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# The brain structure and genetic mechanisms underlying the nonlinear association between sleep duration, cognition and mental health

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**Sleep duration, psychiatric disorders and dementias are closely interconnected in older adults. However, the underlying genetic mechanisms and brain structural changes are unknown. Using data from the UK Biobank for participants primarily of European ancestry aged 38–73 years, including 94% white people, we identified a nonlinear association between sleep, with approximately 7 h as the optimal sleep duration, and genetic and cognitive factors, brain structure, and mental health as key measures. The brain regions most significantly underlying this interconnection included the precentral cortex, the lateral orbitofrontal cortex and the hippocampus. Longitudinal analysis revealed that both insufficient and excessive sleep duration were significantly associated with a decline in cognition on follow up. Furthermore, mediation analysis and structural equation modeling identified a unified model incorporating polygenic risk score (PRS), sleep, brain structure, cognition and mental health. This indicates that possible genetic mechanisms and brain structural changes may underlie the nonlinear relationship between sleep duration and cognition and mental health.**

Sleep serves critical functions in cognitive processing and maintenance of psychological health, including consolidation of memories[1] and emotion processing[2]. Sleep also provides a critical neuroprotective function through the clearance of waste products[3]. Changes in sleep duration, a critical sleep characteristic, have been linked to several diseases and psychiatric disorders, including cardio-cerebral vascular disease and dementia[4–6]. Sleep duration of less than 4–5 h per night is associated with increased mortality[7]. Prolonged sleep duration has been recognized as a potential marker of incident dementia[8].

Alteration in sleep patterns, including difficulty falling asleep and staying asleep, decreased quantity and quality of sleep and decreased sleep efficiency are important characteristics of the aging process[9–11]. Therefore, sleep disturbances are prevalent in the aging population and may be accompanied by cognitive decline and poorer well-being[12,13]. Relevant to this, a recent study showed an inverted U-shaped association between sleep duration and global cognitive decline, with sleep duration less than 4 h or more than 10 h being detrimental[14]. In addition, a U-shaped association was observed between nocturnal sleep duration and cerebrospinal fluid (CSF) biomarkers of amyloid deposition in older adults, with optimal sleep duration around 6 h[15]. However, the optimal level of sleep duration and its relationship with genetics and brain mechanisms in addition to cognition and mental health in a large cohort remains to be determined.

Abnormal sleep is associated with detrimental changes in brain structures in older populations. Previous studies showed that each hour of reduced sleep duration was associated with a 0.59% increase in ventricular volume in participants aged over 55 years[16]. Shorter total sleep duration in middle-aged and older adults was related to impairment in white matter microstructure[17]. A longitudinal study showed that age-related atrophy of the brain regions involved in sleep regulation may contribute to the emergence of sleep disorders in the aging population[18]. Despite some previous discussion of possible nonlinear relationships between sleep and behavioral measures[19–21], the previous reports considering sleep duration and brain structure were focused on linear relationships.

To address whether brain and genetic mechanisms underlie the nonlinear association between sleep duration, cognition and mental health, this study focused on the sleep durations of mid-to-late life adults using the large cohort of the UK Biobank. This large cohort enables us to precisely determine the interaction between age and sleep. The UK Biobank is a large-scale database containing cognitive assessments, mental health questionnaires (MHQs) and brain imaging and in-depth genetic information from participants in the UK. The objectives of the current study were fourfold. First, to investigate whether a nonlinear association exists between sleep duration and various mental health conditions and cognitive performance. Second, to investigate the relationship between sleep duration and brain structure using neuroimaging data. Third, to explore the relationship between sleep, PRS, brain structure, mental health and cognitive functioning using structural equation modeling. Finally, to test the directional and direct association of sleep

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**Table 1 | Demographic characteristics of participants**

| Variables | Baseline (2006–2010) $n=498,277$ | Imaging visit (2014+) $n=48,511$ | Online follow up (2016–2017) $n=156,884$ |
|---|---|---|---|
| Age (years; mean ± s.d.) | 56.5 ± 8.1 | 64.2 ± 7.7 | 63.9 ± 7.7 |
| Sex (female, percent) | 270,814 (54.3%) | 25,002 (51.5%) | 88,774 (56.6%) |
| Townsend deprivation index | −1.3 ± 3.1 | −1.9 ± 2.7 | −1.7 ± 2.8 |
| BMI | 27.4 ± 4.8 | 26.6 ± 4.4 | 26.8 ± 4.6 |
| Educational qualification (%) | | | |
| Degree level | 160,774 (32.3%) | 23,493 (48.4%) | 70,893 (45.2%) |
| Other | 244,714 (49.1%) | 21,662 (44.6%) | 73,729 (47%) |
| Missing data | 92,789 (18.6%) | 3,356 (7.0%) | 12,262 (7.8%) |
| Smoking status (%) | | | |
| Never | 271,798 (54.5%) | 30,023 (61.9%) | 90,135 (57.5%) |
| Previous | 172,170 (34.6%) | 16,639 (34.3%) | 55,143 (35.1%) |
| Current | 52,478 (10.5%) | 1,693 (3.5%) | 11,309 (7.2%) |
| Missing data | 1,831 (0.4%) | 156 (0.3%) | 297 (0.2%) |
| Drinking status (%) | | | |
| Never | 22,018 (4.4%) | 1,602 (3.3%) | 4,493 (2.9%) |
| Previous | 17,840 (3.6%) | 1,640 (3.4%) | 4,269 (2.7%) |
| Current | 457,862 (91.9%) | 45,251 (93.3%) | 148,055 (94.4%) |
| Missing data | 557 (0.1%) | 18 (0.037%) | 67 (0.043%) |
| Sleep duration (h; mean ± s.d.) | 7.15 ± 1.11 | 7.15 ± 1.05 | NA |

BMI, body mass index; NA, not available.

duration, cognition and mental health via longitudinal analysis and mediation analysis. We hypothesized that there is a nonlinear association between sleep duration and mental health, cognition and brain structure. Non-optimal sleep duration would be associated with subsequent inferior cognitive performance and mental health symptoms. In addition, we hypothesized that this nonlinear association between sleep duration and behavioral measures may be supported by brain and genetic mechanisms.

## Results

**Population characteristics.** Of the 502,536 participants in the UK Biobank cohort, 498,277 participants aged 38–73 years (55% female) completed touchscreen questions about sleep duration at baseline, with mean sleep duration 7.15 ± 1.11 h (mean ± s.d.), of which 48,511 participants aged 44–82 years had data measured at the follow-up neuroimaging visit (7.15 ± 1.05 h, mean ± s.d.; Extended Data Fig. 1). The baseline data were assessed between 2006 and 2010, and neuroimaging data were collected from 2014, which explains the difference in the age range. A total of 156,886 participants completed an online mental health questionnaire (MHQ) at follow up. Brain imaging and genetic data of 39,692 participants were used in the current study. Table 1 showed the demographic information of the participants used in the study. Fig. 1 provides a general schema of the current study.

**Nonlinear association between sleep duration and key measures.** There were quadratic associations between cognitive function and sleep duration (cognitive function ~ sleep + sleep$^2$, with covariates adjusted; Extended Data Fig. 2), significant after Bonferroni correction ($P<0.001$), encompassing fluid intelligence ($F=473.5$, $P=9.12\times10^{-206}$), numeric memory ($F=111.5$, $P=4.75\times10^{-49}$), pair matching ($F=79.3$, $P=3.72\times10^{-35}$), reaction time ($F=130.6$, $P=2.07\times10^{-57}$) and trail making ($F=26.9$, $P=2.14\times10^{-12}$). Sleep duration illustrated an inverted U shape with fluid intelligence and numeric memory, and U-shaped associations were found for pair matching, trail making, prospective memory and reaction time. This demonstrated the positive association of both insufficient and excessive sleep duration with inferior performance on cognitive tasks (Fig. 2a and Table 2).

Sleep duration was significantly quadratically correlated with multiple follow-up mental health measures (mental health ~ sleep + sleep$^2$, with covariates adjusted) including anxiety symptoms ($F=1,027.4$, $P<1\times10^{-300}$), depressive symptoms ($F=1,013.7$, $P<1\times10^{-300}$), mania symptoms ($F=182.5$, $P=6.71\times10^{-80}$), mental distress ($F=244.0$, $P=1.52\times10^{-106}$), psychotic experience ($F=328.3$, $P=4.94\times10^{-143}$), self-harm ($F=444.3$, $P=4.02\times10^{-193}$), trauma ($F=1,106.9$, $P<1\times10^{-300}$) and well-being ($F=923.2$, $P<1\times10^{-300}$) after adjusting for covariates. Results were consistent after additionally adjusting interval years between sleep duration and online follow-up mental health measurements. Specifically, sleep duration showed a U-shaped association with anxiety symptoms, depressive symptoms, mental distress, mania symptoms and self-harm behaviors, whereas well-being showed an inverted U shape. This indicated that both insufficient and excessive sleep duration were positively correlated with mental health symptoms (Fig. 2b and Table 2). Significant nonlinear associations were also revealed between sleep duration and similar baseline mental health symptoms, including depressive symptoms ($F=4,283.0$, $P<1\times10^{-300}$), mania symptoms ($F=668.9$, $P=4.24\times10^{-290}$) and well-being ($F=1,850.4$, $P<1\times10^{-300}$). All the associations between sleep duration and mental health scores were significant after Bonferroni correction ($P<0.001$).

**Sleep duration was quadratically associated with brain structures.** To determine how sleep duration and brain structure were associated, measures of total area, mean thickness, total cortical gray matter volume and total subcortical gray matter volume were used. Significant quadratic associations (brain structures ~ sleep + sleep$^2$, with covariates adjusted) were revealed between sleep duration and total surface area (left hemisphere (lh), $F=28.88$, $P=2.91\times10^{-13}$; right hemisphere (rh), $F=29.92$, $P=1.04\times10^{-13}$), global mean thickness (lh, $F=23.88$, $P=4.32\times10^{-11}$; rh, $F=20.42$, $P=1.37\times10^{-9}$), cortical gray matter volume ($F=41.13$, $P=1.43\times10^{-18}$) and subcortical gray matter volume ($F=12.64$, $P=3.24\times10^{-6}$) (Fig. 3a and Table 2). Inverted U-shaped associations were found between sleep duration and the above brain structure measures. Restricted cubic splines were also used to model the association between sleep duration and brain structures, which also demonstrated significant nonlinearity (Supplementary Table 5). Therefore, a nonlinear model analysis was conducted to determine which brain regions had significant nonlinear associations with sleep duration with intracranial volume and other covariates adjusted. The most significant cortical volumes nonlinearly associated with sleep duration included the precentral cortex, the superior frontal gyrus (lh), the lateral orbitofrontal cortex, the pars orbitalis, the frontal pole (lh) and the middle temporal cortex (with all mentioned regions Bonferroni corrected ($P<0.05$)). Cortical areas of the isthmus cingulate gyrus and cortical thicknesses of the superior frontal gyrus, the rostral middle frontal gyrus, the superior temporal gyrus, the pars opercularis and the triangularis and the frontal pole showed the most significant nonlinear association with sleep duration (with all mentioned regions Bonferroni corrected ($P<0.05$); Fig. 3b). The corresponding results for the cortical area and thickness are shown in Extended Data Fig. 3. The subcortical volumes significantly quadratically

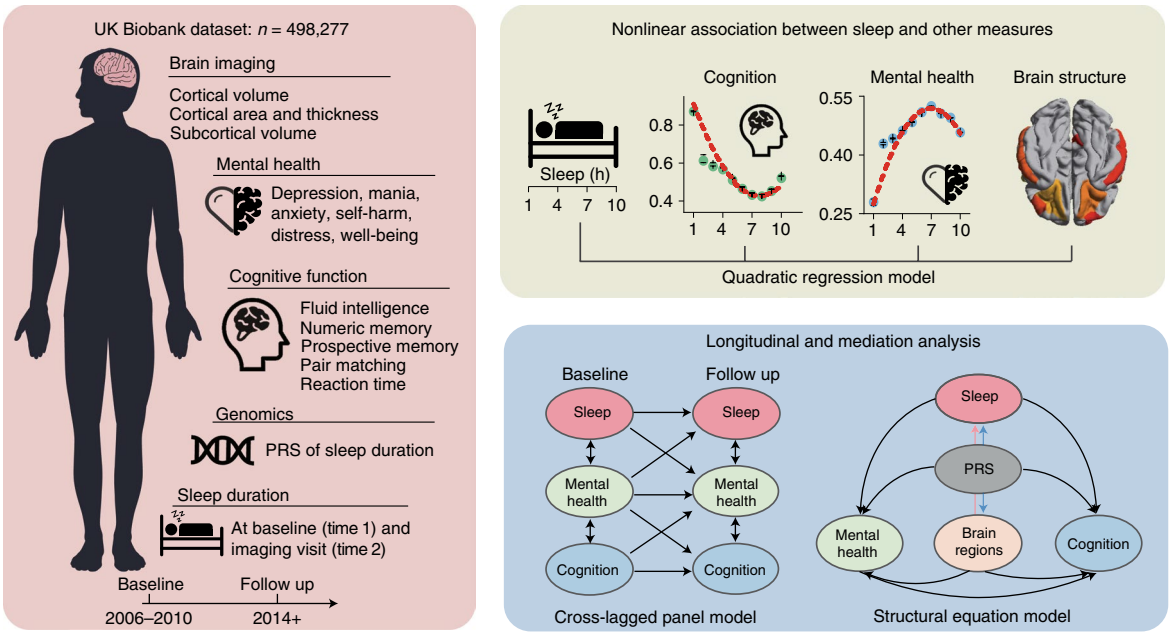


**Fig. 1 | Guideline of the study.** Left, UK Biobank data used in the study including brain imaging, mental health, cognitive function, genomics and sleep duration. Top right, nonlinear association between sleep duration and cognitive function, mental health and brain structure. Bottom right, longitudinal analysis between sleep duration, cognition and mental health and structural equation model specifying the directional association between PRS, sleep, mental health, cognition and brain structure.

correlated with sleep duration included the hippocampus (lh, $F=13.7$, $P=1.10\times10^{-6}$; rh, $F=14.3$, $P=6.0\times10^{-7}$), the inferior lateral ventricle (lh, $F=12.9$, $P=2.38\times10^{-6}$; rh, $F=11.7$, $P=8.15\times10^{-6}$) and the corpus callosum anterior midbody ($F=11.3$, $P=1.22\times10^{-5}$) (with all mentioned regions Bonferroni corrected ($P<0.05$); Fig. 3c).

Additionally, two-line tests were conducted to identify the breakpoint of these quadratic regressions between sleep duration and cognitive function, mental health symptoms and brain structure. Consistent with the quadratic regression, the two-line test showed that 7 h was the breakpoint with an opposite slope sign of regression between sleep duration below and above 7 h and all these key measures (Supplementary Table 6). It is worth noting that only integer values of sleep duration were available in the questionnaire.

**The effect of age on the associations between sleep duration and key measures.** We further investigated whether there were differences in the association pattern between sleep duration, cognition, mental health and brain structure between groups with different ages. The participants were divided into three age groups, ensuring approximately the same number of individuals in each subgroup for baseline behavioral analysis and follow-up neuroimaging analysis, respectively. The results revealed that, with increasing age, there was a decrease in brain volume and a greater impairment in cognitive function. However, the same pattern was not found for mental health. The nonlinear relationship between sleep duration and cortical volumes was most significant in the group aged 44–59 years, and the association curve gradually flattened with increasing age ($F_{\text{age }44-59}=20.16$, $F_{\text{age }60-67}=18.36$, $F_{\text{age }68-82}=10.63$), which was also shown in subcortical volumes ($F_{\text{age }44-59}=10.15$, $F_{\text{age }60-67}=6.79$, $F_{\text{age }68-82}=2.25$). A similar trend was also observed in the association between sleep duration and several cognitive function and mental health measures including reaction time ($F_{\text{age }39-52}=200.7$, $F_{\text{age }53-61}=194.4$, $F_{\text{age }62-70}=48.8$), depressive symptoms ($F_{\text{age }39-52}=420.3$, $F_{\text{age }53-61}=360.2$, $F_{\text{age }62-70}=205.5$) and mania ($F_{\text{age }39-52}=129.2$, $F_{\text{age }53-61}=94.0$, $F_{\text{age }62-70}=47.9$) (Fig. 4 and Supplementary Table 7). These findings showed the frequently reported interaction between sleep duration and age. Furthermore, 'sleep × age' and 'sleep$^2$ × age' terms were added in the nonlinear regression model to validate the significance of the interaction terms. Details of results are provided in Supplementary Table 8.

Noticeably, even for the older age groups with a relatively flatter nonlinear curve, the nonlinear associations were still significant between sleep duration and the above-mentioned cognitive function, mental health symptoms and cortical volumes compared to a linear relationship (Supplementary Table 9).

We further explored the interaction between sleep duration and sex; interaction terms 'sleep × sex' and 'sleep$^2$ × sex' were added to the original nonlinear regression model (Extended Data Fig. 4 and Supplementary Tables 10 and 11).

**The longitudinal association between sleep duration and key measures.** To examine the association between sleep variability and behavioral assessments, we calculated the difference in sleep duration between baseline and neuroimaging visits and associated this difference with cognitive function and mental health. Similar nonlinear associations were found between sleep duration difference and these assessments, with approximately 0 h being associated with optimal cognitive performance ($F$-value range from 6.69 to 50.6, all $P$ values $<1.2\times10^{-3}$) and mental health ($F$-value range from 38.9 to 158.9, all $P$ values $<1.4\times10^{-17}$). These findings highlight the close association of stable sleep duration and health (Fig. 5). Detailed $F$ and $P$ values are displayed in Supplementary Table 12.

Based on the quadratic associations between sleep duration and mental health and cognitive function, participants with both longitudinal sleep and behavioral data were separated into two groups with sleep duration ≤7 h and sleep duration >7 h. The longitudinal analysis was conducted for depressive symptoms (Patient Health Questionnaire (PHQ)-4, fluid intelligence and sleep duration at baseline and at the neuroimaging visit. Histograms of the changes in these variables over time are shown in Extended Data Fig. 5. The results revealed that, for participants with sleep duration ≤7 h

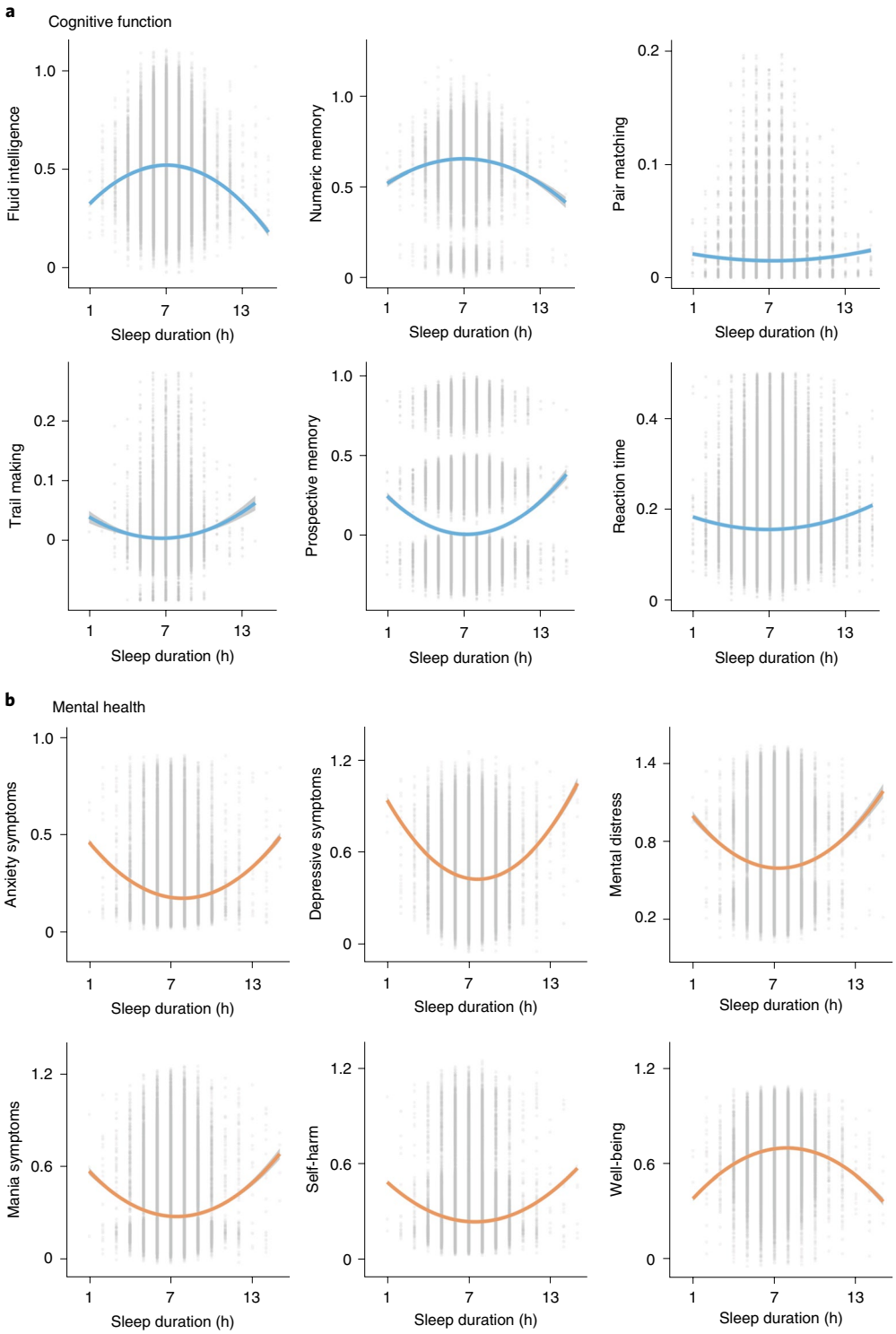


**Fig. 2 | Nonlinear association of sleep duration with mental health and with cognitive function. a**, Significant nonlinear association between sleep duration and cognitive function including fluid intelligence, numeric memory, pair matching, trail making, perspective memory and reaction time (Bonferroni corrected, $P < 0.01$). **b**, Significant nonlinear association between sleep duration and mental health including anxiety symptoms, depressive symptoms, mental distress, mania symptoms, self-harm and well-being (Bonferroni corrected, $P < 0.01$). The variables shown in the figure were adjusted for covariates comprising age, sex, body mass index, Townsend deprivation index, educational qualification, smoking status and drinking status. *F*-tests were used to assess statistical significance and derive *F* statistics and corresponding one-sided *P* values adjusted for multiple comparisons. Lines are fitted nonlinear models indicating fitted mean values, and shaded areas are 95% confidence intervals (CIs); gray points are individual data points.

($n = 9{,}753$) longer sleep duration was significantly associated with lower PHQ-4 scores and higher fluid intelligence scores at follow up ($\beta = -0.038$, $P = 1.3 \times 10^{-5}$ and $\beta = 0.021$, $P = 0.01$, Fig. 6a). Baseline PHQ-4 scores were significantly associated with follow-up fluid intelligence scores ($\beta = -0.018$, $P = 0.029$). All mentioned longitudinal associations were significant after false discovery rate (FDR)

**Table 2 | The nonlinear correlation between sleep duration and key measures**

| Cognitive function (baseline) | *F* value | *r* value | *P* value |
|---|---|---|---|
| Fluid intelligence | 473.5 | 0.0057 | $9.12\times10^{-206}$ |
| Matrix pattern completion | 30.2 | 0.0022 | $8.21\times10^{-14}$ |
| Numeric memory | 111.5 | 0.0043 | $4.75\times10^{-49}$ |
| Pair matching | 79.3 | 0.0007 | $3.72\times10^{-35}$ |
| Prospective memory | 223.1 | 0.0026 | $1.76\times10^{-97}$ |
| Reaction time | 130.6 | 0.0012 | $2.07\times10^{-57}$ |
| Symbol-digit substitution | 28.3 | 0.0017 | $5.10\times10^{-13}$ |
| Tower rearranging | 17.5 | 0.0011 | $2.58\times10^{-8}$ |
| Trail making | 26.9 | 0.0016 | $2.14\times10^{-12}$ |
| **Mental health** | | | |
| Anxiety symptoms | 1,027.4 | 0.0131 | $<1\times10^{-300}$ |
| Depressive symptoms | 1,013.7 | 0.0128 | $<1\times10^{-300}$ |
| Mania symptoms | 280.9 | 0.0037 | $1.70\times10^{-122}$ |
| Mental distress | 244.0 | 0.0031 | $1.52\times10^{-106}$ |
| Psychotic experience | 328.3 | 0.0042 | $4.94\times10^{-143}$ |
| Self-harm | 444.3 | 0.0056 | $4.02\times10^{-193}$ |
| Trauma | 1,106.9 | 0.0139 | $<1\times10^{-300}$ |
| Well-being | 923.2 | 0.0116 | $<1\times10^{-300}$ |
| **Brain structure** | | | |
| Area of total surface (lh, $mm^2$) | 28.88 | 0.0015 | $2.91\times10^{-13}$ |
| Area of total surface (rh, $mm^2$) | 29.92 | 0.0015 | $1.04\times10^{-13}$ |
| Mean thickness (lh, mm) | 23.88 | 0.0012 | $4.32\times10^{-11}$ |
| Mean thickness (rh, mm) | 20.42 | 0.0010 | $1.37\times10^{-9}$ |
| Total gray volume ($mm^3$) | 39.81 | 0.0020 | $5.36\times10^{-18}$ |
| Subcortical gray volume ($mm^3$) | 12.64 | 0.0006 | $3.24\times10^{-6}$ |
| Cortex volume (lh, $mm^3$) | 42.68 | 0.0021 | $3.04\times10^{-19}$ |
| Cortex volume (rh, $mm^3$) | 35.68 | 0.0018 | $3.29\times10^{-16}$ |
| Cortical gray volume ($mm^3$) | 41.13 | 0.0021 | $1.43\times10^{-18}$ |

*F*-tests were used to assess statistical significance and derive *F* statistics and corresponding one-sided *P* values adjusted for multiple comparisons (Bonferroni correction). *F* statistics were converted to effect-size *r* values with the equation $r = \sqrt{F \times df_1 \,(F \times df_1 + df_2)^{-1}}$, where $df_1$ is the numerator degrees of freedom and $df_2$ is the denominator degrees of freedom. lh, left hemisphere; rh, right hemisphere.

correction (FDR corrected $P<0.05$; Supplementary Table. 13). For participants with sleep duration of more than 7 h ($n=5{,}247$), longer sleep duration at baseline correlated with lower fluid intelligence scores at follow up ($\beta=0.025$, $P=0.027$, Extended Data Fig. 6a).

**Serial mediation between PRSs of sleep and behavioral measures.** Based on the longitudinal association of baseline sleep duration with subsequent depressive symptoms and the significant association between sleep duration and brain structure, we further examined whether sleep duration and brain structure contributed to the association between PRSs for sleep and behavioral measures. Therefore, we first conducted three mediation pathway analyses for depressive symptoms, namely (1) PRS → sleep duration → brain structure → depressive symptoms, (2) PRS → sleep duration → depressive symptoms and (3) PRS → brain structure → depressive symptoms.

For participants with sleep duration ≤7 h, the results of first model demonstrated that PRS for sleep had a significant negative effect on depressive symptoms ($\beta=-0.033$, $P=2.3\times10^{-4}$), PRS was associated with sleep duration ($\beta=0.058$, $P=1.4\times10^{-10}$) and sleep duration was associated with brain structure ($\beta=0.046$, $P=3.7\times10^{-7}$), and, in addition, brain structure was associated with depressive score ($\beta=-0.027$, $P=2.2\times10^{-3}$). The indirect pathway of the effect of PRS on depressive symptoms via sleep duration and brain structure was significant (Fig. 6b, path $\beta_1=-7.3\times10^{-5}$, $P=0.025$). The results of the second model showed that sleep duration significantly mediated the association between PRS and depressive symptoms (Fig. 6b, path $\beta_2=-0.0071$, $P=9.3\times10^{-9}$). The third model revealed that brain structure was also a significant mediator for the association between PRS and depressive symptoms (Fig. 6b, path $\beta_3=-7.7\times10^{-4}$, $P=0.035$). A mediation analysis of PRS → depressive symptoms → brain structures → sleep was also conducted (Extended Data Fig. 7a), with depressive symptoms and brain structures serially mediating the association between PRS and sleep duration ($\beta=4.11\times10^{-5}$, $P=0.049$).

Three mediation pathway analyses were also conducted for the cognitive function of fluid intelligence for participants with sleep duration ≤7 h: (1) PRS → sleep duration → brain structure → fluid intelligence, (2) PRS → sleep duration → fluid intelligence and (3) PRS → brain structure → fluid intelligence. PRSs of sleep showed a significant positive association with fluid intelligence in the model ($\beta=0.044$, $P=2.5\times10^{-8}$). The serial mediation pathway via sleep and brain structure was significant ($\beta_1=3.8\times10^{-4}$, $P=1.3\times10^{-5}$). Specifically, sleep duration was significantly associated with PRS ($\beta=0.061$, $P=1.2\times10^{-14}$), and brain volume was positively associated with sleep duration ($\beta=0.045$, $P=1.3\times10^{-8}$) and, in addition, brain volume was significantly associated with fluid intelligence ($\beta=0.14$, $P=0$). The result of model 2 and model 3 showed that sleep duration and brain structure were also separately significant mediators for this association (Fig. 6b; $\beta_2=0.004$, $P=2.8\times10^{-8}$; $\beta_3=0.004$, $P=7.9\times10^{-5}$). Additionally, mediation analyses examining how depressive symptoms mediated the association between sleep duration and fluid intelligence were also conducted and are presented in Extended Data Fig. 7b.

For participants with sleep duration >7 h, mediation analysis was also conducted (sleep duration → brain structure → fluid intelligence). The results revealed that the association between sleep duration and fluid intelligence was also significantly mediated by brain structure (Extended Data Fig. 6b; $\beta=-0.004$, $P=1.4\times10^{-5}$). The mediation analysis between sleep duration and depressive symptoms did not yield significant results for participants with sleep duration >7 h.

Five other cognitive functions were also used to conduct mediation analysis (Extended Data Fig. 8). For participants with sleep duration ≤7 h, brain structure related to sleep significantly mediated the association between sleep duration and numeric memory (path $\beta=0.006$, $P=1.4\times10^{-11}$), trail making (path $\beta=-0.003$, $P=7.8\times10^{-7}$) and prospective memory (path $\beta=-8.8\times10^{-4}$, $P=0.021$). The association between these cognitive functions and sleep duration was also significantly mediated by brain structures related to sleep for participants with sleep duration >7 h, including symbol–digit substitution (path $\beta=-0.002$, $P=0.019$), numeric memory (path $\beta=-0.003$, $P=0.0039$), etc.

**Structural equation model.** Confirmatory factor analysis was used to examine the latent variables in the structural equation model including brain structure, mental health and cognitive function. For participants with sleep duration ≤7 h, the results demonstrated that depressive symptoms and anxiety symptoms were the main components of the mental health latent variable ($\beta=0.84$ and 0.71, respectively, $P<0.001$). The volume of the cortex was the most significant predictor of brain volume ($\beta=0.98$, $P<0.001$). The latent variable cognitive function was represented by fluid intelligence, perspective memory, the reaction time test and the pair-matching test ($\beta=1$, 0.15, 0.10 and 0.12, respectively; $P<0.001$).

Structural equation modeling was used to specify the directional association between PRS and sleep duration, brain structure, mental

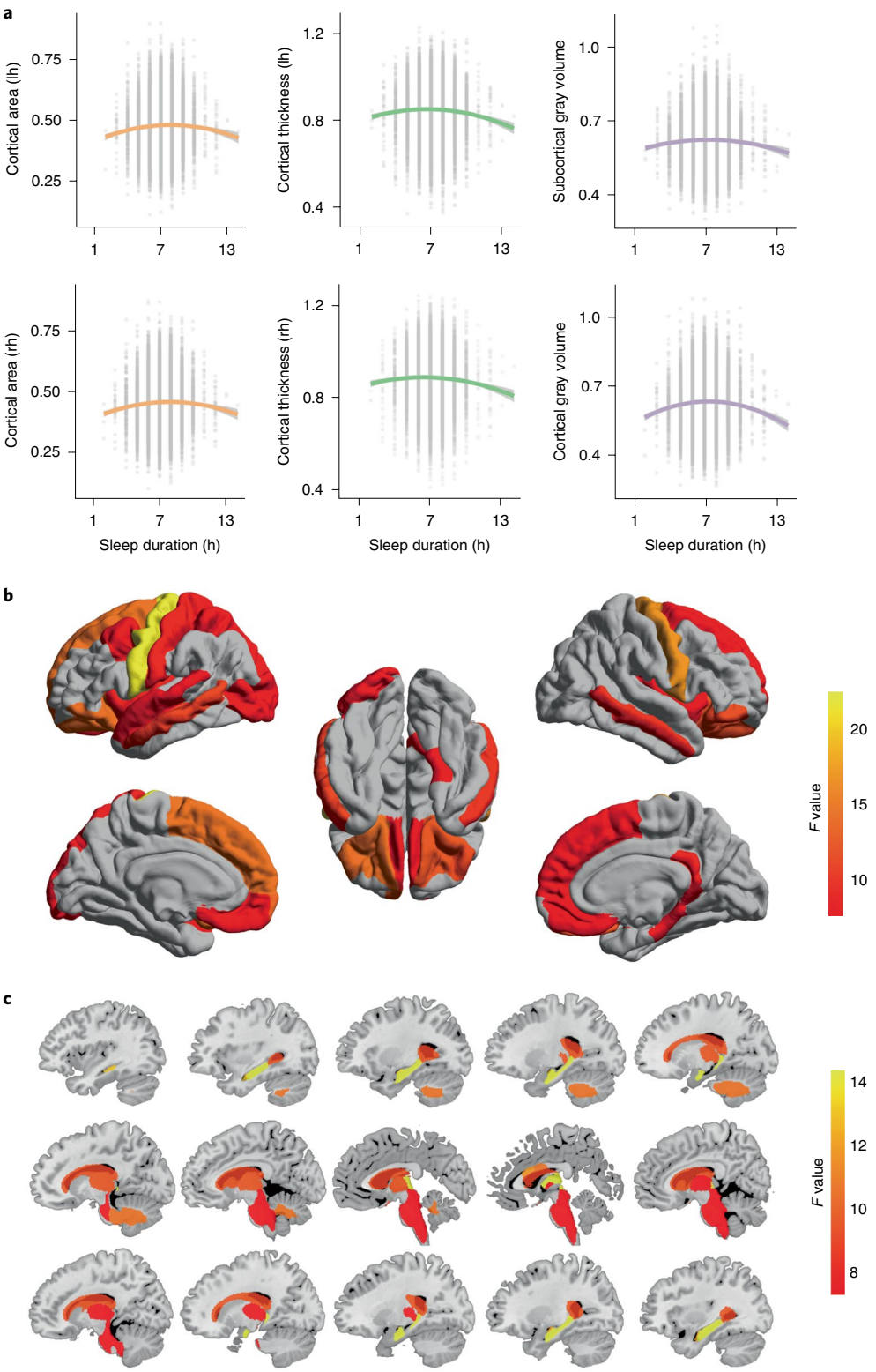


**Fig. 3 | Nonlinear association between sleep duration and brain structure. a**, Significant nonlinear association of sleep duration with area of total surface, global mean thickness and cortical and subcortical gray matter volumes (Bonferroni corrected, $P < 0.005$). Lines are fitted nonlinear models indicating fitted mean values, and shaded areas are 95% CIs; gray points are individual data points. **b**, Cortical regions with their volume significantly and nonlinearly associated with sleep duration adjusted for intracranial volume, age, sex, body mass index, Townsend deprivation index, educational qualification, smoking status, drinking status and imaging scanning sites (Bonferroni corrected, $P < 0.05$). **c**, Subcortical regions with their volumes significantly nonlinearly associated with sleep duration adjusted for intracranial volume, age, sex, body mass index, Townsend deprivation index, educational qualification, smoking status, drinking status and imaging scanning sites (Bonferroni corrected, $P < 0.05$). *F*-tests were used to assess statistical significance and derive *F* statistics and corresponding one-sided *P* values adjusted for multiple comparisons.

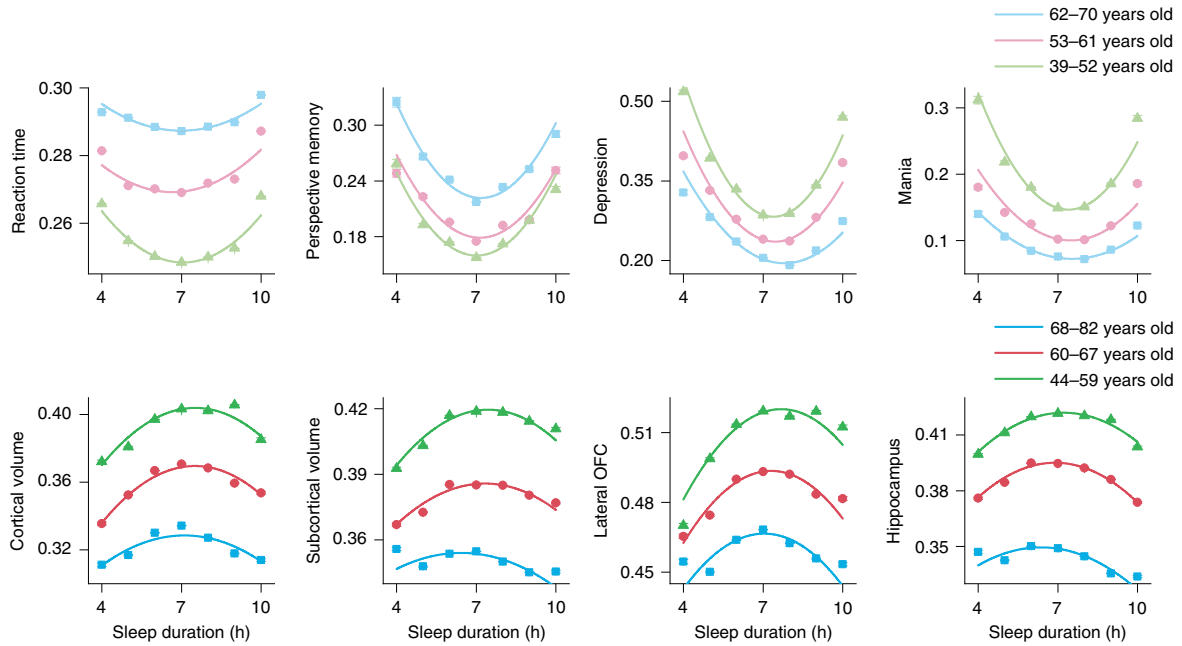


**Fig. 4 | The interaction between age and sleep duration.** Participants were divided into three age groups: 39–52, 53–61 and 62–70 years of age for behavioral measures; and 44–59, 60–67 and 68–82 years of age for imaging data collected at follow up. Top, each age group showed nonlinear associations between sleep duration and cognitive function and mental health. With increasing age, the nonlinear curve gradually tended to flatten, and the *F* value decreased simultaneously, especially for reaction time, depressive symptoms and mania symptoms. Bottom, each age group showed nonlinear associations between sleep duration and brain structures. The nonlinear association between sleep duration and brain structures gradually flattened with aging. Lines are fitted nonlinear models. OFC, orbitofrontal cortex.

health and cognitive function. All associations in the path model (Fig. 6c) were in the expected direction. All paths were significant (with $P<0.01$). PRS was significantly associated with sleep duration ($\beta=0.059$, $P=9.2\times10^{-10}$), mental health ($\beta=-0.033$, $P=9.0\times10^{-8}$) and brain gray matter volume ($\beta=0.034$, $P<1.0\times10^{-20}$). Brain volume was a better predictor of cognitive function ($\beta=-0.14$, $P<1.0\times10^{-20}$) than mental health ($\beta=0.041$, $P=5.0\times10^{-11}$) or sleep duration ($\beta=-0.049$, $P=5.3\times10^{-7}$). Sleep duration was the most significant predictor of mental health ($\beta=-0.15$, $P<1.0\times10^{-20}$) compared to PRS and brain volume ($\beta=-0.016$, $P=5.8\times10^{-11}$). Sleep duration was a significant predictor of brain volume ($\beta=0.048$, $P<1.0\times10^{-20}$). The results of the analysis of data from sleep duration >7 h are provided in Extended Data Fig. 6c.

## Discussion

The present study revealed consistent nonlinear associations between sleep duration and cognitive function, mental health and brain structure in middle-aged to older adults, with approximately 7 h as the optimal sleep duration. Our study demonstrated a coherent mediated pathway involving genetics, sleep duration, brain structure, cognition and mental health using structural equation modeling. The brain areas that were significantly quadratically associated with sleep duration included the precentral cortex, the lateral orbitofrontal cortex, the superior frontal cortex and the hippocampus. Initially, we took genetics and brain structure into consideration to explore the nonlinear association between sleep duration, mental health and cognition. The result of the longitudinal analysis supported our hypothesis that both insufficient and excessive sleep duration are associated with follow-up impaired cognitive performance of a middle-aged to older adult population. The mediation analyses further suggested that the genetic constructs of sleep may contribute to behavioral measures, such as depressive symptoms and cognition, through the mediation of brain structure.

**Nonlinear associations between sleep duration and behavioral measures.** We found a beneficial association with cognitive function and mental health with a sleep duration of approximately 7 h in a middle-aged to older adult population. A previous study reported a nonlinear association between sleep duration and cognitive decline in memory and executive functions[14]. The current findings were consistent with this study and extend the findings to a broader range of cognitive functions including processing speed, visual attention, memory and problem-solving ability as well as a much larger cohort of middle-aged to older adults[22]. This association between sleep duration and cognitive performance potentially suggests that insufficient or excessive sleep duration may be a risk factor for cognitive decline in aging. This is supported by previous reports of a nonlinear relationship between nocturnal sleep duration and the risk of developing Alzheimer's disease and dementia, in which cognitive decline is a hallmark symptom[23,24]. A possible reason for the association between insufficient sleep duration and cognitive decline may be due to the disruption of slow-wave sleep, which has been identified as having a close association with memory consolidation[25] as well as amyloid deposition[26–28]. A reduction in sleep time may have detrimental consequences to the clearance of toxins[29]. It is possible that prolonged sleep duration results from poor-quality and fragmented sleep[30].

Our results also indicate the close association between optimal sleep duration and mental health including symptoms of anxiety, symptoms of depression, mania and well-being. Inadequate or excessive sleep duration are both considered criteria for severity of depressive symptoms in the PHQ-9 (ref. [31]). Insomnia and depression have been shown to share overlapping genetic and environmental causal influences in twin studies[32,33]. Our longitudinal association between baseline sleep duration and follow-up depressive symptoms supported the finding that non-optimal sleep duration may contribute to psychiatric disorders in middle-aged to older adults. Our findings further support the idea that interventions that

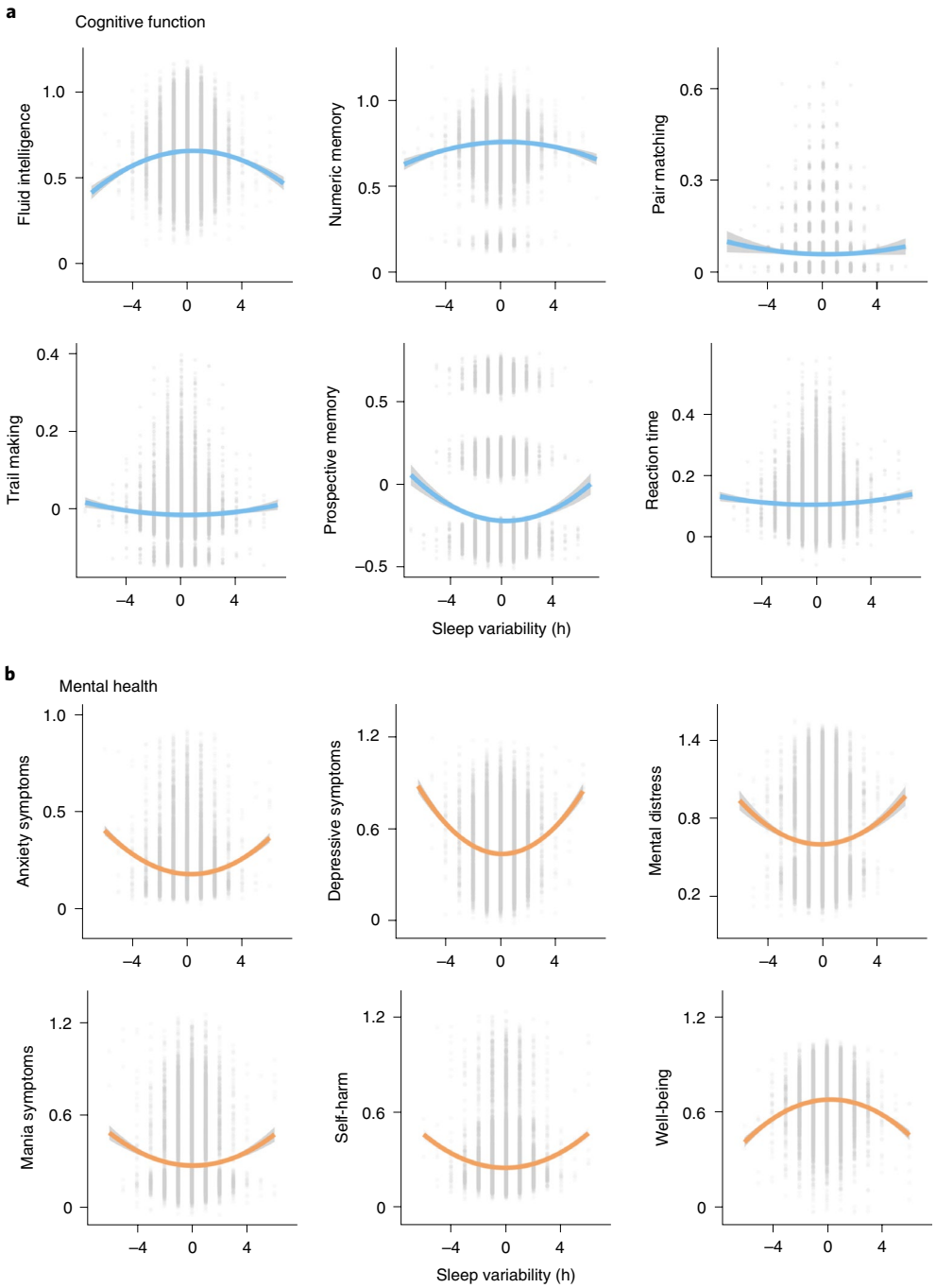


**Fig. 5 | Nonlinear association between sleep variability, mental health, cognitive function and brain structures. a**, Sleep variability between baseline and imaging follow up showed nonlinear significant associations with cognitive function including fluid intelligence, numeric memory, pair matching, trail making, perspective memory and reaction time (Bonferroni corrected, $P < 0.05$), with almost 0 h as the inflection point. **b**, Sleep variability between baseline and imaging follow up showed nonlinear significant associations with mental health including anxiety symptoms, depressive symptoms, mental distress, mania symptoms, self-harm and well-being (Bonferroni corrected, $P < 0.05$), with almost 0 h as the inflection point. *F*-tests were used to assess statistical significance and derive *F* statistics and corresponding one-sided *P* values adjusted for multiple comparisons. Lines are fitted nonlinear models indicating fitted mean values, and shaded areas are 95% CIs; gray points are individual data points.

are able to optimize a 7-h sleep duration on a regular basis may be beneficial for mental health and reducing psychiatric symptoms[34].

**Nonlinear associations between sleep duration and brain structure.** Nonlinear associations between sleep duration and brain structure were found in the current study and suggested that insufficient or excessive sleep duration was associated with smaller brain volume, area and thickness. The brain regions involved were the precentral gyrus, the lateral orbitofrontal cortex, the left insula and the hippocampus. Previous studies have shown that reduced gray matter in the lateral orbitofrontal cortex and hippocampal damage were associated with disrupted sleep patterns in older adults[35,36]. Furthermore, poorer sleep quality and efficiency have been associated with a greater rate of decline in hippocampal volume[37]. Our results are consistent with these findings. Moreover, the involvement of the lateral orbitofrontal cortex and the hippocampus corresponds

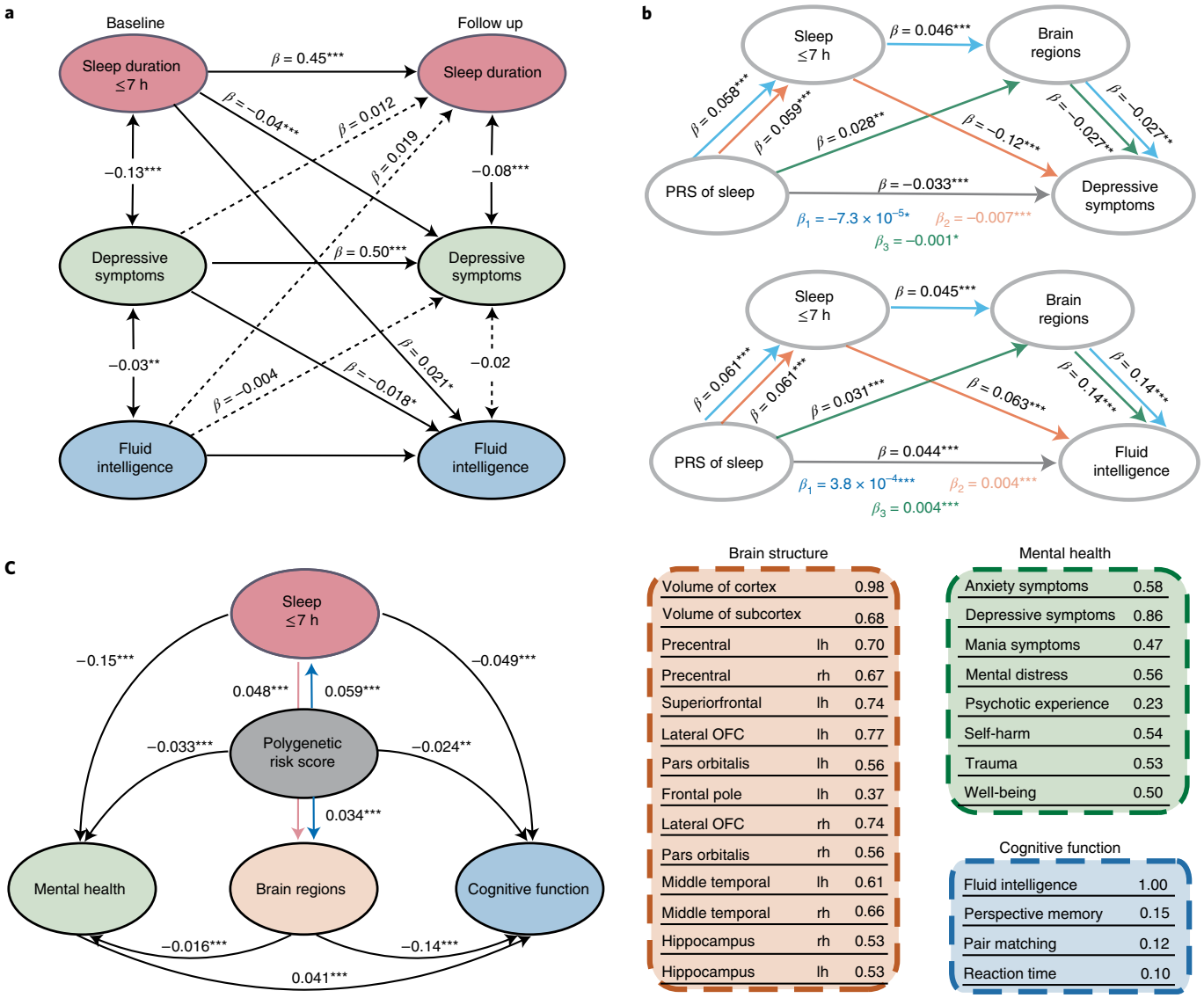


**Fig. 6 | Structural equation model, longitudinal analysis and mediation analysis. a**, The longitudinal association between sleep duration, depressive symptoms and fluid intelligence revealed by a cross-lagged panel model. The baseline sleep duration was significantly associated with severe depressive symptoms and fluid intelligence at follow up ($\beta = -0.038$, $P = 1.3 \times 10^{-5}$ and $\beta = 0.021$, $P = 0.01$, respectively); baseline depressive symptoms were significantly associated with follow-up fluid intelligence ($\beta = -0.018$, $P = 0.029$). The reverse (dashed line) was not significant. The associations between baseline and follow-up sleep duration ($\beta = 0.45$, $P < 1.0 \times 10^{-20}$), depressive symptoms ($\beta = 0.50$, $P < 1.0 \times 10^{-20}$) and fluid intelligence ($\beta = 0.59$, $P < 1.0 \times 10^{-20}$) were significant. **b**, Mediation analysis. Three mediation models were conducted to analyze the direct relationship between PRSs of sleep and depressive symptoms simultaneously, with sleep duration, brain structure and both of them as mediators, respectively. The indirect pathway of the effect of PRS on depressive symptoms via sleep duration and brain structure was significant (path $\beta_1 = -7.3 \times 10^{-5}$, $P = 0.025$). Meanwhile, sleep duration and brain structure significantly mediated the association between PRS and depressive symptoms, respectively (path $\beta_2 = -0.0071$, $P = 9.3 \times 10^{-9}$; path $\beta_3 = -0.001$, $P = 0.035$). Similarly, three mediation models were conducted to analyze the direct relationship between sleep and fluid intelligence simultaneously, with brain structure and depressive symptoms as mediators, respectively. The serial mediation pathway via sleep and brain structure was significant ($\beta_1 = 3.8 \times 10^{-4}$, $P = 1.3 \times 10^{-5}$). Meanwhile, sleep duration and brain structure were also separately significant mediators for this association ($\beta_2 = 0.004$, $P = 2.8 \times 10^{-8}$; $\beta_3 = 0.004$, $P = 7.9 \times 10^{-5}$). These three models are presented using orange, green and blue lines. Data from participants with sleep duration less than 8 h were used. **c**, Full frame model. Standardized coefficients are shown. PRS was significantly associated with sleep duration ($\beta = 0.059$, $P = 9.2 \times 10^{-10}$), mental health ($\beta = -0.033$, $P = 9.0 \times 10^{-8}$) and brain regions ($\beta = 0.034$, $P < 1.0 \times 10^{-20}$). Brain volumes were a better predictor of cognitive function ($\beta = -0.14$, $P < 1.0 \times 10^{-20}$) than mental health ($\beta = 0.041$, $P = 5.0 \times 10^{-11}$) or sleep duration ($\beta = -0.049$, $P = 7.2 \times 10^{-7}$). Sleep duration was the most significant predictor of mental health ($\beta = -0.15$, $P < 1.0 \times 10^{-20}$) compared to PRS and brain volume ($\beta = -0.016$, $P = 5.8 \times 10^{-11}$). Sleep duration was a significant predictor of brain volume ($\beta = 0.048$, $P < 1.0 \times 10^{-20}$). All paths represent significant associations except for the one between PRS and cognitive function. Latent variables including brain structure, mental health and cognitive function were estimated in the model, which are shown with orange, green and blue boxes, respectively. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$. Wald tests were used to derive the two-sided $P$ values adjusted for multiple comparisons (FDR correction).

to our finding of a nonlinear association between sleep duration and cognitive function and mental health. A previous study also showed that the lateral orbitofrontal cortex, the insula and the hippocampus mediate the relationship between sleep quality and depressive symptoms[38], further emphasizing the importance of these brain regions. Our study also demonstrated that brain structure may play

a critical role in the mediation of the association between genetics, cognitive function and mental health.

Additionally, the above-mentioned nonlinear association was also demonstrated between sleep variability and cognition and mental health. A stable sleep pattern, indicated by a 0-h difference between baseline and neuroimaging visit sleep durations, was closely associated with cognition and mental health. Consistent with our findings, a previous study showed that increased intra-individual variability in sleep duration is related to psychosocial and physiological stress[39]. Moreover, high variability in sleep behaviors has been associated with increased inflammation, indicating susceptibility to age-related diseases in older people[40]. Our findings further indicate that a consistent sleep duration of approximately 7 h should be maintained long term. For those who have occupations that require shift work or traveling, this recommendation may be particularly important to preserve mental health and well-being as well as cognition[41].

**Age-varying nonlinear association between sleep duration and other measures.** Our study identifies the distinct nonlinear association between sleep duration and cognition and mental health across different age groups. The gradually flattening nonlinear curve with increasing age illustrates that the association between sleep duration and cognitive function and mental health gradually diminishes in a population aged above 65 years compared with a middle-aged population of 40 years in age. This distinction might be explained by the gradual increase in sleep disturbances with age and the frequent occurrence of fragmented sleep[42], which may contribute to the attenuated nonlinear association between optimal sleep duration and mental and cognitive health in a population aged over 66 years. Furthermore, age-related atrophy of brain regions involved in the regulation of sleep and wakefulness may contribute to circadian dysfunction and decreased production and secretion of melatonin in older adults[43,44]. Our results demonstrate that optimal sleep duration may be more beneficial to the middle-aged population, which is likely related to their engagement in occupational activities and skills.

**Strengths and limitations.** One of the strengths of the current study is the large sample size from the UK Biobank. In addition, we comprehensively describe the nonlinear association between sleep duration and brain structure, mental health and cognitive function. Based on the large cohort from the UK Biobank, we demonstrate that these nonlinear associations vary from middle-aged to older adults. Our study also suggested a longitudinal association between baseline sleep duration and depressive symptoms and cognition 8 years later. Finally, the possible mechanistic paths underlying this process ranging from genetics, brain structure and eventual behavior were specified in current study.

Our study also has some limitations. One limitation of the current study is that we only used total sleep duration and did not have access to other measures of sleep hygiene. Future investigations could focus on enriching sleep measures. In addition, sleep duration was assessed via a self-reported questionnaire, which may introduce some bias. Nevertheless, given the large sample size of the UK Biobank, the measures of sleep duration used in the current study should be robust. Supporting the robustness of this measure, a previous study found that self-reported sleep duration showed consistent direction with accelerometer-based sleep duration in association with genetic variants in the UK Biobank sample[45]. Second, compared with the general UK population, the UK Biobank has a 'healthy volunteer' selection bias[46]. Sleep durations used in our study were mainly reported by healthier people, and future investigations could further focus on sleep pattern in patients with brain disorders. Third, online MHQs were used in our study and these provided quantitative measures of mental health symptoms but not a Diagnostic and Statistical Manual (DSM)-5 diagnosis. Additionally, the MHQ scores were obtained several years after the baseline assessment; nonetheless, the nonlinear associations between sleep duration and mental health were consistent after adjusting for the interval years between these two assessment time points. MHQ participants were better educated, of higher socioeconomic status and healthier than the entire UK Biobank cohort[47]. To minimize bias from this demographic difference, we have adjusted for related confounders such as educational qualifications, Townsend deprivation index, etc. in all statistical analyses. Finally, the results of our study reflect the demographic makeup of the UK Biobank and may not fully extrapolate to other populations.

Future studies could investigate the potential different mechanisms for the association between excessive or insufficient sleep with mental health and cognitive function. Previous investigations mainly focused on sleep deprivation; therefore, the mechanism for the association between excessive sleep and well-being should be further investigated. In addition, in view of brain atrophy as a critical characteristic of the aging process, longitudinal neuroimaging data and sleep measures are needed for further investigation of the possible contribution of non-optimal sleep duration to brain atrophy in older adults. As mentioned above, more detailed sleep hygiene measures, including sleep timing, sleep efficiency and circadian rhythm, as well as objective sleep measures could be combined in future studies to provide more detailed sleep recommendations for the general population. Interestingly, in contrast to the non-monotonic relationship identified in adults, previous studies have reported a monotonic relationship between sleep duration and behavioral and neuroimaging measures in adolescents[47]. Therefore, we would dedicate future studies to exploring the lifespan associations of sleep duration with physical and mental health, particularly investigating the critical transition period when the relationship shifts from monotonic to non-monotonic.

**Conclusion.** In conclusion, nonlinear associations between sleep duration and mental health, cognitive function and brain structure were found in a large cohort of middle-aged to older participants from the UK Biobank. The most significant brain structures were found to include the precentral cortex, the lateral orbitofrontal cortex and the hippocampus. Given the role of the hippocampus in memory processes and in Alzheimer's disease, the nonlinear association between sleep duration and this brain region is of particular importance. Furthermore, baseline non-optimal sleep duration was significantly associated with decreased cognitive function and increased psychiatric symptoms on follow up. Our findings have emphasized the importance of sleep regulation for cognition, mental health and well-being of adults. In addition, we identified a possible unified pathway that includes genetics and brain mechanisms.

## Methods

**Participants.** We used data from the UK Biobank with application ID 19542, which included 498,277 participants primarily of European ancestry aged between 38 and 73 years. The participants include 94.3% white people, 0.6% mixed people, 2.0% Asian people, 1.6% Black people, 0.3% Chinese people, 0.9% other ethnic groups and 0.3% with missing data. The UK Biobank has research tissue bank approval from the North West Multi-centre Research Ethics Committee (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics) and provided oversight for this study. Written informed consent was obtained from all participants. Participation is voluntary, and participants are free to withdraw at any time without giving any reason. The data consisted of detailed demographic, health, behavioral and cognitive assessments at baseline and ongoing longitudinal follow up. Neuroimaging data were collected from 48,511 participants, and 156,884 participants completed online follow-up MHQs 6–8 years after the baseline assessment. Neuroimaging data of 39,692 participants were available and used in the current analyses under the application number 19542. All participants provided written informed consent.

**Sleep measures.** Sleep duration was recorded through touchscreen questionnaires including questions such as 'About how many hours sleep do you get in every

24 hours? (please include naps)'. Answers <1 h or >23 h were rejected, and answers <3 h or >12 h required confirmation by the participants. If the participant activated the help button, they were shown the message: 'If the time you spend sleeping varies a lot, give the average time for a 24 hour day in the last 4 weeks'. The sleep-duration data from the baseline assessment (2006–2010, $n=498{,}277$) and neuroimaging visit (2014+, $n=48{,}511$) were used in the analyses. Sleep duration assessed at baseline was used to determine the association between cognitive function and online follow-up mental health assessments. Sleep duration assessed at the neuroimaging visit was used to determine the association with brain structure. Histograms of sleep duration are shown in Supplementary Fig. 1; only integer values of sleep duration were available in the questionnaire.

**Mental health.** Measurement of depressive symptoms via the four-item PHQ-4 was first assessed in the UK Biobank Assessment Centre (2006–2010, $n=499{,}585$) and then repeated at the neuroimaging visit (2014–2017, $n=48{,}571$). Furthermore, a detailed and comprehensive mental health questionnaire (MHQ) was administered online (2016–2017, $n=157{,}366$), which assessed self-reported symptoms of mental disorders and major environmental exposures for mental disorders including mental distress, depressive symptoms, mania symptoms, anxiety symptoms, alcohol use, cannabis use, psychotic experiences, traumatic events, self-harm, addiction and well-being (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=136). Based on these questionnaires, we obtained quantitative measures of various mental health symptoms. The items used to assess each mental health symptom are provided in Supplementary Table 2. Briefly, the scores of items in one subcategory of the MHQ were adjusted to same direction such that higher values indicated more symptoms of mental disorder (except for well-being, with a higher value indicating better well-being). Next, each item was normalized by mapping the minimum and maximum to (0, 1) using the MATLAB function 'mapminmax' to maintain the same scale between items. Finally, all items in one subcategory were averaged to measure overall symptoms of mental health. Summary information for each mental health symptom is provided in Supplementary Table 3.

**Cognitive testing.** Cognitive tests were first administered via a touchscreen interface in the UK Biobank Assessment Centre at the baseline visit and repeated at the neuroimaging visit. Six cognitive tests including reaction time, numeric memory, fluid intelligence, trail-making, prospective memory and pair-matching tests were used in the current study. Supplementary Table 1 illustrates the sample sizes for each cognitive task used in the current study. The scores were normalized by mapping the minimum and maximum to (0, 1) using the MATLAB function 'mapminmax' before analysis.

**Structural magnetic resonance imaging data.** Quality-controlled $T_1$-weighted neuroimaging data, processed with FreeSurfer, were used in current study. Details of the imaging protocol can be found in an open-source document (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf). Neuroimaging data were collected with a standard Siemens Skyra 3T scanner with a 32-channel head coil. $T_1$ images were processed with FreeSurfer; surface templates were used to extract imaging-derived phenotypes referred to as atlas regions' surface area, volume and mean cortical thickness[48]. Subcortical regions were extracted via FreeSurfer's aseg tool[49]. FreeSurfer aparc (ID 192) and aseg (ID 190) atlases corresponding to 68 cortical regions and 40 subcortical regions were used in this study. The intracranial volume (field ID 26521) generated by aseg was used as a covariate in the neuroimaging analyses. The Qoala-T approach was used to check FreeSurfer outputs, supplemented by manual checking of outputs close to the threshold. Any FreeSurfer outputs that failed to pass quality control were not included in the FreeSurfer imaging-derived phenotypes.

**Polygenic risk score for sleep duration.** Genotype data were available for all 500,000 participants in the UK Biobank cohort. Detailed genotyping and quality-control procedures for the UK Biobank are available in a previous publication[50]. We excluded single-nucleotide polymorphisms (SNPs) with call rates <95%, minor allele frequency <0.1% or deviation from the Hardy–Weinberg equilibrium with $P<1\times10^{-10}$ and selected individuals that were estimated to have recent British ancestry and have no more than ten putative third-degree relatives in the kinship table, consistent with the previous study[51]. After the quality-control procedures, we obtained a total of 616,339 SNPs and 337,199 participants. To avoided the issue of circular analysis, participants with neuroimaging data ($n=39{,}692$) were used for subsequent estimation of PRS and therefore were removed from the genome-wide association study (GWAS) sample.

We performed genome-wide association analysis, adjusting for age, sex and the top 20 ancestry principal components, using PLINK 1.90 (ref. [52]) to assess the association between genotype and sleep duration. To determine the nonlinear effects of sleep duration, we performed genome-wide association analyses for sleep duration in 114,419 individuals who sleep >7 h and 193,056 individuals who sleep ≤7 h separately. To avoid data-overlap bias, individuals for whom brain MRI was collected were removed from the above genome-wide association analysis.

LD-score regression (GenomicSEM version 0.0.3 in R) was used to assess the SNP-based heritability of sleep duration ≤7 h and >7 h, respectively, and its genetic correlation with a previous published GWAS of sleep duration (http://www.t2diabetesgenes.org/data/). HapMap3 SNPs were used as the reference SNP list. European ancestral background LD scores from the 1000 Genomes Project were used as the reference panel. The heritability for sleep duration ≤7 h and >7 h was 0.0636 (s.e.m. = 0.0051) and 0.0194 (s.e.m. = 0.0068), respectively. The heritability for sleep duration >7 h was lower than the suggested threshold of $z$ ($h^2z=2.83$), which implied potential bias of genetic correlation. The genetic correlation between sleep duration ≤7 h and the previous GWAS of sleep duration was 0.687 (s.e.m. = 0.074, $P=1.67\times10^{-20}$). A positive genetic correlation between sleep duration >7 h and previous GWAS results was also found (0.3382; s.e.m. = 0.1416, $P=0.0168$).

PRSs for sleep duration in individuals with brain MRI measures were calculated using PRSice software (http://www.prsice.info). $P$-value-informed clumping with a cutoff of $r^2=0.1$ in a 250-kb window was used in the analysis. PRSs were calculated using the mean of $P$ values at the threshold ranging from 0.005 to 0.5 with 0.005 as the step size.

**Statistical analysis.** *Nonlinear association analysis.* A nonlinear regression model ($y=bx^2+ax+c$) was used to investigate the association of sleep duration ($x$) with the measures of interest ($y$), including mental health variables (online follow up), cognitive tests scores and brain morphometric measures. The following variables were used as covariates of no interest in the model: age, sex, body mass index, the scanning site of imaging, Townsend deprivation index measuring socioeconomic status, educational qualifications, smoking status and drinking status (Supplementary Fig. 2). Furthermore, we adjusted for intracranial volumes, derived using the FreeSurfer aseg tool in the regression model examining sleep and brain structures. *An F* statistic was obtained for each quadratic model to reflect the association of sleep duration and the measures of interest. $F$ statistics were transferred to effect-size $r$ values using the equation $r=\sqrt{F\times df_1\,(F\times df_1+df_2)^{-1}}$, where $df_1$ is the numerator degrees of freedom and $df_2$ is the denominator degrees of freedom[53]. Bonferroni corrections were conducted for multiple comparisons. Restricted cubic splines (package rms 6.2-0 in R) with three knots at the tenth, 50th and 90th percentiles were also used to model the association between sleep duration and brain structures and validate the nonlinearity.

Two-line tests were conducted to estimate an interrupted regression and to identify the breakpoint between lines with opposite sign of slope[54]. The breakpoint was set to maximize the power of detecting nonlinear relationships (two-lines test version 0.52 implemented in R).

**Longitudinal analysis.** The longitudinal association of sleep duration with depressive scores (PHQ-4) and with cognitive function was explored using a classic two-wave cross-lagged panel model (implemented with the lavaan 0.8 package in R). The analysis was conducted separately for participants with sleep duration ≤7 h and >7 h at baseline assessment. PHQ-4 scores and fluid intelligence scores at the baseline assessment and at the neuroimaging visit assessment were used. Covariates including age, sex, body mass index, Townsend deprivation index, educational qualification, smoking status and drinking status were regressed out before the analysis. Model parameters were estimated by maximum likelihood estimation. Standardized regression coefficients and their standard errors were reported throughout.

**Structural equation model.** A structural equation model was estimated separately for participants with sleep duration ≤7 h and >7 h (implemented in R (lavaan 0.8)). Three latent variables were estimated in the model using confirmatory factor analysis. A latent variable representing cognitive function was estimated via reaction time, fluid intelligence, perspective memory and pair-matching performance, which were all significantly quadratically associated with sleep duration. The latent variable of mental health was also measured in the model using anxiety symptom, cannabis, depressive symptom, mania symptom, mental distress, psychotic experience, self-harm, trauma and well-being scores in the MHQ. Finally, the latent variable for brain structures was derived from the first ten cortical and five subcortical brain gray matter volumes significantly correlated with sleep duration, adjusted for intracranial volume and the other specified covariates. These three latent variables were investigated to determine the directional dependencies with PRS and sleep duration via path modeling.

**Mediation analysis.** Three mediation models were used in the current study. First, the serial mediation model was used to investigate whether the association of PRS with depressive symptoms was mediated by brain structures and sleep duration, adjusting for age, sex, educational qualification, body mass index, scanning sites, PRS components, smoking status and drinking status. The mean values of brain gray matter volumes significantly associated with sleep duration that survived Bonferroni correction ($P<0.05$ adjusted for intracranial volume) were used in the model. PRS was calculated separately based on sleep duration >7 h or ≤7 h. Depressive symptoms used in the model were measured (category ID 138) in an online follow-up questionnaire (Supplementary Table 2). Two other mediation analyses were conducted, specifically to determine whether the association between PRS and depressive symptoms could be mediated only by brain regions or sleep duration; the same covariates as in the first model were used in the second model and the third model excluded scanning sites.

Similarly, three mediation models were also conducted to investigate the association between PRS for sleep and fluid intelligence. The first model was used to investigate whether the association between PRS and fluid intelligence could be serially mediated by sleep and brain structures. The second and third models were used to investigate whether the association between PRS and fluid intelligence could be mediated by sleep or brain structures, respectively. The mediation model used the same covariates as mentioned above. Analyses were conducted separately for sleep duration less than 8 h and greater than 7 h. Finally, serial mediation analysis of the path sleep duration → brain structure → depressive symptoms → fluid intelligence was also conducted. Additionally, five other cognitive functions were also used to conduct mediation analysis via the path sleep duration → brain structure → cognitive function including symbol–digit substitution, numeric memory, trail making, prospective memory and reaction time. Total, direct and indirect associations were estimated by the 10,000-iteration nonparametric bootstrap approach. Analysis was performed in R with lavaan 0.8.

**Interaction between age and sleep duration.** To explore whether sleep duration was associated with mental health, cognitive function and brain structure across various ages, participants were first divided into three age groups, ensuring similar numbers of participants in each group; these were 39–52 years old, 53–61 years old and 62–70 years old for behavioral data. Binomial fitting was conducted for each age group to observe the interaction between age and sleep duration. Neuroimaging data were collected at a follow-up visit around 4 years later, and participants were also divided into three age groups to determine the association between sleep duration and brain structures; these were 44–59, 60–67 and 68–82 years old.

Furthermore, to test the significance of the interaction between sleep duration and age, the linear interaction term 'sleep × age' and the nonlinear interaction term 'sleep$^2$ × age' were added to the original nonlinear regression model[55] (implemented with the AER 1.2-9 package in R). *t*-tests were conducted to identify the significance of the coefficient of each interaction term. Additionally, *F*-tests were conducted to test the joint hypotheses that both coefficients of interaction terms were zero. A similar method was also used to explore the interaction between sleep duration and sex, with 'sleep × sex' and 'sleep$^2$ × sex' added to the nonlinear regression model.

**Reporting Summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

## Data availability

This project corresponds to UK Biobank application ID 19542. Neuroimaging, genotype and behavioral data from the UK Biobank dataset are available at https://biobank.ndph.ox.ac.uk/ by application. The variables used here are detailed in Supplementary Table 1. The previously published GWAS of sleep duration was downloaded from http://www.t2diabetesgenes.org/data/. European ancestral background LD scores from the 1000 Genomes Project were downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/.

## Code availability

MATLAB 2018b was used to perform nonlinear association analysis. FreeSurfer version 6.0 was used to process imaging data. PLINK 1.90 and PRSice (http://www.prsice.info) were used to perform genome-wide association analysis and calculate the PRS, respectively. lavaan 0.8 in R version 3.6.0 was used to perform longitudinal and mediation analyses and make the structural equation model. AER 1.2-9 in R version 3.6.0 was used to perform the interaction test; rms 6.2-0 was used to conduct restricted cubic spine analysis; GenomicSEM version 0.0.3 was used to calculate heritability and genetic correlation; two-lines test version 0.52 was used to identify the breakpoints of the nonlinear model. Scripts used to perform the analyses are available at https://github.com/yuzhulineu/UKB_sleep.

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## Author contributions

J.F. and W.C. proposed the study. Y.L., J.K. and W.Z. analyzed data. S.X. preprocessed data. W.C., J.F. and B.J.S. contributed to interpretation of results. Y.L. drafted the manuscript. B.J.S., C.L., J.Y. and W.C. edited the manuscript. Y.L., C.X. and W.C. contributed to visualization. All authors considered how to analyze data and approved the manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

**Extended data** is available for this paper at https://doi.org/10.1038/s43587-022-00210-2.

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s43587-022-00210-2.

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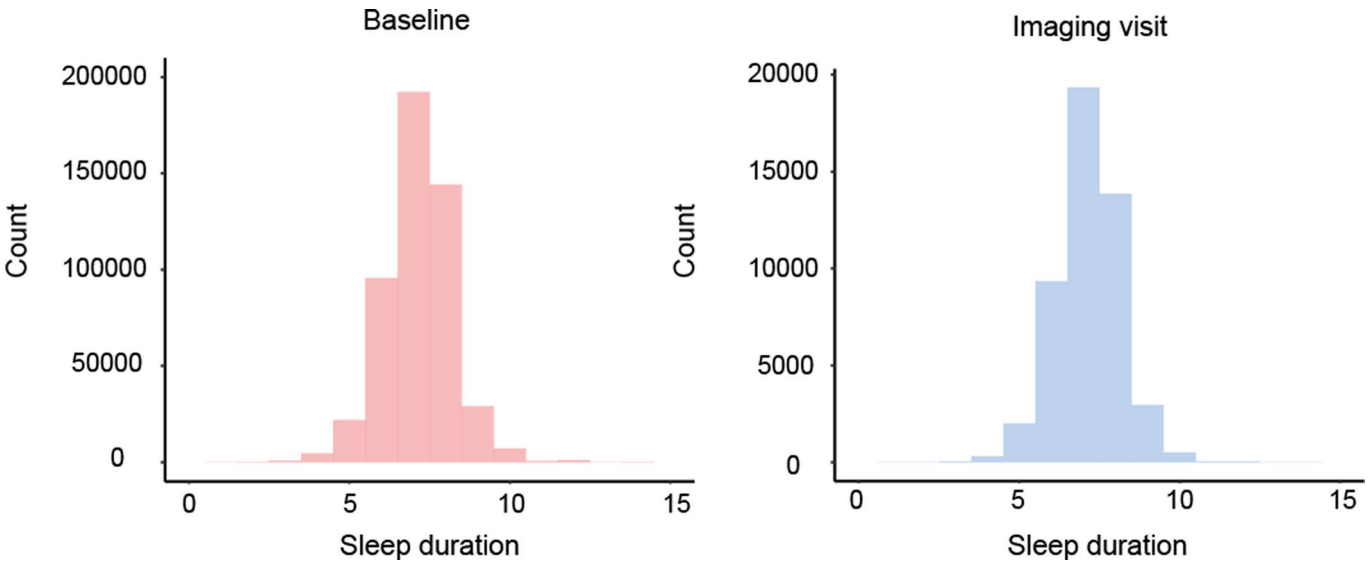
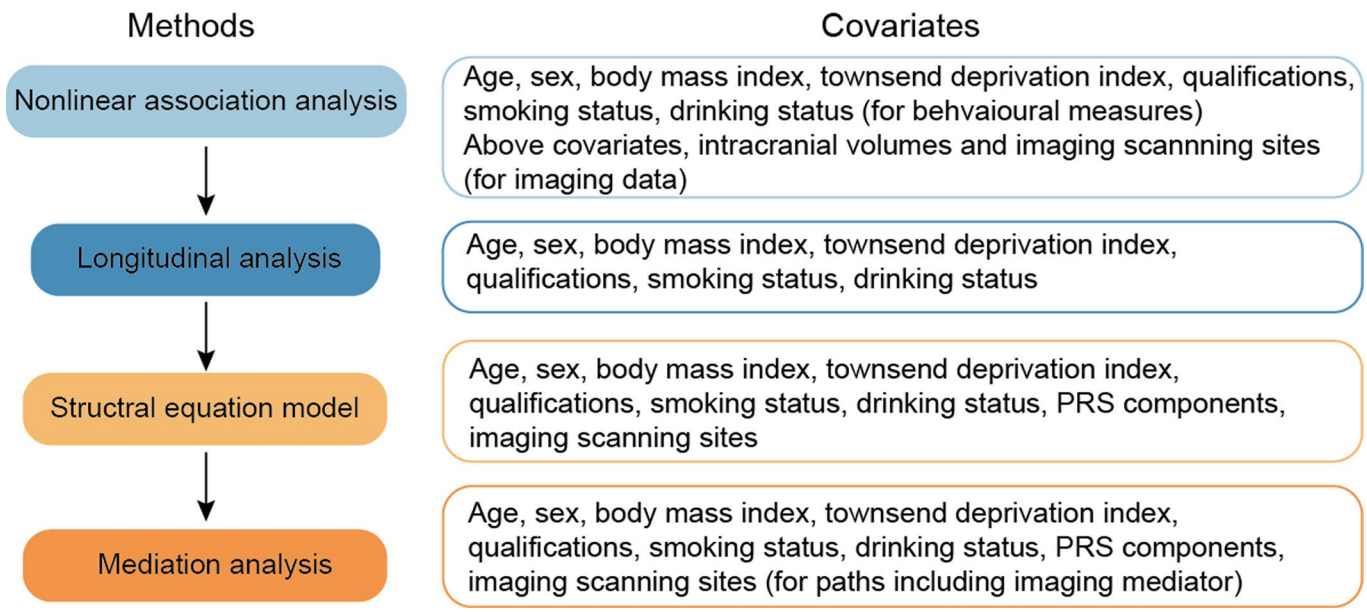
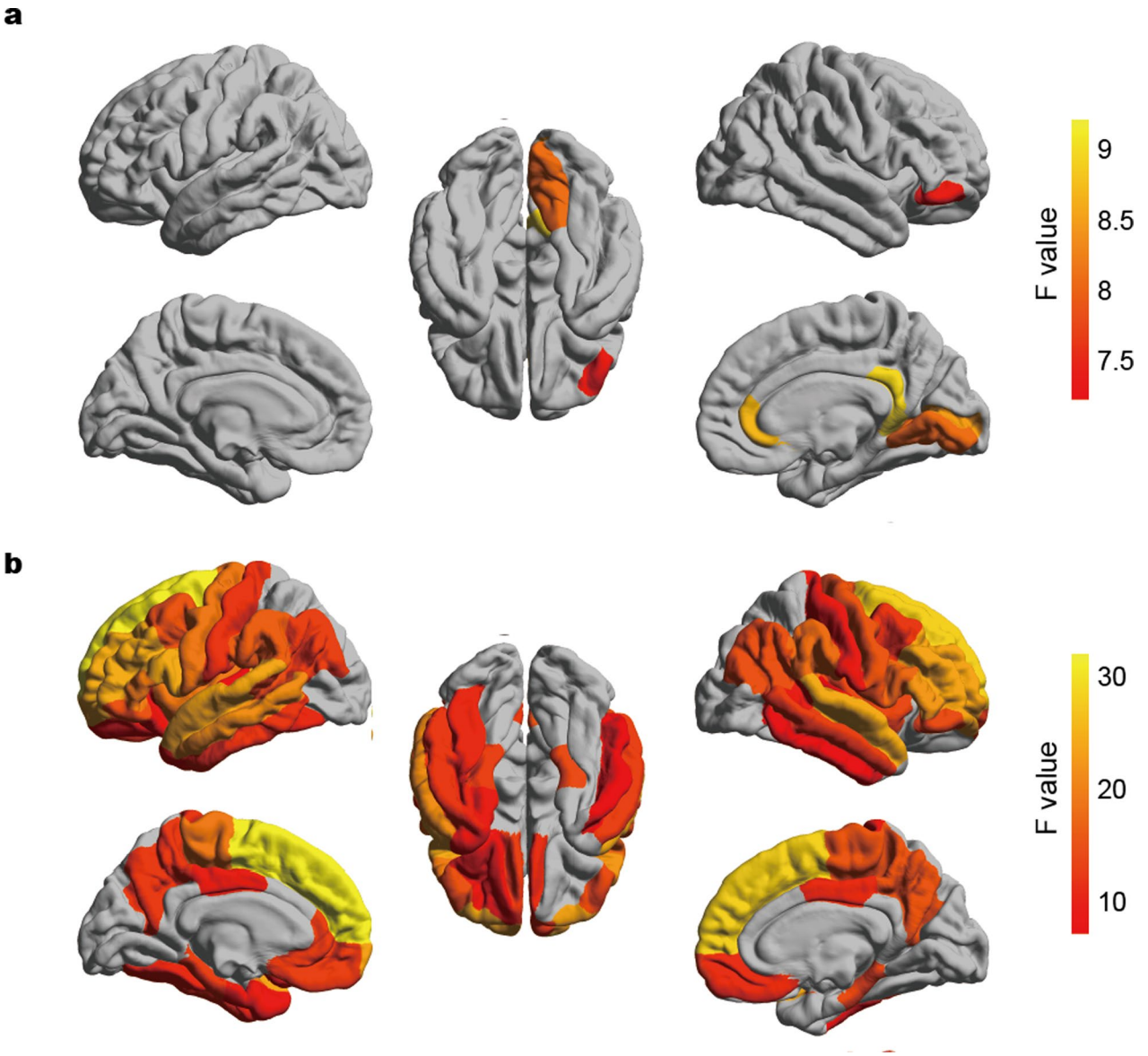


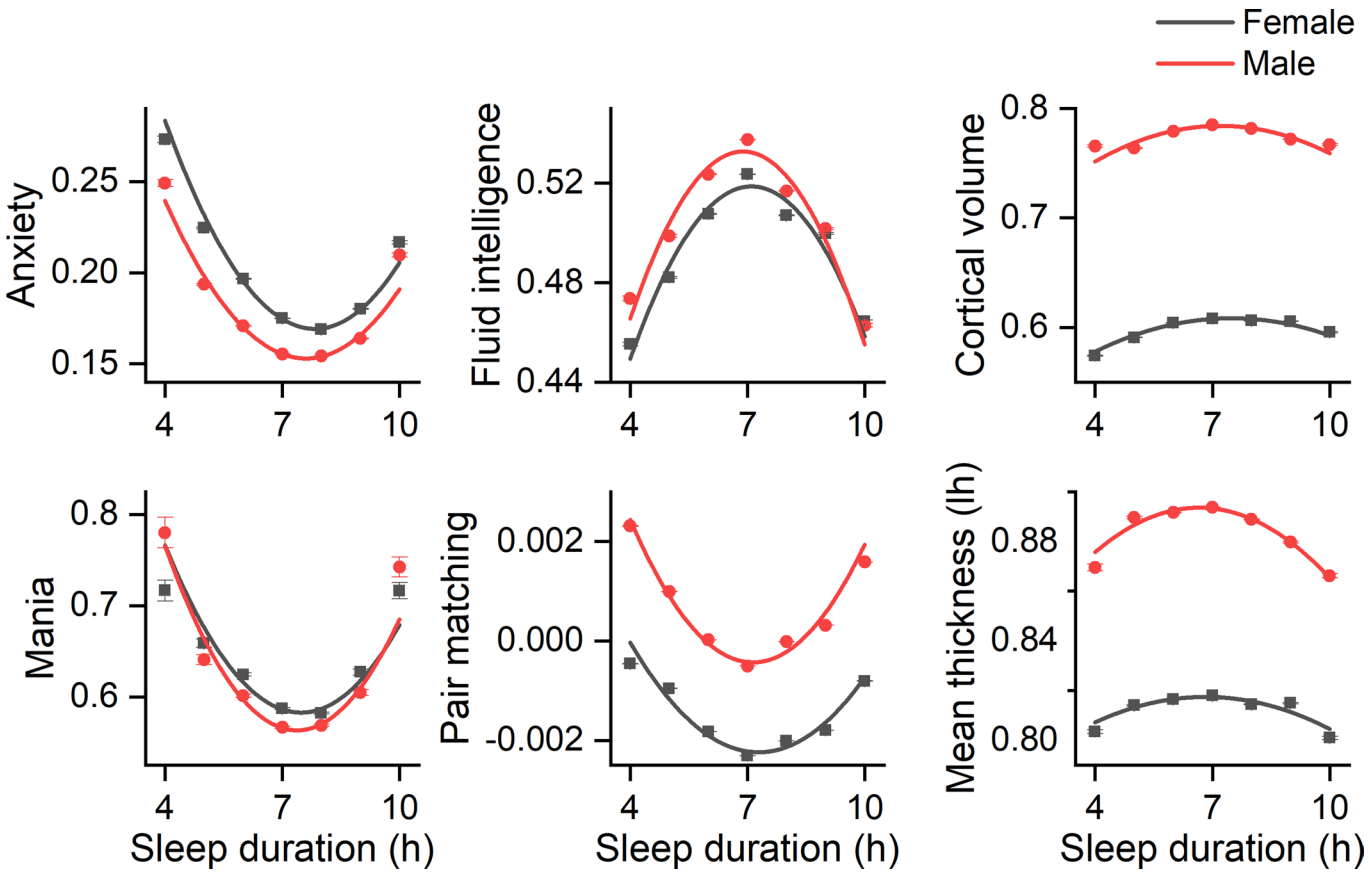

**Extended Data Fig. 1 | Histograms of sleep duration in baseline and imaging assessment.** The sleep duration data from the baseline assessment (2006–2010, n = 498,277) and neuroimaging visit (2014+, n = 48,511) were used in the analyses. Sleep duration assessed at baseline was utilized to determine the association between cognitive function and online follow-up mental health assessments. Sleep duration assessed at the neuroimaging visit was used to determine the association with brain structure.



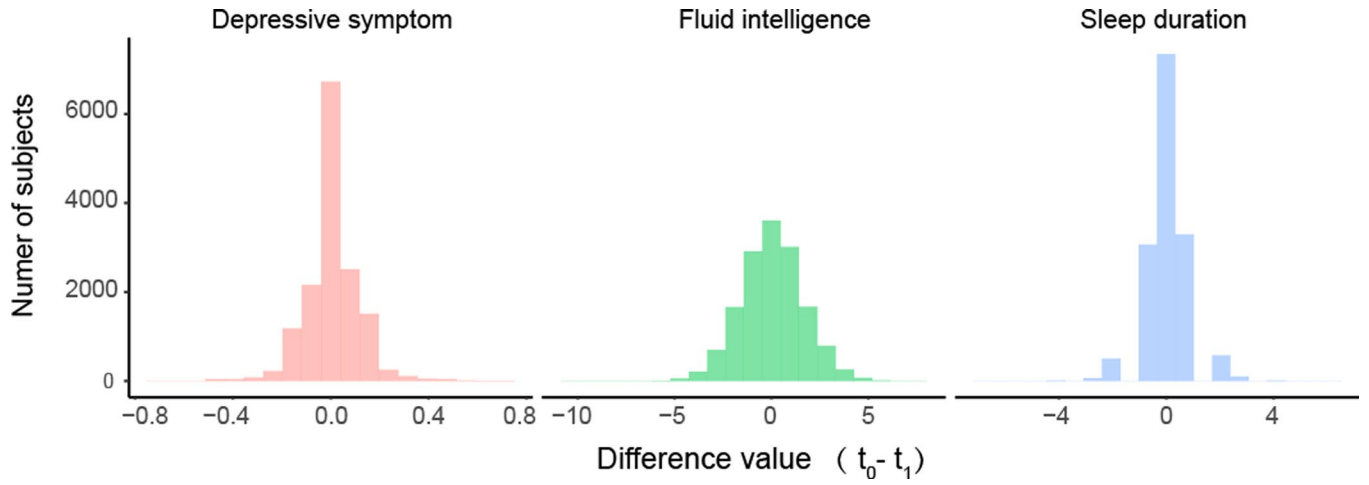

**Extended Data Fig. 2 | Covariates utilized in the statistical analyses.** Age, sex, body mass index, Townsend deprivation index, educational qualification, smoking status and drinking status were adjusted in all analyses. In addition, for analysis involving neuroimaging data and polygenetic risk score, intracranial volumes, neuroimaging scanning sites and PRS components were further added as covariates respectively.



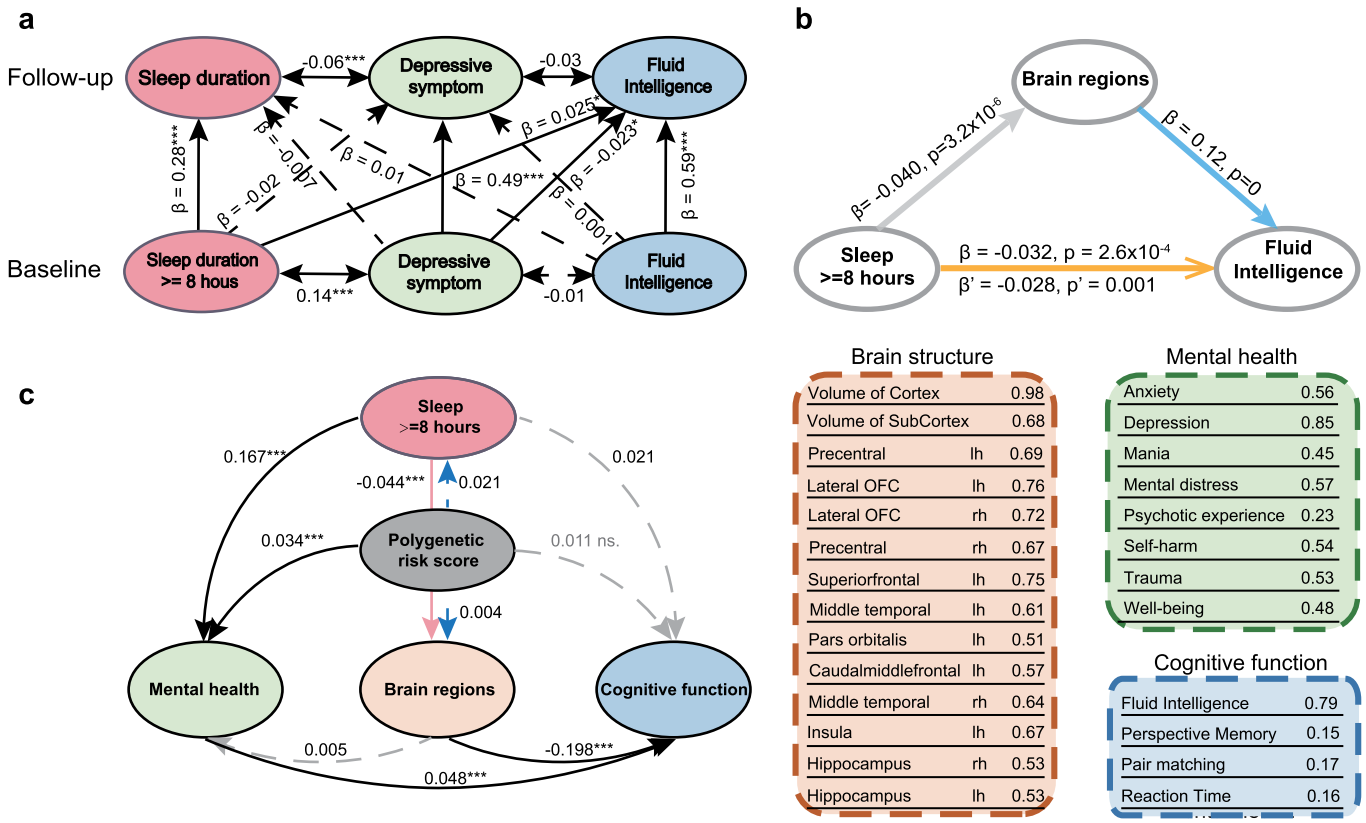

**Extended Data Fig. 3 | Nonlinear association between sleep duration and cortical area and thickness.** Cortical regions with their a) area and b) thickness significantly and nonlinearly associated with sleep duration adjusted for sleep duration with intracranial volume, age, sex, sex, body mass index, Townsend deprivation index, educational qualification, smoking status and drinking status, imaging scanning sites (Bonferroni corrected, $p < 0.05$). F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons.



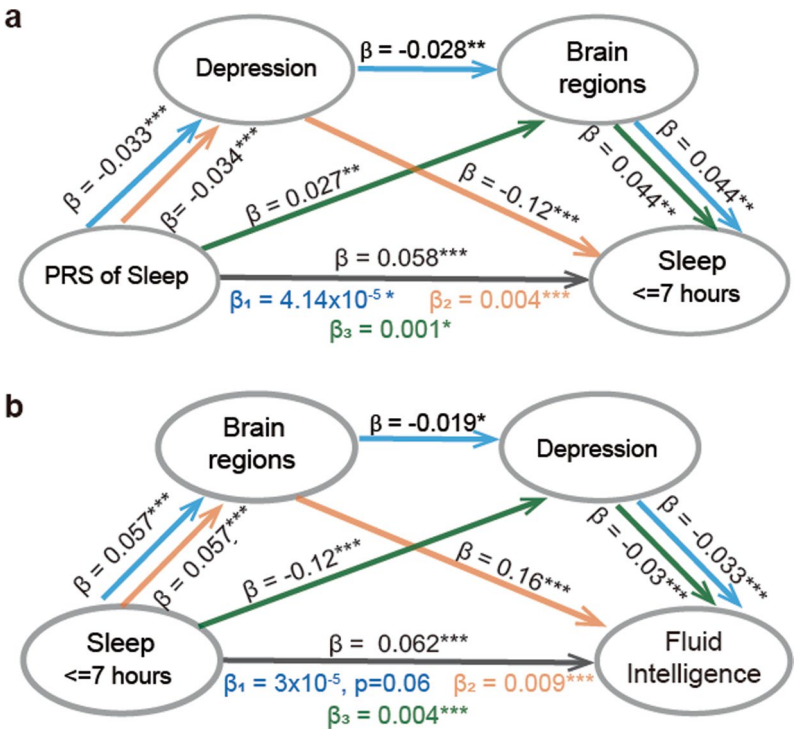

**Extended Data Fig. 4 | Sex difference of the association between sleep duration and mental health, cognitive function and brain structure.** The nonlinear association between sleep duration and anxiety symptom was more significant in female participants ($F_{female}$ = 622.6, n = 533, 2878, 15240, 36239, 26712, 4712 and 1000 participants respectively; $F_{male}$ = 417.2, n = 347, 2126, 12587, 29710, 18677, 3229 and 665 participants respectively), whereas mania symptoms showed more significant association with sleep duration for male participants ($F_{female}$ = 140.3, n = 550, 2928, 15466, 36672, 26988, 4774 and 1025 participants respectively; $F_{male}$ = 145.0 respectively, n = 354, 2148, 12673, 29893, 18780, 3252 and 670 participants respectively).Fluid intelligence were found to have a greater nonlinear association with sleep duration in females compared with males ($F_{female}$ = 272.7, n = 940, 3981, 16606, 32724, 25625, 5051 and 1502 participants respectively; $F_{male}$ = 205.4, n = 673, 3144, 14934, 29192, 20019, 4018 and 1223 participants respectively) while pair matching were more associated with sleep duration in males ($F_{female}$ = 85.8, n = 3087, 11892, 48704, 98567, 79070, 15934 and 4922 participants respectively; $F_{male}$ = 104.1, n = 2367, 9356, 44236, 88501, 61182, 12315 and 3980 participants respectively). For brain structure, female participants demonstrated a more significant association between sleep duration and cortical volumes (rh, $F_{female}$ = 29.1, n = 192, 991, 4221, 8375, 5746, 1158 and 249 participants respectively; $F_{male}$ = 14.7, n = 118, 631, 3445, 7523, 5592, 1231 and 238 participants respectively) while cortical thickness was more significantly associated with sleep duration for males ($F_{female}$ = 2.89, n = 192, 991, 4221, 8375, 5746, 1158 and 249 participants respectively; $F_{male}$ = 20.0, n = 118, 631, 3445, 7523, 5592, 1231 and 238 participants respectively). Lines are fitted nonlinear model indicating fitted mean value and error bar is standard error of the mean.



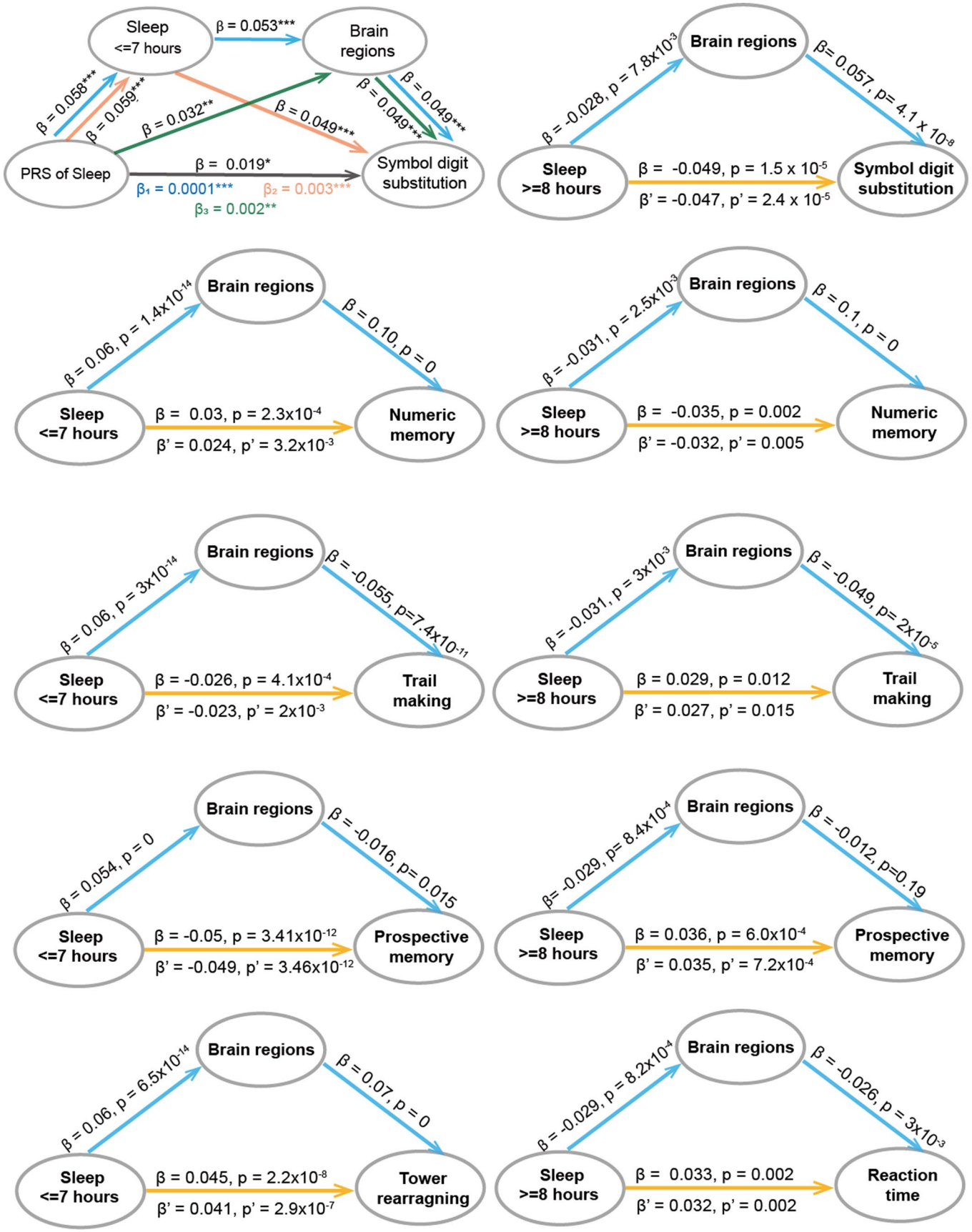

**Extended Data Fig. 5 | Histograms of the change of variables over time in the longitudinal analysis.** Baseline sleep duration is 0.031 hours longer than the follow-up sleep duration (std = 0.94). At baseline, participants were more depressed compared with the measurement at follow-up (difference = 0.0069, std = 0.11). Fluid intelligence of participants at baseline was also higher than at follow-up (difference = 0.043, std = 1.73).




**Extended Data Fig. 6 | Structural equation model, longitudinal analysis and mediation analysis for participants with more than 7 hours sleep. a**. The longitudinal association between the sleep duration, depression and fluid intelligence revealed by cross-lagged panel model. The baseline sleep duration ($\beta$= 0.025, p = $1.3\times10^{-5}$) and depressive symptom ($\beta$= −0.023, p = $1.3\times10^{-5}$) was significantly associated with fluid intelligence in the follow-up. **b**. Mediation analysis. The mediation models were conducted to analyze the direct relationship between sleep duration and fluid intelligence, with sleep duration, brain structure and both of them as mediator respectively. Brain regions significantly mediated the association between sleep duration and fluid intelligence ($\beta$= −0.0046, p = $1.4\times10^{-5}$). These figures utilized participants with sleep duration more than 7 hours. **c**. Full frame model. Standardized coefficients were showed in the figure. PRS was significantly associated with mental health ($\beta$ = −0.034, $p = 4.7\times10^{-5}$). Brain volumes were a better predictor of cognitive function ($\beta$= −0.198, $p < 1.0\times10^{-20}$) compared to mental health ($\beta$ = 0.048, $p = 3.5\times10^{-6}$). Sleep duration was the most significant predictor of mental health ($\beta$ = 0.167, $p < 1.0\times10^{-20}$) and brain regions ($\beta$= −0.044, $p < 1.0\times10^{-20}$). Latent variable including brain structure, mental health and cognitive function were estimated in the model which showed in the figure with orange, green and blue box respectively. Wald tests were utilized to derive the two-sided p value adjusted for multiple comparisons (FDR correction). * represented p < 0.05, ** represented p < 0.01 and *** represented p < 0.001.




**Extended Data Fig. 7 | Mediation analysis. a**. Three mediation analysis were conducted between PRS and sleep duration, 1) PRS →depressive symptoms→brain structure →sleep, 2) PRS →depressive symptoms→sleep, 3) PRS→brain structure →sleep. Depressive symptoms and brain structure serially mediated the association between PRS and sleep duration ($\beta$=4.14×10$^{-5}$, p = 0.044). Specifically, with depression significantly associated with PRS ($\beta$ = −0.033, p = 1.6×10$^{-4}$) and brain volumes positively associated with depression ($\beta$ = −0.028, p = 1.4×10$^{-3}$), and in addition, brain volumes significantly associated with sleep duration ($\beta$ = 0.044, p = 1.4×10$^{-6}$). Meanwhile, depressive symptoms and brain structure also separately significantly mediated the association between PRS and sleep duration ($\beta_2$ = 0.004, $p$ = 3.3×10$^{-4}$, $\beta_3$ = 0.001, $p$ = 0.01). **b**. Three mediation pathway analyses were conducted for the cognitive function of fluid intelligence for participants with less than 8 hours sleep duration, 1) sleep duration→brain structure→ depression→ fluid intelligence, 2) sleep duration→ brain structure → fluid intelligence, 3) sleep duration→ depression→ fluid intelligence. Sleep duration showed a significant positive association with fluid intelligence in the model ($\beta$ = 0.062, p = 2×10$^{-15}$). The serial mediation pathway via brain structure and depression was not significant ($\beta_1$ = 3×10$^{-5}$, $p$ = 0.06), but brain structure and depression were separately significant mediators for this association. Brain structure accounted for the association between sleep duration and fluid intelligence ($\beta_2$ = 0.009, $p$ = 2×10$^{-7}$; $\beta_3$ = 0.004, $p$ = 5.6×10$^{-5}$). Wald tests were utilized to derive the two-sided p value adjusted for multiple comparisons (FDR correction). * represented p < 0.05, ** represented p < 0.01 and *** represented p < 0.001.




**Extended Data Fig. 8 | See next page for caption.**

**Extended Data Fig. 8 | Mediation analysis between sleep duration and cognitive functions.** For participants with sleep duration ≤ 7 hours, brain structure related to sleep significantly mediated the association between sleep duration and numeric memory (path $\beta$= 0.006, p = $1.4\times10^{-11}$), trail making (path $\beta$= −0.003, p = $7.8\times10^{-7}$), prospective memory (path $\beta$= $-8.8\times10^{-4}$, p = 0.02) and tower rearranging (path $\beta$= 0.004, p = $9.5\times10^{-9}$). Meanwhile, sleep duration and brain regions related to sleep significantly mediated the association between PRS of sleep and symbol digit substitution (path $\beta = 1.5\times10^{-4}$, p = 0.001). Specifically, with sleep duration significantly associated with PRS ($\beta = 0.058$, p = $4.5\times10^{-10}$) and brain volumes positively associated with sleep duration ($\beta = 0.053$, p = $1.1\times10^{-8}$), and in addition, brain volumes significantly associated with symbol digit substitution ($\beta = 0.049$, p = $1.1\times10^{-7}$). Sleep duration ($\beta = 0.003$, p = $6.3\times10^{-5}$) and brain volumes ($\beta = 0.002$, p = $4.2\times10^{-3}$) also separately mediated the association between PRS and symbol digit substitution. The association between these cognitive functions and sleep duration were also significantly mediated by brain structure related to sleep for participants with sleep duration > 7 hours, including symbol digit substitution (path $\beta$= −0.002, p = 0.019), numeric memory (path $\beta$= −0.003, p = 0.004) and trail making (path $\beta$= 0.002, p = 0.017). Reaction time and sleep duration were also mediated by brain structure for participants with sleep duration > 7 hours (path $\beta$= 0.001, p = 0.031). Wald tests were utilized to derive the two-sided p value adjusted for multiple comparisons (FDR correction). * represented p < 0.05, ** represented p < 0.01 and *** represented p < 0.001.

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*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| | |
|---|---|
| Data collection | No software was involved in data collection (data used is all directly available from UK Biobank, as described in detail in the paper ) |
| Data analysis | Matlab 2018b was used to perform nonlinear association analysis.<br>Freesurfer v6.0 was used to process the imaging data.<br>PLINK 1.90 and PRSice version 1.25 (www.PRSice.info) were used to perform genome-wide association analysis and calculate the polygenic risk score respectively.<br>R version 3.6.0 package:<br>lavaan 0.8 was used to perform longitudinal analysis, mediation analysis and structural equation model,<br>AER 1.2-9 was used to perform interaction test, rms 6.2-0 was utilized to conduct restricted cubic spine analysis,<br>GenomicSEM version 0.0.3 was utilized to calculate the heritability and genetic correlation,<br>two-lines test version 0.52 was utilized to identify the breakpoints of the nonlinear model.<br>Scripts used to perform the analyses are available at https://github.com/yuzhulineu/UKB_sleep |

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## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

This project corresponds to UK Biobank application ID 19542. Neuroimaging, genotype and behavioral data from UK Biobank dataset are available from https://biobank.ndph.ox.ac.uk/ by application. The variables utilized here are detailed in Supplemental Table 1. Previous published GWAS of sleep duration was downloaded via http://www.t2diabetesgenes.org/data/. European ancestral background LD scores from the 1000 Genomes Project were downloaded from https://alkesgroup.broadinstitute.org/LDSCORE/.

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# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | No statistical methods were used to predetermine sample sizes and all currently available sample in the UK Biobank were used including 498,277 subjects with behavioral data, 156,884 subjects with follow-up mental health data and 39,692 subjects with imaging and genotype data. The sample sizes were provided in the method section. |
| Data exclusions | For calculation of polygenetic risk score, we excluded single-nucleotide polymorphisms (SNPs) with call rates < 95%, minor allele frequency < 0.1%, deviation from the Hardy–Weinberg equilibrium with p < 1E-10 and selected subjects that were estimated to have recent British ancestry and have no more than ten putative third-degree relatives in the kinship table, consistent with the previous study. |
| Replication | All available data were used to maximize statistical power of the analysis therefore we did not repeat the analysis. |
| Randomization | In our nonlinear association analysis, we regressed out covariates including age, sex, body mass index, scanning site of imaging, Townsend deprivation index measuring socioeconomic status, qualifications, smoking status and drinking status. |
| Blinding | Blinding was not applicable to this study as this study is observational. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☒ | ☐ Clinical data |
| ☒ | ☐ Dual use research of concern |

### Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☐ | ☒ MRI-based neuroimaging |

## Human research participants

Policy information about studies involving human research participants

| | |
|---|---|
| Population characteristics | A total of 498,277 participants aged between 38 and 73 (54% females) was obtained from the UK biobank study, which is a large-scale database containing cognitive assessment, mental health questionnaires, brain imaging and in-depth genetic information from UK participants. Neuroimaging data of 39,694 participants were available and utilized in the current analyses. See Method section for further details. Population characteristics of the participants are listed in Table 1. |

| | |
|---|---|
| Recruitment | The UK Biobank recruited over 500,000 people aged 40-69 since 2006 at 22 recruitment centers across the UK. Previous investigation showed UK biobank subject to a healthy sample bias. |
| Ethics oversight | UK Biobank has approval from the North West Multi-centre Research Ethics Committee (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics) as a Research Tissue Bank approval and provides oversight for this study. Written informed consent was obtained from all participants. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

# Magnetic resonance imaging

## Experimental design

| | |
|---|---|
| Design type | Structural MRI |
| Design specifications | UK Biobank designed the imaging acquisition protocals including 6 modalities, covering structural, diffusion and functional imaging. The collection order is T1-weighted structural image, resting-state functional MRI, task functional MRI, T2-weighted FLAIR structural image, Diffution MRI and susceptibility-weighted imaging. T1-weighted structural image was acquired using straight sagittal orientation for 5 minutes. |
| Behavioral performance measures | Cognitive tests were first administered via touchscreen interface in the UK biobank assessment center at the baseline visit and repeated at the neuroimaging visit. Six cognitive tests including reaction time, numeric memory, fluid intelligence, trail making, prospective memory and pair matching test were utilized in the current study. Measurement of depressive symptoms via 4-item Patient Health Questionnaire-4 (PHQ-4) was first assessed in the UK biobank assessment center (2006-2010, n=499,585) and then repeated at the neuroimaging visit (2014-2017, n=48,571). |

## Acquisition

| | |
|---|---|
| Imaging type(s) | T1-weighted structural imaging |
| Field strength | 3T |
| Sequence & imaging parameters | The EPI-based acquisitions utilize simultaneous multi-slice (multiband) acceleration. Biobank uses pulse sequences and reconstruction code from the Center for Magnetic Resonance Research (CMRR), University of Minnesota https://www.cmrr.umn.edu/multiband. The resolution is 1x1x1 mm and field of view is 208x256x256 matrix. Straight sagittal orientation is used. TR and TE are 2000ms and 2.01ms respectively. The flip angle is 8 deg. Detailed sequence and imaging parameters are openly available here: https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/ brain_mri.pdf |
| Area of acquisition | Whole brain |

Diffusion MRI ☐ Used ☒ Not used

## Preprocessing

| | |
|---|---|
| Preprocessing software | Imaging derived phenotypes (IDP) generated by an imaging-processing pipeline developed and run on behalf of UK Biobank were used in the study. 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 thickness42. Subcortical regions were extracted via FreeSurfer's aseg tool. The full processing pipeline is openly available here: http://doi.org/10.1016/j.neuroimage.2017.10.034 |
| Normalization | see above |
| Normalization template | fsaverage |
| Noise and artifact removal | see above |
| Volume censoring | see above |

## Statistical modeling & inference

| | |
|---|---|
| Model type and settings | mass univariate, nonlinear regression model, cross-lagged panel model, structural equation modeling |
| Effect(s) tested | For nonlinear regression model, F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons. For cross-lagged panel model and structural equation modeling, Wald tests were utilized to derive the two-sided p value. |

Specify type of analysis: ☒ Whole brain ☐ ROI-based ☐ Both

| | |
|---|---|
| Statistic type for inference (See Eklund et al. 2016) | voxel-wise association, voxel-wise Bonferroni correction |
| Correction | Bonferroni |

## Models & analysis

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ Functional and/or effective connectivity |
| ☒ | ☐ Graph analysis |
| ☒ | ☐ Multivariate modeling or predictive analysis |