Title Page

The title:

Sleep and physical activity in relation to all-cause, cardiovascular disease, and cancer mortality risk.

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ABSTRACT

Objectives Although both physical inactivity and poor sleep are deleteriously associated with mortality, the joint effects of these two behaviours remain unknown. This study aimed to investigate the joint association of physical activity (PA) and sleep with all-cause/cause-specific mortality risks.

Methods 380,055 participants (55.9±8.1 years, 55% female) from the UK Biobank were included. Baseline PA levels were categorized as high, medium, low, and no moderate-to-vigorous PA (MVPA) based on public health guidelines. We categorized sleep into healthy, intermediate, and poor with an established composited sleep score of chronotype, sleep, insomnia, snoring, and daytime sleepiness. We derived twelve PA–sleep combinations, accordingly. Mortality risks were ascertained to May 2020 for all-cause, total cardiovascular disease (CVD), CVD sub-types (coronary heart disease, hemorrhagic stroke, ischemic stroke), as well as total cancer and lung cancer.

Results After an average follow-up of 11.1 years, sleep scores showed dose-response associations with all-cause, total CVD, and ischemic stroke mortality. Compared to high PA-healthy sleep group (reference), the no MVPA-poor sleep group had the highest mortality risks for all-cause (hazard ratio [95% confidence intervals], (1.39 [1.20 to 1.61]), total CVD (1.44 [1.09 to 1.88]), total cancer (1.30 [1.06 to 1.59]), and lung cancer (1.59 [1.08 to 2.34]). The deleterious associations of poor sleep with all outcomes, except for stroke, was amplified with lower PA.

Conclusion The detrimental associations of poor sleep with both all-cause and cause-specific mortality risks are exacerbated by low PA, suggesting likely synergistic effects. Our study supports the need to target both behaviours in research and clinical practice.

Keywords:

sleep patterns; cohort study; risk factor; synergistic effect.

KEY MESSAGES

what are the new findings?

Among middle-aged UK adults without obstructive sleep apnea history or class III obesity, PA at levels above the WHO guideline (600 MET-mins/wk) threshold eliminated most of the deleterious associations of poor sleep with mortality.

how might it impact on clinical practice in the near future?

As emerging evidence supports a synergistic effect of sleep and PA on health outcomes, future trials concurrently targeting both behaviours are warranted.

INTRODUCTION

Both physical inactivity and poor sleep are deleteriously associated with all-cause, cardiovascular diseases (CVD), and cancer mortality.[1-5] Both behaviours are complex, and their health effects are dependent upon various characteristics. For example, health-related sleep characteristics include duration, quality, and timing. Sleep duration has shown a curvilinear relationship (U-shaped) with all-cause, CVD, and cancer mortality, with the lowest risk observed among those obtaining between 7-8 hours per night.[1-3, 6] Based on a Swedish cohort (n = 70,973) with a 15-year follow-up, Bellavia et al. (2014) suggested that a low physical activity (PA) level could exaggerate the detrimental association between inadequate sleep duration and all-cause and CVD mortality risk.[6] Although sleep quality and timing (*e.g.*, snoring and chronotype) are also associated with all-cause and cause-specific mortality,[7] to our knowledge, very few studies have examined the synergistic effect of PA and sleep quality on mortality while the results were inconsistent.[8, 9] The lack of a standardized sleep measurement might hinder the investigation of sleep concerning health and the joint effects with other behaviours.[3]

Besides the independent health effects of sleep duration, quality, and timing, these sleep characteristics have shown a potential joint effect on health outcomes. Poor sleep quality, in combination with either inadequate or excess sleep,[7, 10] is associated with increased mortality risk. Based on the Sleep Heart Health Study with an 11.4-year follow-up (n = 4,994), Bertisch et al. (2018) found that only the combination of inadequate sleep duration and poor sleep quality was associated with incident CVD risk.[11] This interaction between sleep characteristics, as well as the heterogeneity of the sleep characteristics chosen between studies, might produce less consistent results.[3, 12] Recently, Fan et al. (2020) proposed a novel score integrating both duration, quality, and timing into a single sleep measurement.[12] They demonstrated its capacity to identify high-risk populations for incident CVD based on the UK Biobank cohort with an 8.5-year follow-up (n = 385,292).

PA and sleep could be co-dependent and influence health conditions through related pathways.[6, 8, 9, 13-16] For example, PA might improve health outcomes through improving metabolic fitness (e.g., reducing insulin resistance), maintaining a stable circadian rhythm and a healthy sleep pattern, and enhancing energy expenditure.[8, 14, 15] Prolonged sleep duration may decrease the time available for PA due to the time-dependency between the two behaviours.[6] Beyond their independent health effects, the potential joint effects of these two key behaviours remain largely unknown.[17] We investigated the joint association of PA and a novel comprehensive sleep score with all-cause and subtype-specific CVD and cancer mortality risks.

METHODS

The UK Biobank is a prospective cohort of 502,616 participants of adults aged 37-73 years, recruited from 22 centres across the UK between 2006-2010, with ethical approval by the National Research Ethics Service (Ref 11/NW/0382). Participants completed questionnaires, interviews, physical measurements at baseline assessments, and consented to the use of their de-identified data and access to their national health-related hospital and death records. Detailed methods are described elsewhere.[18]

Outcomes

Date of death was obtained from death certificates through data linkage with national datasets from the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). The cause of death (including both primary and contributory causes of death) was defined based on the international classification of diseases, 10th revision (ICD10)(**Supplementary File, Table S1**). In short, total CVD was defined as diseases of the circulatory system, excluding hypertension, diseases of arteries and lymph. Total cancer was defined as neoplasms, excluding *in situ*, benign, uncertain, or non-well-defined cancers. Three CVD sub-types and one cancer site which have been previously linked to sleep disorders in published systematic reviews were also defined: coronary heart disease, hemorrhagic stroke, ischemic stroke, and lung cancer.[5, 16] The censoring date was May 2020. Participants were followed up from the date of attendance at the recruitment centre to the date of death or censorship, whichever came first. The data linkage was updated two or three times per year.

Exposures

PA was quantified using the modified short-form International Physical Activity Questionnaire (IPAQ), which assessed the duration and frequency of PA in leisure time.[19] Weekly PA was summarized using weekly total Metabolic Equivalent Task (MET), calculated by multiplying the MET value of activity by the number of PA hours per week. Based on the lower and upper limits of the World Health Organization (WHO) PA guideline,[19] PA was categorized as low (0 to $<$ 600 MET-mins/wk), medium (600 to $<$ 1200 MET-mins/wk), and high ($\geq$ 1200 MET-mins/wk). Another no moderate-to-vigorous PA (MVPA) category was further defined to reflect the potential health benefits of insufficient PA compared to no MVPA.[4, 21]

A novel healthy sleep score, comprising five sleep characteristics, was applied.[12] Morning chronotype, adequate sleep duration (7-8 hr/d), not usually insomnia, no snoring, and no frequent daytime sleepiness, represented healthy sleep characteristics. **Supplementary File, Table S2** provides a detailed questionnaire and definition of each item. Participants were scored from 0 to 5, according to their number of the healthy characteristics and were categorized into three groups: "healthy sleep" (≥ 4 sleep score); "intermediate sleep" (2-3 sleep score); and "poor sleep" (≤ 1 sleep score). This score has been used in the UK Biobank to distinguish high-risk middle-aged populations for incident CVD.[12] We generated twelve combined joint categories of PA and sleep accordingly (**Supplementary File, Table S3**).

Covariates

To reduce the effect of potential confounding, demographics and contextual covariates were selected based on previous literature,[3, 12, 15] and included age, sex, socioeconomic status, employment status, body mass index (BMI), cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, mental health issues, and PA or sleep scores when applicable. **Supplementary File, Table S4** describes the definitions in detail.

Statistics and data analysis

All tests were performed using SAS 9.4 or R 3.6.3 software and were two-sided. Descriptive statistics are presented stratified by the sleep score, while chi-square tests, analysis of variance (ANOVA), and Kruskal-Wallis tests were conducted as applicable. Kaplan-Meier estimation, the scaled Schoenfeld residuals, and supremum tests of functional forms were used to examine the proportional hazards assumption, although no noticeable violations were observed. We also performed models excluding 15 potential outliers with extreme values of confounding detected by the *dfβ* measure-based influence diagnostics. Since the effect sizes of all the effects were unaffected after exclusion (data not shown), the present analyses reserved them in all models.

Both the independent and joint association between PA and sleep scores with mortality were examined using Cox-proportional hazard models, with a high PA level, healthy sleep, or the combination of both as the reference as applicable. Each of the described analyses started with a minimally adjusted Cox model including only age and sex as covariates (Model 1), and a second model additionally adjusted for socioeconomic status, employment status, body mass index (BMI), cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, mental health issues, and PA or sleep scores when applicable (Model 2).[3, 12, 15] In the sensitivity analysis, we further examined the potential synergistic effect between the two main exposures by performing additional analysis of both the additive and multiplicative interactions between the two primary exposures (PA and sleep).[22]

RESULTS

For this study, participants were excluded if they had history of total CVD (n = 30,696), total cancer (n = 21,257), or both (n = 2,585) at baseline (**Supplementary File, Figure S1)**. Participants were also excluded if they had obstructive sleep apnea history (n = 1,825), class III obesity (body mass index (BMI) ≥ 40 kg/m^2) (n = 7,937), missing or unusable data on sleep characteristics (n = 10,633), PA (n = 35,754), or any confounders (n = 10,737). We also excluded those who died from coronavirus disease (COVID-19) (either a primary or contributory cause) (n = 235). To reduce the potential reverse causality,[23] we further excluded those who died in the first two years of follow-up (n = 902). The comparison between included and excluded samples was also provided in **Supplementary File, Table S5.** A total of 380,055 participants (55.9 ± 8.1 years old, 55% female) were included in the present study. Among those, the average follow-up time was 11.1 ± 1.2 years, with 15,503 all-cause deaths (4,095 events from total CVD and 9,064 from total cancer, including 1,932 from coronary heart diseases, 359 from hemorrhagic stroke, 450 from ischemic stroke, and 1,595 from lung cancer). **Table 1** presents the characteristics of participants stratified by sleep scores. The majority (56%) of the participants had a healthy sleep, followed by having intermediate (42%) or poor sleep (3%), demonstrating the same distribution as the work by Fan et al. (2020).[12] Individuals with different sleep categorizations had significant differences in all the covariates. Participants who were younger, female, faced less socioeconomic deprivation, were employed in non-shift work, never smoked, had higher vegetable and fruit intakes, drank less alcohol, sat less, had no mental health issues, and were more PA, tended to have healthier sleep scores.

Independent association of exposures with mortality

Table 2 (and **Supplementary File, Figure S2)** shows the independent (and mutually adjusted) association of sleep scores and PA with mortality risks. There was a dose-response increase toward poorer sleep in mortality risks for all-cause, total CVD, and ischemic stroke. Relative to healthy sleep, with full adjustment for selected confounders and PA levels (Model 2), poor and intermediate sleep was associated with higher mortality risks for all-cause (hazard ratio, HR, [95% confidence intervals]: 1.05 [1.02 to 1.09], for intermediate sleep; 1.23 [1.13 to 1.34], for poor sleep) and total CVD (1.09 [1.03 to 1.17], for intermediate sleep; 1.39 [1.19 to 1.62], for poor sleep). Poor sleep was further associated with ischemic stroke mortality (1.94 [1.29 to 2.94]), while intermediate sleep was further associated with coronary heart diseases (1.16 [1.06 to 1.27]).

Compared to participants with a high PA level, those with all the other PA levels had an incrementally higher risk for all-cause mortality after full adjustment (1.05 [1.01 to 1.10], for medium level; 1.08 [1.02 to 1.14], for low level; 1.25 [1.20 to 1.31], for no MVPA, respectively). Those with no MVPA also had higher risks for all the other conditions except for hemorrhagic stroke (for all-cause, 1.25 [1.20 to 1.31]; for total CVD, 1.31 [1.21 to 1.42]; for total cancer, 1.16 [1.10 to 1.23]; for coronary heart diseases, 1.35 [1.21 to 1.52]; for ischemic stroke, 1.38 [1.07 to 1.77]; and for lung cancer, 1.34 [1.19 to 1.53]).

Joint association of exposures with mortality

Figure 1 and 2, and **Supplementary File, Table S6 and S7** illustrate the HR for each condition of exposure combinations compared to the referent high PA-healthy sleep group. After full adjustment, participants with no MVPA had higher mortality risks for all outcomes except for hemorrhagic stroke, while those mutually with poor sleep had the highest risks (for all-cause, 1.57 [1.35 to 1.82]; for total CVD, 1.67 [1.27 to 2.19]; for total cancer, 1.45 [1.18 to 1.77]; for coronary heart diseases, 1.59 [1.07 to 2.37]; for ischemic stroke, 2.96 [1.43 to 6.11]; and for lung cancer, 1.91 [1.30 to 2.81], respectively). Participants with low PA-poor sleep combination had higher mortality risks for all-cause, total CVD, coronary heart disease, and lung cancer. In the sensitivity analysis, we found statistically significant additive interaction in total CVD, and multiplicative interactions in all the outcomes except for stroke **(Supplementary File, Table S8 and S9)**.

DISCUSSION

To our knowledge, this is the first prospective study investigating the association of a composite score reflecting both sleep duration, quality, and timing with mortality outcomes, as well as the largest investigation examining the joint effect of sleep and PA with all-cause and cause-specific mortality. The PA measurement in the UK Biobank captured frequency, intensity, and duration (time) in the leisure-time domain. Our results suggest that, among middle-aged adults, poorer sleep, after adjustment for PA, remained associated with higher mortality risks for all-cause, total CVD, and ischemic stroke. Besides, there was a potential synergistic effect of sleep and PA with mortality risks for all-cause, total CVD, total cancer, and lung cancer. Compared to no MVPA, levels of PA above the lower threshold recommended by WHO (600 MET-mins/wk),[20] appeared to eliminate most of the detrimental associations of poor sleep and mortality.

Comparison with other studies

Sleep duration, quality, and timing are interrelated dimensions of healthy sleep characteristics [7 9 11 16].[7-,12, 16] Previous meta-analyses and systematic reviews based on single sleep characteristics provided mixed results in relation to poor sleep and all-cause mortality risk.[3, 24] Yin et al. (2017) suggested that inadequate sleep duration (shorter or longer than 7 hr/d) was associated with all-cause mortality risk (pooled relative risk, RR: 1.06 [1.04 to 1.07] per hour reduction for short sleepers, and 1.13 [1.11 to 1.15] per hour increment for long sleepers).[24] Alternatively, Kwok et al. (2018) proposed that only long sleepers (≥ 8 hr/d) but not short sleepers (< 7 hr/d) had a higher risk for all-cause mortality (*e.g.*, pooled RR: 1.14 [1.05 to 1.25] for 9-hr sleeper) compared to healthy sleepers (7 hr/d), while sleep quality showed no significant association with mortality risk (pooled RR: 1.03 [0.93 to 1.14]).[3] With a multicomponent sleep characteristic score, the present study shows that people with poor or intermediate sleep, with adjustment for PA, still had a 23% or 5% higher risk for all-cause mortality and a 39% or 9% higher risk for total CVD mortality (**Table 2**). As poor sleep was further associated with 94% higher mortality risk for ischemic stroke but not for hemorrhagic stroke, our finding extends the work by Fan et al. (2020), which did not distinguish the subtypes of stroke.[12] The adverse health effects of poor sleep remain even within participants with a high PA level (**Figure 1**). Besides, our results indicate that not participating in any MVPA could result in 16% to 38% higher mortality risks for all-cause, total CVD, total cancer, and the sub-types (**Table 2**). In agreement with a previous prospective study and public health guidelines,[4, 21] our finding suggested that a below-guideline MVPA level could be beneficial.

Recent studies have suggested the synergistic health effect of physical inactivity and poor sleep.[6, 8, 9, 15, 17] Cassidy et al. (2016) reported that people with CVD or type 2 diabetes tended to simultaneously report physical inactivity and poor sleep, based on a cross-sectional analysis of the same cohort as the present study.[15] In a 15-year follow-up of a Taiwanese cohort (n = 341,248), short sleep duration (defined as < 6 hr) increased all-cause and CVD mortality risk only among physically inactive participants (< 450 MET-mins/wk).[9] Wennman et al. (2017) found that the combination of insufficient sleep duration (≤ 6 hr) and low leisure-time PA (< 450 MET-mins/wk) was associated with higher mortality risks for all-cause (HR: 1.49 [1.05 to 2.11]) and CVD (HR: 1.98 [1.25 to 3.12]), compared to the referent combination of adequate sleep (6.5 to 8.5 hr) and high leisure-time PA (≥ 450 MET-mins/wk), based on a male cohort comprising 60% of former elite athletes with a 26-year follow-up (n = 1,638).[8] However, the same study also suggested no synergistic effect of sleep quality and PA on mortality. Likewise, Xiao et al. (2014) found no significant relative excess risk of insufficient sleep (< 7 hr) and low MVPA (<1 hr/wk) for all-cause mortality, based on a large US cohort with a 14-year follow-up (n = 239,896).[25] The present study extended the findings from the above studies by capturing different perspectives of sleep and death causes. Compared to those with the high PA-healthy sleep combination, participants with the no MVPA-poor sleep combination had higher mortality risks (*e.g.*, 57% for all-cause; 67% for total CVD; 45% for total cancer). Moreover, the detrimental effect of poorer sleep with mortality risks could potentially be exaggerated among participants with lower PA levels (**Figure 1 and 2**; **Supplementary File, Table S6 to S9**).

Several explanations of the deleterious associations of poor sleep with health have been put forward,[6, 8, 9, 15, 16] although none of them has been widely established. In particular, the mechanisms surrounding the deleterious associations of prolonged sleep duration with mortality outcomes are controversial.[5] One possibility is that these associations are not causal and are due to residual confounding, *e.g.*, fatigue, sleep fragmentation, substance use, or undiagnosed mental disorders.[26] Another hypothetical mechanism is that prolonged sleep duration might compromise the time available for health-enhancing behaviours such as PA.[15] In the present sample, however, the average total PA volume was not very different in prolonged sleepers compared to those in the adequate sleep range (adequate vs prolonged sleep: 43.0 vs 42.2 MET-hrs/wk), despite the large difference in average sleep times between the two groups (adequate vs prolonged sleepers: 7.4 vs 9.3 hr). We used a composite sleep score that relied on self-reported data and did not allow us to incorporate time sequence or patterns of the sleep-related behaviours in this study.[27] Future studies featuring wearable devices that measure sleep and physical activity will shed further light on the time-dependent aspects of these behaviours and their impact on health. Although an emerging body of evidence suggests that excessive PA might worsen sleep and potentially increase cardiovascular health risks,[28-30] the proportion of high PA (≥ 1200 MET-mins/wk) in the present study was higher in those with the healthiest sleep score (**Table 1**). Our results also showed that, among participants with PA higher than the upper limit of the WHO guideline (1200 MET-mins /week),[20] PA may attenuate the deleterious effects of poor sleep. However, in populations at the very top end of the activity spectrum, *e.g.*, athletes, excessive PA might compromise sleep.[28] The combination of very high PA and poor sleep could, in the long term, even increase the risks for injuries and infections.[30] As the point past which PA might be harmful is unknown,[29] we acknowledge that our results may not be applicable to extremely active populations.

Study strengths and limitations

The strengths of the present study include the prospective study design with large sample size and long follow up and extensive measurement of covariates, which allowed us to perform several sensitivity analyses to strengthen our interpretation. The novel sleep score integrating various aspects of the sleep characteristics provides a convenient yet thorough way for investigating the joint effects of sleep with other time-dependent behaviours like PA. Our study had some potential limitations. Firstly, the observational nature of our data precludes a definitive causal interpretation of our findings, although we took several measures to minimize risks for reverse causalities and confounding, such as exclusion criteria and a wide range of covariates included. Second, our exposures were measured by self-reported, random measurement error may have biased results toward the null, and thereby underestimating the true magnitude of the associations. Third, all the exposures and confounders were collected at recruitment and were assumed to be relatively constant over the course of the follow-up period. In a UK Biobank sub-sample with at least one repeated measurement of both exposures over a seven-year follow-up (n = 35,466), 59% and 68%of the participants maintained their PA and sleep, respectively. Future studies investigating changes of the two behaviours over time will further elucidate the synergistic effects of the two behaviours. Fourth, the PA measurement of the UK Biobank did not include other domains like occupation, transportation, and household.[15, 31] The relatively low sample size in some joint groups (*e.g.*, the low PA-poor sleep combination) may have compromised our statistical power to detect the differences in risk. Lastly, the UK Biobank had a response rate of 5.5%, and it is not representative of the UK population.[32] However, a recent UK Biobank study showed that poor representativeness does not materially affect the associations of physical activity and other lifestyle behaviours with mortality.[33]

CONCLUSIONS

Poor sleep was associated with a higher risk for all-cause and cause-specific mortality, and these risks were markedly exacerbated among participants with insufficient PA. Meeting the lower threshold of the current PA guidelines (600 MET-mins/wk) eliminated most of the deleterious associations of poor sleep with mortality. Our results support the value of interventions to concurrently target PA and sleep to improve health. Future prospective studies with device-based sleep and PA assessments and trials concurrently targeting both behaviours are warranted.

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Competing interests: None declared.

References

1 Ma QQ, Yao Q, Lin L, et al. Sleep duration and total cancer mortality: a meta-analysis of prospective studies. *Sleep Med* 2016;27-28:39-44.

2 Dohrn M, Sjöström M, Kwak L, et al. Accelerometer-measured sedentary time and physical activity—a 15 year follow-up of mortality in a Swedish population-based cohort. *J Sci Med Sport* 2018;21(7):702-07.

3 Kwok CS, Kontopantelis E, Kuligowski G, et al. Self-Reported Sleep Duration and Quality and Cardiovascular Disease and Mortality: A Dose-Response Meta-Analysis. *J Am Heart Assoc* 2018;7(15):e008552.

4 US Department of Health and Human Services. 2018 Physical Activity Guidelines Advisory Committee Scientific Report U.S. Department of Health and Human Services. Available: https://health.gov/our-work/physical-activity/current-guidelines/scientific-report/ [Accessed Aug 2020].

5 Jike M, Itani O, Watanabe N, et al. Long sleep duration and health outcomes: A systematic review, meta-analysis and meta-regression. *Sleep Med Rev* 2018;39:25-36.

6 Bellavia A, Akerstedt T, Bottai M, et al. Sleep duration and survival percentiles across categories of physical activity. *Am J Epidemiol* 2014;179(4):484-91.

7 Chien KL, Chen PC, Hsu HC, et al. Habitual sleep duration and insomnia and the risk of cardiovascular events and all-cause death: report from a community-based cohort. *Sleep* 2010;33(2):177-84.

8 Wennman H, Kronholm E, Heinonen OJ, et al. Leisure Time Physical Activity and Sleep Predict Mortality in Men Irrespective of Background in Competitive Sports. *Prog Prev Med (N Y)* 2017;2(6):e0009.
9 Li-Jung C, Mark H, Yun-Ju L, et al. Can physical activity eliminate the mortality risk associated with poor sleep? A 15-year follow-up of 341,248 MJ Cohort participants. J Sport Health Sci 2021. Available: https://doi.org/10.1016/j.jshs.2021.03.001 [Accessed Apr 2021].
10 Rod NH, Kumari M, Lange T, et al. The Joint Effect of Sleep Duration and Disturbed Sleep on Cause-Specific Mortality: Results from the Whitehall II Cohort Study. *PLOS ONE* 2014;9(4):e91965.
11 Bertisch SM, Pollock BD, Mittleman MA, et al. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. *Sleep* 2018;41(6)
12 Fan M, Sun D, Zhou T, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. *Eur Heart J* 2020;41(11):1182-89.
13 Kline CE. The bidirectional relationship between exercise and sleep: implications for exercise adherence and sleep improvement. *Am J Lifestyle Med* 2014;8(6):375-79.
14 Huang BH, Hamer M, Duncan MJ, et al. The bidirectional association between sleep and physical activity: A 6.9 years longitudinal analysis of 38,601 UK Biobank participants. *Prev Med* 2021;143:106315.
15 Cassidy S, Chau JY, Catt M, et al. Cross-sectional study of diet, physical activity, television viewing and sleep duration in 233,110 adults from the UK Biobank; the behavioural phenotype of cardiovascular disease and type 2 diabetes. *BMJ Open* 2016;6(3):e010038.
16 Stone CR, Haig TR, Fiest KM, et al. The association between sleep duration and cancer-specific mortality: A systematic review and meta-analysis. *Cancer Causes Control* 2019;30(5):501-25.
17 Rayward AT, Duncan MJ, Brown WJ, et al. A cross-sectional cluster analysis of the combined association of physical activity and sleep with sociodemographic and health characteristics in mid-aged and older adults. *Maturitas* 2017;102:56-61.

18 Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12(3):e1001779.

19 Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35(8):1381-95.

20 World Health Organization. Physical Activity and Adults: World Health Organization. Available: https://www.who.int/dietphysicalactivity/factsheet_adults/en/ [Accessed Aug 2020].

21 O'Donovan G, Lee IM, Hamer M, et al. Association of "Weekend Warrior" and Other Leisure Time Physical Activity Patterns With Risks for All-Cause, Cardiovascular Disease, and Cancer Mortality. *JAMA Intern Med* 2017;177(3):335-42.

22 Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol* 2012;41(2):514-20.

23 Strain T, Wijndaele K, Sharp SJ, et al. Impact of follow-up time and analytical approaches to account for reverse causality on the association between physical activity and health outcomes in UK Biobank. *Int J Epidemiol* 2020;49(1):162-72.

24 Yin J, Jin X, Shan Z, et al. Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc* 2017;6(9):e005847.

25 Xiao Q, Keadle SK, Hollenbeck AR, et al. Sleep duration and total and cause-specific mortality in a large US cohort: interrelationships with physical activity, sedentary behavior, and body mass index. *Am J Epidemiol* 2014;180(10):997-1006.

26 Ding D, Rogers K, Macniven R, et al. Revisiting lifestyle risk index assessment in a large Australian sample: should sedentary behavior and sleep be included as additional risk factors? *Prev Med* 2014;60:102-6.

27 Huang B-H, Inan-Eroglu E, Hamer M, et al. Joint associations of device-measured physical activity and sleep duration with cardiometabolic health in the 1970 British Cohort Study. *J Sci Med Sport* 2020;23(12):1191-6.

28 Falck RS, Stamatakis E, Liu-Ambrose T. The athlete's sleep paradox prompts us to reconsider the dose-response relationship of physical activity and sleep. *Br J Sports Med* 2021. Available: https://doi.org/10.1136/bjsports-2020-103835 [Accessed Mar 2021].

29 Eijsvogels TMH, Thompson PD, Franklin BA. The "Extreme Exercise Hypothesis": Recent Findings and Cardiovascular Health Implications. *Curr Treat Options Cardiovasc Med* 2018;20(10):84.

30 Walsh NP, Halson SL, Sargent C, et al. Sleep and the athlete: narrative review and 2021 expert consensus recommendations. *Br J Sports Med* 2020. Available: https://doi.org/10.1136/bjsports-2020-102025 [Accessed Mar 2021].

31 DiPietro L, Al-Ansari SS, Biddle SJH, et al. Advancing the global physical activity agenda: recommendations for future research by the 2020 WHO physical activity and sedentary behavior guidelines development group. *Int J Behav Nutr Phys Act* 2020;17(1):143.32 Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017;186(9):1026-34.

33 Stamatakis E, Owen KB, Shepherd L, Drayton B, Hamer M, Bauman AE. Is Cohort Representativeness Passé? Poststratified Associations of Lifestyle Risk Factors with Mortality in the UK Biobank. *Epidemiology* 2021;32(2):179.

Figure legends

Figure 1. The Joint Association of Physical Activity and Sleep Scores with Mortality for All-Cause, Total Cardiovascular Disease, and Total Cancer (n = 380,055)

a, all-cause; b, total cardiovascular disease; c, total cancer. Physical activity levels were categorized based on public health guidelines: no MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk). Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

Models were adjusted for age, sex, socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, and mental health.

Figure 2. The Joint Association of Physical Activity and Sleep Scores with Mortality for Sub-Type Conditions (n = 380,055)

a, coronary heart disease; b, hemorrhagic stroke; c, ischemic stroke; d, lung cancer. Physical activity levels were categorized based on public health guidelines: no MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk. Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

Models were adjusted for age, sex, socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, and mental health.

Text tables

Table 1. The Descriptive Statistics by Sleep Scores (n = 380,055)

Characteristics	All	Sleep Scores [a]		
		Poor	Intermediate	Healthy
n (%)	380,055 (100)	10,166 (3)	158,103 (42)	211,786 (56)
Follow-up (yr) (mean (SD))	11.1 (1.2)	11.0 (1.4)	11.1 (1.3)	11.1 (1.2)
Age (mean (SD))	55.9 (8.1)	56.1 (7.7)	56.1 (7.9)	55.6 (8.2)
Male (n (%))	171,315 (45)	890 (48)	76,819 (49)	89,606 (42)
Body mass index (kg/m^2) (mean (SD))	26.9 (4.1)	28.7 (4.5)	27.5 (4.2)	26.4 (4.0)
Socioeconomic Status (mean (SD)) [b]	-1.5 (3.0)	-0.8 (3.3)	-1.4 (3.1)	-1.6 (2.9)
Vegetable and Fruit Intake (serves/d) (mean (SD))	4.4 (2.9)	4.2 (3.1)	4.3 (3.0)	4.5 (2.9)
Sedentary Behaviour (hr/d) (mean (SD))	4.7 (2.4)	5.5 (2.8)	5.0 (2.5)	4.5 (2.3)
Mental Health Issue (n (%)) [c]	127,943 (34)	5,108 (50)	59,207 (37)	63,628 (30)

Cigarette Smoking (n (%))				
Never	213,618 (56)	4,758 (47)	82,786 (52)	126,074 (60)
Previous Smoker	128,597 (34)	3773 (37)	56,135 (36)	68,689 (32)
Current Smoker	37,840 (10)	1,635 (16)	19,182 (12)	17,023 (8)
Employment Status (n (%))				
Retired/not in the workforce	144,090 (38)	4,626 (46)	61,893 (39)	77,571 (37)
Employed not in shift work	197,803 (52)	4,225 (42)	78,439 (50)	115,139 (54)
Employed in night shift work	19,365 (5)	752 (7)	9,584 (6)	9,029 (4)
Employed in day shift work	18,797 (5)	563 (6)	8,187 (5)	10,047 (5)
Physical Active (n (%)) [d]				
No MVPA	59,541 (16)	2,510 (25)	28,289 (18)	28,742 (14)
Low	9,298 (10)	1,291 (13)	17,757 (11)	20,250 (10)
Medium	57,771 (15)	1,384 (14)	24,110 (15)	32,277 (15)
High	223,445 (59)	4,981 (49)	87,947 (56)	130,517 (62)
Alcohol Consumption (n (%)) [e]				

Never	13,843 (4)	389 (4)	5,567 (4)	7,887 (4)
Previous Drinker	11,512 (3)	525 (5)	4,980 (3)	6,007 (3)
Occasional Drinker	81,191 (21)	2,555 (25)	33,930 (22)	44,706 (21)
Within Guideline	130,901 (34)	2,712 (27)	50,203 (32)	77,986 (37)
Above Guideline	84,936 (22)	1,967 (19)	35,409 (22)	47,560 (23)
Above Double Guideline	57,672 (15)	2,018 (20)	28,014 (18)	27,640 (13)

a. Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5. There were significant differences ($p < 0.05$) across sleep score groups in all the characteristics shown in the table.

b. Townsend area deprivation index was used.

c. Had ever seen a doctor or psychiatrist for nerves, anxiety or depression.

d. Categorization based on public health guidelines: no MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk).

e. The UK guideline (14 UK units/wk) was used.

MET = metabolic equivalent task; MVPA = moderate-to-vigorous physical activity

Table 2. The Independent (and Mutually Adjusted) Associations of Physical Activity and Sleep Scores with Mortality (n = 380,055)

Exposure [a]	Hazard Ratio for Mortality Risks (95% confidence interval)							
	All-cause		Total cardiovascular disease		Total cancer			
	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]
Sleep Pattern								
Poor	**1.56**	**1.23**	**1.92**	**1.39**	**1.35**	1.13		
(n = 10,166)	**(1.44, 1.70)**	**(1.13, 1.34)**	**(1.65, 2.23)**	**(1.19, 1.62)**	**(1.20, 1.52)**	(1.00, 1.27)		
Intermediate	**1.16**	**1.05**	**1.24**	**1.09**	**1.12**	1.03		
(n = 158,103)	**(1.13, 1.20)**	**(1.02, 1.09)**	**(1.17, 1.33)**	**(1.03, 1.17)**	**(1.08, 1.17)**	(0.99, 1.08)		
Healthy (n = 211,786)				1.00				
	Coronary heart diseases		Hemorrhagic stroke		Ischemic stroke		Lung cancer	
Poor	**1.83**	1.26	1.23	1.05	**2.46**	**1.94**	**1.93**	1.25
(n = 10,166)	**(1.46, 2.29)**	(1.00, 1.59)	(0.67, 2.26)	(0.57, 1.95)	**(1.64, 3.70)**	**(1.29, 2.94)**	**(1.51, 2.46)**	(0.98, 1.60)

Intermediate (n = 158,103)	**1.34 (1.22, 1.46)**	**1.16 (1.06, 1.27)**	1.12 (0.90, 1.38)	1.04 (0.84, 1.29)	1.18 (0.97, 1.43)	1.06 (0.87, 1.29)	**1.29 (1.17, 1.43)**	1.05 (0.95, 1.16)
Healthy (n = 211,786)				1.00				
Physical Activity	All-cause		Total cardiovascular disease		Total cancer			
No MVPA (n = 59,541)	**1.39 (1.33, 1.44)**	**1.25 (1.20, 1.31)**	**1.52 (1.41, 1.65)**	**1.31 (1.21, 1.42)**	**1.28 (1.21, 1.35)**	**1.16 (1.10, 1.23)**		
Low (n = 9,298)	**1.1 (1.04, 1.16)**	**1.08 (1.02, 1.14)**	**1.14 (1.02, 1.26)**	1.09 (0.98, 1.21)	1.07 (0.99, 1.14)	1.03 (0.96, 1.11)		
Medium (n = 57,771)	**1.05 (1.01, 1.10)**	**1.05 (1.01, 1.10)**	1.07 (0.98, 1.17)	1.06 (0.97, 1.16)	1.03 (0.97, 1.09)	1.02 (0.96, 1.08)		
High (n = 223,445)				1.00				
	Coronary heart diseases		Hemorrhagic stroke		Ischemic stroke		Lung cancer	
No MVPA	**1.61**	**1.35**	**1.32**	1.26	**1.51**	**1.38**	**1.68**	**1.35**

(n = 59,541)	**(1.44, 1.81)**	**(1.21, 1.52)**	**(1.01, 1.73)**	(0.96, 1.66)	**(1.18, 1.92)**	**(1.07, 1.77)**	**(1.48, 1.89)**	**(1.19, 1.53)**
Low	1.13	1.08	0.95	0.97	1.16	1.16	1.13	1.09
(n = 9,298)	(0.97, 1.32)	(0.93, 1.26)	(0.65, 1.39)	(0.67, 1.43)	(0.83, 1.61)	(0.83, 1.61)	(0.96, 1.35)	(0.92, 1.30)
Medium	0.99	0.98	1.02	1.04	**1.46**	**1.47**	1.03	1.04
(n = 57,771)	(0.86, 1.13)	(0.86, 1.13)	(0.75, 1.38)	(0.77, 1.41)	**(1.14, 1.88)**	**(1.15, 1.89)**	(0.89, 1.20)	(0.89, 1.21)
High (n = 223,445)				1.00				

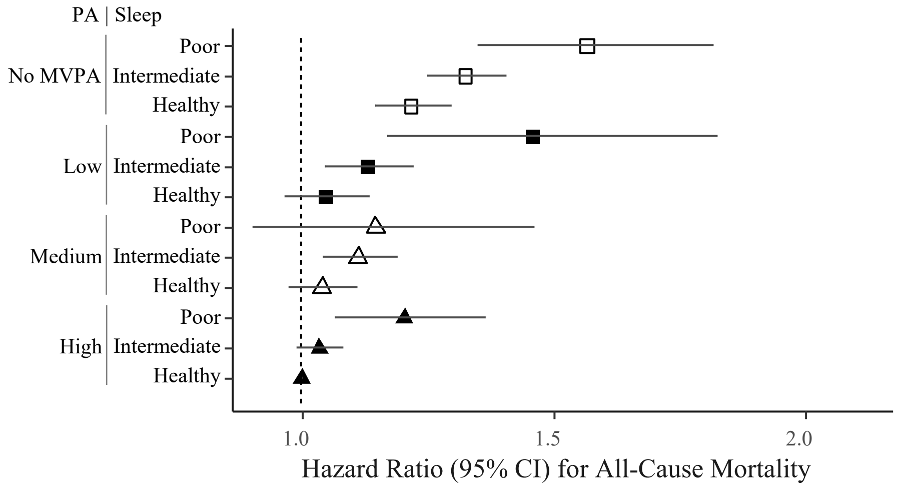
a. Physical activity levels were categorized based on public health guidelines: no MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk). Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

b. Adjusted for age and sex.

c. Further adjusted for socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, mental health, and mutually adjusted for sleep scores or physical activity levels as appropriate.

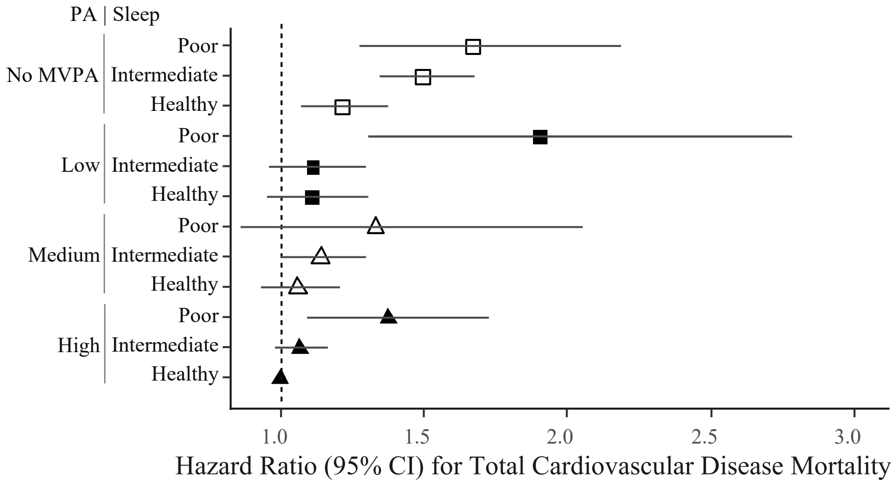
BMI = body mass index; MET = metabolic equivalent task; MVPA = moderate-to-vigorous physical activity.

1a



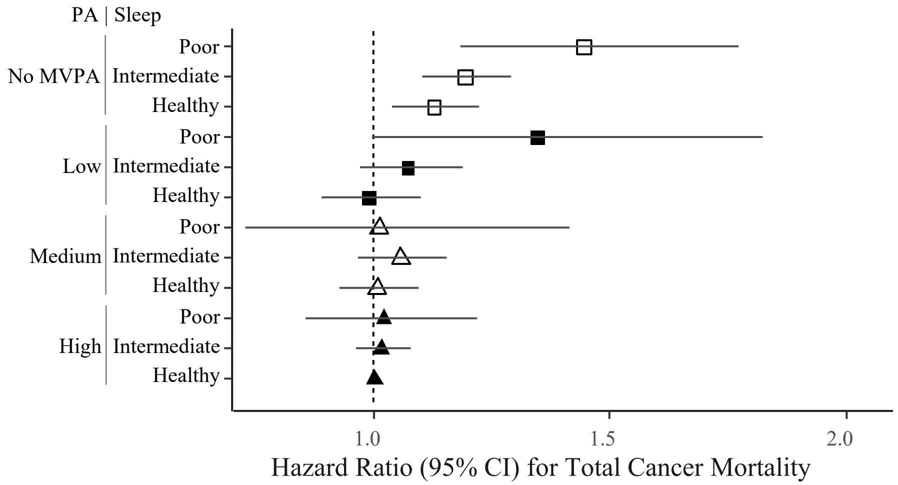
PA | Sleep
No MVPA
Low
Medium
High
Poor
Intermediate
Healthy
1.0
1.5
2.0
Hazard Ratio (95% CI) for All-Cause Mortality

1b

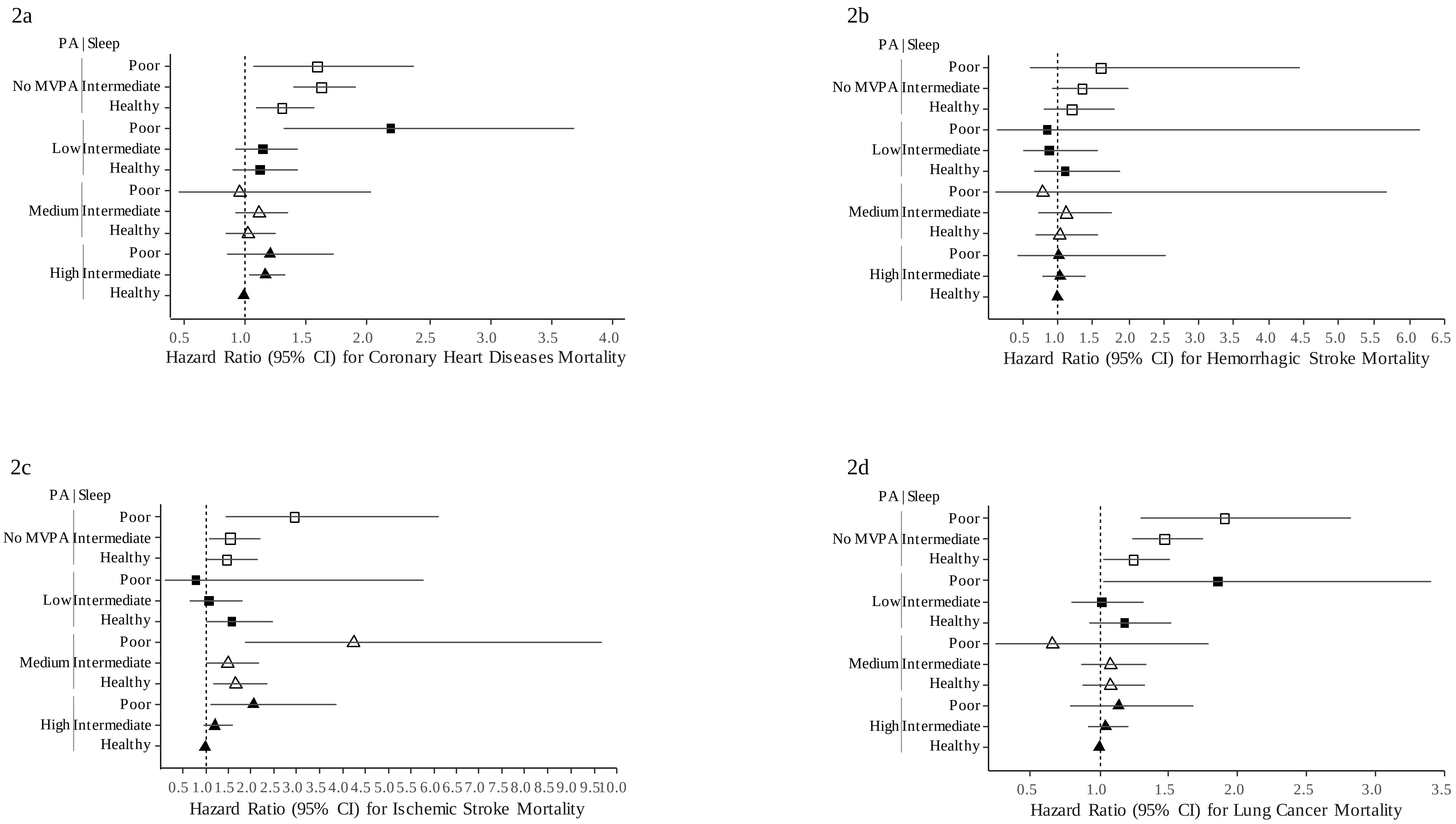


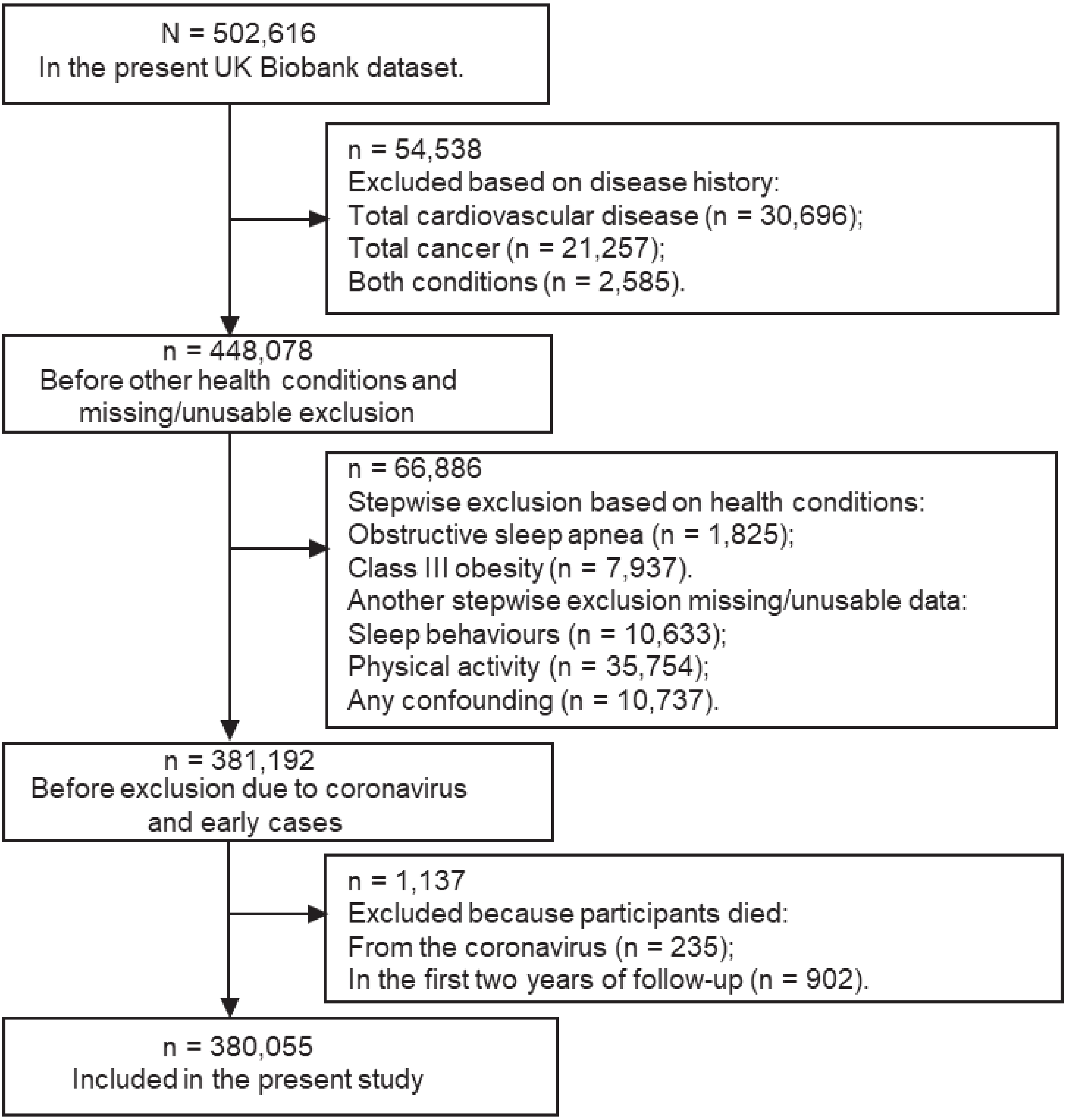
PA | Sleep
No MVPA
Low
Medium
High
Poor
Intermediate
Healthy
1.0
1.5
2.0
2.5
3.0
Hazard Ratio (95% CI) for Total Cardiovascular Disease Mortality

1c



PA | Sleep
No MVPA
Low
Medium
High
Poor
Intermediate
Healthy
1.0
1.5
2.0
Hazard Ratio (95% CI) for Total Cancer Mortality

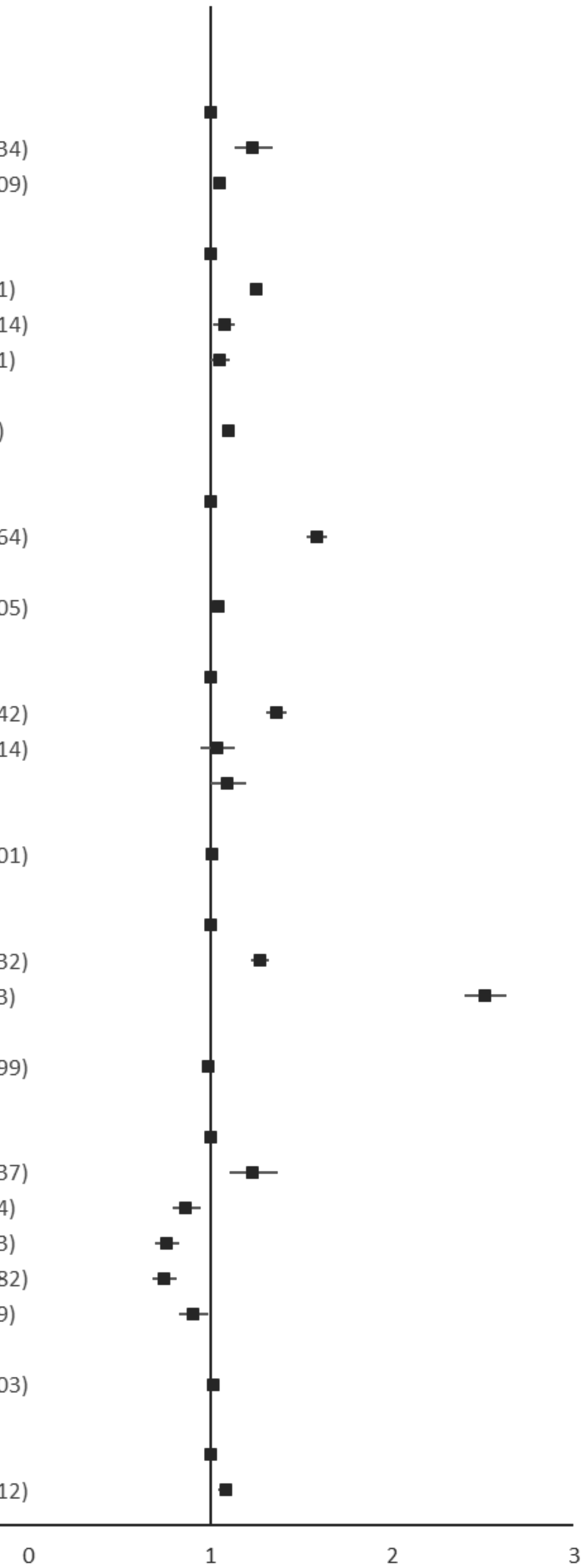

2a
PA | Sleep
No MVPA
Low
Medium
High
Poor
Intermediate
Healthy
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Hazard Ratio (95% CI) for Coronary Heart Diseases Mortality
2b
PA | Sleep
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5
Hazard Ratio (95% CI) for Hemorrhagic Stroke Mortality
2c
PA | Sleep
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0
Hazard Ratio (95% CI) for Ischemic Stroke Mortality
2d
PA | Sleep
0.5 1.0 1.5 2.0 2.5 3.0 3.5
Hazard Ratio (95% CI) for Lung Cancer Mortality



Supplementary Figure S1. Participants recruitment flowchart

(a) All-cause mortality

Variables	Hazard ratio
Sleep	
Healthy	1
Poor	1.23 (1.13, 1.34)
Intermediate	1.05 (1.02, 1.09)
Physical Activity	
High	1
No MVPA	1.25 (1.2, 1.31)
Low	1.08 (1.02, 1.14)
Medium	1.05 (1.01, 1.1)
Age	
Each year older	1.1 (1.09, 1.1)
Sex	
Female	1
Male	1.59 (1.53, 1.64)
Socioeconomic status	
Each one unit up*	1.04 (1.03, 1.05)
Employment status	
Employed not in shift work	1
Retired/not in the workforce	1.36 (1.31, 1.42)
Employed in night shift work	1.04 (0.95, 1.14)
Employed in day shift work	1.09 (1, 1.2)
Body mass index	
Each 1 kg/m^2 more	1.01 (1.01, 1.01)
Cigarette smoking	
Never	1
Previous smoker	1.27 (1.23, 1.32)
Current smoker	2.51 (2.4, 2.63)
Vegetable and fruit intake	
Each serve more	0.99 (0.98, 0.99)
Alcohol consumption	
Never	1
Previous drinker	1.23 (1.11, 1.37)
Occasional drinker	0.87 (0.8, 0.94)
Within guidelines	0.76 (0.7, 0.83)
Above guidelines	0.75 (0.69, 0.82)
Double guidelines	0.9 (0.83, 0.99)
Sedentary behaviour	
Each hour more	1.02 (1.01, 1.03)
Mental health issue	
No	1
Yes	1.08 (1.05, 1.12)

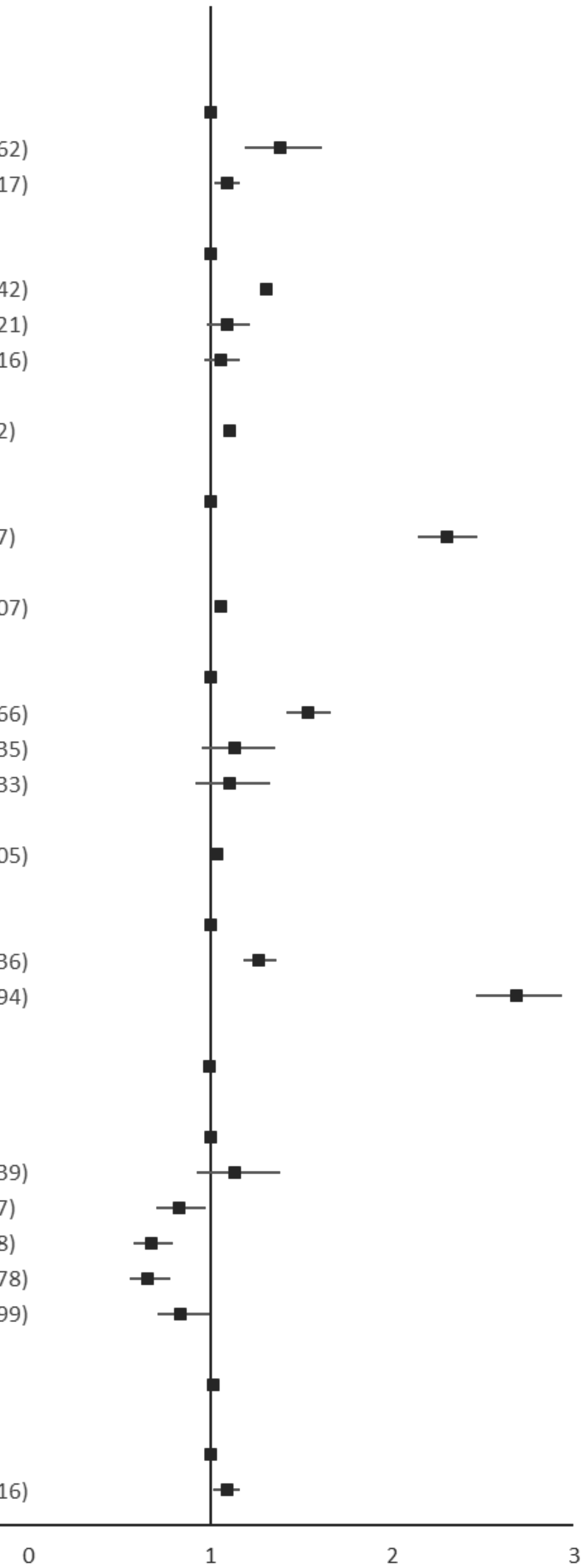


Supplementary Figure S2. The Independent (and Mutually Adjusted) Associations of All Selected Variables with Mortality (n = 380,055) of (a) All-Cause, (b) Total Cardiovascular Disease, and (c) Total Cancer.

* 'Townsend area deprivation index' served as an indicator of socioeconomic status, with higher scores indicating greater socioeconomic deprivation.

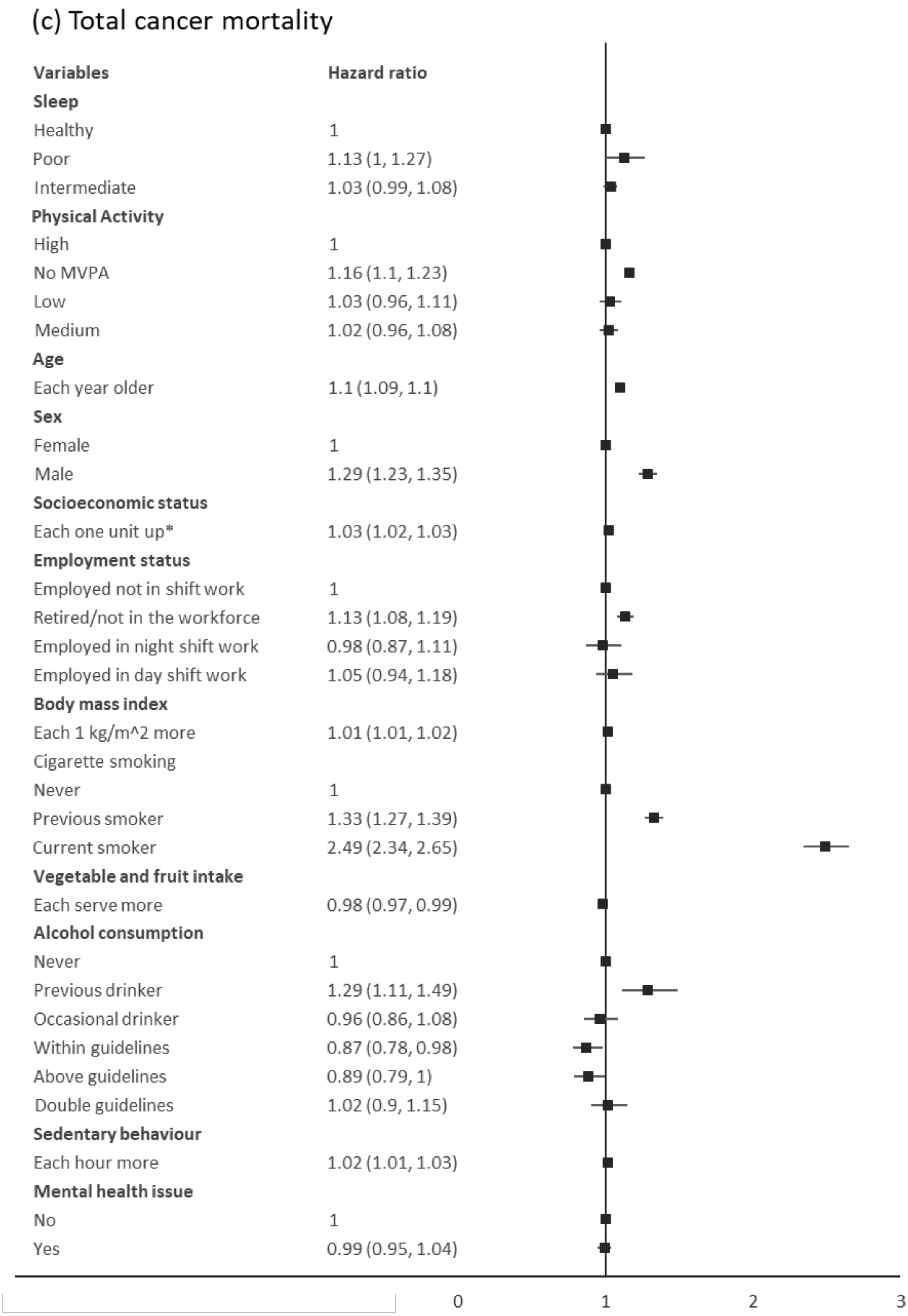
(b) Total cardiovascular disease mortality

Variables	Hazard ratio
Sleep	
Healthy	1
Poor	1.39 (1.19, 1.62)
Intermediate	1.09 (1.03, 1.17)
Physical Activity	
High	1
No MVPA	1.31 (1.21, 1.42)
Low	1.09 (0.98, 1.21)
Medium	1.06 (0.97, 1.16)
Age	
Each year older	1.11 (1.1, 1.12)
Sex	
Female	1
Male	2.3 (2.14, 2.47)
Socioeconomic status	
Each one unit up*	1.06 (1.05, 1.07)
Employment status	
Employed not in shift work	1
Retired/not in the workforce	1.54 (1.42, 1.66)
Employed in night shift work	1.14 (0.95, 1.35)
Employed in day shift work	1.11 (0.92, 1.33)
Body mass index	
Each 1 kg/m^2 more	1.04 (1.03, 1.05)
Cigarette smoking	
Never	1
Previous smoker	1.27 (1.18, 1.36)
Current smoker	2.69 (2.46, 2.94)
Vegetable and fruit intake	
Each serve more	0.99 (0.98, 1)
Alcohol consumption	
Never	1
Previous drinker	1.13 (0.93, 1.39)
Occasional drinker	0.83 (0.7, 0.97)
Within guidelines	0.68 (0.58, 0.8)
Above guidelines	0.66 (0.56, 0.78)
Double guidelines	0.84 (0.71, 0.99)
Sedentary behaviour	
Each hour more	1.01 (1, 1.03)
Mental health issue	
No	1
Yes	1.09 (1.02, 1.16)



Supplementary Figure S2 (cont.). The Independent (and Mutually Adjusted) Associations of All Selected Variables with Mortality (n = 380,055) of (a) All-Cause, (b) Total Cardiovascular Disease, and (c) Total Cancer.

* 'Townsend area deprivation index' served as an indicator of socioeconomic status, with higher scores indicating greater socioeconomic deprivation.



Supplementary Figure S2 (cont.). The Independent (and Mutually Adjusted) Associations of All Selected Variables with Mortality (n = 380,055) of (a) All-Cause, (b)Total Cardiovascular Disease, and (c) Total Cancer.

* 'Townsend area deprivation index' served as an indicator of socioeconomic status, with higher scores indicating greater socioeconomic deprivation..

Supplementary Table S1. The Definition of Diseases

Variable	Definition
Total cardiovascular disease (CVD)	The total CVD definition is aligned with Zao et al. (2020) (https://doi.org/10.1136/bmj.m2031). In brief, the ICD-10 code described in the Chapter IX Diseases of the circulatory system (I0, I11, I13, I20-I51, I60-I69) or the ICD-9 code within (390.0-398.9/ 402.0- 402.9/ 404.0-404.9/ 411.1-436.9) were included.
Sub-type CVD	
Coronary heart diseases	The ICD-10 code described in Chapter IX Diseases of the circulatory system – Ischemic heart disease (I20-I25) was included.
Hemorrhagic stroke	The definition of hemorrhagic stroke (both intracerebral and subarachnoid) is aligned with UK Biobank. The ICD-10 code beginning with ('I60' 'I61') was included.
Ischemic stroke	The definition of ischemic stroke is aligned with UK Biobank. The ICD-10 code beginning with ('I63' 'I64') was included.
Total cancers	The definition of total cancer excludes in situ, benign, uncertain, or non-well-defined cancers. In brief, the ICD-10 code beginning with ('C0' 'C1' 'C2' 'C3' 'C4' 'C5' 'C6' 'C70' 'C71' 'C72' 'C73' 'C74' 'C75' 'C7A' 'C8' 'C9') or the ICD-9 code within (140.0-194.9/ 199.0-209.3) were included.
Sub-type malignant neoplasm	
Lung cancer	The ICD-10 code beginning with ('C33' 'C34') was included.
Others	
Obstructive sleep apnea	The ICD-10 code 'G47.3' and ICD-9 code '327.2' and '780.5' were applied.
Coronavirus disease (COVID-19)	The ICD-10 code 'U07.1' and 'U07.2' were applied.

Primary/secondary inpatient diseases diagnosis is based on both ICD-9 and ICD-10 code. All death cause was based on both primary and secondary cause of death with ICD-10 code only.

Supplementary Table S2. The Scoring System of Sleep

Characteristics	UK BioBank Code	UK BioBank Questionnaire	Healthy Answer (%)	Unhealthy Answer (%)
Chronotype	1180	Do you consider yourself to be?	Definitely a "morning" person; More a "morning" than "evening" person. (57%)	More an "evening" than a "morning person; Definitely an "evening" person. (43%)
Sleep Duration	1160	About how many hours sleep do you get in every 24 hours? (please include naps)	7-8 hr/d. (69%)	<7 or >=9 hr/d. (31%)
Insomnia	1200	Do you have trouble falling asleep at night or do you wake up in the middle of the night?	Never/rarely; Sometimes (73%)	Usually (27%)
Snoring	1210	Does your partner or a close relative or friend complain about your snoring?	No (60%)	Yes (40%)
Daytime Sleepiness	1220	How likely are you to doze off or fall asleep during the daytime when you don't mean to? (e.g. when working, reading or driving)	Never/rarely; Sometimes (98%)	Often; All the Time (2%)

Supplementary Table S3. Number of Mortality Events by Joint Category of Physical Activity and Sleep Scores (n = 380,055)

Joint Category [a]	N With/Without Events						
Physical Activity, Sleep Scores	All-cause	Total cardiovascular disease	Total cancer	Coronary heart diseases	Hemorrhagic stroke	Ischemic stroke	Lung cancer
No MVPA, Poor (n = 2,510)	187/2,323	56/2,454	99/2,411	26/2,484	4/2,506	8/2,502	28/2,482
No MVPA, Intermediate (n = 28,289)	1,570/26,719	469/27,820	851/27,438	237/28,052	36/28,253	43/28,246	201/28,088
No MVPA, Healthy (n = 28,742)	1,293/27,449	325/28,417	738/28,004	155/28,587	31/28,711	37/28,705	138/28,604
Low, Poor (n = 1,291)	79/1,212	28/1,263	43/1,248	15/1,276	1/1,290	1/1,290	11/1,280
Low, Intermediate (n = 17,757)	765/16,992	197/17,560	442/17,315	95/17,662	13/17,744	17/17,740	72/17,685
Low, Healthy (n = 20,250)	689/19,561	182/20,068	406/19,844	83/20,167	17/20,233	24/20,226	72/2,0178
Medium, Poor (n = 1,384)	67/1,317	21/1,363	35/1,349	7/1,377	1/1,383	6/1,378	4/1,380
Medium, Intermediate (n = 24,110)	1,050/23,060	279/23,831	605/23,505	125/23,985	24/24,086	34/24,076	103/24,007
Medium, Healthy (n = 32,277)	1,128/31,149	283/31,994	675/31,602	121/32,156	27/32,250	43/32,234	110/32,167
High, Poor (n = 4,981)	262/4,719	80/4,901	130/4,851	33/4,948	5/4,976	11/4,970	28/4,953
High, Intermediate (n = 87,947)	3,704/84,243	996/86,951	2,176/85,771	506/87,441	86/87,861	109/87,838	384/87,563
High, Healthy (n = 130,517)	4,709/125,808	1,179/129,338	2,864/127,653	529/129,988	114/130,403	117/130,400	444/130,073
Overall (n = 380,055)	15,503/364,552	4,095/375,960	9,064/370,991	1,932/378,123	359/379,696	450/379,605	1,595/378,460

a. Physical activity levels were categorized based on public health guidelines: No MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk). Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

Supplementary Table S4. The Resource and Definition of the Selected Covariates (except for Age, Sex, and BMI)

Covariates	UK BioBank Code	Description	Type	Category
Socioeconomic status	189	The existing variable 'Townsend area deprivation index' (189) served as an indicator of socioeconomic status, with higher scores indicating greater socioeconomic deprivation.	Continuous	-
Vegetable and fruit intake	1299, 1309	The sum of the daily servings of 'salad /raw vegetable intake' (1299) and 'fresh fruit intake' (1309) served as a proxy of a healthy diet.	Continuous	-
Sedentary behaviour	1070, 1080, 1090	The total daily hours of television viewing (1070), computer use (1080), and driving (1090) as a marker of sedentary behaviour.	Continuous	-
Mental health issue	2090, 2100	Participants having ever seen a doctor (GP) (2090) or psychiatrist (2100) for nerves, anxiety, or depression were classified as having mental health issues.	Categorical	Yes; No
Cigarette smoking	20116	The existing variable 'smoking status' (20116) was applied.	Categorical	never; previous smoker; current smoker
Employment	6142 3426 826	We derived four groups based on 'Current employment status' (6142), 'Job involves night shift work' (3426), and 'Job involves shift work' (826).	Categorical	retired/not in the workforce; employed not in shift work; employed in night shift work; employed in day shift work
Alcohol consumption	1558, 1568, 1578, 1588, 1598, 1608, 5364. 20117	The level of overall alcohol consumption as the number of UK units of alcohol (10 mL/unit) consumed per week was calculated; participants were categorized based on the consumption according to the UK guideline (14 UK units/wk).	Categorical	never; previous drinker; occasional drinker; within guidelines (14 units per week); above guidelines (14-28 units/wk); double guidelines (>28 units/wk).

Supplementary Table S5. Comparison of the Characteristics between Included and Excluded Samples.

Characteristics	Included Sample (n = 380,055)	Excluded Sample (n = 122,561)	Missing Count in Excluded Sample
Age (mean (SD))	55.9 (8.1)	58.60 (7.7)	-
Male (n (%))	171,315 (45)	57848 (47)	-
BMI (kg/m^2) (mean (SD))	26.9 (4.1)	29.13 (6.17)	3,194
Socioeconomic Status (mean (SD)) [a]	-1.5 (3.0)	-0.65 (3.4)	627
Vegetable and Fruit Intake (serves/d) (mean (SD))	4.4 (2.9)	4.43 (3.2)	8,801
Sedentary Behaviour (hr/d) (mean (SD))	4.7 (2.4)	5.10 (2.6)	7,763
Mental Health Issue (n (%)) [b]	127,943 (34)	45257 (38)	2,179
Cigarette Smoking (n (%))			2,952
Never	213,618 (56)	59,970 (50)	
Previous Smoker	128,597 (34)	44,494 (37)	
Current Smoker	37,840 (10)	15,145 (13)	
Employment Status (n (%))			5,759
Retired/not in the workforce	144,090 (38)	65,557 (56)	
Employed not in shift work	197,803 (52)	39,725 (34)	
Employed in night shift work	19,365 (5)	6,006 (5)	
Employed in day shift work	18,797 (5)	5,514 (5)	
Alcohol Consumption (n (%)) [c]			1,658
Never	13,843 (4)	8,551 (7)	
Previous Drinker	11,512 (3)	6,599 (5)	
Occasional Drinker	81,191 (21)	32,704 (27)	
Within Guideline	130,901 (34)	36,254 (30)	
Above Guideline	84,936 (22)	21,627 (18)	
Above Double Guideline	57,672 (15)	15,168 (13)	
Sleep Score (n (%)) [d]			12,458
Poor	10,166 (3)	5,401 (5)	
Intermediate	158,103 (42)	53,394 (48)	
Healthy	211,786 (56)	51,308 (47)	
Physical Active (n (%)) [e]			47,153
No MVPA	59,541 (16)	9871 (13)	
Low	9,298 (10)	14344 (19)	
Medium	57,771 (15)	12290 (16)	
High	223,445 (59)	38903 (52)	

a. Townsend area deprivation index was used.

b. Had ever seen a doctor or psychiatrist for nerves, anxiety or depression.

c. The UK guideline (14 UK units/wk) was used.

d. Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

e. Categorization based on public health guidelines: no MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk).

Supplementary Table S6. The Joint Association of Physical Activity and Sleep Scores with Mortality for All-Cause, Total Cardiovascular Disease, and Total Cancer (n = 380,055)

Joint Category [a]	Hazard Ratio for Mortality Risks (95% CI)					
Guideline Physical Activity, Sleep Scores	All-cause		Total cardiovascular disease		Total cancer	
	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]
No MVPA, Poor (n = 2,510)	**2.18 (1.88, 2.52)**	**1.57 (1.35, 1.82)**	**2.64 (2.02, 3.45)**	**1.67 (1.27, 2.19)**	**1.89 (1.55, 2.31)**	**1.45 (1.18, 1.77)**
No MVPA, Intermediate (n = 28,289)	**1.56 (1.48, 1.65)**	**1.33 (1.25, 1.40)**	**1.88 (1.69, 2.09)**	**1.50 (1.34, 1.67)**	**1.39 (1.29, 1.5)**	**1.19 (1.10, 1.29)**
No MVPA, Healthy (n = 28,742)	**1.3 (1.22, 1.38)**	**1.22 (1.15, 1.30)**	**1.34 (1.19, 1.52)**	**1.22 (1.07, 1.38)**	**1.21 (1.12, 1.31)**	**1.13 (1.04, 1.22)**
Low, Poor (n = 1,291)	**1.8 (1.44, 2.24)**	**1.46 (1.17, 1.83)**	**2.58 (1.78, 3.76)**	**1.91 (1.31, 2.78)**	**1.6 (1.18, 2.16)**	1.35 (1.00, 1.82)
Low, Intermediate (n = 17,757)	**1.24 (1.15, 1.34)**	**1.13 (1.05, 1.22)**	**1.28 (1.10, 1.49)**	1.11 (0.96, 1.30)	**1.19 (1.07, 1.31)**	1.07 (0.97, 1.19)
Low, Healthy (n = 20,250)	1.04 (0.96, 1.12)	1.05 (0.97, 1.13)	1.11 (0.95, 1.30)	1.11 (0.95, 1.30)	1 (0.90, 1.11)	0.99 (0.89, 1.1)
Medium, Poor (n = 1,384)	**1.33 (1.05, 1.69)**	1.15 (0.90, 1.46)	**1.66 (1.08, 2.56)**	1.33 (0.86, 2.05)	1.15 (0.82, 1.6)	1.01 (0.72, 1.41)
Medium, Intermediate (n = 24,110)	**1.19 (1.12, 1.28)**	**1.11 (1.04, 1.19)**	**1.26 (1.11, 1.44)**	1.14 (1.00, 1.30)	**1.13 (1.04, 1.24)**	1.06 (0.97, 1.15)
Medium, Healthy (n = 32,277)	1.04 (0.97, 1.11)	1.04 (0.98, 1.11)	1.06 (0.93, 1.21)	1.06 (0.93, 1.21)	1.01 (0.93, 1.1)	1.01 (0.93, 1.09)
High, Poor (n = 4,981)	**1.44 (1.27, 1.63)**	**1.21 (1.06, 1.37)**	**1.74 (1.39, 2.18)**	**1.37 (1.09, 1.72)**	1.18 (0.99, 1.40)	1.02 (0.86, 1.22)
High, Intermediate (n = 87,947)	**1.12 (1.07, 1.17)**	1.03 (0.99, 1.08)	**1.18 (1.09, 1.29)**	1.07 (0.98, 1.16)	**1.09 (1.03, 1.15)**	1.02 (0.96, 1.07)
High, Healthy (n = 130,517)	1.00					

[a] Physical activity levels were categorized based on public health guidelines: No MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk). Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

[b] Adjusted for age and sex.

[c] Further adjusted for socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, and mental health.

Supplementary Table S7. The Joint Association of Physical Activity and Sleep Scores with Mortality for Sub-Type Conditions (n = 380,055)

Joint Category [a]	Hazard Ratio for Mortality Risks (95% CI)							
Guideline Physical Activity,	Coronary heart disease		Hemorrhagic stroke		Ischemic stroke		Lung cancer	
Sleep Scores	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]	Model 1 [b]	Model 2 [c]
No MVPA, Poor (n = 2,510)	**2.70 (1.82, 4.00)**	**1.59 (1.07, 2.37)**	1.95 (0.72, 5.29)	1.63 (0.60, 4.44)	**3.98 (1.95, 8.15)**	**2.96 (1.43, 6.11)**	**3.48 (2.38, 5.10)**	**1.91 (1.30, 2.81)**
No MVPA, Intermediate (n = 28,289)	**2.11 (1.81, 2.46)**	**1.63 (1.40, 1.91)**	**1.48 (1.02, 2.16)**	1.35 (0.92, 1.98)	**1.78 (1.25, 2.52)**	**1.55 (1.08, 2.21)**	**2.13 (1.80, 2.52)**	**1.47 (1.24, 1.75)**
No MVPA, Healthy (n = 28,742)	**1.47 (1.23, 1.76)**	**1.31 (1.09, 1.56)**	1.24 (0.83, 1.84)	1.20 (0.81, 1.80)	**1.53 (1.06, 2.22)**	**1.47 (1.01, 2.14)**	**1.46 (1.20, 1.76)**	**1.25 (1.03, 1.51)**
Low, Poor (n = 1,291)	**3.09 (1.85, 5.15)**	**2.20 (1.31, 3.69)**	0.94 (0.13, 6.75)	0.86 (0.12, 6.15)	0.96 (0.13, 6.88)	0.81 (0.11, 5.78)	**2.66 (1.46, 4.84)**	**1.87 (1.02, 3.40)**
Low, Intermediate (n = 17,757)	**1.34 (1.07, 1.66)**	1.15 (0.92, 1.44)	0.91 (0.52, 1.62)	0.89 (0.50, 1.58)	1.17 (0.70, 1.94)	1.09 (0.65, 1.82)	1.27 (0.99, 1.63)	1.02 (0.79, 1.31)
Low, Healthy (n = 20,250)	1.12 (0.89, 1.42)	1.13 (0.90, 1.43)	1.07 (0.64, 1.79)	1.12 (0.67, 1.86)	1.54 (0.99, 2.39)	**1.60 (1.03, 2.49)**	1.16 (0.91, 1.49)	1.18 (0.92, 1.52)
Medium, Poor (n = 1,384)	1.22 (0.58, 2.57)	0.96 (0.46, 2.03)	0.84 (0.12, 5.99)	0.79 (0.11, 5.67)	**4.86 (2.14, 11.03)**	**4.24 (1.86, 9.66)**	0.85 (0.32, 2.27)	0.67 (0.25, 1.79)
Medium, Intermediate (n = 24,110)	**1.24 (1.02, 1.51)**	1.12 (0.92, 1.36)	1.15 (0.74, 1.79)	1.12 (0.72, 1.75)	**1.58 (1.08, 2.32)**	**1.49 (1.01, 2.18)**	**1.25 (1.01, 1.55)**	1.08 (0.87, 1.33)
Medium, Healthy (n = 32,277)	1.02 (0.84, 1.25)	1.03 (0.84, 1.25)	1.01 (0.66, 1.54)	1.03 (0.68, 1.57)	**1.65 (1.16, 2.33)**	**1.67 (1.18, 2.37)**	1.07 (0.87, 1.32)	1.08 (0.88, 1.33)
High, Poor (n = 4,981)	**1.57 (1.10, 2.23)**	1.21 (0.85, 1.73)	1.16 (0.48, 2.85)	1.03 (0.42, 2.52)	**2.47 (1.33, 4.58)**	**2.07 (1.11, 3.86)**	**1.64 (1.12, 2.41)**	1.14 (0.78, 1.68)
High, Intermediate (n = 87,947)	**1.31 (1.16, 1.48)**	**1.17 (1.04, 1.32)**	1.11 (0.84, 1.47)	1.05 (0.79, 1.39)	**1.32 (1.02, 1.72)**	1.22 (0.94, 1.59)	**1.24 (1.08, 1.42)**	1.05 (0.91, 1.20)
High, Healthy (n = 130,517)	1.00							

[a] Physical activity levels were categorized based on public health guidelines: No MVPA (those reported 0 MET-mins/wk from MVPA, regardless of total MET-mins/wk); low (< 600 MET-mins/wk); medium (600 to < 1200 MET-mins/wk); and high (≥ 1200 MET-mins/wk). Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

[b] Adjusted for age and sex.

[c] Further adjusted for socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, and mental health.

Supplementary Table S8. Analyses on Interaction of Sleep Scores [a] and Physical Activity [b] with Mortality Risks for All-Cause, Total Cardiovascular Disease, and Total Cancer (n = 380,055)

	Healthy Sleep		Intermediate and Poor Sleep		Hazard Ratio [c] (95% CI) for Sleep Scores within Strata of Physical Activity Level
	N With/Without Events	Hazard Ratio [c] (95% CI)	N With/Without Events	Hazard Ratio [c] (95% CI)	
All-cause death					
Any MVPA	6,526/183,044	1.00	5,927/137,470	**1.06 (1.02, 1.10)** ***P* = 0.0021**	**1.06 (1.01, 1.11)** ***P* = 0.0021**
No MVPA	1,293/28,742	**1.20 (1.13, 1.28)** ***P* < .0001**	1,757/30,799	**1.33 (1.26, 1.40)** ***P* < .0001**	**1.10 (1.03, 1.19)** ***P* = 0.0073**
Hazard Ratio [c] (95% CI) for No MVPA within Strata of Sleep		**1.20 (1.13, 1.28)** ***P* < .0001**		**1.33 (1.26, 1.40)** ***P* < .0001**	
Total cardiovascular disease death					
Any MVPA	1,644/183,044	1.00	1,601/137,470	**1.08 (1.01, 1.16)** ***P* = 0.0236**	**1.08 (1.01, 1.16)** ***P* = 0.0236**
No MVPA	325/28,742	**1.19 (1.05, 1.34)** ***P* = 0.0050**	525/30,799	**1.48 (1.34, 1.63)** ***P* < .0001**	**1.24 (1.08, 1.43)** ***P* = 0.0021**
Hazard Ratio [c] (95% CI) for No MVPA y within Strata of Sleep		**1.19 (1.05, 1.34)** ***P* = 0.0050**		**1.48 (1.34, 1.63)** ***P* < .0001**	
Total cancer death					
Any MVPA	3,945/183,044	1.00	3,431/137,470	1.03 (0.99, 1.08) *P* = 0.1763	1.03 (0.99, 1.08) *P* = 0.1763
No MVPA	738/28,742	**1.13 (1.04, 1.22)** ***P* = .0033**	9,50/30,799	**1.21 (1.13, 1.30)** ***P* < .0001**	1.08 (0.98, 1.19) *P* = 0.1324
Hazard Ratio [c] (95% CI) for No MVPA y within Strata of Sleep		**1.13 (1.04, 1.22)** ***P* = .0033**		**1.21 (1.13, 1.30)** ***P* < .0001**	

Measure of interaction on additive scale: for all-cause death, RERI (95% CI) = 0.07 (-0.03, 0.16), AP (95% CI) = 0.05 (-0.02, 0.12), and S = 1.26 (0.89, 1.79); for cardiovascular diseases death, RERI (95% CI) = 0.21 (0.01, 0.40), AP (95% CI) = 0.14 (0.02, 0.26), and S = 1.76 (0.93, 3.31); for total cancers death, RERI (95% CI) = 0.05 (-0.07, 0.18), AP (95% CI) = 0.05 (-0.05, 0.14), and S = 1.34 (0.66, 2.73).

Measure of interaction on multiplicative scale: for all-cause death, hazard ratios (HR) (95% CI) = 1.25 (1.19, 1.32), *P* < .0001; for cardiovascular diseases death, HR (95% CI) = 1.36 (1.23, 1.51), *P* < .0001; for total cancers death, HR (95% CI) = 1.17 (1.09, 1.26), *P* < .0001.

[a] Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

[b] Physical activity levels were categorized based on MET-mins/wk from MVPA, regardless of total MET-mins/wk.

[c] Hazard ratios were adjusted for age, sex, socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, and mental health.

Supplementary Table S9. Analyses on Interaction of Sleep Scores [a] and Physical Activity [b] with Sub-Type Conditions Mortality (n = 380,055)

	Healthy Sleep		Intermediate and Poor Sleep		Hazard Ratio [c] (95% CI) for Sleep Scores within Strata of Physical Activity Level
	N With/Without Events	Hazard Ratio [c] (95% CI)	N With/Without Events	Hazard Ratio [c] (95% CI)	
Coronary heart diseases death					
Any MVPA	733/183,044	1.00	781/137,470	**1.15 (1.04, 1.27) *P* = 0.0081**	**1.15 (1.04, 1.27) *P* = 0.0081**
No MVPA	155/28,742	**1.28 (1.08, 1.52) *P* = 0.0055**	263/30,799	**1.60 (1.38, 1.84) *P* < .0001**	**1.24 (1.02, 1.52) *P* = 0.0300**
Hazard Ratio [c] (95% CI) for No MVPA within Strata of Sleep		**1.28 (1.08, 1.52) *P* = 0.0055**		**1.60 (1.38, 1.84) *P* < .0001**	
Hemorrhagic stroke death					
Any MVPA	158/183,044	1.00	130/137,470	1.02 (0.81, 1.29) *P* = 0.8688	1.02 (0.81, 1.29) *P* = 0.8688
No MVPA	31/28,742	1.18 (0.80, 1.75) *P* = 0.3908	40/30,799	1.35 (0.95, 1.93) *P* = 0.0944	1.14 (0.71, 1.83) *P* = 0.5804
Hazard Ratio [c] (95% CI) for No MVPA within Strata of Sleep		1.18 (0.80, 1.75) *P* = 0.3908		1.35 (0.95, 1.93) *P* = 0.0944	
Ischemic stroke death					
Any MVPA	184/183,044	1.00	178/137,470	1.12 (0.91, 1.38) *P* = 0.2868	1.12 (0.91, 1.38) *P* = 0.2868
No MVPA	37/28,742	1.25 (0.88, 1.79) *P* = 0.2143	51/30,799	**1.42 (1.03, 1.94) *P* = 0.0315**	1.13 (0.74, 1.73) *P* = 0.5724
Hazard Ratio [c] (95% CI) for No MVPA within Strata of Sleep		1.25 (0.88, 1.79) *P* = 0.2143		**1.42 (1.03, 1.94) *P* = 0.0315**	
Lung cancer death					
Any MVPA	626/183,044	1.00	602/137,470	1.02 (0.91, 1.15) *P* = 0.6868	1.02 (0.91, 1.15) *P* = 0.6868
No MVPA	138/28,742	**1.21 (1.00, 1.45) *P* = 0.0476**	2,29/30,799	**1.46 (1.25, 1.71) *P* < .0001**	1.21 (0.98, 1.50) *P* = 0.0765
Hazard Ratio [c] (95% CI) for No MVPA within Strata of Sleep		**1.21 (1.00, 1.45) *P* = 0.0476**		**1.46 (1.25, 1.71) *P* < .0001**	

Measure of interaction on additive scale: for coronary heart diseases death, RERI (95% CI) = 0.17 (-0.13, 0.46), AP (95% CI) = 0.11 (-0.07, 0.29), and S = 1.39 (0.74, 2.64); for hemorrhagic stroke death, RERI (95% CI) = 0.15 (-0.48, 0.78), AP (95% CI) = 0.11 (-0.34, 0.56), and S = 1.72 (0.11, 26.53); for ischemic stroke death, RERI (95% CI) = 0.04 (-0.56, 0.64), AP (95% CI) = -0.03 (-0.39, 0.45), and S = 1.12 (0.24, 5.31); for lung cancer death, RERI (95% CI) = 0.23 (-0.06, 0.53), AP (95% CI) = 0.16 (-0.03, 0.35), and S = 2.01 (0.63, 6.35).

Measure of interaction on multiplicative scale: for coronary heart diseases death, HR (95% CI) = 1.39 (1.21, 1.60), *P* < .0001; for hemorrhagic stroke death, HR (95% CI) = 1.33 (0.93, 1.90), *P* = 0.1211; for ischemic stroke death, hazard ratios (HR) (95% CI) = 1.26 (0.92, 1.73), *P* = 0.1438; for lung cancer death, HR (95% CI) = 1.43 (1.22, 1.67), *P* < .0001.

[a] Sleep scores were categorized into: poor, 0~1; intermediate, 2~3; healthy, 4~5.

[b] Physical activity levels were categorized based on MET-mins/wk from MVPA, regardless of total MET-mins/wk.

[c] Hazard ratios were adjusted for age, sex, socioeconomic status, employment status, BMI, cigarette smoking, vegetable and fruit intake, alcohol consumption, sedentary behaviour, and mental health.