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Complete List of Authors:	Gadie, Andrew; MRC Cognition and Brain Sciences Unit Shafto, Meredith; University of Cambridge, Center for Speech, Language and the Brain Leng, Yue; University of Cambridge; University of California San Francisco, School of Medicine Cam-CAN, _; University of Cambridge, Center for Sleep, language and the brain Kievit, Rogier; MRC CBSU
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Age-related differences in self-reported sleep quality predict healthy ageing across multiple domains: a multi-modal cohort of 2406 adults

Andrew Gadié¹

Meredith Shafto²

Yue Leng³

Cam-CAN⁴

Rogier A. Kievit^{1*}

*Corresponding author: rogier.kievit@mrc-cbu.cam.ac.uk

1 MRC Cognition and Brain Sciences Unit, 15 Chaucer Rd, Cambridge, CB2 7EF, United Kingdom

2 Department of Psychology, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom

3 University of California, San Francisco

4 Cambridge Centre for Ageing and Neuroscience (Cam-CAN), University of Cambridge and MRC Cognition and Brain Sciences Unit, Cambridge, UK, www.cam-can.com

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2
3 13 Abstract

4
5 14 **Objectives** To examine lifespan changes in self-reported sleep quality and their associations
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7 15 with health outcomes across four domains: Physical Health, Cognitive Health, Mental Health and
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9 16 Neural Health.

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11 17 **Setting** Cam-CAN is a cohort study in East Anglia/England, which collected self-reported
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13 18 health and lifestyle questions as well as a range of objective measures from healthy adults.

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15 19 **Participants** 2406 healthy adults (age 18-98) answered questions about their sleep quality
16
17 20 (Pittsburgh Sleep Quality Index) and measures of Physical, Cognitive, Mental, and Neural Health. A
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19 21 subset of 641 individuals provided measures of brain structure.

20
21 22 **Main outcome measures** Pittsburgh Sleep Quality Index scores (PSQI) of sleep, and scores
22
23 23 across tests within the four domains of health. Latent Class Analysis (LCA) is used to identify sleep
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25 24 types across the lifespan. Bayesian regressions quantify the presence, and absence, of relationships
26
27 25 between sleep quality and health measures.

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29 30 **Results** LCA identified four sleep types: 'Good sleepers' (68.1%, most frequent in middle
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31 31 age), 'inefficient sleepers' (14.01%, most frequent in old age), 'Delayed sleepers' (9.28%, most
32
33 32 frequent in young adults) and 'poor sleepers' (8.5%, most frequent in old age). Better sleep is
34
35 28 generally associated with better health outcomes, strongly so for mental health, moderately for
36
37 29 cognitive and physical health, but not for sleep quality and neural health. There is little evidence for
38
39 30 interactions between sleep quality and age on health outcomes.

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41 42 **Conclusions** Lifespan changes in sleep quality are multifaceted and not captured well by
42
43 43 summary measures, but instead as partially independent symptoms that vary in prevalence across
44
45 44 the lifespan. Better self-reported sleep is associated with better health outcomes, and the strength
46
47 45 of these associations differs across health domains. Notably, observed absence of associations
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49 46 between sleep quality and white matter suggests that previous associations may depend on clinical
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51 47 samples with pathological sleep deficiencies and may not generalise to healthy cohorts.
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4
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6
7 40 Medical Research Council (MC-A060-5PR61).
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11 42 **Keywords**

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14 43 Ageing, sleep quality, healthy ageing, cognition, mental health, cognition, white matter, physical
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16 44 health
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20 46 **Strengths and limitations of this study**

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22 47 • Broad phenotypic assessment of healthy ageing across multiple health domains
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24 48 • Advanced analytic techniques (i.e. Latent Class Analysis regression) allows new insights
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26 49 • Uniquely large neuroimaging sample combined with Bayesian inference allows for
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28 50 quantification of evidence for the null hypothesis
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31 51 • Subjective sleep measures may have drawbacks in older samples
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33 52 • Cross-sectional data precludes modelling of within subject changes
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3 54 **BACKGROUND**
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5 55 Sleep is a fundamental human behaviour, with humans spending almost a third of their lives asleep.
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7 56 Regular and sufficient sleep has been shown to benefit human physiology through a number of
8
9 57 different routes, ranging from consolidation of memories (1) to removal of free radicals (2) and
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11 58 neurotoxic waste (3). Sleep patterns are known to change across the lifespan in various ways,
12
13 59 including decreases in quantity and quality of sleep (4), changes in the alignment of homeostatic and
14
15 60 circadian rhythms (5), decreases in sleep efficiency (6) the amount of slow-wave sleep, and an
16
17 61 increase in daytime napping(7). Importantly, interruption and loss of sleep has been shown to have
18
19 62 wide ranging adverse effects on health (8), leaving open the possibility that age-related changes in
20
21 63 sleep patterns and quality may contribute to well-documented age-related declines in various health
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23 64 domains.
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27 65 In the current study, we examine self-reported sleep habits in a large, population-based
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29 66 cohort Cambridge Centre for Ageing and Neuroscience (Cam-CAN, (9)). We relate sleep measures to
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31 67 measures of health across four health domains: cognitive, brain health, physical and mental health.
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33 68 Our goal is to quantify and compare the associations between typical age-related changes in sleep
34
35 69 quality and a range of measures of health measures that commonly decline in later life. We assess
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37 70 sleep using a self-reported measure of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) (10).
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39 71 The PSQI has good psychometric properties (11) and has been shown to correlate reliably with
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41 72 diseases of aging and mortality (12–14). Although actigraphy (measuring sleep quality in the lab) is
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43 73 commonly considered the gold standard of sleep quality measurement, it is often prohibitively
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45 74 challenging to employ in large samples. A recent direct comparison of sleep measures (15) suggests
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47 75 that although subjective sleep measures (such as PSQI) may have certain drawbacks in older
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49 76 samples, they also capture complementary aspects of sleep quality not fully captured by actigraphy.
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51 77 Moreover, collecting self-report sleep quality data in a large, deeply phenotyped cohort offers
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53 78 several additional benefits.
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3 79 First, previous work on the effects of sleep has tended to focus on the pathological extremes
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5 80 of sleep problems (16), leaving open the question whether these findings generalise to how non-
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7 81 pathological differences in sleep quality affect health outcomes in non-clinical samples. Second,
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9 82 smaller studies often focus on specific health outcomes such as metabolism (17) or cognition (18). By
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11 83 instead studying a range of health outcomes in the same population, we can compare and contrast
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13 84 the associations between sleep quality and health domains in multiple domains.

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16 85 We will focus on three questions within each health domain: First, is there a relationship
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18 86 between sleep quality and health? Second, does the strength and nature of this relationship change
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20 87 when age is included as a covariate? Third, does the strength and nature of the relationship change
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22 88 across the lifespan? We will examine these questions across each of the four health domains.
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26 27 90 **METHODS**

28 29 91 **Sample**

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31 92 Participants were recruited as part of the population-based Cambridge Centre for Ageing and
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33 93 Neuroscience (Cam-CAN) cohort (www.cam-can.com). For details of the project protocol see (19)
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35 94 and (20), and for further details of the Cam-CAN dataset visit [http://www.mrc-](http://www.mrc-cbu.cam.ac.uk/datasets/camcan/)
36
37 95 [cbu.cam.ac.uk/datasets/camcan/](http://www.mrc-cbu.cam.ac.uk/datasets/camcan/). A further subset participated in a neuroimaging session (20).
38
39 96 Participants included were native English speakers, had normal or corrected to normal vision and
40
41 97 hearing, and scored 25 or higher on the mini mental state exam (MMSE; Folstein, Folstein, &
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43 98 McHugh, 1975). Ethical approval for the study was obtained from the Cambridgeshire 2 (now East of
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45 99 England- Cambridge Central) Research Ethics Committee (reference: 10/H0308/50). Participants
46
47 100 gave written informed consent. The raw data and analysis code are available upon signing a data
48
49 101 sharing request form (see <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/> for more detail).
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3 105 **Variables**

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5 106 *Sleep Measures*

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7 107 Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a well-validated
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9 108 self-report questionnaire (10,15) designed to assist in the diagnosis of sleep disorders. The questions
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11 109 concern sleep patterns, habits, and lifestyle questions, grouped into seven components, each
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13 110 yielding a score ranging from 0 (good sleep/no problems) to 3 (poor sleep/severe problems), that
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15 111 are commonly summed to a PSQI Total score ranging between 0 and 21, with higher scores
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17 112 reflecting poorer sleep quality.

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20 113 **Health Measures**

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22 114 *Cognitive health.* A number of studies have found associations between poor sleep and
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24 115 cognitive decline, including in elderly populations. Poor sleep affects cognitive abilities such as
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26 116 executive functions (e.g. 22) and learning and memory processes (23), whereas short term
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28 117 pharmaceutical interventions such as administration of melatonin improve both sleep quality and
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30 118 cognitive performance. Scullin & Bliwise (2015, p. 97) conclude that “maintaining good sleep quality,
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32 119 at least in young adulthood and middle age, promotes better cognitive functioning and serves to
33
34 120 protect against age-related cognitive declines”. As sleep may affect various aspects of cognition
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36 121 differently (18), we include measures that cover a range of cognitive domains including memory,
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38 122 reasoning, response speed, and verbal fluency, as well as including a measure of general cognition
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40 123 (See Table 1 and (19) for more details).

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43 124 *Neural health.* Previous research suggests that individuals with a severe disruption of sleep
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45 125 are significantly more likely to exhibit signs of poor neural health (25,26). Specifically, previous
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47 126 studies have observed decreased white matter health in clinical populations suffering from
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49 127 conditions such as chronic insomnia (16), obstructive sleep apnoea (27,28), excessively long sleep in
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51 128 patients with diabetes (29), and REM Sleep Behaviour Disorder (30). Many of these studies focus on
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53 129 white matter hyperintensities (WMH), a measure of the total volume or number of (regions)
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55 130 showing low-level neural pathology (although some study grey matter, e.g. Alena et al., 2010;
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3 131 Macey et al., 2002). White matter hyperintensities are often used as a clinical marker, as longitudinal
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5 132 increases in WMHs are associated with increased risk of stroke, dementia and death (32) and are
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7 133 more prevalent in patients with pathological sleep problems (28,29). However, use of this metric in
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9 134 clinical cohorts largely leaves open the question of the impact of sleep quality on neural (white
10
11 135 matter) health in non-clinical, healthy populations. To address this question, we use a more general
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13 136 indicator of white matter neural health; *Fractional Anisotropy* (FA). FA is associated with white
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15 137 matter integrity and myelination (see Mädler, Drabycz, Kolind, Whittall, & MacKay, 2008, for more
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17 138 discussion on the interpretation of FA). We use FA as recent evidence (34) suggests that WMHs
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19 139 represent the extremes (foci) of white matter damage, and that FA is able to capture the full
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21 140 continuum of white matter integrity. For more information regarding the precise white matter
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23 141 pipeline, see (35)

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27 142 *Physical health.* Sleep quality is also an important marker for physical health, with poorer
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29 143 sleep being associated with conditions such as obesity, diabetes mellitus (17), overall health (8,36)
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31 144 and increased all-cause mortality (37,38). We focus on a set of variables that capture three types of
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33 145 health domains commonly associated with poor sleep: Cardiovascular health measured by pulse,
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35 146 systolic and diastolic blood pressure (39), self-reported health, both in general and for the past 12
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37 147 months, (e.g. Strine & Chapman, 2005) and body-mass index (e.g. Taheri, Lin, Austin, Young, &
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39 148 Mignot, 2004).

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42 149 *Mental health.* Previous work has found that disruptions of sleep quality are a central
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44 150 symptom of forms of psychopathology such as Major Depressive Disorder, including both
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46 151 hypersomnia and insomnia (36,42), and episodes of insomnia earlier greatly increased the risk of
47
48 152 later episodes of major depression (43). Kaneita et al., (2006) found a U-shaped association between
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50 153 sleep and depression, such that individuals regularly sleeping less than 6, or more than 8, hours were
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52 154 more likely to be depressed. Both depression (e.g. Fried & Nesse, 2015) and anxiety (46,47) are
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54 155 commonly associated with sleep problems. To capture these dimensions we used both scales of the
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3 156 Hospital Anxiety and Depression Scale (HADS) (48), a widely used and standardized questionnaire
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5 157 that captures self-reported frequency and intensity of anxiety and depression symptoms.
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182 **Table 1.** Description of health variables across each of four domains (cognitive, neural, physical,
 183 mental). For each variable details are given including a description of the task it is derived from,
 184 relevant citations, a brief definition and descriptive statistics.

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Health domain	Task and Description	Variable	Descriptives	Citation
Cognitive	Story Recall Immediate: Participants hear a short story and are asked to recall as accurately as possible.	Recall manually scored for similarity and precision (min=0, max=24)	M=13.14, SD=4.66, Range=(0-24)	(49)
Cognitive	Story Recall Delayed: Same as above but recall after 30 minute delay	Recall manually scored for similarity and precision (min=0, max=24)	M=11.47, SD=4.92, Range=(0-24)	(49)
Cognitive	Letter Fluency (phonemic fluency): Participants have one minute to generate as many words as possible beginning with the letter 'p'.	Total words generated (min=0,max=30)	M=25.38, SD=3.96, Range=(0-30)	(49)
Cognitive	Animal Fluency (semantic fluency): Participants have one minute to generate as many words as possible in the category 'animals'.	Total words generated (min=0,max=30)	M=25.85, SD=4.47, Range=(0-30)	(49)
Cognitive	Cattell Culture Fair: Test of fluid reasoning using four subtests (series completions, odd-one-out, matrices and topology)	Total correct summed across four subtests. Min=0, max=46	M=31.8, SD=6.79, Range=(11-44)	(50)
Cognitive	Simple reaction time: Speed in a simple reaction time task	1/response time in seconds	M=0.37, SD=0.08, Range=(0.24-0.93)	(9)
Cognitive	Addenbrookes Cognitive Examination, Revised: Screening test for dementia using seven subtests (orientation, attention and concentration, memory, fluency, language, visuospatial abilities, perceptual abilities)	Performance on multiple tests converted to min=0, max=100 range	M=89.25, SD=13.4, Range=(0-100)	(51)
Neural	White matter health: Measure of tract integrity using fractional anisotropy	Fractional Anisotropy (min=0, max=1, averaged across 10 tracts)	M=0.5, SD=0.03, Range=(0.3-0.56)	(52)
Physical	Self-reported Health, in general: Participants use a 4-point scale to respond to the prompt "Would you say for someone of your age, your own health in	Score from 1 = Excellent to 4= Poor	M=2.02, SD=0.79, Range=(1-3)	(53)

	general is..."			
Physical	Self-reported Health, last 12 months: Participants use a 3-point scale to respond to the prompt "Over the last twelve months would you say your health has on the whole been..."	Score from 1 = Good to 3= Poor	M=1.46, SD=0.71, Range=(1-3)	(53)
Physical	Systolic blood pressure	Mean systolic blood pressure in mmHg, averaged across three consecutive measurements	M=120.11, SD=17, Range=(78.5-186)	
Physical	Diastolic blood pressure	Mean diastolic blood pressure in mmHg, averaged across three consecutive measurements	M=73.14, SD=10.48, Range=(49-115.5)	
Physical	Resting pulse	Mean pulse in beats per minute, averaged across three consecutive measurements	M=65.69, SD=10.5, Range=(40-110.5)	
Physical	Body Mass Index (BMI)	(weight in kg) / (height in m) ²	M=25.77, SD=4.59, Range=(16.75-48.32)	(54)
Mental health	Anxiety Subscale (Hospital Anxiety and Depression Scale (HADS)): Participants response to seven questions about anxiety-related behaviours	Seven questions rated on 0 to 3 scale ('Often' to 'Very seldom'). Min=0, Max=21	M=5.17, SD=3.4, Range=(0-19)	(48)
Mental health	Depression Subscale (Hospital Anxiety and Depression Scale (HADS)): Participants response to seven questions about depression-related behaviours	Seven questions rated on 0 to 3 scale ('Often' to 'Very seldom'). Min=0, Max=21	M=3.32, SD=2.91, Range=(0-14)	

STATISTICAL ANALYSES

We examine whether self-reported sleep patterns change across the lifespan, both for the PSQI sum score and for each of the seven PSQI components. We then examine the relationships between the sleep quality and the four health domains in three ways: First, simple regression of the health outcome on sleep variables, to determine evidence for association between poor sleep quality and poor health outcomes. Second, we include age as a covariate. Finally, we include a (standard normal rescaled) continuous interaction term to examine whether there is evidence for a changing relationship between sleep and outcomes across the lifespan.

For all regressions we will use a default Bayesian approach advocated by Liang, Paulo, Molina, Clyde, & Berger, (2008); Rouder & Morey, (2012); Wagenmakers, (2007); Wei et al., (2012); Wetzels et al., (2011), which avoids several well-documented issues with p-values (57), allows for quantification of null effects, and decreases the risk of multiple comparison problems (e.g. Gelman, Hill, & Yajima, 2012). Bayesian regressions allows us to symmetrically quantify evidence in favour of, or against, some substantive model as compared to a baseline (e.g. null) model. This evidentiary strength is expressed as a Bayes Factor (see Jeffreys (61), which can be interpreted as the relative likelihood of one model versus another given the data and a certain prior expectation. A Bayes Factor of, e.g., 7, in favour of a regression model suggests that the data are seven times *more likely* under that model than an intercept only model (for an empirical comparison of p-values and Bayes factors, see Wetzels et al., 2011). A heuristic summary of evidentiary interpretation can be seen in Figure 1.

[insert Figure 1 here]

We report log Bayes Factors for large effects and regular Bayes Factors for smaller effects. To compute Bayes Factors we will use Default Bayes Factor approach for model selection (55,56) in the package BayesFactor (62) using the open source software package R (63). As previous papers report associations between sleep and outcomes ranging from absent to considerable in size we utilize the default, symmetric Cauchy prior with width $\frac{\sqrt{2}}{2}$ which translates to a 50% confidence that

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3 the true effect will lie between $-.707$ and $.707$. Prior to further analysis, scores on all outcomes were
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5 transformed to a standard normal distribution, and any scores exceeding a z-score of 4 or -4 were
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7 recoded as missing (aggregate percentage outliers across the four health domains: Cognitive, 0.41%,
8
9 Mental, 0.16%, Neural, 0.37% Physical, 0.031%).
10

11 To better elucidate individual differences in sleep quality we next use *Latent Class Analysis*
12 (64). This technique will allow us examine individual differences in sleep quality across the lifespan in
13
14 more detail than afforded by simple linear regressions: Rather than examining continuous variation
15
16 in sleep components, LCA classifies individuals into different *sleep types*, each associated with a
17
18 distinct profile of 'sleep symptoms'. If there are specific constellations of sleep problems across
19
20 individuals, we can quantify and visualize such sleep types. Moreover, by using Latent Class
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22 Regression, we can examine whether the likelihood of belonging to any sleep 'type' changes as a
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24 function of age. To analyse the data in this manner, we binarized the responses on each component
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26 into 'good' (0 or 1) or 'poor' (2 or 3).
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33 RESULTS

34 Age-related differences in sleep quality

35 First, we examined sleep changes across the lifespan by examining age-related differences in the
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37 PSQI sum score (N= 2178, M=5.16, SD=3.35, Range=0-19). Regressing the PSQI global score on age,
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39 (see Supplementary Figure 1) showed evidence for a positive relationship across the lifespan
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41 (logBF₁₀= 10.45). This suggests that on the whole, sleep quality decreases across the lifespan (note
42
43 that *higher* PSQI scores correspond to worse sleep). Although we observe strong statistical evidence
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45 for an age-related difference ('Extreme' according to Jeffreys, (1961)), age explained only 1.23 % of
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47 the variance in the PSQI Total score. Next, we examined each of the seven components on age in the
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49 same manner. In Supplementary Figure 2 we see that that age has varying and specific effects on
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51 different aspects of sleep quality, and did not worsen uniformly across the lifespan. For example, we
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53 observed moderate evidence that sleep latency did not change across the lifespan (Sleep Latency,
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3 $BF_{01} = 9.25$, in favour of the null), Sleep Quality showed no evidence for either change or stasis ($BF_{10} =$
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5 1.63) and one sleep component, Daytime Dysfunction, improved slightly across the lifespan ($BF_{10} =$
6
7 7.03). Medication). The strongest age-related decline is that of Efficiency, showing an R-squared of
8
9 6.6%.

10
11 Finally, we entered all seven components into a Bayesian multiple regression
12 simultaneously, to examine to what extent they could, together, predict age. The best model
13 included every component except Sleep Latency ($\log BF_{10} = 142.71$). Interestingly, this model
14 explained 13.41% of the variance in age, compared to 1.23% for the PSQI Total score, and 6.4% for
15 the strongest single component. This shows that lifespan changes in self-reported sleep are
16 heterogeneous and partially independent, and that specific patterns and components need to be
17 taken into account simultaneously to fully understand age-related differences in sleep quality. These
18 finding shows that neither the PSQI sum score nor the sleep components in isolation fully capture
19 differences in sleep quality across the lifespan.

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31 Next we examined evidence for distinct sleep types using Latent Class Analysis (64). We fit a
32 set of possible models (varying from 2 to 6 sleep types) We found that the four class solution gives
33 the best solution, according to the Bayesian Information Criterion (65) (BIC for 4 Classes = 11825.65,
34 lowest BIC for other solutions = 11884.92 (5 classes) (with 50 repetitions per class, at 5000 maximum
35 iterations). Next we inspected the nature of the sleep types, the prevalence of each 'sleep type' in
36 the population, and whether the likelihood of belonging to a certain sleep type changes across the
37 lifespan. See Figure 2 for the component profiles of the four sleep types identified.

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46 [insert Figure 2 here]

47
48 Class 1, 'Good sleepers', make up 68.1% of participants. Their sleep profile is shown in Figure
49 2A, top left, and is characterised by a low probability of responding 'poor' to any of the sleep
50 components. Class 2, 'inefficient sleepers', make up 14.01% of the participants, and are
51 characterized by poor sleep Efficiency: Members of this group uniformly (100%) report poor sleep
52 Efficiency, despite relatively low prevalence of other sleep problems, as seen in Figure 2A, top right.

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2
3 Class 3, 'Delayed Sleepers' seen in the bottom left of Figure 2a, makes up 9.28% of the participants:
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5 characterized by modestly poor sleep across the board, but a relatively high probability of poor
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7 scores on Sleep Latency (59%), Sleep Quality (51%) and sleep Disturbance (31%). Finally, Class 4,
8
9 'Poor sleepers', make up 8.5% of the participants, shown bottom right in Figure 2A. Their responses
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11 to any of the seven sleep components are likely to be 'poor' or 'very poor', almost universally so for
12
13 'sleep quality' (94%) and 'Sleep Efficiency' (97.7%).
14

15
16 Next, we including age as a covariate (simultaneously including a covariate is known as
17
18 *latent class regression* or concomitant-variable latent class models (66). This analysis, visualised in
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20 Figure 2b, shows that the probability of membership of each classes compared to the reference class
21
22 (good sleepers) changes significantly across the lifespan for each of the classes (Class 2 versus class
23
24 1: beta/SE= 0.05/0.00681, t=7.611, Class 3 versus class 1: beta/SE= -0.01948/0.0055, t=-3.54), Class 4
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26 versus class 1: beta/SE 0.01269/0.00478, t=2.655, for more details on generalized logit coefficients ,
27
28 see Linzer & Lewis, 2011, p. 21). The frequency of Class 1 (Good sleepers) peaks in middle to late
29
30 adulthood, dropping increasingly quickly after age 50. Class 2 (Inefficient sleepers) are relatively rare
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32 in younger individuals, but the prevalence increases rapidly in individuals over age 50. On the other
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34 hand, Class 3 (Delayed sleepers) shows a steady decrease in the probability of an individual showing
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36 this profile across the lifespan, suggesting that this specific pattern of poor sleep is more commonly
37
38 associated with younger adults. Finally, the proportion of Class 4 (poor sleepers) members increases
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40 only slightly across the lifespan. Together, the latent class analysis provides additional evidence that
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42 the PSQI sum score as an indicator of sleep quality does not fully capture the subtleties of age-
43
44 related differences. Age-related changes in sleep patterns are characterized by specific, clustered
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46 patterns of sleep problems that cannot be adequately characterized by summation of the
47
48 component scores. The above analyses show how both a summary measure and individual measures
49
50 of sleep quality change across the lifespan. Next, we examined the relationships between sleep
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52 quality measures (seven components and the global PSQI score) and health variables (specific
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54 variables across four domains, as shown in Table 1).
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Sleep, health domains and age

Cognitive health

First, we examined the relationships between sleep quality and seven measures of cognitive health (see Table 1 for details). As can be seen in Figure 3, several relationships exist between measures of cognitive health and measures of sleep quality. We visualise these results using a tile plot (68), as shown in Figure 3.

[Insert Figure 3 here]

Each cell shows the numeric effect size (R-squared, 0-100) of the bivariate association between a sleep component and a health outcome, colour coded by the statistical evidence for a relationship using the Bayes Factor. If the parameter estimate is positive, the r-squared value has the symbol '+' added (note the interpretation depends on the nature of the variable, cf. Table 1). The strongest associations were found for poorer Total Sleep, poorer sleep Efficiency and use of Sleep Medication, all associated with poorer performance on cognitive tests. The cognitive abilities most strongly associated with poor sleep are immediate and delayed memory, fluid reasoning and a measure of general cognitive health, ACE-R. Two patterns emerged: First, the strongest predictor across the simple and multiple regressions was for the PSQI Total score. Tentatively this suggests that a cumulative index of sleep problems, rather than any specific pattern of poor sleep, is the biggest risk factor for poorer cognitive performance. Secondly, after controlling for age, the most strongly affected cognitive measure is phonemic fluency, the ability to generate name as many different words as possible starting with a given letter within a minute. Verbal fluency is commonly used as a neuropsychological test (e.g. Miller, 1984). Previous work suggests it depends on both the ability to cluster (generating words within a semantic cluster) and to switch (switching between categories), and is especially vulnerable to frontal lobe damage. Although modest in size, our findings suggest this task, dependent on multiple executive processes, is particularly affected by poor sleep quality (70). The second strongest association was with the ACE-R, a general cognitive test battery

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2
3 similar in style and content to the MMSE. The associations with cognition were slightly attenuated
4
5 when age was included as a covariate (Supplementary Figure 3) but the basic effects remained.
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8 When an interaction term with age was included, no evidence for interactions with age were
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10 observed (mean $\log BF_{10} = -2.08$, see Supplementary Figure 4), suggesting that the negative
11
12 associations between sleep and cognitive performance are a constant feature across the lifespan,
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14 rather than specifically in elderly individuals. Together this suggests that poor sleep quality is
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16 modestly and consistently associated with poorer general cognitive performance across the lifespan,
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18 most strongly with semantic fluency.
19

20 21 22 *Neural Health*

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24 Using Diffusion Tensor Imaging, we estimated a general index of white matter integrity in 10 tracts
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26 (52) (shown in Supplementary Figure 5), by taking the average Fractional Anisotropy in each white
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28 matter ROI (see (71) for more information). We use the data from a subsample of 641 individuals
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30 (age $M = 54.87$, range 18.48-88.96) who were scanned in a 3T MRI scanner (for more details regarding
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32 the pipeline, sequence and processing steps, see (71)). Regressing neural WM ROI's on sleep quality,
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34 we find several small effects, with the strongest associations between sleep efficiency and neural
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36 health (see Supplementary Figure 6). All effects are such that poorer sleep is associated with poorer
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38 neural health, apart from a small effect in the opposite direction for Uncinate and Daytime
39
40 Dysfunction ($BF_{10} = 6.20$). However, when age is included as a covariate, the negative associations
41
42 between sleep quality and white matter health are attenuated virtually to zero (Figure 4,
43
44 mean/median $BF_{10} = 0.18/.10$), with Bayes Factors providing strong evidence for the lack of
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46 associations between sleep quality and white matter integrity. One exception was observed: The use
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48 of Sleep Medication is associated with *better* neural health in the corticospinal tract, a region
49
50 previously found to be affected by pathological sleep problems such as sleep apnoea (28). However,
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52 this effect is very small ($BF_{10} = 3.24$) given the magnitude of the sample and the range of comparisons,
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54 so should be interpreted with caution.
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[Insert Figure 4 here]

Finally, we tested for any interactions by including a mean-scaled interaction term (sleep*age, Supplementary Figure 7). This analysis found evidence for a significant interaction, between the Superior Longitudinal Fasciculus (SLF) and Sleep Medication ($BF_{10}=13.77$), such that better neural health in the SLF was associated with the use of Sleep Medication more strongly in older adults. Together, these findings suggest that in general, once age is taken into account, self-reported sleep problems in a non-clinical sample are *not* associated with poorer neural health, although there is some evidence for a modest associations between better neural health in specific tracts and the use of sleep medication in the elderly.

Physical health

Next we examined whether sleep quality is associated with physical health. Figure 5 shows the simple regressions between sleep quality and physical health. Strong associations were found between poor overall sleep (PSQI sum score) and poor self-reported health, both in general ($\log BF_{10}=77.51$) and even more strongly for health in the past 12 months ($\log BF_{10}=91.25$). This may be because poorer sleep, across all components, directly affects general physical health (Briones et al., 1996; Spiegel et al., 2009) or because people subjectively experience sleep quality as a fundamental part of overall general health. A second association was between BMI and poor sleep quality, most strongly poor Duration ($\log BF_{10}=4.69$).

[Insert Figure 5 here]

This not only replicates previous findings but is in line with an increasing body of evidence that suggests that shorted sleep duration causes metabolic changes, which in turn increases the risk of both diabetes mellitus and obesity (17,73,74). Next, we examined whether these effects were attenuated once age was included. We show that although the relationships are slightly weaker, the overall pattern remains (Supplementary Figure 8), suggesting these associations are not merely co-

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3 occurrences across the lifespan. Our findings suggest self-reported sleep quality, especially sleep
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5 Duration, is related to differences in physical health outcomes in a healthy sample.
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7 Finally, there was evidence of a single interaction with age (Supplementary Figure 9):

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9 Although poor sleep Duration was associated with *higher* diastolic blood pressure in younger adults,
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11 it was associated with *lower* diastolic blood pressure in older individuals ($BF_{10} = 8.53$). This may
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13 reflect the fact that diastolic blood pressure is related to cardiovascular health in a different way
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15 across the lifespan, although given the small effect size it should be interpreted with caution.
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18 19 20 *Mental health*

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22 Finally, we examined the relationship between sleep quality and mental health, as measured by the
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24 Hospital Anxiety and Depression Scale (48). One benefit of the HADS in this context is that, unlike
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26 some other definitions (e.g. the DSM-V), sleep quality is not an integral (scored) symptom of these
27
28 dimensions. As shown in Supplementary Figure 10, there are very strong relationships between all
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30 aspects of sleep quality and measures of both anxiety and depression. The strongest predictors of
31
32 Depression are Daytime Dysfunction ($\log BF_{10} = 245.9$, $R^2 = 20.9\%$), followed by the overall sleep
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34 score ($\log BF_{10} = 170.5$, $R^2 = 14.6\%$) and sleep quality ($\log BF_{10} = 106.8$, $R^2 = 9.7\%$). The effects size for
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36 Anxiety was comparable but slightly smaller in magnitude. When age is included as a covariate the
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38 relationships remained virtually unchanged (Supplementary Figure 11), suggesting these
39
40 relationships are present throughout across the lifespan. These findings replicate and extend
41
42 previous work, suggesting that sleep quality is strongly associated with both anxiety and depression
43
44 across the lifespan.
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48 Finally we examined a model with an interaction term (Supplementary Figure 12). Most
49
50 prominently we found interactions with age in the relationship between HADS depression and the
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52 PSQI Total, and in the relationship between HADS depression and Sleep Duration, such that for the
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54 relationship between anxiety and overall sleep quality is stronger in younger adults ($BF_{10} = 9.91$, see
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3 Figure 6). Together our findings show that poor sleep quality is consistently, strongly and stably
4
5 associated with poorer mental health across the adult lifespan.
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7 [Insert Figure 6 here]
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10 11 **DISCUSSION**

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13 In this study, we report on the associations between age-related differences in sleep quality and
14 health outcomes in a large, age-heterogeneous sample of community dwelling adults of the
15 Cambridge Neuroscience and Aging (Cam-CAN) cohort. We find that sleep quality generally
16 decreases across the lifespan, most strongly for sleep Efficiency. However age-related changes in
17 sleep patterns are complex and multifaceted, so we used Latent Class Analysis to identify 'sleep
18 types' associated with specific sleep quality profiles. We found that Younger adults are more likely
19 than older adults to display a pattern of sleep problems characterised by poor sleep quality and
20 longer sleep latency, whereas older adults are more likely to display inefficient sleeping,
21 characterised by long periods spent in bed whilst not asleep. Moreover, the probability of being a
22 'good' sleeper, unaffected by any adverse sleep symptoms, decreases considerably after age fifty.
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35 Our broad phenotypic assessment allows for direct comparison of the different measures of
36 sleep quality and four key health domains We find strongest associations between sleep quality and
37 mental health, moderate relations between sleep quality and physical health and cognitive health
38 and sleep, virtually all such that poorer sleep is associated with poorer health outcomes. We did not
39 find evidence for associations between self-reported sleep and neural health. Notably, the
40 relationships we observe are mostly stable across the lifespan, affecting younger and older
41 individuals alike. A notable exception to these effects is the absence of any strong relation (after
42 controlling for age) between sleep quality and neural health as indexed by tract-based average
43 fractional anisotropy. Using a Bayesian framework we observed evidence in favour of the null
44 hypothesis, suggesting that the adverse effects of poor sleep on brain structure found in more
45 extreme clinical samples (e.g. insomnia, sleep apnoea) do not necessarily generalize to a non-clinical
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3 population for self-reported sleep. Notably, as we found strong relationships in the same sample
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5 between sleep and other outcomes (e.g. mental health, Figure 10) and there is previous evidence
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7 from this cohort linking white matter health and cognition, the absence of the relationship between
8
9 poor sleep and neural health cannot be (fully) explained away by the possible noisiness of self-report
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11 measures or white matter measures. For this reason, our study provides a potentially reassuring
12
13 message that for typically-ageing, healthy individuals, poorer self-reported sleep quality is not
14
15 associated with poorer brain health.
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18 While there are limitations of self-report measures including in older cohorts (15), including
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20 the fact that they likely reflect different aspects of sleep health than actigraphy (sleep in the lab), our
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22 results suggest there are considerable advantages in using self-reported sleep measures: first,
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24 obtaining sleep quality data in a large and broadly phenotyped sample is feasible; and second, our
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26 results demonstrated clear and consistent associations across multiple domains for both subjective
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28 (e.g. self-reported health) and objective measures (e.g. memory tests, BMI), which both replicate
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30 and extend previous lab-based sleep findings. Future work should ideally simultaneously measure
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32 actigraphy and self-report in large scale cohorts to fully capture the range of overlapping and
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34 complementary relations between different aspects of sleep quality and health outcomes (15).
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38 For both self-report and objective measures of sleep quality an open question is that of
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40 causality: Does poor sleep affect health outcomes, do health problems affect sleep, are they both
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42 markers of some third problem, or do causal influences go both ways? Most likely, all these patterns
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44 occur to varying degrees. Previous studies have shown that sleep quality causally affects health
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46 outcomes such as diabetes (17) and memory consolidation (1) while other evidence suggests that
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48 depression directly affect sleep quality (Lustberg & Reynolds, 2000; Sbarra & Allen, 2009) and that
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50 damage to neural structures may affect sleep regulation (77). Although our findings are in keeping
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52 with previous findings, our cross-sectional sample cannot tease apart the causal direction of the
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54 observed associations, more work remains to be done to disentangle these complex causal
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56 pathways.
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3 In our paper we focus on a healthy, age-heterogeneous community dwelling sample. This
4 allows us to study the associations between healthy aging and self-reported sleep quality, but comes
5 with two key limitations of the interpretations of our findings. First and foremost, our findings are
6 cross-sectional, not longitudinal. This means we can make inferences about age-related *differences*,
7 but not necessarily age-related *changes* (Raz & Lindenberger, 2011; Schaie, 1994). One reason why
8 cross-sectional and longitudinal estimates may diverge is that older adults can be thought of as
9 cohorts that differ from the younger adults in more ways than age alone. For example, our age range
10 includes individuals born in the twenties and thirties of the 20th century. Compared to someone
11 born in the 21st century, these individuals will likely have experience various differences during early
12 life development (e.g. less broadly accessible education, lower quality of healthcare, poorer
13 nutrition and similar patterns). For some of our measures, these are inherent limitations –*truly*
14 longitudinal study of neural aging is inherently impossible as scanner technology has not been
15 around sufficiently long. This means our findings likely reflect a combination of effects attributable
16 to age-related changes as well as baseline differences between subpopulations that may affect both
17 mean differences as well as developmental trajectories.

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Second, our sample reflects an atypical population in the sense that they are willing and able to visit the laboratory on multiple occasions for testing sessions. This subsample is likely a more healthy subset of the full population, which will mean the range of (poor) sleep quality as well as (poorer) health outcomes will likely be less extreme than in the full population. However, this challenge is not specific to our sample. In fact, as the Cam-CAN cohort was developed using stratified sampling based on primary healthcare providers, our sample is likely as population-representative as is feasible for a cohort of this magnitude and phenotypic breadth (see Shafto et al., 2014b) for further details). Nonetheless, a healthier subsample may lead to restriction of range (80), i.e. an attenuation of the strength of the associations observed between sleep quality and health outcomes. Practically, this means that our results likely generalise to comparable, healthy

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3 community dwelling adults, but not necessarily to populations that include those affected by either
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5 clinical sleep deprivation or other serious health conditions.
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7 8 **Conclusions**

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10 Taken together, our study allows several conclusions. First, although we replicate the age-
11 related deterioration in some aspects of sleep quality, other aspects remain stable or even improve.
12
13 Second, we show that the profile of sleep quality changes across the lifespan. This is important
14 methodologically, as it suggests that PSQI sum scores do not capture the full picture, especially in
15 age-heterogeneous samples. Moreover, it is important from a psychological standpoint: We show
16 that 'sleep quality' is a multidimensional construct and should be treated as such if we wish to
17 understand the complex effects and consequences of sleep quality across the lifespan. Third,
18 moderate to strong relations exist between sleep quality and cognitive, physical and mental health,
19 and these relations largely remain stable across the lifespan. In contrast, we show evidence that in
20 non-clinical populations, poorer self-reported sleep is not reliably associated with poorer neural
21 health. Together with previous experimental and longitudinal evidence, our findings suggest that at
22 least some age-related decreases in health outcomes may be due to poorer sleep quality. We show
23 that self-reported sleep quality can be an important indicator of other aspects of healthy functioning
24 throughout the lifespan, especially for mental and general physical health. Our findings suggest
25 accurate understanding of sleep quality is essential in understanding and supporting healthy aging
26 across the lifespan.
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Author contributions

AG, MS and MS designed the study. AG and RAK performed the analyses. CC organized and conducted the data collection. AG, MS and RAK wrote the manuscript. YL provided considerable expertise on sleep and poor sleep outcomes. All authors approved the final manuscript.

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4
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Legends

Figure 1. Descriptive interpretation of Bayes Factors

Figure 2. Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

Figure 3. Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction Time were measured only in the imaging cohort: mean N = 648, N=11.11. Sample sizes for 5 other domains are similar: mean N= 2300.25, SD= 65.57)

Figure 4. Multiple regressions between sleep components and Neural Health. Each cell represents the relationship between a sleep component and the mean neural health in a given tract as index by Fractional Anisotropy. Numbers represent R-squared, the sample size is show in the last column. Strong associations are observed between measures of Sleep Efficiency and multiple tracts, along with sporadic associations between other components and tracts. White matter tracts abbreviations: Uncinate fasciculus (UNC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior Fronto-occipital fasciculus (IFOF), forceps minor (FMin), forceps major (FMaj), cerebrospinal tract (CST), the ventral cingulate gyrus (CINGHipp), the dorsal cingulate gyrus (CING), and the anterior thalamic radiations (ATR). N varies slightly across components due to varying missingness (N mean = 631.325, SD = 10.32).

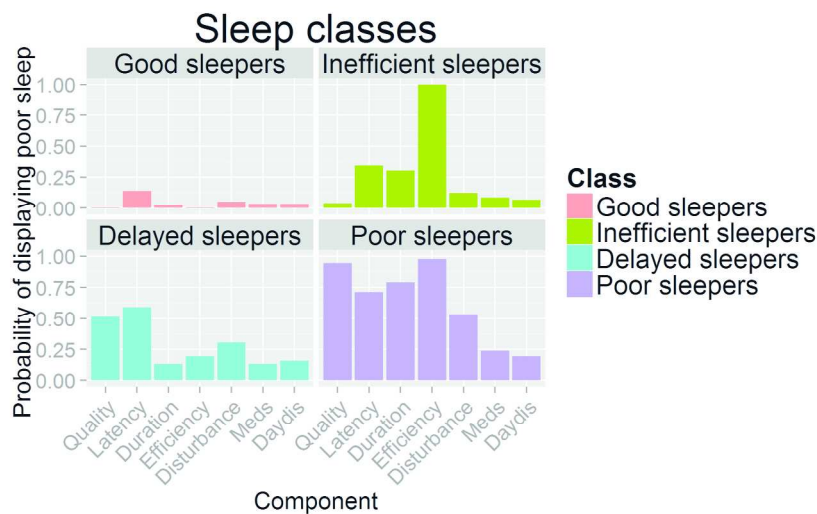
Figure 5 Physical health and sleep quality. Numbers represent Rsquared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and General) were measured in the full cohort (Mean = 2315.37, SD=66.29), the other indicators were measured in the imaging cohort only (Mean = 569.87, SD= 11.16).

Figure 6. Interaction between sleep quality and anxiety. (N=724, age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to 98.88).

Bayes Factor BF ₁₀	Log BF ₁₀	Tileplot colour	Description (Jeffreys, 1961)
>100	>4.6	Red	Extreme evidence for H1
30 – 100	3.4 – 4.6	Red	Very strong evidence for H1
10 – 30	2.3 – 3.4	Red	Strong evidence for H1
3 – 10	1.098 – 2.3	Light red	Substantial evidence for H1
1 – 3	1 – 1.098	Light red	Anecdotal evidence for H1
1	0	White	No evidence either way
1/3 – 1	-1.098 – -1	Light blue	Anecdotal evidence for H0
1/3 - 1/10	-2.3 – -1.098	Light blue	Substantial evidence for H0
1/10 - 1/30	-3.4 – -2.3	Light blue	Strong evidence for H0
1/30 - 1/100	-4.6 – -3.4	Light blue	Very strong evidence for H0
<1/100	< -4.6	Blue	Extreme evidence for H0

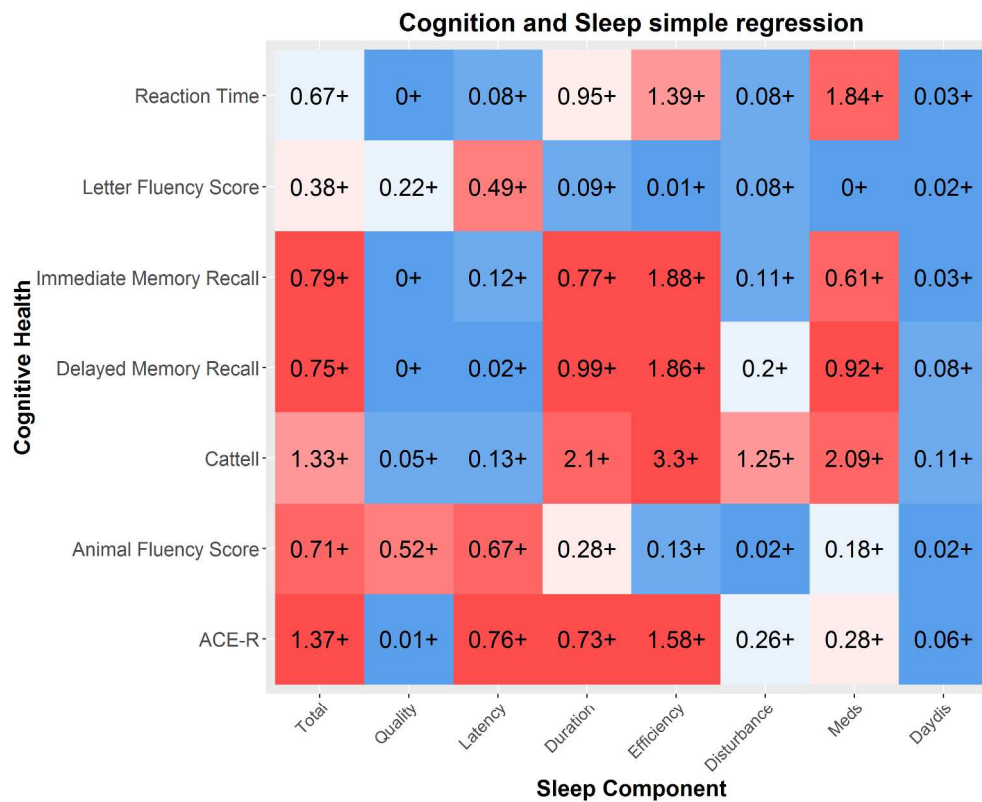
Descriptive interpretation of Bayes Factors
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Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

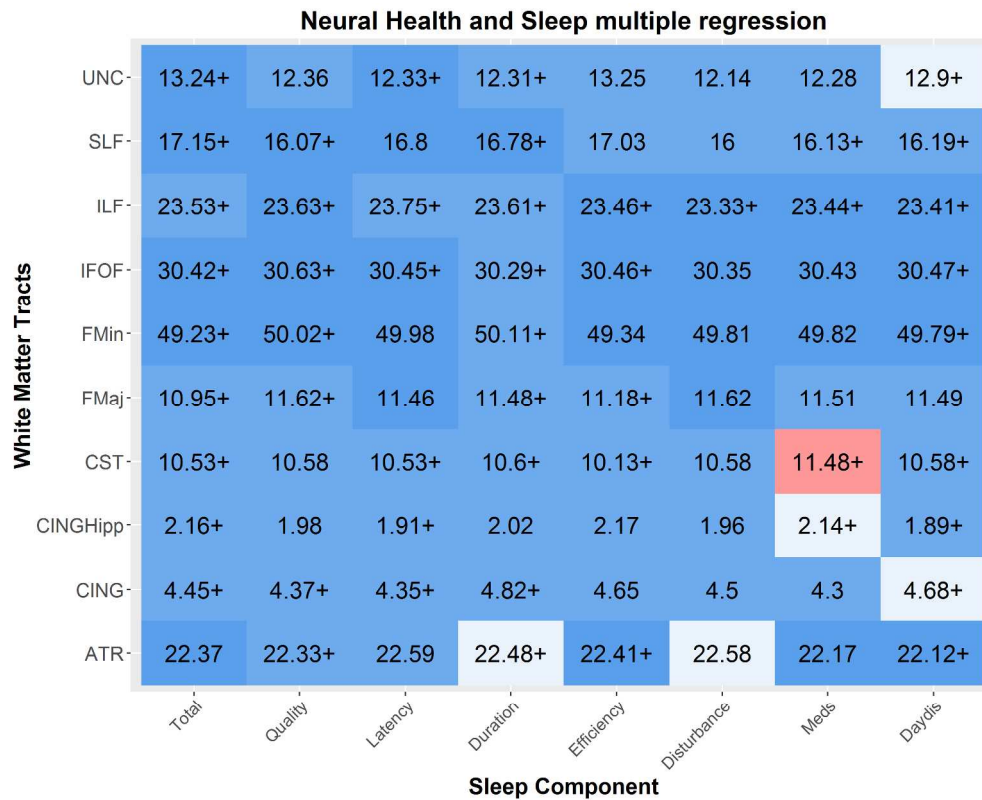
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Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction Time were measured only in the imaging cohort: mean N = 648, N=11.11. Sample sizes for 5 other domains are similar: mean N= 2300.25, SD= 65.57)

insert Figure 3 here
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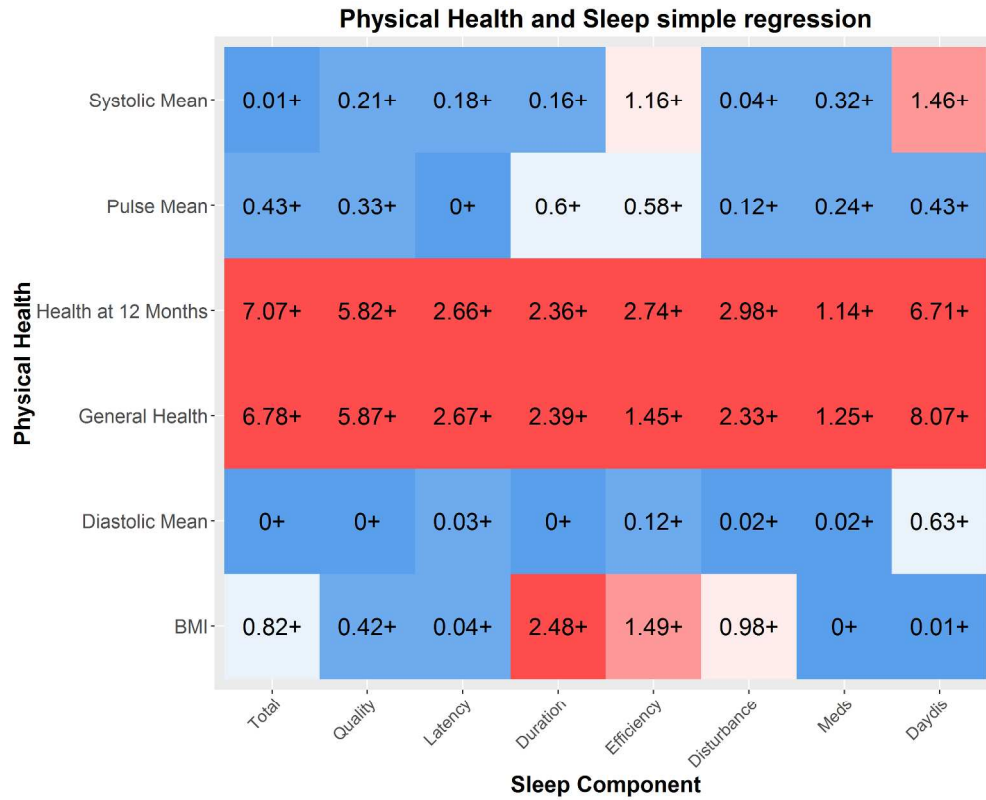


Multiple regressions between sleep components and Neural Health. Each cell represents the relationship between a sleep component and the mean neural health in a given tract as index by Fractional Anisotropy. Numbers represent R-squared, the sample size is show in the last column. Strong associations are observed between measures of Sleep Efficiency and multiple tracts, along with sporadic associations between other components and tracts. White matter tracts abbreviations: Uncinate fasciculus (UNC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior Fronto-occipital fasciculus (IFOF), forceps minor (FMin), forceps major (FMaj), cerebrospinal tract (CST), the ventral cingulate gyrus (CINGHipp), the dorsal cingulate gyrus (CING), and the anterior thalamic radiations (ATR). N varies slightly across components due to varying missingness (N mean = 631.325, SD = 10.32).

insert Figure 4 here
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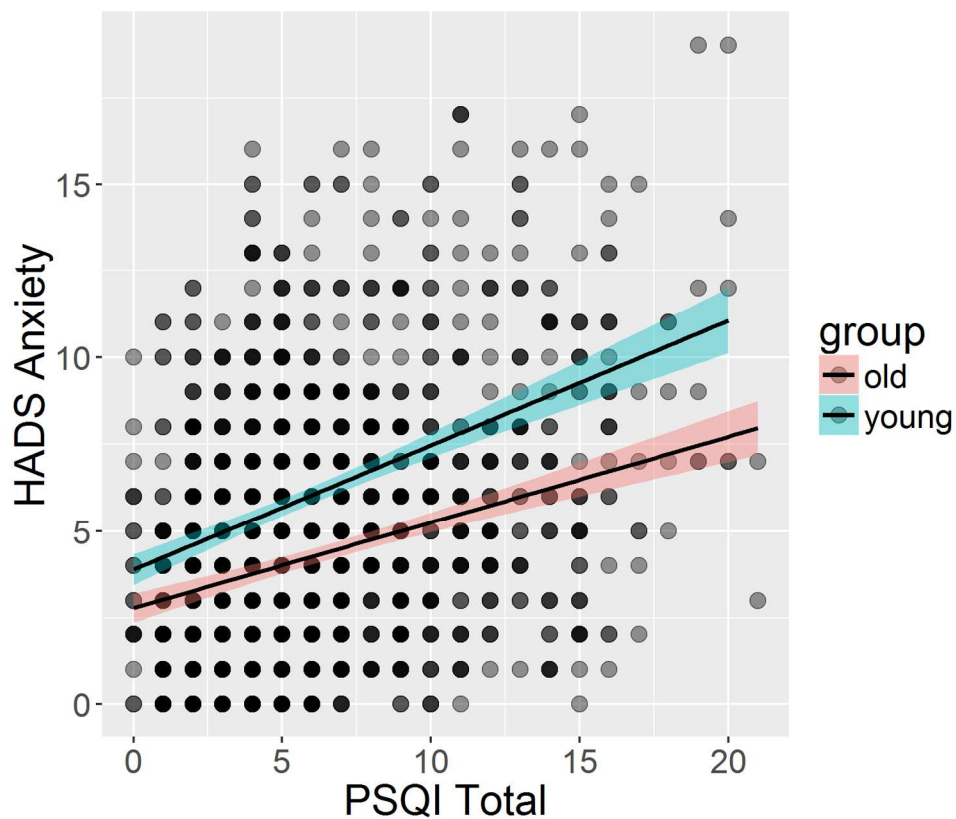


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Physical health and sleep quality. Numbers represent Rsquared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and General) were measured in the full cohort (Mean = 2315.37, SD=66.29), the other indicators were measured in the imaging cohort only (Mean = 569.87, SD= 11.16).
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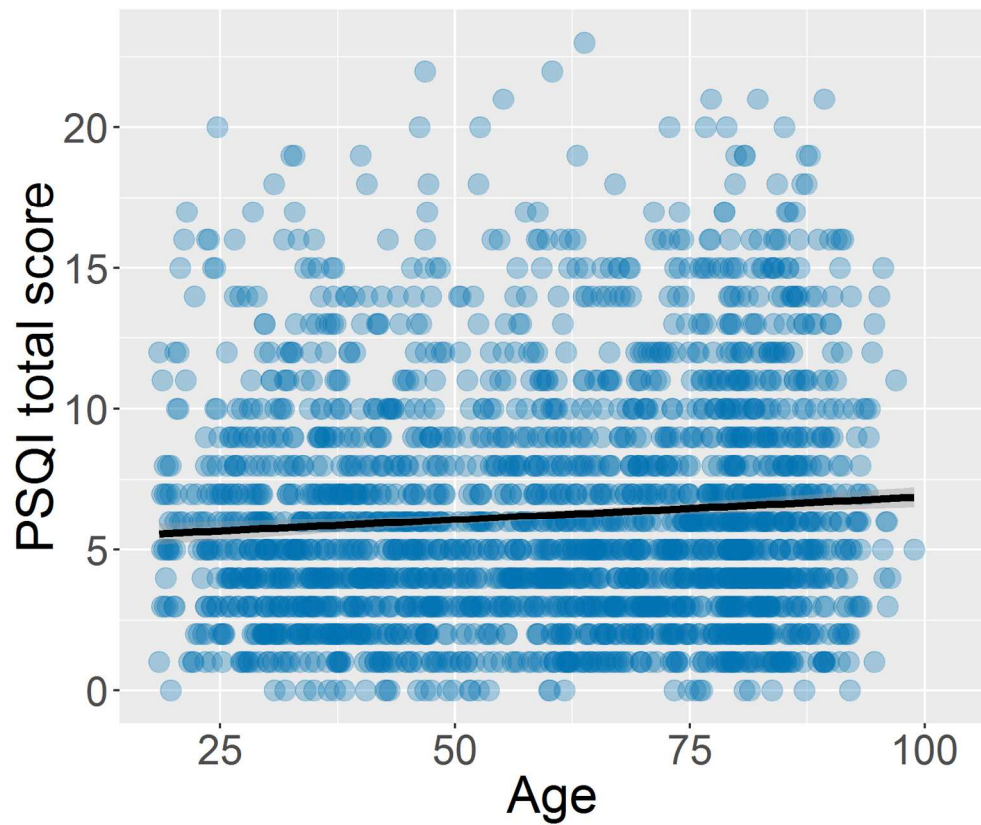


Interaction between sleep quality and anxiety. (N=724, age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to
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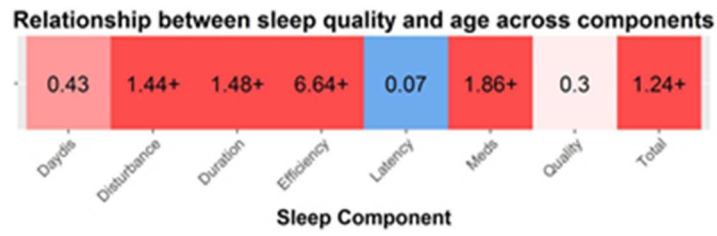
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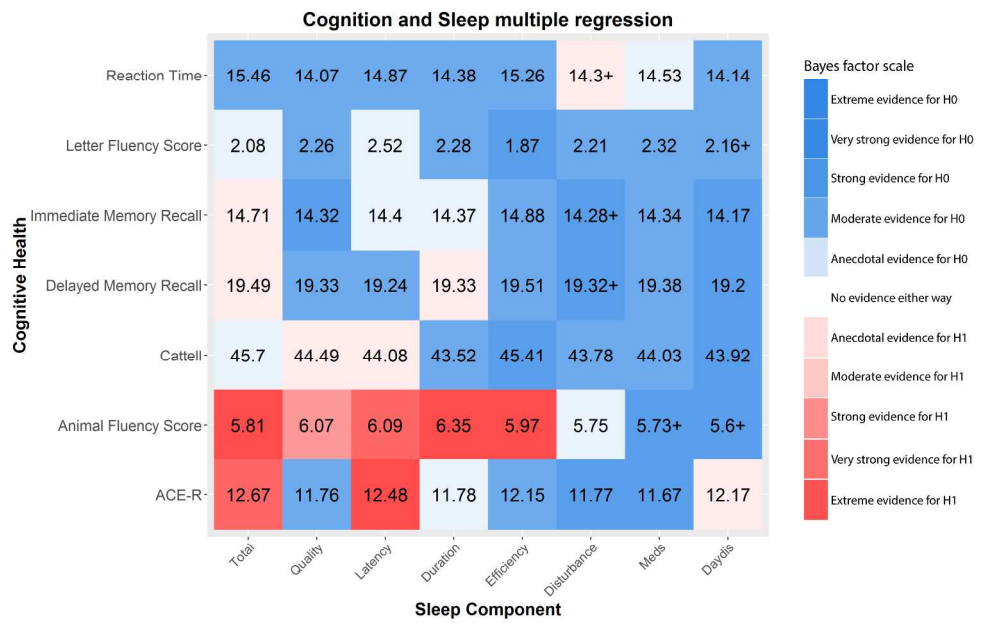
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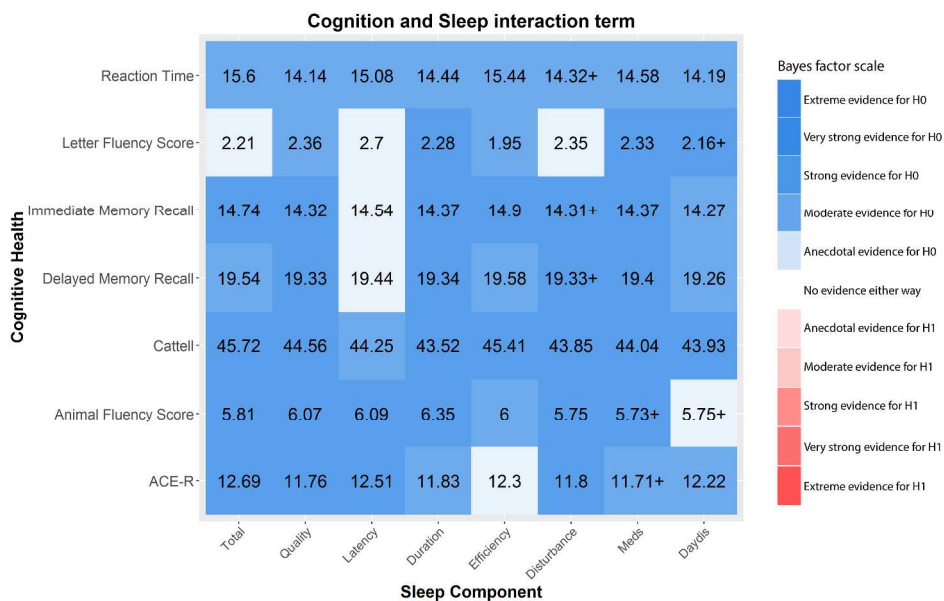
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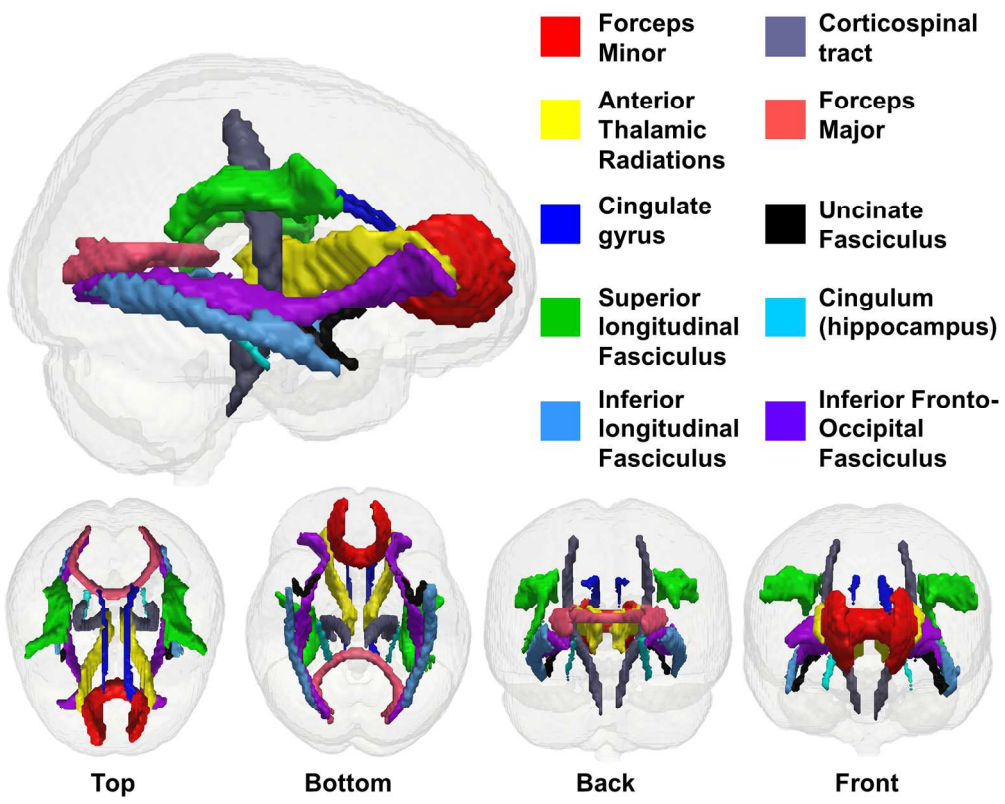
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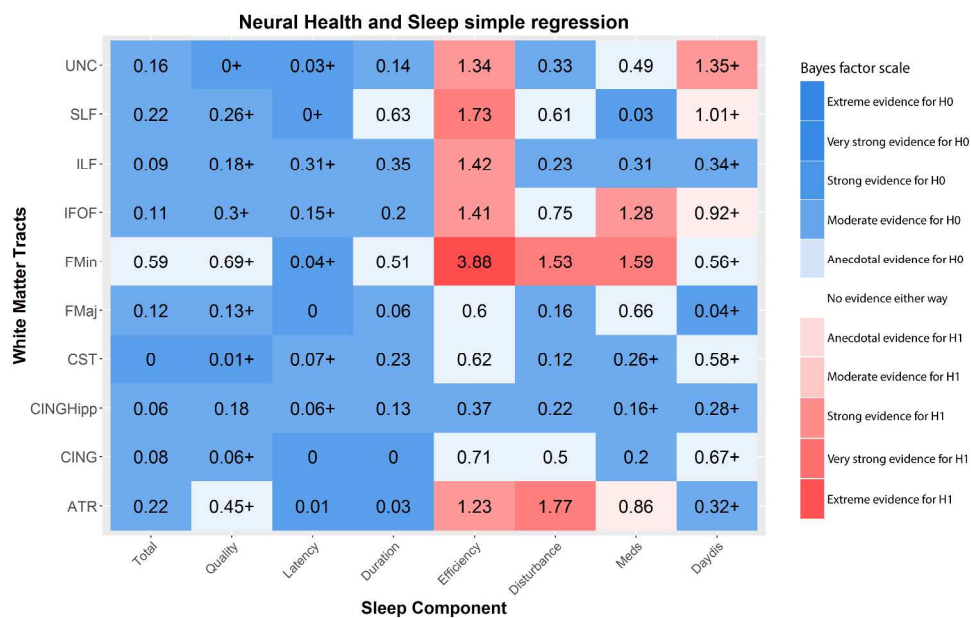
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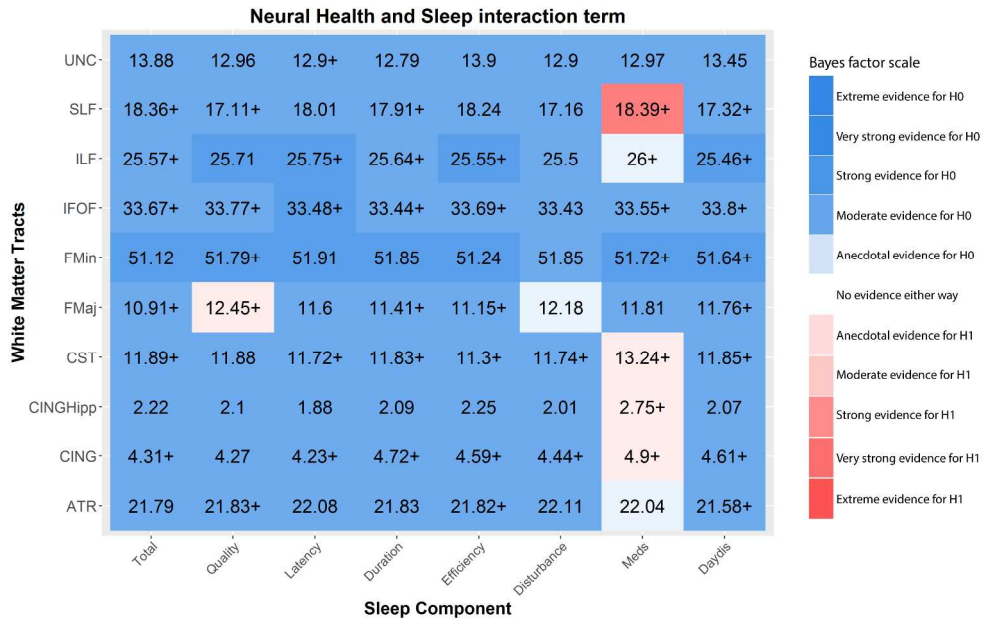
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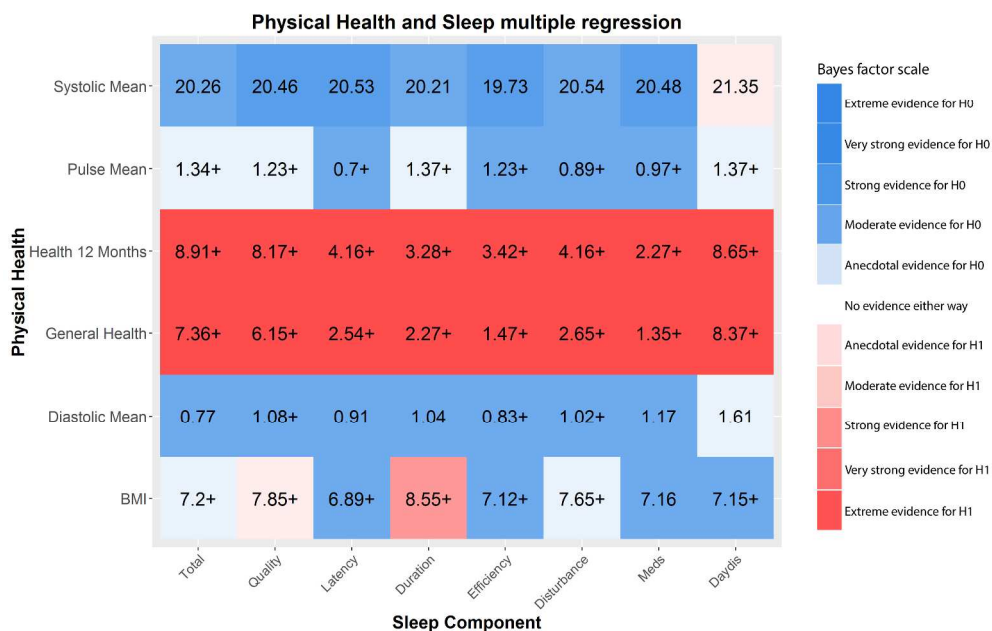
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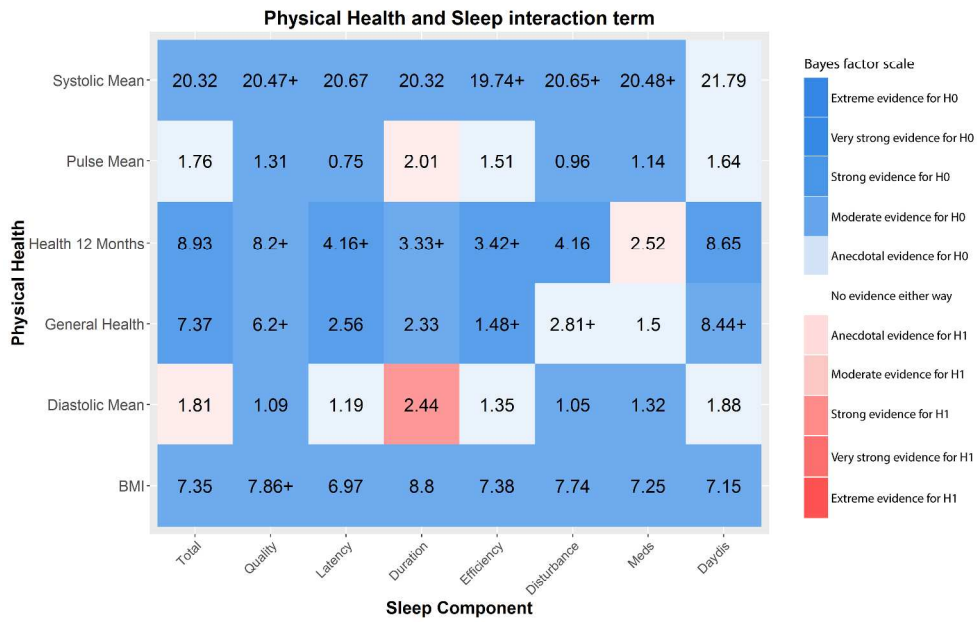


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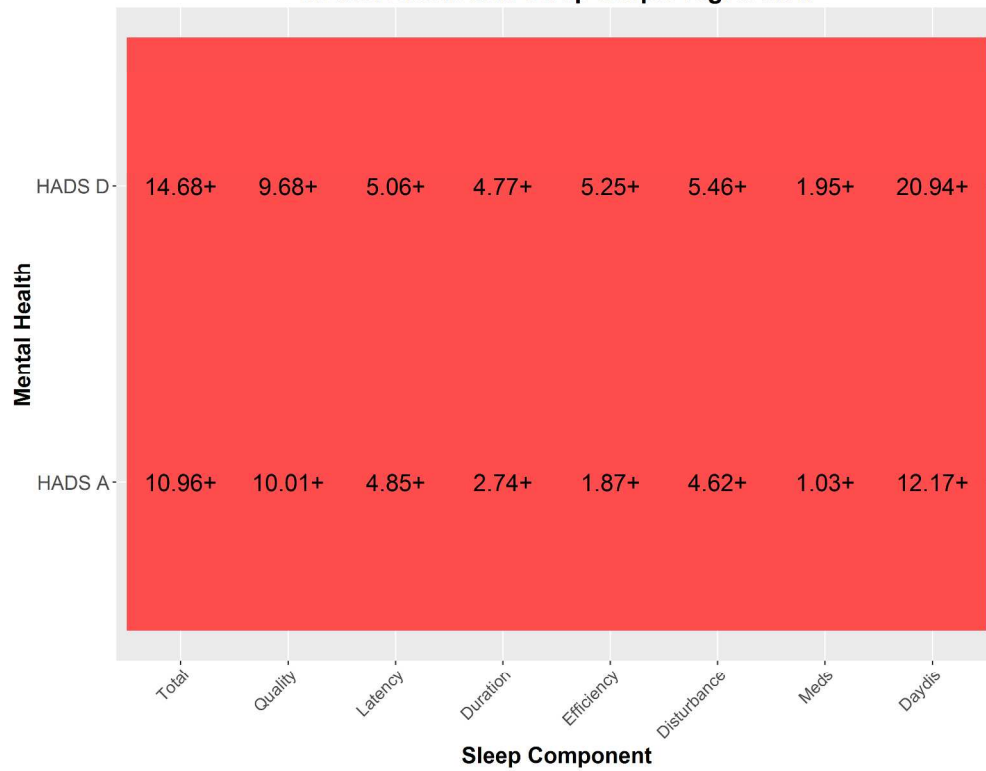


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Mental Health and Sleep simple regression



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5 (lines 87-91)
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 (project protocol)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 (project protocol)
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-11
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	(project protocol)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10-13
		(b) Describe any methods used to examine subgroups and interactions	10
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14-22
		(b) Give reasons for non-participation at each stage	(Project Proposal)
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	(Project Protocol)
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	(Project Protocol)
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-22
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-22
Discussion			
Key results	18	Summarise key results with reference to study objectives	22-26
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	25-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	25-26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

How are age-related differences in sleep quality associated with health outcomes? An epidemiological investigation in a UK cohort of 2406 adults

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014920.R1
Article Type:	Research
Date Submitted by the Author:	15-Feb-2017
Complete List of Authors:	Gadie, Andrew; MRC Cognition and Brain Sciences Unit Shafto, Meredith; University of Cambridge, Center for Speech, Language and the Brain Leng, Yue; University of Cambridge; University of California San Francisco, School of Medicine Cam-CAN, _; University of Cambridge, Center for Sleep, language and the brain Kievit, Rogier; MRC CBSU
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology, Mental health, Public health, Geriatric medicine
Keywords:	Ageing, SLEEP MEDICINE, cognition, MENTAL HEALTH, Neurobiology < BASIC SCIENCES

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2 How are age-related difference in sleep quality associated with health outcomes? An
3 epidemiological investigation in a UK cohort of 2406 adults

4
5 Andrew Gadie¹

6 Meredith Shafto²

7 Yue Leng³

8 Cam-CAN⁴

9 Rogier A. Kievit^{1*}

For peer review only

*Corresponding author: rogier.kievit@mrc-cbu.cam.ac.uk

1 MRC Cognition and Brain Sciences Unit, 15 Chaucer Rd, Cambridge, CB2 7EF, United Kingdom

2 Department of Psychology, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom

3 University of California, San Francisco

4 Cambridge Centre for Ageing and Neuroscience (Cam-CAN), University of Cambridge and MRC Cognition and Brain Sciences Unit, Cambridge, UK, www.cam-can.com

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2
3 12 Abstract
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5 13 **Objectives** To examine age related differences in self-reported sleep quality and their
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7 14 associations with health outcomes across four domains: Physical Health, Cognitive Health, Mental
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9 15 Health and Neural Health.

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11 16 **Setting** Cam-CAN is a cohort study in East Anglia/England, which collected self-reported
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13 17 health and lifestyle questions as well as a range of objective measures from healthy adults.

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15 18 **Participants** 2406 healthy adults (age 18-98) answered questions about their sleep quality
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17 19 (Pittsburgh Sleep Quality Index) and measures of Physical, Cognitive, Mental, and Neural Health. A
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19 20 subset of 641 individuals provided measures of brain structure.
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21

22 21 **Main outcome measures** Pittsburgh Sleep Quality Index scores (PSQI) of sleep, and scores
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24 22 across tests within the four domains of health. Latent Class Analysis (LCA) is used to identify sleep
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26 23 types across the lifespan. Bayesian regressions quantify the presence, and absence, of relationships
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28 24 between sleep quality and health measures.
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30
31 25 **Results** Better sleep is generally associated with better health outcomes, strongly so for
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33 26 mental health, moderately for cognitive and physical health, but not for sleep quality and neural
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35 27 health. Latent Class Analysis identified four sleep types: 'Good sleepers' (68.1%, most frequent in
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37 28 middle age), 'inefficient sleepers' (14.01%, most frequent in old age), 'Delayed sleepers' (9.28%,
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39 29 most frequent in young adults) and 'poor sleepers' (8.5%, most frequent in old age). There is little
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41 30 evidence for interactions between sleep quality and age on health outcomes. Finally, we observe u-
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43 31 shaped associations between sleep duration and mental health (depression and anxiety) as well as
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45 32 self-reported general health, such that both short and long sleep were associated with poorer
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47 33 outcomes.
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50 34 **Conclusions** Lifespan changes in sleep quality are multifaceted and not captured well by
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52 35 summary measures, but instead as partially independent symptoms that vary in prevalence across
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54 36 the lifespan. Better self-reported sleep is associated with better health outcomes, and the strength
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3 37 of these associations differs across health domains. Notably, we do observed associations between
4
5 38 self-reported sleep quality and white matter.
6

7 39 **Funding** Biotechnology and Biological Sciences Research Council (grant number
8
9 40 BB/H008217/1). RAK is supported by the Wellcome Trust (grant number 107392/Z/15/Z and the UK
10
11 41 Medical Research Council (MC-A060-5PR61).
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16 43 **Keywords**

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18 44 Ageing, sleep quality, healthy ageing, cognition, mental health, cognition, white matter, physical
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20 45 health
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25 47 **Strengths and limitations of this study**

- 26
27 48 • Broad phenotypic assessment of healthy ageing across multiple health domains
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29 49 • Advanced analytic techniques (i.e. Latent Class Analysis regression) allows new insights
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31 50 • A uniquely large neuroimaging sample combined with Bayesian inference allows for
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33 51 quantification of evidence for the null hypothesis
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35 52 • Subjective sleep measures may have drawbacks in older samples
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37 53 • Cross-sectional data precludes modelling of within subject changes
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3 55 **BACKGROUND**
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5 56 Sleep is a fundamental human behaviour, with humans spending almost a third of their lives asleep.
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7 57 Regular and sufficient sleep has been shown to benefit human physiology through a number of
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9 58 different routes, ranging from consolidation of memories (1) to removal of free radicals (2) and
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11 59 neurotoxic waste (3). Sleep patterns are known to change across the lifespan in various ways.
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13 60 including decreases in quantity and quality of sleep (4), with up to 50% of older adults report
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15 61 difficulties initiating and/or maintaining sleep (5). A meta-analysis of over 65 studies reflecting 3577
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17 62 subjects across the lifespan reported a complex pattern of changes, including an increase of stage 1
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19 63 but a decrease of stage 2 sleep in old age, as well as a decrease in REM sleep (6). An epidemiological
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21 64 investigation of self-reported sleep in older adults observed marker sex differences in age-related
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23 65 sleep changes, with females more likely to report disturbed sleep onset but men reporting night-
24
25 66 time awakenings (7). Other findings age-related physiological changes in the alignment of
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27 67 homeostatic and circadian rhythms (8), decreases in sleep efficiency (9) the amount of slow-wave
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29 68 sleep, and an increase in daytime napping (10). Importantly, interruption and loss of sleep has been
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31 69 shown to have wide ranging adverse effects on health (11), leaving open the possibility that age-
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33 70 related changes in sleep patterns and quality may contribute to well-documented age-related
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35 71 declines in various health domains.
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40 72 In the current study, we examine self-reported sleep habits in a large, population-based
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42 73 cohort Cambridge Centre for Ageing and Neuroscience (Cam-CAN (12)). We relate sleep measures to
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44 74 measures of health across four health domains: cognitive, brain health, physical and mental health.
45
46 75 Our goal is to quantify and compare the associations between typical age-related changes in sleep
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48 76 quality and a range of measures of health measures that commonly decline in later life. We assess
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50 77 sleep using a self-reported measure of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) (13).
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52 78 The PSQI has good psychometric properties (14) and has been shown to correlate reliably with
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54 79 diseases of aging and mortality (15–17). Although polysomnography (18) is commonly considered
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56 80 the gold standard of sleep quality measurement, it is often prohibitively challenging to employ in
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3 81 large samples. A recent direct comparison of sleep measures (19) suggests that although subjective
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5 82 sleep measures (such as PSQI) may have certain drawbacks in older samples, they also capture
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7 83 complementary aspects of sleep quality not fully captured by polysomnography. Moreover,
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9 84 collecting self-report sleep quality data in a large, deeply phenotyped cohort offers several
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11 85 additional benefits.

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14 86 By utilising a population cohort of healthy adults, and studying a range of health outcomes in
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16 87 the same population, we can circumvent challenges associated with studying clinical populations
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18 88 and provide new insights. First and foremost, by investigating associations between sleep and
19
20 89 outcomes across multiple health domains in the same sample, we can make direct comparisons of
21
22 90 the relative magnitude of these effects. Second, larger samples allow us to can generate precise
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24 91 effect size estimates, as well as adduce in favour of the null hypothesis. Third, we investigate the
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26 92 associations between sleep quality and neural health in a uniquely large healthy population.

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29 93 Previous investigations of the consequences of poor sleep on especially neural health have generally
30
31 94 focuses on clinical populations such as those suffering from insomnia (20,21). Although such studies
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33 95 are crucial for understanding pathology, the demographic idiosyncrasies and often modest sample
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35 96 sizes of these approaches make it hard to generalize to healthy, community dwelling lifespan
36
37 97 populations. Moreover, most studies that study age-related changes or differences focus on (very)
38
39 98 old age, while far less is known about young and middle aged adults (6). For these reasons, our focus
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41 99 on a healthy, multimodal lifespan cohort is likely to yield novel insights into the subtle changes in
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43 100 sleep quality across the lifespan.

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45
46 101 We will focus on three questions within each health domain: First, is there a relationship
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48 102 between sleep quality and health? Second, does the strength and nature of this relationship change
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50 103 when age is included as a covariate? Third, does the strength and nature of the relationship change
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52 104 across the lifespan? We will examine these questions across each of the four health domains.

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3 107 **METHODS**

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5 108 **Sample**

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7 109 A cohort of 2544 (12) was recruited as part of the population-based Cambridge Centre for Ageing
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9 110 and Neuroscience (Cam-CAN) cohort (www.cam-can.com), drawn from the general population via
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11 111 Primary Care Trust (PCT)'s lists within the Cambridge City (UK) area 10,520 invitation letters were
12
13 112 sent between 2010 and 2012, and willing participants were invited to have an interview conducted
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15 113 in their home, with questions on health, lifestyle demographics and core cognitive assessments.
16
17 114 Sample size was chosen to allow for 100 participants per decile in further acquisition stages, giving
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19 115 sufficient power to separate age-related change from other sources of individual variation. For
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21 116 additional details of the project protocol see (12,22) and for further details of the Cam-CAN dataset
22
23 117 visit <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/>. A further subset of participants who were
24
25 118 MRI compatible with no serious cognitive impairment participated in a neuroimaging session (22)
26
27 119 between the 2011 and 2013. Participants included were native English speakers, had normal or
28
29 120 corrected to normal vision and hearing, scored 25 or higher on the mini mental state (23). Note that
30
31 121 other, more stringent cut-offs are sometimes employed to screen for premorbid dementia, such as a
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33 122 score of 88 or higher in the Addenbrookes Cognitive Examination – Revised (24). For the sake of
34
35 123 comprehensiveness we repeated our analyses using this more stringent cut off (ACE-R>88), but
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37 124 observed no noteworthy differences in our findings, so we only report the findings based on the
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39 125 MMSE. Ethical approval for the study was obtained from the Cambridgeshire 2 (now East of England-
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41 126 Cambridge Central) Research Ethics Committee (reference: 10/H0308/50). Participants gave written
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43 127 informed consent. The raw data and analysis code are available upon signing a data sharing request
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45 128 form (see <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/> for more detail).
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52 130 **Variables**

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54 131 *Sleep Measures*
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3 132 Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a well-validated
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5 133 self-report questionnaire (13,19) designed to assist in the diagnosis of sleep disorders. The questions
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7 134 concern sleep patterns, habits, and lifestyle questions, grouped into seven components, each
8
9 135 yielding a score ranging from 0 (good sleep/no problems) to 3 (poor sleep/severe problems), that
10
11 136 are commonly summed to a PSQI Total score ranging between 0 and 21, with higher scores
12
13 137 reflecting poorer sleep quality.

16 138 **Health Measures**

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18 139 *Cognitive health.* A number of studies have found associations between poor sleep and
19
20 140 cognitive decline, including in elderly populations. Poor sleep affects cognitive abilities such as
21
22 141 executive functions (25) and learning and memory processes (26), whereas short term
23
24 142 pharmaceutical interventions such as administration of melatonin improve both sleep quality and
25
26 143 cognitive performance (27,28). Recent work (29) concluded that “maintaining good sleep quality, at
27
28 144 least in young adulthood and middle age, promotes better cognitive functioning and serves to
29
30 145 protect against age-related cognitive declines”. As sleep may affect various aspects of cognition
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32 146 differently (30), we include measures that cover a range of cognitive domains including memory,
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34 147 reasoning, response speed, and verbal fluency, as well as including a measure of general cognition
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36 148 (See Table 1 and (12) for more details).

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39 149 *Neural health.* Previous research suggests that individuals with a severe disruption of sleep
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41 150 are significantly more likely to exhibit signs of poor neural health (20,31). Specifically, previous
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43 151 studies have observed decreased white matter health in clinical populations suffering from
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45 152 conditions such as chronic insomnia (21), obstructive sleep apnoea (32,33), excessively long sleep in
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47 153 patients with diabetes (34), and REM Sleep Behaviour Disorder (35). Many of these studies focus on
48
49 154 white matter hyperintensities (WMH), a measure of the total volume or number of (regions)
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51 155 showing low-level neural pathology (although some study grey matter, e.g. (36,37). White matter
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53 156 hyperintensities are often used as a clinical marker, as longitudinal increases in WMHs are
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55 157 associated with increased risk of stroke, dementia and death (38) and are more prevalent in patients
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3 158 with pathological sleep problems (33,34). However, use of this metric in clinical cohorts largely
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5 159 leaves open the question of the impact of sleep quality on neural (white matter) health in non-
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7 160 clinical, healthy populations. To address this question, we use a more general indicator of white
8
9 161 matter neural health; *Fractional Anisotropy* (FA). FA is associated with white matter integrity and
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11 162 myelination (39,40). We use FA as recent evidence suggests that WMHs represent the extremes
12
13 163 (foci) of white matter damage, and that FA is able to capture the full continuum of white matter
14
15 164 integrity (41). For more information regarding the precise white matter pipeline, see (12,22,42).

16 165 *Physical health.* Sleep quality is also an important marker for physical health, with poorer
17
18 166 sleep being associated with conditions such as obesity, diabetes mellitus (43), overall health (11,44)
19
20 167 and increased all-cause mortality (45,46). We focus on a set of variables that capture three types of
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22 168 health domains commonly associated with poor sleep: Cardiovascular health measured by pulse,
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24 169 systolic and diastolic blood pressure (47), self-reported health, both in general and for the past 12
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26 170 months (48) and body-mass index (49).

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29 171 *Mental health.* Previous work has found that disruptions of sleep quality are a central
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31 172 symptom of forms of psychopathology such as Major Depressive Disorder, including both
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33 173 hypersomnia and insomnia (44,50), and episodes of insomnia earlier greatly increased the risk of
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35 174 later episodes of major depression (51). Kaneita et al. (52) found a U-shaped association between
36
37 175 sleep and depression, such that individuals regularly sleeping less than 6, or more than 8, hours were
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39 176 more likely to be depressed. Both depression (53) and anxiety (54,55) are commonly associated with
40
41 177 sleep problems. To capture these dimensions we used both scales of the Hospital Anxiety and
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43 178 Depression Scale (HADS) (56), a widely used and standardized questionnaire that captures self-
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45 179 reported frequency and intensity of anxiety and depression symptoms.

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Health	Task and Description	Variable	Descriptives	Citati
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domain				on
Cognitive	Story Recall Immediate: Participants hear a short story and are asked to recall as accurately as possible.	Recall manually scored for similarity and precision (min=0, max=24)	N = 2379, M=13.14, SD=4.66, Range=(0-24)	(57)
Cognitive	Story Recall Delayed: Same as above but recall after 30 minute delay	Recall manually scored for similarity and precision (min=0, max=24)	N = 2366, M=11.47, SD=4.92, Range=(0-24)	(57)
Cognitive	Letter Fluency (phonemic fluency): Participants have one minute to generate as many words as possible beginning with the letter 'p'.	Total words generated (min=0,max=30)	N = 2360, M=25.38, SD=3.96, Range=(0-30)	(57)
Cognitive	Animal Fluency (semantic fluency): Participants have one minute to generate as many words as possible in the category 'animals'.	Total words generated (min=0,max=30)	N = 2346, M=25.85, SD=4.47, Range=(0-30)	(57)
Cognitive	Cattell Culture Fair: Test of fluid reasoning using four subtests (series completions, odd-one-out, matrices and topology)	Total correct summed across four subtests. Min=0, max=46	N = 658, M=31.8, SD=6.79, Range=(11-44)	(58)
Cognitive	Simple reaction time: Speed in a simple reaction time task	1/response time in seconds	N = 657, M=0.37, SD=0.08, Range=(0.24-0.93)	(12)
Cognitive	Addenbrookes Cognitive Examination, Revised: Screening test for dementia using seven subtests (orientation, attention and concentration, memory, fluency, language, visuospatial abilities, perceptual abilities)	Performance on multiple tests converted to min=0, max=100 range	N = 2406, M=89.25, SD=13.4, Range=(0-100)	(24)
Neural	White matter health: Measure of tract integrity using fractional anisotropy	Fractional Anisotropy (min=0, max=1, averaged across 10 tracts)	N = 641, M=0.5, SD=0.03, Range=(0.3-0.56)	(59)
Physical	Self-reported Health, in general: Participants use a 4-point scale to respond to the prompt "Would you say for someone of your age, your own health in general is..."	Score from 1 = Excellent to 4= Poor	N = 2404, M=2.02, SD=0.79, Range=(1-3)	(60)
Physical	Self-reported Health, last 12 months: Participants use a 3-point scale to respond to the prompt "Over the last twelve months would you say your health has on the whole been..."	Score from 1 = Good to 3= Poor	N = 2398, M=1.46, SD=0.71, Range=(1-3)	(60)

Physical	Systolic blood pressure	Mean systolic blood pressure in mmHg, averaged across three consecutive measurements	N = 577, M=120.11, SD=17, Range=(78.5-186)	
Physical	Diastolic blood pressure	Mean diastolic blood pressure in mmHg, averaged across three consecutive measurements	N = 577, M=73.14, SD=10.48, Range=(49-115.5)	
Physical	Resting pulse	Mean pulse in beats per minute, averaged across three consecutive measurements	N = 578, M=65.69, SD=10.5, Range=(40-110.5)	
Physical	Body Mass Index (BMI)	(weight in kg) / (height in m) ²	N = 584, M=25.77, SD=4.59, Range=(16.75-48.32)	(61)
Mental health	Anxiety Subscale (Hospital Anxiety and Depression Scale (HADS)): Participants response to seven questions about anxiety-related behaviours	Seven questions rated on 0 to 3 scale ('Often' to 'Very seldom'). Min=0, Max=21	N = 2393, M=5.17, SD=3.4, Range=(0-19)	(56)
Mental health	Depression Subscale (Hospital Anxiety and Depression Scale (HADS)): Participants response to seven questions about depression-related behaviours	Seven questions rated on 0 to 3 scale ('Often' to 'Very seldom'). Min=0, Max=21	N = 2373, M=3.32, SD=2.91, Range=(0-14)	

183

Table 1. Description of health variables across each of four domains (cognitive, neural, physical, mental). For each variable details are given including a description of the task it is derived from, relevant citations, a brief definition and descriptive statistics.

184 **STATISTICAL ANALYSES**

185 We examine whether self-reported sleep patterns change across the lifespan, both for the PSQI sum
186 score and for each of the seven PSQI components. We then examine the relationships between the
187 sleep quality and the four health domains in three ways: First, simple regression of the health
188 outcome on sleep variables, to determine evidence for association between poor sleep quality and
189 poor health outcomes. Second, we include age as a covariate. Finally, we include a (standard normal
190 rescaled) continuous interaction term to examine whether there is evidence for a changing
191 relationship between sleep and outcomes across the lifespan.

192 For all regressions we will use a default Bayesian approach advocated by (62–65) which
193 avoids several well-documented issues with p-values (64), allows for quantification of null effects,
194 and decreases the risk of multiple comparison problems (66). Bayesian regressions allows us to
195 symmetrically quantify evidence in favour of, or against, some substantive model as compared to a
196 baseline (e.g. null) model. This evidentiary strength is expressed as a Bayes Factor (67), which can be
197 interpreted as the relative likelihood of one model versus another given the data and a certain prior
198 expectation. A Bayes Factor of, e.g., 7, in favour of a regression model suggests that the data are
199 seven times *more likely* under that model than an intercept only model for a given prior (for an
200 empirical comparison of p-values and Bayes factors, see (65)). A heuristic summary of evidentiary
201 interpretation can be seen in Figure 1.

202 [insert Figure 1 here]

203 We report log Bayes Factors for (very) large effects and regular Bayes Factors for smaller
204 effects. To compute Bayes Factors we will use Default Bayes Factor approach for model selection
205 (62,63) in the package BayesFactor (68) using the open source software package R (69). As previous
206 papers report associations between sleep and outcomes ranging from absent to considerable in size
207 we utilize the default, symmetric Cauchy prior with width $\frac{\sqrt{2}}{2}$ which translates to a 50% confidence
208 that the true effect will lie between -.707 and .707. Prior to further analysis, scores on all outcomes
209 were transformed to a standard normal distribution, and any scores exceeding a z-score of 4 or -4

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3 210 were recoded as missing (aggregate percentage outliers across the four health domains: Cognitive,
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5 211 0.41%, Mental, 0.16%, Neural, 0.37% Physical, 0.031%).
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11 213 **RESULTS**

12 214 **Age-related differences in sleep quality**

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14 215 First, we examined sleep changes across the lifespan by examining age-related differences in the
15
16 216 PSQI sum score (N= 2178, M=5.16, SD=3.35, Range=0-19). Regressing the PSQI global score on age,
17
18 217 (see Supplementary Figure 1) showed evidence for a positive relationship across the lifespan
19
20 218 ($\log BF_{10} = 10.45$). This suggests that on the whole, sleep quality decreases across the lifespan (note
21
22 219 that *higher* PSQI scores correspond to worse sleep). Although we observe strong statistical evidence
23
24 220 for an age-related difference ('Extreme' according to (70)) age explained only 1.23 % of the variance
25
26 221 in the PSQI Total score. Next, we examined each of the seven components on age in the same
27
28 222 manner. In Supplementary Figure 2 we see that that age has varying and specific effects on different
29
30 223 aspects of sleep quality, and did not worsen uniformly across the lifespan. For example, we observed
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32 224 moderate evidence that sleep latency did not change across the lifespan (Sleep Latency, $BF_{01} = 9.25$,
33
34 225 in favour of the null), Sleep Quality showed no evidence for either change or stasis ($BF_{10} = 1.63$) and
35
36 226 one sleep component, Daytime Dysfunction, improved slightly across the lifespan ($BF_{10} = 7.03$).
37
38 227 Medication). The strongest age-related decline is that of Efficiency, showing an R-squared of 6.6%.
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41
42 229 Finally, we entered all seven components into a Bayesian multiple regression
43
44 230 simultaneously, to examine to what extent they could, together, predict age. The best model
45
46 231 included every component except Sleep Latency ($\log BF_{10} = 142.71$). Interestingly, this model
47
48 232 explained 13.66% of the variance in age, compared to 1.23% for the PSQI Total score, and 6.6% for
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50 233 the strongest single component (efficiency). This shows that lifespan changes in self-reported sleep
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52 234 are heterogeneous and partially independent, and that specific patterns and components need to be
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3 235 finding shows that neither the PSQI sum score nor the sleep components in isolation fully capture
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5 236 differences in sleep quality across the lifespan.
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7 237 The analysis above suggests that conceptualizing 'poor sleep' as a single dimension does not
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9 238 reflect the subtleties in lifespan changes – An often computed sumscore changes little across the
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11 239 lifespan, whereas the totality of sleep symptoms shows far stronger, and more subtle, patterns. To
12
13 240 better elucidate individual differences in sleep quality we next use *Latent Class Analysis* (71). This
14
15 241 technique will allow us examine individual differences in sleep quality across the lifespan in more
16
17 242 detail than afforded by simple linear regressions: Rather than examining continuous variation in
18
19 243 sleep components, LCA classifies individuals into different *sleep types*, each associated with a distinct
20
21 244 profile of 'sleep symptoms'. If there are specific constellations of sleep problems across individuals,
22
23 245 we can quantify and visualize such sleep types.
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25

26 246 To analyse the data in this manner, we binarized the responses on each component into
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28 247 'good' (0 or 1) or 'poor' (2 or 3). Our measures of PSQI symptoms straddle the border between
29
30 248 continuous and categorical – Although some are fully continuous (e.g. sleep latency) others are less
31
32 249 so. For instance, although scored on a range of four several of the scales (such as Subjective Sleep
33
34 250 quality) have implicitly binary response options of 'Very good' and 'fairly good' on the one hand and
35
36 251 'fairly bad' and 'very bad' on the other. As analytical work in psychometrics (72) suggests that likert-
37
38 252 like graded scales can be treated as continuous only from five ordinal categories upwards, by fitting
39
40 253 an LCA we are erring on the side of caution (although a latent profile analysis would likely give
41
42 254 similar results). Note that although our analysis divides individuals into discrete classes with specific
43
44 255 profiles, it is still possible to examine the conditional response likelihood of responding 'yes' to each
45
46 256 symptom as a continuous metric (between 0 and 1) that reflects the nature of the association
47
48 257 between the class and the outcome. By modelling sleep 'types' we hope to illustrate the complex
49
50 258 patterns in a more intelligible manner – notably, doing so allows us to examine whether the
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52 259 likelihood of belonging to any sleep 'type' changes as a function of age.
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3 260 Next we examined evidence for distinct sleep types using We fit a set of possible models
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5 261 (varying from 2 to 6 sleep types) We found that the four class solution gives the best solution,
6
7 262 according to the Bayesian Information Criterion (73) (BIC for 4 Classes = 11825.65, lowest BIC for
8
9 263 other solutions= 11884.92 (5 classes) (with 50 repetitions per class, at 5000 maximum iterations).

10
11 264 Next we inspected the nature of the sleep types, the prevalence of each 'sleep type' in the
12
13 265 population, and whether the likelihood of belonging to a certain sleep type changes across the
14
15 266 lifespan. See Figure 2 for the component profiles of the four sleep types identified.

16
17
18 267 [insert Figure 2 here]

19
20 268 Class 1, 'Good sleepers', make up 68.1% of participants. Their sleep profile is shown in Figure
21
22 269 2A, top left, and is characterised by a low probability of responding 'poor' to any of the sleep
23
24 270 components. Class 2, 'inefficient sleepers', make up 14.01% of the participants, and are
25
26 271 characterized by poor sleep Efficiency: Members of this group uniformly (100%) report poor sleep
27
28 272 Efficiency, despite relatively low prevalence of other sleep problems, as seen in Figure 2A, top right.
29
30 273 Class 3, 'Delayed Sleepers' seen in the bottom left of Figure 2a, makes up 9.28% of the participants:
31
32 274 characterized by modestly poor sleep across the board, but a relatively high probability of poor
33
34 275 scores on Sleep Latency (59%), Sleep Quality (51%) and sleep Disturbance (31%). Finally, Class 4,
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36 276 'Poor sleepers', make up 8.5% of the participants, shown bottom right in Figure 2A. Their responses
37
38 277 to any of the seven sleep components are likely to be 'poor' or 'very poor', almost universally so for
39
40 278 'sleep quality' (94%) and 'Sleep Efficiency' (97.7%).

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44 279 Next, we including age as a covariate (simultaneously including a covariate is known as
45
46 280 *latent class regression* or concomitant-variable latent class models (74). This analysis, visualised in
47
48 281 Figure 2b, shows that the probability of membership of each classes compared to the reference class
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50 282 (good sleepers) changes significantly across the lifespan for each of the classes (Class 2 versus class
51
52 283 1: beta/SE= 0.05/0.00681, t=7.611, Class 3 versus class 1: beta/SE= -0.01948/0.0055, t=-3.54), Class 4
53
54 284 versus class 1: beta/SE 0.01269/0.00478, t=2.655, for more details on generalized logit coefficients ,
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56 285 see (71). The frequency of Class 1 (Good sleepers) peaks in middle to late adulthood, dropping
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3 286 increasingly quickly after age 50. Class 2 (Inefficient sleepers) are relatively rare in younger
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5 287 individuals, but the prevalence increases rapidly in individuals over age 50. On the other hand, Class
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7 288 3 (Delayed sleepers) shows a steady decrease in the probability of an individual showing this profile
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9 289 across the lifespan, suggesting that this specific pattern of poor sleep is more commonly associated
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11 290 with younger adults. Finally, the proportion of Class 4 (poor sleepers) members increases only
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13 291 slightly across the lifespan. Together, the latent class analysis provides additional evidence that the
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15 292 PSQI sum score as an indicator of sleep quality does not fully capture the subtleties of age-related
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17 293 differences. Age-related changes in sleep patterns are characterized by specific, clustered patterns
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19 294 of sleep problems that cannot be adequately characterized by summation of the component scores.
20
21 295 The above analyses show how both a summary measure and individual measures of sleep quality
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23 296 change across the lifespan. Next, we examined the relationships between sleep quality measures
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25 297 (seven components and the global PSQI score) and health variables (specific variables across four
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27 298 domains, as shown in Table 1).
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303 **Sleep, health domains and age**

304 *Cognitive health*

305 First, we examined the relationships between sleep quality and seven measures of cognitive health
306 (see Table 1 for details). We visualize our findings using tileplots (75). Each cell shows the numeric
307 effect size (R-squared, 0-100) of the bivariate association between a sleep component and a health
308 outcome, colour coded by the statistical evidence for a relationship using the Bayes Factor. If the
309 parameter estimate is positive, the r-squared value has the symbol '+' added (note the
310 interpretation depends on the nature of the variable, cf. Table 1).
311 As can be seen in Supplementary Figure 3, several relationships exist between measures of cognitive
312 health and measures of sleep quality. However, these results attenuate in a multiple regression
313 model including age as shown in Figure 3.

[Insert Figure 3 here]

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3 312 The cognitive abilities most strongly associated with poor sleep are a measure of general cognitive
4
5 313 health, ACE-R, and a test of verbal phonemic fluency. Two patterns emerged: First, the strongest
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7 314 predictor across the simple and multiple regressions was for the PSQI Total score. Tentatively this
8
9 315 suggests that a cumulative index of sleep problems, rather than any specific pattern of poor sleep, is
10
11 316 the biggest risk factor for poorer cognitive performance. Secondly, after controlling for age, the most
12
13 317 strongly affected cognitive measure is phonemic fluency, the ability to generate name as many
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15 318 different words as possible starting with a given letter within a minute. Verbal fluency is commonly
16
17 319 used as a neuropsychological test (76). Previous work suggests it depends on both the ability to
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19 320 cluster (generating words within a semantic cluster) and to switch (switching between categories),
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21 321 and is especially vulnerable to frontal and temporal lobe damage (with specific regions dependant
22
23 322 on either a semantic or phonemic task (77)). Although modest in size, our findings suggests this task,
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25 323 dependent on multiple executive processes, is particularly affected by poor sleep quality (78). The
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27 324 second strongest association was with the ACE-R, a general cognitive test battery similar in style and
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29 325 content to the MMSE. When an interaction term with age was included, little evidence for
30
31 326 interactions with age (mean $\log_{10}BF_{10} = -2.08$, see Supplementary Figure 4), suggesting that the
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33 327 negative associations between sleep and cognitive performance are a constant feature across the
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35 328 lifespan, rather than specifically in elderly individuals. Together this suggests that poor sleep quality
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37 329 is modestly but consistently associated with poorer general cognitive performance across the
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39 330 lifespan, most strongly with semantic fluency.
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46 332 *Neural Health*

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48 333 Using Diffusion Tensor Imaging, we estimated a general index of white matter integrity in 10 tracts
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50 334 (59) (shown in Supplementary Figure 5), by taking the average Fractional Anisotropy in each white
51
52 335 matter ROI (see (79) for more information). We use the data from a subsample of 641 individuals
53
54 336 (age $M=54.87$, range 18.48-88.96) who were scanned in a 3T MRI scanner (for more details regarding
55
56 337 the pipeline, sequence and processing steps, see (22,79). Regressing neural WM ROI's on sleep
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3 338 quality, we find several small effects, with the strongest associations between sleep efficiency and
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5 339 neural health (see Supplementary Figure 6). All effects are such that poorer sleep is associated with
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7 340 poorer neural health, apart from a small effect in the opposite direction for Uncinate and Daytime
8
9 341 Dysfunction ($BF_{10}= 6.20$). However, when age is included as a covariate, the negative associations
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11 342 between sleep quality and white matter health are attenuated virtually to zero (Figure 4,
12
13 343 mean/median $BF_{10}= 0.18/.10$), with Bayes Factors providing strong evidence for the lack of
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15 344 associations between sleep quality and white matter integrity. One exception was observed: The use
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17 345 of Sleep Medication is associated with *better* neural health in the corticospinal tract, a region
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19 346 previously found to be affected by pathological sleep problems such as sleep apnoea (33). However,
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21 347 this effect is very small ($BF_{10}=3.24$) given the magnitude of the sample and the range of comparisons,
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23 348 so should be interpreted with caution.

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27 [Insert Figure 4 here]

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29 350 Finally, we tested for any interactions by including a mean-scaled interaction term (sleep*age,
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31 351 Supplementary Figure 7). This analysis found evidence for a significant interaction, between the
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33 352 Superior Longitudinal Fasciculus (SLF) and Sleep Medication ($BF_{10}= 13.77$), such that better neural
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35 353 health in the SLF was associated with the use of Sleep Medication more strongly in older adults.
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37 354 Together, these findings suggest that in general, once age is taken into account, self-reported sleep
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39 355 problems in a non-clinical sample are *not* associated with poorer neural health, although there is
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41 356 some evidence for a modest associations between better neural health in specific tracts and the use
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43 357 of sleep medication in the elderly.

44 45 46 47 48 359 *Physical health*

49
50 360 Next we examined whether sleep quality is associated with physical health. Figure 5 shows
51
52 361 the simple regressions between sleep quality and physical health. Strong associations were found
53
54 362 between poor overall sleep (PSQI sum score) and poor self-reported health, both in general
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56 363 ($\log BF_{10}=77.51$) and even more strongly for health in the past 12 months ($\log BF_{10}=91.25$). This may
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3 364 be because poorer sleep, across all components, directly affects general physical health (43,80) or
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5 365 because people subjectively experience sleep quality as a fundamental part of overall general health.
6
7 366 A second association was between BMI and poor sleep quality, most strongly poor Duration
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9 367 ($\log BF_{10}=4.69$).

11 [Insert Figure 5 here]

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13 369 This not only replicates previous findings but is in line with an increasing body of evidence
14
15 370 that suggests that shorted sleep duration causes metabolic changes, which in turn increases the risk
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17 371 of both diabetes mellitus and obesity (43,81,82). Next, we examined whether these effects were
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19 372 attenuated once age was included. We show that although the relationships are slightly weaker, the
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21 373 overall pattern remains (Supplementary Figure 8), suggesting these associations are not merely co-
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23 374 occurrences across the lifespan. Our findings suggest self-reported sleep quality, especially sleep
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25 375 Duration, is related to differences in physical health outcomes in a healthy sample.
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29 376 Finally, there was evidence of a single interaction with age (Supplementary Figure 9):
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31 377 Although poor sleep Duration was associated with *higher* diastolic blood pressure in younger adults,
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33 378 it was associated with *lower* diastolic blood pressure in older individuals ($BF_{10}= 8.53$). This may
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35 379 reflect the fact that diastolic blood pressure is related to cardiovascular health in a different way
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37 380 across the lifespan, although given the small effect size it should be interpreted with caution.
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41 382 *Mental health*

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43 383 Finally, we examined the relationship between sleep quality and mental health, as measured by the
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45 384 Hospital Anxiety and Depression Scale (56). One benefit of the HADS in this context is that, unlike
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47 385 some other definitions (e.g. the DSM-V), sleep quality is not an integral (scored) symptom of these
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49 386 dimensions. As shown in Supplementary Figure 10, there are very strong relationships between all
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51 387 aspects of sleep quality and measures of both anxiety and depression. The strongest predictors of
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53 388 Depression are Daytime Dysfunction ($\log BF_{10}= 245.9$, $R^2=20.9\%$), followed by the overall sleep
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55 389 score ($\log BF_{10}= 170.5$, $R^2=14.6\%$) and sleep quality ($\log BF_{10}= 106.8$, $R^2=9.7\%$). The effects size for
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3 390 Anxiety was comparable but slightly smaller in magnitude. When age is included as a covariate the
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5 391 relationships remained virtually unchanged (Supplementary Figure 11), suggesting these
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7 392 relationships are present throughout across the lifespan. These findings replicate and extend
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9 393 previous work, suggesting that sleep quality is strongly associated with both anxiety and depression
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11 394 across the lifespan.

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13 395 Finally we examined a model with an interaction term (Supplementary Figure 12). Most
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15 396 prominently we found interactions with age in the relationship between HADS depression and the
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17 397 PSQI Total, and in the relationship between HADS depression and Sleep Duration, such that for the
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19 398 relationship between anxiety and overall sleep quality is stronger in younger adults ($BF_{10} = 9.91$, see
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21 399 Figure 6). Together our findings show that poor sleep quality is consistently, strongly and stably
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23 400 associated with poorer mental health across the adult lifespan.

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27 401 [Insert Figure 6 here]

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30 31 403 **Non-linear associations between sleep and health outcomes**

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33 404 In the above analyses, we focused on linear associations between symptoms and health outcomes.
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35 405 However, for one aspect of sleep, namely sleep duration (in hours), evidence exists that these
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37 406 associations are likely to be non-linear, such that both shorter and longer than average sleep are
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39 407 associated with poorer health outcomes (e.g. (83–85). This is echoed in clinical criteria for
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41 408 depression, which commonly include that include both hyper- and hypo-somnia as ‘sleep disruption’
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43 409 symptoms – In other words, both too much or too little sleep are suboptimal. To examine whether
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45 410 we observe evidence for non-linearities we examined the relationship between raw scores on sleep
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47 411 duration (in hours, not transformed to PSQI norms) and health outcomes across the four domains. If
48
49 412 the association between sleep and outcomes is indeed u-shaped (or inverted U, depending on the
50
51 413 scale) then a Bayesian regression would prefer the less parsimonious model that includes the
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53 414 quadratic term. We observed no non-linear associations between any neural or cognitive health
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55 415 variables. We find strong evidence for a quadratic (subscript q) over a linear (subscript l) associations
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3 416 between sleep duration and HADS anxiety ($\log BF_{qi} = 19.98$), even more strongly so with HADS
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5 417 Depression ($\log BF_{qi} = 25.83$, see Figure 7A shows the strongest curvilinear association, namely with
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7 418 depression). We find a similar u-shaped curve with general health ($BF_{qi} = 277.81$) and self-reported
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9 419 health over the last 12 months ($BF_{qi} = 887.59$), the latter shown in Figure 7b. Together, these analyses
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11 420 support previous conclusions that some (although not all) poorer health outcomes can be associated
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13 421 with both too much and too little sleep.

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16 422 [Insert Figure 7 here]

17 423 DISCUSSION

18 424 In this study, we report on the associations between age-related differences in sleep quality and
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20 425 health outcomes in a large, age-heterogeneous sample of community dwelling adults of the
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22 426 Cambridge Neuroscience and Aging (Cam-CAN) cohort. We find that sleep quality generally
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24 427 decreases across the lifespan, most strongly for sleep Efficiency. However age-related changes in
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26 428 sleep patterns are complex and multifaceted, so we used Latent Class Analysis to identify 'sleep
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28 429 types' associated with specific sleep quality profiles. We found that Younger adults are more likely
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30 430 than older adults to display a pattern of sleep problems characterised by poor sleep quality and
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32 431 longer sleep latency, whereas older adults are more likely to display inefficient sleeping,
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34 432 characterised by long periods spent in bed whilst not asleep. Moreover, the probability of being a
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36 433 'good' sleeper, unaffected by any adverse sleep symptoms, decreases considerably after age fifty.

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38 434 Notably, closer investigation of the sleep classes reveals likely further complexities of age-
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40 435 related differences. The category 'poor sleepers', most prevalent in older adults, shows high
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42 436 conditional likelihood of 'poor sleep' across all symptoms except 'daytime dysfunction'. One possible
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44 437 explanation is that almost all individuals in this group are beyond retirement age. For this reason,
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46 438 they likely have greater flexibility in tailoring their day to day activities to their energy levels (as
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48 439 opposed to individuals working fulltime), and are therefore less likely to consider themselves
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50 440 'disrupted' even in the presence of suboptimal sleep. Although more detailed, interview-based
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3 441 investigations would be necessary to examine the precise nature of these findings, it stands to
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5 442 reason that certain symptoms change not just in prevalence but also in meaning across the lifespan.
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7 443 One key strength of our broad phenotypic assessment allows for direct comparison of the
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9 444 different measures of sleep quality and four key health domains. We find strongest associations
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11 445 between sleep quality and mental health, moderate relations between sleep quality and physical
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13 446 health and cognitive health and sleep, virtually all such that poorer sleep is associated with poorer
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15 447 health outcomes. We did not find evidence for associations between self-reported sleep and neural
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17 448 health. Notably, the relationships we observe are mostly stable across the lifespan, affecting
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19 449 younger and older individuals alike. A notable exception to these effects is the absence of any strong
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21 450 relation (after controlling for age) between sleep quality and neural health as indexed by tract-based
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23 451 average fractional anisotropy. Perhaps surprisingly, given we found strong relationships in the same
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25 452 sample between sleep and other outcomes (e.g. mental health, Figure 10) we find that self-reported
26
27 453 sleep problems in a non-clinical sample are not associated with fractional anisotropy above and
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29 454 beyond old age. This is despite the fact that previous work within the same cohort observed
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31 455 moderate to strong associations between white matter and various cognitive outcomes (42,86,87).
32
33 456 However, although notable, our finding does not rule out that such associations do exist with other
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35 457 white matter metrics, that they would be observed with objective measures of sleep such as
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37 458 polysomnography, or that the co-occurrence of age-related declines in sleep quality and white
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39 459 matter share an underlying causal association that cannot be teased apart in a cross-sectional
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41 460 sample.
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45 461 One strength of our study is the assessment of neuroimaging metrics, namely fractional
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47 462 anisotropy, in a large, community-dwelling healthy population. Fractional anisotropy is often used in
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49 463 studies of aging (e.g. Madden, is relatively reliable (88)) and is sensitive to clinical anomalies such as
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51 464 white matter hyperintensities. However, the relationship between FA and white-matter health is
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53 465 indirect (40,89) and drawbacks include its inability to distinguish crossing fibers (e.g. (40,89) and
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55 466 vulnerability to movement and the fact that it likely reflects a combination of underlying
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3 467 physiological properties. Various alternative white matter metrics exist, including summary
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5 468 measures of diffusivity (e.g. axial/radial/mean diffusivity), volumetric measures of white matter
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7 469 hyperintensity (e.g.) and various innovative measures currently in development, but their
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9 470 physiological validity is ongoing (89,90).

11 471 While there are limitations of self-report measures including in older cohorts (19), including
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13 472 the fact that they likely reflect different aspects of sleep health than polysomnography (sleep in the
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15 473 lab), our results suggest there are considerable advantages in using self-reported sleep measures:
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17 474 first, obtaining sleep quality data in a large and broadly phenotyped sample is feasible; and second,
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19 475 our results demonstrated clear and consistent associations across multiple domains for both
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21 476 subjective (e.g. self-reported health) and objective measures (e.g. memory tests, BMI), which both
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23 477 replicate and extend previous lab-based sleep findings. Future work should ideally simultaneously
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25 478 measure polysomnography and self-report in longitudinal, large scale cohorts to fully capture the
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27 479 range of overlapping and complementary relations between different aspects of sleep quality and
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29 480 health outcomes (19).

31 481 For both self-report and objective measures of sleep quality an open question is that of
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33 482 causality: Does poor sleep affect health outcomes, do health problems affect sleep, are they both
34
35 483 markers of some third problem, or do causal influences go both ways? Most likely, all these patterns
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37 484 occur to varying degrees. Previous studies have shown that sleep quality causally affects health
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39 485 outcomes such as diabetes (43) and memory consolidation (1) while other evidence suggests that
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41 486 depression directly affect sleep quality (91,92) and that damage to neural structures may affect
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43 487 sleep regulation (93). Although our findings are in keeping with previous findings, our cross-sectional
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45 488 sample cannot tease apart the causal direction of the observed associations, more work remains to
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47 489 be done to disentangle these complex causal pathways.

50 490 In our paper we focus on a healthy, age-heterogeneous community dwelling sample. This
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52 491 allows us to study the associations between healthy aging and self-reported sleep quality, but comes
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54 492 with two key limitations of the interpretations of our findings. First and foremost, our findings are
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3 493 cross-sectional, not longitudinal. This means we can make inferences about age-related *differences*,
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5 494 but not necessarily age-related *changes* (94,95). One reason why cross-sectional and longitudinal
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7 495 estimates may diverge is that older adults can be thought of as cohorts that differ from the younger
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9 496 adults in more ways than age alone. For example, our age range includes individuals born in the
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11 497 twenties and thirties of the 20th century. Compared to someone born in the 21st century, these
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13 498 individuals will likely have experience various differences during early life development (e.g. less
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15 499 broadly accessible education, lower quality of healthcare, poorer nutrition and similar patterns). For
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17 500 some of our measures, these are inherent limitations –*truly* longitudinal study of neural aging is
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19 501 inherently impossible as scanner technology has not been around sufficiently long. This means our
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21 502 findings likely reflect a combination of effects attributable to age-related changes as well as baseline
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23 503 differences between subpopulations that may affect both mean differences as well as
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25 504 developmental trajectories.
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29 505 Second, our sample reflects an atypical population in the sense that they are willing and able
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31 506 to visit the laboratory on multiple occasions for testing sessions. This subsample is likely a more
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33 507 healthy subset of the full population, which will mean the range of (poor) sleep quality as well as
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35 508 (poorer) health outcomes will likely be less extreme than in the full population. However, this
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37 509 challenge is not specific to our sample. In fact, as the Cam-CAN cohort was developed using stratified
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39 510 sampling based on primary healthcare providers, our sample is likely as population-representative as
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41 511 is feasible for a cohort of this magnitude and phenotypic breadth (see (12) for further details).
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43 512 Nonetheless, a healthier subsample may lead to restriction of range (96), i.e. an attenuation of the
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45 513 strength of the associations observed between sleep quality and health outcomes. Practically, this
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47 514 means that our results likely generalise to comparable, healthy community dwelling adults, but not
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49 515 necessarily to populations that include those affected by either clinical sleep deprivation or other
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51 516 serious health conditions.
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Conclusions

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520 Taken together, our study allows several conclusions. First, although we replicate the age-
521 related deterioration in some aspects of sleep quality, other aspects remain stable or even improve.
522 Second, we show that the profile of sleep quality changes across the lifespan. This is important
523 methodologically, as it suggests that PSQI sum scores do not capture the full picture, especially in
524 age-heterogeneous samples. Moreover, it is important from a psychological standpoint: We show
525 that 'sleep quality' is a multidimensional construct and should be treated as such if we wish to
526 understand the complex effects and consequences of sleep quality across the lifespan. Third,
527 moderate to strong relations exist between sleep quality and cognitive, physical and mental health,
528 and these relations largely remain stable across the lifespan. In contrast, we show evidence that in
529 non-clinical populations, poorer self-reported sleep is not reliably associated with poorer neural
530 health. Finally, we find that for absolute sleep duration, we replicate previous findings that both
531 longer and shorter than average amounts of sleep are association with poorer self-reported general
532 health and higher levels of depression and anxiety.

533 Together with previous experimental and longitudinal evidence, our findings suggest that at
534 least some age-related decreases in health outcomes may be due to poorer sleep quality. We show
535 that self-reported sleep quality can be an important indicator of other aspects of healthy functioning
536 throughout the lifespan, especially for mental and general physical health. Our findings suggest
537 accurate understanding of sleep quality is essential in understanding and supporting healthy aging
538 across the lifespan.

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3 545**Author contributions**

4
5 546 AG, MS and MS designed the study. AG and RAK performed the analyses. CC organized and
6
7 547 conducted the data collection. AG, MS and RAK wrote the manuscript. YL provided considerable
8
9 548 expertise on sleep and poor sleep outcomes. All authors approved the final manuscript.
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34
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36
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38
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40
41 563 Samu, Jason R Taylor, Matthias Treder, Kamen Tsvetanov, Janna van Belle, Nitin Williams; Research
42
43 564 Assistants: Lauren Bates, Tina Emery, Sharon Erzinçlioglu, Sofia Gerbase, Stanimira Georgieva, Claire
44
45 565 Hanley, Beth Parkin, David Troy; Affiliated Personnel: Tibor Auer, Marta Correia, Lu Gao, Emma
46
47 566 Green, Rafael Henriques; Research Interviewers: Jodie Allen, Gillian Amery, Liana Amunts, Anne
48
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5 572 Mitchell, Laura Willis.

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Legends

Figure 1. Descriptive interpretation of Bayes Factors

Figure 2. Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

Figure 3. Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction Time were measured only in the imaging cohort: mean N = 648, N=11.11. Sample sizes for 5 other domains are similar: mean N= 2300.25, SD= 65.57)

Figure 4. Multiple regressions between sleep components and Neural Health. Each cell represents the relationship between a sleep component and the mean neural health in a given tract as index by Fractional Anisotropy. Numbers represent R-squared, the sample size is show in the last column. Strong associations are observed between measures of Sleep Efficiency and multiple tracts, along with sporadic associations between other components and tracts. White matter tracts abbreviations: Uncinate fasciculus (UNC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior Fronto-occipital fasciculus (IFOF), forceps minor (FMin), forceps major (FMaj), cerebrospinal tract (CST), the ventral cingulate gyrus (CINGHipp), the dorsal cingulate gyrus (CING), and the anterior thalamic radiations (ATR). N varies slightly across components due to varying missingness (N mean = 631.325, SD = 10.32).

Figure 5 Physical health and sleep quality. Numbers represent Rsquared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and General) were measured in the full cohort (Mean = 2315.37, SD=66.29), the other indicators were measured in the imaging cohort only (Mean = 569.87, SD= 11.16).

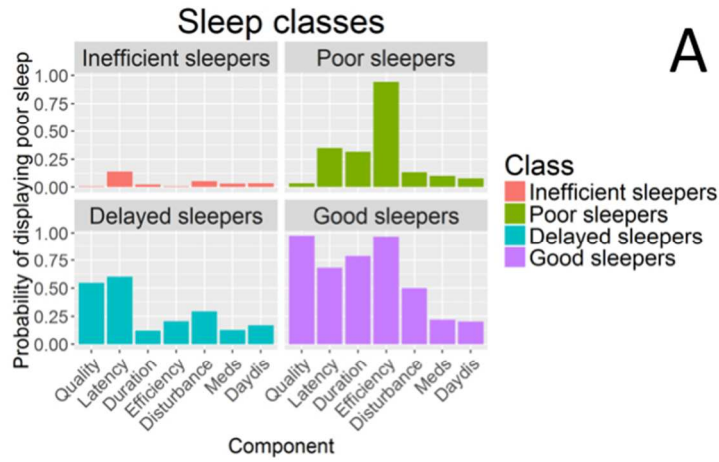
Figure 6. Interaction between sleep quality and anxiety. (N=724, age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to 98.88).

Figure 7. Curvilinear associations between sleep duration in hours and A) HADS depression and B) general health (self-reported). For visual clarity a small amount of random jitter was added to the data points.

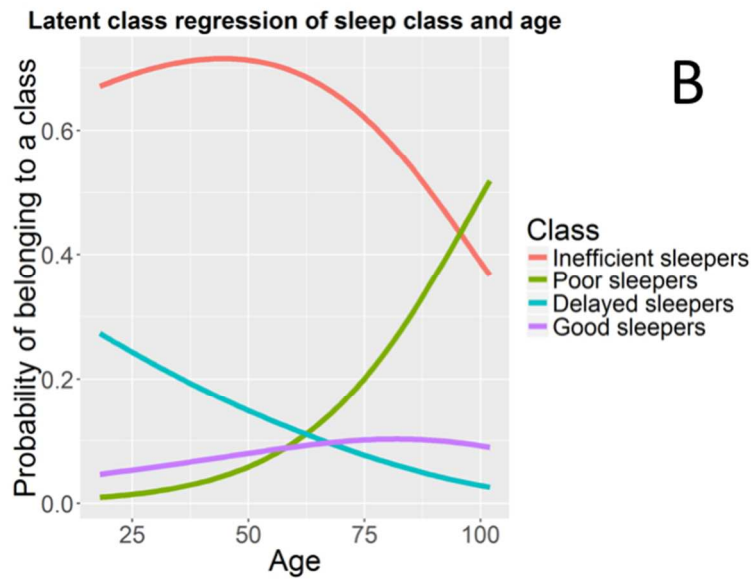
Bayes Factor BF ₁₀	Log BF ₁₀	Tileplot colour	Description (Jeffreys, 1961)
>100	>4.6	Red	Extreme evidence for H1
30 – 100	3.4 – 4.6	Red	Very strong evidence for H1
10 – 30	2.3 – 3.4	Red	Strong evidence for H1
3 – 10	1.098 – 2.3	Light red	Substantial evidence for H1
1 – 3	1 – 1.098	Light red	Anecdotal evidence for H1
1	0	White	No evidence either way
1/3 – 1	-1.098 – -1	Light blue	Anecdotal evidence for H0
1/3 - 1/10	-2.3 – -1.098	Light blue	Substantial evidence for H0
1/10 - 1/30	-3.4 – -2.3	Light blue	Strong evidence for H0
1/30 - 1/100	-4.6 – -3.4	Light blue	Very strong evidence for H0
<1/100	< -4.6	Blue	Extreme evidence for H0

Figure 1. Descriptive interpretation of Bayes Factors

Insert Figure 1 here
338x190mm (96 x 96 DPI)



A



B

Figure 2. Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

Insert Figure 2 here
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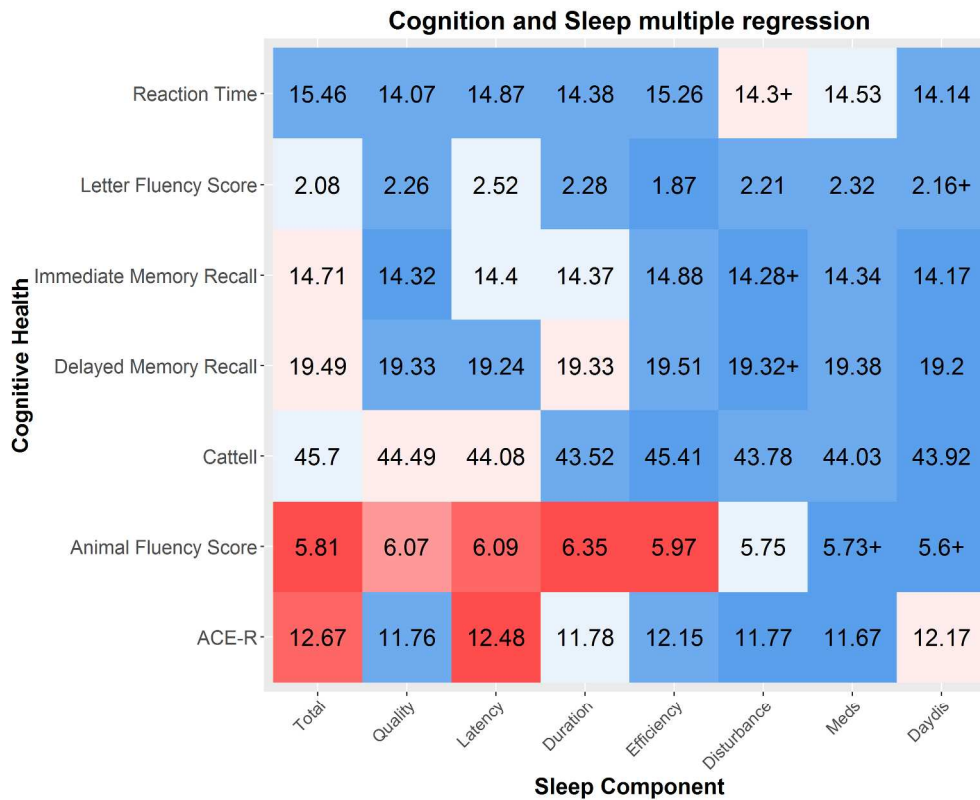


Figure 3. Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction Time were measured only in the imaging cohort: mean N = 648, N=11.11. Sample sizes for 5 other domains are similar: mean N= 2300.25, SD= 65.57)

Insert Figure 3 here
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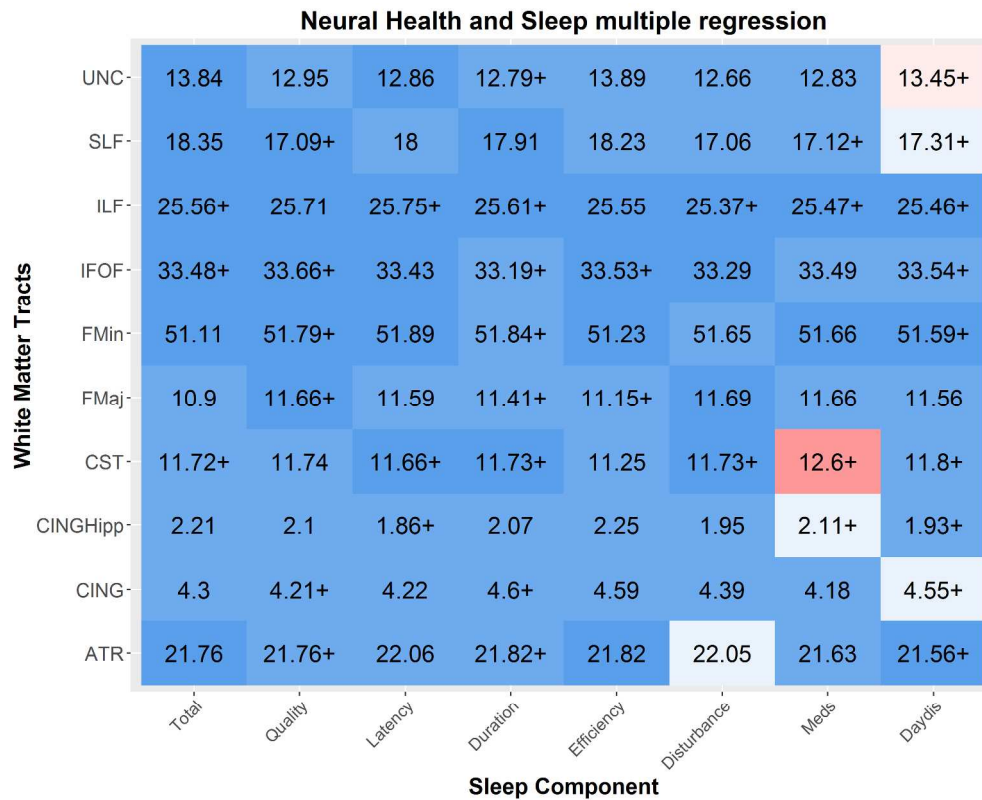


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Insert Figure 4 here
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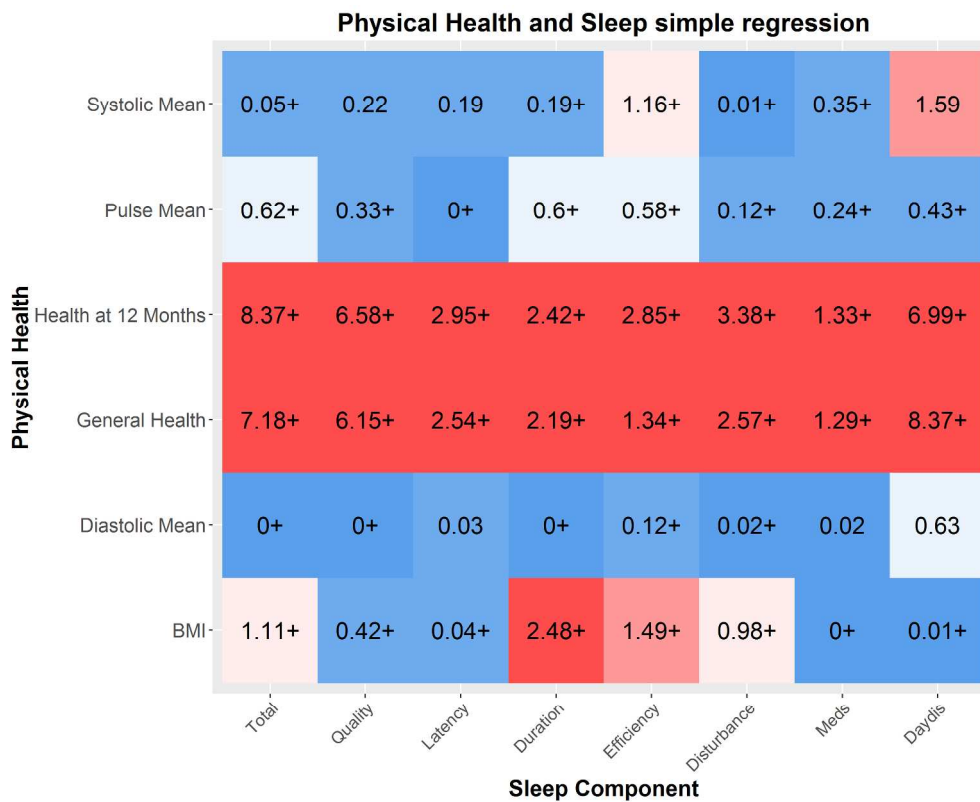


Figure 5 Physical health and sleep quality. Numbers represent Rsquared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and General) were measured in the full cohort (Mean = 2315.37, SD=66.29), the other indicators were measured in the imaging cohort only (Mean = 569.87, SD= 11.16).

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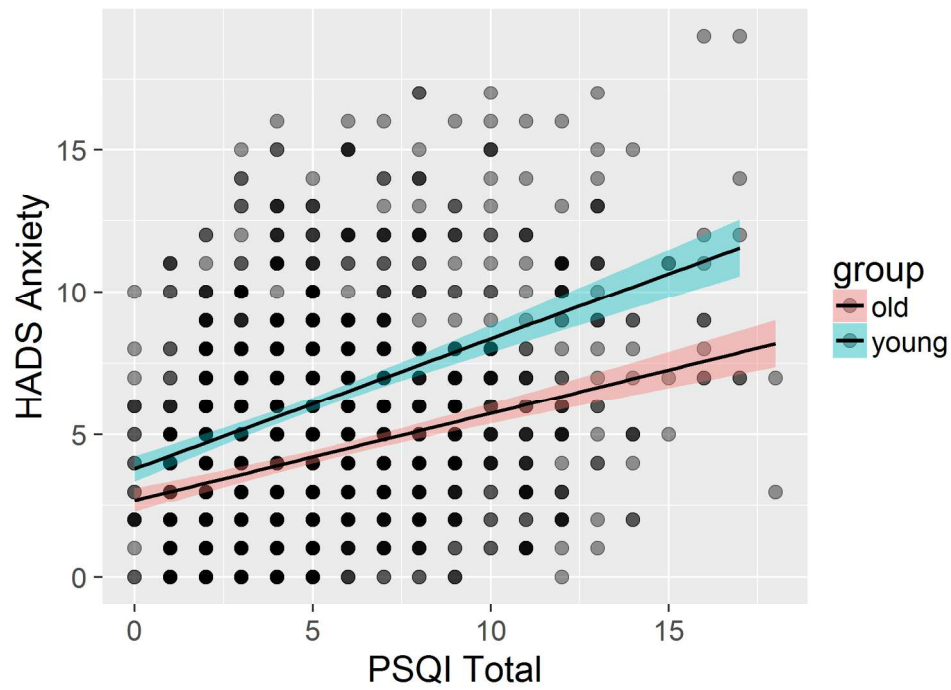


Figure 6. Interaction between sleep quality and anxiety. (N=724, age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to 98.88).

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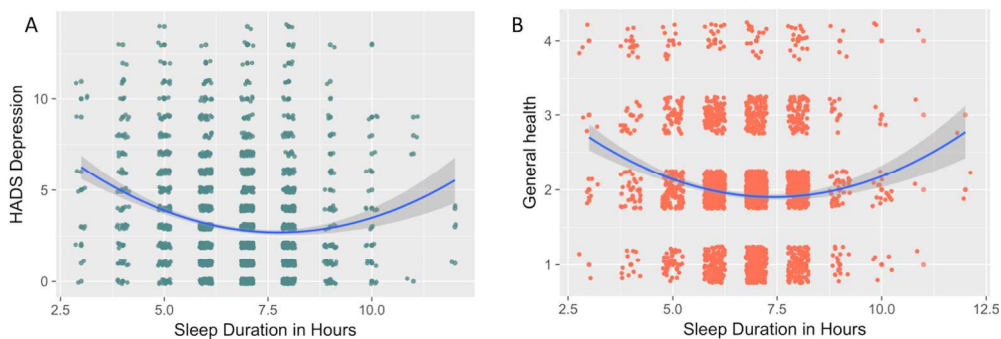


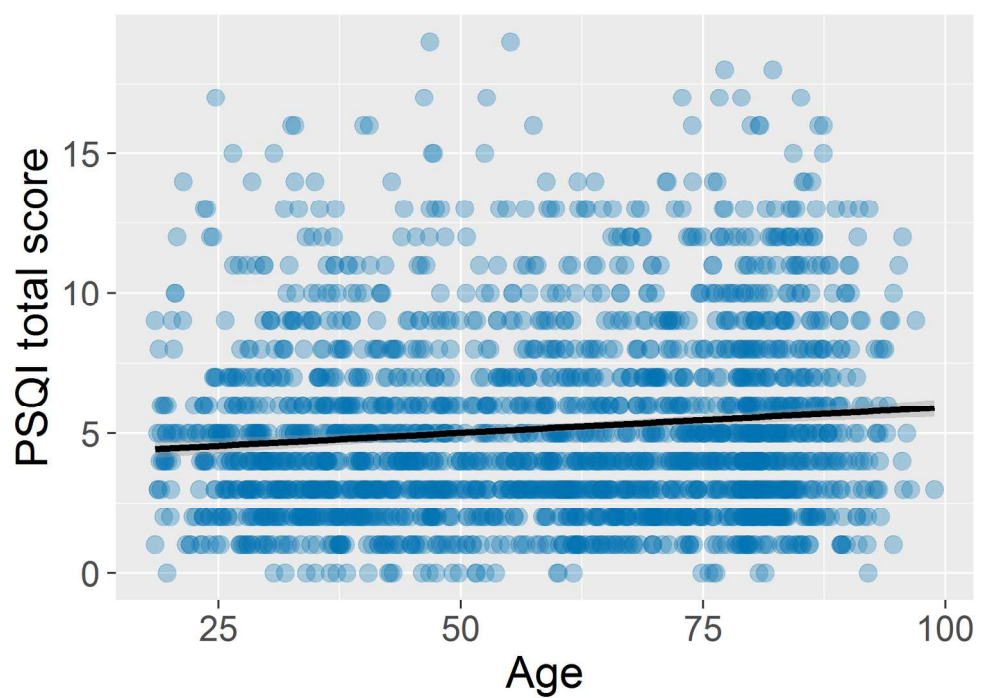
Figure 7. Curvilinear associations between sleep duration in hours and A) HADS depression and B) general health (self-reported). For visual clarity a small amount of random jitter was added to the data points.

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Peer review only

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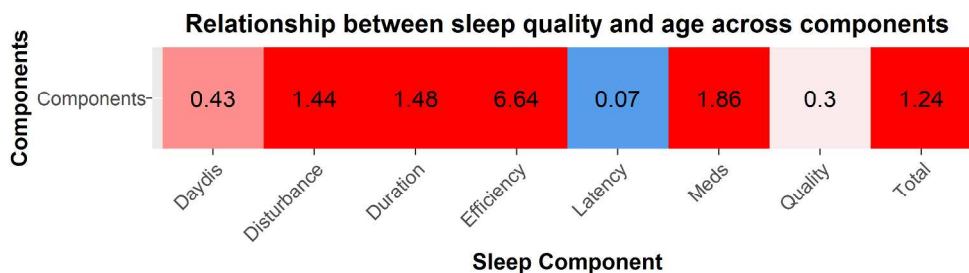
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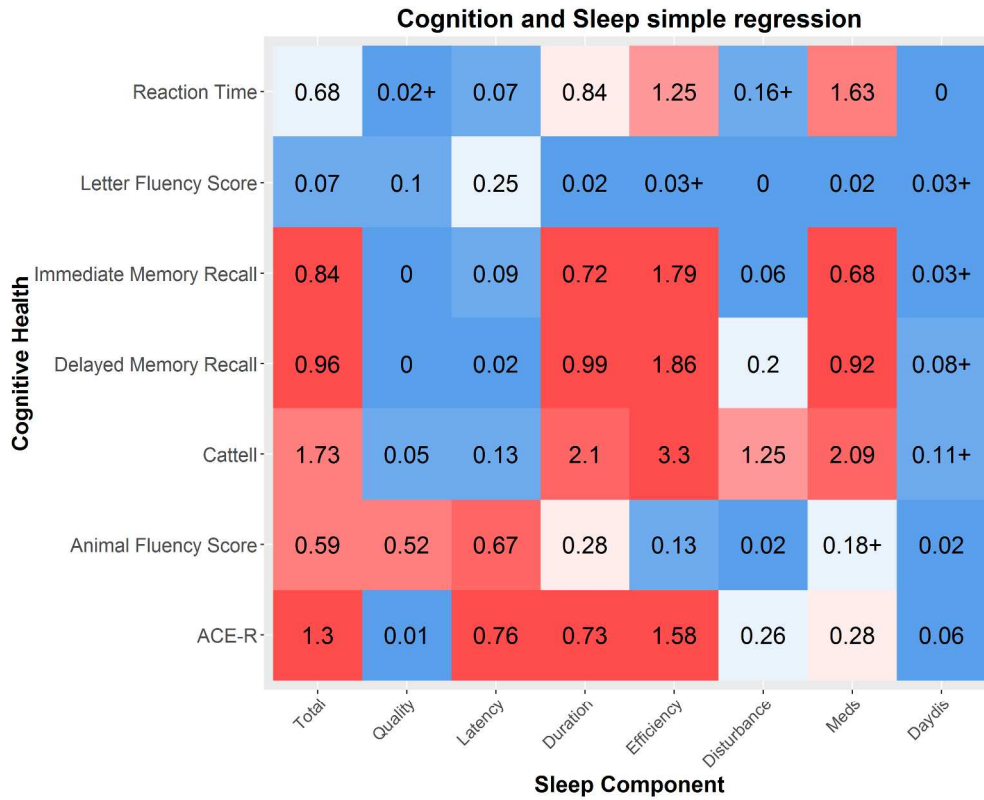
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Cognition and Sleep interaction term

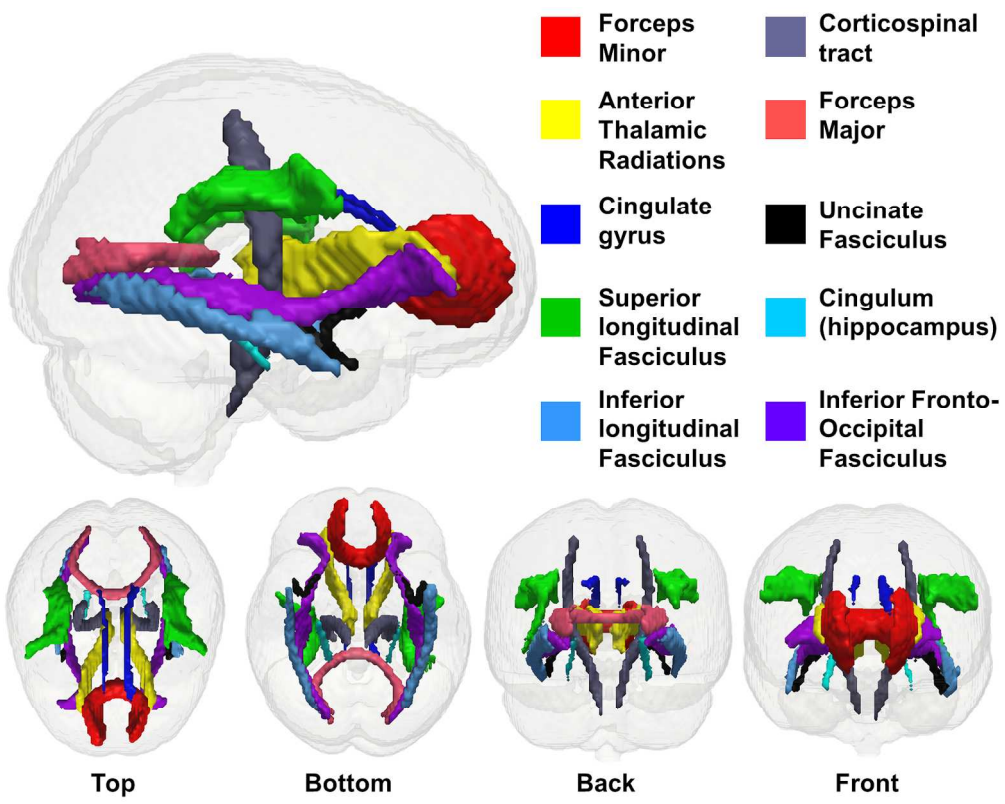
Cognitive Health	Cognition and Sleep interaction term							
	Total	Quality	Latency	Duration	Efficiency	Disturbance	Medts	Daydis
Reaction Time	15.6	14.14	15.08	14.44	15.44	14.32+	14.58+	14.19
Letter Fluency Score	2.21	2.36	2.7	2.28	1.95	2.35	2.33	2.16
Immediate Memory Recall	14.74+	14.32	14.54+	14.37+	14.9+	14.31	14.37+	14.27+
Delayed Memory Recall	19.54+	19.33+	19.44+	19.34+	19.58+	19.33	19.4+	19.26+
Cattell	45.72	44.56	44.25	43.52	45.41+	43.85	44.04	43.93
Animal Fluency Score	5.81+	6.07+	6.09	6.35	6	5.75+	5.73+	5.75+
ACE-R	12.69	11.76+	12.51	11.83	12.3	11.8+	11.71	12.22+

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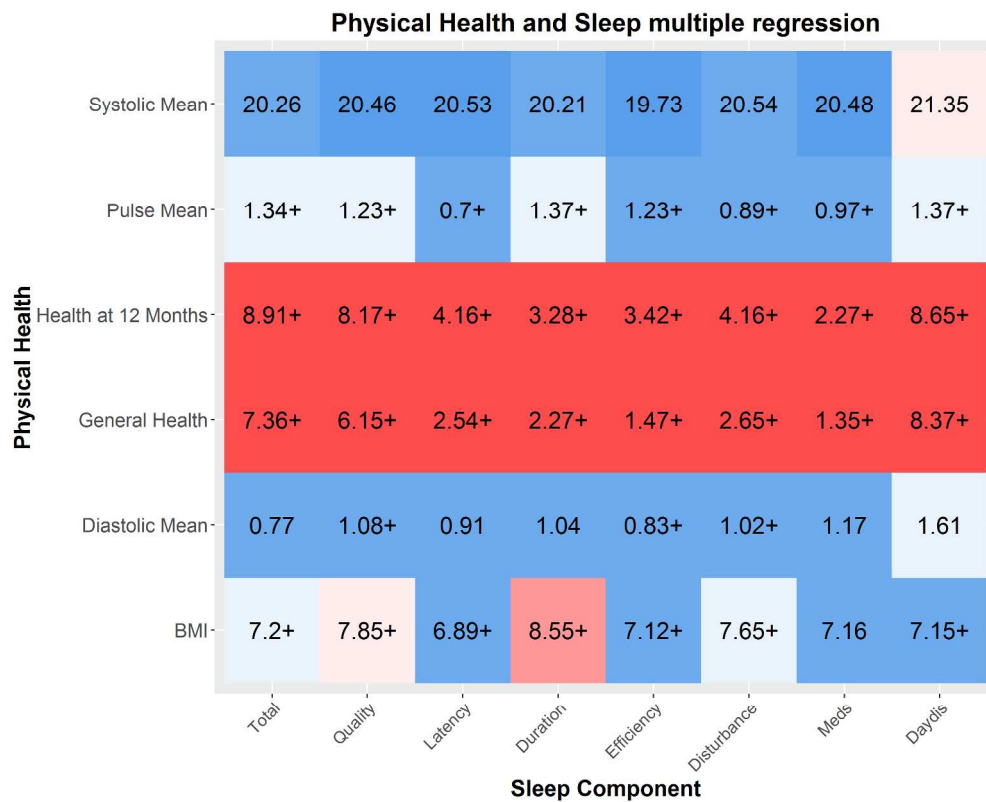
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Neural Health and Sleep interaction term

White Matter Tracts	Neural Health and Sleep interaction term							
	Total	Quality	Latency	Duration	Efficiency	Disturbance	Medts	Daydis
UNC	13.88	12.96	12.9+	12.79	13.9	12.9	12.97	13.45
SLF	18.36+	17.11+	18.01	17.91+	18.24	17.16	18.39+	17.32+
ILF	25.57+	25.71	25.75+	25.64+	25.55+	25.5	26+	25.46+
IFOF	33.67+	33.77+	33.48+	33.44+	33.69+	33.43	33.55+	33.8+
FMin	51.12	51.79+	51.91	51.85	51.24	51.85	51.72+	51.64+
FMaj	10.91+	12.45+	11.6	11.41+	11.15+	12.18	11.81	11.76+
CST	11.89+	11.88	11.72+	11.83+	11.3+	11.74+	13.24+	11.85+
CINGHipp	2.22	2.1	1.88	2.09	2.25	2.01	2.75+	2.07
CING	4.31+	4.27	4.23+	4.72+	4.59+	4.44+	4.9+	4.61+
ATR	21.79	21.83+	22.08	21.83	21.82+	22.11	22.04	21.58+

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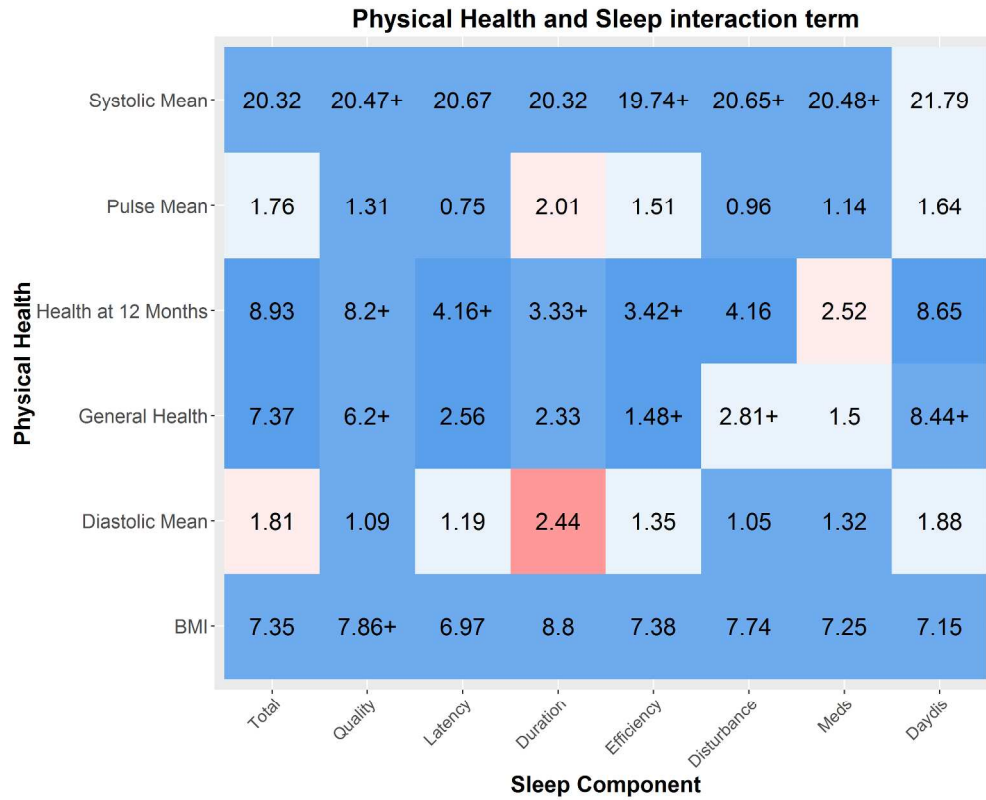


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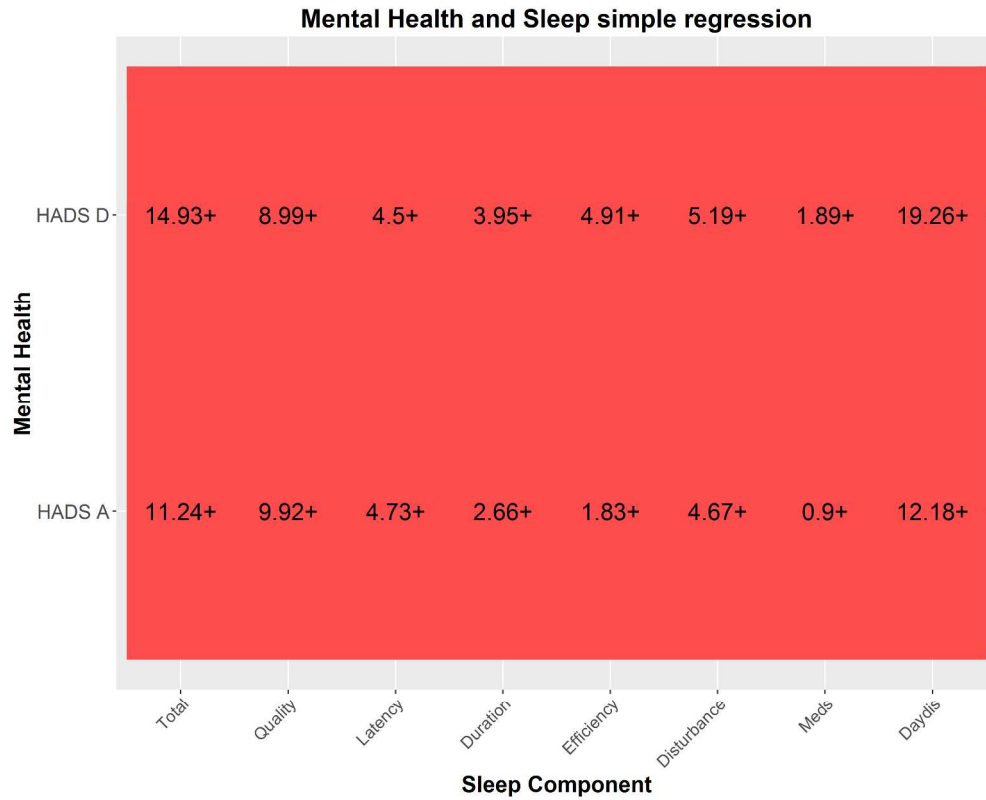
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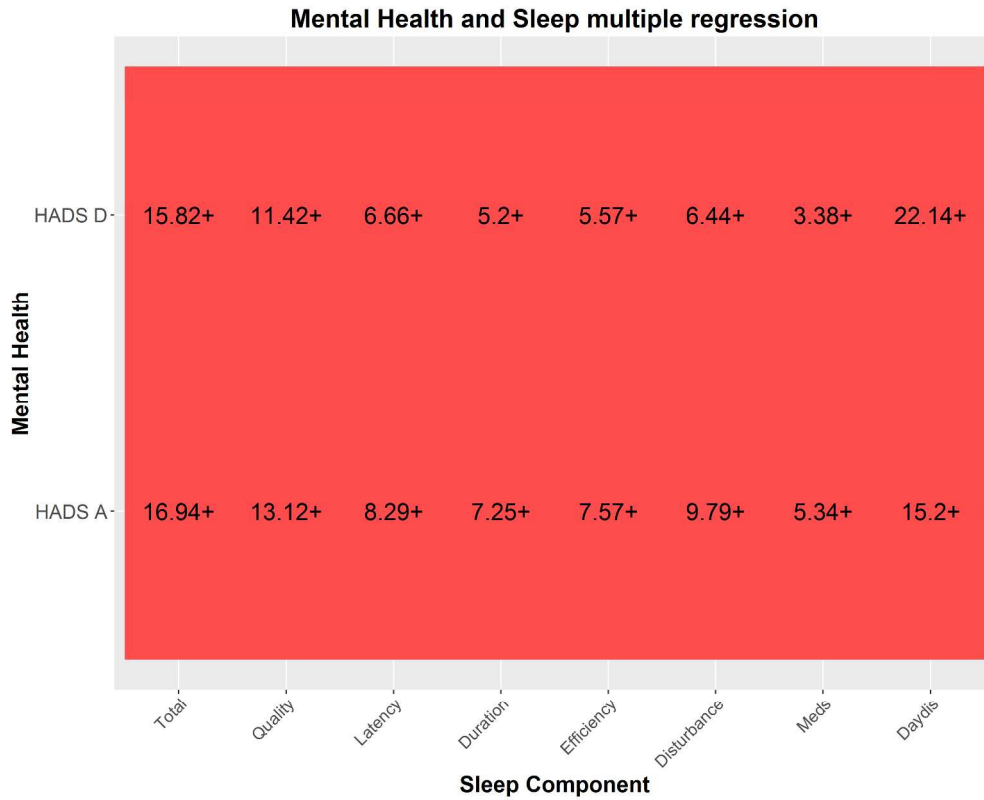
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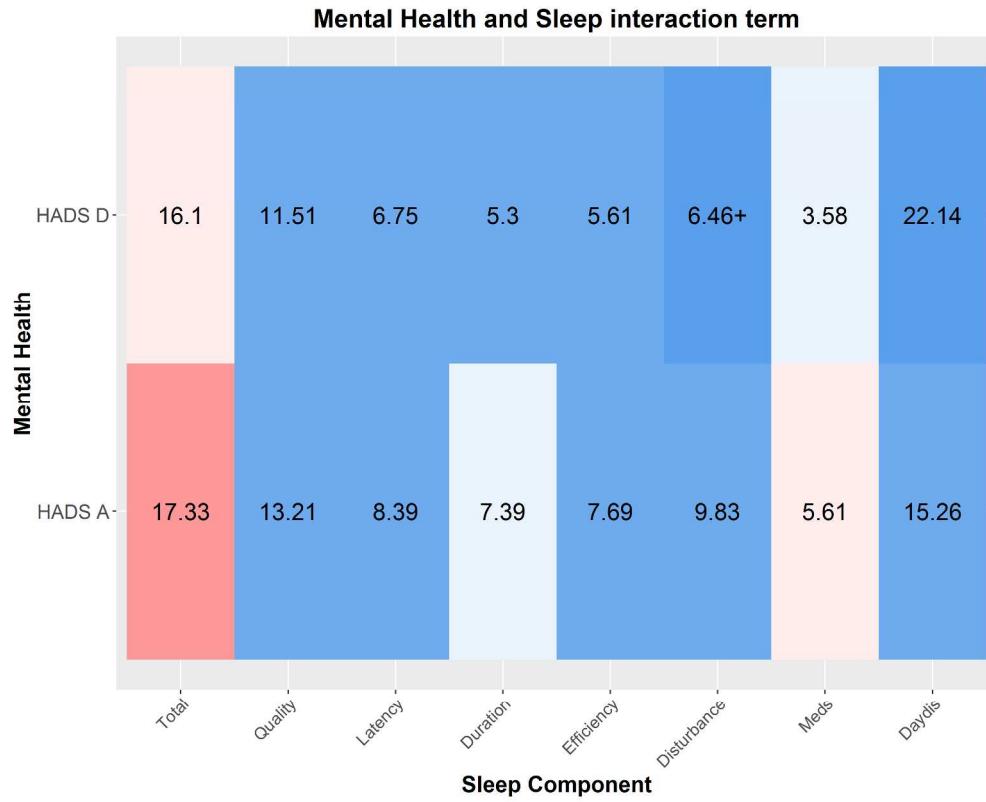
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-11
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10-13
		(b) Describe any methods used to examine subgroups and interactions	10
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14-22
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	9,10
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-22
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-22
Discussion			
Key results	18	Summarise key results with reference to study objectives	22-26
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	25-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	25-26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

How are age-related differences in sleep quality associated with health outcomes? An epidemiological investigation in a UK cohort of 2406 adults

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014920.R2
Article Type:	Research
Date Submitted by the Author:	07-Mar-2017
Complete List of Authors:	Gadie, Andrew; MRC Cognition and Brain Sciences Unit Shafto, Meredith; University of Cambridge, Center for Speech, Language and the Brain Leng, Yue; University of Cambridge; University of California San Francisco, School of Medicine Cam-CAN, _; University of Cambridge, Center for Sleep, language and the brain Kievit, Rogier; MRC CBSU
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Neurology, Mental health, Public health, Geriatric medicine
Keywords:	Ageing, SLEEP MEDICINE, cognition, MENTAL HEALTH, Neurobiology < BASIC SCIENCES

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2 How are age-related difference in sleep quality associated with health outcomes? An
3 epidemiological investigation in a UK cohort of 2406 adults

4
5 Andrew Gadie¹

6 Meredith Shafto²

7 Yue Leng³

8 Cam-CAN⁴

9 Rogier A. Kievit^{1*}

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*Corresponding author: rogier.kievit@mrc-cbu.cam.ac.uk

1 MRC Cognition and Brain Sciences Unit, 15 Chaucer Rd, Cambridge, CB2 7EF, United Kingdom

2 Department of Psychology, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom

3 University of California, San Francisco

4 Cambridge Centre for Ageing and Neuroscience (Cam-CAN), University of Cambridge and MRC Cognition and Brain Sciences Unit, Cambridge, UK, www.cam-can.com

1
2
3 12 Abstract
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5 13 **Objectives** To examine age related differences in self-reported sleep quality and their
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7 14 associations with health outcomes across four domains: Physical Health, Cognitive Health, Mental
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9 15 Health and Neural Health.

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11 16 **Setting** Cam-CAN is a cohort study in East Anglia/England, which collected self-reported
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13 17 health and lifestyle questions as well as a range of objective measures from healthy adults.

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15 18 **Participants** 2406 healthy adults (age 18-98) answered questions about their sleep quality
16
17 19 (Pittsburgh Sleep Quality Index) and measures of Physical, Cognitive, Mental, and Neural Health. A
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19 20 subset of 641 individuals provided measures of brain structure.
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21

22 21 **Main outcome measures** Pittsburgh Sleep Quality Index scores (PSQI) of sleep, and scores
23
24 22 across tests within the four domains of health. Latent Class Analysis (LCA) is used to identify sleep
25
26 23 types across the lifespan. Bayesian regressions quantify the presence, and absence, of relationships
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28 24 between sleep quality and health measures.
29

30
31 25 **Results** Better sleep is generally associated with better health outcomes, strongly so for
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33 26 mental health, moderately for cognitive and physical health, but not for sleep quality and neural
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35 27 health. Latent Class Analysis identified four sleep types: 'Good sleepers' (68.6%, most frequent in
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37 28 middle age), 'inefficient sleepers' (13.05%, most frequent in old age), 'Delayed sleepers' (9.76%,
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39 29 most frequent in young adults) and 'poor sleepers' (8.6%, most frequent in old age). There is little
40
41 30 evidence for interactions between sleep quality and age on health outcomes. Finally, we observe u-
42
43 31 shaped associations between sleep duration and mental health (depression and anxiety) as well as
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45 32 self-reported general health, such that both short and long sleep were associated with poorer
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47 33 outcomes.
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50 34 **Conclusions** Lifespan changes in sleep quality are multifaceted and not captured well by
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52 35 summary measures, but instead as partially independent symptoms that vary in prevalence across
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54 36 the lifespan. Better self-reported sleep is associated with better health outcomes, and the strength
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3 37 of these associations differs across health domains. Notably, we do observed associations between
4
5 38 self-reported sleep quality and white matter.
6

7 39 **Funding** Biotechnology and Biological Sciences Research Council (grant number
8
9 40 BB/H008217/1). RAK is supported by the Wellcome Trust (grant number 107392/Z/15/Z and the UK
10
11 41 Medical Research Council (MC-A060-5PR61).
12

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16 43 **Keywords**

17
18 44 Ageing, sleep quality, healthy ageing, cognition, mental health, cognition, white matter, physical
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20 45 health
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25 47 **Strengths and limitations of this study**

- 26
27 48 • Broad phenotypic assessment of healthy ageing across multiple health domains
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29 49 • Advanced analytic techniques (i.e. Latent Class Analysis regression) allows new insights
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31 50 • A uniquely large neuroimaging sample combined with Bayesian inference allows for
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33 51 quantification of evidence for the null hypothesis
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35 52 • Subjective sleep measures may have drawbacks in older samples
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37 53 • Cross-sectional data precludes modelling of within subject changes
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3 55 **BACKGROUND**
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5 56 Sleep is a fundamental human behaviour, with humans spending almost a third of their lives asleep.
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7 57 Regular and sufficient sleep has been shown to benefit human physiology through a number of
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9 58 different routes, ranging from consolidation of memories (1) to removal of free radicals (2) and
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11 59 neurotoxic waste (3). Sleep patterns are known to change across the lifespan in various ways.
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13 60 including decreases in quantity and quality of sleep (4), with up to 50% of older adults report
14
15 61 difficulties initiating and/or maintaining sleep (5). A meta-analysis of over 65 studies reflecting 3577
16
17 62 subjects across the lifespan reported a complex pattern of changes, including an increase of stage 1
18
19 63 but a decrease of stage 2 sleep in old age, as well as a decrease in REM sleep (6). An epidemiological
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21 64 investigation of self-reported sleep in older adults observed marker sex differences in age-related
22
23 65 sleep changes, with females more likely to report disturbed sleep onset but men reporting night-
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25 66 time awakenings (7). Other findings age-related physiological changes in the alignment of
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27 67 homeostatic and circadian rhythms (8), decreases in sleep efficiency (9) the amount of slow-wave
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29 68 sleep, and an increase in daytime napping (10). Importantly, interruption and loss of sleep has been
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31 69 shown to have wide ranging adverse effects on health (11), leaving open the possibility that age-
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33 70 related changes in sleep patterns and quality may contribute to well-documented age-related
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35 71 declines in various health domains.
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40 72 In the current study, we examine self-reported sleep habits in a large, population-based
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42 73 cohort Cambridge Centre for Ageing and Neuroscience (Cam-CAN (12)). We relate sleep measures to
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44 74 measures of health across four health domains: cognitive, brain health, physical and mental health.
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46 75 Our goal is to quantify and compare the associations between typical age-related changes in sleep
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48 76 quality and a range of measures of health measures that commonly decline in later life. We assess
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50 77 sleep using a self-reported measure of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) (13).
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52 78 The PSQI has good psychometric properties (14) and has been shown to correlate reliably with
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54 79 diseases of aging and mortality (15–17). Although polysomnography (18) is commonly considered
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56 80 the gold standard of sleep quality measurement, it is often prohibitively challenging to employ in
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3 81 large samples. A recent direct comparison of sleep measures (19) suggests that although subjective
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5 82 sleep measures (such as PSQI) may have certain drawbacks in older samples, they also capture
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7 83 complementary aspects of sleep quality not fully captured by polysomnography. Moreover,
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9 84 collecting self-report sleep quality data in a large, deeply phenotyped cohort offers several
10
11 85 additional benefits.

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14 86 By utilising a population cohort of healthy adults, and studying a range of health outcomes in
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16 87 the same population, we can circumvent challenges associated with studying clinical populations
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18 88 and provide new insights. First and foremost, by investigating associations between sleep and
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20 89 outcomes across multiple health domains in the same sample, we can make direct comparisons of
21
22 90 the relative magnitude of these effects. Second, larger samples allow us to can generate precise
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24 91 effect size estimates, as well as adduce in favour of the null hypothesis. Third, we investigate the
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26 92 associations between sleep quality and neural health in a uniquely large healthy population.

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28
29 93 Previous investigations of the consequences of poor sleep on especially neural health have generally
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31 94 focuses on clinical populations such as those suffering from insomnia (20,21). Although such studies
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33 95 are crucial for understanding pathology, the demographic idiosyncrasies and often modest sample
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35 96 sizes of these approaches make it hard to generalize to healthy, community dwelling lifespan
36
37 97 populations. Moreover, most studies that study age-related changes or differences focus on (very)
38
39 98 old age, while far less is known about young and middle aged adults (6). For these reasons, our focus
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41 99 on a healthy, multimodal lifespan cohort is likely to yield novel insights into the subtle changes in
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43 100 sleep quality across the lifespan.

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45
46 101 We will focus on three questions within each health domain: First, is there a relationship
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48 102 between sleep quality and health? Second, does the strength and nature of this relationship change
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50 103 when age is included as a covariate? Third, does the strength and nature of the relationship change
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52 104 across the lifespan? We will examine these questions across each of the four health domains.

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3 107 **METHODS**
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5 108 **Sample**
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7 109 A cohort of 2544 (12) was recruited as part of the population-based Cambridge Centre for Ageing
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9 110 and Neuroscience (Cam-CAN) cohort (www.cam-can.com), drawn from the general population via
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11 111 Primary Care Trust (PCT)'s lists within the Cambridge City (UK) area 10,520 invitation letters were
12
13 112 sent between 2010 and 2012, and willing participants were invited to have an interview conducted
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15 113 in their home, with questions on health, lifestyle demographics and core cognitive assessments.
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17 114 Sample size was chosen to allow for 100 participants per decile in further acquisition stages, giving
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19 115 sufficient power to separate age-related change from other sources of individual variation. For
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21 116 additional details of the project protocol see (12,22) and for further details of the Cam-CAN dataset
22
23 117 visit <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/>. A further subset of participants who were
24
25 118 MRI compatible with no serious cognitive impairment participated in a neuroimaging session (22)
26
27 119 between the 2011 and 2013. Participants included were native English speakers, had normal or
28
29 120 corrected to normal vision and hearing, scored 25 or higher on the mini mental state (23). Note that
30
31 121 other, more stringent cut-offs are sometimes employed to screen for premorbid dementia, such as a
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33 122 score of 88 or higher in the Addenbrookes Cognitive Examination – Revised (24). For the sake of
34
35 123 comprehensiveness we repeated our analyses using this more stringent cut off (ACE-R>88), but
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37 124 observed no noteworthy differences in our findings, so we only report the findings based on the
38
39 125 MMSE. Ethical approval for the study was obtained from the Cambridgeshire 2 (now East of England-
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41 126 Cambridge Central) Research Ethics Committee (reference: 10/H0308/50). Participants gave written
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43 127 informed consent. The raw data and analysis code are available upon signing a data sharing request
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45 128 form (see <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/> for more detail).
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53 130 **Variables**
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55 131 *Sleep Measures*
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3 132 Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a well-validated
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5 133 self-report questionnaire (13,19) designed to assist in the diagnosis of sleep disorders. The questions
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7 134 concern sleep patterns, habits, and lifestyle questions, grouped into seven components, each
8
9 135 yielding a score ranging from 0 (good sleep/no problems) to 3 (poor sleep/severe problems), that
10
11 136 are commonly summed to a PSQI Total score ranging between 0 and 21, with higher scores
12
13 137 reflecting poorer sleep quality.

138 **Health Measures**

139 *Cognitive health.* A number of studies have found associations between poor sleep and
140
141 cognitive decline, including in elderly populations. Poor sleep affects cognitive abilities such as
142
143 executive functions (25) and learning and memory processes (26), whereas short term
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145 pharmaceutical interventions such as administration of melatonin improve both sleep quality and
146
147 cognitive performance (27,28). Recent work (29) concluded that “maintaining good sleep quality, at
148
149 least in young adulthood and middle age, promotes better cognitive functioning and serves to
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151 protect against age-related cognitive declines”. As sleep may affect various aspects of cognition
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153 differently (30), we include measures that cover a range of cognitive domains including memory,
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155 reasoning, response speed, and verbal fluency, as well as including a measure of general cognition
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157 (See Table 1 and (12) for more details).

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149 *Neural health.* Previous research suggests that individuals with a severe disruption of sleep
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151 are significantly more likely to exhibit signs of poor neural health (20,31). Specifically, previous
152
153 studies have observed decreased white matter health in clinical populations suffering from
154
155 conditions such as chronic insomnia (21), obstructive sleep apnoea (32,33), excessively long sleep in
156
157 patients with diabetes (34), and REM Sleep Behaviour Disorder (35). Many of these studies focus on
158
159 white matter hyperintensities (WMH), a measure of the total volume or number of (regions)
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161 showing low-level neural pathology (although some study grey matter, e.g. (36,37). White matter
162
163 hyperintensities are often used as a clinical marker, as longitudinal increases in WMHs are
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165 associated with increased risk of stroke, dementia and death (38) and are more prevalent in patients

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3 158 with pathological sleep problems (33,34). However, use of this metric in clinical cohorts largely
4
5 159 leaves open the question of the impact of sleep quality on neural (white matter) health in non-
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7 160 clinical, healthy populations. To address this question, we use a more general indicator of white
8
9 161 matter neural health; *Fractional Anisotropy* (FA). FA is associated with white matter integrity and
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11 162 myelination (39,40). We use FA as recent evidence suggests that WMHs represent the extremes
12
13 163 (foci) of white matter damage, and that FA is able to capture the full continuum of white matter
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15 164 integrity (41). For more information regarding the precise white matter pipeline, see (12,22,42).

16 165 *Physical health.* Sleep quality is also an important marker for physical health, with poorer
17
18 166 sleep being associated with conditions such as obesity, diabetes mellitus (43), overall health (11,44)
19
20 167 and increased all-cause mortality (45,46). We focus on a set of variables that capture three types of
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22 168 health domains commonly associated with poor sleep: Cardiovascular health measured by pulse,
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24 169 systolic and diastolic blood pressure (47), self-reported health, both in general and for the past 12
25
26 170 months (48) and body-mass index (49).

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29 171 *Mental health.* Previous work has found that disruptions of sleep quality are a central
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31 172 symptom of forms of psychopathology such as Major Depressive Disorder, including both
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33 173 hypersomnia and insomnia (44,50), and episodes of insomnia earlier greatly increased the risk of
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35 174 later episodes of major depression (51). Kaneita et al. (52) found a U-shaped association between
36
37 175 sleep and depression, such that individuals regularly sleeping less than 6, or more than 8, hours were
38
39 176 more likely to be depressed. Both depression (53) and anxiety (54,55) are commonly associated with
40
41 177 sleep problems. To capture these dimensions we used both scales of the Hospital Anxiety and
42
43 178 Depression Scale (HADS) (56), a widely used and standardized questionnaire that captures self-
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45 179 reported frequency and intensity of anxiety and depression symptoms.

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Health	Task and Description	Variable	Descriptives	Citati
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domain				on
Cognitive	Story Recall Immediate: Participants hear a short story and are asked to recall as accurately as possible.	Recall manually scored for similarity and precision (min=0, max=24)	N = 2379, M=13.14, SD=4.66, Range=(0-24)	(57)
Cognitive	Story Recall Delayed: Same as above but recall after 30 minute delay	Recall manually scored for similarity and precision (min=0, max=24)	N = 2366, M=11.47, SD=4.92, Range=(0-24)	(57)
Cognitive	Letter Fluency (phonemic fluency): Participants have one minute to generate as many words as possible beginning with the letter 'p'.	Total words generated (min=0,max=30)	N = 2360, M=25.38, SD=3.96, Range=(0-30)	(57)
Cognitive	Animal Fluency (semantic fluency): Participants have one minute to generate as many words as possible in the category 'animals'.	Total words generated (min=0,max=30)	N = 2346, M=25.85, SD=4.47, Range=(0-30)	(57)
Cognitive	Cattell Culture Fair: Test of fluid reasoning using four subtests (series completions, odd-one-out, matrices and topology)	Total correct summed across four subtests. Min=0, max=46	N = 658, M=31.8, SD=6.79, Range=(11-44)	(58)
Cognitive	Simple reaction time: Speed in a simple reaction time task	1/response time in seconds	N = 657, M=0.37, SD=0.08, Range=(0.24-0.93)	(12)
Cognitive	Addenbrookes Cognitive Examination, Revised: Screening test for dementia using seven subtests (orientation, attention and concentration, memory, fluency, language, visuospatial abilities, perceptual abilities)	Performance on multiple tests converted to min=0, max=100 range	N = 2406, M=89.25, SD=13.4, Range=(0-100)	(24)
Neural	White matter health: Measure of tract integrity using fractional anisotropy	Fractional Anisotropy (min=0, max=1, averaged across 10 tracts)	N = 641, M=0.5, SD=0.03, Range=(0.3-0.56)	(59)
Physical	Self-reported Health, in general: Participants use a 4-point scale to respond to the prompt "Would you say for someone of your age, your own health in general is..."	Score from 1 = Excellent to 4= Poor	N = 2404, M=2.02, SD=0.79, Range=(1-3)	(60)
Physical	Self-reported Health, last 12 months: Participants use a 3-point scale to respond to the prompt "Over the last twelve months would you say your health has on the whole been..."	Score from 1 = Good to 3= Poor	N = 2398, M=1.46, SD=0.71, Range=(1-3)	(60)

Physical	Systolic blood pressure	Mean systolic blood pressure in mmHg, averaged across three consecutive measurements	N = 577, M=120.11, SD=17, Range=(78.5-186)	
Physical	Diastolic blood pressure	Mean diastolic blood pressure in mmHg, averaged across three consecutive measurements	N = 577, M=73.14, SD=10.48, Range=(49-115.5)	
Physical	Resting pulse	Mean pulse in beats per minute, averaged across three consecutive measurements	N = 578, M=65.69, SD=10.5, Range=(40-110.5)	
Physical	Body Mass Index (BMI)	(weight in kg) / (height in m) ²	N = 584, M=25.77, SD=4.59, Range=(16.75-48.32)	(61)
Mental health	Anxiety Subscale (Hospital Anxiety and Depression Scale (HADS)): Participants response to seven questions about anxiety-related behaviours	Seven questions rated on 0 to 3 scale ('Often' to 'Very seldom'). Min=0, Max=21	N = 2393, M=5.17, SD=3.4, Range=(0-19)	(56)
Mental health	Depression Subscale (Hospital Anxiety and Depression Scale (HADS)): Participants response to seven questions about depression-related behaviours	Seven questions rated on 0 to 3 scale ('Often' to 'Very seldom'). Min=0, Max=21	N = 2373, M=3.32, SD=2.91, Range=(0-14)	

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Table 1. Description of health variables across each of four domains (cognitive, neural, physical, mental). For each variable details are given including a description of the task it is derived from, relevant citations, a brief definition and descriptive statistics.

184 **STATISTICAL ANALYSES**

185 We examine whether self-reported sleep patterns change across the lifespan, both for the PSQI sum
186 score and for each of the seven PSQI components. We then examine the relationships between the
187 sleep quality and the four health domains in three ways: First, simple regression of the health
188 outcome on sleep variables, to determine evidence for association between poor sleep quality and
189 poor health outcomes. Second, we include age as a covariate. Finally, we include a (standard normal
190 rescaled) continuous interaction term to examine whether there is evidence for a changing
191 relationship between sleep and outcomes across the lifespan.

192 For all regressions we will use a default Bayesian approach advocated by (62–65) which
193 avoids several well-documented issues with p-values (64), allows for quantification of null effects,
194 and decreases the risk of multiple comparison problems (66). Bayesian regressions allows us to
195 symmetrically quantify evidence in favour of, or against, some substantive model as compared to a
196 baseline (e.g. null) model. This evidentiary strength is expressed as a Bayes Factor (67), which can be
197 interpreted as the relative likelihood of one model versus another given the data and a certain prior
198 expectation. A Bayes Factor of, e.g., 7, in favour of a regression model suggests that the data are
199 seven times *more likely* under that model than an intercept only model for a given prior (for an
200 empirical comparison of p-values and Bayes factors, see (65)). A heuristic summary of evidentiary
201 interpretation can be seen in Figure 1.

202 [insert Figure 1 here]

203 We report log Bayes Factors for (very) large effects and regular Bayes Factors for smaller
204 effects. To compute Bayes Factors we will use Default Bayes Factor approach for model selection
205 (62,63) in the package BayesFactor (68) using the open source software package R (69). As previous
206 papers report associations between sleep and outcomes ranging from absent to considerable in size
207 we utilize the default, symmetric Cauchy prior with width $\frac{\sqrt{2}}{2}$ which translates to a 50% confidence
208 that the true effect will lie between -.707 and .707. Prior to further analysis, scores on all outcomes
209 were transformed to a standard normal distribution, and any scores exceeding a z-score of 4 or -4

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3 210 were recoded as missing (aggregate percentage outliers across the four health domains: Cognitive,
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5 211 0.41%, Mental, 0.16%, Neural, 0.37% Physical, 0.031%).
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213 RESULTS

214 Age-related differences in sleep quality

215 First, we examined sleep changes across the lifespan by examining age-related differences in the
216 PSQI sum score (N= 2178, M=5.16, SD=3.35, Range=0-19). Regressing the PSQI global score on age,
217 (see Supplementary Figure 1) showed evidence for a positive relationship across the lifespan
218 ($\log BF_{10} = 10.45$). This suggests that on the whole, sleep quality decreases across the lifespan (note
219 that *higher* PSQI scores correspond to worse sleep). Although we observe strong statistical evidence
220 for an age-related difference ('Extreme' according to (70)) age explained only 1.11 % of the variance
221 in the PSQI Total score. Next, we examined each of the seven components on age in the same
222 manner. In Supplementary Figure 2 we see that that age has varying and specific effects on different
223 aspects of sleep quality, and did not worsen uniformly across the lifespan. For example, we observed
224 moderate evidence that sleep latency did not change across the lifespan (Sleep Latency, $BF_{01} = 9.66$,
225 in favour of the null), Sleep Quality showed no evidence for either change or stasis ($BF_{10} = 1.64$) and
226 one sleep component, Daytime Dysfunction, improved slightly across the lifespan ($BF_{10} = 7.04$).
227 Medication). The strongest age-related decline is that of Efficiency, showing an R-squared of 6.6%.

228 Finally, we entered all seven components into a Bayesian multiple regression
229 simultaneously, to examine to what extent they could, together, predict age. The best model
230 included every component except Sleep Duration ($\log BF_{10} = 142.98$). Interestingly, this model
231 explained 13.66% of the variance in age, compared to 1.12% for the PSQI Total score, and 6.6% for
232 the strongest single component (efficiency). This shows that lifespan changes in self-reported sleep
233 are heterogeneous and partially independent, and that specific patterns and components need to be
234 taken into account simultaneously to fully understand age-related differences in sleep quality. These

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3 235 finding shows that neither the PSQI sum score nor the sleep components in isolation fully capture
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5 236 differences in sleep quality across the lifespan.
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7 237 The analysis above suggests that conceptualizing 'poor sleep' as a single dimension does not
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9 238 reflect the subtleties in lifespan changes – An often computed sumscore changes little across the
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11 239 lifespan, whereas the totality of sleep symptoms shows far stronger, and more subtle, patterns. To
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13 240 better elucidate individual differences in sleep quality we next use *Latent Class Analysis* (71). This
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15 241 technique will allow us examine individual differences in sleep quality across the lifespan in more
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17 242 detail than afforded by simple linear regressions: Rather than examining continuous variation in
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19 243 sleep components, LCA classifies individuals into different *sleep types*, each associated with a distinct
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21 244 profile of 'sleep symptoms'. If there are specific constellations of sleep problems across individuals,
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23 245 we can quantify and visualize such sleep types.
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26 246 To analyse the data in this manner, we binarized the responses on each component into
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28 247 'good' (0 or 1) or 'poor' (2 or 3). Our measures of PSQI symptoms straddle the border between
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30 248 continuous and categorical – Although some are fully continuous (e.g. sleep latency) others are less
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32 249 so. For instance, although scored on a range of four several of the scales (such as Subjective Sleep
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34 250 quality) have implicitly binary response options of 'Very good' and 'fairly good' on the one hand and
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36 251 'fairly bad' and 'very bad' on the other. As analytical work in psychometrics (72) suggests that likert-
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38 252 like graded scales can be treated as continuous only from five ordinal categories upwards, by fitting
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40 253 an LCA we are erring on the side of caution (although a latent profile analysis would likely give
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42 254 similar results). Note that although our analysis divides individuals into discrete classes with specific
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44 255 profiles, it is still possible to examine the conditional response likelihood of responding 'yes' to each
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46 256 symptom as a continuous metric (between 0 and 1) that reflects the nature of the association
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48 257 between the class and the outcome. By modelling sleep 'types' we hope to illustrate the complex
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50 258 patterns in a more intelligible manner – notably, doing so allows us to examine whether the
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52 259 likelihood of belonging to any sleep 'type' changes as a function of age.
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3 260 Next we examined evidence for distinct sleep types using We fit a set of possible models
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5 261 (varying from 2 to 6 sleep types) We found that the four class solution gives the best solution,
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7 262 according to the Bayesian Information Criterion (73) (BIC for 4 Classes = 11874.67, lowest BIC for
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9 263 other solutions= 11892.17 (5 classes) (with 50 repetitions per class, at 5000 maximum iterations).

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11 264 Next we inspected the nature of the sleep types, the prevalence of each 'sleep type' in the
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13 265 population, and whether the likelihood of belonging to a certain sleep type changes across the
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15 266 lifespan. See Figure 2 for the component profiles of the four sleep types identified.

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18 267 [insert Figure 2 here]

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20 268 Class 1, 'Good sleepers', make up 68.62% of participants. Their sleep profile is shown in
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22 269 Figure 2A, top left, and is characterised by a low probability of responding 'poor' to any of the sleep
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24 270 components. Class 2, 'inefficient sleepers', make up 13.05% of the participants, and are
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26 271 characterized by poor sleep Efficiency: Members of this group uniformly (100%) report poor sleep
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28 272 Efficiency, despite relatively low prevalence of other sleep problems, as seen in Figure 2A, top right.
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30 273 Class 3, 'Delayed Sleepers' seen in the bottom left of Figure 2a, makes up 9.76% of the participants:
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32 274 characterized by modestly poor sleep across the board, but a relatively high probability of poor
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34 275 scores on Sleep Latency (60%), Sleep Quality (54%) and sleep Disturbance (29.2%). Finally, Class 4,
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36 276 'Poor sleepers', make up 8.6% of the participants, shown bottom right in Figure 2A. Their responses
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38 277 to any of the seven sleep components are likely to be 'poor' or 'very poor', almost universally so for
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40 278 'sleep quality' (97%) and 'Sleep Efficiency' (96.6%).

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43 279 Next, we including age as a covariate (simultaneously including a covariate is known as
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45 280 *latent class regression* or concomitant-variable latent class models (74). This analysis, visualised in
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47 281 Figure 2b, shows that the probability of membership of each classes compared to the reference class
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49 282 (good sleepers) changes significantly across the lifespan for each of the classes (Class 2 versus class
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51 283 1: beta/SE= 0.054/0.0069, t=7.9, Class 3 versus class 1: beta/SE= -0.020/0.0057, t=-3.63, Class 4
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53 284 versus class 1: beta/SE 0.015/0.0049, t=3.05), for more details on generalized logit coefficients , see
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55 285 (71). The frequency of Class 1 (Good sleepers) peaks in middle to late adulthood, dropping
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3 286 increasingly quickly after age 50. Class 2 (Inefficient sleepers) are relatively rare in younger
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5 287 individuals, but the prevalence increases rapidly in individuals over age 50. On the other hand, Class
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7 288 3 (Delayed sleepers) shows a steady decrease in the probability of an individual showing this profile
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9 289 across the lifespan, suggesting that this specific pattern of poor sleep is more commonly associated
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11 290 with younger adults. Finally, the proportion of Class 4 (poor sleepers) members increases only
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13 291 slightly across the lifespan. Together, the latent class analysis provides additional evidence that the
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15 292 PSQI sum score as an indicator of sleep quality does not fully capture the subtleties of age-related
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17 293 differences. Age-related changes in sleep patterns are characterized by specific, clustered patterns
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19 294 of sleep problems that cannot be adequately characterized by summation of the component scores.
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21 295 The above analyses show how both a summary measure and individual measures of sleep quality
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23 296 change across the lifespan. Next, we examined the relationships between sleep quality measures
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25 297 (seven components and the global PSQI score) and health variables (specific variables across four
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27 298 domains, as shown in Table 1).
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33 300 **Sleep, health domains and age**

35 301 *Cognitive health*

37 302 First, we examined the relationships between sleep quality and seven measures of cognitive health
38
39 303 (see Table 1 for details). We visualize our findings using tileplots (75). Each cell shows the numeric
40
41 304 effect size (R-squared, 0-100) of the bivariate association between a sleep component and a health
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43 305 outcome, colour coded by the statistical evidence for a relationship using the Bayes Factor. If the
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45 306 parameter estimate is positive, the r-squared value has the symbol '+' added (note the
46
47 307 interpretation depends on the nature of the variable, cf. Table 1).
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50 308 As can be seen in Supplementary Figure 3, several relationships exist between measures of cognitive
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52 309 health and measures of sleep quality. However, these results attenuate in a multiple regression
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54 310 model including age as shown in Figure 3.
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57 311 [Insert Figure 3 here]
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3 312 The cognitive abilities most strongly associated with poor sleep are a measure of general cognitive
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5 313 health, ACE-R, and a test of verbal phonemic fluency. Two patterns emerged: First, the strongest
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7 314 predictor across the simple and multiple regressions was for the PSQI Total score. Tentatively this
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9 315 suggests that a cumulative index of sleep problems, rather than any specific pattern of poor sleep, is
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11 316 the biggest risk factor for poorer cognitive performance. Secondly, after controlling for age, the most
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13 317 strongly affected cognitive measure is phonemic fluency, the ability to generate name as many
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15 318 different words as possible starting with a given letter within a minute. Verbal fluency is commonly
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17 319 used as a neuropsychological test (76). Previous work suggests it depends on both the ability to
18
19 320 cluster (generating words within a semantic cluster) and to switch (switching between categories),
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21 321 and is especially vulnerable to frontal and temporal lobe damage (with specific regions dependant
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23 322 on either a semantic or phonemic task (77)). Although modest in size, our findings suggests this task,
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25 323 dependent on multiple executive processes, is particularly affected by poor sleep quality (78). The
26
27 324 second strongest association was with the ACE-R, a general cognitive test battery similar in style and
28
29 325 content to the MMSE. When an interaction term with age was included, little evidence for
30
31 326 interactions with age (mean $\log_{10}BF_{10} = -2.09$, see Supplementary Figure 4), suggesting that the
32
33 327 negative associations between sleep and cognitive performance are a constant feature across the
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35 328 lifespan, rather than specifically in elderly individuals. Together this suggests that poor sleep quality
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37 329 is modestly but consistently associated with poorer general cognitive performance across the
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39 330 lifespan, most strongly with semantic fluency.
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46 332 *Neural Health*

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48 333 Using Diffusion Tensor Imaging, we estimated a general index of white matter integrity in 10 tracts
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50 334 (59) (shown in Supplementary Figure 5), by taking the average Fractional Anisotropy in each white
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52 335 matter ROI (see (79) for more information). We use the data from a subsample of 641 individuals
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54 336 (age $M=54.87$, range 18.48-88.96) who were scanned in a 3T MRI scanner (for more details regarding
55
56 337 the pipeline, sequence and processing steps, see (22,79). Regressing neural WM ROI's on sleep
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3 338 quality, we find several small effects, with the strongest associations between sleep efficiency and
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5 339 neural health (see Supplementary Figure 6). All effects are such that poorer sleep is associated with
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7 340 poorer neural health, apart from a small effect in the opposite direction for Uncinate and Daytime
8
9 341 Dysfunction ($BF_{10}= 6.20$). However, when age is included as a covariate, the negative associations
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11 342 between sleep quality and white matter health are attenuated virtually to zero (Figure 4,
12
13 343 mean/median $BF_{10}= 0.18/.10$), with Bayes Factors providing strong evidence for the lack of
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15 344 associations between sleep quality and white matter integrity. One exception was observed: The use
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17 345 of Sleep Medication is associated with *better* neural health in the corticospinal tract, a region
18
19 346 previously found to be affected by pathological sleep problems such as sleep apnoea (33). However,
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21 347 this effect is very small ($BF_{10}=3.24$) given the magnitude of the sample and the range of comparisons,
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23 348 so should be interpreted with caution.

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27 [Insert Figure 4 here]

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29 350 Finally, we tested for any interactions by including a mean-scaled interaction term (sleep*age,
30
31 351 Supplementary Figure 7). This analysis found evidence for a significant interaction, between the
32
33 352 Superior Longitudinal Fasciculus (SLF) and Sleep Medication ($BF_{10}= 13.77$), such that better neural
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35 353 health in the SLF was associated with the use of Sleep Medication more strongly in older adults.
36
37 354 Together, these findings suggest that in general, once age is taken into account, self-reported sleep
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39 355 problems in a non-clinical sample are *not* associated with poorer neural health, although there is
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41 356 some evidence for a modest associations between better neural health in specific tracts and the use
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43 357 of sleep medication in the elderly.

44 45 46 47 48 359 *Physical health*

49
50 360 Next we examined whether sleep quality is associated with physical health. Figure 5 shows
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52 361 the simple regressions between sleep quality and physical health. Strong associations were found
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54 362 between poor overall sleep (PSQI sum score) and poor self-reported health, both in general
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56 363 ($\log BF_{10}=77.51$) and even more strongly for health in the past 12 months ($\log BF_{10}=91.25$). This may
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3 364 be because poorer sleep, across all components, directly affects general physical health (43,80) or
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5 365 because people subjectively experience sleep quality as a fundamental part of overall general health.
6
7 366 A second association was between BMI and poor sleep, most strongly for Duration ($\log BF_{10}=4.69$).
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9
10 367 [Insert Figure 5 here]

11 368 This not only replicates previous findings but is in line with an increasing body of evidence
12
13 369 that suggests that shorted sleep duration causes metabolic changes, which in turn increases the risk
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15 370 of both diabetes mellitus and obesity (43,81,82). Next, we examined whether these effects were
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17 371 attenuated once age was included. We show that although the relationships are slightly weaker, the
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19 372 overall pattern remains (Supplementary Figure 8), suggesting these associations are not merely co-
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21 373 occurrences across the lifespan. Our findings suggest self-reported sleep quality, especially sleep
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23 374 Duration, is related to differences in physical health outcomes in a healthy sample.
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27 375 Finally, there was evidence of a single interaction with age (Supplementary Figure 9):
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29 376 Although poor sleep Duration was associated with *higher* diastolic blood pressure in younger adults,
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31 377 it was associated with *lower* diastolic blood pressure in older individuals ($BF_{10}= 8.43$). This may
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33 378 reflect the fact that diastolic blood pressure is related to cardiovascular health in a different way
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35 379 across the lifespan, although given the small effect size it should be interpreted with caution.
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39 381 *Mental health*

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41 382 Finally, we examined the relationship between sleep quality and mental health, as measured by the
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43 383 Hospital Anxiety and Depression Scale (56). One benefit of the HADS in this context is that, unlike
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45 384 some other definitions (e.g. the DSM-V), sleep quality is not an integral (scored) symptom of these
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47 385 dimensions. As shown in Supplementary Figure 10, there are very strong relationships between all
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49 386 aspects of sleep quality and measures of both anxiety and depression. The strongest predictors of
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51 387 Depression are Daytime Dysfunction ($\log BF_{10}= 245.9$, $R^2=19.26\%$), followed by the overall sleep
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53 388 score ($\log BF_{10}= 170.5$, $R^2=14.92\%$) and sleep quality ($\log BF_{10}= 106.8$, $R^2=8.9\%$). The effects size for
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55 389 Anxiety was comparable but slightly smaller in magnitude. When age is included as a covariate the
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3 390 relationships remained virtually unchanged (Supplementary Figure 11), suggesting these
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5 391 relationships are present throughout across the lifespan. These findings replicate and extend
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7 392 previous work, suggesting that sleep quality is strongly associated with both anxiety and depression
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9 393 across the lifespan.

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11 394 Finally we examined a model with an interaction term (Supplementary Figure 12). Most
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13 395 prominently we found interactions with age in the relationship between HADS depression and the
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15 396 PSQI Total, and in the relationship between HADS depression and Sleep Duration, such that for the
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17 397 relationship between anxiety and overall sleep quality is stronger in younger adults ($BF_{10} = 9.91$, see
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19 398 Figure 6). Together our findings show that poor sleep quality is consistently, strongly and stably
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21 399 associated with poorer mental health across the adult lifespan.

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24 400 [Insert Figure 6 here]

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28 29 402 **Non-linear associations between sleep and health outcomes**

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31 403 In the above analyses, we focused on linear associations between symptoms and health outcomes.
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33 404 However, for one aspect of sleep, namely sleep duration (in hours), evidence exists that these
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35 405 associations are likely to be non-linear, such that both shorter and longer than average sleep are
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37 406 associated with poorer health outcomes (e.g. (83–85). This is echoed in clinical criteria for
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39 407 depression, which commonly include that include both hyper- and hypo-somnia as ‘sleep disruption’
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41 408 symptoms – In other words, both too much or too little sleep are suboptimal. To examine whether
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43 409 we observe evidence for non-linearities we examined the relationship between raw scores on sleep
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45 410 duration (in hours, not transformed to PSQI norms) and health outcomes across the four domains. If
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47 411 the association between sleep and outcomes is indeed u-shaped (or inverted U, depending on the
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49 412 scale) then a Bayesian regression would prefer the less parsimonious model that includes the
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51 413 quadratic term. We observed no non-linear associations between any neural or cognitive health
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53 414 variables. We find strong evidence for a quadratic (subscript q) over a linear (subscript l) associations
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55 415 between sleep duration and HADS anxiety ($\log BF_{q|l} = 19.98$), even more strongly so with HADS
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3 416 Depression ($\log BF_{qi} = 25.83$, see Figure 7A shows the strongest curvilinear association, namely with
4 depression). We find a similar u-shaped curve with general health ($BF_{qi} = 277.81$) and self-reported
5 417 health over the last 12 months ($BF_{qi} = 887.59$), the latter shown in Figure 7b. Together, these analyses
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7 418 support previous conclusions that some (although not all) poorer health outcomes can be associated
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9 419 with both too much and too little sleep.
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14 421 [Insert Figure 7 here]

15 422 DISCUSSION

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17 423 In this study, we report on the associations between age-related differences in sleep quality and
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19 424 health outcomes in a large, age-heterogeneous sample of community dwelling adults of the
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21 425 Cambridge Neuroscience and Aging (Cam-CAN) cohort. We find that sleep quality generally
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23 426 decreases across the lifespan, most strongly for sleep Efficiency. However age-related changes in
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25 427 sleep patterns are complex and multifaceted, so we used Latent Class Analysis to identify 'sleep
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27 428 types' associated with specific sleep quality profiles. We found that Younger adults are more likely
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29 429 than older adults to display a pattern of sleep problems characterised by poor sleep quality and
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31 430 longer sleep latency, whereas older adults are more likely to display inefficient sleeping,
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33 431 characterised by long periods spent in bed whilst not asleep. Moreover, the probability of being a
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35 432 'good' sleeper, unaffected by any adverse sleep symptoms, decreases considerably after age fifty.
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40 433 Notably, closer investigation of the sleep classes reveals likely further complexities of age-
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42 434 related differences. The category 'poor sleepers', most prevalent in older adults, shows high
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44 435 conditional likelihood of 'poor sleep' across all symptoms except 'daytime dysfunction'. One possible
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46 436 explanation is that almost all individuals in this group are beyond retirement age. For this reason,
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48 437 they likely have greater flexibility in tailoring their day to day activities to their energy levels (as
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50 438 opposed to individuals working fulltime), and are therefore less likely to consider themselves
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52 439 'disrupted' even in the presence of suboptimal sleep. Although more detailed, interview-based
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54 440 investigations would be necessary to examine the precise nature of these findings, it stands to
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56 441 reason that certain symptoms change not just in prevalence but also in meaning across the lifespan.
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3 442 One key strength of our broad phenotypic assessment allows for direct comparison of the
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5 443 different measures of sleep quality and four key health domains. We find strongest associations
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7 444 between sleep quality and mental health, moderate relations between sleep quality and physical
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9 445 health and cognitive health and sleep, virtually all such that poorer sleep is associated with poorer
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11 446 health outcomes. We did not find evidence for associations between self-reported sleep and neural
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13 447 health. Notably, the relationships we observe are mostly stable across the lifespan, affecting
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15 448 younger and older individuals alike. A notable exception to these effects is the absence of any strong
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17 449 relation (after controlling for age) between sleep quality and neural health as indexed by tract-based
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19 450 average fractional anisotropy. Perhaps surprisingly, given we found strong relationships in the same
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21 451 sample between sleep and other outcomes (e.g. mental health, Figure 10) we find that self-reported
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23 452 sleep problems in a non-clinical sample are not associated with fractional anisotropy above and
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25 453 beyond old age. This is despite the fact that previous work within the same cohort observed
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27 454 moderate to strong associations between white matter and various cognitive outcomes (42,86,87).
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29 455 However, although notable, our finding does not rule out that such associations do exist with other
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31 456 white matter metrics, that they would be observed with objective measures of sleep such as
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33 457 polysomnography, or that the co-occurrence of age-related declines in sleep quality and white
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35 458 matter share an underlying causal association that cannot be teased apart in a cross-sectional
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37 459 sample.
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42 460 One strength of our study is the assessment of neuroimaging metrics, namely fractional
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44 461 anisotropy, in a large, community-dwelling healthy population. Fractional anisotropy is often used in
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46 462 studies of aging (e.g. Madden, is relatively reliable (88)) and is sensitive to clinical anomalies such as
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48 463 white matter hyperintensities. However, the relationship between FA and white-matter health is
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50 464 indirect (40,89) and drawbacks include its inability to distinguish crossing fibers (e.g. (40,89) and
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52 465 vulnerability to movement and the fact that it likely reflects a combination of underlying
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54 466 physiological properties. Various alternative white matter metrics exist, including summary
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56 467 measures of diffusivity (e.g. axial/radial/mean diffusivity), volumetric measures of white matter
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3 468 hyperintensity (e.g.) and various innovative measures currently in development, but their
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5 469 physiological validity is ongoing (89,90).
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7 470 While there are limitations of self-report measures including in older cohorts (19), including
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9 471 the fact that they likely reflect different aspects of sleep health than polysomnography (sleep in the
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11 472 lab), our results suggest there are considerable advantages in using self-reported sleep measures:
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13 473 first, obtaining sleep quality data in a large and broadly phenotyped sample is feasible; and second,
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15 474 our results demonstrated clear and consistent associations across multiple domains for both
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17 475 subjective (e.g. self-reported health) and objective measures (e.g. memory tests, BMI), which both
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19 476 replicate and extend previous lab-based sleep findings. Future work should ideally simultaneously
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21 477 measure polysomnography and self-report in longitudinal, large scale cohorts to fully capture the
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23 478 range of overlapping and complementary relations between different aspects of sleep quality and
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25 479 health outcomes (19).
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29 480 For both self-report and objective measures of sleep quality an open question is that of
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31 481 causality: Does poor sleep affect health outcomes, do health problems affect sleep, are they both
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33 482 markers of some third problem, or do causal influences go both ways? Most likely, all these patterns
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35 483 occur to varying degrees. Previous studies have shown that sleep quality causally affects health
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37 484 outcomes such as diabetes (43) and memory consolidation (1) while other evidence suggests that
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39 485 depression directly affect sleep quality (91,92) and that damage to neural structures may affect
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41 486 sleep regulation (93). Although our findings are in keeping with previous findings, our cross-sectional
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43 487 sample cannot tease apart the causal direction of the observed associations, more work remains to
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45 488 be done to disentangle these complex causal pathways.
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49 489 In our paper we focus on a healthy, age-heterogeneous community dwelling sample. This
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51 490 allows us to study the associations between healthy aging and self-reported sleep quality, but comes
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53 491 with two key limitations of the interpretations of our findings. First and foremost, our findings are
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55 492 cross-sectional, not longitudinal. This means we can make inferences about age-related *differences*,
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57 493 but not necessarily age-related *changes* (94,95). One reason why cross-sectional and longitudinal
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3 494 estimates may diverge is that older adults can be thought of as cohorts that differ from the younger
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5 495 adults in more ways than age alone. For example, our age range includes individuals born in the
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7 496 twenties and thirties of the 20th century. Compared to someone born in the 21st century, these
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9 497 individuals will likely have experience various differences during early life development (e.g. less
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11 498 broadly accessible education, lower quality of healthcare, poorer nutrition and similar patterns). For
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13 499 some of our measures, these are inherent limitations –*truly* longitudinal study of neural aging is
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15 500 inherently impossible as scanner technology has not been around sufficiently long. This means our
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17 501 findings likely reflect a combination of effects attributable to age-related changes as well as baseline
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19 502 differences between subpopulations that may affect both mean differences as well as
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21 503 developmental trajectories.

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24 504 Second, our sample reflects an atypical population in the sense that they are willing and able
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26 505 to visit the laboratory on multiple occasions for testing sessions. This subsample is likely a more
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28 506 healthy subset of the full population, which will mean the range of (poor) sleep quality as well as
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30 507 (poorer) health outcomes will likely be less extreme than in the full population. However, this
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32 508 challenge is not specific to our sample. In fact, as the Cam-CAN cohort was developed using stratified
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34 509 sampling based on primary healthcare providers, our sample is likely as population-representative as
35
36 510 is feasible for a cohort of this magnitude and phenotypic breadth (see (12) for further details).
37
38 511 Nonetheless, a healthier subsample may lead to restriction of range (96), i.e. an attenuation of the
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40 512 strength of the associations observed between sleep quality and health outcomes. Practically, this
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42 513 means that our results likely generalise to comparable, healthy community dwelling adults, but not
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44 514 necessarily to populations that include those affected by either clinical sleep deprivation or other
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46 515 serious health conditions.

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Conclusions

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3 519 Taken together, our study allows several conclusions. First, although we replicate the age-
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5 520 related deterioration in some aspects of sleep quality, other aspects remain stable or even improve.
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7 521 Second, we show that the profile of sleep quality changes across the lifespan. This is important
8
9 522 methodologically, as it suggests that PSQI sum scores do not capture the full picture, especially in
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11 523 age-heterogeneous samples. Moreover, it is important from a psychological standpoint: We show
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13 524 that 'sleep quality' is a multidimensional construct and should be treated as such if we wish to
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15 525 understand the complex effects and consequences of sleep quality across the lifespan. Third,
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17 526 moderate to strong relations exist between sleep quality and cognitive, physical and mental health,
18
19 527 and these relations largely remain stable across the lifespan. In contrast, we show evidence that in
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21 528 non-clinical populations, poorer self-reported sleep is not reliably associated with poorer neural
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23 529 health. Finally, we find that for absolute sleep duration, we replicate previous findings that both
24
25 530 longer and shorter than average amounts of sleep are association with poorer self-reported general
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27 531 health and higher levels of depression and anxiety.

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31 532 Together with previous experimental and longitudinal evidence, our findings suggest that at
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33 533 least some age-related decreases in health outcomes may be due to poorer sleep quality. We show
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35 534 that self-reported sleep quality can be an important indicator of other aspects of healthy functioning
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37 535 throughout the lifespan, especially for mental and general physical health. Our findings suggest
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39 536 accurate understanding of sleep quality is essential in understanding and supporting healthy aging
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41 537 across the lifespan.

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Author contributions

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3 545 AG, MS and MS designed the study. AG and RAK performed the analyses. CC organized and
4
5 546 conducted the data collection. AG, MS and RAK wrote the manuscript. YL provided considerable
6
7 547 expertise on sleep and poor sleep outcomes. All authors approved the final manuscript.
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31
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33
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35
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37
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39
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41
42 564 Hanley, Beth Parkin, David Troy; Affiliated Personnel: Tibor Auer, Marta Correia, Lu Gao, Emma
43
44 565 Green, Rafael Henriques; Research Interviewers: Jodie Allen, Gillian Amery, Liana Amunts, Anne
45
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47
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49
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51
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4

5 571 Mitchell, Laura Willis.
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Legends

Figure 1. Descriptive interpretation of Bayes Factors

Figure 2. Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

Figure 3. Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction Time were measured only in the imaging cohort: mean N = 648, N=11.11. Sample sizes for 5 other domains are similar: mean N= 2300.25, SD= 65.57)

Figure 4. Multiple regressions between sleep components and Neural Health. Each cell represents the relationship between a sleep component and the mean neural health in a given tract as index by Fractional Anisotropy. Numbers represent R-squared, the sample size is show in the last column. Strong associations are observed between measures of Sleep Efficiency and multiple tracts, along with sporadic associations between other components and tracts. White matter tracts abbreviations: Uncinate fasciculus (UNC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior Fronto-occipital fasciculus (IFOF), forceps minor (FMin), forceps major (FMaj), cerebrospinal tract (CST), the ventral cingulate gyrus (CINGHipp), the dorsal cingulate gyrus (CING), and the anterior thalamic radiations (ATR). N varies slightly across components due to varying missingness (N mean = 631.325, SD = 10.32).

Figure 5 Physical health and sleep quality. Numbers represent Rsquared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and General) were measured in the full cohort (Mean = 2315.37, SD=66.29), the other indicators were measured in the imaging cohort only (Mean = 569.87, SD= 11.16).

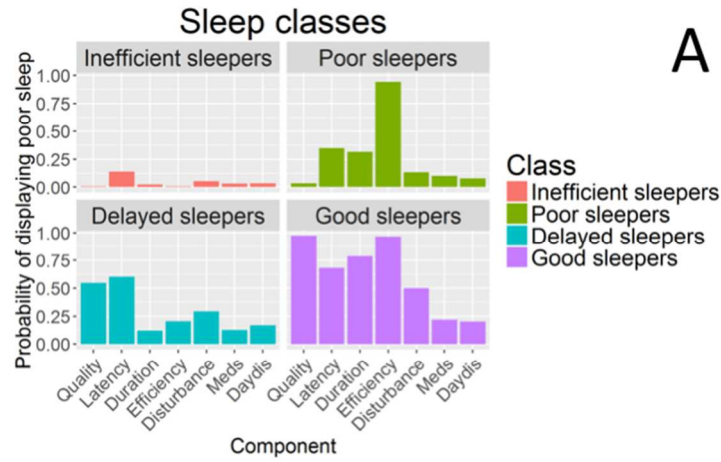
Figure 6. Interaction between sleep quality and anxiety. (N=724, age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to 98.88).

Figure 7. Curvilinear associations between sleep duration in hours and A) HADS depression and B) general health (self-reported). For visual clarity a small amount of random jitter was added to the data points.

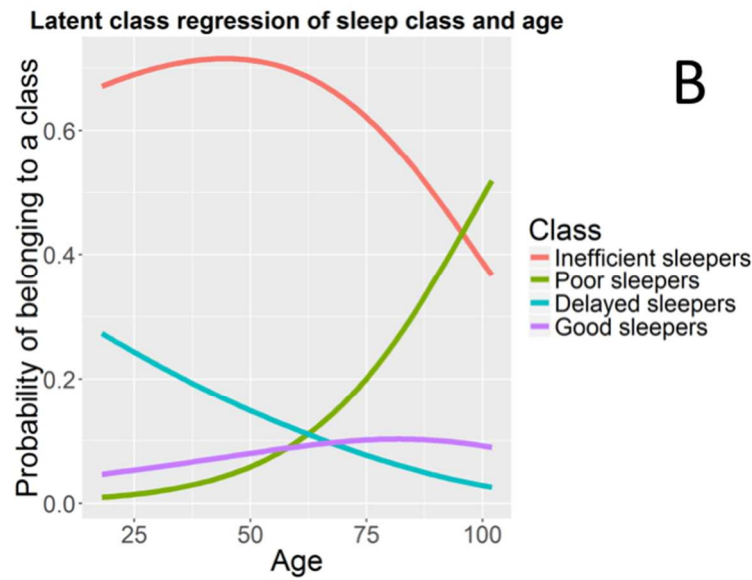
Bayes Factor BF ₁₀	Log BF ₁₀	Tileplot colour	Description (Jeffreys, 1961)
>100	>4.6	Red	Extreme evidence for H1
30 – 100	3.4 – 4.6	Red	Very strong evidence for H1
10 – 30	2.3 – 3.4	Red	Strong evidence for H1
3 – 10	1.098 – 2.3	Light red	Substantial evidence for H1
1 – 3	1 – 1.098	Light red	Anecdotal evidence for H1
1	0	White	No evidence either way
1/3 – 1	-1.098 – -1	Light blue	Anecdotal evidence for H0
1/3 - 1/10	-2.3 – -1.098	Light blue	Substantial evidence for H0
1/10 - 1/30	-3.4 – -2.3	Light blue	Strong evidence for H0
1/30 - 1/100	-4.6 – -3.4	Light blue	Very strong evidence for H0
<1/100	< -4.6	Blue	Extreme evidence for H0

Figure 1. Descriptive interpretation of Bayes Factors

Insert Figure 1 here
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A



B

Figure 2. Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

Insert Figure 2 here
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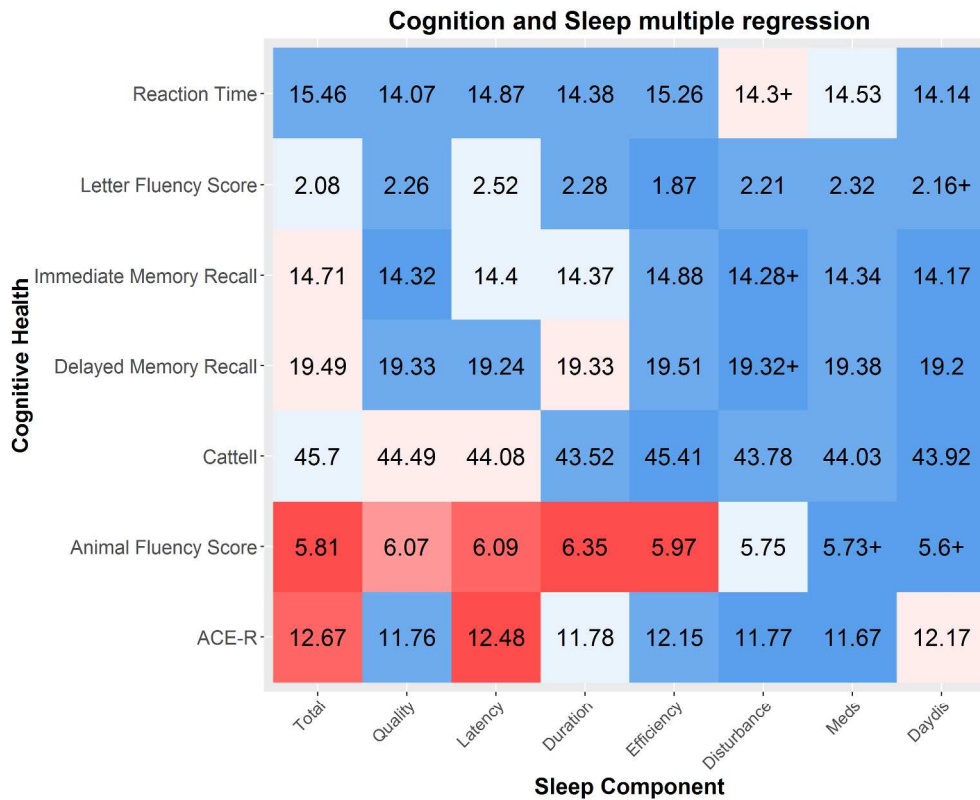


Figure 3. Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction Time were measured only in the imaging cohort: mean N = 648, N=11.11. Sample sizes for 5 other domains are similar: mean N= 2300.25, SD= 65.57)

Insert Figure 3 here
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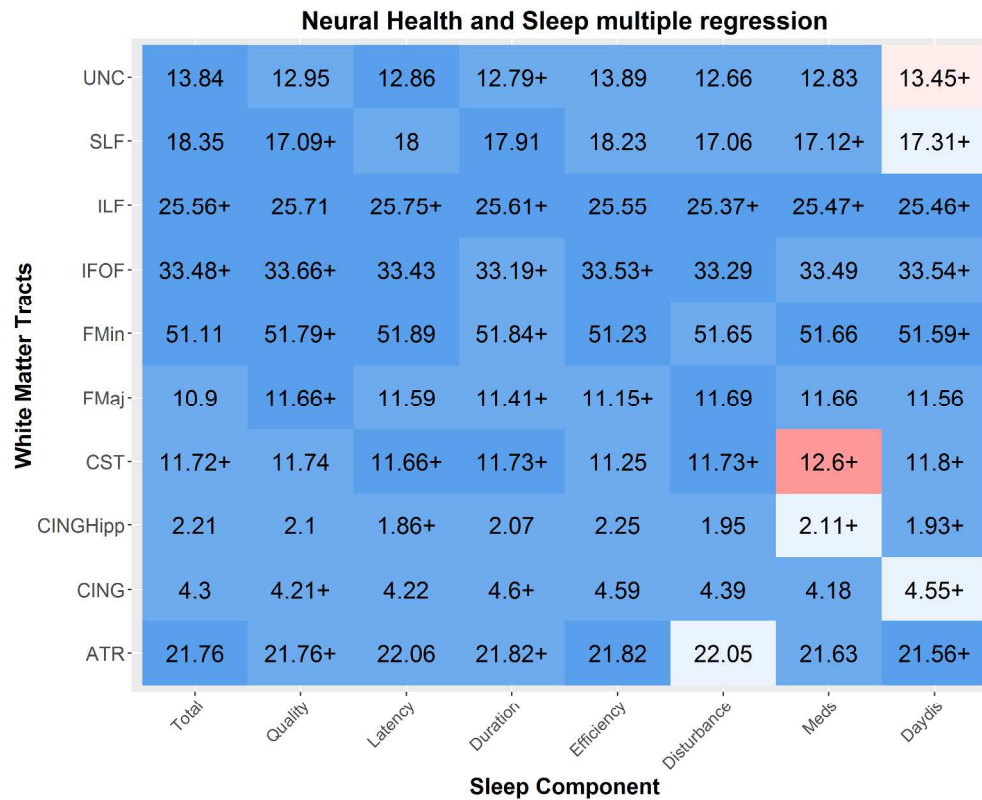


Figure 4. Multiple regressions between sleep components and Neural Health. Each cell represents the relationship between a sleep component and the mean neural health in a given tract as index by Fractional Anisotropy. Numbers represent R-squared, the sample size is show in the last column. Strong associations are observed between measures of Sleep Efficiency and multiple tracts, along with sporadic associations between other components and tracts. White matter tracts abbreviations: Uncinate fasciculus (UNC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior Fronto-occipital fasciculus (IFOF), forceps minor (FMin), forceps major (FMaj), cerebrospinal tract (CST), the ventral cingulate gyrus (CINGHipp), the dorsal cingulate gyrus (CING), and the anterior thalamic radiations (ATR). N varies slightly across components due to varying missingness (N mean = 631.325, SD = 10.32).

Insert Figure 4 here
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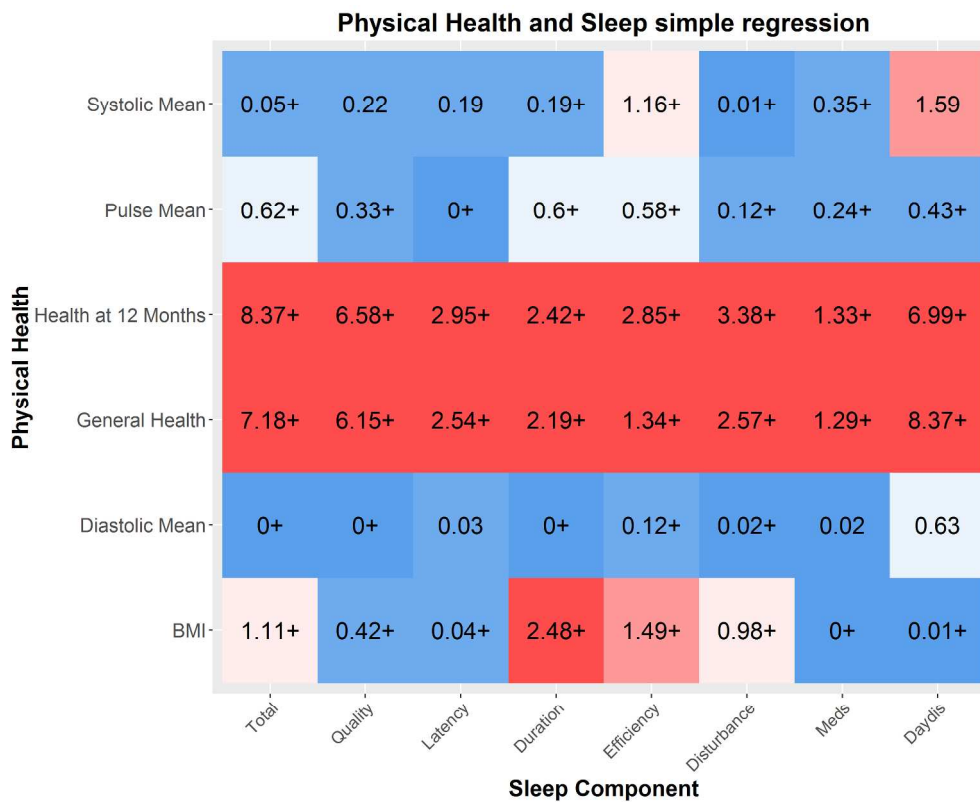


Figure 5 Physical health and sleep quality. Numbers represent Rsquared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and General) were measured in the full cohort (Mean = 2315.37, SD=66.29), the other indicators were measured in the imaging cohort only (Mean = 569.87, SD= 11.16).

Insert Figure 5 here
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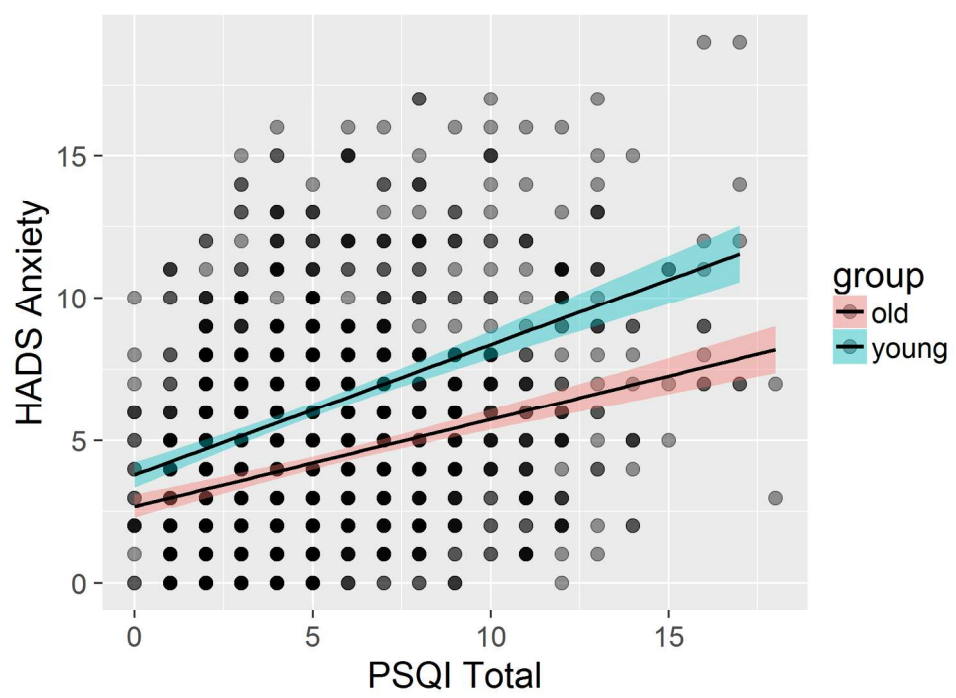


Figure 6. Interaction between sleep quality and anxiety. (N=724, age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to 98.88).

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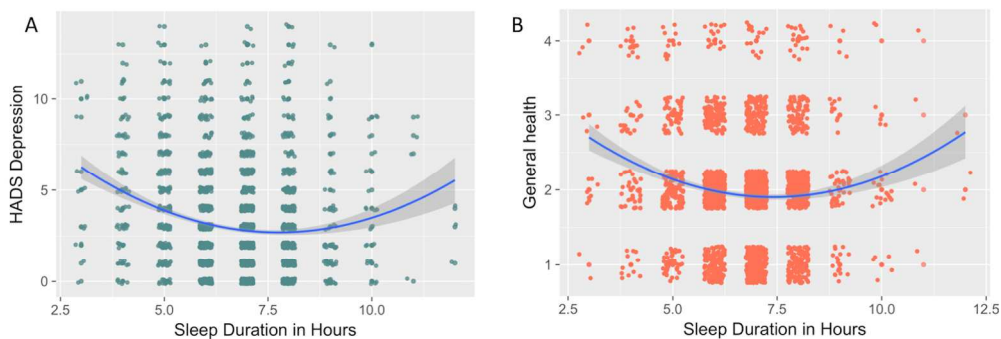


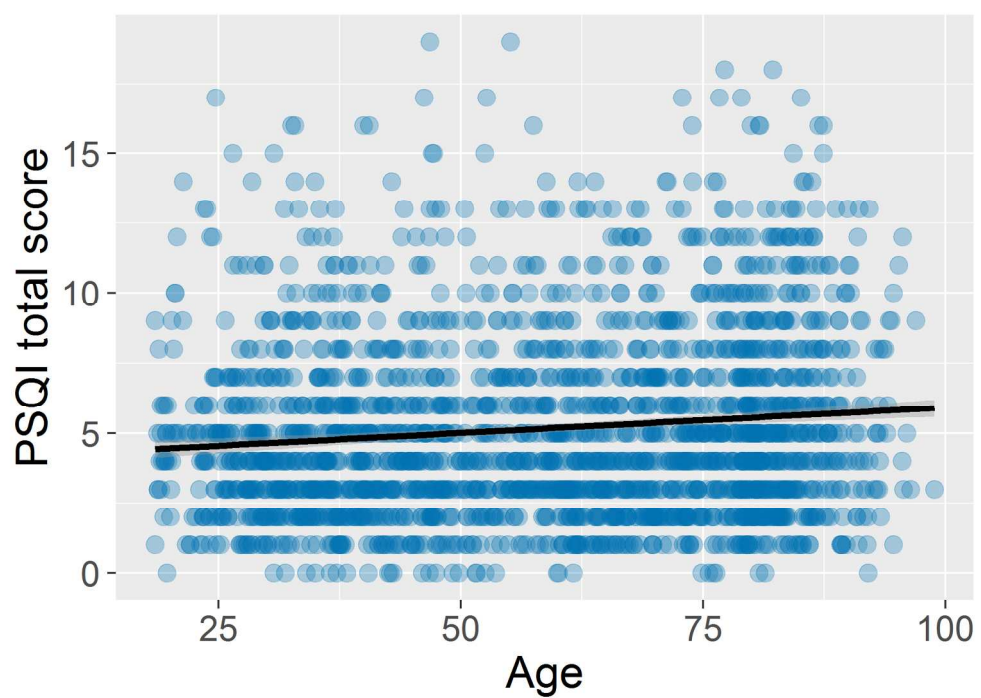
Figure 7. Curvilinear associations between sleep duration in hours and A) HADS depression and B) general health (self-reported). For visual clarity a small amount of random jitter was added to the data points.

Insert Figure 7 here
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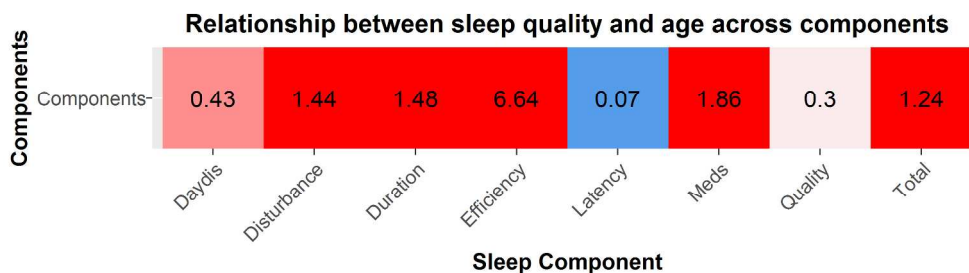
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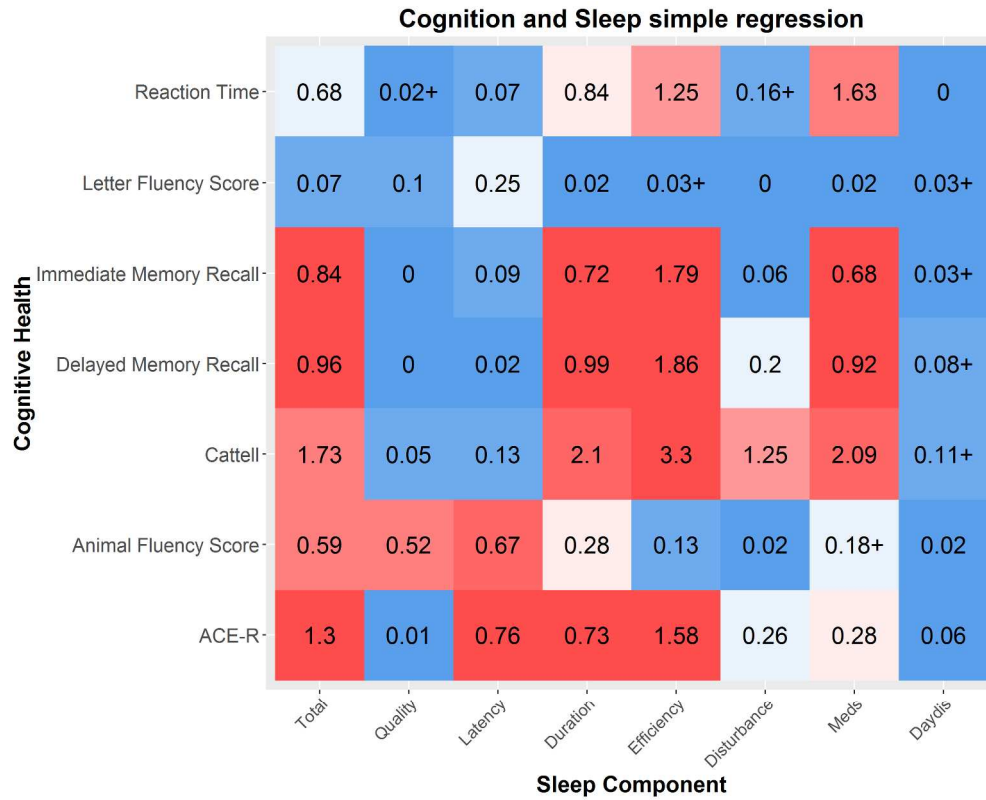
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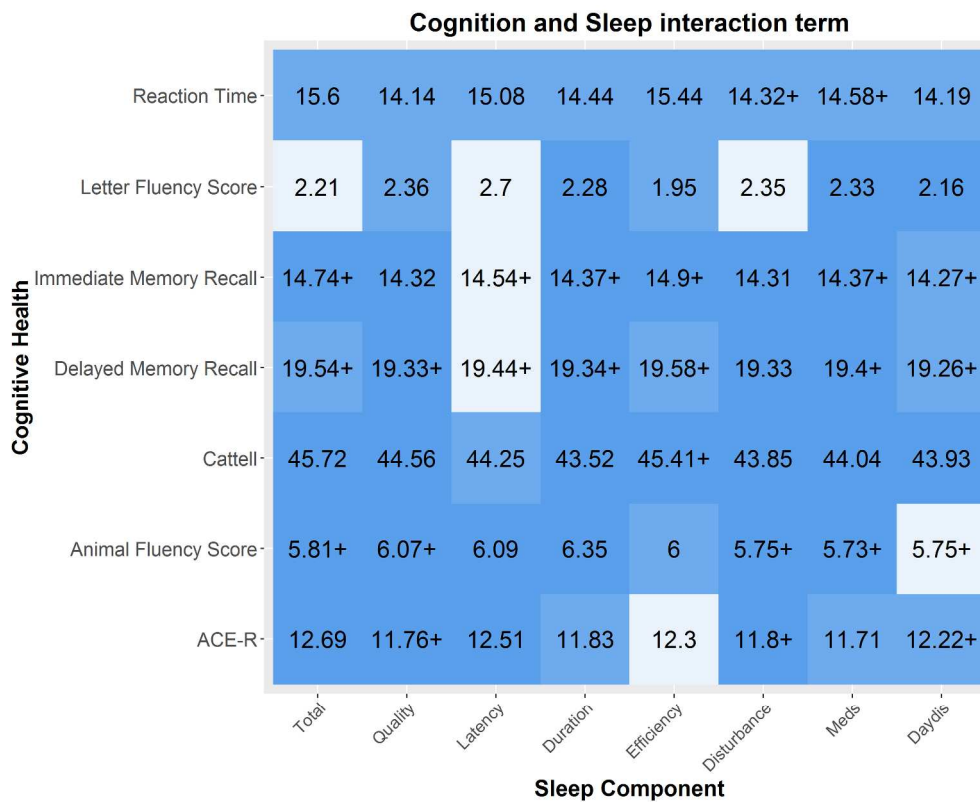
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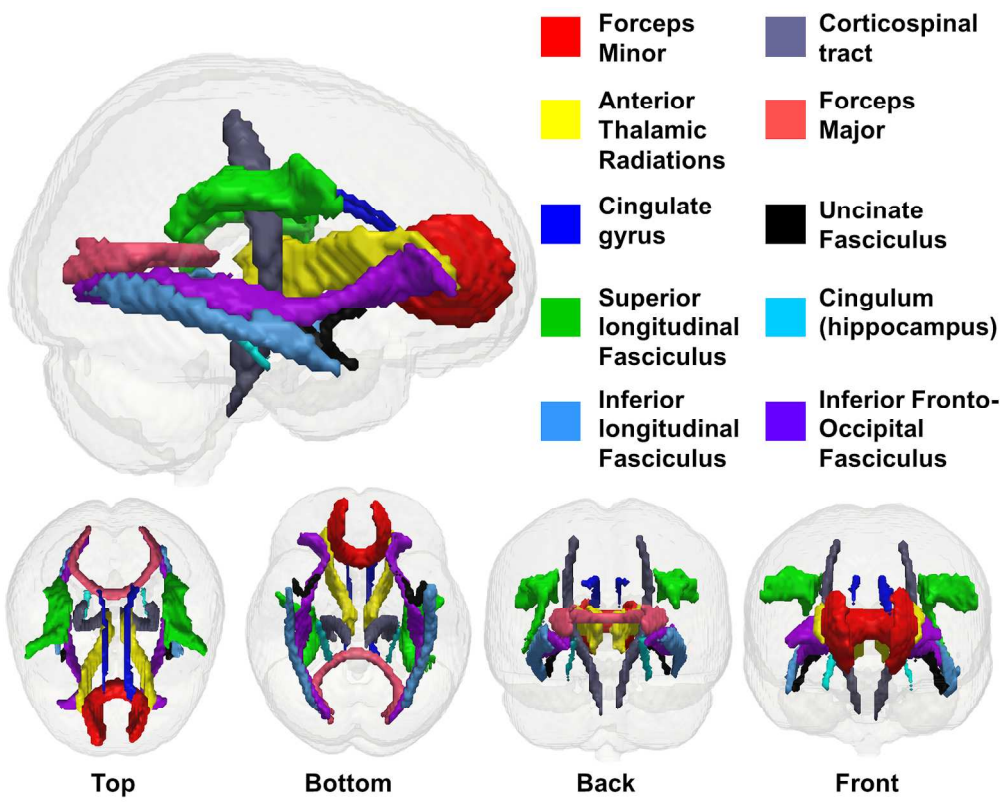


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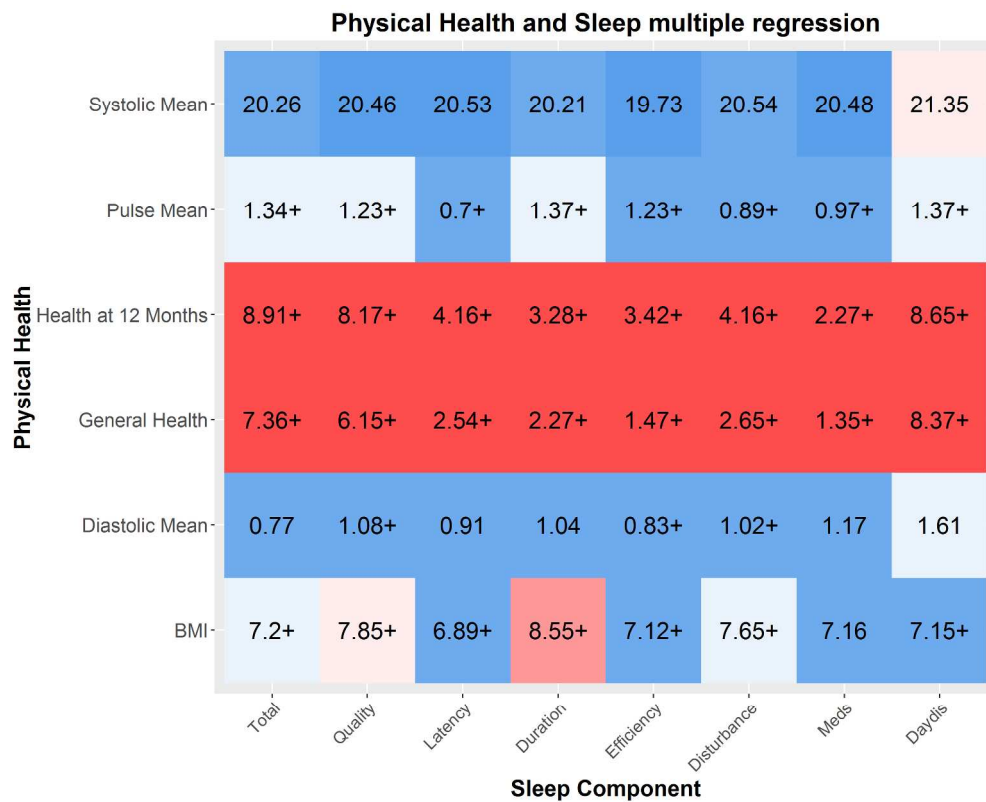
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Neural Health and Sleep interaction term

White Matter Tracts	Neural Health and Sleep interaction term							
	Total	Quality	Latency	Duration	Efficiency	Disturbance	Medts	Daydis
UNC	13.88	12.96	12.9+	12.79	13.9	12.9	12.97	13.45
SLF	18.36+	17.11+	18.01	17.91+	18.24	17.16	18.39+	17.32+
ILF	25.57+	25.71	25.75+	25.64+	25.55+	25.5	26+	25.46+
IFOF	33.67+	33.77+	33.48+	33.44+	33.69+	33.43	33.55+	33.8+
FMin	51.12	51.79+	51.91	51.85	51.24	51.85	51.72+	51.64+
FMaj	10.91+	12.45+	11.6	11.41+	11.15+	12.18	11.81	11.76+
CST	11.89+	11.88	11.72+	11.83+	11.3+	11.74+	13.24+	11.85+
CINGHipp	2.22	2.1	1.88	2.09	2.25	2.01	2.75+	2.07
CING	4.31+	4.27	4.23+	4.72+	4.59+	4.44+	4.9+	4.61+
ATR	21.79	21.83+	22.08	21.83	21.82+	22.11	22.04	21.58+

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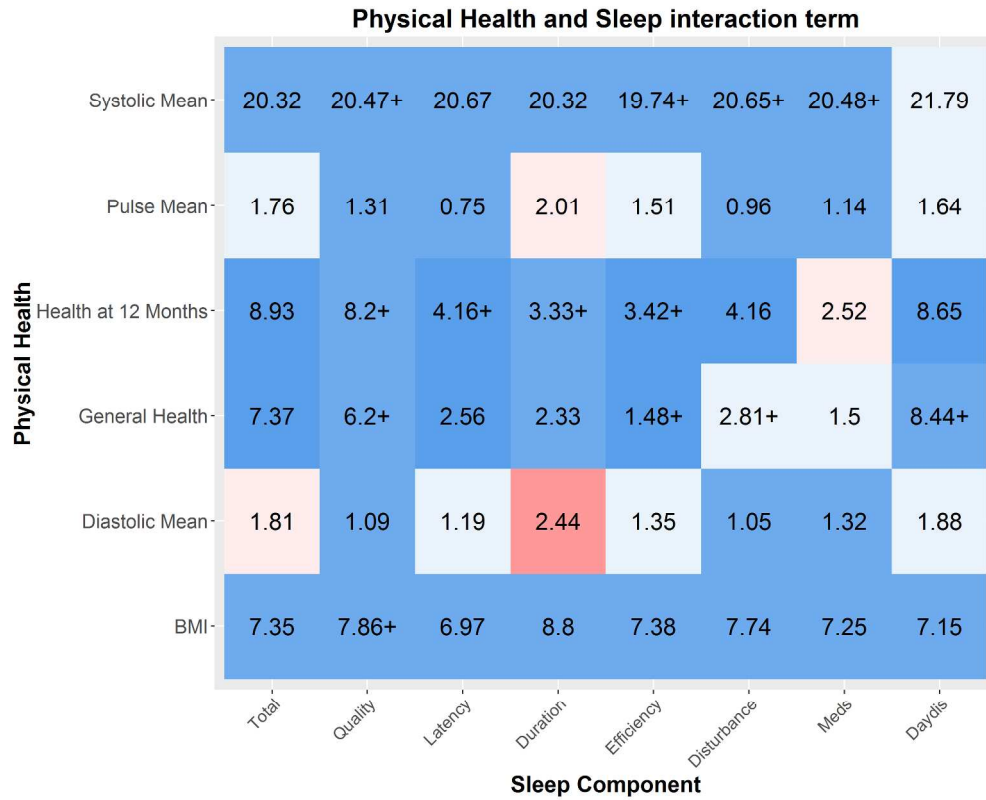


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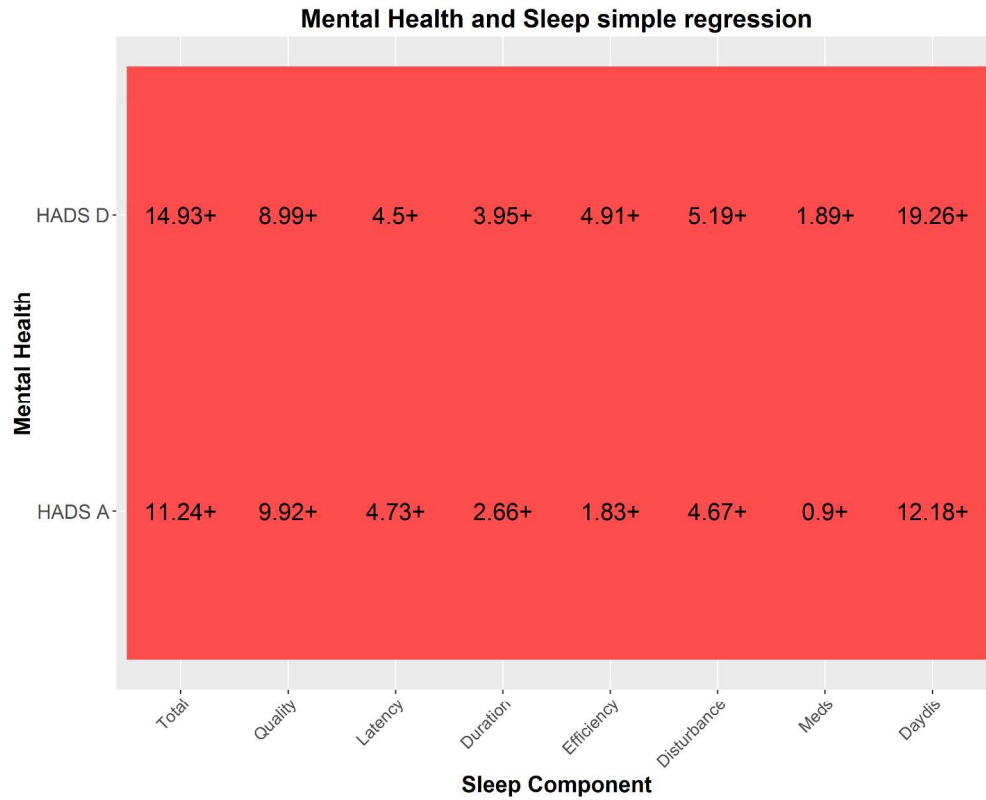
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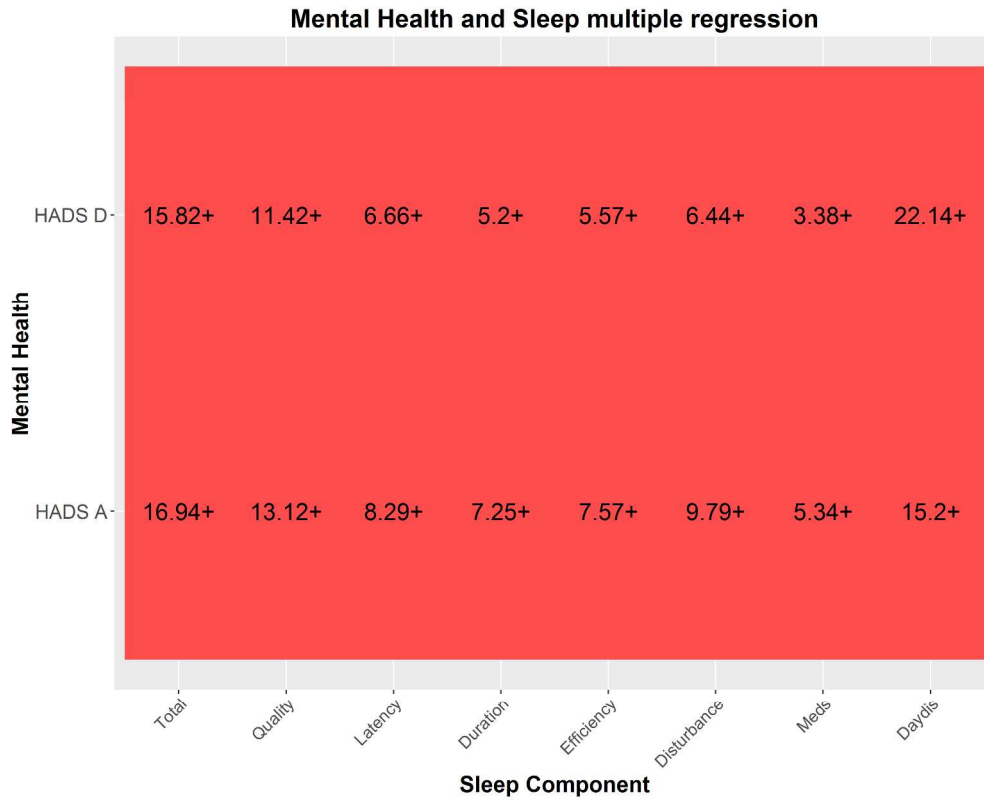
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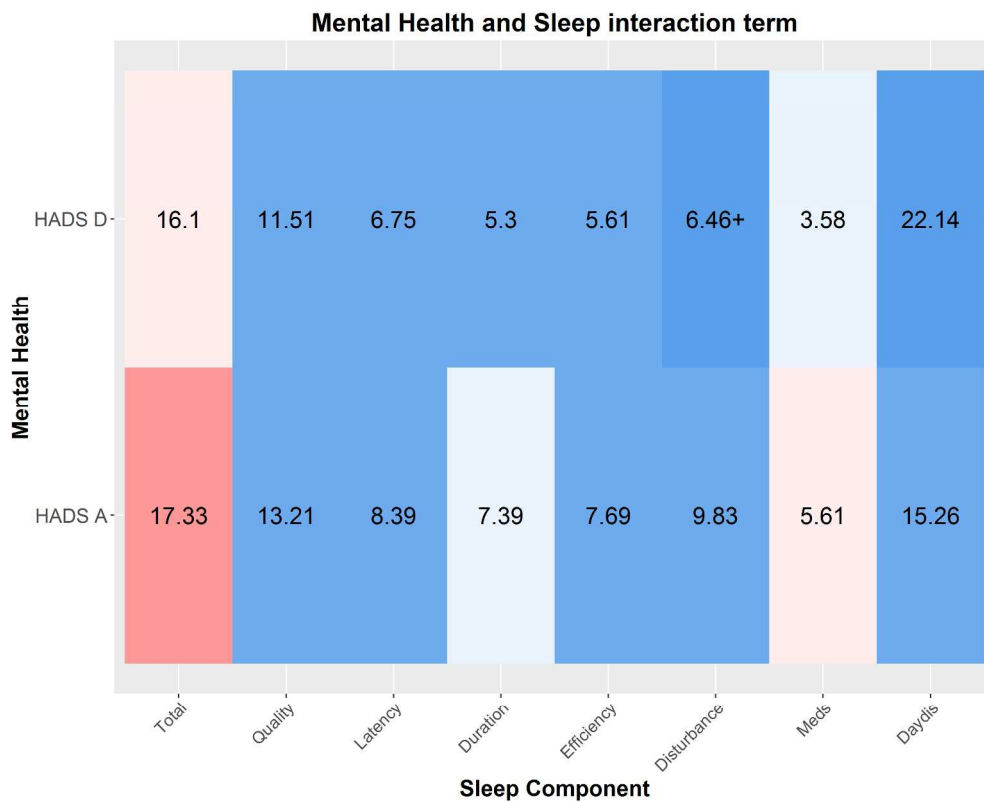
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-11
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10-13
		(b) Describe any methods used to examine subgroups and interactions	10
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14-22
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	9,10
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-22
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-22
Discussion			
Key results	18	Summarise key results with reference to study objectives	22-26
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	25-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	25-26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.