ARTICLE

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Sleep, physical activity, sedentary behavior, and risk of incident dementia: a prospective cohort study of 431,924 UK Biobank participants

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Although sleep, physical activity and sedentary behavior have been found to be associated with dementia risk, findings are inconsistent and their joint relationship remains unclear. This study aimed to investigate independent and joint associations of these three modifiable behaviors with dementia risks. A total of 431,924 participants (median follow-up 9.0 years) without dementia from UK Biobank were included. Multiple Cox regressions were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Models fitted with restricted cubic spline were conducted to test for linear and nonlinear shapes of each association. Sleep duration, leisure-time physical activity (LTPA), and screen-based sedentary behavior individually associated with dementia risks in different non-linear patterns. Sleep duration associated with dementia in a U-shape with a nadir at 7 h/day. LTPA revealed a curvilinear relationship with dementia in diminishing tendency, while sedentary behavior revealed a J-shaped relationship. The dementia risk was 17% lower in the high LTPA group (HR[95%CI]: 0.83[0.76–0.91]) and 22% higher in the high sedentary behavior group (1.22[1.10–1.35]) compared to the corresponding low-level group, respectively. A combination of seven-hour/day sleep, moderate-to-high LTPA, and low-to-moderate sedentary behavior showed the lowest dementia risk (0.59[0.50–0.69]) compared to the referent group (longer or shorter sleep/low LTPA/high sedentary behavior). Notably, each behavior was non-linearly associated with brain structures in a pattern similar to its association with dementia, suggesting they may affect dementia risk by affecting brain structures. Our findings highlight the potential to change these three daily behaviors individually and simultaneously to reduce the risk of dementia.

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INTRODUCTION

The increasing number of people with dementia and the lack of effective treatment highlight the urgency of a better understanding of modifiable risk factors, which might account for one quarter to one third of the population's risk for dementia [1]. Emerging evidence have found that sleep, physical activity (PA), and sedentary behavior (SB) are three of modifiable daily behaviors in association with the risk of dementia. Each of them has been suggested to be related to dementia risk or cognitive performance [2–4]. Nevertheless, findings of these associations have been inconsistent [5–9], possibly due to insufficient length of follow-up, limited statistical power resulting from insufficient sample size, or neglecting possible nonlinear relationships. Additionally, the synergistic effects of sleep, PA, and SB have been examined in fields other than dementia [10, 11]. For instance, participating in moderate-to-vigorous PA has been reported as ameliorating the health risks of high SB or poor sleep [12–14]. However, to our knowledge, no reported studies have discussed the joint effects of the three main components of daily behaviors on the risk of all-cause dementia in large cohorts.

It is well-established that brain atrophy assessed by structural magnetic resonance imaging is a valid marker of neurodegeneration [15]. Sleep deprivation and lack of PA is likely to exacerbate brain atrophy, and even influence neurogenesis and cell proliferation in hippocampus [16, 17], and thus may be one of the mechanisms affecting dementia risks. However, current

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evidence on the associations of sleep and PA with whole/regional grey volumes is sparse and inconclusive, and are based on relatively small numbers of participants [18, 19]. Benefitting from the collected large-scale brain imaging data in UK Biobank (UKB), we are able to investigate the association between each behavior and brain structure.

The aim of this study was to investigate the independent and joint effects of sleep duration, PA, and SB on risk of all-cause dementia using data from the large-scale population-based UKB cohort ($N = 431,924$). To explore the underlying mechanisms, we investigated the association between each behavior of interest and brain structural measures. Because these three behaviors are in relation to cerebrovascular health which can affect dementia risk, we also assessed whether each behavior affected dementia risk through its association with cerebrovascular risks.

SUBJECTS AND METHODS

Data source and study population

This study is based on data from the UKB study that received approval from the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee [20]. All participants provided informed consent through electronic signature at baseline assessment. UKB is a population-based cohort of more than 500,000 participants aged 37 to 73 years recruited across the United Kingdom between 2006 and 2010 [20]. After excluding participants with dementia at baseline, participants with error records, and those with unavailable baseline and/or follow-up data, 431,924 participants remained for the main analysis (Supplementary Fig. 1). The present analyses were conducted under UK Biobank application number 19542.

Dementia diagnosis

Dementia diagnoses were ascertained using hospital inpatient records from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales. Additional cases were detected through linkage to death register data from the National Health Service Digital, National Health Service Central Register, and the National Records of Scotland. Diagnoses were recorded according to the International Classification of Diseases (ICD) system codes, which presented as a primary or secondary diagnosis in the health records or a potential cause of death in the death register. Dementia diagnoses were also retrieved from primary care data using read codes (version 2 [Read v2] and version 3 [CTV3 or Read v3]). The list of read codes used in the study was presented in Supplementary Table 1. Date and source of first diagnoses were derived from first occurrence categories in the UKB of mental and behavioral disorders (Fields 130836–130843) and nervous system disorders (Fields 131036-131037).

Sleep duration, physical activity, and sedentary behavior measurements

To measure sleep duration (Field 1160), participants were asked "About how many hours sleep do you get in every 24 h?". Total hours per day of sleep duration was divided into three categories according to tertiles: low (0–6 h), moderate (7 h) and high (≥8 h) [21].

Total physical activity (TPA) was measured based on a modified version of the International Physical Activity Questionnaire (IPAQ), including the frequency and duration of walking (Field 864 and 874), moderate (Field 884 and 894), and vigorous activity (Field 904 and 914) on a typical day/week over the past four weeks [22]. These measures were combined to create a composite score by multiplying the metabolic equivalents (METs) for each type of PA by the minutes performed per week. One MET is considered the resting metabolic rate obtained during quiet sitting [23]. To get a continuous TPA score (MET-minutes/week), we considered walking to be 3.3 METs, moderate activity to be 4 METs, and vigorous activity to be 8 METs [22]. Following IPAQ guidelines [24], duration of PA less than 10 min per day for any category was recoded to 0. Participants with duration of any type of PA greater than 16 h per day were excluded from the analysis as unreasonably high data were outliers. According to the IPAQ guidelines [24], all walking, moderate and vigorous time variables exceeding "four hours" or "240 minutes" are truncated to be equal to 240 min in a new variable. These data processing rules will ensure that highly active people remain highly active, while decreasing the chances that less active individuals are coded as highly active [24]. TPA was categorized into three mutually exclusive groups according to tertiles: low (<800 MET-min/week), moderate (800 to 2400 MET-min/week), and high (≥2400 MET-min/week).

For leisure-time physical activity (LTPA), the frequency and duration of five activities undertaken in the previous four weeks were asked, and the intensity was also expressed in terms of MET values: 3.5 METs for walking for pleasure (Field 971 and 981), 2.5 METs for light DIY (do-it-yourself, i.e., home maintenance and improvement and gardening activities; Field 1011 and 1021), 5.5 METs for heavy DIY (e.g., using heavy tools, weeding, lawn mowing, digging, carpentry; Field 2624 and 2634), 8.0 METs for strenuous sports (i.e., sports that make you sweat or breathe hard; Field 991 and 1001), and 4.0 METs for other activities (e.g., swimming, cycling, keep fit, bowling; Field 3637 and 3647) [23]. LTPA was categorized into low (<400 MET-min/week), moderate (400 to 1200 MET-min/week), and high (≥1200 MET-min/week) according to tertiles.

Screen-based SB time was estimated as the sum of self-reported hours spent watching TV and using a computer (do not include using a computer at work) during a typical day (Field 1070 and 1080) [25], two of the most wide-spread leisure-time SB in adults. Values greater than 24 h per day were excluded, and in those reporting over 16 h sedentary time values were winsorized at 16 h [26]. When TV viewing or computer using were assessed individually, the data processing was the same. Participants were grouped into three predefined categories by tertiles for total SB (low (0–2 h per day), moderate (>2–4 h) and high (>4 h)), TV viewing (low (0–2 h), moderate (>2–3 h) and high (≥4 h)), and computer using (low (0 h), moderate (1 h) and high (2–5 h)).

For note, when we analyzed the association between the combination of three behaviors and dementia, the three behaviors (sleep duration, LTPA, and SB) were sometimes simplified to binary classification to avoid small sample size in subgroups caused by excessive grouping. LTPA was reclassified in binary as light intensity of LTPA (LIPA; <400 MET-min/week) and moderate-to-vigorous intensity of LTPA (MVPA, ≥400 MET-min/week); sleep duration was reclassified in binary as typical (sleeping 7 h/day) and atypical sleep (sleeping less or more than 7 h/day); SB was reclassified in binary as low-to-moderate (0–4 h) and high SB group (>4 h).

Covariates and cerebrovascular disease

Relevant covariates include age at baseline (Field 21022); sex (Field 31); education (Field 6138), categorized as higher (college/university degree or other professional qualifications) or lower; *APOE* ε4 carrier status (carrier/non-carrier status as defined by genetic information); self-reported ethnicity (White/non-White; Field 21000); Townsend deprivation index (Field 189; referring to an area-based measure of socioeconomic deprivation), categorized as quintiles 1, 2 to 4, and 5; employment status (Field 6142 and 20119), categorized as working, retired, and other (unemployed, looking after home and/or family, unable to work because of sickness or disability, unpaid/voluntary work, full/part time student, or did not answer); body mass index (BMI; Field 21001); smoking status (current/non-current, Field 20116); alcohol intake (daily intake, less than 14 units per week, or never or special occasions only; Field 1558); depression status defined as a combined score of >3 (Field 2050 and 2060); the average total household income before tax (Field 738) was categorized as <£18,000, £18,000-£30,999, £31,000-£51,999, ≥£52,000; sleep medications (Field 20003) were self-reported to the research nurse, and the participants were dichotomized according to whether they were taking sleep medication (benzodiazepines and non-benzodiazepine sedative-hypnotics); physical impairment was dichotomized according to doctor restricts physical activity due to heart condition (Field 6014) and attendance/disability/mobility allowance (Field 6146; options of "disability living allowance" or "blue badge" were considered physical impairment); cerebrovascular disease was ascertained at baseline from different sources (Fields 42006-42013, and ICD10 code within I60-I69).

Structural magnetic resonance imaging (MRI) data

Quality-controlled T1-weighted neuroimaging data, processed with FreeSurfer, were used in this study. Details of the imaging protocol can be found in the open-source document (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf). Neuroimaging data were collected on a standard Siemens Skyra 3T scanner with a 32-channel head coil. T1 images were processed with FreeSurfer, surface templates were utilized to extract imaging derived phenotypes (IDP) referring to atlas regions' surface area, volume, and mean cortical thickness. Subcortical regions were extracted via FreeSurfer's aseg tool. The FreeSurfer aparc (ID = 192) and ASEG (ID = 190) atlas corresponding to 68 cortical regions

and 16 subcortical regions were used in this study. Qoala-T approach was used to check FreeSurfer outputs, supplemented by manual checking of outputs close to threshold. Any FreeSurfer outputs that failed to pass quality control were not included in the FreeSurfer IDPs.

Diffusion tensor imaging (DTI) measures

We used the quality-controlled imaging-derived phenotypes from the DTI assessments released by the UK Biobank Imaging Study. Details of the dataset and imaging protocol can be found in the online documentation (https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Major processing steps are described here in brief. Two commonly used DTI microstructure measures were extracted from the preprocessed diffusion MRI: FA (fractional anisotropy) and MD (mean diffusivity). FA and MD were calculated using DTIFIT (FMRIB Software Library's Diffusion Toolbox). Then, the probabilistic tractography-based method using the AutoPtx package from FSL was used to map 27 tracts over the whole brain [27]. Masks of tracts derived from FA data were used to locate the tracts on MD. Finally, weighted tract-averaged FA and MD for each tract were generated.

Statistical analysis

To avoid the effects of extreme values of exposure data, outliers located outside ±4 standard deviation from the mean were excluded (i.e., 1573 outliers for sleep duration, 9284 outliers for TPA, 8733 outliers for LTPA, and 3115 outliers for SB). An overview flow chart of study design is shown in Supplementary Fig. 1. Cox proportional hazard regression models were used to estimate the independent and joint association between sleep duration, PA, and SB with incident all-cause dementia. Missing data were deleted in the Cox analyses. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of incident dementia were calculated in complete-case analysis. The number and proportion of all the missing data were presented in Supplementary Table 2. Participants were considered at risk for dementia from baseline (2006–2010) and were followed up until the date of first diagnosis, death, loss to follow-up, or the last date with available information (April, 2021), whichever came first. The independent analysis started with a minimally adjusted Cox model including only age and sex as covariates (Model 1), and a second model adjusted for age, sex, education, and *APOE* ε4 status (Model 2). The joint associations were examined through combination of different behavior categories, adjusting for age, sex, education, and *APOE* ε4 status. Proportional hazards were tested using scaled Schoenfeld's residuals, although no noticeable violations were observed. We used restricted cubic spline models fitted for Cox proportional hazards models with three knots to flexibly model and visualize the dose-response association of each exposure with incident dementia. Potential non-linearity was tested using a likelihood ratio test as described previously [28].

In sensitivity analyses, we further adjusted for socioeconomic status, smoking status, alcohol intake, BMI, employment status, depression status, income, and sleep medication/physical impairment in addition to covariates in Model 2 (Model 3). Model 4 was further mutually adjusted for sleep duration, TPA, and SB in addition to the covariates in Model 3. We also analyzed data after imputing missing covariates (Supplementary Table 3). Missing values were imputed by multiple imputations using chained equations with 5 imputations and all other covariates and the outcome as predictors, as implemented in the R package "mice". For note, the imputed values of *APOE* ε4 genotypes were derived from UK Biobank, based on merged UK10K and 1000Genomes phase 3 panels [29]. Additionally, participants with a follow-up time less than eight years were systematically excluded to test for potential reverse causation bias. We further examined the potential synergistic effect between the three exposures by performing additional analysis of both the additive and multiplicative interactions. Stratum-specific analyses were conducted according to age at baseline (<60 and ≥60 years), sex (male and female), *APOE* ε4 status, and education levels (high and low). In mediation analyses, we examine whether the association between sleep duration, LTPA, SB, and risk of dementia were mediated by cerebrovascular disease. Cox proportional hazards models and logistic regression models were fitted [30]. Each path of the model was corrected for age, sex, education, and *APOE* ε4 status.

Cox proportional hazards models and logistic regression models were fitted in mediation analyses to examine whether the association between sleep duration, LTPA, SB and risk of dementia were mediated by cerebrovascular disease. Each path of the model was corrected for age, sex, education, and APOE ε4 status. The first equation regressed the mediator (i.e., cerebrovascular disease) on the independent variable (i.e., sleep, LTPA, or SB). The second equation regressed the dependent variable (i.e., dementia) on the independent variable. Mediation effects were established according to the following criteria: (1) sleep, LTPA, and SB must be significantly related to cerebrovascular disease; (2) sleep, LTPA, and SB must be significantly related to incident dementia; (3) cerebrovascular disease must be significantly related to incident dementia; and (4) the association between sleep, LTPA, SB and incident dementia must be attenuated when cerebrovascular disease (the mediator) is included in the regression model. Furthermore, the attenuation or indirect effect was estimated, with the significance determined using 1000 bootstrapped iterations.

A non-linear regression model ($y = \beta x^2 + ax + c$) was utilized to examine the association between each behavior (x) and brain morphometric measures (y) of participants with adjustment of age, sex, education, and *APOE* ε4 status. An F-statistic was obtained for each quadratic model to reflect the association of each behavior and the brain morphometric measures. Bonferroni and false discovery rate (FDR) corrections were conducted for multiple comparisons of 68 cortical regions, 16 subcortical regions, and 27 white matter tracts.

All p values were two-sided. R software version 4.1.0 and GraphPad Prism version 8.00 (GraphPad Software, San Diego, CA) were used for statistical analyses and figure preparation.

RESULTS

A total of 431,924 individuals from UKB were included in this study. Among those, the median age was 58 (interquartile range [IQR]: 51–64) years; 46% participants were men. During a median follow-up of 9.04 years (7.03–10.61), 5390 incident dementia events were recorded. Baseline characteristics of the participants stratified by incident dementia status are provided in Table 1. The distribution of each exposure data was depicted in Supplementary Fig. 2. The median age was 67 (59–73) years at the end of the follow-up period (Supplementary Fig. 3).

Independent association of each behavior with incident dementia

After adjustments for age, sex, education, and *APOE* ε4 status, a cubic spline model showed a significant non-linear U-shaped association between sleep duration and risk of dementia (p-value for non-linearity < 0.001; Fig. 1), with a nadir at 7 h/day. When compared with the moderate sleep group (7 h/day), HRs for incident dementia were higher for low sleep (HR [95% CI]) = 1.19 [1.07–1.31]) and high sleep group (1.23[1.13–1.34]; Supplementary Table 3), independent of full adjustments. There was no significant difference in the risk of dementia in low sleep group compared to the high sleep group, either in Model 1 (1.05 [0.99–1.13], p = 0.128) or Model 2 (0.97 [0.88–1.06], p = 0.480). To examine the quantitative change in dementia risk for each 1 h/day increase of sleep duration, sleep duration was regarded as a continuous variable and divided into two parts by the change point (<7 h/day and ≥7 h/day). When sleep was less than 7 h/day, the risk of dementia was 27% lower per 1 h/day increase of sleep duration (0.73[0.64–0.82]); while when above 7 hours/day, the risk of dementia was 24% higher per 1 h/day increase of sleep duration (1.24[1.18–1.31]; Supplementary Table 4).

Both TPA and LTPA showed inverse associations with dementia (Fig. 2). Compared with the low TPA group, the high TPA group showed 15% lower risk of dementia (0.85[0.77–0.93]) independent of full adjustment in Model 2. The risk of dementia was 22% lower in high LTPA group (0.78[0.70, 0.93] in Model 2), compared to low LTPA group. The cubic spline model showed a significant non-linear association between LTPA and dementia (p-value for non-linearity = 0.025). The risk of dementia was 12% lower per 600 MET-mins/week increase of LTPA (0.88[0.81–0.96]) when less than the change point of 1200 MET-min/week, while there was little additional benefit when above it. As for the individual components of TPA, moderate (p-value for non-linearity = 0.024) and vigorous activity (p-value for non-linearity < 0.001) both showed a significant U-shaped association with incident dementia (Supplementary Fig. 4).

Table 1. Baseline characteristics of study participants by incident dementia status.

	Non-dementia ($N = 426534$)	Dementia ($N = 5390$)	Total ($N = 431924$)	*p*-value
Age (years)	58.0 (51.0–63.0)	66.0 (62.0–68.0)	58.0 (51.0–64.0)	<0.001
Sex				
Male	195115 (46%)	2870 (53%)	197985 (46%)	<0.001
Female	231419 (54%)	2520 (47%)	233939 (54%)	
Education level				
High	194363 (57%)	1750 (54%)	196113 (57%)	<0.001
Low	147580 (43%)	1521 (46%)	149101 (43%)	
APOE ε4				
APOE carrier	103447 (28%)	2504 (55%)	105951 (29%)	<0.001
APOE non-carrier	261791 (72%)	2071 (45%)	263862 (71%)	
Ethnicity				
Non-white	18356 (4%)	209 (4%)	18565 (4%)	0.135
White	402169 (96%)	5104 (96%)	407273 (96%)	
Socioeconomic status*				
Quintile 1	84399 (20%)	990 (18%)	85389 (20%)	<0.001
Quintile 2–4	255842 (60%)	3040 (56%)	258882 (60%)	
Quintile 5	85747 (20%)	1355 (25%)	87102 (20%)	
Employment status				
Working	228331 (54%)	833 (16%)	229164 (53%)	<0.001
Retire	156777 (37%)	4025 (75%)	160802 (37%)	
Other	39067 (9%)	495 (9%)	39562 (9%)	
Smoking status				
Current	45920 (11%)	581 (11%)	46501 (11%)	0.871
Non-current	378106 (89%)	4745 (89%)	382851 (89%)	
Alcohol intake				
Daily intake	86210 (20%)	1085 (20%)	87295 (20%)	<0.001
Less than 14 units per week	253973 (60%)	2702 (50%)	256675 (60%)	
Never or special occasions only	85114 (20%)	1569 (29%)	86683 (20%)	
BMI	26.9 (24.2–30.1)	27.2 (24.4–30.5)	26.9 (24.2–30.1)	<0.001
Depression status				
No	347564 (83%)	4205 (80%)	351769 (83%)	<0.001
Yes	71391 (17 %)	1028 (20 %)	72419 (17%)	
Average total household income before tax				
<£18,000	86071 (24%)	1880 (48%)	87951 (24%)	<0.001
£18,000–£30,999	93755 (26%)	1202 (30%)	94957 (26%)	
£31,000–£51,999	93383 (26%)	561 (14%)	93944 (26%)	
≥£52,000	87243 (24%)	304 (8%)	87547 (24%)	
Physical impairment				
Yes	28809 (7%)	1042 (19%)	29851 (7%)	<0.001
No	397153 (93%)	4329 (80%)	401482 (93%)	
Sleep medication intake				
Yes	4700 (1%)	154 (3%)	4854 (1%)	<0.001
No	421834 (99%)	5236 (97%)	427070 (99%)	
TPA (MET-min/week)	1460 (594–3090)	1330 (494–2880)	1460 (594–3090)	<0.001
TPA group				
Low	126601 (32%)	1754 (36%)	128355 (32%)	<0.001
Moderate	136537 (35%)	1617 (33%)	138154 (35%)	
High	130484 (33%)	1481 (31%)	131965 (33%)	

Table 1. continued

	Non-dementia (*N* = 426534)	Dementia (*N* = 5390)	Total (*N* = 431924)	*p*-value
LTPA (MET-min/week)	705 (278–1440)	668 (235–1410)	704 (278–1440)	0.0898
LTPA group				
Low	125877 (33%)	1599 (37%)	127476 (33%)	<0.001
Moderate	135861 (36%)	1458 (33%)	137319 (36%)	
High	117340 (31%)	1319 (30%)	118659 (31%)	
Sedentary behavior (h/day)	4.00 (2.00–5.00)	4.00 (3.00–5.00)	4.00 (2.00–5.00)	<0.001
Sedentary behavior group				
Low	114102 (28%)	1124 (22%)	115226 (28%)	<0.001
Moderate	174864 (42%)	2060 (40%)	176924 (42%)	
High	124421 (30%)	2018 (39%)	126439 (30%)	
TV viewing (h/day)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	<0.001
TV viewing group				
Low	175188 (44%)	1516 (30%)	176704 (44%)	<0.001
Moderate	100085 (25%)	1221 (24 %)	101306 (25%)	
High	125541 (31%)	2271 (45 %)	127812 (31%)	
Computer using (h/day)	1.00 (0–2.00)	0 (0–1.00)	1.00 (0–2.00)	<0.001
Computer using group				
Low	119118 (37%)	2448 (55 %)	121566 (37%)	<0.001
Moderate	118632 (37%)	975 (22%)	119607 (36%)	
High	85979 (27%)	1021 (23%)	87000 (27%)	
Sleep duration (h/day)	7.00 (6.00–8.00)	7.00 (6.00–8.00)	7.00 (6.00–8.00)	<0.001
Sleep group				
Low	106080 (25%)	1379 (26%)	107459 (25%)	<0.001
Normal	160948 (38%)	1579 (30%)	162527 (38%)	
High	154349 (37%)	2275 (43%)	156624 (37%)	

Shown are numbers (%) or median (interquartile range). *p*-values are derived using either Student's *t*-test or Chi-square test.
*Socioeconomic status quintiles according to Townsend deprivation index combining information on social class, employment, car availability, and housing. Higher scores represent higher levels of area-based socioeconomic deprivation.
APOE apolipoprotein, *BMI* body mass index, *LTPA* leisure-time physical activity, *MET* metabolic equivalent of task, *TPA* total physical activity, *TV* television.

The risk of dementia was relatively flat until around 3 h/day of SB and then started to increase rapidly thereafter (*p*-value for non-linearity = 0.027). When compared with low SB group, the risk of dementia was 22% higher in high SB group (1.22[1.10–1.35]), independent of full adjustment in Model 2. No significant differences between low and moderate SB group were detected. Above 3 h/day of SB, the risk of dementia was 6% higher for 1 h/day increase of SB; while the corresponding change below the change point was non-significant. In greater detail, two components of SB, TV viewing (*p*-value for non-linearity = 0.009) and computer using (*p*-value for non-linearity < 0.001; Fig. 1), were also non-linearly associated with dementia.

Individual associations between each behavior and dementia remained stable when further adjusted for additional confounders (Supplementary Table 5), except for the TPA. Low sleep group approached significance (1.11[0.99, 1.25], $p = 0.068$) when compared to the moderate sleep group in Model 3. The association between SB and dementia was also approximately significant in Model 3 (*p* for trend = 0.077), but was significant when additionally adjusted for sleep and physical activity (*p* for trend = 0.047 in Model 4). The main results, including the independent and joint associations, were also confirmed in the sensitivity analysis using imputed datasets (Supplementary Tables 7–9 and Supplementary Fig. 5). When the follow-up time was restricted to more than eight years, the individual association of sleep, SB, and LTPA with the risk of dementia remained significant after adjustments for age, sex, education, and *APOE* ε4 status, except for TPA (Supplementary Table 10). The two types of PA exposures were positively correlated (Pearson's $r = 0.36$, $p < 0.001$). Thus, LTPA was chosen to include in further analysis. In stratified analyses, the effect estimates of LTPA were more significant in midlife and male; that of TV viewing were more significant in midlife and male (Supplementary Tables 11–14). The interactions between each exposure and stratification variables were significant (Supplementary Table 15). In mediation analysis, the relationships between sleep duration, LTPA, SB, and dementia were partially mediated by cerebrovascular disease (Supplementary Fig. 6). A simplified overview of associations between each behavior and dementia risks is depicted in Supplementary Fig. 7.

Joint association of behaviors with incident dementia

Participants with high levels of LTPA had a lower risk of dementia among those with high levels of sleep (0.79[0.68, 0.92]; Fig. 3) or low levels of sleep (0.72[0.59, 0.89], $p = 0.002$). Participants with high LTPA also had lower risk of dementia even among those with high SB (0.73[0.62, 0.86]; Fig. 3). When the joint associations of sleep, SB, and LTPA were estimated, each exposure was re-categorized in binary and eight combination subgroups were created (Fig. 3). Participants with a combination of typical sleep-low-to-moderate SB-MVPA showed the lowest dementia risks (0.59 [0.50, 0.69]) compared to the referent atypical sleep-high SB-LIPA group. In the sensitivity analysis, we found statistically significant additive interaction in incident dementia (Supplementary Tables 16–18).

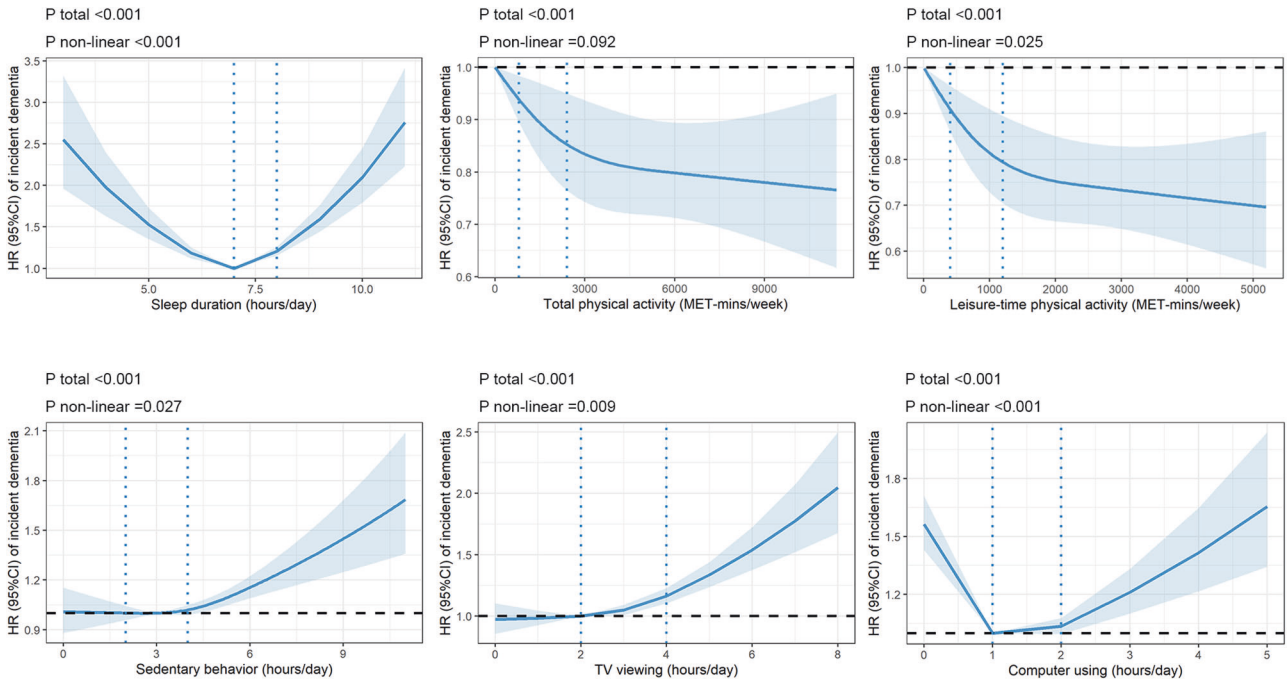

Fig. 1 The independent associations between exposures and incident dementia using a restricted cubic spline regression model. Restricted cubic spline models fitted for Cox proportional hazards models with three knots. Dashed vertical lines represent the category thresholds of each exposure as described in the Methods. Results were adjusted for age, sex, education, and *APOE* ε4 status. CI confidence interval, HR hazard ratio, MET metabolic equivalent of task.

Associations of each behavior and brain structural measures

A nonlinear association model was utilized to explore which brain structures showed significant associations with sleep duration, LTPA and SB. For note, the results of associations with brain volume were much more significant than that of DTI microstructures. Hence, the more rigorous Bonferroni correction was performed instead of FDR in the analysis of brain volume in order to highlight the most important brain regions. The cortical volumes demonstrating the most significant nonlinear associations with sleep were the lateral orbitofrontal cortex, insula, medial orbitofrontal cortex, and precentral cortex (Fig. 4A). Subcortical regions nonlinearly associated with sleep included the hippocampus and thalamus. LTPA was mostly highly associated with cortical volumes in the middle temporal gyrus, medial orbitofrontal cortex, and inferior parietal cortex (Fig. 4C). Subcortical regions showed significant associations with LTPA in the pallidum, thalamus, and hippocampus. SB showed most significant associations with cortical volumes in insula gyrus, middle temporal gyrus, and inferior parietal cortex (Fig. 4E). Subcortical regions demonstrating significant associations with SB were the pallidum, thalamus, and caudate (Bonferroni corrected across regions, p-value < 0.01; Supplementary Tables 19, 20). These cortical and subcortical regions including the middle temporal gyrus and hippocampus have been reported as having a close association with dementia in previous studies [31].

To further explore optimal sleep duration, LTPA and SB for brain structures, mean cortical and subcortical grey volume were utilized. The results demonstrated that sleep duration of around 7 h, LTPA above 1000 MET-min/week, and lower exposure to sedentary behavior is associated with larger cortical and subcortical grey matter volumes (Fig. 4B, D, F), which is consistent with the result of the Cox model for incident dementia (Fig. 1). Additionally, the only white matter tract fractional anisotropy that showed significant association with all these three behaviors was the posterior thalamic radiation (FDR corrected p-value < 0.05; Fig. 4G), with an association with vascular dementia reported in a previous study [32]. In addition, both sleep and SB showed significant association with the medial lemniscus (Supplementary Table 21). Results of white matter tract weighted-mean diffusivity were presented in Supplementary Table 22.

DISCUSSION

In this study of 431,924 UKB participants, we found sleep duration, PA, and SB were the independently and jointly associated with dementia risks. To our knowledge, this is the first investigation examining the joint effects of sleep, PA, and SB with incident dementia. Additionally, each behavior of interest was associated with the volume of brain regions including middle temporal gyrus, orbitofrontal cortex, and hippocampus, which were implicated in the neuropathology of dementia.

In the present study, the recommended optimal sleep duration was 7 h/day, with longer or shorter sleep duration being associated with a higher risk of dementia. The more sleep deviates from 7 h/day, the higher the risk of dementia. The U-shaped relationship between sleep and dementia is consistent with many previous studies [2, 33]. However, we did not find a difference in the risk of dementia between the low sleep group and the high sleep group. It should be mentioned that the HR value of low sleep group was higher than the high group when compared with the moderate group in Model 1, while it yielded the opposite in Model 2. This difference is due to the exclusion of missing samples of education and *APOE* ε4 status in Model 2, but we kept them in Model 1. When we excluded these samples, the results of Model 1 were consistent with Model 2: the HR value of low sleep group (HR [95% CI] = 1.20 [1.08–1.32], $p = 0.0005$) was lower than that of high sleep group (1.22 [1.12–1.33], $p = 9.01 \times 10^{-6}$) when compared to the moderate group. Although some studies have questioned reverse casualty [5, 21], we observed a significant association even in a long follow-up subgroup, which is consistent with other long follow-up studies [34–36]. Sleep might contribute to dementia by influencing amyloid metabolism [37], increasing the risk of cerebrovascular disease (Supplementary Fig. 5), or inducing neuroinflammation [38]. A better

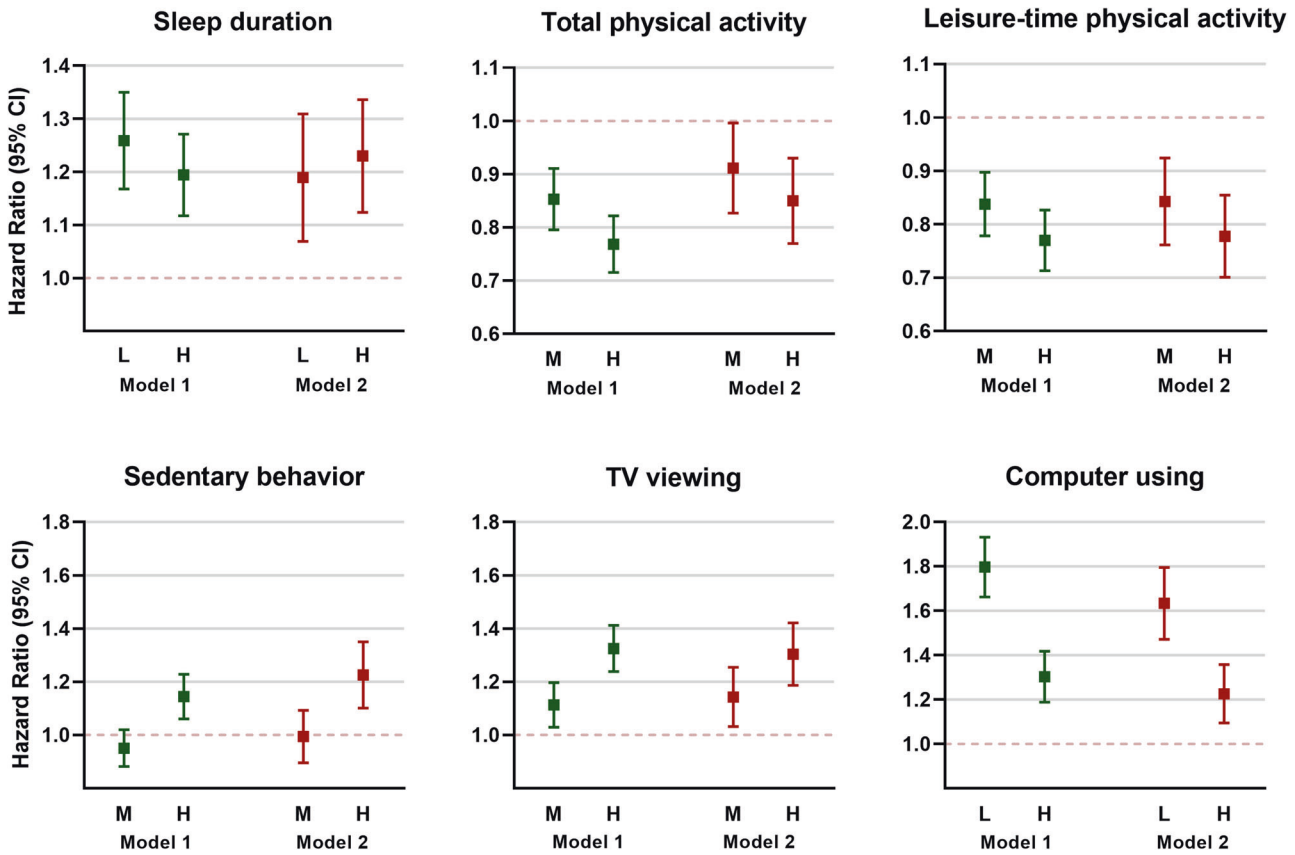

Fig. 2 The independent associations of sleep duration, physical activity, and sedentary behavior with incident dementia. Each behavior was categorized as low (L), moderate (M), and high (H). Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, education, and *APOE* ε4 status. CI confidence interval.

understanding of how sleep features shape the risk of dementia would be helpful to identify windows of opportunity for therapeutic interventions to reduce the risk or delay the progression of dementia and its subtypes.

The curvilinear relationship between PA and dementia is in line with earlier studies [39, 40], suggesting that low-to-moderate exercise is sufficient to lower the dementia risk, without a further reduction in risk with greater levels of PA [40]. In the association with reduced dementia risks, the HRs revealed a stronger effect estimate of LTPA than TPA. Conceptually, TPA includes LTPA, and work-, transport-, domestic and garden-related activity. Previous studies found that LTPA confers protection against AD [41], but not work-related or transport-related PA [42, 43]. It is suggested LTPA and occupational PA are differentially associated with dementia [44]. The next step can be considered to analysis whether the LTPA is associated with dementia even among those who are physically active at work. Furthermore, analyses of the individual components of TPA showed that moderate and vigorous activity had a U-shaped association with the risk of dementia. It is consistent with previous findings that prolonged bouts of strenuous exercise can induce a large number of free radicals, which cause an increase in oxidative stress and further lead to organ damages and pathological protein modifications in AD [45, 46]. Thus, a combination of different types of PA and avoidance of high intensity of moderate-to-vigorous physical activity could be a better recommendation, if future studies support our findings.

Additionally, some studies differ on whether the association between PA and dementia is a reverse causation [47–50]. We found the significant association between LTPA and dementia remained in the long follow-up subgroup, but that of TPA was completely attenuated. This attenuated result may be related to a reverse causation effect, but also may due to the heterogeneity of different PA domains. Despite the controversial evidences for such an association, there are some biologically plausible explanations. One hypothesis relates to vascular protection, which results from positive changes in the cerebral vasculature that is stimulated by PA [51]. Another hypothesis purports enlargement of cognitive reserve, suggesting that PA fostering neuroplasticity in cerebral areas including the hippocampus and neocortex, as well as the pathways between these two regions [52]. Another mechanism suggests PA can limit stress, which in turn diminishes the risk for dementia [53]. These hypotheses are not mutually exclusive, and may act in combination to produce the observed reduction in risk. As some long-term follow-up studies and randomized controlled trials have supported the protective effects of PA on dementia, cognitive function, and hippocampal volume loss [50, 54–57], the potential protection of PA cannot be completely dismissed.

Consistent with previous studies [58], engaging in extended periods of SB (i.e., approximately when longer than 3 h/day) is associated with a higher risk of dementia, but shorter periods are acceptable. Interestingly, the relationship between computer usage and dementia was U-shaped. Participants never using a computer showed a much higher risk of dementia compared to those engaged for a limited time. Specific components of SB may differentially influence cognition. Watching TV is a mentally passive SB, whereas using computer is considered an active type [59]. Therefore, previous non-significant reports of associations between SB and dementia are possibly due to the heterogeneity of SB types [9], and our finding underlines the importance of recording the type of SB when establishing the range of sedentary times that are a potential target for dementia protection.

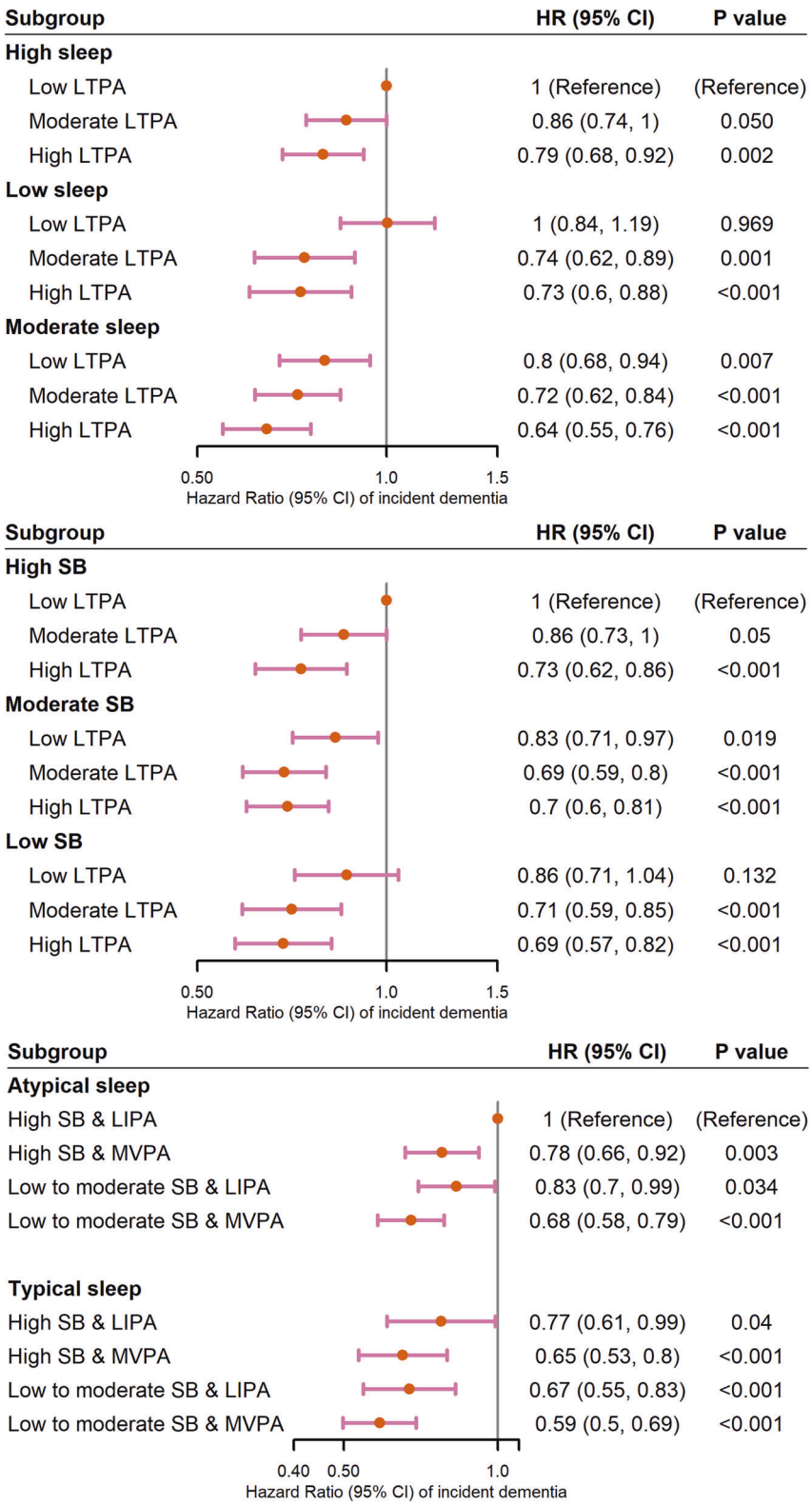

Fig. 3 The joint association of sleep duration, physical activity, and sedentary behavior with incident dementia. The upper panel displays the joint association of sleep duration and leisure-time physical activity with dementia. The middle panel displays the joint association of sedentary behavior and leisure-time physical activity with dementia. When we analyzed the association between each combination of three behaviors and dementia (the bottom panel), LTPA was reclassified in binary as light intensity of LTPA (LIPA, that is, the original low LTPA group) and moderate-to-vigorous intensity of LTPA (MVPA, that is, a combination of original moderate and high LTPA groups); sleep duration was reclassified in binary as typical (sleeping 7 h/day, that is, the original moderate sleep group) and atypical sleep (sleeping less or more than 7 h/day, that is, a combination of original low and high sleep groups); SB was reclassified in binary as low-to-moderate SB (i.e., a combination of original low and moderate SB groups) and high SB group. CI confidence interval, LTPA leisure-time physical activity, SB sedentary behavior, HR hazard ratio, LIPA light intensity of leisure-time physical activity, MVPA, moderate to vigorous intensity of leisure-time physical activity.

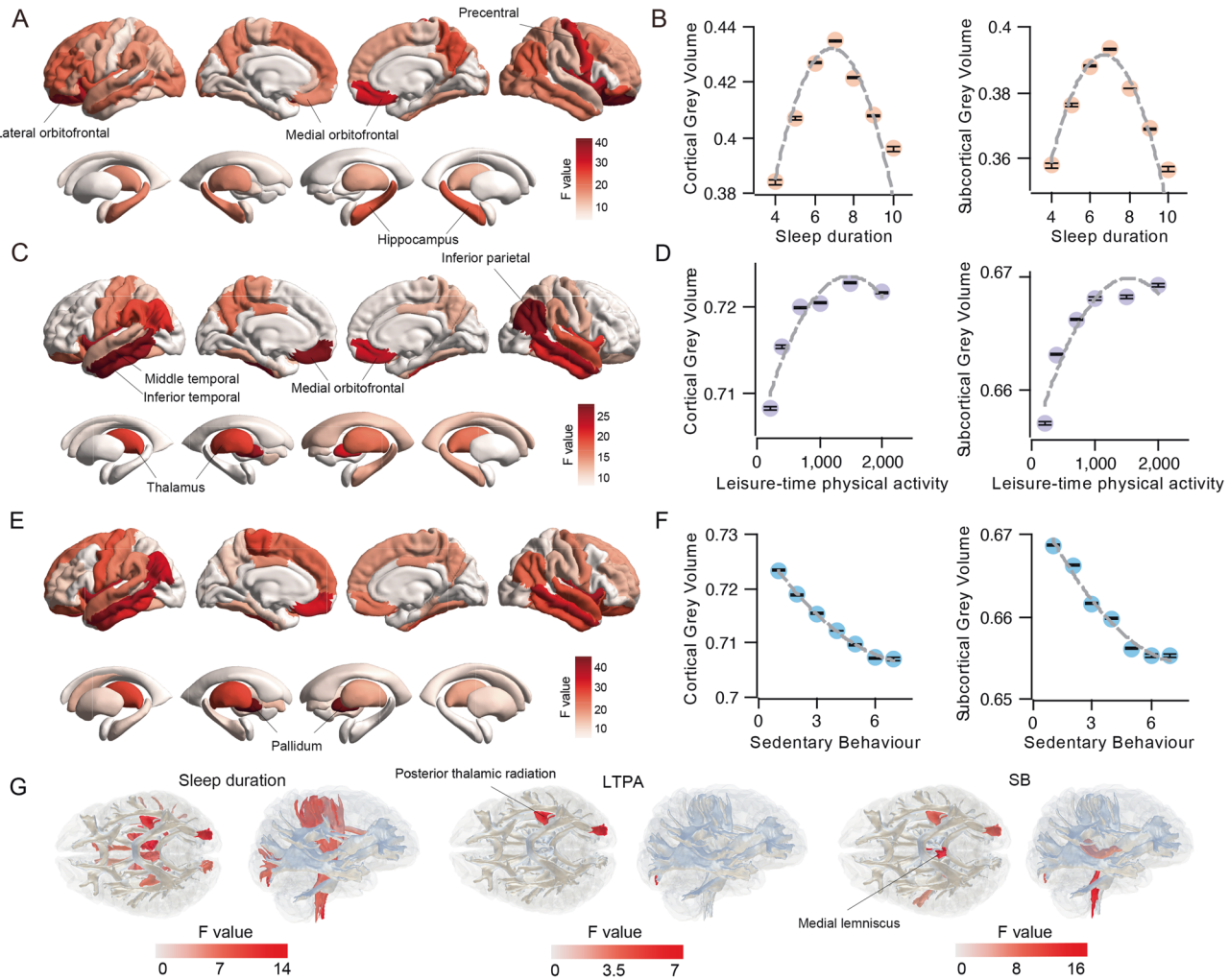

Fig. 4 Associations between sleep duration, physical activity, sedentary behavior and brain structure. The volumes of cortical and subcortical regions were non-linearly associated with sleep duration (**A**), leisure-time physical activity (**C**), and sedentary behavior (**E**). Curve graphs in the right panel show the non-linear associations of mean cortical and subcortical grey volume with sleep duration, leisure-time physical activity, and sedentary behavior (**B**, **D**, **F**). Note that the bottom panel shows the non-linear association between fractional anisotropy of white matter tracts and each exposure (**G**). The magnitude of F value reflects the degree of the non-linear association of each behavior and the brain morphometric measures. LTPA leisure-time physical activity, SB sedentary behavior.

Regarding the synergistic associations, a study reported that replacing SB with MVPA, or replacing excessive sleep with PA was associated with favorable cognitive function [60]. In agreement, we found PA significantly associated with lower dementia risk even among high SB or excessive sleep groups. A speculation is that increasing PA may even reduce the high dementia risk associated with high SB or excessive sleep duration. Nevertheless, the co-dependent associations between the three behaviors were not considered in the present study. Future studies are recommended to consider the competing nature of the three behaviors and examine the associations of replacing different behaviors with incident dementia in longitudinal studies.

The correlations between the three behaviors and brain structure are in line with expectations that proper intensity/time-spending of each behavior was associated with higher grey matter volumes in dementia-related brain regions [15], such as the temporal cortex (involved in perception and semantic representation), medial orbitofrontal cortex (involved in emotion and executive function) [61], posterior cingulate (involved in memory) [62], basal ganglia, as well as the hippocampal formation and entorhinal cortex (involved in episodic memory). Previous studies have found that sleep, PA, and SB are all related to these brain structures [63–66]. A possible hypothesis is that the three behaviors may affect the risk of dementia through protective changes to these dementia-corelated brain structures.

Strengths of the present study include the large sample size, long follow-up, extensive measurement of covariates, as well as the available brain imaging data, which allow us performing several sensitivity analyses and exploring underlying mechanisms. By integrating data from multiple modes, we explored possible mechanisms behind these associations. Also, this is the first study to examine the association of sleep, PA, and SB with dementia simultaneously. This study has some limitations. First, exposure data were measured by self-report, which may lead to biased results. Second, participants in the UKB are primarily of European ancestry and are volunteers with slightly higher representation from affluent groups. Further research is warranted to investigate to what extent these findings generalize to other populations. Third, 34,644 of 466,568 participants were excluded from the survival analyses due to unavailable dementia diagnostic data during follow-up, which was considered as loss of follow-up (accounting for 7.5%). However, it is unlikely to be biased as the

loss of follow-up was less than 20%. Besides, the complete case-analysis may bias the effect estimates and reduce power if data are missing not completely at random. However, it is not possible to distinguish between missing at random and missing not at random using observed data [67]; we also performed sensitivity analysis using imputed data and the main findings were well confirmed. In addition, although an eight-year wash-out period were added in the sensitivity analysis, it is still insufficient to completely exclude the possibility of reverse causation. Also, it should be highlighted that the median age of participants was 67 years at the end of the follow-up period. Most of the participants might not reach age at dementia onset, which limited the number of incident dementia cases despite large sample size and long follow-up period. However, the prevalence of incident dementia in our study was similar as previous literatures using UKB cohort for analyses [68, 69], suggesting the reasonability and usability of the current data. Additionally, as these behaviors are closely linked to long-standing culture, habits, and environment, which are difficult to alter, there may be difficulties in real-world practice.

Taken together, our findings have important implications for advancing the development of dementia prevention strategies. Briefly, 7 h/day can be the best sleep duration in reducing the risk of dementia. Although higher levels of LTPA are associated a lower risk of dementia, moderate levels of exercise have been shown to be significantly associated with a reduced risk of dementia in the present study. Notably, prolonged strenuous exercise may even be counterproductive, despite further validation in independent cohorts are needed. In addition, lower levels of sedentary behaviors are recommended. Importantly, our findings emphasize the difference between mentally active and passive sedentary types. A moderate level of mentally active sedentary behavior such as using computer in non-work time may also reduce the dementia risks. Regarding the joint effects of these three behaviors, a combination of 7-hour/day sleep, higher levels of LTPA (above 400 MET-mins/week), and lower sedentary time (less than 4 h/day) could be the best recommendation in association with lower dementia risk. Considering the difficulty in changing these three daily behaviors simultaneously, the present findings have also suggested that a higher level of leisure-time physical activity appeared to attenuate the high dementia risk associated with atypical sleep duration or high sedentary time.

CONCLUSIONS

In conclusion, we found sleep duration, LTPA, and screen-based SB each associated with the risk of dementia in different non-linear association modes. High LTPA appeared to be associated with lower dementia risk even among participants with atypical sleep duration or high sedentary time. And each behavior may affect dementia risk through its association with brain structures and cerebrovascular disease risks. Our results support the potential of changing these three daily behaviors individually or simultaneously to mitigate dementia risks.

DATA AVAILABILITY

The data that support the findings of this study are available from UK Biobank project site, subject to registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

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AUTHOR CONTRIBUTIONS

JTY and WC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JFF and WC were responsible for the cohort data. SYH performed the statistical analysis between sleep, physical activity, sedentary behaviors and incident dementia. YZL and WZ conducted the brain imaging analysis. SYH, YZL, and YRZ wrote the first draft of the report and YYH, BSW, YTD, SDC, XYH, SFC, QD, CZ, RJC, JS, ETR, JFF, WC, and JTY helped in revising the text. QD, JFF, WC, and JTY provide administrative, technical and material support. All authors read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All participants gave written informed consent prior data collection. The UK Biobank has ethical approval by the National Research Ethics Service (Ref 11/NW/0382).

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