Age-related differences in self-reported sleep quality predict healthy ageing across multiple domains: a multi-modal cohort of 2406 adults

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Abstract

Background

Sleep is a fundamental human behaviour with many functions, and disruptions to sleep can lead to a variety of adverse health outcomes. Previous research suggests that age can impair sleep quality, contributing to age-related declines in health. In the current study we examine lifespan changes in self-reported sleep quality and their associations with health outcomes across four domains: Physical Health, Cognitive Health, Mental Health and Neural Health.

Methods

This paper reports on analyses of a large (N=2406) sample of healthy adults (age 18-98) from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN; www.cam-can.com) cohort. We measured sleep quality (Pittsburgh Sleep Quality Index) and measures of Physical, Cognitive, Mental, and Neural Health. We use Latent Class Analysis to identify sleep 'types' across the lifespan. Using Bayesian regressions we quantified the presence, and absence, of relationships between sleep quality and health measures and how these are affected by age.

Results

Using LCA we identified four sleep types: 'Good sleepers' (68.1% of the population, most frequent in middle age), 'inefficient sleepers' (14.01% of the population, most frequent in old age), 'Delayed sleepers' (9.28%, most frequent in young adults) and 'poor sleepers' (8.5% of the population, most frequent in old age). Second, we find that better sleep is generally associated with better health outcomes, strongly so for mental health, moderately for cognitive and physical health, but not for sleep quality and neural health. Finally, we find little evidence for interactions between sleep quality and age on health outcomes.

Conclusions

Lifespan changes in sleep quality are multifaceted and not captured well by summary measures. Instead, we find distinct sleep subtypes that vary in prevalence across the lifespan. Second, better self-reported sleep is associated with better health outcomes, and the strength of these associations

39 differs across health domains. Notably, the absence of associations between sleep quality and white
40 matter suggests that previously observed associations may depend on clinical samples with
41 pathological sleep deficiencies that do not necessarily generalise to healthy cohorts. While our
42 measure of sleep quality is self-reported, these findings suggest that such measures can provide
43 valuable insight when examining large, typically-ageing samples.
44

45 **Keywords**
46 Ageing, sleep quality, healthy ageing, cognition, mental health, cognition, white matter, physical
47 health
48

Background

Sleep is a fundamental human behaviour, with humans spending almost a third of their lives asleep. Regular and sufficient sleep has been shown to benefit human physiology through a number of different routes, ranging from consolidation of memories [1]to removal of free radicals [2] and neurotoxic waste [3]. Sleep patterns are known to change across the lifespan in various ways, including decreases in quantity and quality of sleep [4], changes in the alignment of homeostatic and circadian rhythms [5], decreases in sleep efficiency [6] the amount of slow-wave sleep, and an increase in daytime napping[7]. Importantly, interruption and loss of sleep has been shown to have wide ranging adverse effects on health [8], leaving open the possibility that age-related changes in sleep patterns and quality may contribute to well-documented age-related declines in various health domains. Recent work suggests sleep disruption may present a novel mechanistic pathway and treatment target for Alzheimer's disease [9].

In the current study, we examine self-reported sleep habits in a large, population-based cohort Cambridge Centre for Ageing and Neuroscience (Cam-CAN, [10]). We relate sleep measures to measures of health across four health domains: cognitive, brain health, physical and mental health. Our goal is to quantify and compare the associations between typical age-related changes in sleep quality and a range of measures of health measures that commonly decline in later life.

We assess sleep using a self-reported measure of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) [11]. The PSQI has good psychometric properties [12] and has been shown to correlate reliably with diseases of aging and mortality [13–15]. Although actigraphy (measuring sleep quality in the lab) is commonly considered the gold standard of sleep quality measurement, it is often prohibitively challenging to employ in large samples. A recent direct comparison of sleep measures [16] suggests that although subjective sleep measures (such as PSQI) may have certain drawbacks in older samples, they also capture complementary aspects of sleep quality not fully covered by actigraphy. Moreover, collecting self-report sleep quality data in a large, deeply phenotyped cohort allows for several additional benefits.

First, previous work on the effects of sleep has tended to focus on either the pathological extremes of sleep problems [17], leaving open the question whether these findings generalise to how non-pathological differences in sleep quality affect health outcomes in non-clinical samples. Second, smaller studies often focus on specific health measures such as metabolism [18] or cognition [19]. By instead studying a range of health outcomes in the same population, we can compare and contrast the effect of sleep quality on multiple health domains in the same individuals. Finally, previous studies, especially neuroimaging samples, have relied on relatively small sample sizes [19, 20], although see [22].

Small samples both limit statistical power and the extent to which optimal statistical methodology can be employed. The large sample size in the current study allows us to use advanced analytic techniques such as latent class analysis to examine whether sleep quality can be described not just as a continuum, but in terms of a discrete set of sleep profiles across individuals. Moreover, the large sample size allows us to use Bayesian statistics to quantify both the presence and absence of associations between sleep quality and health. Together, this suggests considerable value in assessing the relationship between self-reported sleep quality and health outcomes in a large, population-based, age-heterogeneous sample.

Methods

Sample

Participants were recruited as part of the population-based Cambridge Centre for Ageing and Neuroscience (Cam-CAN) cohort (www.cam-can.com). For details of the project protocol see [10] and [23], and for further details of the Cam-CAN dataset visit http://www.mrc-cbu.cam.ac.uk/datasets/camcan/. The raw data are available upon signing a data sharing request form (see http://www.mrc-cbu.cam.ac.uk/datasets/camcan/ for more detail). A further subset participated in a neuroimaging session [23] . Participants included were native English speakers, had normal or corrected to normal vision and hearing, and scored 25 or higher on the mini mental state

exam (MMSE; Folstein, Folstein, & McHugh, 1975). Ethical approval for the study was obtained from the Cambridgeshire 2 (now East of England- Cambridge Central) Research Ethics Committee (reference: 10/H0308/50). Participants gave written informed consent.

Sleep Measures

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a well-validated self-report questionnaire [11, 16] designed to assist in the diagnosis of sleep disorders. The questions concern sleep patterns, habits, and lifestyle questions, grouped into seven components, each yielding a score ranging from 0 (good sleep/no problems) to 3 (poor sleep/severe problems). The seven sleep components in the PSQI are as follows:

Component 1: Subjective Sleep Quality. The participant self-reports the quality of their sleep, on a scale between "Very good" (0) to "Very bad" (3), with this value representing their overall 'Quality' score.

Component 2: Sleep Latency. Assessing how long it takes participants to fall asleep, and whether falling asleep often causes any sleeping problems.

Component 3: Sleep Duration. Self-report of how many hours on average of 'actual' sleep per night (>7 hours=0, 6-7 hours=1, 5-6 hours = 2, <5 hours =3).

Component 4: Sleep Efficiency. Computed by dividing 'hours slept' by 'hours in bed'. This percentage is stratified to give four scores ranging from <65% (3, for highly inefficient sleep) to >85% (0, for efficient sleep).

Component 5: Sleep Disturbance. A number of sub questions regarding disruptions are summed to quantify the extent and regularity of disruptions to sleep (e.g. 'Not during the past month' (0) to 'Three or more times a week' (3).

Component 6: Use of sleep medication. The participant rates how often they have taken medicine (prescribed or 'over the counter') to aid their sleep ('not during the last month'=0, 'three or more times a week'=3).

Component 7: Daytime Dysfunction. Uses two questions to assess the extent and frequency to which lack of sleep impacts on daily activities, ranging from 'No problem at all' (0) to 'A very big problem'/'Three or more times a week' (3).

These component scores are summed to a PSQI Total score ranging between 0 and 21, with higher scores reflecting poorer sleep quality.

Health Measures

Many conceptualisations of healthy ageing exist [25]. Here we aim to capture the relationship between sleep and health across a broad range of variables in four key domains - cognitive, brain, physical and mental health across the lifespan. We describe these four health domains and variables below, and Table 1 provides an overview of each variable, including distributional characteristics and relevant citations.

Cognitive health. A number of studies have found associations between poor sleep and cognitive decline, including in elderly populations. Poor sleep affects cognitive abilities such as executive functions (e.g. Regestein et al., 2004) and learning and memory processes [27], whereas short term pharmaceutical interventions such as administration of melatonin improve both sleep quality and cognitive performance . Scullin & Bliwise (2015, p. 97) conclude that "maintaining good sleep quality, at least in young adulthood and middle age, promotes better cognitive functioning and serves to protect against age-related cognitive declines". Because sleep may affect various aspects of cognition differently [19], we include measures that cover a range of cognitive domains including memory, reasoning, response speed, and verbal fluency, as well as including a measure of general cognition. See Table 1 and [10] for more details.

Neural health. Previous research suggests that individuals with a severe disruption of sleep are significantly more likely to exhibit signs of poor neural health [20, 29]. Specifically, previous studies have observed decreased white matter health in clinical populations suffering from conditions such as chronic insomnia [17], obstructive sleep apnoea [30, 31], excessively long sleep in patients with diabetes [32], and REM Sleep Behaviour Disorder [33]. Many of these studies focus on

white matter hyperintensities (WMH), a measure of the total volume or number of low-level neural pathological regions (although some study grey matter, e.g. [20, 34, 35]). White matter hyperintensities are often used as a clinical marker, as longitudinal increases in WMHs are associated with increased risk of stroke, dementia and death [36] and are more prevalent in patients with pathological sleep problems [31, 32]. However, use of this metric in clinical cohorts largely leaves open the question of the impact of sleep quality on neural (white matter) health in non-clinical, healthy populations. To address this question, we use a more general indicator of white matter neural health, namely *Fractional Anisotropy* (FA). Fractional anisotropy quantifies the directional coherence of the diffusion of water molecules, and is associated with white matter integrity and myelination (see [37, 38] for further discussion regarding white matter measures). We use FA as recent evidence [39] suggests that WMHs represent the extremes (foci) of white matter damage, and that FA is able to capture the full continuum of white matter integrity. This suggests that using fractional anisotropy provides a sensitive marker of neural health suitable for large, non-clinical healthy cohorts.

Physical health. Sleep quality is also an important marker for physical health, with poorer sleep being associated with conditions such as obesity, diabetes mellitus [18], overall health [8, 22] and increased all-cause mortality [40]. These associations have been observed in both directions, such that longer sleep was associated with greater risk of stroke [41]. We focus on a set of variables that capture three types of health domains commonly associated with poor sleep: Cardiovascular health measured by pulse, systolic and diastolic blood pressure [42], self-reported health, both in general and for the past 12 months, (e.g. Strine & Chapman, 2005) and body-mass index (e.g. Taheri, Lin, Austin, Young, & Mignot, 2004).

Mental health. Previous work has found that disruptions of sleep quality are a central symptom of forms of psychopathology such as Major Depressive Disorder, including both hypersomnia and insomnia [22, 45], and episodes of insomnia earlier greatly increased the risk of later episodes of major depression [46]. Kaneita et al., (2006) found a U-shaped association between

177 sleep and depression, such that individuals regularly sleeping less than 6, or more than 8, hours were
178 more likely to be depressed. A prospective study by Roberts et al., (2000) in an ageing population
179 showed a strong association between depression and sleep problems. At the other end of the
180 lifespan, [48] found that in late adolescence and early adulthood people self-reporting a diagnosis of
181 insomnia were more likely to report mental health symptoms and have lower working memory
182 capacity. Both depression (e.g. Fried & Nesse, 2015) and anxiety [50, 51] are commonly associated
183 with sleep problems. To capture these dimensions we used both scales of the Hospital Anxiety and
184 Depression Scale (HADS) [52], a widely used and standardized questionnaire that captures self-
185 reported frequency and intensity of anxiety and depression symptoms.
186

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 definition of the variable, and descriptive statistics.

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)	(Wechsler, 1999)
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)	(Wechsler, 1999)
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)	(Wechsler, 1999)
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)	(Wechsler, 1999)
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)	(Cattell, 1971)
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)	(Shafto et al., 2014)
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)	(Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006)
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)	(Hua et al., 2008)
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	M=2.02, SD=0.79, Range=(1-3)	(McGee, Liao, Cao, & Cooper, 1999)

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)	(McGee et al., 1999)
Physical	Systolic blood pressure	Mean systolic blood pressure in mmHg, averaged across three consecutive measurements	M=120.11, SD=17, Range=(78.5-186)	Hishida, H. (1993). *U.S. Patent No. 5,220,925*. Washington, DC: U.S. Patent and Trademark Office.
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)	Hishida, H. (1993). *U.S. Patent No. 5,220,925*. Washington, DC: U.S. Patent and Trademark Office.
Physical	Resting pulse	Mean pulse in beats per minute, averaged across three consecutive measurements	M=65.69, SD=10.5, Range=(40-110.5)	Hishida, H. (1993). *U.S. Patent No. 5,220,925*. Washington, DC: U.S. Patent and Trademark Office.
Physical	Body Mass Index (BMI)	(weight in kg) / (height in m)^2	M=25.77, SD=4.59, Range=(16.75-48.32)	(Deurenberg, Weststrate, & Seidell, 2007)
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)	(Zigmond & Snaith, 1983)
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)	(Zigmond & Snaith, 1983)

Analyses

Below, 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, we examine the simple regression of the health outcome on sleep variables, to determine whether there is evidence for an association between poor sleep quality and poor health outcomes. Second, we examine whether the relationship between sleep and health is attenuated when we include age as a covariate. Finally, we include a continuous interaction term (by adding a sleep*age term to a regression model after scaling both variables to have a standard normal distribution) 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) and others. This approach has avoids several well-documented problems known to plague p-values [55]. Moreover, Bayesian approach allows for the quantification of null effects, such that we can draw conclusions about the *absence* of certain associations in our data. Such null findings can be of considerable scientific value, as they may suggest the absence of risk factors in the non-clinical range of sleep quality. Third, Bayesian analyses are commonly considered to be less prone to multiple comparison problems (e.g. Gelman, Hill, & Yajima, 2012), which is useful given the breadth of our outcome measures. We can compare the evidence from a Bayesian regression to a null model (say, without a slope) to and compute aa *Bayes Factor*, a continuous measure of evidence of the model being tested compared to some other reference model (such as an 'intercept only' model compared to a linear regression). Although this is a continuous measure of evidence, it can be useful to use descriptive heuristics to quantify the strength of the evidence. Jeffreys [59] proposed a categorisation of Bayes Factors as seen in Figure 1:

Bayes Factor BF_{10}	Log BF_{10}	Tileplot colour	Description (Jeffreys, 1961)
>100	>4.6		Extreme evidence for H1
30 – 100	3.4 – 4-6		Very strong evidence for H1
10 – 30	2.3 – 3.4		Strong evidence for H1
3 – 10	1.098 – 2.3		Substantial evidence for H1
1 – 3	1 – 1.098		Anecdotal evidence for H1
1	0		No evidence either way
1/3 – 1	-1.098 – -1		Anecdotal evidence for H0
1/3 - 1/10	-2.3 – -1.098		Substantial evidence for H0
1/10 - 1/30	-3.4 – -2.3		Strong evidence for H0
1/30 - 1/100	-4.6 – - 3.4		Very strong evidence for H0
<1/100	< -4.6		Extreme evidence for H0

Figure 1. Descriptive interpretation of Bayes Factors.

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). Note that Bayes Factors are symmetrical: a Bayes Factor of .1 in favour of the model of interest (BF_{10}=0.1) is equivalent to a Bayes Factor of 10 in favour of the null model (BF_{01}=10). 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 [53, 54] in the package BayesFactor [60] using the open source software package R [61]. 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 the true effect will lie between -.707 and .707. Prior to further analysis, scores on all outcomes were transformed to a standard normal distribution, and any scores exceeding a z-score of 4 or -4 were recoded as missing (aggregate percentage outliers across the four health domains: Cognitive, 0.41%, Mental, 0.16%, Neural, 0.37% Physical, 0.031%).

Results

1. *Age-related differences in sleep quality*

First, we examined sleep changes across the lifespan by examining age-related differences in the PSQI sum score (N= 2178, M=5.16, SD=3.35, Range=0-19). Regressing the PSQI global score on age, shown in Figure 2, showed evidence for a positive relationship across the lifespan ($logBF_{10}$= 10.45). This suggests that on the whole, sleep quality decreases across the lifespan (note that *higher* PSQI scores correspond to worse sleep).

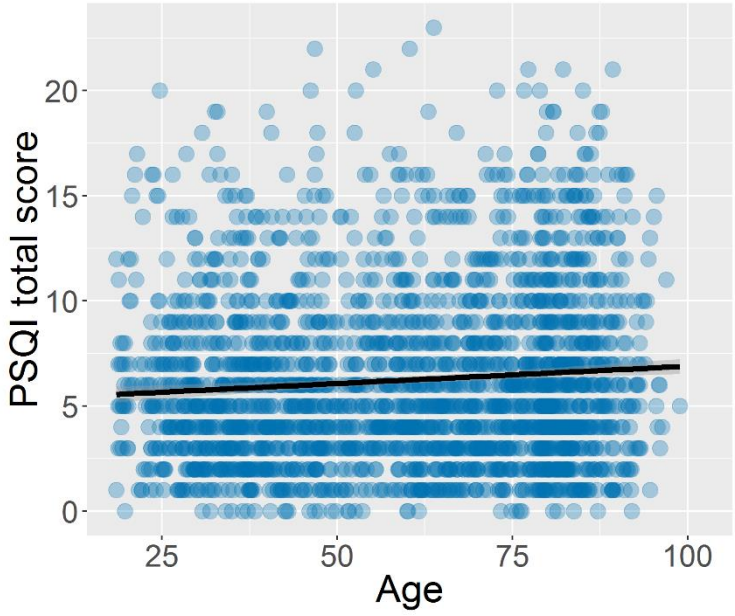

Figure 2. The relation of age to general sleep quality (PSQI sum-score across the lifespan

Although this amounts to strong statistical evidence for an age-related difference ('Extreme' according to Jeffreys, (1961), the effect was modest in size, with age explaining 1.23 % of the variance in the PSQI Total score. Next, we examined which subcomponents were driving this effect, regressing each of the seven components on age in the same manner. We visualise these results using a tile plot [62], as shown in Figure 3. 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 of the

regression is positive, the r-squared value has the symbol '+' added (note that this may mean sleep quality is associated with 'better' or 'worse' outcomes depending on the nature of the variable, cf. Table 1). In Figure 3 we see that that age has varying and specific effects on different aspects of sleep quality. In line with the overall age-related worsening of the PSQI Total score, four components showed a worsening of sleep quality across the lifespan (Total, Duration, Efficiency, Daytime Dysfunction and Sleep Medication). The strongest age-related decline is that of Efficiency, showing an R-squared of 6.6%.

However, sleep did not worsen uniformly across the lifespan. For example, we observed moderate evidence that sleep latency did not change across the lifespan (Sleep Latency, BF_{01}= 9.25, in favour of the null), Sleep Quality showed no evidence for either change or stasis (BF_{10}= 1.63) and one sleep component, Daytime Dysfunction, improved slightly across the lifespan (BF_{10}= 7.03).

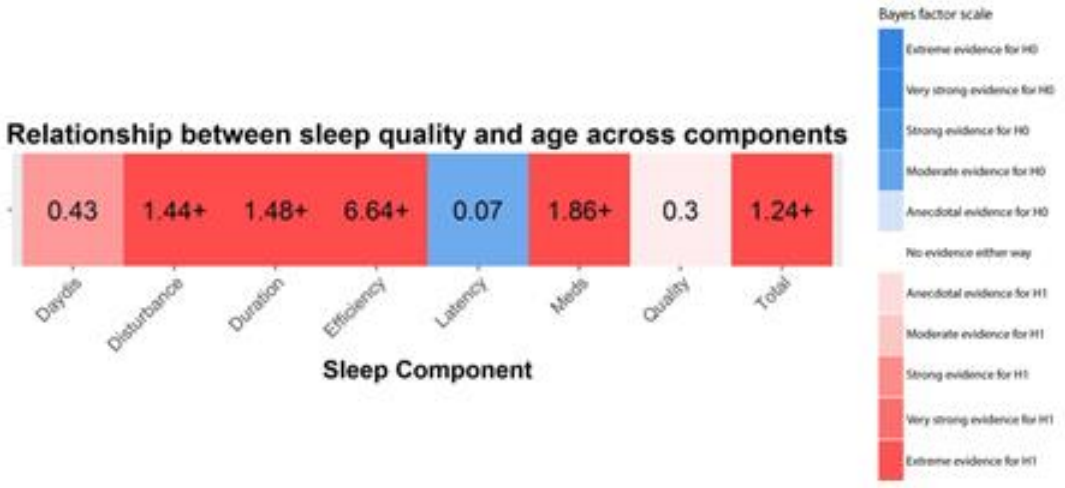

Figure 3. Bayesian Regressions between individual PSQI components and age. Values represent r-squared. Positive parameter estimates are denoted with a + symbol next to the r-squared value. Here, a positive relationship between age and sleep components denotes a worsening of sleep quality across the lifespan. N varies slightly across components due to varying missingness (N mean = 2320.20, N SD = 68.5]

Finally, we entered all seven components into a Bayesian multiple regression simultaneously, to examine to what extent they could, together, predict age. The best model included every component except Sleep Latency ($logBF_{10}$= 142.71). Interestingly, this model

explained 13.41% of the variance in age, compared to 1.23% for the PSQI Total score, and 6.4% for the strongest single component. This shows that lifespan changes in self-reported sleep are heterogeneous and partially independent, and that specific patterns and components need to be taken into account simultaneously to fully understand age-related differences in sleep quality.

These finding shows that neither the PSQI sum score nor the sleep components in isolation fully capture differences in sleep quality across the lifespan. To better elucidate individual differences in sleep quality we next use *Latent Class Analysis* [63]. This technique will allow us examine individual differences in sleep quality across the lifespan in more detail than afforded by simple linear regressions: Rather than examining continuous variation in sleep components, LCA classifies individuals into different *sleep types*, each associated with a distinct profile of 'sleep symptoms'. If there are specific constellations of sleep problems across individuals, we can quantify and visualize such sleep types. Moreover, by using Latent Class Regression, we can examine whether the likelihood of belonging to any sleep 'type' changes as a function of age. To analyse the data in this manner, we binarized the responses on each component into 'good' (0 or 1) or 'poor' (2 or 3). We fit a series of Latent Class solutions varying from 2 to 6 sleep types, including age as a covariate (simultaneously including a covariate is known as *latent class regression* or concomitant-variable latent class models [64]. We repeated each class solution 50 times with a maximum of 5000 iterations to ensure that the model fit was not affected by local minima of the log-likelihood. We found that the four class solution gives the best solution, according to the Bayesian Information Criterion [65] (BIC for 4 Classes = 11825.65, lowest BIC for other solutions= 11884.92 (5 classes). Next we inspected the nature of the sleep types, the prevalence of each 'sleep type' in the population, and whether the likelihood of belonging to a certain sleep type changes across the lifespan. Figure 4a shows the component profile for the four sleep types we identified.

Class 1, which we refer to as 'Good sleepers', make up 68.1% of participants. Their sleep profile is shown in Figure 4A, top left, and is characterised by a low probability of responding 'poor' to any of the sleep components. Class 2, 'inefficient sleepers', make up 14.01% of the participants,

and are characterized by poor sleep Efficiency: Members of this group uniformly (100%) report poor sleep Efficiency, despite relatively low prevalence of other sleep problems, as seen in Figure 4A, top right. Class 3, seen in the bottom left of Figure 4a, makes up 9.28% of the participants and can be described as 'Delayed sleepers': They are characterized by modestly poor sleep across the board, but a relatively high probability of poor scores on Sleep Latency (59%), Sleep Quality (51%) and sleep Disturbance (31%). Finally, Class 4, 'Poor sleepers', make up 8.5% of the participants, shown bottom right in Figure 4A. Their responses to any of the seven sleep components are likely to be 'poor' or 'very poor', almost universally so for 'sleep quality' (94%) and 'Sleep Efficiency' (97.7%).

Next, we examined whether age predicts the likelihood of belonging to any particular class using latent class regression. This analysis, visualised in Figure 4b, shows that the probability of membership of each classes compared to the reference class (good sleepers) changes significantly across the lifespan for each of the classes (Class 2 versus class 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 versus class 1: beta/SE 0.01269/0.00478, t=2.655, for more details on generalized logit coefficients , see Linzer & Lewis, 2011, p. 21). The frequency of Class 1 (Good sleepers) peaks in middle to late adulthood, dropping increasingly quickly after age 50. Class 2 (Inefficient sleepers) are relatively rare in younger individuals, but the prevalence increases rapidly in individuals over age 50. On the other hand, Class 3 (Delayed sleepers) shows a steady decrease in the probability of an individual showing this profile across the lifespan, suggesting that this specific pattern of poor sleep is more commonly associated with younger adults. Finally, the proportion of Class 4 (poor sleepers) members increases only slightly across the lifespan. Together, the latent class analysis provides additional evidence that the PSQI sum score as an indicator of sleep quality does not fully capture the subtleties of age-related differences. Age-related changes in sleep patterns are characterized by specific, clustered patterns of sleep problems that cannot be adequately characterized by summation of the component scores. Next, we examine the relationships between sleep components and measures of health across different domains.

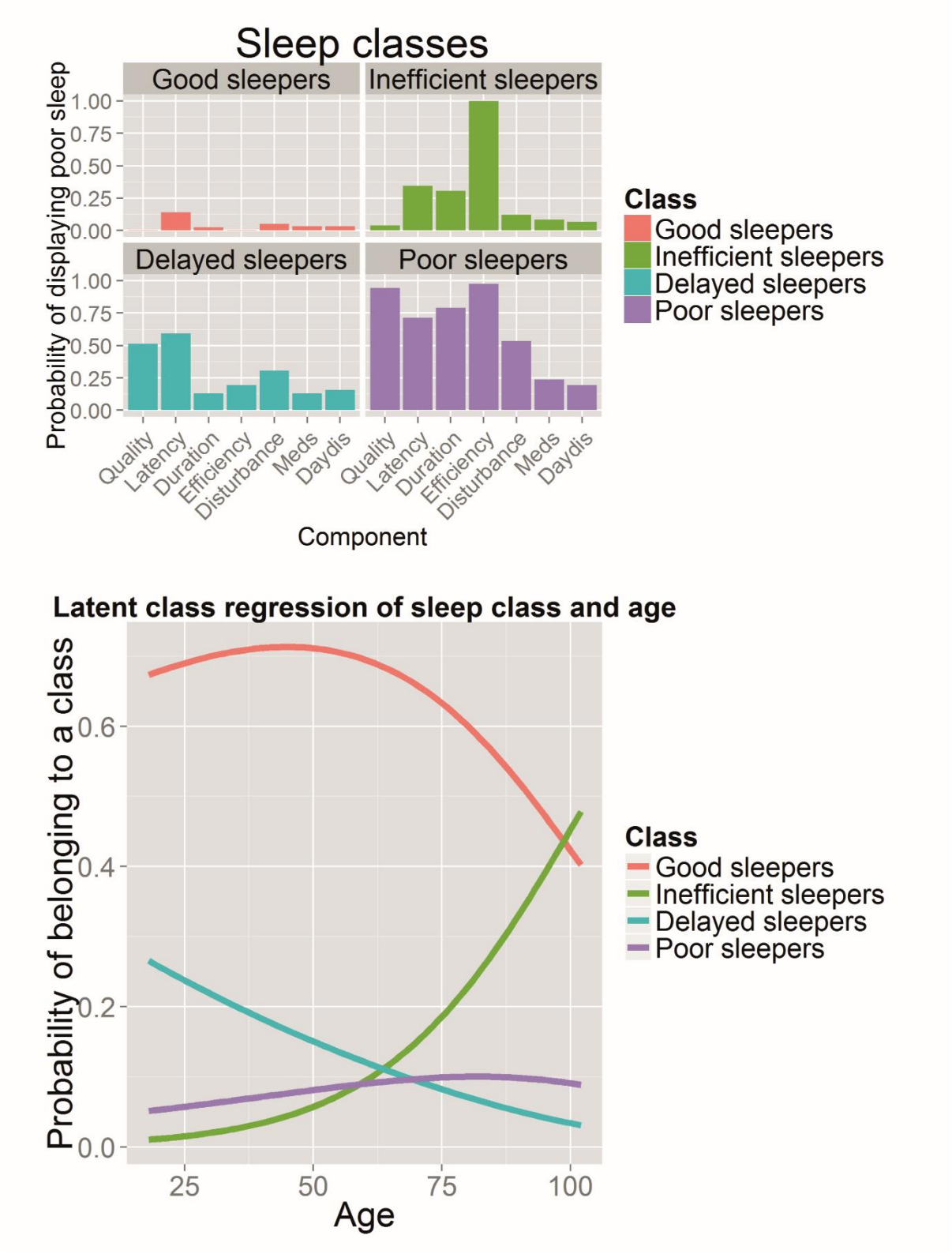

Figure 4. Latent Class Analysis. Panel A shows the sleep quality profiles for each of the four classes. Panel B shows the conditional probability of belonging to each class across the lifespan.

Sleep, health domains and age

The above analyses show how both a summary measure and individual measures of sleep quality change across the lifespan. Next, we examined the relationships between sleep quality measures (seven components and the global PSQI score) and health variables (specific variables across four domains, as shown in Table 1). We will focus on three questions within each health domain: First, is there a relationship between sleep quality and health? Second, does the strength and nature of this relationship change when age is included as a covariate? Third, does the strength and nature of the relationship change across the lifespan? We will examine these questions across each of the four health domains.

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 5, several relationships exist between measures of cognitive health and measures of sleep quality. 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 suggests this task, dependent on multiple executive processes, is particularly affected by poor sleep quality [68]. The second strongest association was

with the ACE-R, a general cognitive test battery similar in style and content to the MMSE. The associations with cognition were slightly attenuated when age was included as a covariate (Supplementary Figure A) but the basic effects remained.

When an interaction term with age was included, no evidence for interactions with age were observed (mean $logBF_{10}$=-2.08, see Supplementary Figure B), suggesting that the negative associations between sleep and cognitive performance are a constant feature across the lifespan, rather than specifically in elderly individuals. Together this suggests that poor sleep quality is modestly and consistently associated with poorer general cognitive performance across the lifespan, most strongly with semantic fluency. Next, we examine whether there is evidence for a relationship between poor sleep and poorer neural health.

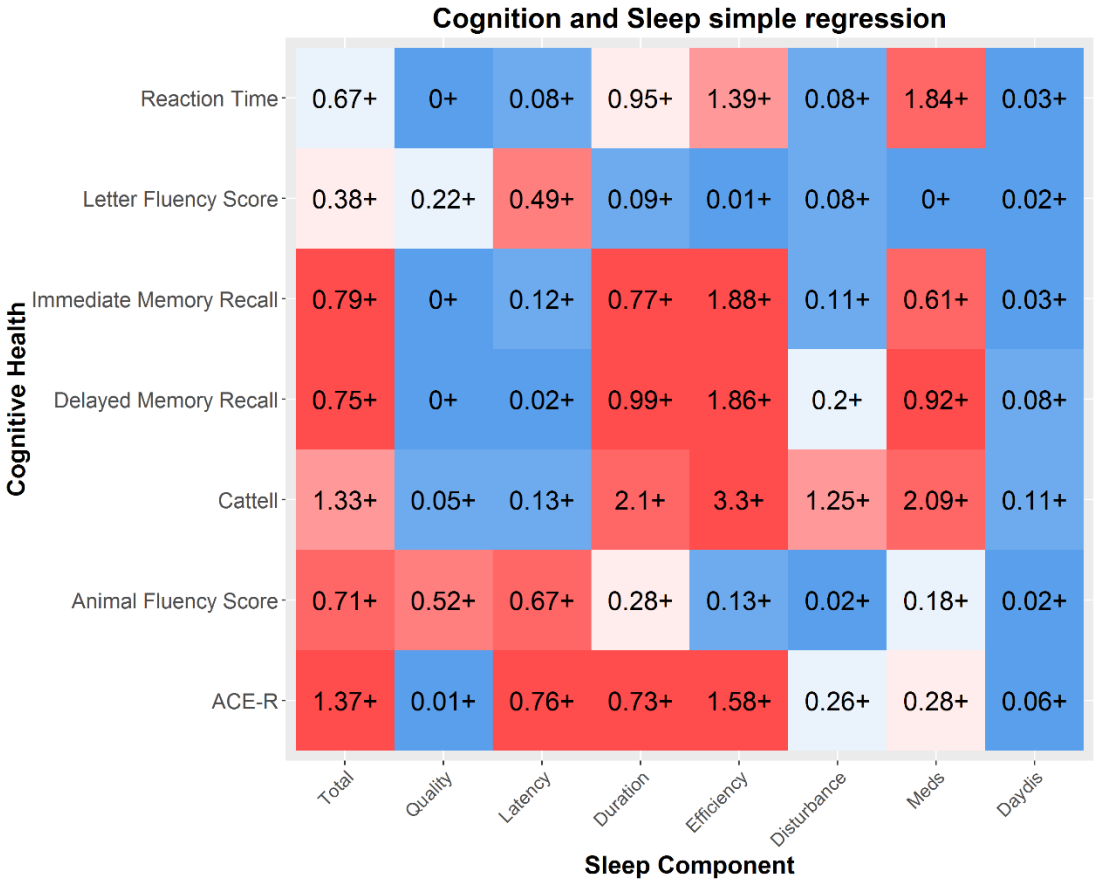

Figure 5. Simple regressions between sleep components and Cognitive Health. The strength of the effect is colour-coded by Bayes Factor, and the effect size is shown as r-squared (as a percentage out of 100). Sample varies across components and measures due to varying missingness. Cattell and Reaction 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)]

Neural Health

Next we examined the relationship between sleep quality and neural health. As described in the Methods, we focus on white matter health as indexed by fractional anisotropy. Using Diffusion Tensor Imaging, we estimated a general index of white matter integrity in 10 tracts [69] shown in Figure 6, by taking the average Fractional Anisotropy in each white matter ROI.

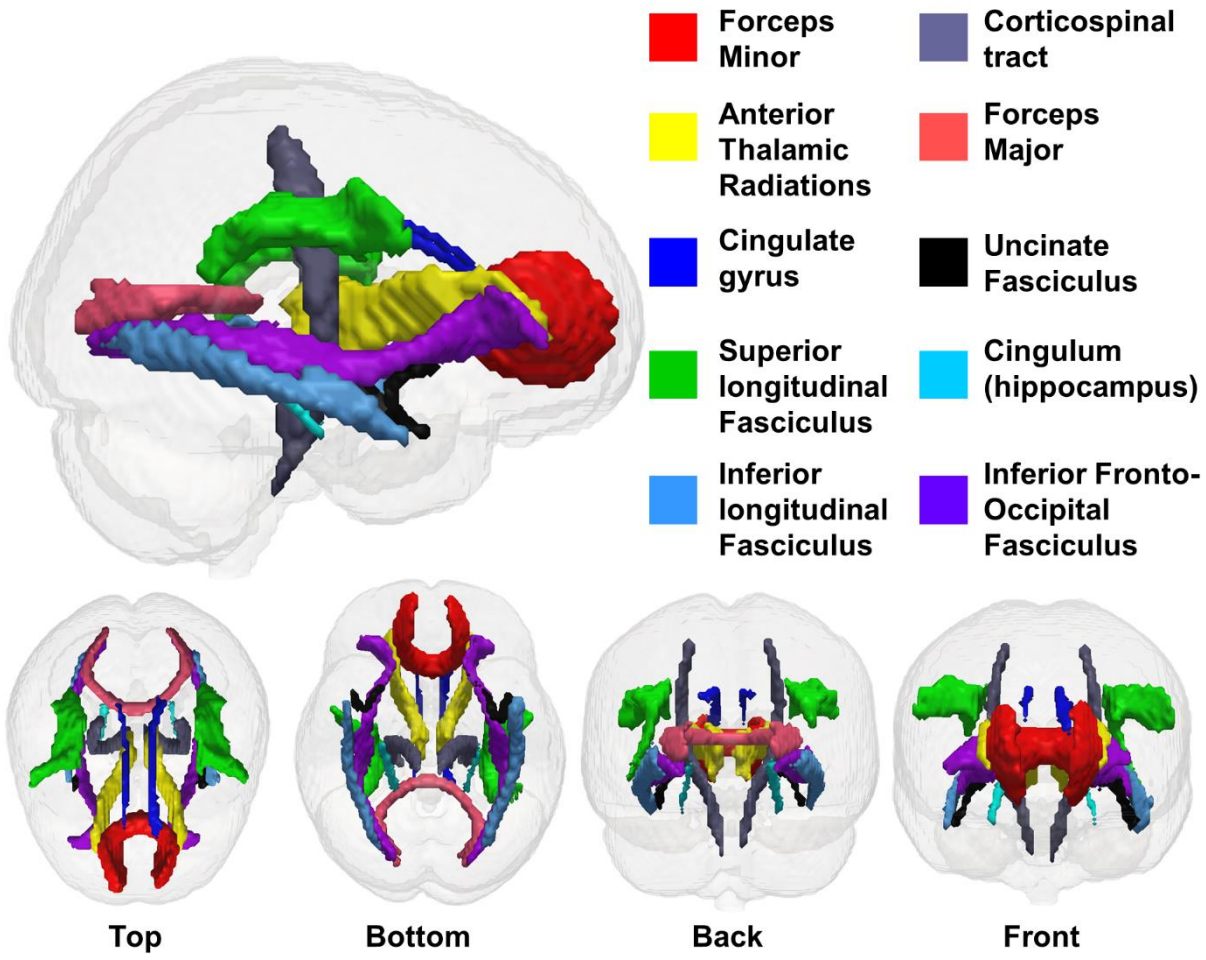

Figure 6. Ten white matter ROIS based on Hua et al. (2008). Mean FA per ROI was averaged bilaterally and used in further analysis.

We use the data from a subsample of 641 individuals (age M=54.87, range 18.48-88.96) who were scanned in a 3T MRI scanner (for more details regarding the pipeline, sequence and processing steps, see [70]). Regressing neural WM ROI's on sleep quality, we find several small effects, with the strongest associations between sleep efficiency and neural health (see Supplementary Figure C). All effects are such that poorer sleep is associated with poorer neural health, apart from a small effect

in the opposite direction for Uncinate and Daytime Dysfunction (BF_{10}= 6.20). However, when age is included as a covariate, the negative associations between sleep quality and white matter health are attenuated virtually to zero (Figure 7, mean/median BF_{10}= 0.18/.10), with Bayes Factors providing strong evidence for the lack of associations between sleep quality and white matter integrity. One exception was observed: The use of Sleep Medication is associated with *better* neural health in the corticospinal tract, a region previously found to be affected by pathological sleep problems such as sleep apnoea [31]. However, this effect is very small (BF_{10}=3.24), so should be interpreted with caution. Finally, we tested for any interactions by including a mean-scaled interaction term (sleep*age, Supplementary Figure D). This analysis found evidence for a significant interaction, between the Superior Longitudinal Fasciculus (SLF) and Sleep Medication (BF_{10}= 13.77), such 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.

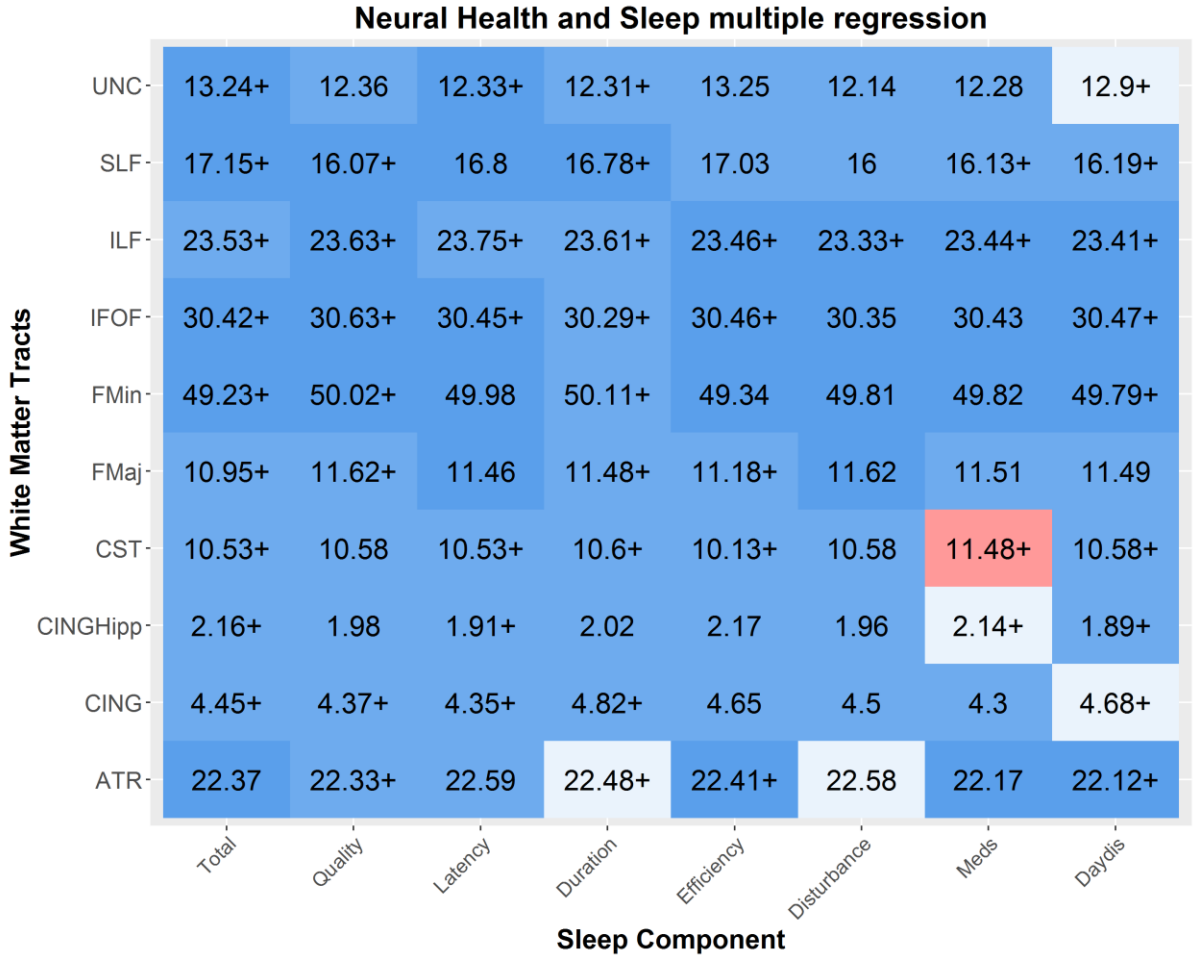

Figure 7. Multiple regressions between sleep components and Neural Health. Each cell represents the relationship between a sleep component and the mean neural health in a given tract as index by Fractional Anisotropy. Numbers represent R-squared, the sample size is show in the last column. Strong associations 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).

Physical health

Next we examined whether sleep quality is associated with physical health. Figure 8 shows the simple regressions between sleep quality and physical health. Strong associations were found between poor overall sleep (PSQI sumscore) and poor self-reported health, both in general ($logBF_{10}$=77.51) and even more strongly for health in the past 12 months ($logBF_{10}$=91.25). One

explanation is that poorer sleep, across all components, directly affects general physical health (Briones et al., 1996; Spiegel et al., 2009). A second, possibly complementary pattern is that 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). 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 [18, 72, 73]. 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 E), suggesting these associations are not merely co-occurences across the lifespan. Our findings suggest self-reported sleep quality, especially sleep Duration, is related to differences in physical health outcomes in a healthy sample.

Finally, there was evidence of a single interaction with age (Supplementary Figure F): Although poor sleep Duration was associated with *higher* diastolic blood pressure in younger adults, it was associated with *lower* diastolic blood pressure in older individuals (BF_{10}= 8.53), as can be seen in Supplementary Figure F. This may reflect the fact that diastolic blood pressure is related to cardiovascular health in a different way across the lifespan, although given the small effect size it should be interpreted with caution.

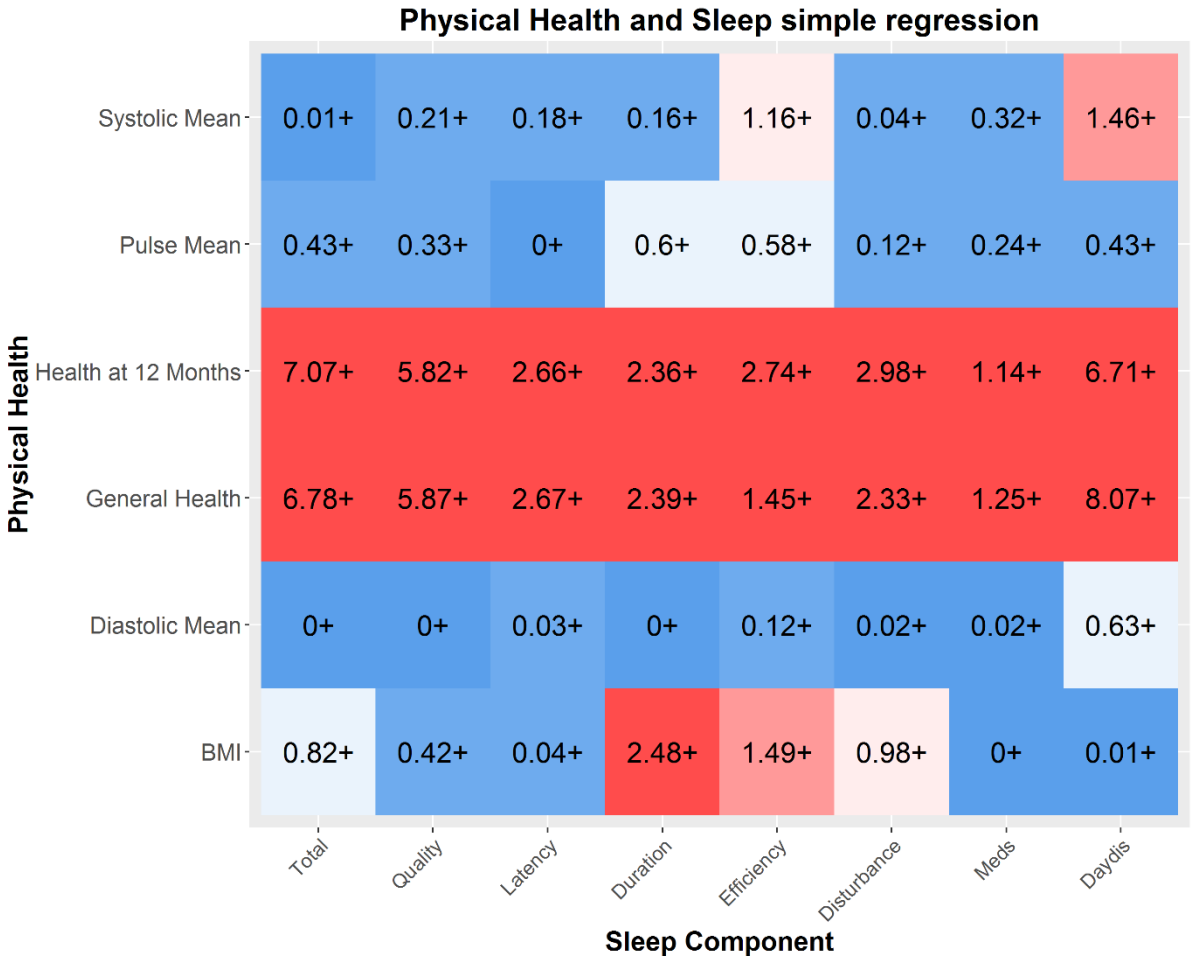

Figure 8. Physical health and sleep quality. Numbers represent R-squared, the sample size is show in the last column. Strong associations between general indices of health and sleep quality are found, and several more modest relationships with BMI and sleep quality. Self-reported health (12 month and 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).

Mental health

Finally, we examined the relationship between sleep quality and mental health, as measured by the Hospital Anxiety and Depression Scale [52]. One benefit of the HADS in this context is that, unlike some other definitions (e.g. the DSM-V), sleep quality is not an integral (scored) part of these dimensions. As shown in Figure 9, there are very strong relationships between all aspects of sleep quality and measures of both anxiety and depression. The strongest predictors of Depression are Daytime Dysfunction ($logBF_{10}$= 245.9, R^2=20.9%), followed by the overall sleep score ($logBF_{10}$= 170.5, R^2=14.6%) and sleep quality ($logBF_{10}$= 106.8, R^2=9.7%). The effects size for Anxiety was

comparable but slightly smaller in magnitude. When age is included as a covariate the relationships remained virtually unchanged (Supplementary Figure G), suggesting these relationships are present throughout across the lifespan. These findings replicate and extend previous work, suggesting that sleep quality is strongly associated with both anxiety and depression across the lifespan.

Figure 9. Mental health and sleep quality. N varies slightly across components due to varying missingness (N mean = 2303.62, N SD = 65.32). The + symbols signify positive parameter estimates, such that poorer (higher) sleep quality is associated with higher scores on anxiety and depression.

Next we examined a model with an interaction term (Supplementary Figure H). Most prominently we found interactions with age in the relationship between HADS depression and the PSQI Total, and in the relationship between HADS depression and Sleep Duration, such that for the relationship between anxiety and overall sleep quality is stronger in younger adults (BF_{10} =9.91, see Figure 10). Together our findings show that poor sleep quality is consistently, strongly and stably associated with poorer mental health across the adult lifespan.

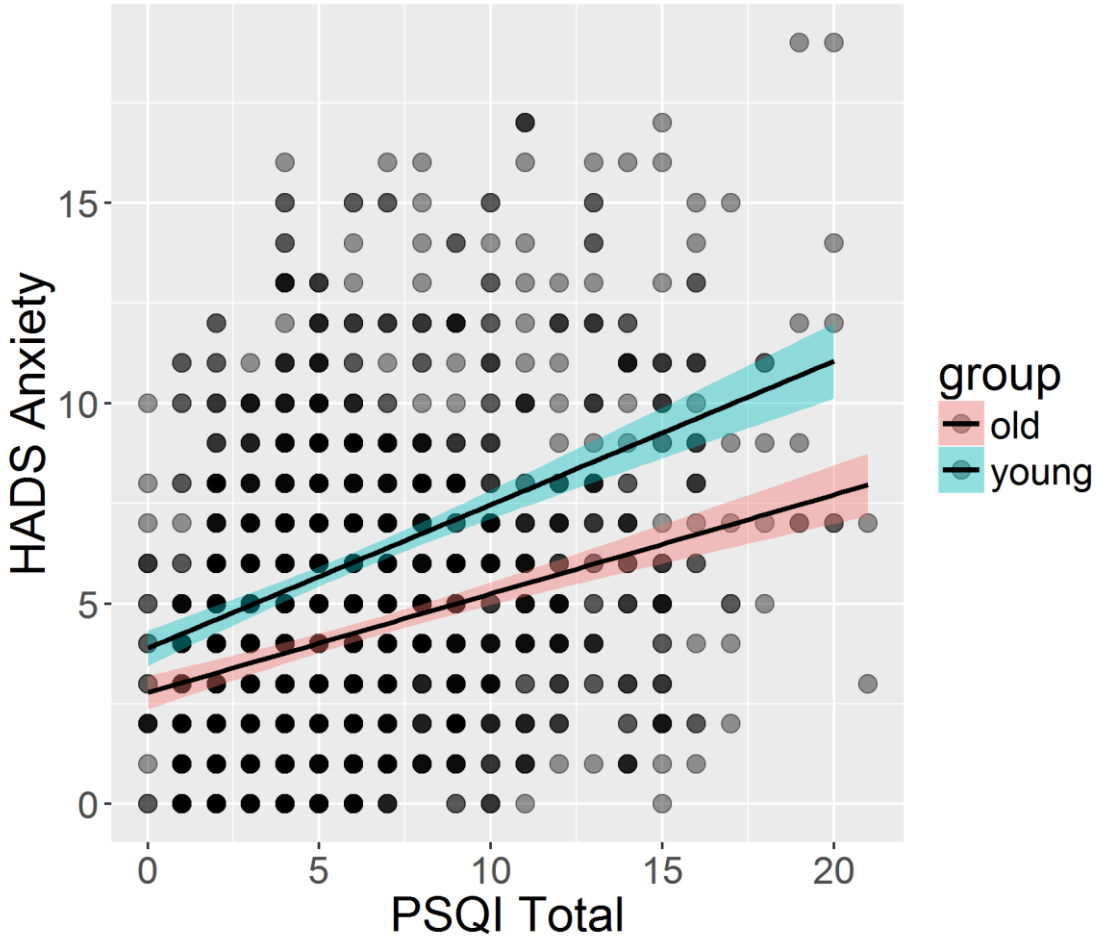

***Figure 10**:* interaction between sleep quality and anxiety. (N=724,age 18.48 to 46.2) compared to the oldest third of participants (N=725, age 71.79 to 98.88).

Discussion

In this study, we report on the associations between age-related differences in sleep quality and health outcomes in a large, age-heterogeneous sample of community dwelling adults of the Cambridge Neuroscience and Aging (Cam-CAN) cohort. We find that sleep quality generally decreases across the lifespan, most strongly for sleep Efficiency (the proportion of time spent in bed actually asleep). However, components such as 'Daytime Dysfunction' improve slightly across the lifespan, whereas 'sleep latency' does not change. As this pattern suggests that age-related changes in sleep patterns are complex and multifaceted, we used Latent Class Analysis to identify 'sleep types' associated with specific sleep quality profiles. We find evidence for four such sleep types, and show that the likelihood of belonging to certain sleep type varied across the lifespan. Younger adults

are more likely than older adults to display a pattern of sleep problems characterised by poor sleep quality and longer sleep latency, whereas older adults are more likely to display inefficient sleeping, characterised by long periods spent in bed whilst not asleep. Moreover, the probability of being a 'good' sleeper, unaffected by any adverse sleep symptoms, decreases considerably after age fifty.

A key strength of our sample is the broad phenotypic assessment of healthy ageing across multiple health domains in a large cohort. This allows, contrary to most previous studies, for direct comparison of the different measures of sleep quality and four key health domains: cognitive, neural, physical and mental health. We find strongest associations between sleep quality and mental health, moderate relations between sleep quality and physical health and cognitive health and sleep, virtually all such that poorer sleep is associated with poorer health outcomes. We did not find evidence for associations between self-reported sleep and neural health. Notably, the relationships we observe are mostly stable across the lifespan, affecting younger and older individuals alike. A notable exception to these effects is the absence of any strong relation (after controlling for age) between sleep quality and neural health as indexed by tract-based average fractional anisotropy. Using a Bayesian framework we are able to provide evidence in favour of the null hypothesis, suggesting that the adverse effects of poor sleep on brain structure found in more extreme clinical samples (e.g. insomnia, sleep apnoea) do not generalize to a non-clinical population for self-reported sleep. Notably, as we found strong relationships in the same sample between sleep and other outcomes (e.g. mental health, Figure 10) and there is previous evidence from this cohort linking white matter health and cognition, the absence of the relationship between poor sleep and neural health cannot be (fully) explained away by the possible noisiness of self-report measures. For this reason, our study provides a potentially reassuring message that for typically-ageing, healthy individuals, poorer self-reported sleep quality is not associated with poorer brain health.

While there are limitations of self-report measures including in older cohorts [16], including the fact that they likely reflect different aspects of sleep health than actigraphy (sleep in the lab), our results suggest there are considerable advantages in using self-reported sleep measures: first,

obtaining sleep quality data in a large and broadly phenotyped sample is feasible; and second, our results demonstrated clear and consistent associations across multiple domains for both subjective (e.g. self-reported health) and objective measures (e.g. memory tests, BMI), which both replicate and extend previous lab-based sleep findings. Future work should ideally simultaneously measure actigraphy and self-report in large scale cohorts to fully capture the range of overlapping and complementary relations between different aspects of sleep quality and health outcomes [16].

For both self-report and objective measures of sleep quality an open question is that of causality: Does poor sleep affect health outcomes, do health problems affect sleep, are they both markers of some third problem, or do causal influences go both ways? Most likely, all these patterns occur to varying degrees. Previous studies have shown that sleep quality causally affects health outcomes such as diabetes [18] and memory consolidation [1] while other evidence suggests that depression directly affect sleep quality (Lustberg & Reynolds, 2000; Sbarra & Allen, 2009) and that damage to neural structures may affect sleep regulation [76]. Although our findings are in keeping with previous findings, our cross-sectional sample cannot tease apart the causal direction of the observed associations, so more work remains to be done to disentangle these complex causal pathways.

In our paper we focus on a healthy, age-heterogeneous community dwelling sample. This allows us to study the associations between healthy aging and self-reported sleep quality, but comes with two key limitations of the interpretations of our findings. First and foremost, our findings are cross-sectional, not longitudinal. This means we can make inferences about age-related *differences*, but not necessarily age-related *changes* (Raz & Lindenberger, 2011; Schaie, 1994). One reason why cross-sectional and longitudinal estimates may diverge is that older adults can be thought of as cohorts that differ from the younger adults in more ways than age alone. For example, our age range includes individuals born in the twenties and thirties of the 20th century. Compared to someone born in the 21st century, these individuals will likely have experience various differences during early life development (e.g. less broadly accessible education, lower quality of healthcare, poorer

nutrition and similar patterns). For some of our measures, these are inherent limitations – Neuroimaging technology means that of *truly* longitudinal study of aging is inherently impossible. This means our findings likely reflect a combination of effects attributable to age-related changes as well as baseline differences between subpopulations that may affect both mean differences as well as developmental trajectories.

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 that 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 [10] for further details). Nonetheless, a healthier subsample may lead to restriction of range [79], 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 community dwelling adults, but not necessarily to populations that include those affected by either clinical sleep deprivation or other serious health conditions.

Conclusions

Taken together, our study allows several conclusions. First, although we replicate the age-related deterioration in some aspects of sleep quality, other aspects remain stable or even improve. Second, we show that the profile of sleep quality changes across the lifespan. This is important methodologically, as it suggests (PSQI) sum scores do not capture the full picture, especially in age-heterogeneous samples. Moreover, it is important from a psychological standpoint: We show that 'sleep quality' is a multidimensional construct and should be treated as such if we wish to understand the complex effects and consequences of sleep quality across the lifespan. Third,

moderate to strong relations exist between sleep quality and cognitive, physical and mental health, and these relations largely remain stable across the lifespan. In contrast, we show evidence that in non-clinical populations, poorer self-reported sleep is not associated with poorer neural health. Together with previous experimental and longitudinal evidence, our findings suggest that at least some age-related decreases in health outcomes may be due to poorer sleep quality. We show that self-reported sleep quality can be an important indicator of other aspects of healthy functioning throughout the lifespan, especially for mental and general physical health. Our findings suggest accurate understanding of sleep quality is essential in understanding and supporting healthy aging across the lifespan.

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Cambridgeshire 2 (now East of England-Cambridge Central) Research Ethics Committee (reference: 10/H0308/50). Participants gave written informed consent.

Consent for publication

Not applicable

Availability of data and material

The raw data are available upon signing a data sharing request form (see http://www.mrc-cbu.cam.ac.uk/datasets/camcan/ for more detail).

Competing interests

The authors declare no competing interests

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Authors' contributions

A.G., M. S. and R. A. K. conceived of the paper. Cam-CAN organised the study. Y. L. contributed to writing and revising. A. G. and R. A. K. analysed the data and created the figures.

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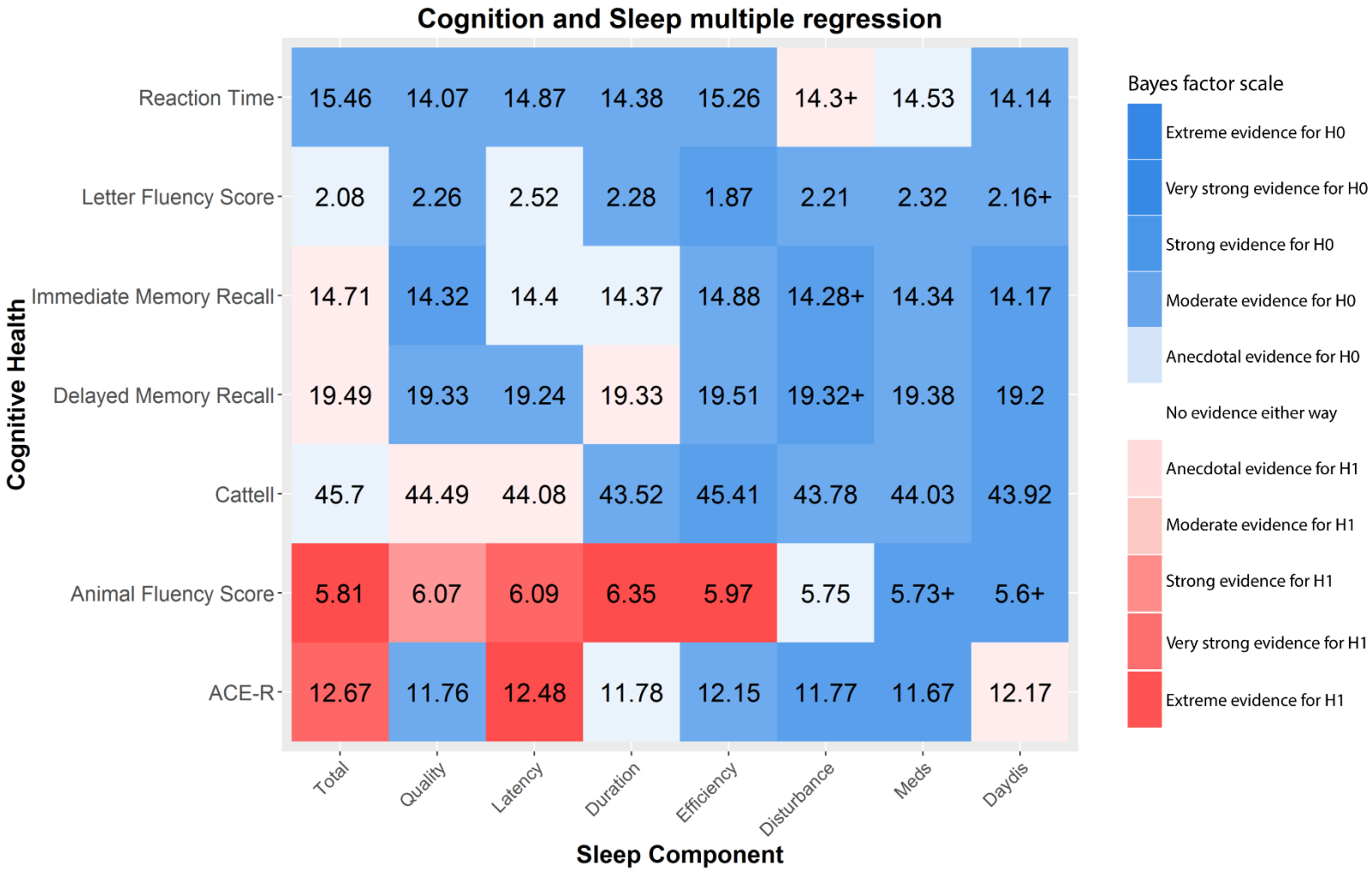
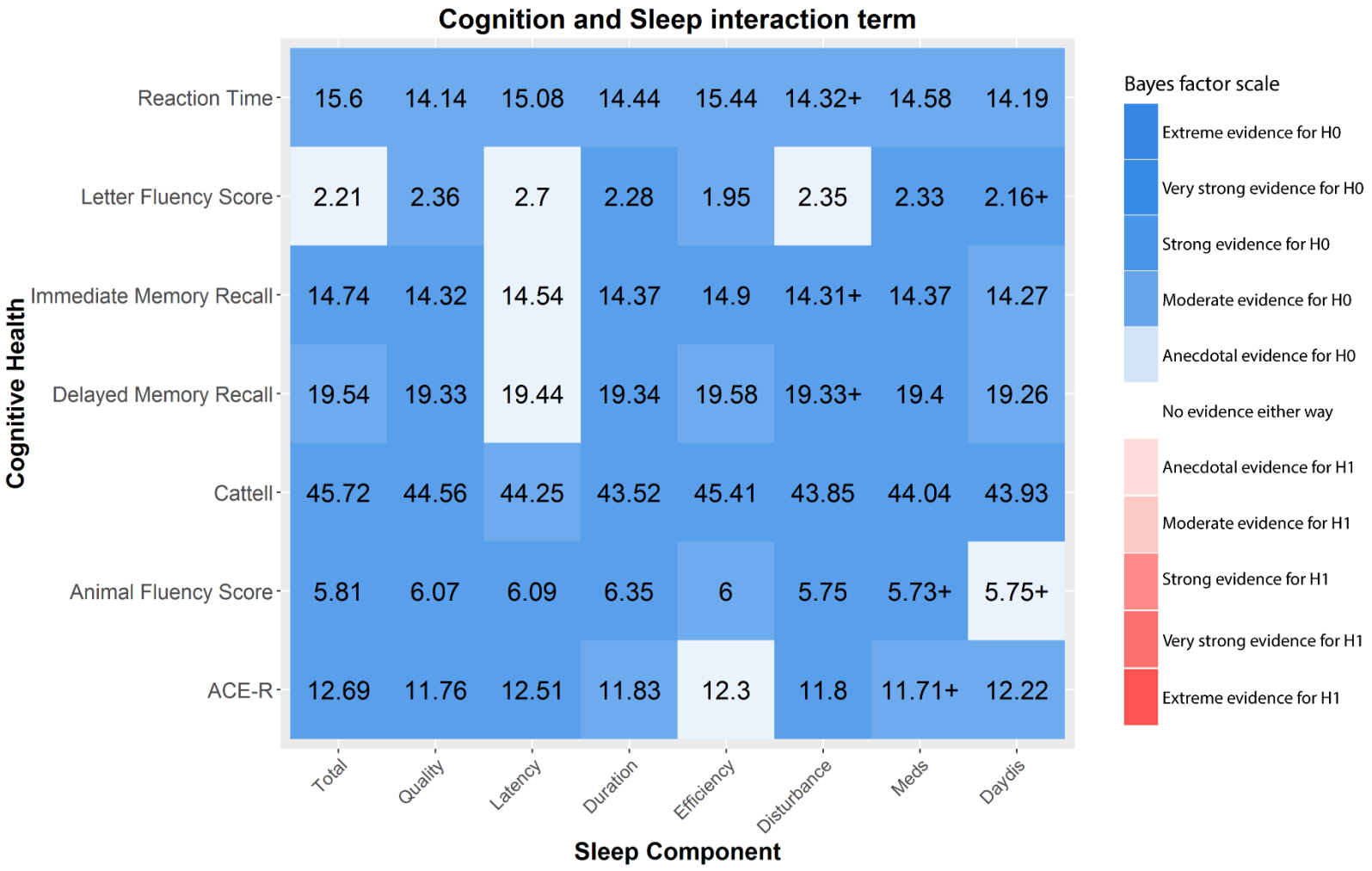
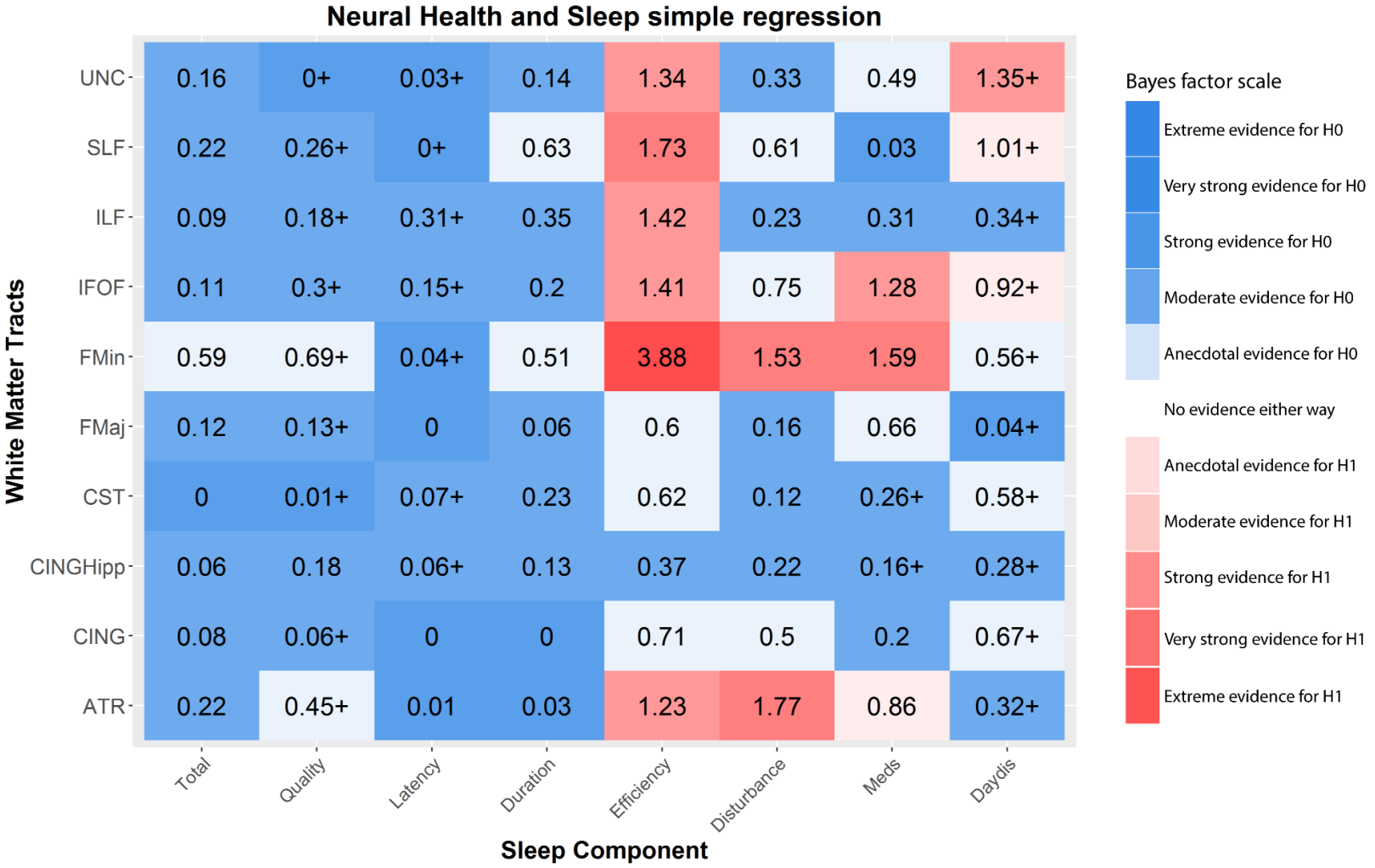


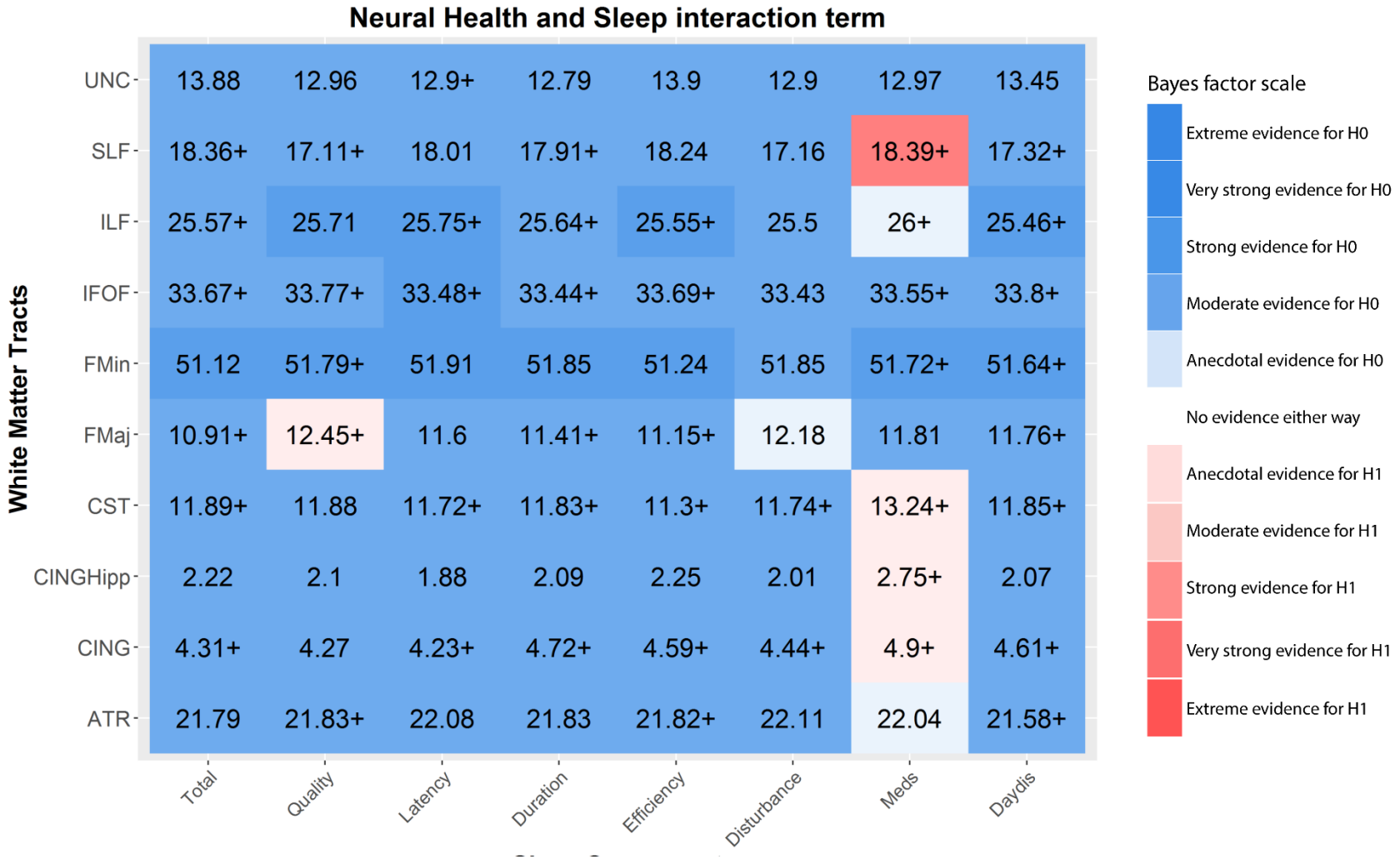
Supplementary Figure A. Multiple regression of sleep and age on cognitive health measures



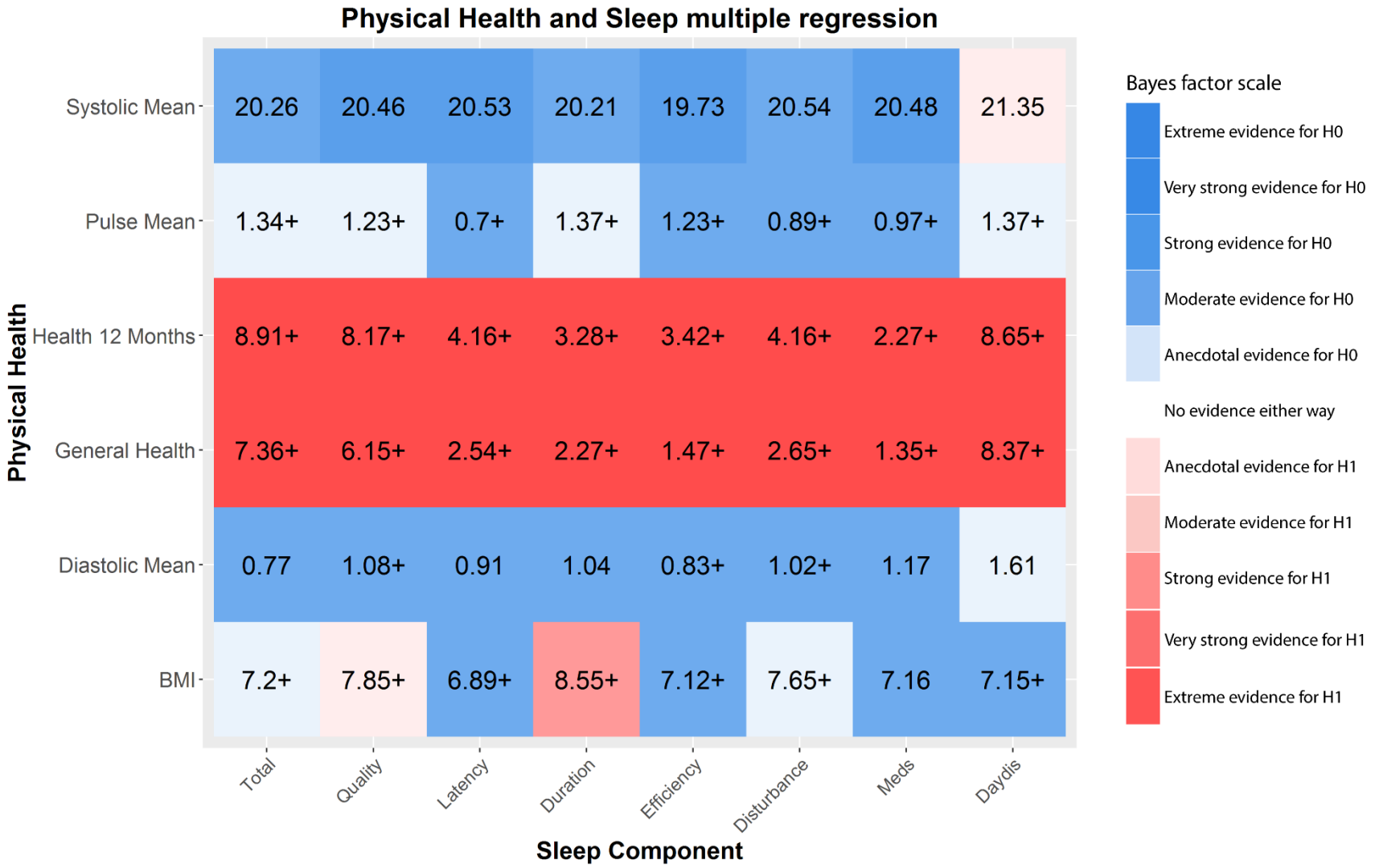
Supplementary Figure B. Multiple regression of sleep and age and an interaction of sleep* age on cognitive health measures



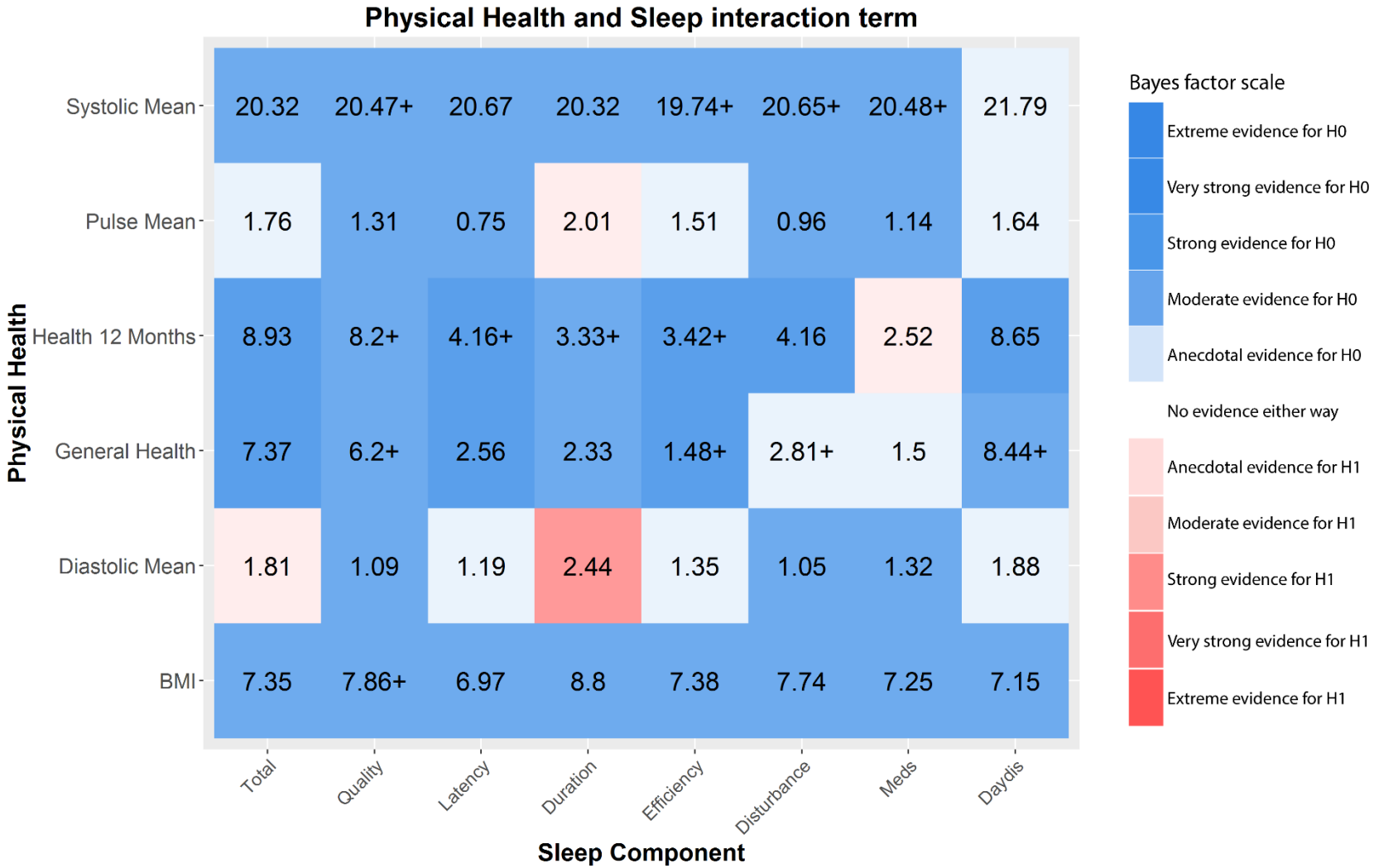
Supplementary Figure C. Simple regression of white matter health on sleep quality



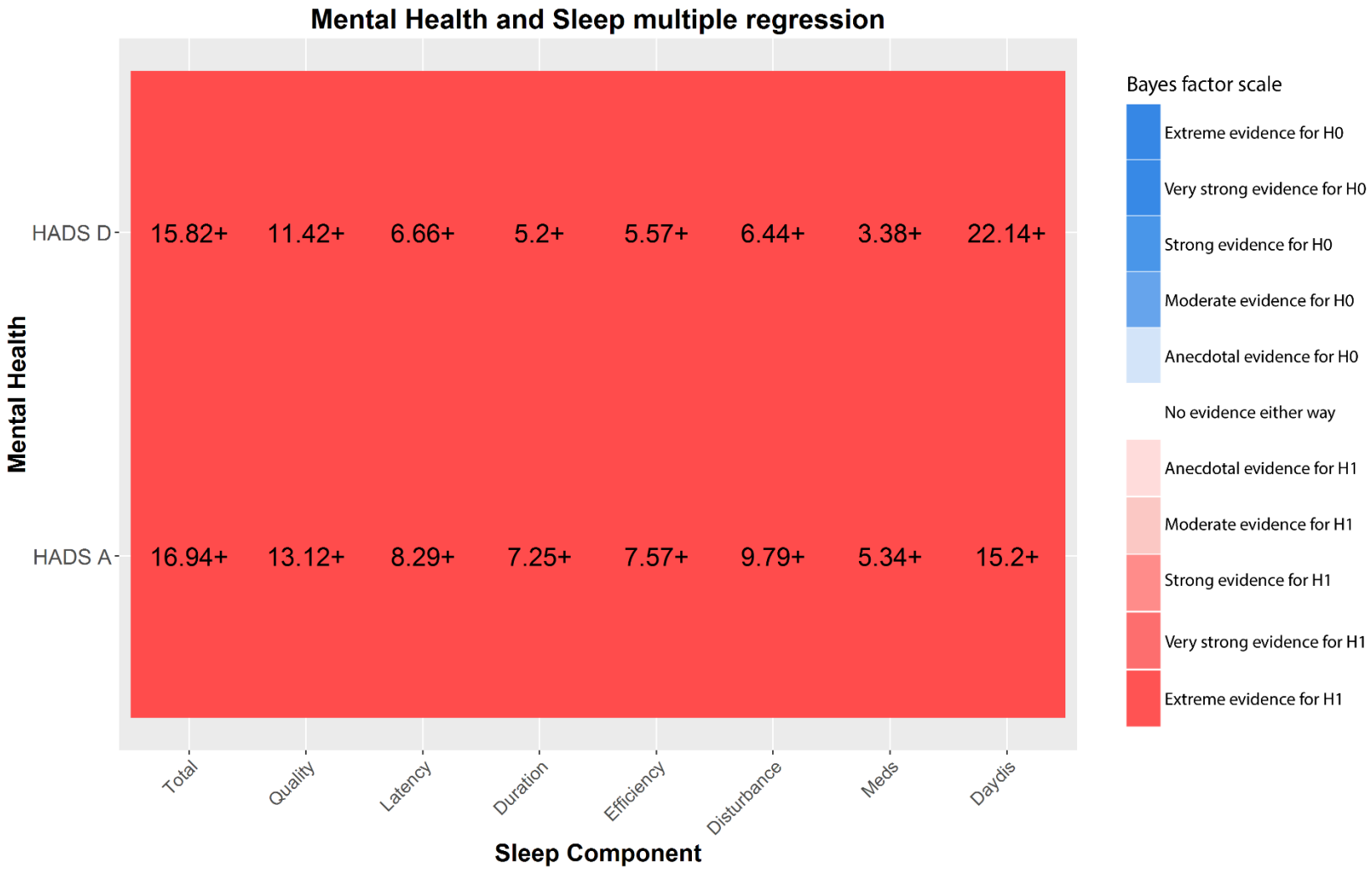
Supplementary Figure D. Multiple regression of neural health on sleep, age and an interaction term.



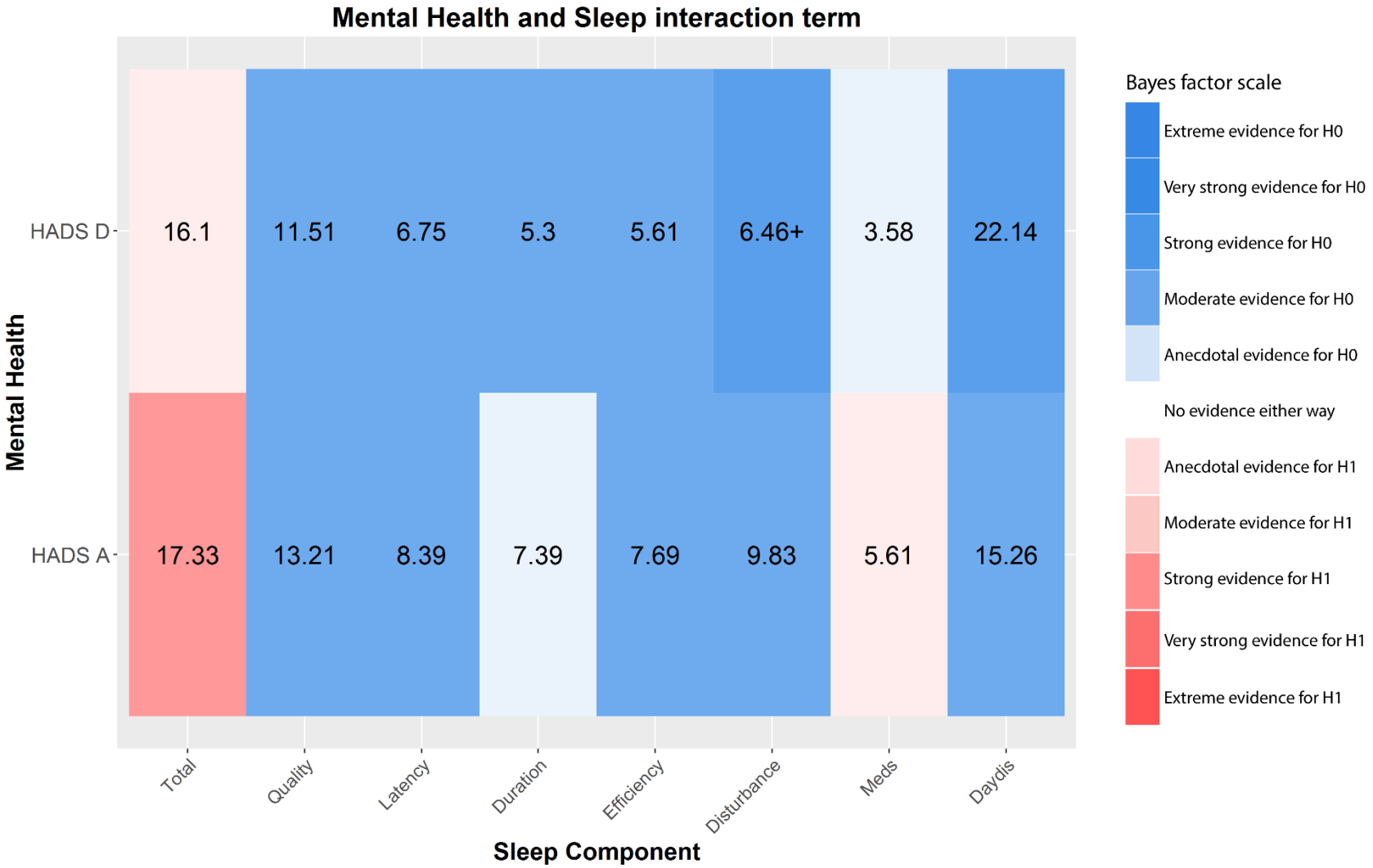
Supplementary Figure E. Multiple regression of physical health on sleep and age



Supplementary Figure F. Multiple regression of physical health on sleep and age and an interaction term of sleep*age.



Supplementary Figure G. Multiple regression of mental health on sleep and age



Supplementary Figure H. Multiple regression of physical health on sleep and age, including an interaction term (sleep*age).