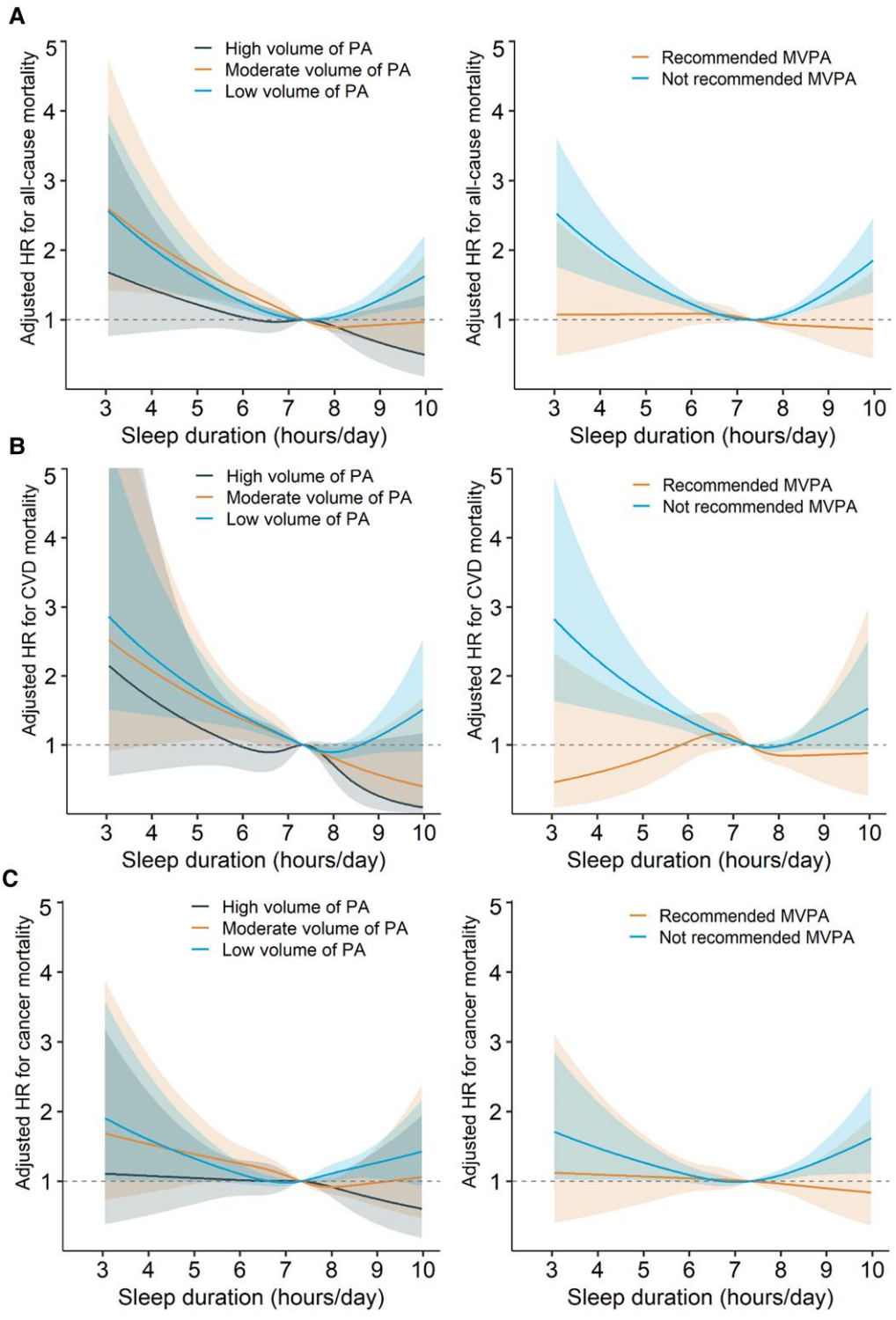


Figure 2 Dose–response associations between accelerometer-measured sleep duration, the total volume of physical activity, moderate-to-vigorous physical activity with all-cause (*A*), cardiovascular disease (*B*), and cancer mortality (*C*) stratified by categories of the total volume of physical activity and moderate-to-vigorous physical activity, respectively. Restricted cubic splines were constructed with five knots located at the 5th, 35th, 65th, and 95th percentiles of each exposure. The total volume of physical activity was categorized by low (≤ 24 mg), intermediate (24–30.37 mg), and high (>30.37 mg), while moderate-to-vigorous physical activity was categorized as not recommended moderate-to-vigorous physical activity (<150 min/week) and recommended moderate-to-vigorous physical activity (≥150 min/week) based on the WHO guideline. Adjusted hazard rations (95% CI) were calculated with adjustment for age, sex, ethnicity, Townsend deprivation index, recruitment centre, education level, season of accelerometer wear, body mass index, healthy diet score, smoking status, alcohol intake, and shift work history.

Table 2 Associations of accelerometer-measured sleep duration with all-cause, cardiovascular disease, and cancer mortality stratified by the total volume of physical activity and moderate-to-vigorous physical activity

		All-cause mortality			CVD mortality			Cancer mortality		
		Events/*n*	Incidence rate, (%) per 1000 person-years	HR (95% CI)[a]	Events/*n*	Incidence rate, (%) per 1000 person-years	HR (95% CI)[a]	Events/*n*	Incidence rate, (%) per 1000 person-years	HR (95% CI)[a]
Total volume of PA[b]										
High	Short sleep duration	61/2758	3.2	1.19 (0.90–1.56)	21/2758	1.1	1.41 (0.88–2.28)	35/2758	1.8	1.01 (0.71–1.45)
	Normal sleep duration	409/24 189	2.4	1.00 [Reference]	106/24 189	0.6	1.00 [Reference]	285/24 189	1.7	1.00 [Reference]
	Long sleep duration	59/3771	2.2	0.90 (0.68–1.18)	8/3771	0.3	0.49 (0.24–1.01)	43/3771	1.6	0.93 (0.68–1.29)
Moderate	Short sleep duration	81/1998	5.8	1.41 (1.11–1.78)[d]	28/1998	2.0	1.41 (0.94–2.11)	44/1998	3.2	1.18 (0.86–1.62)
	Normal sleep duration	611/22 940	3.8	1.00 [Reference]	196/22 940	1.2	1.00 [Reference]	407/22 940	2.5	1.00 [Reference]
	Long sleep duration	137/5768	3.4	0.90 (0.75–1.09)	37/5768	2.0	0.77 (0.54–1.10)	92/5768	2.3	0.90 (0.72–1.13)
Low	Short sleep duration	145/1789	12.0	1.37 (1.15–1.63)[d]	76/1789	6.3	1.69 (1.32–2.16)[d]	67/1789	5.5	1.15 (0.89–1.49)
	Normal sleep duration	1071/20 390	7.7	1.00 [Reference]	425/20 390	3.0	1.00 [Reference]	600/20 390	4.3	1.00 [Reference]
	Long sleep duration	506/8618	8.6	1.16 (1.04–1.29)[d]	177/8618	3.0	1.04 (0.87–1.24)	298/8618	5.1	1.21 (1.05–1.39)[d]
MVPA[c]										
Recommended MVPA	Short sleep duration	56/2468	3.2	1.11 (0.84–1.47)	19/2468	1.1	1.16 (0.72–1.87)	31/2468	1.8	0.96 (0.66–1.39)
	Normal sleep duration	533/27 157	2.8	1.00 [Reference]	160/27 157	0.8	1.00 [Reference]	355/27 157	1.9	1.00 [Reference]
	Long sleep duration	136/6406	3.0	0.98 (0.81–1.18)	38/6406	0.9	0.91 (0.63–1.30)	92/6406	2.1	0.99 (0.78–1.25)
Not	Short sleep duration	231/4077	8.3	1.31 (1.14–1.51)[d]	106/4077	3.8	1.52 (1.23–1.88)[d]	115/4077	4.1	1.12 (0.92–1.36)

Continued

Table 2 *Continued*

		All-cause mortality			CVD mortality			Cancer mortality		
		Events/*n*	Incidence rate, (%) per 1000 person-years	HR (95% CI)[a]	Events/*n*	Incidence rate, (%) per 1000 person-years	HR (95% CI)[a]	Events/*n*	Incidence rate, (%) per 1000 person-years	HR (95% CI)[a]
recommended MVPA	Normal sleep duration	1558/40 362	5.6	1.00 [Reference]	567/40 362	2.0	1.00 [Reference]	937/40 362	3.4	1.00 [Reference]
	Long sleep duration	566/11 751	7.0	1.20 (1.09–1.32)[d]	184/11 751	2.3	1.07 (0.91–1.27)	341/11 751	4.2	1.21 (1.07–1.37)[d]

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; FDR, false discovery rate; HR, hazard ratio; MVPA, moderate-to-vigorous physical activity; PA, physical activity.
[a]Multivariable Cox model was adjusted for age, sex, ethnicity, Townsend Deprivation Index, recruitment centre, education, season of accelerometer wear, body mass index, healthy diet score, smoking status, alcohol intake, and shift work history.
[b]Total volume of PA was categorized by tertiles (low: ≤ 24 mg; intermediate: 24–30.37 mg; high: > 30.37 mg).
[c]MVPA was dichotomized based on the WHO guideline (not recommended MVPA: < 150 min/week; recommended MVPA: ≥ 150 min/week).
[d]*P* values remained significant after multiple testing with the FDR method.

combinations of the intermediate volume of PA with short (HR, 1.63; 95% CI, 1.28–2.07) and long sleep duration (HR, 1.10; 95% CI, 0.91–1.34). Likewise, the total volume of PA protected against the risks of CVD and cancer mortality associated with short and long sleep duration in a gradient dose–response manner. Similarly, when grouped by MVPA threshold (150 min/week), the HRs of all-cause mortality associated with short (HR, 1.88; 95% CI, 1.61–2.20) and long (HR, 1.69; 95% CI, 1.49–1.90) sleep duration among participants not meeting MVPA recommended target significantly declined into 1.06 (95% CI, 0.80–1.39) and 1.01 (95% CI, 0.83–1.21), respectively, when engaging MVPA well above the recommended threshold (*Figure 3B*). Similar gradient patterns were observed regarding the outcomes of CVD and cancer mortality. In addition, we found significant additive and/or multiplicative interactions of short sleep duration, the total volume of PA, and MVPA with all mortality outcomes (see Supplementary material online, *eTables S8 and S9*). The results of joint analyses remained consistently significant even after multiple testing correction using the FDR method.

Sensitivity analyses

The mortality risks were slightly attenuated in some sensitivity analyses. However, most of the results remained robustly consistent in all the sensitivity analyses, for instance, restricting the analyses to the sample without missing data (see Supplementary material online, *eTables S10 and S11*) and to the samples where the accelerometer was worn for seven whole days (see Supplementary material online, *eTables S12 and S13*), further adjusting for prevalent illnesses (see Supplementary material online, *eTables S14–S17*), excluding baseline CVD and cancer (see Supplementary material online, *eTables S18 and S19*), performing the time lag analyses (see Supplementary material online, *eTables S20 and S21*), or censoring data up to 31 December 2019 (see Supplementary material online, *eTables S22 and S23*).

Discussion

To our knowledge, the present study was the first to use accelerometry to document the joint association of PA and sleep duration with all-cause, CVD, and cancer mortality. We reported several important findings. First, accelerometer-measured PA (total volume of PA and time spent in MVPA) and sleep duration were independently associated with mortality in a curvilinear dose–response manner. The most striking finding was that objectively measured PA and sleep duration had significantly additive and interactive effects on mortality risks. Short and long sleep duration was associated with the greatest mortality risks among participants with the lowest volume of total PA. In contrast, the mortality risks of short and long sleep duration were similar to those of normal sleep duration among participants with a higher volume of total PA. More importantly, we found that engaging MVPA well above the lower threshold recommended by the WHO seemed to be able to mitigate most detrimental associations of unusual sleep duration with mortality.

Our study using accelerometry offered robust evidence supporting the large body of research relying on self-reported data, showing independent associations of PA and sleep duration with mortality.[3,4] Similar to previous studies,[3,4] we observed that both short and long sleep duration increased the risks of mortality, particularly all-cause and CVD mortality. Likewise, this study revealed a curvilinear dose–response between time spent in PA and mortality risks, which are largely consistent with previous observations.[2,24] The spline analyses suggested that the maximal risk reduction was observed at about 25 mg for the total volume of PA and 150 min per week for MVPA, nearly meeting the lower threshold of the WHO recommendation for PA.[21] Our study replicated the previous observations in a much larger sample using

A **Total volume of PA**

Subgroup	N	Incidence rate (%), per 1000 person-years	Hazard Ratio (95% CI)	P value
All-cause mortality				
High volume of PA				
Normal sleep duration	24 189	2.4	1.00 [Reference]	
Short sleep duration	2 758	3.2	1.17 (0.89-1.53)	0.253
Long sleep duration	3 771	2.2	0.91 (0.69-1.20)	0.498
Moderate volume of PA				
Normal sleep duration	22 940	3.8	1.21 (1.06-1.37)*	0.004
Short sleep duration	1 998	5.8	1.63 (1.28-2.07)*	<0.001
Long sleep duration	5 768	3.4	1.10 (0.91-1.34)	0.329
Low volume of PA				
Normal sleep duration	20 390	7.7	1.79 (1.59-2.02)*	<0.001
Short sleep duration	1 789	12.0	2.51 (2.07-3.05)*	<0.001
Long sleep duration	8 618	8.6	2.06 (1.80-2.36)*	<0.001
CVD mortality				
High volume of PA				
Normal sleep duration	24 189	0.6	1.00 [Reference]	
Short sleep duration	2 758	1.1	1.40 (0.88-2.25)	0.156
Long sleep duration	3 771	0.3	0.49 (0.24-1.01)	0.053
Moderate volume of PA				
Normal sleep duration	22 940	1.2	1.38 (1.08-1.75)*	0.009
Short sleep duration	1 998	2.0	1.77 (1.16-2.69)*	0.008
Long sleep duration	5 768	0.9	1.09 (0.75-1.59)	0.654
Low volume of PA				
Normal sleep duration	20 390	3.0	2.27 (1.82-2.84)*	<0.001
Short sleep duration	1 789	6.3	3.93 (2.90-5.32)*	<0.001
Long sleep duration	8 618	3.0	2.35 (1.84-3.01)*	<0.001
Cancer mortality				
High volume of PA				
Normal sleep duration	24 189	1.7	1.00 [Reference]	
Short sleep duration	2 758	1.8	1.00 (0.70-1.42)	0.989
Long sleep duration	3 771	1.6	0.95 (0.69-1.30)	0.73
Moderate volume of PA				
Normal sleep duration	22 940	2.5	1.19 (1.02-1.38)*	0.028
Short sleep duration	1 998	3.2	1.35 (0.98-1.86)	0.064
Long sleep duration	5 768	2.3	1.08 (0.86-1.37)	0.501
Low volume of PA				
Normal sleep duration	20 390	4.3	1.55 (1.33-1.79)*	<0.001
Short sleep duration	1 789	5.5	1.83 (1.39-2.40)*	<0.001
Long sleep duration	8 618	5.1	1.85 (1.56-2.19)*	<0.001

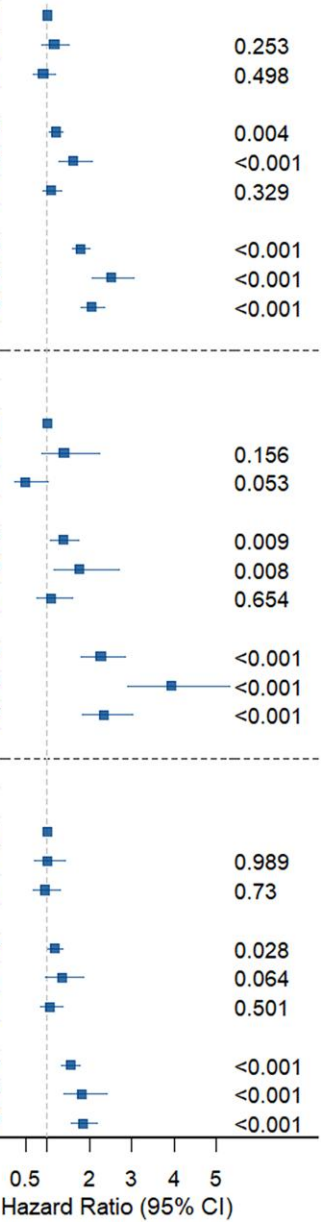


Figure 3 Joint associations of accelerometer-measured sleep duration, and total volume of physical activity (*A*) or moderate-to-vigorous physical activity (*B*) with all-cause, cardiovascular disease, and cancer mortality. Multivariable Cox model was adjusted for age, sex, ethnicity, Townsend deprivation index, recruitment centre, education level, season of accelerometer wear, body mass index, healthy diet score, smoking status, alcohol intake, and shift work history. **P* values remained significant after multiple testing with false discovery rate method.

accelerometer-measured data, which can substantially offset the pitfalls of self-reported data and provide more reliable estimates of prospective associations of sleep and PA with mortality.

To our knowledge, this is the first study to reveal an interactive joint association of the two time-dependent lifestyles, PA and sleep duration as objectively measured by an accelerometer, with mortality risk. To date, several studies have attempted to explore the additive effects of sleep duration and PA on mortality risk, reproducing some conflicting findings.[7,8,25] An earlier Swedish cohort with a 15-year follow-up demonstrated that the detrimental effects on survival associated with long

B MVPA

Subgroup	N	Incidence rate (%), per 1000 person-years	Hazard Ratio (95% CI)	P value
All-cause mortality				
Recommended MVPA				
Normal sleep duration	27 157	2.8	1 [Reference]	
Short sleep duration	2 468	3.2	1.06 (0.80-1.39)	0.699
Long sleep duration	6 406	3.0	1.01 (0.83-1.21)	0.955
Not recommended MVPA				
Normal sleep duration	40 362	5.6	1.41 (1.27-1.56)*	<0.001
Short sleep duration	4 077	8.3	1.88 (1.61-2.20)*	<0.001
Long sleep duration	11 751	7.0	1.69 (1.49-1.90)*	<0.001
CVD mortality				
Recommended MVPA				
Normal sleep duration	27 157	0.8	1 [Reference]	
Short sleep duration	2 468	1.1	1.09 (0.68-1.76)	0.719
Long sleep duration	6 406	0.9	0.94 (0.66-1.34)	0.722
Not recommended MVPA				
Normal sleep duration	40 362	2.0	1.55 (1.30-1.86)*	<0.001
Short sleep duration	4 077	3.8	2.40 (1.86-3.09)*	<0.001
Long sleep duration	11 751	2.3	1.66 (1.33-2.06)*	<0.001
Cancer mortality				
Recommended MVPA				
Normal sleep duration	27 157	1.9	1 [Reference]	
Short sleep duration	2 468	1.8	0.90 (0.63-1.31)	0.591
Long sleep duration	6 406	2.1	1.02 (0.81-1.29)	0.849
Not recommended MVPA				
Normal sleep duration	40 362	3.4	1.31 (1.15-1.48)*	<0.001
Short sleep duration	4 077	4.1	1.49 (1.20-1.85)*	<0.001
Long sleep duration	11 751	4.2	1.57 (1.35-1.83)*	<0.001

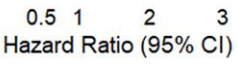


Figure 3 Continued

sleep duration, but not short sleep duration, were most evident among individuals with low levels of PA.[7] Conversely, in a cohort of former elite male athletes, Wennman H *et al.* observed that leisure time PA levels modified the associations of short sleep duration, but not long sleep duration, with all-cause mortality.[8] Another study in a Taiwan Chinese population–based cohort showed that short and long sleep duration was no longer associated with the risk of all-cause and CVD mortality when achieving a PA level of 15 metabolic equivalent of task (MET)-h/week or above.[9,25] The inconsistent observations concerning short or long sleep duration possibly arise from heterogeneities of study populations or daily light exposure associated with the geographical location, insufficient statistical power due to smaller sample size, or measurement bias. Our study testified the research question in a larger population with more reliable measures of sleep duration and PA using an accelerometer. In the same cohort as in the current study, Huang BH *et al.* found that the association of a composited sleep score that included self-reported sleep duration with all-cause and CVD mortality risks was only partly attenuated by even the highest level of MVPA.[9] By using accelerometer-measured sleep duration and PA, our study revealed directly that the detrimental effect of short or long sleep could be fully eliminated by recommended level of MVPA or by a higher volume of PA at any intensity.

Another important finding was that meeting the guideline-recommended PA target (150 min/week for MVPA) can diminish the most detrimental effects on all-cause and CVD mortality associated with either short or long sleep duration. This threshold also nearly approached the turning point, as reported by the Taiwanese cohort study (15 MET-h/week).[25] Our findings support the need to encourage the maintenance of guideline-recommended PA levels to improve longevity, especially among individuals with extremely short or long sleep duration.

We speculated that PA alleviated mortality risk associated with short or long sleep duration through differential mechanisms. As for short sleep duration, the suggested causal links to adverse health outcomes included a series of pathologies including, hyperactivation of the sympathetic nervous system,[26] insulin resistance,[27] endothelial dysfunctions,[28] and inflammation.[29] Sleep deprivation significantly promotes excess energy intake and visceral obesity.[30] Instead, PA reinforces cardiorespiratory fitness,[31] inhibits inflammatory responses,[32] and improves glucose metabolism.[33] Exercise training effectively alleviates endothelial

dysfunction triggered by sleep loss, possibly through inflammation pathways.[34] The multiple health benefits of PA may potentially serve as a mechanism for attenuation of PA or elimination of the detrimental association of short sleep duration with mortality. However, unlike short sleep, long sleep may act as a surrogate marker of residual confounding due to poor health.[35] Of note, we found a steeper decline in mortality risk immediately after improving PA levels among long sleepers compared with short sleepers. Since PA and sleep are time-dependent behaviours, sleeping for extremely long durations might compromise the time available for PA.[36] These findings likely support the hypothesis that the detrimental associations between long sleep duration and death might partly be compensated by prolonging the time for engaging in PA.

Our findings highlight that the promotions targeting both PA and sleep duration may be more effective in preventing or delaying premature death among the middle-aged population than solely targeting either behaviour. Maintaining normal sleep duration is important but not sufficient; long-term engagement in PA meeting recommendations combined with healthy sleep may yield greater benefits in maintaining longevity. Notably, if sleep restriction or excessive time spent in bed is inevitably avoided, engaging a sufficient amount of PA would be considered as a practical and feasible strategy to partly compensate for the harmful effects resulting from unhealthy sleep.

The present study had some strengths, including a large sample size and the adoption of accelerometer. An accelerometer largely offsets the recall bias occurring in the application of self-reported questionnaires.[11]

However, the results should be considered in the setting of some potential limitations. First, our study did not account for prospective changes in sleep duration and PA. However, previous analyses of the data from the UK Biobank suggest that the pattern of sleep and PA remain relatively stable over time.[37,38] Second, the definition of unusual sleep duration was not adjusted according to age, which may introduce a misclassification bias. However, the distributions of normal, short, and long sleep duration in this study were similar to that in other middle-aged and older populations.[39] Third, despite careful consideration of confounding factors, due to the observational nature of the study, the issues of residual confounding and reverse causation could not be completely ruled out. Therefore, we further adjusted for prevalent illness at baseline, removed deaths in the first two years of follow-up, and excluded participants with baseline CVD and cancer in the sensitivity analyses. Fourth, most covariates were assessed during the physical visits to the assessment centres, nearly six years before the present study baseline (date of accelerometer mail-out). However, these covariates have been proven to be stable over time,[40] indicating that such a time lag is not likely to affect the reliability of the current findings. Fifth, sedentary behaviour is not included in the current analyses due to its possible association with PA and sleep, which would violate the premise of Cox proportional hazards regression models. We analysed the association of sedentary behaviour with PA by defining sedentary as any epoch with a mean acceleration <30 mg outside the SPT window according to similar studies,[41] and did find a significant correlation between them (Spearman's correlation: ρtotal volume of PA = −0.706, ρMVPA = −0.357). Sixth, besides sleep duration, various sleep patterns and sleep behavioural issues have been found to be associated with excessive mortality risks.[9,25] These parameters are not investigated in the current study because accelerometer is limited in measuring parameters other than sleep/wake states.[42] Last, the sample from the UK Biobank is not representative of the population of the UK, which may limit the generalization of the current findings. A previous analysis, however, revealed that the exposure–outcome associations of the UK Biobank are comparable to observations from other more representative samples.[43] More prospective multi-centre evaluation are expected to help us learn more about the associations worldwide in the future.

Conclusions

This population-based cohort study suggested that PA and sleep duration were jointly associated with all-cause, CVD, and cancer-caused mortality risks among middle-aged and older adults, by using objective measures. The majority of the detrimental associations of unusual sleep duration with mortality may be mitigated by engaging in a higher volume of PA or meeting the lower threshold of the WHO recommendation for MVPA.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Ethics approval and consent to participate

The UK Biobank has ethical approval from the National Research Ethics Service (Ref 11/NW/0382). All participants included provided written informed consent.

Disclaimer

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Author contributions

Y.Y.L., Q.S.G., and J.H.Z. contributed to the conception and design of the work. F.H.L. was responsible for the acquisition of data. H.L.F. and Y.Y.L. performed all data analyses. Y.Y.L., Y.L.C., H.L.F., and X.Y.J. drafted the manuscript. All the authors gave comments and revised the manuscript. All the authors approved the final version to be submitted.

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Conflict of interest: None declared.

Data availability

Individual-level data from the UK Biobank are not publicly available due to their policy, but they will be available after applying the UK Biobank (https://www.ukbiobank.ac.uk/).

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