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Diffusion tensor imaging analysis along the perivascular space in the UK biobank

Oliver Clark [a,*], Ariane Delgado-Sanchez [a], Natalia Cullell [b], Sonia A.L. Correa [c], Jurek Krupinski [b,c,d], Nicola Ray [a]

[a] Faculty of Health and Education, Manchester Metropolitan University, Brooks Building, Manchester Metropolitan University, Bonsall Street, Manchester. M15 6GX, UK
[b] Fundació Docència i Recerca MútuaTerrassa: Grupo Neurociencias Mútua, Spain
[c] Faculty of Science and Engineering, Department of Life Sciences John, Manchester Metropolitan University, Chester Street, Manchester, M1 5GD, UK
[d] Department of Neurology, F.Ass. Mútua Terrassa, Terrassa, Barcelona, Spain

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ABSTRACT

Background: The recently discovered glymphatic system may support the removal of neurotoxic proteins, mainly during sleep, that are associated with neurodegenerative diseases such as Alzheimer's and Parkinson's Disease. Diffusion tensor image analysis along the perivascular space (DTI-ALPS) has been suggested as a method to index the health of glymphatic system (with higher values indicating a more intact glymphatic system). Indeed, in small-scale studies the DTI-ALPS index has been shown to correlate with age, cognitive health, and sleep, and is higher in females than males.

Objective: To determine whether these relationships are stable we replicated previous findings associating the DTI-ALPS index with demographic, sleep-related, and cognitive markers in a large sample of participants from the UK Biobank.

Methods: We calculated the DTI-ALPS index in UK Biobank participants (n = 17723). Using Bayesian and Frequentist analysis approaches, we replicate previously reported relationships between the DTI-ALPS index.

Results: We found the predicted associations between the DTI-ALPS index and age, longest uninterrupted sleep window (LUSWT) on a typical night, cognitive performance, and sex. However, these effects were substantially smaller than those found in previous studies. Parameter estimates from this study may be used as priors in subsequent studies using a Bayesian approach. These results suggest that the DTI-ALPS index is consistently, and therefore predictably, associated with demographics, LUWST, and cognition.

Conclusion: We propose that the metric, calculated for the first time in a large-scale, population-based cohort, is a stable measure, but one for which stronger links to glymphatic system function are needed before it can be used to understand the relationships between glymphatic system function and health outcomes reported in the UK Biobank.

The glymphatic system is a brain-wide vascular network that may remove toxic proteins, and is therefore proposed to slow the formation of plaques (including those associated with neurodegenerative conditions like Alzheimer's [1]), and other waste materials from the brain parenchyma [1,2]. This system is proposed to become more active during sleep [3–5], and may therefore explain the relationship between impaired sleep and increased risk of neurodegenerative disease [6]. Since sleep could represent a population-level, modifiable risk factor for progression of neurodegenerative cognitive conditions, it is necessary to explore relationships between sleep, the glymphatic system, and cognitive ability in a large population.

A proposed method for measuring glymphatic system health is the calculation of the Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS) index [7]. This method mathematically isolates the diffusion of fluid towards in the anterior-posterior direction using the Apparent Diffusion Coefficients (ADC) of water molecules in regions within projection and association fibers at the level of the lateral ventricles. By isolating movement in the anterior-posterior direction, a single value (the DTI-ALPS index) that is proportional to the degree of diffusivity may be calculated to reflect glymphatic system integrity.

* Corresponding author. Brooks Building, Manchester Metropolitan University, Manchester, M15 6GX, UK.
E-mail address: o.clark@mmu.ac.uk (O. Clark).

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Indeed, the DTI-ALPS index has been closely associated with the classical measure of glymphatic activity using clearance of intrathecal gadolinium [8]. Clearance of this tracer has been shown to be slower in sleep deprived subjects than in subjects who had a normal night's sleep [9].

Previous research indicates the DTI-ALPS index is lower in people with Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) than those without [7,10]. It is positively correlated with global cognitive ability as measured by the Mini-Mental State exam [7], negatively correlated with progression of Parkinson's disease [11], and negatively correlated with severity of vascular conditions [12]. In addition, the DTI-ALPS index has been shown to mediate the relationship between white matter hyperintensity volume, amyloid beta deposition, and memory in participants with AD [13]. These studies imply that a reduction of the DTI-ALPS index may increase risk of neurodegenerative conditions, and lead to more serious symptoms in those who develop them.

There is pre-clinical and human evidence that sleep plays a large role in the activation of glymphatic clearance of cerebral waste materials [3,5]. More specifically, an increase in efficacy of protein removal during slow wave activity stage 3 NREM sleep state has been reported [14]. Indeed, time spent in NREM stage 3 sleep decreases with increasing age [15], and there is evidence of a relationship between poor quality of sleep and the development of dementia [6].

Although previous research has yielded promising findings, the studies using the DTI-ALPS index have drawn valid criticism for making causal claims from associative research and the simplified use of water molecule movement within a small region of interest to represent a brain-wide complex process [16]. Moreover, current recommendations are that the DTI-ALPS index should not be described as a proxy for glymphatic system efficacy, and should be interpreted cautiously until further validation has been achieved [17]. The inclusion of the DTI-ALPS index in a large-scale dataset will give researchers the statistical freedom to either corroborate the indexes relationship to glymphatic function or investigate alternative explanations for the previous findings that demonstrate its utility.

Therefore, in the current study we calculated the DTI-ALPS index in a subset of the participants in the UK Biobank who provided seven days of wrist-worn accelerometer data. This can be used to estimate the longest time period spent in uninterrupted sleep [18,19]. Sample sizes in studies using the DTI-ALPS index range between 31 [7], and 146 [12]. The purpose of this paper is to determine if findings from studies with smaller sample sizes are stable in a large population-based cohort. This would provide the necessary confirmation that the DTI-ALPS index is a meaningful research tool that behaves consistently across larger samples. As such, we expect to see reductions in the DTI-ALPS index associated with age, poorer cognitive performance, and worse sleep. Based on previous findings we also expect to see larger values in women than men [12].

A synthetic dataset and all analysis scripts are available to access https://osf.io/6twca/.

1. Methods

1.1. Participants

Participant data was accessed from the UK Biobank [20]. Participants were included if they had data for both sleep and MRI imaging. Of the 44073 participants with DWI images that had been preprocessed according to the above pipeline, 17723 had wrist-worn accelerometer derived sleep estimates provided by Doherty et al. [18]. There were 9812 females and 7911 males available for this analysis. Several participants had incomplete cognitive ability so sample sizes for each task may be found in the sections that describe the cognitive tasks. All participants were included regardless of dementia status.

1.2. Imaging data

Diffusion- Weighted Images (DWIs) were collected following the published protocol (https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367). Participants were scanned using one of three identical 3T Siemens Skyra scanners with a Siemens 32 channel RF receiver head coils. MRI scans took place from 2014 in Cheadle, Manchester until 2017 when two identical centres were set up in Reading and Newcastle. The use of identical scanners precluded the need to adjust data for variations in scanner hardware [21]. At the time of the current analysis there were 44073 first instance images available. Images were processed using the Oxford fsl pipeline [21] which included registration, eddy correction, and DTI Tensor fitting.

1.2.1. DTI-ALPS index

The DTI-ALPS index was calculated using the fMRIB software library [22,23] for both left and right hemispheres following Taoka et al. [7]. The size of the UK biobank precludes manual identification of regions of interest. Instead, 5 mm spherical regions of interest (ROI) were created in MNI 152 space (Montreal Neurological Institute, Montreal, Québec, Canada) centered on co-ordinates for association (Left: x = 50, y = 104, z = 100; Right: x = 128, y = 104, z = 100) and projection areas (Left: x = 62, y = 104, z = 100; Right: x = 116, y = 104, z = 100) reported by Y. Zhang et al. [12]. The anatomical locations are presented in Supplemental Image S1. Then, for each participant, the affine transformations and non-linear warps that were available on the UK Biobank as part of a tract-based spatial statistics pre-processing pipeline were applied to the MNI space ROI images to transform them to individual subject space. Next, the b1000 shell was isolated from the pre-processed DWI (based on the recommendations of [7]) and fsl's dtifit was executed with the -save tensor flag to create Apparent Diffusion Coefficients (ADC) in six directions (xx, xy, xz, yy, yz, zz) Finally, mean ADC within each of the ROIs described above were extracted for calculation of the DTI-ALPS index (below). A selection of images were visually inspected by first and last authors to ensure that the MNI space ROIs were accurately transformed into subject space. DTI-ALPS indexes for left and right hemispheres were then calculated for each participant using the equation:

$$DTI\ ALPS_{Index} = \frac{mean(Projection_x, Association_x)}{mean(Projection_y, Association_z)} \quad (1)$$

In line with Y. Zhang et al. [12], the mean average of the left and right DTI-ALPS index was used as the final value which provides an estimate of the diffusivity of water in the anterior-posterior direction.

1.3. Sleep data

The calculated sleep metric was based on probabilities derived from accelerometer data using machine learning [18,19], and validated in a study on cardiovascular risk factors [24]. Data were collected between June 2013 and December 2015, and the derived data yielded a set of per-hour probabilities averaged over 7 consecutive 24 h periods [19]. Because the glymphatic system is reported to be most active during slow-wave sleep [3] the sleep predictor used in this study was longest period of uninterrupted sleep (hereafter longest uninterrupted sleep window on a typical night, or LUSWT). That is, a person might sleep for 8 h in one day, but this might be broken before they enter NREM3 sleep. The low resolution of the derived metric (one reading per hour) means that pinpointing the most likely period of N3 sleep is impossible. Instead we assume thata person with a longer uninterrupted sleep window on a typical night is likely to have spent more time in NREM3 sleep than someone who sleeps in shorter bursts. To estimate the longest uninterrupted sleep window on a typical night, 1-h periods in which the probability that the participant was asleep exceeded 0.9 was treated as an hour in which they were solidly asleep. One-hour periods in which the probability of sleep was below 0.9 was treated as either awake or

interrupted sleep. A string of consecutive 1-h periods where the probability of sleep was above 0.9 was treated as a window of uninterrupted sleep. The longest stretch of probabilities exceeding 0.9 averaged over seven days was taken to be the longest uninterrupted sleep window. An example may be found in Supplemental Table S2. We favoured this method over other measures of sleep such as sleep efficiency (ratio of time actually spent asleep to time spent and time dedicated to sleeping) since this would rely on the unstandardised sleep-related items provided in the UK Biobank.

Out of 17723 participants participants in this study, 150 had extreme values of either 0 h or over 15 h daily total sleep. These participants were removed from further analysis.

1.3.1. Cognitive tasks

In all cases, cognitive tests were conducted at the first scanning session. The following tests from the UK Biobank were included: Numeric memory (n = 12026), Paired associate learning (n = 11789), Prospective memory (n = 16677) (binary outcome of success/not successful on first attempt), Picture Vocabulary test (n = 11153), Fluid Reasoning (n = 16383), Matrix completion, (n = 11666), and the Trail Making Task Part A and B were completed (n = 11789). Participants who did not complete the trail were scored as 0 and were not included in the completion time analysis (numeric trail: n = 121; alpha-numeric trail: n = 356).

Field numbers and short descriptions of how the metrics were calculated are presented in the Supplemental Materials (Table S1).

2. Statistical analysis

Correlations between the DTI-ALPS index and all study variables were calculated using the correlation package in R [25]. To examine the relationship between the DTI-ALPS index and demographics (age, sex), longest uninterrupted sleep window on a typical night, and cognitive health we used a combination of frequentist and Bayesian approaches. To make results comparable with previous literature, variables were z transformed. Frequentist linear regressions were fitted using the lm function from base R [26]. The brms package [27] was used to convert the models to the stan language [28] and provide Bayesian posterior distributions for the regression parameters. Posterior distributions were estimated over 8 chains each with 10,000 iterations (5000 iteration burn-in).

First, bi-variate correlations were run to examine the zero order correlations between the DTI-ALPS index and age, longest uninterrupted sleep window on a typical night, and cognitive tasks. In addition, a between-groups *t*-test was used to compare the DTI-ALPS index between males and females. To determine whether the DTI-ALPS index could be predicted by sex, age, and longest uninterrupted sleep window on a typical night, these variables were entered into a regression model, and relevant interactions were explored in a separate follow-up model. In the Bayes analysis, priors for sex and age were normal distributions centered on the standardised beta estimates for these two variables reported by Y. Zhang et al [12] with a liberal standard deviation of 0.2 to reflect the smaller sample size in their study. Priors for the relationship between longest uninterrupted sleep window and the DTI-ALPS index were taken from estimates reported by Saito et al. [29]. Their overall self-reported sleep quality estimate for using the Pittsburgh Sleep Quality Index (PSQI) was −0.27, where the subscale for sleep duration yielded a non-significant standardised beta of −0.051. Given the uncertainty around the duration estimate and the fact that the measure was self-reported, a weakly informative prior of $N(0.1, 0.2)$ was chosen to favour the positive parameter space (a lower score on the PSQI scale means healthier sleep), but also allow the Monte Carlo algorithm to explore negative values. Both p values (with a liberal alpha level of 0.05) and Bayes Factors using the simplified cutoffs suggested by Royall were used to draw inferences (BF < 8 being weak evidence, 8<BF < 32 being moderate evidence, and BF > 32 being strong evidence for the hypothesis, [30]).

Finally, to determine if cognitive health could be predicted by the DTI-ALPS index independently of age, sex, and longest uninterrupted sleep window on a typical night, we first selected all cognitive tasks that were found to be significantly associated at a corrected p < .05 with DTI-ALPS index in the bivariate correlations for further analysis. Age, sex, and longest uninterrupted sleep window on a typical night were then entered alongside DTI-ALPS index to predict each of the selected cognitive tasks (in separate models for each task). Here we carried out frequentist analysis only as there was no prior information available on the relationship between the DTI-ALPS index and the cognitive tasks used by the UK Biobank. For the cognitive task analysis p values were Bonferrioni corrected to 0.005 to account for multiple analyses. The parameters reported here may be used to inform future Bayesian analyses.

Data were analysed using the R programming language. The lm function was used to model the data where responses were expected to follow a normal distribution. In cases where responses would not be expected to fit a normal distribution, generalised Poisson models were applied to count metrics, and binomial regression to dichotomous metrics using the glm function in R.

3. Results

3.1. Demographics

After removal of extreme values there were 17573 participants entered into the final analysis. Of these 9724 were female and 7849 were male.

Table 1 presents the descriptive statistics for all study variables split by sex.

3.2. Bivariate correlations

Bivariate correlations between all study variables and the DTI-ALPS index are presented in Table 1. Scatter plots for DTI-ALPS and Age and DTI-ALPS and longest uninterrupted sleep window on a typical night are presented in Figs. 1 and 2. In brief, the DTI-ALPS index significantly correlated with participant age (r = −0.27, 95 % CI [−0.28, −0.25], t (11431) = −29.52, p < 0.001), and there was a significant difference in

Table 1
Means and standard deviations for age, longest uninterrupted sleep window on a typical night, DTI-ALPS index, and performance on cognitive tasks grouped by sex.

Variable	Female		Male		Pearsons r
	Mean	SD	Mean	SD	
Age	63.98	(7.50)	65.75	(7.89)	r = −0.27, p < 0.001***
LUSWT	5.29	(1.79)	5.06	(1.83)	r = 0.03, p < 0.001***
ALPS	1.62	(0.20)	1.50	(0.19)	–
Prosp	0.12	(0.31)	0.12	(0.31)	r = −0.05, p < 0.001***
Picv	0.40	(0.08)	0.41	(0.08)	r = −0.06, p < 0.001***
Fintel	6.64	(1.94)	6.84	(2.05)	r = 8.00e-03, p = .393
Ntrail	5.34	(0.61)	5.39	(0.62)	r = −0.15, p < 0.001***
Atrail	6.24	(1.13)	6.28	(1.12)	r = −0.15, p < 0.001***
Passo	7.50	(2.48)	6.55	(2.57)	r = 0.13, p < 0.001***
Matrix	8.06	(2.08)	8.24	(2.13)	r = 0.06, p < 0.001***
BDS	6.69	(1.38)	6.83	(1.44)	r = 0.04, p < 0.001***

Note. Age = Participant age at scan session; LUSWT = Longest uninterrupted sleep window on a typical night; ALPS = Mean DTI-ALPS index over two hemispheres; Prosp = Binarised prospective memory; Picv = Derived intelligence score from picture vocabulary task; Fintel = Number of fluid intelligence questions answered; Ntrail = Log completion time on numeric trail making task; Atrail = log completion time on alpha-numeric trail making task; Passo = Number of correct responses on verbal paired associates task; Matrix = Number of correct answers on matrix reasoning task; BDS = Maximum number of digits recalled on backward digits span task.

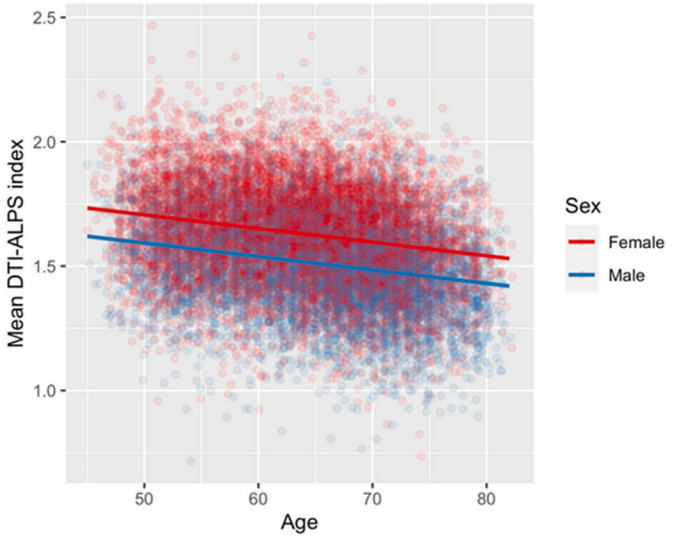

Fig. 1. Plot of correlations between age and DTI-ALPS index split by sex.

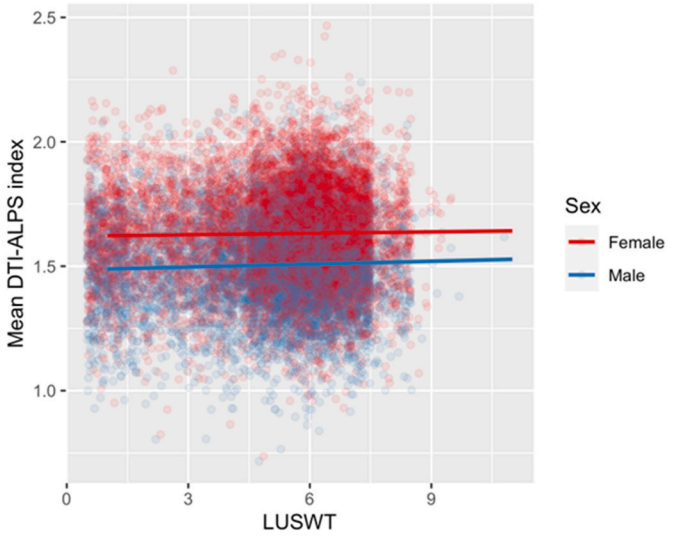

Fig. 2. Plot of correlations between longest uninterrupted sleep window on a typical night and DTI-ALPS index split by sex. Regression line controls for age.

DTI-ALPS index between males and females ($\Delta M = 0.13$, 95 % CI [0.12, 0.13], $t(17062.86) = 42.82$, $p < .001$). A higher DTI-ALPS index was associated with a longer uninterrupted sleep window on a typical night (r = 0.03, 95 % CI [0.01, 0.05], t(11431) = 3.34, p < 0.001). Correlations with cognitive tasks were mostly weaker but, with the exception of fluid intelligence (r = 8.00e-03, 95 % CI [−0.01, 0.03], t(11378) = 0.85, p = .393) and prospective memory (r = −0.05, 95 % CI [−0.07, −0.03], t(11431) = −5.39, p < 0.001), a higher DTI-ALPS index was associated with better performance.

3.3. Linear regression

Linear regression with age, sex and longest uninterrupted sleep window entered together revealed that all these variables could independently predict the DTI-ALPS index (Age: $b = -0.17$, 95 % CI [−0.19, −0.16], $t(17569) = -23.83$, $p < .001$; Sex: $b = -0.49$, 95 % CI [−0.52, −0.46], $t(17569) = -33.90$, $p < .001$; LUSWT: $b = 0.02$, 95 % CI [0.01, 0.03], $t(17569) = 2.70$, $p = .007$).

No significant interaction was found between age and LUSWT ($b = 0.01$, 95 % CI [−0.01, 0.02], $t(17568) = 0.97$, $p = .330$). The full regression tables for these analyses may be found in Supplemental Table S3.

3.3.1. Bayesian analysis

The Bayesian analysis replicated the frequentist analysis in that the distribution of possible parameters did not cross zero in cases where frequentist analysis showed a non-significant estimate. Parameter point value and 95 % credible interval estimates can be found in Supplemental Table S4.

Parameters of interest from the Bayesian models were tested against a null hypothesis of zero using the hypothesis function of the brms package.

We found very strong evidence for the hypothesis that there would be sex differences the DTI-ALPS index ($\beta = -0.49$, SE = 0.01, 95 % CI [−0.51, −0.47], EvidenceRatio > 1000 , PosteriorProbability > 0.99).

We found very strong evidence for the hypothesis that age predicts the DTI-ALPS index ($\beta = -0.17$, SE = 0.01, 95 % CI [−0.18, −0.16], EvidenceRatio > 1000 , PosteriorProbability > 0.99).

We found strong evidence that longest uninterrupted sleep window on a typical night was associated with the DTI-ALPS index ($\beta = 0.02$, SE = 0.01, 95 % CI [0.01, 0.03], EvidenceRatio = 297.51, PosteriorProbability = 1.00).

There was only very weak evidence to support an interaction between age and longest uninterrupted sleep window ($\beta = 0.01$, SE = 0.01, 95 % CI[0.00, 0.02], EvidenceRatio = 4.88, PosteriorProbability = 0.83).

3.4. Cognitive tasks

Parameters are reported in Table 2 for all tests. Bonferroni corrections were applied to the alpha level such that the threshold for significance was 0.005. In brief, after controlling for age, sex, and LUSWT, the DTI-ALPS index significantly predicted backwards digit span ($p < .001$), verbal paired associates ($p < .001$), log completion times for numeric ($p < .001$) and alpha-numeric ($p < .001$) trail making tasks.

4. Discussion

In this study we calculated a proposed index of glymphatic activity (DTI-ALPS index) on a large number of MRI scans from the UK Biobank. To validate the calculation of the index, we replicated previously established relationships between age, sex, and the DTI-ALPS index, and investigated the association between the index and longest uninterrupted sleep window on a typical night. Finally, we established a positive, independent relationship between several of the cognitive tasks completed by UK Biobank participants and the DTI-ALPS index.

Although yielding smaller effect sizes, our findings in this very large sample, are consistent with previous reports in studies with smaller samples showing that the DTI-ALPS index decreases with age [31], and is greater in female participants [12,29]. We also found that longest uninterrupted sleep window on a typical night was positively associated with the DTI-ALPS index which supports previous findings [3,29] and is consistent with findings from studies that used more direct measures of glymphatic efficacy [5]. Importantly, all these findings are independent of one another, therefore each variable can be assumed to be providing a unique contribution to variance in the ALPS-index.

The effect sizes in our study were smaller than those reported previously on the relationship between the DTI-ALPS index, age and sex. Although this is in agreement with previous meta-scientific findings in which sample size negatively correlates with effect size [32,33], the explanations offered may not be compatible. For instance, it is claimed that publication bias and selective reporting is largely responsible for inflated effect sizes in psychological literature [32], and the correlation between standard errors and effect sizes is a function of appropriately powering studies [33]. There are still too few studies available to determine whether this might be the case, but future meta-analytic

Table 2
Inferential test statistics for each cognitive task by domain.

Task	Domain	Sex	Age	LUSWT	ALPS Index
Fluid Reasoning	Executive	b = 0.30, 95 % CI [0.24, 0.37]	b = −0.03, 95 % CI [-0.03, −0.03]	b = 0.02, 95 % CI [0.00, 0.04]	b = 0.05, 95 % CI [-0.12, 0.21]
Matrix Reasoning	Executive	b = 0.34, 95 % CI [0.27, 0.42]	b = −0.07, 95 % CI [-0.07, −0.06]	b = 0.05, 95 % CI [0.03, 0.07]	b = 0.18, 95 % CI [-0.02, 0.38]
Prospective Memory	Memory	b = −0.16, 95 % CI [-0.32, −0.01]	b = −0.06, 95 % CI [-0.08, −0.05]	b = 0.04, 95 % CI [0.00, 0.07]	b = 0.34, 95 % CI [-0.05, 0.73]
Verbal Paired Associates	Memory	b = −0.76, 95 % CI [-0.86, −0.67]	b = −0.07, 95 % CI [-0.07, −0.06]	b = 0.04, 95 % CI [0.02, 0.07]	b = 0.46, 95 % CI [0.22, 0.70]
Word Naming	Memory	b = 0.00, 95 % CI [0.00, 0.01]	b = 0.00, 95 % CI [0.00, 0.00]	b = 0.00, 95 % CI [0.00, 0.00]	b = −0.01, 95 % CI [-0.02, 0.00]
Trail Making A - Finish	Visuo Spatial	b = 0.18, 95 % CI [-0.20, 0.56]	b = −0.08, 95 % CI [-0.11, −0.05]	b = −0.02, 95 % CI [-0.11, 0.08]	b = 0.41, 95 % CI [-0.54, 1.37]
Trail Making A - Time	Visuo Spatial	b = 0.02, 95 % CI [0.01, 0.03]	b = 0.01, 95 % CI [0.01, 0.01]	b = 0.00, 95 % CI [-0.01, 0.00]	b = −0.04, 95 % CI [-0.07, −0.02]
Trail Making B - Finish	Visuo Spatial	b = 0.27, 95 % CI [0.04, 0.49]	b = −0.10, 95 % CI [-0.12, −0.09]	b = 0.02, 95 % CI [-0.04, 0.07]	b = 0.10, 95 % CI [-0.47, 0.67]
Trail Making B - Time	Visuo-Spatial	b = −0.01, 95 % CI [-0.02, 0.00]	b = 0.02, 95 % CI [0.02, 0.02]	b = −0.01, 95 % CI [-0.01, 0.00]	b = −0.08, 95 % CI [-0.11, −0.04]
Digit Span Backwards	Working Memory	b = 0.25, 95 % CI [0.20, 0.29]	b = −0.02, 95 % CI [-0.03, −0.02]	b = 0.00, 95 % CI [-0.01, 0.02]	b = 0.26, 95 % CI [0.14, 0.38]

research would contribute to this explanation.

It must be noted that the effect sizes we find for the relationship between sleep and DTI-ALPS is very small. Indeed, other studies report no association between self-reported sleep and global grey matter volume in the UK Biobank despite using a sample that was twice the size of ours [34]. It is possible that our measure of sleep (LUSWT) was either more sensitive or measured a more relevant sleep phenotype than the self-report measures available on the Biobank. With increasingly sensitive and specific sleep metrics, findings between studies may become more consistent.

The relationship between age and the DTI-ALPS index is consistent with previously reported negative associations between age and glymphatic activity [35]. This association has been explained as being driven by age-related factors such as loss of arterial wall integrity and senescent astrocyte pathology. There are fewer attempts at explaining sex differences in glymphatic activity, with one possibility being differences in CSF influx between sexes [12]. A recent mouse study found no association between biological sex and glymphatic influx [36], and a subsequent study found that female mice produced more CSF, but that the transport kinetics of the fluid did not vary between sexes [37]. The calculation of the DTI-ALPS index in the UK Biobank dataset will allow the exploration of lifestyle (e.g. alcohol and tobacco consumption) and socio-demographic (e.g. education) factors which may yield useful findings; especially since these factors are absent from mouse models.

Taoka et al. [7] did not control for age and sex in their analysis of the relationship between the MMSE and the DTI-ALPS index. Given the strength of association between these demographic variables and the DTI-ALPS index we recommend that, as a minimum, age and sex be controlled for in future studies using this measure.

We also explored whether age would modify the impact of sleep on the DTI-ALPS index, under the assumption that glymphatic health may deteriorate more quickly due to changes in sleep patterns in older people. However, we found no interaction between age and longest uninterrupted sleep window on a typical night. This was confirmed via a combination of a non-significant frequentist interaction in such a large sample and a Bayes Factor of above 1, but below our lower threshold. That said, our sleep metric does not comprehensively capture sleep integrity, and exploring this interaction within more detailed analysis of sleep may be warranted.

We found that the DTI-ALPS index significantly correlated with performance on a range of neuropsychological tests. Upon follow-up analysis this relationship was also present when controlling for age, sex, and longest uninterrupted sleep window on a typical night. A higher DTI-ALPS index was associated with shorter log completion time in both numeric and alphanumeric versions of the trail making task, the number of words correctly recalled in the verbal paired associates task, and backwards digit span. Previous research has shown a relationship between the DTI-ALPS index and global screening measures of cognitive ability (e.g. the MMSE), however these were not corrected for age [7]. Unfortunately, no screening tasks were available on the UK Biobank dataset, however our findings are consistent with the expected performances based on previous research on correlations between MMSE scores and more in-depth cognitive tasks (e.g. Ref. [38]) even after accounting for age and sex.

Categorisation of dementia was not an aim of this study, however it is promising that the DTI-ALPS index predicted performance on versions of several measures that are sensitive to cognitive decline and are regularly used to assess cognitive decline and in the assessment of dementia [39,40]. Performance on the trail making task has been shown to be sensitive to cognitive changes in the early stages of neurodegeneration ([39,41], p. p373; [42]), and the numeric trail alone is sensitive to early or prodromal stages of disease [43]. Likewise, impaired verbal associate learning has been shown to be an early indicator of dementia ([39,44], p. p442). Our findings also reflect known relationships between white-matter integrity and cognition [45], and are importantly still present when controlling for age which is known to sometimes mask smaller white matter effects [46]. The small but independent relationship between the DTI-ALPS index and behaviour demonstrate that, as with other white matter indices, age alone is not sufficient to explain cognitive decline. Although there is debate about the relationship between the DTI-ALPS index and glymphatic activity, this finding parallels reports of glymphatic activity being associated with cognitive decline [1], and provides evidence for the utility of the DTI-ALPS index as a tool in neuroscience research.With the DTI-ALPS index now available on the UK Biobank there is an opportunity to explore more complex relationships such as genetic predictors, longitudinal survival analysis for both dementia and mortality, associations with lifestyle factors, brain age, or other physiological conditions such as cardiovascular disease. More importantly, it is now possible to explore its relationship with therapeutically modifiable factors [47].

4.1. Limitations

The use of probabilities to estimate length and longest uninterrupted window of sleep likely oversimplified the complexities of sleep

behaviour. For instance, there was no distinction between night and day sleeping, no consideration of napping, or distinction between lifestyle-related and physical sleep interruption (e.g. Obstructive Sleep Apnoea). A recent study by Katori, Shi, Ode, Tomita, and Ueda [48] used accelerometer data from the UK Biobank to calculate 23 sleep indices (e.g. average lengths and variances in sleep and wake time, short and long sleep windows, etc). They subsequently categorised participants into sleep phenotype groups such as 'irregular sleep schedule', 'insomnia with short sleep duration', and 'sleep without day-time sleep window'. We believe that using more sophisticated indices of sleep will yield more conclusive findings.

The calculation of the DTI-ALPS index from unsupervised extraction of ROIs mean that the estimate of the scores is liable to be noisy. A semi-automated calculation of the DTI-ALPS index has been previously described [49], although this still required some user input which is unfeasible for large datasets. A key difficulty is in locating the medullary vein [50], which we achieved by relying on a standardised template. The size of the sample and consistency with previous findings suggest that any bias is minimal. However, there is room for improvement. For instance, multiple estimates of measurements could be made at several sites. Jiang et al. [51] used DTI-ALPS index estimates from anterior, middle, and posterior cortical areas. They also estimated glymphatic efficacy using three different methods: Choroid Plexus volume to establish CSF generation propensity; DTI-ALPS index to estimate diffusion in perivascular space; and CSF-Global Blood Oxygen Level Dependent coupling to estimate CSF influx. In future studies multiple measurements and triangulation would facilitate investigation into glymphatic activity.

In a recent critique of the DTI-ALPS index Ringstad [16] presents several limitations of the measure including the use of perivascular space which is rarely observable, and the liklihood that water diffusivity in a small white-matter ROI does not fully capture brain-wide clearance of large molecules from the cortex. Ringstad [16] then warns against making causal assumptions about the measure between the DTI-ALPS index and glymphatic clearance based on association studies alone, suggesting that observed relationships may be due to age- and/or disease-related changes to DTI indices. Our estimation of the DTI-ALPS index in the UK Biobank will allow for further exploration of these criticisms.

Although benefiting from a large number of participants, the UK Biobank sample is limited in its representation of the diversity of UK society. Approximately 95 % of participants are white, with 86 % being white-British (https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=21000). Participants in the UK Biobank are also on average healthier and more educated than the general population [52–54], meaning that the ranges of several variables may be restricted, thus masking true population effects. Moreover, selection bias may result in unobserved causal pathways which may lead to unexpected confounds or collider biases when variables are controlled for [53].

4.2. Conclusion

We have demonstrated that our estimate of the DTI-ALPS index in the UK Biobank can replicate previous findings from smaller studies. We have also shown that in addition to sex and age, longest uninterrupted sleep window on a typical night is positively associated with the DTI-ALPS index. Finally we have shown that the DTI-ALPS index has investigative utility since it is inversely associated with performance on a range of neuropsychological tasks. The inclusion of the DTI-ALPS index in the UK Biobank showcase data will facilitate future study into risk factors associated with perivascular diffusion and the development of dementia. We encourage researchers to contact us for collaborative projects using this metric.

CRediT authorship contribution statement

Oliver Clark: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Ariane Delgado-Sanchez:** Writing – review & editing. **Natalia Cullell:** Writing – review & editing. **Sonia A.L. Correa:** Writing – review & editing. **Jurek Krupinski:** Writing – review & editing. **Nicola Ray:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

None of the authors have any conflict of interest associated with this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.05.007.

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