Behavioral/Cognitive

Is Short Sleep Bad for the Brain? Brain Structure and Cognitive Function in Short Sleepers

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Many sleep less than recommended without experiencing daytime sleepiness. According to prevailing views, short sleep increases risk of lower brain health and cognitive function. Chronic mild sleep deprivation could cause undetected sleep debt, negatively affecting cognitive function and brain health. However, it is possible that some have less sleep need and are more resistant to negative effects of sleep loss. We investigated this using a cross-sectional and longitudinal sample of 47,029 participants of both sexes (20–89 years) from the Lifebrain consortium, Human Connectome project (HCP) and UK Biobank (UKB), with measures of self-reported sleep, including 51,295 MRIs of the brain and cognitive tests. A total of 740 participants who reported to sleep <6 h did not experience daytime sleepiness or sleep problems/disturbances interfering with

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falling or staying asleep. These short sleepers showed significantly larger regional brain volumes than both short sleepers with daytime sleepiness and sleep problems ($n = 1742$) and participants sleeping the recommended 7–8 h ($n = 3886$). However, both groups of short sleepers showed slightly lower general cognitive function (GCA), 0.16 and 0.19 SDs, respectively. Analyses using accelerometer-estimated sleep duration confirmed the findings, and the associations remained after controlling for body mass index, depression symptoms, income, and education. The results suggest that some people can cope with less sleep without obvious negative associations with brain morphometry and that sleepiness and sleep problems may be more related to brain structural differences than duration. However, the slightly lower performance on tests of general cognitive abilities warrants closer examination in natural settings.

Key words: **brain; cognition; hippocampus; MRI; sleep; sleepiness**

Significance Statement

Short habitual sleep is prevalent, with unknown consequences for brain health and cognitive performance. Here, we show that daytime sleepiness and sleep problems are more strongly related to regional brain volumes than sleep duration. However, participants sleeping ≤6 h had slightly lower scores on tests of general cognitive function (GCA). This indicates that sleep need is individual and that sleep duration per se is very weakly if at all related brain health, while daytime sleepiness and sleep problems may show somewhat stronger associations. The association between habitual short sleep and lower scores on tests of general cognitive abilities must be further scrutinized in natural settings.

Introduction

Approximately 50% of people sleep less than the recommended 7–9 h (Hirshkowitz et al., 2015; Watson et al., 2015), with 6.5% sleeping less than six (Kocevska et al., 2021b), many of whom do not report excessive daytime sleepiness. Shorter than recommended sleep is believed to reduce brain health and cognitive performance (Zamore and Veasey, 2022); but guidelines do not take into account two factors. First, partly because of genetic differences (Dashti et al., 2019), sleep need varies. Even vulnerability to sleep loss is a heritable and stable trait, and several genetic polymorphisms are identified (Casale and Goel, 2021). Second, like other physiological systems, sleep need may not be fixed, but is expected to have the ability to adapt to changes in external circumstances (Horne, 2011). This may allow short sleep without sleepiness, reduced brain health and cognitive deficits. Crucially, however, the relationship between sleep duration, daytime sleepiness and neurocognitive function is complex (Horne, 2010). A subset of healthy adults sleeping 7–8 h without daytime sleepiness can still fall asleep within 6 min in the multiple sleep latency test (MSLT; Roehrs et al., 1996). This indicates a level of sleepiness similar to patients with primary sleep disorders, and it was suggested that this could represent accumulated sleep debt from chronically mild insufficient sleep (Roehrs et al., 1996). Lack of daytime sleepiness may result from insensitivity to sleep drive or renormalization in response to chronic sleep deprivation preventing feelings of sleepiness, rather than reflecting lower sleep need (Mander et al., 2017). With extended sleep deprivation, subjective sleepiness can return to baseline levels well before deficits in psychomotor vigilance tasks are normalized (Van Dongen et al., 2003). If such short sleepers are indeed suffering undetected sleep debt despite low levels of daytime sleepiness, neurocognitive deficits may be possible to detect by cognitive tests and brain MRIs. In contrast, if short sleep is due lower sleep need, then such participants are not likely to have poorer cognitive function or brain health.

Duration per se may be a less important indicator of insufficient sleep than daytime sleepiness and problems such as frequently having trouble falling or staying asleep. Short duration (≤6 h) combined with problems and insomnia was associated with higher risk of hypertension, whereas sleeping as short as ≤5 h without problems was not (Vgontzas et al., 2009). Daytime sleepiness was associated with thinner cortex (Carvalho et al., 2017), but sleep duration was not addressed.

Here, we compared cognitive function and brain volumes between short sleepers (≤6 h) with or without sleep problems and daytime sleepiness, and in participants sleeping the recommended 7−8 h. Important aspects of brain health can be measured by structural MRI, which is sensitive to aging (Walhovd et al., 2016) and disease (Fjell et al., 2014). Global brain volume is consistently related to higher general cognitive function (GCA; Walhovd et al., 2022), and atrophy in specific regions has been associated with reduced cognitive function (Gorbach et al., 2020). Brain morphometry and habitual sleep duration form an inverse U-shaped relationship, peaking at ∼7 h (Spira et al., 2016; Fjell et al., 2020b, 2021). We combined data from the Lifebrain consortium (Walhovd et al., 2018), UK Biobank (UKB; Miller et al., 2016), and the Human Connectome Project (HCP; Van Essen et al., 2013) in a mixed cross-sectional and longitudinal design, allowing us to target short (≤6 h) and normal (7−8 h) sleepers with or without daytime sleepiness and sleep problems.

Materials and Methods

Sample

The sample (see Table 1), described in more detail previously (Fjell et al., 2023), consisted of community-dwelling adults from multiple European countries and the United States. All participants gave written informed consent. The Lifebrain project (Walhovd et al., 2018) was approved by the Regional Committees for Medical and Health Research Ethics South East Norway, and substudies approved by the relevant national review boards. For UKB, ethical approval was obtained from the National Health Service National Research Ethics Service (Ref 11/NW/0382). The full sample consisted of 47,029 participants (20−89 years) with information about sleep duration and MRI of the brain and 8694 with general cognitive ability scores, calculated as a g-factor from the available cognitive tests in each sample (for details, see Walhovd et al., 2022). As the specific cognitive test varied across samples (see below), the g-factor was used to reduce the impact of test-specific variance on the results. For 3893 participants, longitudinal MRI examinations were available, yielding a total of 51,295 MRIs (mean follow-up interval 2.5 years, range 0.005–11.2, 26 811 female/24,509 male observations).

Lifebrain

Participants from major European brain studies: Berlin Study of Aging II (BASE II; Bertram et al., 2014; Gerstorf et al., 2016), the BETULA project (Nyberg et al., 2020), the Cambridge Center for Ageing and Neuroscience study (Cam-CAN; Shafto et al., 2014), Whitehall-II (WH-II; Filippini et al., 2014), and Center for Lifespan Changes in Brain and Cognition longitudinal studies (LCBC; Walhovd et al., 2016; Fjell et al., 2018).

UKB

UK Biobank is a national and international health resource open to all bona fide health researchers (https://www.ukbiobank.ac.uk/; Guggenheim et al., 2015), and includes MRI data from a subsample (https://www.ukbiobank.ac.uk/imaging-data/; Miller et al., 2016). The dataset released February 2020 was used.

HCP

HCP freely share data from 1143 young adults (ages 22–35) from families with twins and nontwin siblings, with 3T MRI and behavioral testing. The dataset used was the 1200 Subjects Release.

The general cognitive ability score was calculated as a g-factor per sample, using available tests. More details are given in (Walhovd et al., 2022), but the following test scores were included: the Practical Problems, Figural Analogies, and Letter Series tests (Düzel et al., 2016; Whitehall-II); Block Design test 7, a measure of immediate free recall of 16 enacted verb-noun sentences, a 30-item five-alternative forced choice vocabulary test, four measures of verbal fluency measured during 1 min, as well as a 26-item general knowledge test (Betula; Nilsson et al., 1997), the standard form of the Cattell Culture Fair, Scale 2 Form A (Cattell and Cattell, 1973), the Spot The Word task (Baddeley et al., 1993; CamCAN), Vocabulary and Matrix reasoning from WASI (Wechsler, 1999; LCBC), raw fluid intelligence score from the UKB Data-field 20 016 (UKB), Practical Problems, Figural Analogies, Letter Series (Düzel et al., 2016; BASE-II), Block design and/or vocabulary from WAIS-III (Wechsler, 1997) and National Adult Reading Test (NART; Nelson and Willison, 1991; Barcelona), and for HCP, Flanker, Dimensional Change Card Sort, Picture Sequence Memory, List Sorting and Pattern Comparison, and Picture Vocabulary and Reading Tests.

Table 1. Sample origins of the full sample

Study	Observations	Participants	Age (mean)	Age (min–max)
HCP	974	974	28.8	22–37
BASE-II	675	391	63.2	24–83
Barcelona	113	39	70.9	64–81
Cam-CAN	884	632	55.1	20–88
LCBC	1474	803	49.4	20–89
UK Biobank	45,983	43,137	64.5	45–83
Betula	423	284	62.3	25–85
Whitehall-II	769	769	69.8	60–85
Total	51,295	47,029	63.4	20–89

HCP: Human Connectome Project; BASE-II: Berlin Aging Study II; Barcelona: University of Barcelona brain studies; Cam-CAN: The Cambridge Center for Ageing and Neuroscience; LCBC: Center for Lifespan Changes in Brain and Cognition, University of Oslo.

Table 2. Definition of sleep groups

Groups	Sample	Defining criteria
1 ($\leq$6 h) and 3 (7–8 h)	Lifebrain/HCP	Yes to all of the following: (1) Usual sleep latency (PSQI2) $<$ 30 min (2) Less than once a week (PSQI5a): sleep latency $>$ 30 min (3) Less than once a week (PSQI5b): nightly or early morning awakenings (4) Less than once a week (PSQI8): trouble staying awake during daytime
1 ($\leq$6 h) and 3 (7–8 h)	UKB	Responses to all the following: (1) "Very easy/fairly easy" (field 1170): trouble getting up (2) "Never/rarely" (field 1190): nap during day (3) "Never/rarely" (field 1200): sleeplessness (4) "Never/rarely" (field 1220): daytime dozing
2 ($\leq$6 h) and 4 (7–8 h)	Lifebrain/HCP	Yes on at least two of the following: (1) Usual sleep latency (PSQI2) $>$ 30 min (2) More than once a week (PSQI5a): sleep latency $>$ 30 min (3) More than once a week (PSQI5b): nightly or early morning awakenings (4) More than once a week (PSQI8): trouble staying awake during daytime
2 ($\leq$6 h) and 3 (7–8 h)	UKB	Responses to all the following: (1) "Not very easy/not at all easy" (field 1170): trouble getting up (2) "Sometimes/usually" (field 1190): nap during day (3) "Sometimes/usually" (field 1200): sleeplessness (4) "Sometimes/often" (field 1220): daytime dozing

The PSQI response category "Less than once a week" here also includes the response "Not during the past month."

Classification of participants

Sleep information was available for baseline only for most of the participants. For the small number of participants for whom more than one observation about sleep was available, we used the average value across timepoints. For the HCP and the Lifebrain samples except Betula, sleep characteristics were measured by the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). For Betula, sleep characteristics were measured by The Karolinska Sleep Questionnaire (KSQ; Nordin et al., 2013; Westerlund et al., 2014). For UKB, sleep was measured through multiple questions.

Participants were classified in four groups, according to criteria specified in Table 2. Groups 1 and 2 consisted of short sleepers ($\leq$6 h). Group 1 reported no daytime sleepiness and no sleep problems ("group 1: Short sleep and no sleep problems/sleepiness"), while group 2 reported daytime sleepiness and/or sleep problems ("group 2: Short sleep and sleep problems/sleepiness"). Group 3 and four consisted of participants sleeping the recommended 7−8 h. Like group 1, group 3 participants did not report daytime sleepiness and sleep problems ("group 3: Recommended sleep and no sleep problems/sleepiness"). Like group 2, group 4 participants reported daytime sleepiness and/or sleep problems ("group 4: Recommended sleep and sleep problems/sleepiness"). Since UKB did not include PSQI, the items used for group assignment were not identical for UKB and Lifebrain participants. Participants not satisfying the criteria were ungrouped and not included in the analyses. 19 Lifebrain participants were short sleepers ($\leq$6 h) and experienced daytime sleepiness without reporting sleep problems. This shows that very few participants report to sleep $\leq$ 6 h and feel tired during the day unless they also have sleep problems. We considered this group to be too small for statistical comparisons. Of the total sample, 9611 participants were successfully classified into the predefined sleep groups. Of participants sleeping $\leq$6 h, 740 (6%) and 1742 (14%) were classified as belonging to group 1 or 2, respectively. Of participants sleeping 7−8 h, 3886 (12%) and 3243 (10%) were classified as belonging to group 3 or 4, respectively (see Table 3 for details).

The same sleep categories were used across the age-range, although recommended sleep duration range is not identical for younger and older adults. This was done because mean sleep duration in this sample is relatively stable across the age-range (Fjell et al., 2023), and the recommended lower limit of sleep is the same across adulthood (Paruthi et al., 2016; Hirshkowitz et al., 2015). This led to the exclusion of young and middle-aged participants sleeping 8–9 h, which is within the recommended duration, and hence represent a risk of reducing the representativity of the "recommended sleep" groups. However, 75% of the sample reported to sleep $<$9 h, and so we believe this choice did not bias the results.

Accelerometer-derived sleep duration

We ran validation analyses using sleep duration quantified by accelerometer data for the UKB participants. Raw accelerometer data were

Table 3. Description of sleep groups

Group	Characteristics	*N* (%)	Age (SD)	Sex (f/m)	Sleep duration (SD)
1. Short sleep and no sleep problems/sleepiness	-Short sleep (≤6 h) -No sleep problems -No daytime sleepiness	740 (6%)	55.8 (15.2)	241/499	5.9 (0.4)
2. Short sleep and sleep problems/sleepiness	-Short sleep (≤6 h) -Sleep problems -Daytime sleepiness	1742 (14%)	62.7 (13.1)	848/894	5.8 (0.5)
3. Recommended sleep and no sleep problems/sleepiness	-Recommended sleep (7–8 h) -No sleep problems -No daytime sleepiness	3886 (12%)	58.1 (14.0)	1764/2122	7.6 (0.5)
4. Recommended sleep and sleep problems/sleepiness	-Recommended sleep (7–8 h) -Sleep problems -Daytime sleepiness	3243 (10%)	65.3 (11.3)	1495/1748	7.5 (0.5)

The percentages refer to the total sample with the same sleep duration, i.e., ≤6 h or 7–8 h.

Table 4. MR Acquisition parameters

Sample	Scanner	Field strength (Tesla)	Sequence parameters
BASE-II	Tim Trio Siemens	3.0	TR: 2500 ms, TE: 4.77 ms, TI: 1100 ms, flip angle: 7°, slice thickness: 1.0 mm, FoV 256 × 256 mm, 176 slices
Betula	Discovery GE	3.0	TR: 8.19 ms, TE: 3.2 ms, TI: 450 ms, flip angle: 12°, slice thickness: 1 mm, FOV 250 × 250 mm, 180 slices
Cam-CAN	Tim Trio Siemens	3.0	TR: 2250 ms, TE: 2.98 ms, TI: 900 ms, flip angle: 9°, slice thickness 1 mm, FOV 256 × 240 mm, 192 slices
LCBC	Avanto Siemens	1.5	TR: 2400 ms, TE: 3.61 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 1.2 mm, FoV: 240 × 240 m, 160 slices, iPat = 2
	Avanto Siemens	1.5	TR: 2400 ms, TE = 3.79 ms, TI = 1000 ms, flip angle = 8, slice thickness: 1.2 mm, FoV: 240 × 240 mm, 160 slices
	Skyra Siemens	3.0	TR: 2300 ms, TE: 2.98 ms, TI: 850 ms, flip angle: 8°, slice thickness: 1 mm, FoV: 256 × 256 mm, 176 slices
	Prisma Siemens	3.0	TR: 2400 ms, TE: 2.22 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 0.8 mm, FoV: 240 × 256 mm, 208 slices, iPat = 2
UB	Tim Trio Siemens	3.0	TR: 2300 ms, TE: 2.98, TI: 900 ms, slice thickness 1 mm, flip angle: 9°, FoV 256 × 256 mm, 240 slices
WH-II	Verio Siemens	3.0	TR: 2530 ms, TE: 1.79/3.65/5.51/7.37 ms, TI: 1380 ms, flip angle: 7°, slice thickness: 1.0 mm, FOV: 256 × 256 mm
HCP	Connectome Skyra Siemens*	3.0	TR: 2400 ms, TE: 2.14 ms, TI: 1000 ms, flip angle: 8°, slice thickness: 0.7 mm, FOV: 224 mm, 256 slices, GRAPPA = 2
UKB	Skyra Siemens	3.0	TR: 2000 ms, TI: 880 ms, slice thickness: 1 mm, FoV: 208 × 256 mm, 256 slices, iPAT = 2

TR: repetition time, TE: echo time, TI: inversion time, FoV: field of view, iPat: in-plane acceleration, GRAPPA: GRAPPA acceleration factor. *Customized.

downloaded from UK Biobank bulk data field 90 001. The UKB physical activity data includes a large sample of participants that wore wrist-worn accelerometers (Axivity AX3 wrist-worn triaxial accelerometers) for up to 7 consecutive days. Data were processed using the R-package GGIR v2.4.0 (van Hees et al., 2014, 2015, 2022), using the configuration provided previously (Jones et al., 2019). We excluded accelerometer-derived sleep duration data if any of the UKB derived data fields 90002, 90015, 90016, and 90017 indicated data quality issues. Further, we excluded data when the number of data recording errors, number of interrupted recording periods, or the duration of interrupted recording periods exceeded Q3 + 1.5s²IQR of the sample. The GGIR computed variable SptDurationInSpt (Total sleep duration) was used as the accelerometer derived sleep duration measure.

Magnetic resonance imaging acquisition and analysis

Lifebrain MRI data originated from seven different scanners (for details, see Fjell et al., 2019; processed with FreeSurfer 6.0, https://surfer.nmr.mgh.harvard.edu/; Dale et al., 1999; Fischl et al., 2002; Reuter et al., 2012; Jovicich et al., 2013). Because FreeSurfer is almost fully automated, to avoid introducing possible site-specific biases, gross quality control measures were imposed and no manual editing was done. To assess the influence of scanner on volumetric estimates, seven participants were scanned on seven scanners across the consortium sites (for details, see Fjell et al., 2019). Using hippocampus as test-region, there was a significant main effect of scanner on volume ($F = 4.13$, $p = 0.046$), but the between-participant rank order was close perfectly retained between scanners, with a mean between-scanner Pearson correlation of $r = 0.98$ (range 0.94–1.00). Similar analyses of cortical regions also revealed close correspondence across scanners (Nyberg et al., 2023). Thus, including site as a random effect covariate in the analyses of hippocampal volume is likely sufficient to remove the influence of scanner differences.

UKB participants were scanned using three identical Siemens 3T Prisma scanners (https://www.fmrib.ox.ac.uk/ukbiobank/protocol/). FreeSurfer outputs (Alfaro-Almagro et al., 2018) and the volumetric scaling from T1 head image to standard space as proxy for Intracranial Volume (ICV) were used in the analyses, generated using publicly available tools, primarily based on FSL (FMRIB Software library, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Details of the imaging protocol (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367) and structural image processing are provided on the UK Biobank website (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977).

HCP imaging data were collected and processed (https://www.humanconnectome.org/study/hcp-young-adult) as described previously (Glasser et al., 2013). Imaging data were collected at a customized Siemens 3T "Connectome Skyra" housed at Washington University in St. Louis, using a standard 32-channel Siemens receive head coil and a "body" transmission coil designed by Siemens specifically for the smaller space available using the special gradients of the WU-Minn and MGH-UCLA Connectome scanners. Images were processed using a custom combination of tools from FSL and FreeSurfer (Jenkinson et al., 2002, 2012; Fischl, 2012).

An overview of scanning parameters across all subsamples in the present study is given in Table 4.

Statistical analyses and data availability

Analyses were run in R version 4.0.0 (R Core Team, 2020), by use of Generalized Additive Mixed Models (GAMM) using the packages "gamm4" version 0.2-26 (Wood and Scheipl, 2020) and "mgcv" version 1.8-28 (Wood, 2017). Advantages with GAMM are first that it represents a nonlinear statistical approach which does not require a priori

Table 5. Differences in brain volumes between groups of short sleepers

Region	Mean volume	Group 2 – group 1	
		Difference mm^3 (CI)	% difference (CI)
Accumbens	903	−7 (−19, 6)	−0.8 (−2.2, 0.7)
Amygdala	3290	4 (−25, 34)	0.1 (−0.8, 1)
Brain stem	21,935	−181 (−348, −13)	−0.8 (−1.6, −0.1)
Caudate	6757	−56 (−127, 14)	−0.8 (−1.9, 0.2)
Corpus callosum	3558	−35 (−77, 7)	−1.0 (−2.2, 0.2)
Cerebellum cortex	111,496	−704 (−1567, 160)	−0.6 (−1.4, 0.1)
Cerebellum WM	30,979	−209 (−626, 45)	−0.9 (−2.0, 0.1)
Cerebral WM	475,095	−105 (−2953, 2744)	−0.0 (−0.6, 0.6)
ICV	1,545,244	−2674 (−15197, 9849)	−0.2 (−1.0, 0.6)
Hippocampus	8067	−8 (−68, 51)	−0.1 (−0.8, 0.6)
Pallidum	3994	−36 (−68, −4)	−0.9 (−1.8,−0.1)
Putamen	9221	−27 (−109, 54)	−0.3 (−1.2, 0.6)
Thalamus	13,718	−75 (−163, 13)	−0.6 (−1.2, 0.1)
TGV	662,557	−1799 (−4678, 1081)	−0.3 (−0.7, 0.2)
Ventricles	31,887	116 (−1039, 1270)	0.4 (−3.3, 4.0)

"Group 2: Short sleep and sleep problems/sleepiness" was compared with "group 1: Short sleep and no sleep problems/sleepiness." Negative estimates represent smaller volumes in group 2.

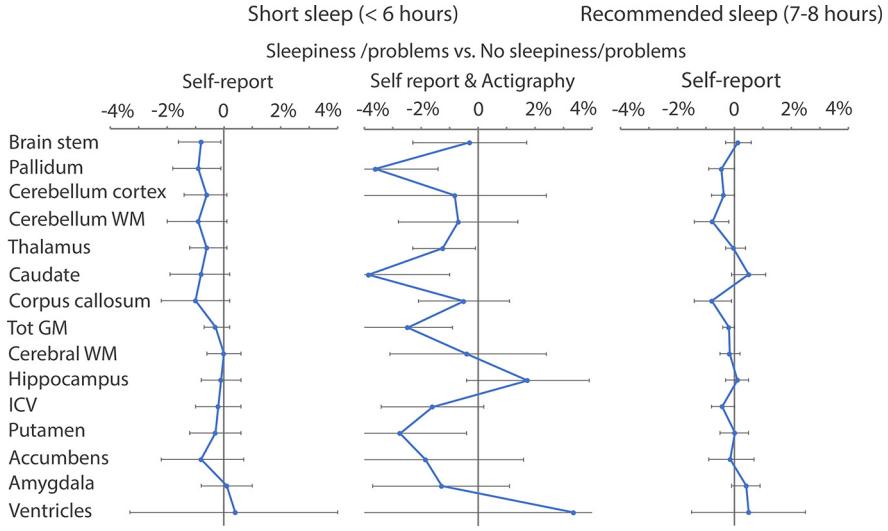

Figure 1. Percent differences in brain volumes between groups. Graphical presentation of the numeric results of Tables 5 (left panel) and 6 (right panel). Left panel, Comparisons between "group 1: Short sleep and no sleep problems/sleepiness" and "group 2: Short sleep and sleep problems/sleepiness," using group 1 as reference (estimate = 0, vertical line). Dots to the left represent smaller volumes of group 2. Lines are sorted from lowest to highest right CI limit. Middle panel, The same comparison as in the left panel, but group classification is based on agreement between self-reports and accelerometer. Lower CIs are trunctade at −4%. Right panel, Comparisons between "group 3: Recommended sleep and no sleep problems/sleepiness" and "group 4: Recommended sleep and sleep problems/sleepiness," using group 3 as reference (estimate = 0, dashed line). Dots to the left represent smaller volumes of group 4. Error bars represent 95% CI.

specification of a polynomial functional form (Sørensen et al., 2021), which is important since the relationship between sleep and brain health may not be linear, and second that it is a mixed model, which means that all data can be included, it deals well with missing data, and the model is optimized to account for both between-subject and within-subject variance. For the main analyses, we ran the model below:

$$\text{mod} <- \text{gamm4}(\text{value} \sim \text{s}(\text{age}) + \text{sex} + \text{site} + \text{sleep} + \text{Group} + \text{icv}, \text{random} = \sim(1|\text{id}), \text{data} = \text{dat})$$

Value represents the brain volume or cognitive score of interest, *sleep* represents sleep duration, *Group* represents the different sleep groups, which were pairwise contrasted. All available data were used, and hence random intercepts were included. Separate analyses were run including the interaction term age x Group. Where appropriate, critical p-values were determined by use of the Benjamini–Hochberg procedure with a 5% false discovery rate to control for multiple comparisons.

As we did not specifically model follow-up time between examinations, the results represent the optimal fit to the longitudinal and cross-sectional observations, and should not be interpreted to signify change in brain volumes per se.

Analyses were run for 12 brain regions, the ventricles, total gray matter volume (TGV) and ICV. We tested for whole-brain effects by computing meta analytic estimates of standardized regression coefficients across the 12 regions, using the R package "metafor" (Viechtbauer, 2010). Data supporting the results of the current study are available from the PI of each substudy on request, given appropriate ethics and data protection approvals. Contact information can be obtained from the corresponding authors. UK Biobank data requests can be submitted to http://www.ukbiobank.ac.uk.

Results

Sleep duration versus sleepiness

For the Lifebrain and HCP samples, we defined "sleepiness" from the Pittsburgh Sleep Quality Index (PSQI) by using the one to four values from item PSQI8 ("trouble staying awake"). Sleepiness and sleep duration correlated $r = -0.11$ ($p < 0.0001$), meaning that short sleep on average was associated with slightly more sleepiness, with ~1% explained variance. Sleep duration and sleepiness hence represents largely independent features.

Brain volumetric comparisons among short sleepers (group 1 vs 2)

Differences in brain volumes between the groups are shown in Table 5 and Figure 1. We performed a meta-analysis across all regions listed in Table 5 (for the ventricles, the sign of the regression coefficient was reversed). Group 2: Short sleep and sleep problems/sleepiness had significantly smaller brain volumes than group 1: Short sleep and no sleep problems/sleepiness (estimate = −0.0041 [CI: −0.0061, −0.0021], SE = 0.001, $z = -4.1$, $p < 0.0001$). Regional comparisons revealed that the differences were most evident for the brain stem and pallidum.

Next, we tested whether each of the two groups of short (≤6 h) sleepers had different volumes from group 3: Recommended sleep and no sleep problems/sleepiness, reporting 7−8 h of sleep. Group 1: Short sleep and no sleep problems/sleepiness had overall larger volumes than group 3 (estimate = 0.0067 [CI: 0.0030, 0.0103], SE = 0.0019, $z = -3.60$, $p < 0.001$), driven by differences in brain stem, caudate, cerebellum white matter and cortex volumes. Group 2: Short sleep and sleep problems/sleepiness did not show an overall significant difference in volume compared with group 3 (estimate = −0.0007 [CI: −0.0019, 0.0034], SE = 0.001, $z = -0.54$, $p = 0.59$).

Brain volumetric comparisons among participants reporting recommended amount of sleep (group 3 vs 4)

Group 4: Recommended sleep and sleep problems/sleepiness showed smaller volumes for cerebellum WM, corpus callosum

Table 6. Differences in brain volumes between groups reporting recommended sleep

Region	Difference mm^3 (CI) Group 3 − group 4	% difference (CI) Group 3 − group 4
Accumbens	−1.3 (−8.4, 5.9)	−0.14 (−0.9, 0.7)
Amygdala	13.9 (−2.6, 30.4)	0.42 (−0.1, 0.9)
Brain stem	28.3 (−64.0, 120.5)	0.13 (−0.3, 0.6)
Caudate	34.4 (−4.1, 72.9)	0.51 (−0.1, 1.1)
Corpus callosum	−28.0 (−50.8, −5.1)	−0.79 (−1.4, −0.1)
Cerebellum cortex	−417.1 (−884.7, 50.5)	−0.37 (−0.8, 0.0)
Cerebellum WM	−237.2 (−419.0, −55.3)	−0.77 (−1.4, −0.2)
Cerebral WM	−756.2 (−2323.9, 816.4)	−0.16 (−0.5, 0.2)
ICV	−6460.9 (−12978.7, 57.0)	−0.42 (−0.8, 0.0)
Hippocampus	8.7 (−23.7, 41.1)	0.11 (−0.3, 0.5)
Pallidum	−17.9 (−35.5, −0.3)	−0.45 (−0.9, 0)
Putamen	2.3 (−42.4, 47.0)	0.02 (−0.5, 0.5)
Thalamus	3.8 (−44.8, 52.3)	−0.03 (−0.3, 0.4)
TGV	−1231.5 (−2784.0, 320.9)	−0.19 (−0.4, 0.0)
Ventricles	164.2 (−479.4, 807.7)	0.51 (−1.5, 2.5)

"Group 4: Recommended sleep and sleep problems/sleepiness" was compared with "group 3: Recommended sleep and no sleep problems/sleepiness." Negative estimates represent smaller volume in group 4.

and pallidum, as well as ICV, compared with group 3: Recommended sleep and no sleep problems/sleepiness (Table 6; Fig. 1). However, the meta-analysis did not show a significant overall difference across regions (estimate = −0.0012 [CI: −0.0028, 0.0004], SE = 0.0008, $z = -1.51$, $p = 0.13$).

Comparisons among participants with daytime sleepiness (group 2 vs 4)

Finally, we compared group 2: Short sleep and sleep problems/sleepiness with group 4: Recommended sleep and sleep problems/sleepiness. The groups differed by 1.7 h in mean sleep duration, but the meta-analysis did not show a significant difference in brain volumes (estimate = 0.0022 [CI: −0.0002, 0.0046], SE = 0.0012, $z = 1.80$, $p = 0.07$).

Age interactions

Age was included as covariate in all analyses, but we also ran additional analyses including an interaction term age × sleep group to formally test whether effect of sleep group differed as a function of age. For no brain region or group contrast did the age × sleep group term survive correction for multiple comparisons.

Cognitive function

General cognitive function (GCA) scores were available for 8694 of the classified participants. GCA was calculated as the principal component of different cognitive scores available for each sample. There were no significant differences between the groups of short sleepers (group 2 vs 1; estimate = −0.077 SD, $t = -1.55$, $p = 0.12$, $n = 2173$). Among those sleeping 7−8 h, group 4: Recommended sleep and sleep problems/sleepiness showed significantly lower GCA than group 3: Recommended sleep and no sleep problems/sleepiness (estimate = −0.078 SD, $t = 6.89$, $p < 5.89e^{-12}$, $n = 6521$). The effect size was however not larger than for the contrast between the two groups of short sleep, so the difference in significance was because of a substantially larger sample for the latter analysis. A significant difference was also seen between the two groups reporting daytime sleepiness (group 2 vs 4; estimate = −0.03 SD, $t = -2.97$, $p = 0.003$). Both group 1: Short sleep and no sleep problems/sleepiness (estimate = −0.16 SD, $t = -3.80$, $p < 0.0002$) and group 2: Short sleep and sleep problems/sleepiness (estimate = −0.19 SD, $t = -9.94$, $p < 2.97e^{-09}$) showed significantly lower scores than group 3: Recommended sleep and no sleep problems/sleepiness.

Table 7. BMI, depression scores, and education level

Group	BMI	Depression (z)	Education (z)
Group 1: Short sleep and no sleep problems/sleepiness	26.8 (4.1)	−0.2 (0.7)	0.1 (0.9)
Group 2: Short sleep and sleep problems/sleepiness	27.3 (4.8)	0.5 (1.5)*	−0.1 (1.1)*
Group 3: Recommended sleep and no sleep problems/sleepiness	25.7 (3.8)*	−0.2 (0.9)	0.0 (0.97)
Group 4: Recommended sleep and sleep problems/sleepiness	26.7 (4.4)	0.2 (1.1)*	0.0 (1.03)

*$p < 0.001$ (uncorrected), using "group 1: Short sleep and no sleep problems/sleepiness" as reference. Depression and education are given in z scores.

Comparing covariates across groups

We compared BMI, depression, and education level across groups (Table 7). ANOVAs showed significant differences across groups for all variables. Comparing groups pairwise for each variable, using group 1: Short sleep and no sleep problems/sleepiness as reference, showed that group 2: Short sleep and sleep problems/sleepiness had higher BMI, more depression symptoms and lower education. Group 3: Recommended sleep and no sleep problems/sleepiness had lower BMI, while group 4: Recommended sleep and sleep problems/sleepiness had more depression symptoms.

We repeated the main group analyses (group 1 vs 2 and group 3 vs 4) using each of the above covariates (Fig. 2; Table 8). This did not affect the main results. Thus, although there were differences between the short sleepers with versus without daytime sleepiness on several of the covariates, these could not explain the volumetric brain differences.

Validation analyses: accelerometer estimated sleep duration

We performed validation analyses on participants from UKB for whom accelerometer data were available. Although not always highly correlated, accelerometer-based estimates and self-reported sleep duration typically show convergent validity (Wrzus et al., 2012). Groups were re-computed based both on accelerometer-estimated sleep duration and on self-reports, i.e., we included only participants with both self-reported and accelerometer estimated sleep ≤6 h. This naturally reduced the sample size (group 1: Short sleep and no sleep problems/sleepiness $n = 92$, group 2: Short sleep and sleep problems/sleepiness $n = 274$). Group 2 still showed significantly smaller regional brain volumes (estimate = −0.014% [CI: −0.0215, −0.007], SE = 0.0037, $z = -3.87$, $p < 0.001$), driven especially by total gray matter, thalamus, putamen, pallidum and caudate, with substantially larger effect sizes compared with classifications based on self-report only (Fig. 1).

Discussion

Sleeping ≤6 h has been associated with smaller regional brain volumes (Fjell et al., 2022). Here, we find that individuals reporting short sleep but not sleep problems or daytime sleepiness show significantly larger volumes than both short sleepers with sleep problem and daytime sleepiness and those sleeping the recommended 7−8 h. One can speculate whether this contributes to explain why these short sleepers do not report feelings of daytime sleepiness. Still, both groups of short sleepers scored

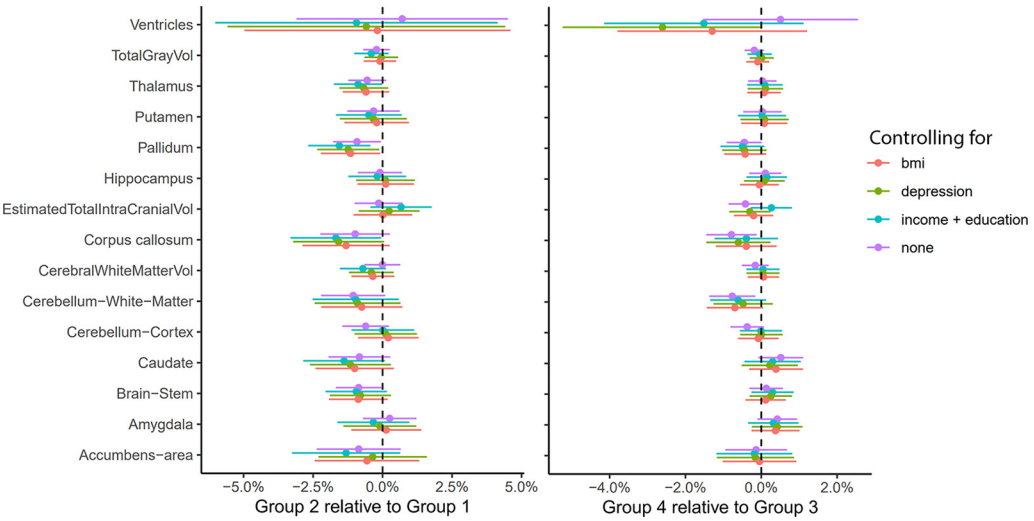

Figure 2. Controlling for additional covariates. Regional brain volumes compared while controlling for additional covariates "group 2: Short sleep and sleep problems/sleepiness" compared with "group 1: Short sleep and no sleep problems/sleepiness." Error bars represent 95%CI.

Table 8. Comparing brain volumes while controlling for additional covariates

Comparison	Additional covariates	Estimate (%)	CI low	CI high	*p*
Group 2 vs 1		−0.0041	−0.0061	−0.0021	0.0000
Group 2 vs 1	BMI	−0.0047	−0.0071	−0.0022	0.003
Group 2 vs 1	Depression	−0.0048	−0.0076	−0.0020	0.007
Group 2 vs 1	Income and education	−0.0065	−0.0094	−0.0035	0.0000
Group 3 vs 4		−0.0012	−0.0028	0.0004	0.13
Group 3 vs 4	BMI	−0.0005	−0.0018	0.0008	0.43
Group 3 vs 4	Depression	−0.0004	−0.0018	0.0010	0.56
Group 3 vs 4	Income and education	0.0001	−0.0012	0.0015	0.84

"Group 2: Short sleep and sleep problems/sleepiness" compared with "group 1: Short sleep and no sleep problems/sleepiness." Estimated differences in regional brain volumes were combined using meta-analysis.

significantly lower on tests of general cognitive function. Although these effect sizes also were minute, this observation warrants further examinations.

Individual differences in sleep need

Short sleepers without daytime sleepiness may need less sleep than the average person, allowing them to sleep in a range that normally is associated with smaller volumes (Fjell et al., 2022). However, as discussed above, lack of daytime sleepiness may not be a good indication of sufficient sleep. Subjective sleepiness tends to normalize faster than performance on psychomotor vigilance tests after sleep deprivation (Van Dongen et al., 2003; Zamore and Veasey, 2022). Still, it is unclear whether vigilance deficits and sleepiness detected in the laboratory reflect real sleep debt (Horne 2010, 2011). Even participants not reporting daytime sleepiness can usually easily fall asleep in a sleep-inducing environment, such as during the multiple sleep-latency test. Sleepiness "unmasked" in the laboratory may be less relevant, as the "sleepiness" is small enough to go unnoticed in more stimulating environments, and one should be cautious inferring "sleep debt" in such cases (Horne, 2010). Hence, it seems clear that self-report measures, as used in the present study, answer different questions about daytime sleepiness than objective assessments (Pérez-Carbonell et al., 2022).

This discussion provides an important context for our findings. If the short sleepers, regardless of experienced daytime sleepiness and sleep problems, had lower regional brain volumes this could indicate undetected sleep debt. The finding of slightly larger volumes in the short sleepers without sleep problems and sleepiness does not necessarily mean that this group has lower sleep need, but is still in line with findings of substantial trait-like individual differences in multiple physiological aspects of sleep, such as sleep homeostasis and duration, which in magnitude have been reported to exceed even effects of 36 h of sleep deprivation (Tucker et al., 2007). Such trait variability may partly be accounted for by genetic differences (Linkowski, 1999; Landolt, 2011; Dashti et al., 2019). This explanation fits previous findings that daytime sleepiness is not solely caused by short sleep (Horne, 2010) and that increased duration does not necessarily cause longer sleep latency and less sleepiness even within individuals (Roehrs et al., 1996). It also concurs with the results from a recent study showing very modest effects of variations in within-participant sleep duration on subjective alertness (Vallat et al., 2022). Recent meta-analyses of twin studies found 38% (Madrid-Valero et al., 2020) and 46% (Kocevska et al., 2021a) of the variability in self-reported sleep duration to be explained by genetics, with GWAS estimates typically being around 10% (Garfield, 2021). Heritability of daytime sleepiness is reported to be 0.38–0.48 in twin studies (Carmelli et al., 2001; Desai et al., 2004; Watson et al., 2006) and 0.08–0.29 (Gottlieb et al., 2007; Lane et al., 2017) with GWAS. Importantly, the genetic overlap between sleep duration, daytime sleepiness, and vulnerability to sleep loss is modest. One study reported a genetic correlation between sleep duration and daytime sleepiness of 0.22 (Wang et al., 2019), and none of the loci associated with duration were associated with sleepiness. The low duration–sleepiness correlation in the present study is in accordance with this, and fits the interpretation that habitual sleep duration and sleepiness are partly independent, trait-like characteristics with different associations to brain health and cognitive function. Differences in sleep quality may further contribute to reduce the relationship between sleep duration and sleepiness. Without taking the individual differences perspective into account, large natural variability in aspects of sleep may lead to spurious, sample-dependent sleep-brain correlations without functional significance (Landolt, 2011).

Still, although short sleep was not associated with smaller regional brain volumes, the short sleepers scored lower on tests of general cognitive abilities. The effect sizes were equal to 2.9 and 2.4 IQ-points for the short sleepers with and without sleep

problems and daytime sleepiness, respectively. This could indicate that these participants sleep less than optimal, in accordance with experimentally induced sleep deprivation yielding reduced cognitive function (Lowe et al., 2017). However, a meta-analysis did not find an effect of sleep deprivation on intelligence and reasoning measures (Lowe et al., 2017), which are the tests most similar to the present measures of cognitive function. In addition, most sleep deprivation experiments involve rapid and dramatic reductions in sleep duration, unlike natural variations in habitual sleep duration between people. A recent very large observational study found ~7 h of sleep to be associated with the highest cognitive function, and <6 h to be associated with mildly lower performance (Coutrot et al., 2022). This fits the results of the present study. Still, we were surprised to find that there were no differences in general cognitive ability between the short sleepers with and without sleep problems and sleepiness, as we expected to see lower scores primarily in the first group. The direction of causality and the possible influence of third variables cannot be decided based on the present data, and must await experimental testing in naturalistic settings, involving modest changes in sleep duration lasting for prolonged periods to mimic everyday sleep duration–cognition relationships.

A complementary account for why the short sleepers in the present study did not show smaller regional brain volumes is that neurocognitive consequences of short sleep depend on adaptation. Sudden sleep deprivation beyond certain limits has negative effects on cognitive performance (Van Dongen et al., 2003; Killgore, 2010) and brain structure (Liu et al., 2014; Saletin et al., 2016; Voldsbekk et al., 2021; Zamore and Veasey, 2022). However, adaptation over time within these limits are unlikely to be harmful to health (Freidmann et al., 1977; Mullaney et al., 1977; Horne, 2011), and may account for the weak relationship between sleep duration and brain morphometry. Reductions in sleep duration can seemingly be obtained without increases in daytime sleepiness or reductions in cognitive performance (Horne and Wilkinson, 1985; Youngstedt et al., 2009). This suggests that sleep duration is adaptable in response to environmental conditions, in line with the present results that variations in sleep duration per se is of less importance for regional brain volume if daytime sleepiness is low. Thus, a combination of adaptation and genetic propensities may create less sleep need and protect from potentially negative consequences of short sleep.

As the present study is correlational and targets brain morphometry, we believe it is not warranted to make strong anatomic interpretations from the results. Still, the regions showing volumetric differences between the short sleepers with versus without sleepiness and sleep problems included the brain stem, which has a critical role in sleep regulation, especially in control of REM sleep (Siegel, 2022). Further, regions of the basal ganglia, especially pallidum and caudate, showed trends toward volumetric differences, and it is suggested that the basal ganglia may play an integral role in the sleep-wake cycle (Hasegawa et al., 2020), with basal ganglia GABAergic neurons possibly representing a functional hub for sleep control (Adamantidis et al., 2021). However, many brain regions are involved on sleep regulation, so we caution about specific neuroanatomical claims based on the present study.

Limitations

(1) Morphometric brain measures and general cognitive ability were used as measures of brain health and cognitive function. Other measures could have yielded different results. e.g., different cognitive domains likely show different relationships to sleep, and the same may be true for other indexes of brain health such as Aβ deposition (Fjell et al., 2020a). (2) The samples were not thoroughly screened for sleep disorders such as sleep apnea, which could affect the observed sleep – brain relationships. (3) The samples are not representative of the populations from which they are drawn, and other sleep-brain patterns may exist in other populations. Further, the majority of participants are white, while sleep loss and sleep problems have been shown to be more prevalent in the United States Black than White population (Jean-Louis et al., 2022). (4) Daytime sleepiness is measured as part of PSQI, but other instruments, like the Epworth Sleepiness Scale, may be more sensitive to excessive daytime sleepiness (Pérez-Carbonell et al., 2022). (5) The strict classification of participants was used to ensure that the groups were as homogenous as possible with regard to sleep variables, but caused most participants to be unclassified. For instance, participants who responded "once or twice a week" on the question of problems sleeping within 30 min, would not be included in the group without sleep problems. Items such as "nap during the day" may both reflect a cultural phenomenon as well as sleep done for pleasure, not necessarily because of sleepiness or sleep need, but would still be assessed as "daytime sleepiness or sleep problems." As a consequence, only 20% of participants sleeping ≤6 h were classified. The remaining 80% had very slight to slight sleep problems or daytime sleepiness, hence not fitting either group. (6) Relationships between sleep and the brain may develop over long time. In the present analyses, sleep duration was for most participants measured at a single time point, making it impossible to distinguish stable from changing sleep patterns. Still, we have previously found good stability in self-reported sleep over time (Fjell et al., 2018; Tsiknia et al., 2023), and another study found current self-reported sleep quality to be as tightly related to brain characteristics as longitudinal measures of sleep (Sexton et al., 2017).

In conclusion, some people sleep ≤6 h without showing lower regional brain volumes, despite sleeping within a range where smaller regional brain volumes are expected. Hence, short sleep is not necessarily associated with negative structural brain outcomes. In contrast, short sleepers showed slightly lower general cognitive abilities, although the causality is unclear. At the same time, the present results suggest that there are large differences in sleep need because of genetic and environmental factors, making general recommendations about sleep duration problematic when it comes to brain health and general cognitive function.

References

Adamantidis A, Fort P, Luppi PH (2021) The neurophysiology of wakefulness and non-rapid eye movement (NREM) sleep. In: Sleep medicine textbook (Bassetti C, McNicholas W, Paunio T, and Peigneux P, eds), Edition 2. Regensburg: European Sleep Research Society.

Alfaro-Almagro F, et al. (2018) Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 166:400–424.

Baddeley A, Emslie H, Nimmo-smith I (1993) The spot-the-word test - a robust estimate of verbal intelligence based on lexical decision. Br J Clin Psychol 32:55–65.

Bertram L, Böckenhoff A, Demuth I, Düzel S, Eckardt R, Li SC, Lindenberger U, Pawelec G, Siedler T, Wagner GG, Steinhagen-Thiessen E (2014) Cohort profile: the Berlin Aging Study II (BASE-II). Int J Epidemiol 43:703–712.

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213.

Carmelli D, Bliwise DL, Swan GE, Reed T (2001) A genetic analysis of the Epworth Sleepiness Scale in 1560 World War II male veteran twins in the NAS-NRC twin registry. J Sleep Res 10:53–58.

Carvalho DZ, St Louis EK, Boeve BF, Mielke MM, Przybelski SA, Knopman DS, Machulda MM, Roberts RO, Geda YE, Petersen RC, Jack CR Jr, Vemuri P (2017) Excessive daytime sleepiness and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults. Sleep Med 32:236–243.

Casale CE, Goel N (2021) Genetic markers of differential vulnerability to sleep loss in adults. Genes (Basel) 12:1317.

Cattell RB, Cattell HEP (1973) Measuring intelligence with the culture fair tests. Champaign: The Institute for Personality and Ability Testing.

Coutrot A, Lazar AS, Richards M, Manley E, Wiener JM, Dalton RC, Hornberger M, Spiers HJ (2022) Reported sleep duration reveals segmentation of the adult life-course into three phases. Nat Commun 13:7697.

Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.

Dashti HS, et al. (2019) Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nat Commun 10:1100.

Desai AV, Cherkas LF, Spector TD, Williams AJ (2004) Genetic influences in self-reported symptoms of obstructive sleep apnoea and restless legs: a twin study. Twin Res 7:589–595.

Düzel S, Voelkle MC, Düzel E, Gerstorf D, Drewelies J, Steinhagen-Thiessen E, Demuth I, Lindenberger U (2016) The Subjective Health Horizon Questionnaire (SHH-Q): assessing future time perspectives for facets of an active lifestyle. Gerontology 62:345–353.

Filippini N, et al. (2014) Study protocol: the Whitehall II imaging sub-study. BMC Psychiatry 14:159.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355.

Fischl B (2012) FreeSurfer. Neuroimage 62:774–781.

Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB; Initiative Alzheimer's Disease Neuroimaging (2014) What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol 117:20–40.

Fjell AM, Idland AV, Sala-Llonch R, Watne LO, Borza T, Brækhus A, Lona T, Zetterberg H, Blennow K, Wyller TB, Walhovd KB (2018) Neuroinflammation and tau interact with amyloid in predicting sleep problems in aging independently of atrophy. Cereb Cortex 28:2775–2785.

Fjell AM, Sederevicius D, Sneve MH, de Lange AG, Bråthen AC, Idland AV, Watne LO, Wang Y, Reinbold C, Dobricic V, Kilpert F, Blennow K, Zetterbergj H, Hong S, Bertram L, Walhovd KB; Initiative Alzheimer's Disease Neuroimaging (2020a) Self-reported sleep problems related to amyloid deposition in cortical regions with high HOMER1 gene expression. Cereb Cortex 30:2144–2156.

Fjell AM, et al. (2020b) Self-reported sleep relates to hippocampal atrophy across the adult lifespan: results from the Lifebrain consortium. Sleep 43:zsz280.

Fjell AM, et al. (2021) Poor self-reported sleep is related to regional cortical thinning in aging but not memory decline-results from the Lifebrain consortium. Cereb Cortex 31:1953–1969.

Fjell AM, et al. (2023) No phenotypic or genotypic evidence for a link between sleep duration and brain atrophy. Nature Human Behavior, in press.

Freidmann J, Globus G, Huntley A, Mullaney D, Naitoh P, Johnson L (1977) Performance and mood during and after gradual sleep reduction. Psychophysiology 14:245–250.

Garfield V (2021) Sleep duration: a review of genome-wide association studies (GWAS) in adults from 2007 to 2020. Sleep Med Rev 56:101413.

Gerstorf D, Bertram L, Lindenberger U, Pawelec G, Demuth I, Steinhagen-Thiessen E, Wagner GG (2016) Editorial. Gerontology 62:311–315.

Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, Xu J, Jbabdi S, Webster M, Polimeni JR, Van Essen DC, Jenkinson M; WU-Minn HCP Consortium (2013) The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage 80:105–124.

Gorbach T, Pudas S, Bartres-Faz D, Brandmaier AM, Düzel S, Henson RN, Idland AV, Lindenberger U, Macia Bros D, Mowinckel AM, Sole-Padulles C, Sorensen O, Walhovd KB, Watne LO, Westerhausen R, Fjell AM, Nyberg L (2020) Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE epsilon4 carriers. Alzheimers Dement (Amst) 12:e12110.

Gottlieb DJ, O'Connor GT, Wilk JB (2007) Genome-wide association of sleep and circadian phenotypes. BMC Med Genet 8 [Suppl 1]:S9.

Guggenheim JA, Williams C; UK Biobank Eye and Vision Consortium (2015) Role of educational exposure in the association between myopia and birth order. Jama Ophthalmol 133:1408–1414.

Hasegawa H, Selway R, Gnoni V, Beniczky S, Williams SCR, Kryger M, Ferini-Strambi L, Goadsby P, Leschziner GD, Ashkan K, Rosenzweig I (2020) The subcortical belly of sleep: new possibilities in neuromodulation of basal ganglia? Sleep Med Rev 52:101317.

Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, Hazen N, Herman J, Adams Hillard PJ, Katz ES, Kheirandish-Gozal L, Neubauer DN, O'Donnell AE, Ohayon M, Peever J, Rawding R, Sachdeva RC, Setters B, Vitiello MV, Ware JC (2015) National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health 1:233–243.

Horne J (2010) Sleepiness as a need for sleep: when is enough, enough? Neurosci Biobehav Rev 34:108–118.

Horne J (2011) The end of sleep: 'sleep debt' versus biological adaptation of human sleep to waking needs. Biol Psychol 87:1–14.

Horne JA, Wilkinson S (1985) Chronic sleep reduction: daytime vigilance performance and EEG measures of sleepiness, with particular reference to "practice" effects. Psychophysiology 22:69–78.

Jean-Louis G, Grandner MA, Seixas AA (2022) Social determinants and health disparities affecting sleep. Lancet Neurol 21:864–865.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.

Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) FSL. Neuroimage 62:782–790.

Jones SE, et al. (2019) Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. Nat Commun 10:1585.

Jovicich J, et al. (2013) Brain morphometry reproducibility in multi-center 3T MRI studies: a comparison of cross-sectional and longitudinal segmentations. Neuroimage 83:472–484.

Killgore WD (2010) Effects of sleep deprivation on cognition. Prog Brain Res 185:105–129.

Kocevska D, Barclay NL, Bramer WM, Gehrman PR, Van Someren EJW (2021a) Heritability of sleep duration and quality: a systematic review and meta-analysis. Sleep Med Rev 59:101448.

Kocevska D, et al. (2021b) Sleep characteristics across the lifespan in 1.1 million people from The Netherlands, United Kingdom and United States: a systematic review and meta-analysis. Nat Hum Behav 5:113–122.

Landolt HP (2011) Genetic determination of sleep EEG profiles in healthy humans. Prog Brain Res 193:51–61.

Lane JM, Liang J, Vlasac I, Anderson SG, Bechtold DA, Bowden J, Emsley R, Gill S, Little MA, Luik AI, Loudon A, Scheer FA, Purcell SM, Kyle SD, Lawlor DA, Zhu X, Redline S, Ray DW, Rutter MK, Saxena R (2017) Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. Nat Genet 49:274–281.

Linkowski P (1999) EEG sleep patterns in twins. J Sleep Res 8 [Suppl 1]:11–13.

Liu C, Kong XZ, Liu X, Zhou R, Wu B (2014) Long-term total sleep deprivation reduces thalamic gray matter volume in healthy men. Neuroreport 25:320–323.

Lowe CJ, Safati A, Hall PA (2017) The neurocognitive consequences of sleep restriction: a meta-analytic review. Neurosci Biobehav Rev 80:586–604.

Madrid-Valero JJ, Rubio-Aparicio M, Gregory AM, Sánchez-Meca J, Ordoñana JR (2020) Twin studies of subjective sleep quality and sleep duration, and their behavioral correlates: systematic review and meta-analysis of heritability estimates. Neurosci Biobehav Rev 109:78–89.

Mander BA, Winer JR, Walker MP (2017) Sleep and human aging. Neuron 94:19–36.

Miller KL, et al. (2016) Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci 19:1523–1536.

Mullaney DJ, Johnson LC, Naitoh JP, Friedmann JK, Globus GG (1977) Sleep during and after gradual sleep reduction. Psychophysiology 14:237–244.

Nelson H, Willison J (1991) The National Adult Reading Test (NART). Windsor: NFER-Nelson.

Nilsson LG, Bäckman L, Erngrund K, Nyberg L, Adolfsson R, Bucht G, Karlsson S, Widing M, Winblad B (1997) The Betula prospective cohort study: memory, health, and aging. Aging Neuropsychol Cogn 4:1–32.

Nordin M, Åkerstedt T, Nordin S (2013) Psychometric evaluation and normative data for the Karolinska Sleep Questionnaire. Sleep Biol Rhythms 11:216–226.

Nyberg L, Boraxbekk CJ, Sörman DE, Hansson P, Herlitz A, Kauppi K, Ljungberg JK, Lövheim H, Lundquist A, Adolfsson AN, Oudin A, Pudas S, Rönnlund M, Stiernstedt M, Sundström A, Adolfsson R (2020) Biological and environmental predictors of heterogeneity in neurocognitive ageing: evidence from Betula and other longitudinal studies. Ageing Res Rev 64:101184.

Nyberg L, et al. (2023) Individual differences in brain aging: heterogeneity in cortico-hippocampal but not caudate atrophy rates. Cereb Cortex 33:5075–5081.

Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF, Rosen CL, Troester MM, Wise MS (2016) Consensus statement of the American Academy of Sleep Medicine on the recommended amount of sleep for healthy children: methodology and discussion. J Clin Sleep Med 12:1549–1561.

Perez-Carbonell L, Mignot E, Leschziner G, Dauvilliers Y (2022) Understanding and approaching excessive daytime sleepiness. Lancet 400:1033–1046.

R Core Team (2020) R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing. Available at: https://www.R-project.org/.

Reuter M, Schmansky NJ, Rosas HD, Fischl B (2012) Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61:1402–1418.

Roehrs T, Shore E, Papineau K, Rosenthal L, Roth T (1996) A two-week sleep extension in sleepy normals. Sleep 19:576–582.

Saletin JM, Goldstein-Piekarski AN, Greer SM, Stark S, Stark CE, Walker MP (2016) Human hippocampal structure: a novel biomarker predicting mnemonic vulnerability to, and recovery from, sleep deprivation. J Neurosci 36:2355–2363.

Sexton CE, Zsoldos E, Filippini N, Griffanti L, Winkler A, Mahmood A, Allan CL, Topiwala A, Kyle SD, Spiegelhalder K, Singh-Manoux A, Kivimaki M, Mackay CE, Johansen-Berg H, Ebmeier KP (2017) Associations between self-reported sleep quality and white matter in community-dwelling older adults: a prospective cohort study. Hum Brain Mapp 38:5465–5473.

Shafto MA, Tyler LK, Dixon M, Taylor JR, Rowe JB, Cusack R, Calder AJ, Marslen-Wilson WD, Duncan J, Dalgleish T, Henson RN, Brayne C, Matthews FE; Cam-CAN (2014) The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study protocol: a cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing. BMC Neurol 14:204.

Siegel JM (2022) Sleep function: an evolutionary perspective. Lancet Neurol 21:937–946.

Sørensen O, Walhovd KB, Fjell AM (2021) A recipe for accurate estimation of lifespan brain trajectories, distinguishing longitudinal and cohort effects. Neuroimage 226:117596.

Spira AP, Gonzalez CE, Venkatraman VK, Wu MN, Pacheco J, Simonsick EM, Ferrucci L, Resnick SM (2016) Sleep duration and subsequent cortical thinning in cognitively normal older adults. Sleep 39:1121–1128.

Tsiknia AA, Parada H Jr, Banks SJ, Reas ET (2023) Sleep quality and sleep duration predict brain microstructure among community-dwelling older adults. Neurobiol Aging 125:90–97.

Tucker AM, Dinges DF, Van Dongen HP (2007) Trait interindividual differences in the sleep physiology of healthy young adults. J Sleep Res 16:170–180.

Vallat R, Berry SE, Tsereteli N, Capdevila J, Khatib HA, Valdes AM, Delahanty LM, Drew DA, Chan AT, Wolf J, Franks PW, Spector TD, Walker MP (2022) How people wake up is associated with previous night's sleep together with physical activity and food intake. Nat Commun 13:7116.

Van Dongen HP, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26:117–126.

Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K; WU-Minn HCP Consortium (2013) The WU-Minn Human Connectome Project: an overview. Neuroimage 80:62–79.

van Hees VT, Fang Z, Langford J, Assah F, Mohammad A, da Silva IC, Trenell MI, White T, Wareham NJ, Brage S (2014) Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. J Appl Physiol (1985) 117:738–744.

van Hees VT, Sabia S, Anderson KN, Denton SJ, Oliver J, Catt M, Abell JG, Kivimäki M, Trenell MI, Singh-Manoux A (2015) A novel, open access method to assess sleep duration using a wrist-worn accelerometer. PLoS One 10:e0142533.

van Hees V, Fang Z, Zhao J, Heywood J, Mirkes E, Sabia S, Migueles J (2022) GGIR: raw accelerometer data analysis. R package version 2.8-2.

Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A (2009) Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep 32:491–497.

Viechtbauer W (2010) Conducting meta-analyses in R with the metafor package. J Stat Soft 36:1–48.

Voldsbekk I, Groote I, Zak N, Roelfs D, Geier O, Due-Tønnessen P, Løkken LL, Strømstad M, Blakstvedt TY, Kuiper YS, Elvsåshagen T, Westlye LT, Bjørnerud A, Maximov II (2021) Sleep and sleep deprivation differentially alter white matter microstructure: a mixed model design utilising advanced diffusion modelling. Neuroimage 226:117540.

Walhovd KB, et al. (2016) Neurodevelopmental origins of lifespan changes in brain and cognition. Proc Natl Acad Sci U S A 113:9357–9362.

Walhovd KB, Fjell AM, Westerhausen R, Nyberg L, Ebmeier KP, Lindenberger U, Bartrés-Faz D, Baaré WFC, Siebner HR, Henson R, Drevon CA, Strømstad Knudsen GP, Ljøsne IB, Penninx BWJH, Ghisletta P, Rogeberg O, Tyler L, Bertram L; Consortium Lifebrain (2018) Healthy minds 0-100 years: optimising the use of European brain imaging cohorts ("Lifebrain"). Eur Psychiatry 50:47–56.

Walhovd KB, et al. (2022) Education and income show heterogeneous relationships to lifespan brain and cognitive differences across European and US cohorts. Cereb Cortex 32:839–854.

Wang H, et al. (2019) Genome-wide association analysis of self-reported daytime sleepiness identifies 42 loci that suggest biological subtypes. Nat Commun 10:3503.

Watson NF, Goldberg J, Arguelles L, Buchwald D (2006) Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. Sleep 29:645–649.

Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA, Kushida C, Malhotra RK, Martin JL, Patel SR, Quan SF, Tasali E (2015) Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep 38:843–844.

Wechsler D (1997) Wechsler adult intelligence scale (WAIS-III): administration and scoring manual, Ed 3. San Antonio: The Psychological Corporation.

Wechsler D (1999) Wchsler abbreviated scale of intelligence. San Antonio: The Psychological Corporation.

Westerlund A, Brandt L, Harlid R, Åkerstedt T, Lagerros YT (2014) Using the Karolinska Sleep Questionnaire to identify obstructive sleep apnea syndrome in a sleep clinic population. Clin Respir J 8:444–454.

Wood SN (2017) Generalized additive models: an introduction with R, Ed 2. Boca Raton: Chapman and Hall/CRC.

Wood SN, Scheipl F (2020) 'gamm4': generalized additive mixed models using 'mgcv' and 'lme4'. R package version 0.2-6. Available at: https://CRAN.R-project.org/package=gamm4.

Wrzus C, Brandmaier AM, von Oertzen T, Müller V, Wagner GG, Riediger M (2012) A new approach for assessing sleep duration and postures from ambulatory accelerometry. PLoS One 7:e48089.

Youngstedt SD, Kline CE, Zielinski MR, Kripke DF, Devlin TM, Bogan RK, Wilcox S, Hardin JW (2009) Tolerance of chronic 90-minute time-in-bed restriction in older long sleepers. Sleep 32:1467–1479.

Zamore Z, Veasey SC (2022) Neural consequences of chronic sleep disruption. Trends Neurosci 45:678–691.