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Supplementary information

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

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Supplementary Information

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

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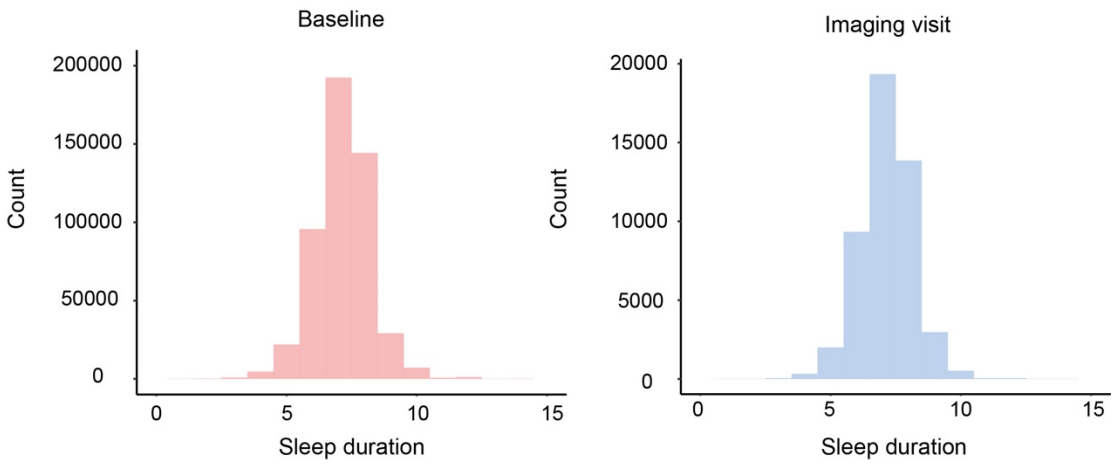
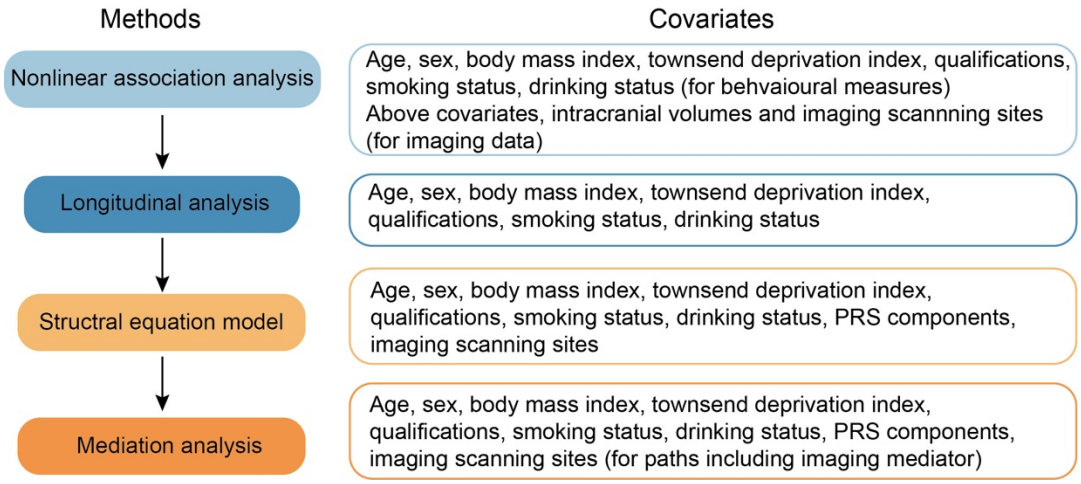
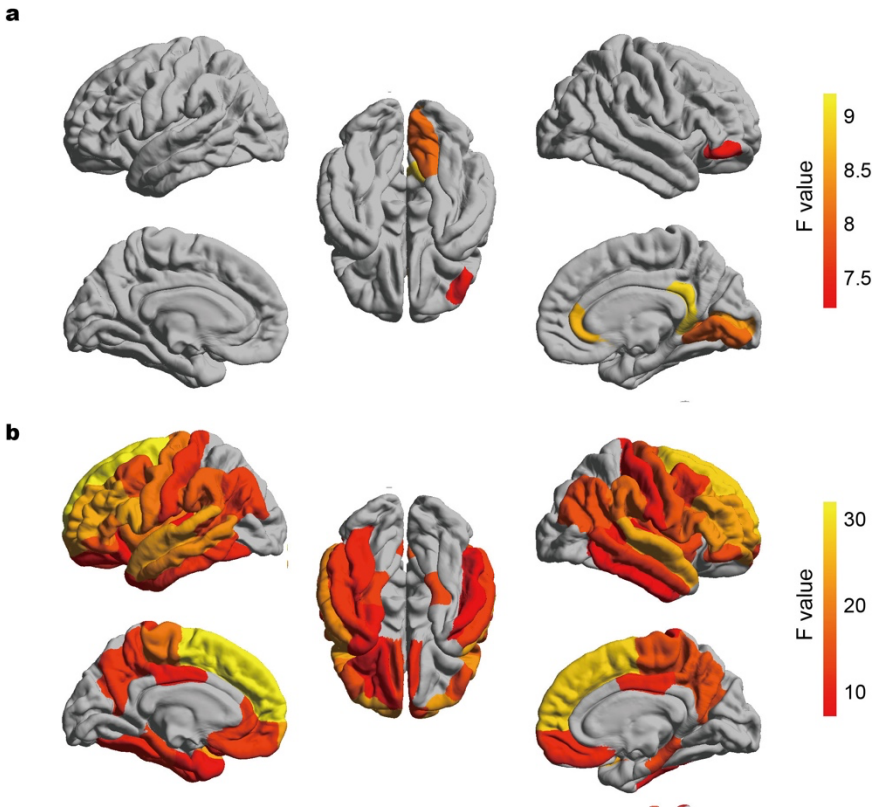


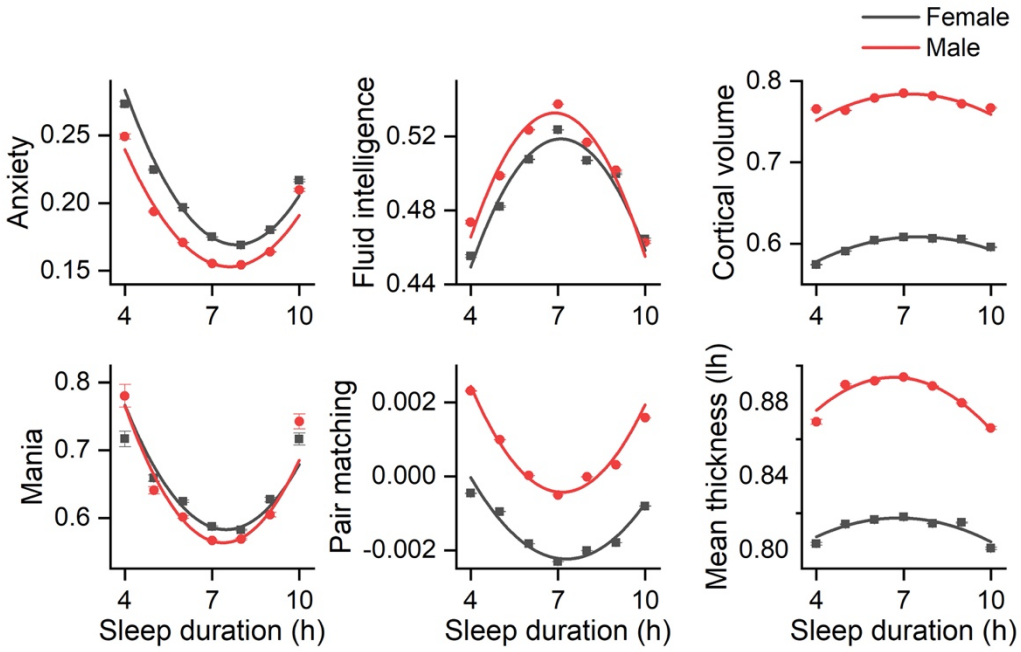
Supplementary Figure 1. Histograms of sleep duration in baseline and imaging assessment. The sleep duration data from the baseline assessment (2006-2010, n=498,277) and neuroimaging visit (2014+, n=48,511) were used in the analyses. Sleep duration assessed at baseline was utilized to determine the association 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.



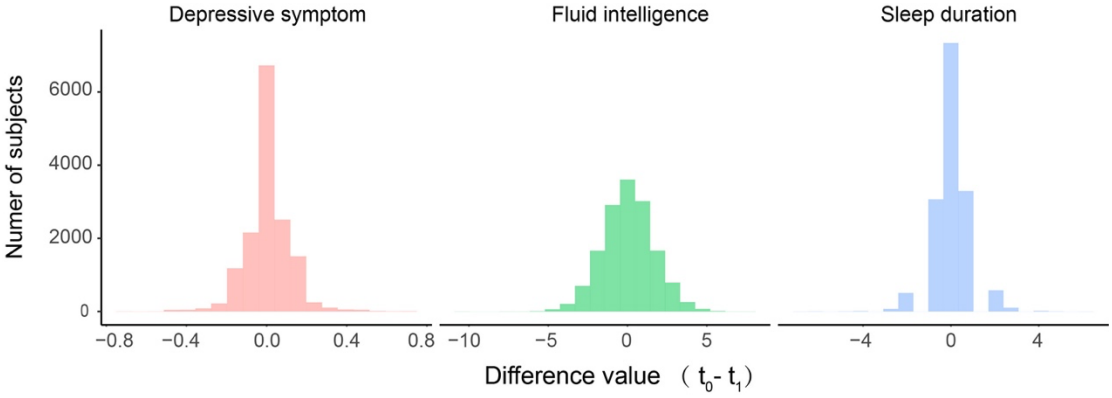
Supplementary Figure 2. Covariates utilized in the statistical analyses. Age, sex, body mass index, Townsend deprivation index, educational qualifications, smoking status and drinking status were adjusted in all analyses. In addition, for analysis involving neuroimaging data and polygenetic risk score,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



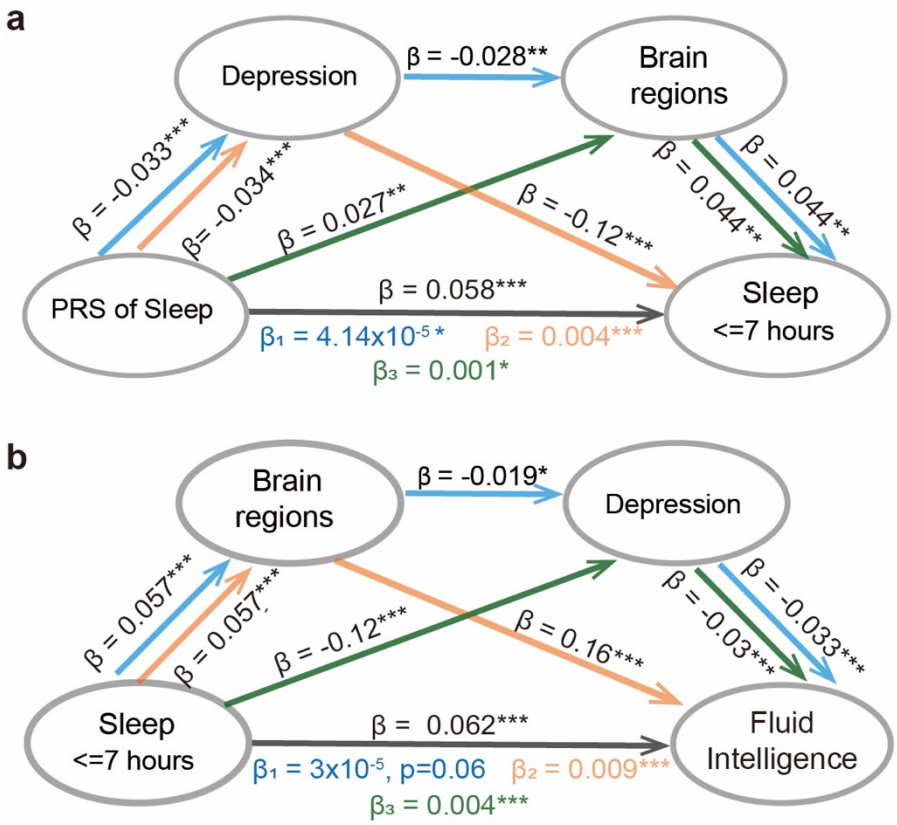
Supplementary Figure 3. Nonlinear association between sleep duration and cortical area and thickness. Cortical regions with their a) area and b) thickness significantly and nonlinearly associated with sleep duration adjusted for sleep duration with intracranial volume, age, sex, sex, body mass index, Townsend deprivation index, educational qualifications, 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.



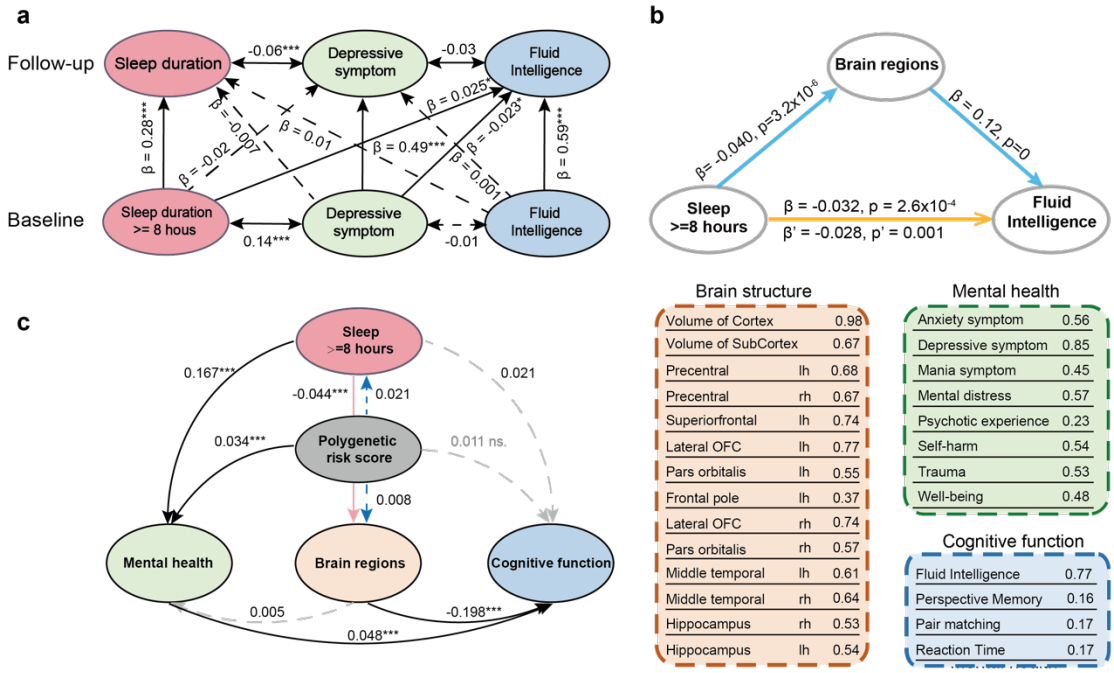
Supplementary Figure 4. Sex difference of the association between sleep duration and mental health, cognitive function and brain structures. The nonlinear association between sleep duration and anxiety symptom was more significant in female participants ($F_{female} = 622.6$, n = 533, 2878, 15240, 36239, 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.



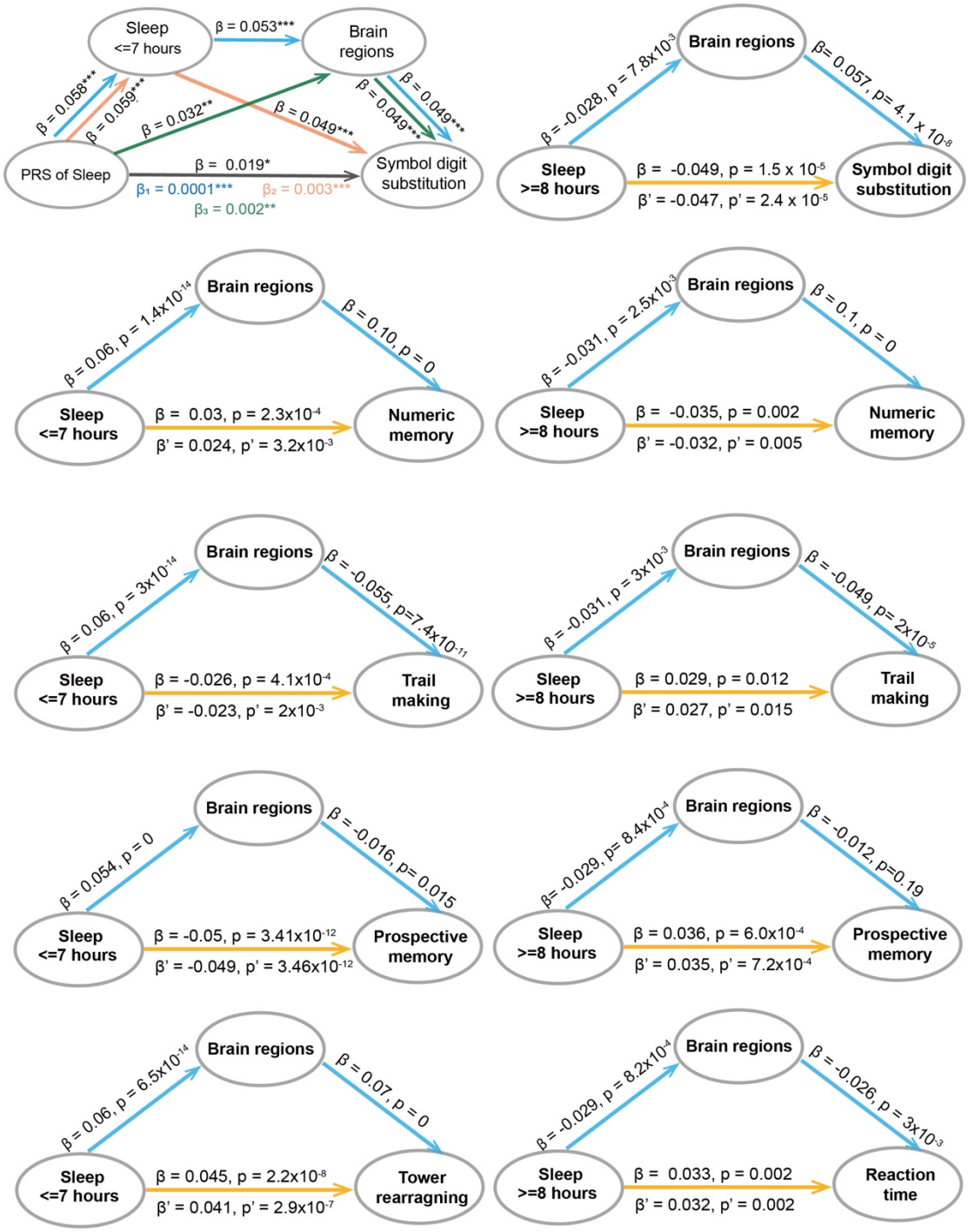
Supplementary Figure 5. Histograms of the change of variables over time in the longitudinal analysis. Baseline sleep duration is 0.031 hours longer than the follow-up sleep duration (std=0.94). At baseline, participants were more depressed compared with the measurement at follow-up (difference=0.0069,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



Supplementary Figure. 6 Mediation analysis. a. Three mediation analysis were conducted between PRS and sleep duration, 1) PRS → depressive symptoms→ brain structures → sleep, 2) PRS → depressive symptoms → sleep, 3) PRS→ brain structures → sleep. Depressive symptoms and brain structures serially mediated the association between PRS and sleep duration (β =4.14×10^{-5}, p = 0.044). Specifically, with depression significantly associated with PRS (β = -0.033, p = 1.6×10^{-4}) and brain volumes positively associated with depression (β = -0.028, p = 1.4×10^{-3}), and in addition, brain volumes significantly associated with sleep duration (β = 0.044, p = 1.4×10^{-6}). Meanwhile, depressive symptoms and brain structures also separately significantly mediated the association between PRS and sleep duration (β_2 = 0.004, p = 3.3×10^{-4}, β_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 structures → fluid intelligence, 3) sleep duration→ depression→ fluid intelligence. Sleep duration showed a significant positive association with fluid intelligence in the model (β = 0.062, p = 2×10^{-15}). The serial mediation pathway via brain structure and depression was not significant (β_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 (β_2 = 0.009, p = 2×10^{-7}; β_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.



Supplementary Figure. 7 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 (β= 0.025, p = 1.3×10^{-5}) and depressive symptom (β= -0.023, p = 1.3×10^{-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 (β= -0.0046, p = 1.4×10^{-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 (β = -0.034, $p = 4.7\times10^{-5}$). Brain volumes were a better predictor of cognitive function (β = -0.198, $p < 1.0\times10^{-20}$) compared to mental health (β = 0.048, $p = 3.5\times10^{-6}$). Sleep duration was the most significant predictor of mental health (β = 0.167, $p < 1.0\times10^{-20}$) and brain regions (β = -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.



Supplementary Figure. 8 Mediation analysis between sleep duration and cognitive functions. For participants with sleep duration ≤ 7 hours, brain structures related to sleep significantly mediated the association between sleep duration and numeric memory (path β= 0.006, p = 1.4×10^{-11}), trail making (path β= -0.003, p = 7.8×10^{-7}), prospective memory (path β= -8.8×10^{-4}, p = 0.02) and tower rearranging (path β= 0.004, p = 9.5×10^{-9}). Meanwhile, sleep duration and brain regions related to sleep significantly mediated the association between PRS of sleep and symbol digit substitution (path β = 1.5×10^{-4}, p = 0.001). Specifically, with sleep duration significantly associated with PRS (β = 0.058, p = 4.5×10^{-10}) and brain volumes positively associated with sleep duration (β = 0.053, p = 1.1×10^{-8}), and in addition, brain

volumes significantly associated with symbol digit substitution (β = 0.049, p = 1.1×10^{-7}). Sleep duration (β = 0.003, p = 6.3×10^{-5}) and brain volumes (β = 0.002, p = 4.2×10^{-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 structures related to sleep for participants with sleep duration >7 hours, including symbol digit substitution (path β= -0.002, p = 0.019), numeric memory (path β= -0.003, p = 0.004) and trail making (path β= 0.002, p = 0.017). Reaction time and sleep duration were also mediated by brain structures for participants with sleep duration >7 hours (path β= 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.

Supplementary Table 1. UK biobank showcase variables used in the paper

Cognitive function	Field ID	Sample size	Time
Fluid intelligence	20016	164609	Instance 0
Matrix pattern completion	6373	26849	Instance 0
Numeric memory	4282	51478	Instance 0
Pairs matching	399	224055	Instance 0
Prospective memory	20018	170433	Instance 0
Reaction time	20023	223662	Instance 0
Symbol digit substitution	23324	32966	Instance 0
Tower rearranging	21004	32652	Instance 0
Trail making	6348	33326	Instance 0
Mental health	**Category ID**	**Sample size**	**Time**
Anxiety	140	154655	Online follow-up
Depression	138	153939	Online follow-up
Mania	139	150994	Online follow-up
Mental distress	137	156783	Online follow-up
Psychotic experience	144	156854	Online follow-up
Self-harm	146	156794	Online follow-up
Trauma	145	156881	Online follow-up
Wellbeing	147	156817	Online follow-up
Brain Imaging	**Field ID**	**Sample size**	**Time**
Area of Total Surface (lh)	26721	39692	Instance 2
Area of Total Surface (rh)	26822	39692	Instance 2
Mean thickness (lh)	26755	39692	Instance 2
Mean thickness (rh)	26856	39692	Instance 2
Subcortical grey volume	26517	39692	Instance 2
Cortex volume (lh)	26552	39692	Instance 2
Cortex volume (rh)	26583	39692	Instance 2

Supplementary Table 2. Variables utilized in mental health symptoms

Wellbeing	Description
20458	In general, how happy are you?
20459	In general, how happy are you with your HEALTH?
20460	To what extent do you feel your life to be meaningful?
Depression	Description
20514	a. Little interest or pleasure in doing things
20510	b. Feeling down, depressed, or hopeless
20517	c. Trouble falling or staying asleep, or sleeping too much
20519	d. Feeling tired or having little energy
20511	e. Poor appetite or overeating
20507	f. Feeling of inadequacy
20508	g. Trouble concentrating on things
20518	h. Changes in speed/amount of moving or speaking
20513	i. Thoughts of suicide or self-harm
20446	Ever had prolonged feelings of sadness or depression
20441	Ever had prolonged loss of interest in normal activities
20532	Did your sleep change?
20435	Difficulty concentrating during worst depression
20438	Duration of worst depression
20449	Feelings of tiredness during worst episode of depression
20450	Feelings of worthlessness during worst period of depression
20436	Fraction of day affected during worst episode of depression
20439	Frequency of depressed days during worst episode of depression
20440	Impact on normal roles during worst period of depression
20437	Thoughts of death during worst depression
20536	Weight change during worst episode of depression
Anxiety (GAD-7)	Over the last 2 weeks, how often have you been bothered by any of the following problems?
20506	a. Feeling nervous, anxious or on edge
20509	b. Not being able to stop or control worrying
20520	c. Worrying too much about different things
20515	d. Trouble relaxing
20516	e. Being so restless that it is hard to sit still
20505	f. Becoming easily annoyed or irritable
20512	g. Feeling afraid as if something awful might happen
Mental distress	Presence and absence of any mental health condition
20499	Ever sought or received professional help for mental distress
20500	Ever suffered mental distress preventing usual activities
20544	Mental health problems ever diagnosed by a professional
Mania	Description
20501	Ever had period of mania / excitability

20502	Ever had period extreme irritability
20548	Manifestations of mania or irritability
20492	Longest period of mania or irritability
20493	Severity of problems due to mania or irritability
Self-harm	Harm behaviors
20479	Ever thought that life not worth living
20485	Ever contemplated self-harm
20480	Ever self-harmed
20482	Number of times self-harmed
20553	Methods of self-harm used
20483	Ever attempted suicide
Trauma	Events in childhood or adult life.
20489	Felt loved as a child
20488	Physically abused by family as a child
20487	Felt hated by family member as a child
20490	Sexually molested as a child
20491	Someone to take to doctor when needed as a child
20522	Been in a confiding relationship as an adult
20523	Physical violence by partner or ex-partner as an adult
20521	Belittlement by partner or ex-partner as an adult
20524	Sexual interference by partner or ex-partner without consent as an adult
20525	Able to pay rent/mortgage as an adult
20531	Victim of sexual assault
20529	Victim of physically violent crime
20526	Been in serious accident believed to be life-threatening
20530	Witnessed sudden violent death
20528	Diagnosed with life-threatening illness
20527	Been involved in combat or exposed to war-zone
20497	Repeated disturbing thoughts of stressful experience in past month
20498	Felt very upset when reminded of stressful experience in past month
20495	Avoided activities or situations because of previous stressful experience in past month
20496	Felt distant from other people in past month
20494	Felt irritable or had angry outbursts in past month
Psychotic experience	Unusual and psychotic experiences.
20471	Ever seen an un-real vision
20463	Ever heard an un-real voice
20474	Ever believed in un-real communications or signs
20468	Ever believed in an un-real conspiracy against self
20467	Frequency of unusual or psychotic experiences in past year
20462	Distress caused by unusual or psychotic experiences

Supplementary Table 3. Summary information of mental health variables

Mental health	Sample size	Mean ± SD
Anxiety symptoms	154655	0.077 ± 0.12
Depressive symptoms	153939	0.26 ± 0.22
Mania symptoms	150994	0.12 ± 0.21
Mental distress	156783	0.28 ± 0.34
Psychotic experience	156854	0.015 ± 0.073
Self-harm	156794	0.077 ± 0.16
Trauma	156881	0.11 ± 0.09
Wellbeing	156817	0.69 ± 0.15

Supplementary Table 4. PHQ-4 Questionnaire in longitudinal analysis

Field ID	Description	Time
2050	Frequency of depressed mood in last 2 weeks	Instance 0&2
2060	Frequency of unenthusiasm / disinterest in last 2 weeks	Instance 0&2
2070	Frequency of tenseness / restlessness in last 2 weeks	Instance 0&2
2080	Frequency of tiredness / lethargy in last 2 weeks	Instance 0&2

Supplementary Table 5. Restricted cubic spline for association between sleep duration and brain structures

Brain Structures	Restricted cubic spline		Quadratic regression	
	F value	P value	F value	P value
Cortical area (lh)	32.2	1.04e-14	28.8	2.91e-13
Cortical area (rh)	33.9	1.99e-15	29.9	1.04e-13
Mean thickness(lh)	26.9	2.19e-12	23.9	4.32e-11
Mean thickness(rh)	21.5	4.69e-10	20.42	1.37e-09
Subcortical grey volume	16.7	5.73e-08	12.64	3.24e-06
Cortical grey volume	48.6	7.83e-22	41.1	1.43e-18

F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons (Bonferroni correction).

Supplementary Table 6. Results of the two-lines test

Cognitive function	Breakpoint	z_1	P value	z_2	P value
Fluid intelligence	7	27.62	<0.0001	-29.96	<0.0001
Numeric memory	7	8.76	<0.0001	-10.95	<0.0001
Pairs matching	7	-17.22	<0.0001	13.79	<0.0001
Prospective memory	7	-18.81	<0.0001	17.18	<0.0001
Reaction time	7	-13.98	<0.0001	20.86	<0.0001
Symbol digit substitution	7	6.14	<0.0001	-5.95	<0.0001
Tower rearranging	7	5.2	<0.0001	-3.35	0.0008
Trail making	7	-2.86	0.0042	7.02	<0.0001
Mental health	Breakpoint	z_1	P value	z_2	P value
Anxiety symptoms	7	-30.29	<0.0001	7.39	<0.0001
Depressive symptoms	7	-34.89	<0.0001	13.79	<0.0001
Mania symptoms	7	-16.4	<0.0001	10.31	<0.0001
Mental distress	7	-15.25	<0.0001	12.65	<0.0001
Psycho experience	7	-11.43	<0.0001	10.38	<0.0001
Self-harm	7	-19.25	<0.0001	11.75	<0.0001
Trauma	7	-33.29	<0.0001	14.59	<0.0001
Wellbeing	7	29.89	<0.0001	-4.94	<0.0001
Brain structure	Breakpoint	z_1	P value	z_2	P value
Area of Total Surface (lh)	7	7.43	<0.0001	-1.52	0.129
Area of Total Surface (rh)	7	7.69	<0.0001	-1.26	0.206
Mean thickness (lh)	7	2.87	0.0041	-6.41	<0.0001
Mean thickness (rh)	7	1.71	0.0881	-5.95	<0.0001
Total grey volume	7	8.52	<0.0001	-5.43	<0.0001
Subcortical grey volume	7	4.95	<0.0001	-3.1	0.002
Cortical grey volume	7	8.69	<0.0001	-5.3	<0.0001

Two-lines tests were utilized to derive the z value and corresponding two-sided p value adjusted for multiple comparisons (Bonferroni correction)

Supplementary Table 7. The nonlinear association between sleep duration and key measures in different age groups

Cognitive function	Age group					
	39-52		53-61		62-70	
	F value	P value	F value	P value	F value	P value
Reaction time	200.7	$8.8x10^{-88}$	194.4	$4.5x10^{-85}$	48.8	$6.2x10^{-22}$
Prospective memory	60.2	$7.4x10^{-27}$	91.7	$1.7x10^{-40}$	73.1	$1.9x10^{-32}$
Mental health	Age group					
	39-52		53-61		62-70	
	F value	P value	F value	P value	F value	P value
Depression	420.3	$8.0x10^{-182}$	360.2	$3x10^{-156}$	205.5	$1.5x10^{-89}$
Mania	129.2	$1.1x10^{-56}$	94.0	$1.7x10^{-41}$	47.9	$1.6x10^{-21}$
Brain structure	Age group					
	44-59		60-67		68-82	
	F value	P value	F value	P value	F value	P value
Cortical grey volume	20.16	$1.8x10^{-9}$	18.36	$1.1x10^{-8}$	10.63	$2.4x10^{-5}$
Subcortical grey volume	10.15	$3.9x10^{-5}$	6.79	0.0011	2.25	0.10
Lateral OFC	19.39	$3.9x10^{-9}$	13.37	$1.6x10^{-6}$	7.09	$8.3x10^{-4}$
Hippocampus	7.2	$7.4x10^{-4}$	9.93	$4.9x10^{-5}$	5.70	0.003

F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons (Bonferroni correction).

Supplementary Table 8. Interactions between age and sleep duration

Cognitive function	Interaction term					
	$sleep * age$		$sleep^2 * age$		$sleep * age + sleep^2 * age$	
	t value	P value	t value	P value	F value	P value
Reaction time	0.63	0.53	-3.8	$1.7x10^{-4}$	7.1	$8.2x10^{-4}$
Prospective memory	-0.14	0.89	0.56	0.57	0.15	0.86
Mental health	t value	P value	t value	P value	F value	P value
Depression	3.5	$4.6x10^{-4}$	-4.3	$1.8x10^{-5}$	15.6	$1.6x10^{-7}$
Mania	2.9	0.003	-5.1	$2.5x10^{-7}$	16.8	$5.2x10^{-8}$
Brain structures	t value	P value	t value	P value	F value	P value
Cortical grey volume	-4.0	$6.7x10^{-5}$	0.27	0.79	7.9	$3.5x10^{-4}$
Subcortical grey volume	-3.4	$7.3x10^{-4}$	1.4	0.16	6.8	$1.1x10^{-3}$
Lateral OFC	-3.4	$7.0x10^{-4}$	0.50	0.62	5.9	$2.8x10^{-3}$
Hippocampus	-3.9	$8.0x10^{-5}$	0.71	0.47	8.21	$2.7x10^{-4}$

T-tests were conducted to identify the significance of the coefficient of each interaction term and derive two-sided p value adjusted multiple comparisons (Bonferroni correction). Additionally, F-tests were conducted to test the joint hypotheses that both coefficients of interaction terms were zero and derive one-sided p value (Bonferroni correction). Interaction of $sleep^2 * age$ is significant in the association between sleep duration and reaction time (t = -3.8, p = 1.7×10^{-4}), depressive symptoms (t = -3.6, p = 3.6×10^{-4}) and mania (t = -3.4, p = 6.8×10^{-4}). Interaction of $sleep * age$ is significant in the association between sleep duration and cortical grey volume (t = -4.0, p = 6.7×10^{-5}), subcortical grey volume (t = -3.4, p = 7.3×10^{-4}), lateral orbitofrontal cortex (t = -3.4, p = 7.0×10^{-4}) and hippocampus (t = -3.9, p = 8.0×10^{-5}).

Supplementary Table 9. Linear regression and quadratic regression for the older age group

Cognitive function	Age group (62-70)			
	Quadratic regression		Linear regression	
	F value	P value	F value	P value
Reaction time	48.8	$6.2x10^{-22}$	9.1	0.0026
Prospective memory	73.1	$1.9x10^{-32}$	0.42	0.52
Mental health	**Age group (62-70)**			
	Quadratic regression		Linear regression	
	F value	P value	F value	P value
Depressive symptoms	519.7	$9.6x10^{-224}$	350.1	$8.2x10^{-78}$
Mania symptoms	47.9	$1.6x10^{-21}$	6.9	0.0085
Brain structure	**Age group (68-82)**			
	Quadratic regression		Linear regression	
	F value	P value	F value	P value
Cortical grey volume	10.63	$2.4x10^{-5}$	1.26	0.262
Subcortical grey volume	2.25	0.10	2.94	0.087
Lateral OFC	7.09	$8.3x10^{-4}$	0.098	0.754
Hippocampus	5.70	0.003	0.027	0.869

F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons (Bonferroni correction).

Supplementary Table 10. Sex difference between sleep duration and cognitive function, mental health and brain structures

Cognitive function	Female		Male	
	F value	P value	F value	P value
Fluid intelligence	272.7	$7.9x10^{-119}$	205.4	$1.1x10^{-89}$
Numeric memory	71.6	$9.7x10^{-32}$	41.1	$1.5x10^{-18}$
Pairs matching	85.8	$5.3x10^{-38}$	104.1	$6.6x10^{-46}$
Prospective memory	120.9	$3.6x10^{-53}$	99.6	$6.5x10^{-44}$
Reaction time	204.0	$2.9x10^{-89}$	193.2	$1.5x10^{-84}$
Symbol digit substitution	11.6	$8.9x10^{-6}$	19.6	$3.1x10^{-9}$
Tower rearranging	5.8	0.0027	13.2	$1.9x10^{-6}$
Trail making	9.4	$8.2x10^{-5}$	21.0	$7.8x10^{-10}$
Mental health	F value	P value	F value	P value
Anxiety	622.6	$3.2x10^{-269}$	417.2	$8.0x10^{-181}$
Depression	600.6	$7.8x10^{-260}$	420.6	$2.8x10^{-181}$
Mania	140.3	$1.4x10^{-61}$	145.0	$1.4x10^{-63}$
Mental distress	122.0	$1.2x10^{-53}$	131.1	$1.4x10^{-57}$
Psycho experience	145.3	$1.0x10^{-63}$	191.4	$1.3x10^{-83}$
Self-harm	213.9	$2.0x10^{-93}$	252.9	$3.5x10^{-110}$
Trauma	714.2	$1.9x10^{-308}$	402.1	$2.5x10^{-174}$
Wellbeing	575.3	$5.5x10^{-249}$	340.2	$1.0x10^{-147}$
Brain structure	F value	P value	F value	P value
Cortical Area (lh)	25.5	$8.6x10^{-12}$	7.38	$6.2\ x10^{-4}$
Cortical Area (rh)	26.6	$2.9x10^{-12}$	7.82	$4.0x10^{-4}$
Cortical thickness (lh)	4.57	0.01	20.9	$8.4x10^{-10}$
Cortical thickness (rh)	2.89	0.055	20.0	$2.2x10^{-9}$
Subcortical GM	9.99	$4.6x10^{-5}$	3.69	0.025
Cortical GM	29.1	$2.4x10^{-13}$	14.7	$4.2x10^{-7}$

F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons (Bonferroni correction).

Supplementary Table 11. The interaction between sex and sleep duration

Cognitive function	Interaction term					
	$sleep * sex$		$sleep^2 * sex$		$sleep * sex + sleep^2 * sex$	
	t value	P value	t value	P value	F value	P value
Fluid intelligence	-3.87	1.1×10^{-4}	-0.34	0.73	7.47	5.7×10^{-4}
Mental health	t value	P value	t value	P value	F value	P value
Anxiety symptoms	5.91	3.4×10^{-9}	0.20	0.84	17.5	2.5×10^{-8}
Depressive symptoms	4.32	1.5×10^{-5}	0.85	0.39	9.54	7.2×10^{-5}
Mania symptoms	-3.90	9.6×10^{-5}	4.47	7.8×10^{-6}	14.0	8.4×10^{-7}
Mental distress	2.60	0.0092	1.80	0.071	4.98	0.0068
Trauma	5.22	1.7×10^{-7}	-1.93	0.054	15.3	8.4×10^{-7}
Wellbeing	-3.33	8.6×10^{-4}	-0.17	0.87	5.58	0.0038
Brain structures	t value	P value	t value	P value	F value	P value
Mean Thickness (lh)	-1.92	0.054	-2.53	0.011	5.41	4.5×10^{-3}
Mean Thickness (rh)	-1.84	0.066	-2.55	0.47	4.91	7.4×10^{-3}

To explore the interaction between sleep duration and sex, interaction terms '$sleep * sex$' and '$sleep^2 * sex$' were added to original nonlinear regression model. T-tests were conducted to identify the significance of the coefficient of each interaction term and derive two-sided p value adjusted multiple comparisons (Bonferroni correction). Additionally, F-tests were conducted to test the joint hypotheses that both coefficients of interaction terms were zero and derive one-sided p value (Bonferroni correction). Joint significance was found for interaction terms of '$sleep * sex$' and '$sleep^2 * sex$' in anxiety symptoms ($F=17.5$, $p = 2.5 \times 10^{-8}$), mania symptoms ($F=14.0$, $p = 8.4 \times 10^{-7}$) etc. Significant interactions of sleep duration and sex were also presented in fluid intelligence ($F =7.47$, $p = 5.7 \times 10^{-4}$) and brain mean thickness (lh, $F =5.41$, $p = 4.5 \times 10^{-3}$; rh, $F =4.91$, $p = 7.4 \times 10^{-3}$).

Supplementary Table 12. The nonlinear correlation between sleep variability and key measures

Cognitive function	F value	P value
Fluid intelligence	50.6	1.09e-22
Numeric memory	29.1	2.44e-13
Pair's matching	6.69	1.20e-03
Prospective memory	32.79	5.82e-15
Reaction time	7.29	6.77e-04
Trail making	9.19	1.01e-04
Mental health	**F value**	**P value**
Anxiety	138.7	9.68e-61
Depression	158.9	1.96e-69
Mania	40.4	2.97e-18
Mental distress	38.9	1.38e-17
Self-harm	102.5	4.06e-45
Wellbeing	138.9	8.49e-61

F-tests were utilized to access statistical significance and derive F-statistics and corresponding one-sided p values adjusted for multiple comparisons (Bonferroni correction).

Supplementary Table 13. Results of Longitudinal analysis

	Coefficient	P value	Fdr-corrected P value
Depression2~			
Depression1	0.5	0	0
Sleep1	-0.038	1.30e-05	2.79e-05
Fluid1	-0.004	0.674	0.674
Sleep2~			
Depression1	0.012	0.199	0.229
Sleep1	0.446	0	0
Fluid1	0.019	0.041	0.0556
Fluid2~			
Depression1	-0.018	0.029	0.0436
Sleep1	0.021	0.011	0.0179
Fluid1	0.593	0	0
Depression1~~			
Sleep1	-0.132	0	0
Fluid1	-0.035	5.59e-04	1.05e-03
Sleep1~~			
Fluid1	0.054	9.51e-08	2.38e-07
.depression2~~			
.sleep2	-0.087	0	0
.fluid2	-0.019	0.0652	0.0814
.sleep2~~			
.fluid2	0.008	0.419	0.449

Wald tests were utilized to derive the two-sided p value adjusted for multiple comparisons (FDR correction).