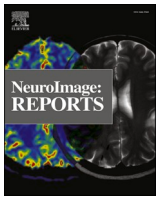
Neuroimage: Reports 3 (2023) 100176

Contents lists available at ScienceDirect

Neuroimage: Reports

journal homepage: www.sciencedirect.com/journal/neuroimage-reports



Normative values of the brain health index in UK biobank

Jodi K. Watt [a,*], David Alexander Dickie [a], Donald M. Lyall [b], Joey Ward [b], Frederick K. Ho [b], Jesse Dawson [a], Terence J. Quinn [a]

[a] School of Cardiovascular and Metabolic Health, University of Glasgow, UK
[b] School of Health and Wellbeing, University of Glasgow, UK

ARTICLE INFO

Keywords:
UK Biobank
Image processing
Magnetic resonance imaging
Ageing

ABSTRACT

Background: The Brain Health Index (BHI) is an automated approach to quantifying brain integrity, combining different types of structural magnetic resonance imaging (MRI). Normative values derived from generally healthy individuals provide a vital baseline for understanding neurodegenerative change. Although commonplace in other areas of medicine, these are not always established when proposing new analytical approaches using MRI. The scale and quality of the UK Biobank imaging cohort (approximately N = 50k, as of 2022) allows for derivation of such values, and the wealth of additional lifestyle, physiological and demographic data enables validation of BHI through comparison with more established variables which may affect brain health.

Aim: This study aimed to: 1) establish normative BHI values in a cohort of 'healthy' participants, and 2) explore associations between BHI and risk factors for brain health.

Methods: The BHI was computed using voxel-based Gaussian mixture model cluster analysis of T1 and T2 FLAIR MRI in a sub-cohort of UK Biobank participants. From these data, normative score curves – with bounds described as 1, 2 and 3 standard deviations from the mean – were produced for males and females, using regression analyses to measure the scale of the BHI values as a function of age. Additional Pearson's correlation testing was used to examine known risk factors to brain health and their relationship to BHI scores, with t-tests and ANOVAs used to determine between-group differences in BHI scoring.

Results: Data from 2,990 participants (50.07% male, 97.05% Caucasian, 43.6% with degree-level education) were used to derive normative BHI curves from 48 to 77 years old. BHI scores were higher in female than male participants (95% CI: 0.0103 to 0.0162, $p < 0.001$, Cohen's d = 0.0416), males with a degree (95% CI: 0.000 to 0.009; $p < 0.05$; Cohen's d = 0.044), and lower in people with type 2 diabetes mellitus (95% CI: 0.018 to 0.033; $p < 0.001$; Cohen's d = 0.0417), hypertension (95% CI: 0.008 to 0.018; $p < 0.001$; Cohen's d = 0.0419), and regular smokers (95% CI: 0.009 to 0.017, $p < 0.001$, Cohen's d = 0.041). BHI scores were higher in those with lower waist-to-hip ratios (WHR; males: $R^2 = 0.02121$, $F(1, 1466) = 31.77$, $p < 0.001$; females: $R^2 = 0.02201$, $F(1, 1454) = 32.72$, $p < 0.001$), and lower pulse pressure (males: $R^2 = 0.06261$, $F(1, 1215) = 81.16$, $p < 0.001$; females: $R^2 = 0.07616$, $F(1, 1205) = 99.34$, $p < 0.001$).

Conclusions: BHI score curves may provide useful reference values for future clinical research. More work is required to determine normative values in more diverse populations.

1. Background

Dementia is a global public health issue, the burden of which is only growing as life expectancy increases. Despite many clinical trials which focused on neurovascular changes and neurodegeneration, we still have no robust disease-modifying treatments and predicting who is most at risk of cognitive decline remains challenging.

Most dementia syndromes exhibit mixed pathology, with both global

Abbreviations: ACER, Addenbrooke's Cognitive Examination Revisited; BHI, Brain Health Index; BP, blood pressure; CPU, central processing unit; GPU, graphical processing unit; HPCC, High Performance Computing Cluster; MRI, magnetic resonance imaging; SVD, small vessel disease; T2DM, Type 2 diabetes mellitus; WHR, waist-to-hip ratio; WMH, white matter hyperintensity.

* Corresponding author. School of Cardiovascular & Metabolic Health, New Lister Building, University of Glasgow, Glasgow Royal Infirmary, 84 Castle Street, G4 0SF, UK.

E-mail address: jodi.watt@glasgow.ac.uk (J.K. Watt).

https://doi.org/10.1016/j.ynirp.2023.100176
Received 21 March 2023; Received in revised form 10 May 2023; Accepted 26 May 2023
Available online 20 June 2023

neurovascular and region-specific structural components, both present attractive targets for prognostic magnetic resonance imaging (MRI) biomarkers in dementia. Vascular changes are thought to occur early in neurodegeneration (Shi and Wardlaw, 2016; Debette et al., 2019), with brain atrophy a well-established risk factor for cognitive decline (Pini et al., 2016; Sweeney et al., 2018). Whilst such markers have limited utility on their own, combining them may enable identification of individuals who are more susceptible to developing dementia, particularly as accelerated brain at the normative level may represent the long preclinical phase of the disorder (Sperling et al., 2011).

Recent work has attempted this using automated image processing of brain MRI scans which combine data from T1, T2, T2* and FLAIR MRI sequences into a single measure: the Brain Health Index (BHI, Dickie et al., 2018), suggests substantial benefit over isolated modalities. This study showed stronger associations between BHI scores and the Addenbrooke's Cognitive Examination Revisited (ACER; standard beta = 0.20 - 0.59, $p<0.05$) than white matter hyperintensity (WMH; standard beta = 0.04 - 0.08, $p>0.05$) volume and total small vessel disease (SVD; standard beta = 0.02 - 0.27, $p>0.05$) score did when compared to the same test, but did not establish normative reference values for the BHI.

Establishing normative values for new analytical metrics in a large-scale cohort provides substantial utility by providing a robust benchmark to aid interpretation of changes seen when the biomarker is clinically applied. Although normative values are common in certain disciplines – psychology, paediatrics – they are less commonly applied to MRI metrics and brain health. UK Biobank (https://www.ukbiobank.ac.uk/) is one of the largest population studies in the world and collects detailed demographic and phenotypic data alongside multi-modal MRI data (Sudlow et al., 2015; Miller et al., 2016). Thus, UK biobank is an ideal resource for deriving normative ranges for the BHI marker.

The UK Biobank can also facilitate an exploration, at scale, of factors associated with differential BHI. Such analyses can assist in validating the BHI. There are many such plausible factors. Education has been associated with greater grey matter volumes (Ho et al., 2011; Boller et al., 2017) and can modulate brain maintenance in pre-symptomatic frontotemporal dementia (Gazzina et al., 2019), but it is currently unknown how education level might affect the BHI. Diagnosed conditions such as type 2 diabetes mellitus (T2DM, Strachan et al., 2011) and hypertension (Sierra, 2020), as well as lifestyle factors such as cigarette smoking (Gray et al., 2020) and alcohol consumption (Topiwala et al., 2021) and physiological measures such as body mass index (BMI, Momtaz et al., 2018), waist-to-hip ratio (WHR, Hamer and Batty, 2019) and pulse pressure (Thorin-Trescases et al., 2018; Levin et al., 2020), have all been negatively implicated in brain health but have not yet been investigated in the context of the BHI.

1.1. Aims and hypothesis

The current study aimed to enhance the practical utility of the BHI by 1) defining normative score curves in older participants without any neurological issues from the UK Biobank MRI cohort and 2) investigating how other physiological and lifestyle factors influence scoring. It was hypothesised that BHI scores would evidence a decrease in structural brain health with increasing age, which may be driven by differences in physiological and lifestyle factors which have been previously associated with brain health.

2. Methods

2.1. Approvals and participant consents

UK Biobank was approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Centre for Research Ethics Committee (Reference: 11/NW/0382). The current study falls under project #17869. Overarchingly, UK Biobank complies with both the Data Protection Act (DPA), and the General Data Protection Regulation (GDPR) which came into effect after commencement of the UK Biobank study.

This paper represents the first in a suite of research into the BHI which is funded by the Chief Scientist Office (Grant reference: TCS/19/31). The ultimate goal of this research is to determine the feasibility of BHI for use within the National Health Service. The code for BHI computation will be released once this research is complete, however it is our hope that releasing information on its normative values and relationship to certain brain health risk factors at this stage will encourage researchers to both use BHI in their own research and consider the benefits of using different MRI scans in combination when attempting to elucidate the nuances of brain ageing.

This secondary-data analysis study was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 13 May 2016, Ref. 16/NW/0274). Written informed consent was obtained from all participants recruited to UK Biobank.

2.2. Participant selection

Random participant selection was carried out by organising participants by age, sex and chronological participant ID number, and then assigning each participant in each age/sex grouping a number from 1 to n, (for participants aged 45–80 years old). A random number generator (https://www.calculator.net/random-number-generator.html) was then used to select 50 participants from each grouping, with those participants used within the norming exercise Sample size was justified by a combination of other attempts to define normative values in different types of MRI (for example Leidhin et al., 2021 for arterial spin labelling), the number of participants required to create structural atlases in cognitive decline cohorts (Dickie et al., 2015), and the available data for each integer year age within the bounds of local computational storage limits. Where participants did not pass quality control or did not have all necessary scans, they were excluded, and the process was repeated with the remaining participants who were not originally selected.

All participants in the final cohort were used for overall BHI analysis, but where additional self-report data was used or a participant preferred not to answer, they were excluded from related analyses.

2.3. Participant demographics

At the assessment centre, participants completed a self-report touchscreen questionnaire pertaining to personal demographics, health, and socioeconomic status. Accuracy of self-reported medical information – including any self-reported diagnoses – was improved by a nurse-led interview addressing a participant's medical history.

Exclusion criteria for the current study was as follows based on MRI-visit self-report: any chronic neurodegenerative condition (including dementias and Parkinson's disease), demyelinating disease, or other condition affecting the brain, such as cancer, haemorrhage, aneurysm, abscess, stroke, head injury, brain trauma, cerebral palsy, or infection affecting the nervous system.

2.4. Risk factors for brain health

Any specific diagnoses of hypertension or T2DM were reported. Alcohol intake data was collected as part of the self-report questionnaire, self-rated from never to daily or almost daily. Cigarette smoking data was collected as part of the same questionnaire, with self-categorisation as smokers, occasional smokers, non-smokers, or ex-smokers. Waist-to-hip ratio was calculated as waist measurement/hip measurement, and body mass index by weight (kg)/height (m^2). Blood pressure was measured twice, successively, and a mean taken (single measures used when mean values unavailable), with pulse pressure calculated as the log-transformed difference between systolic and

diastolic pressure.

2.5. MRI acquisition

The UK Biobank imaging cohort is described at length in Alfaro-Almagro et al. (2018) and Littlejohns et al., (2020). Participants underwent multimodal brain MRI at one of three scanning centres equipped with identical scanners (3T Siemens Skyra,32-channel Siemens receive head coil). The full acquisition protocol took 31 min, with six different imaging sequences. In the current study, BHI utilised sagittal 3D magnetization prepared – rapid gradient echo (MP-RAGE) and T2 Fluid Attenuated Inversion Recovery (FLAIR) sequences, with key acquisition parameters as follows: MP-RAGE – resolution: 1x1x1mm, field-of-view: 208x256x256 matrix, TI/TR = 880/2000ms, 4:54 min; T2 FLAIR – resolution: 1.05x1x1mm, field-of-view: 192x256x256 matrix, TI/TR = 1800/5000ms, 5:52 min.

2.6. Image pre-processing

BHI values are not contained within UK Biobank and were calculated from anonymised MRI scans. Anonymisation was carried out by the UK Biobank team, with raw scans "defaced" using a generic face and ear mask, and back-projected into native participant space, masking out voxels in these regions (Alfaro-Almagro et al., 2018).

In-house, images were registered within-participant using Advanced Normalization Tools (ANTs v2.3.5., Avants et al., 2014). The T1 image was standardised to the MNI152 1 mm template (Mazziotta et al., 1995; 2001a, 2001b) using six-point rigid body registration, before 12-point affine registration of the raw T2 FLAIR image to the standardised T1 image. Both standardised images underwent bias field correction, whereby the erroneous low frequency signal differences which may exist within the image are corrected for to enable accurate computation by the BHI algorithm, using a nonparametric nonuniform intensity normalization algorithm (N4 Bias Field Correction; Tustison et al., 2010).

2.7. Intracranial volume masking

A generic ICV mask was created in Mango (Version 4.1, 1531). The MNI 1 mm brain mask was used as a starting point for this ICV, and overlayed on the MNI 1 mm brain template. The wrapping function within Mango was used to ensure the brain mask (now ICV mask) was as close to the edge of the MNI template as possible, then further eroded by 3 mm^3, due to significant skull inclusion in a sub-cohort of subjects used for testing (sub-cohort n = 10, skull inclusion n = 4). Based on this generic mask, custom ICV masks were produced for each participant using diffeomorphic registration in ANTs (Avants et al., 2014). These custom masks restricted voxels used for BHI computation.

2.8. The brain health index

The computational processes underlying BHI are described in Dickie et al. (2018) and summarised in Fig. 1. In brief, BHI was implemented using the Gaussian mixture model cluster analysis function in Matrix Laboratory (MATLAB) Statistics and Machine Learning Toolbox 2018b (MATLAB, 2018©1994–2018, The MathWorks, Inc.) on the High Performance Computing Cluster (HPCC) at the University of Glasgow (Centos Linux; 1,550 virtual central processing units (CPUs); 8 GeForce GTX 1080 graphics processing units (GPUs); up to 8 Gb RAM per core). The cluster analysis employs co-registered sequences to categorise ICV voxels as either (1) likely normal brain tissue, or (2) likely abnormal tissue or cerebrospinal fluid (CSF). Up to four different sequences can be overlaid here (for example in Dickie et al., 2018, T1, T2, T2* and FLAIR were used; the current study used only T1 and FLAIR), with each voxel given a value from each sequence. The expectation-maximization algorithm then uses the voxel values given by each sequence to compute

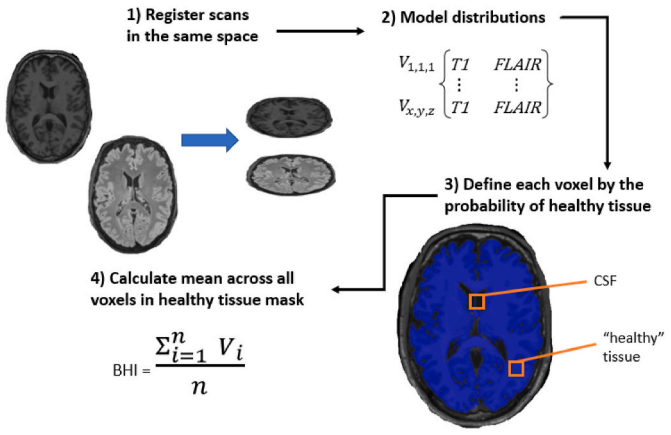


Fig. 1. Flow diagram of processes involved in the computation of the Brain Health Index.

the posterior probability of a given voxel being likely normal or likely 'abnormal'/CSF, across all included sequences. 'Abnormal' brain tissue is categorised alongside CSF by design; the BHI is specifically interested in the 'healthy' tissue of the brain but allows for inter-individual assessment in all the intra-cranial space. This approach is pertinent to the future application in various neurodegenerative diseases and longitudinal studies, given the eventual fate of the diseased brain is a loss of tissue and replacement with CSF.

Computation of BHI first produces a participant-specific 3D mask, with a value pertaining to the probability of "healthy" brain tissue attributed to each voxel within this mask. The mean of the voxel probabilities in each participant is then reported as a value between 0 and 1 (100%). Those closest to 100% are the "healthiest", as defined by BHI.

2.9. Quality control

Quality control of participant-specific ICV and BHI masks was carried out on all datasets using (MATLAB, 2018) to create multi-slice PNG images for visual assessment. For the ICV, the individual mask was overlaid on the participant-specific T1 image to ensure it adequately covered the brain without including skull. The BHI mask was overlaid on the participant-specific, bias field-corrected T1 image.

2.10. Statistical analyses

Statistical analyses were performed using R Studio (RStudio Team, 2020, R version 4.2.1 (2022-06-23)), IBM® SPSS® Statistics (Version: 28.0.0.0 (190) for Windows; IBM Corp, 2017) and GraphPad Prism for Windows (Version 9.4.1. (681), GraphPad Software, San Diego, California USA, www.graphpad.com), with Stata 17.0 (StataCorp, 2021) used to handle and limit the full UK Biobank cohort to those relevant to the current study. The generalized additive model for location, scale and shape (GAMLSS; Rigby and Stasinopoulos, 2005) was used to derive normative values for the BHI, using regression analyses to measure the scale of the BHI values as a P-spline of age, varied by sex. There was no evidence that a more complex distribution was needed (p-value >0.05). There was also no evidence that the standard deviation of the BHI changes with age or sex (p-values >0.05). Further models were produced to determine whether BHI curves varied by degree-level education.

Two-tailed t-tests with Welch's correction were used to test for age-, sex- and education-related differences in BHI scores, as well as how a diagnosis of T2DM or hypertension (vs. not) associated with BHI scores. One-way ANOVAs assessed differences in BHI scores by merit of alcohol intake, and smoking status. Pearson's correlation coefficient assessed relationships between BHI scores and continuous risk factors.

3. Results

Cohort identification and participant attrition are described in Fig. 2. The final cohort comprised two thousand nine hundred and ninety healthy participants aged 48–77 years old. This altered age range was chosen due to scan availability. In all cases of failed BHI computation, this was due to slight misclassification of CSF as grey matter and vice-versa, and minute sections of skull as grey matter. None of these misclassifications were apparent without close visual inspection and were excluded out of an abundance of caution. Participant demographics are provided in Table 1, and example BHI maps in Fig. 3., and Fig. A.1.

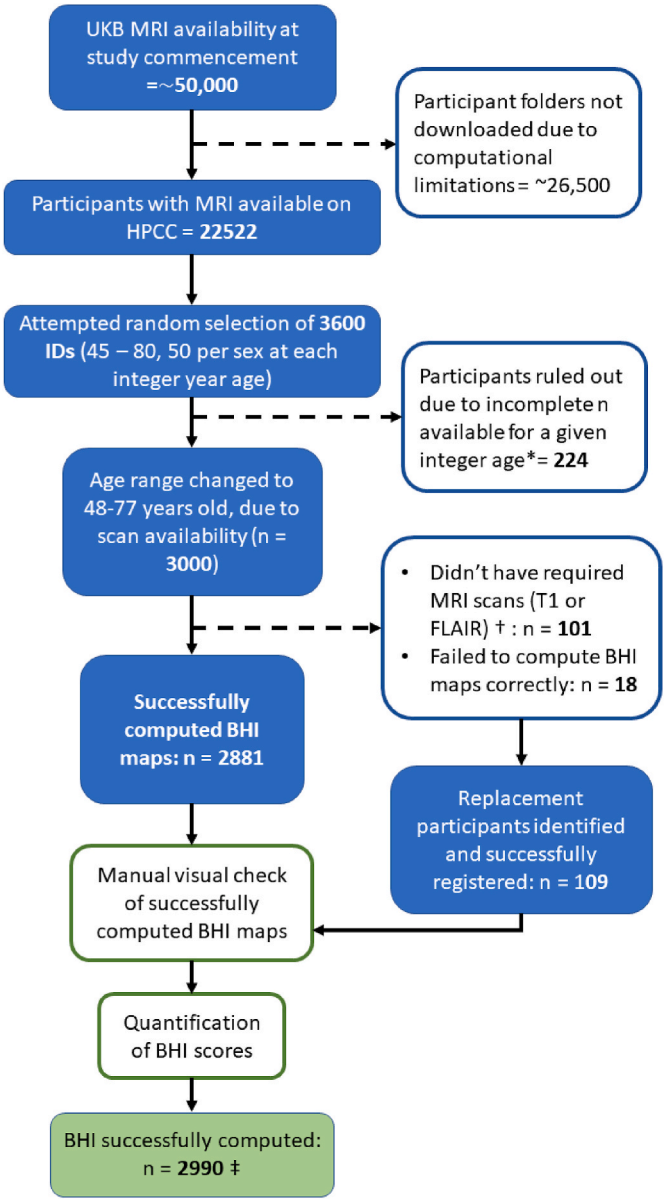


Fig. 2. Participant identification pathway
HPCC: High Performance Computing Cluster; UKB: UK Biobank
* Age (available n of males: females) – 45 (2:3); 46 (11:17); 47 (48:50); 78 (39:28); 79 (14:9); 80 (1:2).
† Manual investigation of folders for those who did not run through analysis pipeline
‡ Age (available n of males: females in incomplete sub-cohorts) – 57 (49:50); 64 (50:48); 68 (49:50); 72 (49:50); 73 (50:49); 77 (50:46).

Table 1
Participant demographics for final cohort.

Variable	Units	Results	N with data available
Demographics			
Age	Years (mean, SD)	48-77 (62.47, 8.65)	2990
Sex	M (% M)	1497 (50.07%)	2990
Ethnicity	Caucasian (%)	97.05%[a]	2979[b]
Education	Degree (%): no degree (%)	1299 (43.6%): 1680 (56.4%)	2979
Vascular Risk Factors at MRI			
T2DM	Yes (% Yes)	149 (5.04%)	2959
Hypertension	Yes (% Yes)	357 (11.94%)	2990
Alcohol intake frequency[c]	Response count (%)	1 – 492 (16.6%) 2 – 799 (26.96%) 3 – 843 (28.44%) 4 – 349 (11.77%) 5 – 290 (9.78%) 6 – 191 (6.44%)	2964
Smoker	Yes (% Yes); Occasionally (% Occasionally): No (% No)	983 (33.28%); 123 (4.16%); 1848 (62.56%)	2954
Pulse pressure	mmHg; range (mean, SD)	20-127 (56.63, 14.1)	2424
BMI	kg/m^2; range (mean, SD)	16-58 (26.66, 4.37)	2915
WHR (males)	Range (mean, SD)	0.73 – 1.21 (0.93, 0.06)	1468
WHR (females)	Range (mean, SD)	0.63 – 1.08 (0.815, 0.06)	1456
Medications	Yes (% Yes)	147 (4.92%)	2990

T2DM: type 2 diabetes mellitus; WHR: waist-to-hip ratio.
N.B. - Percentage values are given in relation to number of responders, not overall cohort size. Data pertaining to medications with specific vascular risks e.g. anticholinergic drugs, not investigated in current cohort.
[a] Other self-reported ethnicities: Chinese (n = 7); Other ethnic group (n = 18); white and black Caribbean (n = 3); white and black African (n = 2); white and Asian (n = 4); any other mixed background (n = 4); Indian (n = 23); Pakistani (n = 7); Bangladeshi (n = 1); any other Asian background (n = 4); Caribbean (n = 12); African (n = 3).
[b] Does not include those who responded "Prefer not to answer" (n = 10) in total.
[c] 1 – Daily or almost daily; 2 – Three to four times per week; 3 – One to two times per week; 4 – One to three times per month; 5 – Special occasions only; 6 – Never.

3.1. Statistical analyses

3.1.1. Normative Brain Health Index curves

Initial analyses suggested that the data was normally distributed, albeit slightly leptokurtic (summary of quantile residuals: mean = 1.435 × 10^{-6}; variance = 1.000335; coefficient of skewness = -0.2689; coefficient of kurtosis = 3.327244).

Normative curves for males and females are given in Fig. 4 (Cox Snell r^2 of full R model = 0.482). A decline in BHI with age is seen in both the full cohort, and males and females independently (r^2 = 0.431, F(1,2988) = 2262, p<0.0001; r^2 = 0.5, F(1,1495) = 1497, p<0.0001; r^2 = 0.382, F(1,1491) = 921.9, p<0.0001).

Higher BHI scores in females than males were found when uncorrected for age (Welch's 95% CI: 0.0103 to 0.0162; p <0.001; Cohen's d = 0.0416). Some ages exhibit significantly higher BHI scores in females than in males. These are summarised in Tables A.1 and A.2. At no age were BHI values significantly higher in males. Using our derived curves, a male aged 75 would be likely to have a BHI score of 0.627 ± 0.024, compared to a female of the same age scoring 0.647 ± 0.034, with lower values suggesting possible neurodegenerative disease.

Mean scores across the full cohort were compared to the work of Dickie et al. (2018). We found a mean score of 0.69 ± 0.04, similar to their work which found a mean of 0.71 ± 0.03 (n = 80).

Female BHI scores did not differ depending on whether the subject

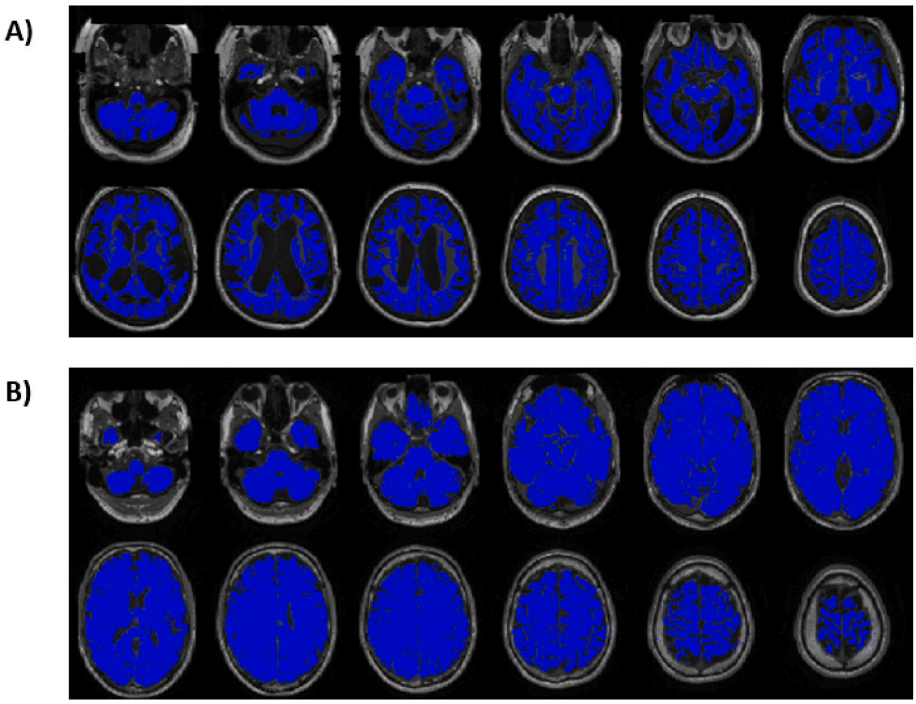


Fig. 3. Example BHI maps of A) a 74-year-old male (score = 0.524) and B) a 50-year-old male (score = 0.74), in native space.

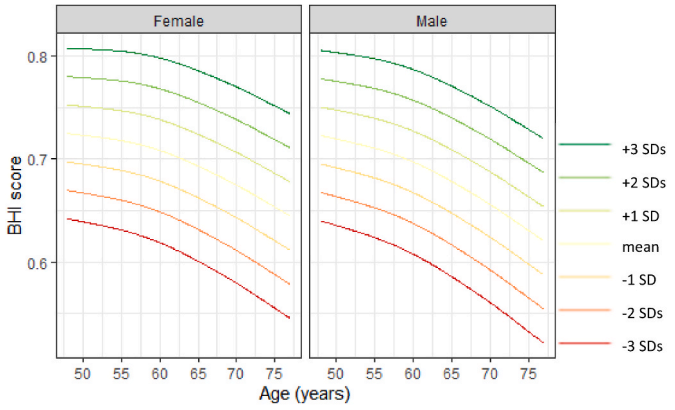


Fig. 4. Uncorrected Brain Health Index score curves for the full cohort (age range: 48–77 years old). Plus or minus X standard deviations are also given.

studied had degree-level education, but males with degrees scored higher than those who did not (Welch's 95% CI: 0.000 to 0.009; $p < 0.05$; Cohen's d = 0.044; see Fig. A.2). However, when sex is not considered here, there is no significant difference in BHI score.

3.1.2. *Associations of brain health risk factors with the brain health index*

Participants with T2DM exhibited lower BHI scores than those without T2DM (95% CI: 0.018 to 0.033; p <0.001; Cohen's d = 0.0417). Similarly, those with hypertension had lower BHI scores than those without hypertension (95% CI: 0.008 to 0.018; p <0.001; Cohen's d = 0.0419).

Alcohol consumption affected BHI scores ($F(5,2958) = 18.49$, $p < 0.001$, $\eta^2 = 0.03$; Table A.3). Lower scores were evidenced in those who consumed alcohol daily or almost daily, when compared with those who drank anywhere between 3 and 4 times per week and on special occasions only (all p <0.001), but not those who never drank (see Fig. A.3).

Participant smoking status had an impact on BHI scores ($F(2,2951) = 33.31$, $p < 0.001$, $\eta^2 = 0.022$). Post-hoc Tukey's analysis suggests scores are higher for non-smokers compared with those who smoked on most or all days (95% CI: 0.009 to 0.017, p <0.001, Cohen's d = 0.041). Occasional smokers scored higher than those who smoked on most or all days (95% CI: 0.003 to 0.021, p < 0.01, Cohen's d = 0.043). Scores did not differ between those who smoked occasionally and those who did not smoke.

The relationships between continuous risk factors and BHI scores are summarised in Fig. 5, with pulse pressure the most significant risk factor in this cohort, other than age. Both WHR and pulse pressure were further investigated to determine if sex is relevant to these findings.

Both males and females with lower waist-to-hip ratios exhibited higher BHI scores ($R^2 = 0.02121$, $F(1, 1466) = 31.77$, p <0.001; $R^2 = 0.02201$, $F(1, 1454) = 32.72$, p <0.001), as did both males ($R^2 =$

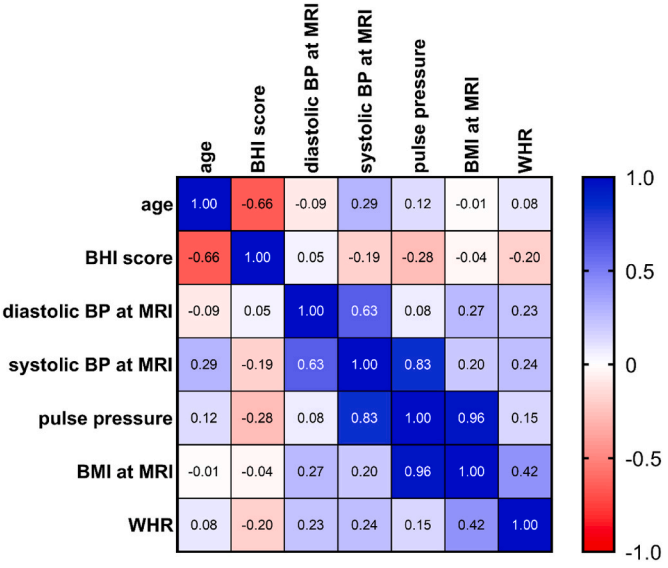


Fig. 5. Two-tailed Pearson's r analysis results for continuous covariates of interest as measured at the MRI assessment centre. BP: blood pressure, BHI: brain health index, WHR: waist-hip ratio.

0.06261, F(1, 1215) = 81.16, p <0.001), and females (R^2 = 0.07616, F (1, 1205) = 99.34, p <0.001) with lower pulse pressure.

4. Discussion

The BHI is an automated image analysis approach which quantifies structural brain integrity by combining different MRI sequences into a single measure. We used data from a subsample of N = 2990 in the UK Biobank imaging cohort (current N = 50k) to create normative BHI curves for individuals with no evidence of neurological issues aged between 48 and 77 years-old. These normalised score curves and SDs provide baseline scores for generally healthy individuals assessed using the BHI, and facilitates clinical application and interpretation of the measure. Use of GAMLSS modelling also allows for harmonization across other studies which assess brain development and ageing using diverse neuroimaging methodology (see Bethlehem et al., 2022).

Mean scores across the full cohort were similar to prior work by Dickie et al. (2018), in their cohort of healthy participants (n = 80). Direct comparison is not possible due to T2 and T2* images additionally being used for BHI computation in their work, but this finding lends support to the idea that BHI can be reliably computed with only T1 and T2 FLAIR images.

We hypothesised that BHI scores would significantly decrease with age, which was supported by our results. This was expected as brain atrophy and vascular health are two major age-related risk factors for cognitive decline and early neurodegeneration (Debette et al., 2019; Pini et al., 2016; Shi and Wardlaw, 2016; Sweeney et al., 2018), with BHI capturing both through the combination of scans used. What is less clear is why BHI scores were significantly lower in males than females for more than half of the age range investigated. Male brains are bigger (Eliot et al., 2021) but significantly more poorly perfused (Lu et al., 2011), which has in turn been linked to pathological vessel changes, progressive neuronal loss, and development of Alzheimer's disease, and possibly underpins this difference we see.

Male participants with degree-level education had significantly higher BHI scores than those who did not. holding degree-level certification has been linked to various socioeconomic benefits (Britton et al., 2020) – including higher lifetime earnings – which may in turn affect brain health. However, degree-level education had no significant effect on scores for female participants. Thus, data on the effect of education on BHI were conflicting. At present, we would recommend adjusting for education level as is common for many other measures of brain function.

When considering specific diagnoses, participants with T2DM and hypertension also evidenced significantly lower BHI scores than those without these conditions. T2DM has been shown to increase the risk of dementia by 1.5–2.5-fold (Strachan et al., 2011), and hypertension contributes to the vascular health risk (Sierra, 2020).

A lack of significant difference in BHI score between participants who never drank and those who drank daily or almost daily was not anticipated, particularly given that lower scores were seen in those who drank daily/almost daily and those who drank anywhere between 3 and 4 times a week and on special occasions only. A study of 25,378 UK Biobank participants found that there was no safe level of alcohol consumption when considering grey matter volume, white matter microstructure, and functional connectivity (Topiwala et al., 2021). Whilst this does assess different aspects of brain health to the BHI, the scale of this study relative to our own highlights the need for further investigation of the relationship between alcohol consumption and the BHI. Contrastingly, significantly higher BHI values in non-smokers compared with participants who smoked on all or most days is unsurprising, given the known links between smoking, brain ageing, and cognition (Linli et al., 2022).

Waist-to-hip ratio and pulse pressure were highlighted as the risk factors most significantly related to BHI score. These findings were expected, with links between these metrics and brain health already established (Cox et al., 2019). High WHR has previously been investigated in 9,652 participants from UK Biobank and highlighted as a risk factor for grey matter atrophy (Hamer and Batty, 2019). A 2018 review by Thorin-Trescases et al. shows that high pulse pressure poses a risk to the structure, metabolism and haemodynamics of the brain, with Levin et al. (2020) suggesting this may be an appropriate target for therapeutic interventions.

The ability of the BHI to mirror certain established risk factors shows promise for its utility in a clinical setting, as do several of its key features. The automated pipeline requires substantially less time investment than more manual image analysis techniques, whilst providing a more cohesive summary of brain health by combining multiple MRI scan types – neurodegenerative conditions affect the whole brain, and BHI captures this, rather than focusing on specific tissue or lesion damage, as other metrics do. Clinical metrics often lack granularity, however scoring BHI on a continuous scale provides easier interpretation and patient comprehension.

Despite these strengths, there are limitations in the current work. The BHI requires T1, T2 FLAIR, T2 and T2* imaging to fully capture structural information, but only T1 and T2 FLAIR were used here. Although Dickie et al. (2018) suggest that this approach would yield unstable results, the similarity of our results with their healthy control findings support the assertion that doing so is possible where necessary. The UK Biobank imaging study uses a state-of-the-art protocol with tight time constraints to enable the volume of scanning required. However, such an approach does not allow for experimentation with alternate imaging parameters to determine whether BHI scoring depends on parameters such as slice thickness or slice gaps. Further work to improve tissue classifications at boundaries is also warranted.

These normative curves are not immediately suited to clinical use and require further development to achieve this. There are many differences in the imaging data used in the clinical routine and data obtained in strict research contexts. As example, due to the high volume of clinical scans performed on a daily basis, clinical data may not be 'complete', in that a field of view covering the whole brain may not be required to answer the clinical question. Additionally, there is a higher degree of variation between both sites and scanner models and manufacturers, thereby necessitating further processing steps to account for this variance. Nevertheless, BHI norms in both clinical and research contexts will provide a benchmark for the understanding of neurodegenerative change. The metric can also be calculated retrospectively from scans which are collected in regular clinical practice, thereby minimising additional costs, and increasing the information gained by the same imaging paradigms. However, currently the age range of participants is fairly narrow, limiting the understanding of the BHI to individuals within this range. Normative BHI scores in the middle aged and the very old would have utility in our understanding of BHI across the lifespan and allow us to determine how BHI values change with age. The limitations of the current cohort also prevent understanding of how risk factors for poor brain health have contributed to BHI scoring over time. Thus, future investigation of the BHI should involve longitudinal, repeated investigation.

The UK Biobank cohort is not representative of the general UK population, with fewer self-reported health conditions and less socioeconomic deprivation (Fry et al., 2017) relative to the general UK population. It is not an ancestrally diverse cohort. The imaging sub-sample shows less deprivation compared with the 'full' N = 502k UK Biobank cohort, among healthy biases in virtually all phenotypes (Lyall et al., 2022). There is also an education bias within the current study – 43.6% of participants held degree-level education, compared with 26.4% of the wider UK population aged 25–64 years (Organisation for Economic Co-operation and Development [OECD], 2021). Furthermore, recent research has shown that the MNI templates used within this study – and which are standard templates – are not always appropriate for use in diverse ancestries (Rao et al., 2017; Bhalerao et al., 2018; Pai et al., 2020; Yang et al., 2020).

5. Conclusions

Normative BHI scores in a generally healthy population of UK Biobank participants were established using regression analyses, providing a baseline against which clinical BHI scoring can be understood in future. More work is required to understand how normative values vary in different populations, and how well vascular risk factors are associated with the BHI.

CRediT author statement

Jodi K Watt: Conceptualization, Methodology, Investigation, Software, Formal analysis, Visualisation, Data Curation Writing – Original Draft, Writing – Review & Editing **David Alexander Dickie**: Conceptualization, Methodology, Software, Resources, Data Curation, Supervision, Writing – Review & Editing **Donald Lyall:** Formal analysis, Writing – Review & Editing **Joey Ward:** Data Curation, Writing – Review & Editing **Frederick K Ho:** Formal analysis, Writing – Review & Editing **Jesse Dawson**: Conceptualization, Methodology, Supervision, Writing – Review & Editing **Terence J Quinn**: Conceptualization, Methodology, Supervision, Writing – Review & Editing.

Funding/acknowledgements

JKW is funded by a Chief Scientist Office Research Grant (Reference: TCS/19/31). JW is funded by the Aitchison Family Bequest. This research has been conducted using the UK Biobank Resource under Application Number 17869.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Researchers can apply to use the UK Biobank resource at https://www.ukbiobank.ac.uk/enable-your-research/register. Code will be released upon completion of the current suite of related research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynirp.2023.100176.

References

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L., Griffanti, L., Douaud, G., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., 2018. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 166, 400–424.

Avants, B.B., Tustison, N.J., Stauffer, M., Song, G., Wu, B., Gee, J.C., 2014. The Insight ToolKit image registration framework. Front. Neuroinf. 8, 44.

Bethlehem, R.A., Seidlitz, J., White, S.R., Vogel, J.W., Anderson, K.M., Adamson, C., Adler, S., Alexopoulos, G.S., Anagnostou, E., Areces-Gonzalez, A., Astle, D.E., 2022. Brain charts for the human lifespan. Nature 604 (7906), 525–533.

Bhalerao, G.V., Parlikar, R., Agrawal, R., Shivakumar, V., Kalmady, S.V., Rao, N.P., Agarwal, S.M., Narayanaswamy, J.C., Reddy, Y.J., Venkatasubramanian, G., 2018. Construction of population-specific Indian MRI brain template: morphometric comparison with Chinese and Caucasian templates. Asian.J. Psychiatr. 35, 93–100.

Boller, B., Mellah, S., Ducharme-Laliberté, G., Belleville, S., 2017. Relationships between years of education, regional grey matter volumes, and working memory-related brain activity in healthy older adults. Brain imaging. Behav. 11 (2), 304–317.

Britton, J., Dearden, L., van der Erve, L., Waltmann, B., 2020. The Impact of Undergraduate Degrees on Lifetime Earnings: Research Report. February 2020.

Cox, S.R., Lyall, D.M., Ritchie, S.J., Bastin, M.E., Harris, M.A., Buchanan, C.R., Fawns-Ritchie, C., Barbu, M.C., De Nooij, L., Reus, L.M., Alloza, C., 2019. Associations between vascular risk factors and brain MRI indices in UK Biobank. Eur. Heart J. 40 (28), 2290–2300.

Debette, S., Schilling, S., Duperron, M.G., Larsson, S.C., Markus, H.S., 2019. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. JAMA Neurol. 76 (1), 81–94.

Dickie, D.A., Job, D.E., Gonzalez, D.R., Shenkin, S.D., Wardlaw, J.M., 2015. Use of brain MRI atlases to determine boundaries of age-related pathology: the importance of statistical method. PLoS One 10 (5), e0127939.

Dickie, D.A., Valdés Hernández, M.D.C., Makin, S.D., Staals, J., Wiseman, S.J., Bastin, M. E., Wardlaw, J.M., 2018. The brain health index: towards a combined measure of neurovascular and neurodegenerative structural brain injury. Int. J. Stroke 13 (8), 849–856.

Eliot, L., Ahmed, A., Khan, H., Patel, J., 2021. Dump the "dimorphism": comprehensive synthesis of human brain studies reveals few male-female differences beyond size. Neurosci. Biobehav. Rev. 125, 667–697.

Fry, A., Littlejohns, T.J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., Allen, N.E., 2017. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am. J. Epidemiol. 186 (9), 1026–1034.

Gazzina, S., Grassi, M., Premi, E., Cosseddu, M., Alberici, A., Archetti, S., Gasparotti, R., Van Swieten, J., Galimberti, D., Sanchez-Valle, R., Moreno, F., 2019. Education modulates brain maintenance in presymptomatic frontotemporal dementia. J. Neurol. Neurosurg. Psychiatr. 90 (10), 1124–1130.

Gray, J.C., Thompson, M., Bachman, C., Owens, M.M., Murphy, M., Palmer, R., 2020. Associations of cigarette smoking with gray and white matter in the UK Biobank. Neuropsychopharmacology 45 (7), 1215–1222.

Hamer, M., Batty, G.D., 2019. Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. Neurology 92 (6), e594–e600.

Ho, A.J., Raji, C.A., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Dinov, I.D., Stein, J.L., Rosano, C., Toga, A.W., Thompson, P.M., 2011. The effects of physical activity, education, and body mass index on the aging brain. Hum. Brain Mapp. 32 (9), 1371–1382.

IBM Corp, 2017. IBM SPSS Statistics for Windows. IBM Corp, Armonk, NY.

Leidhin, C.N., McMorrow, J., Carey, D., Newman, L., Williamson, W., Fagan, A.J., Chappell, M.A., Kenny, R.A., Meaney, J.F., Knight, S.P., 2021. Age-related normative changes in cerebral perfusion: data from the Irish longitudinal study on ageing (TILDA). Neuroimage 229, 117741.

Levin, R.A., Carnegie, M.H., Celermajer, D.S., 2020. Pulse pressure: an emerging therapeutic target for dementia. Front. Neurosci. 14, 669.

Linli, Z., Feng, J., Zhao, W., Guo, S., 2022. Associations between smoking and accelerated brain ageing. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 113, 110471.

Littlejohns, T.J., Holliday, J., Gibson, L.M., Garratt, S., Oesingmann, N., Alfaro-Almagro, F., Bell, J.D., Boultwood, C., Collins, R., Conroy, M.C., Crabtree, N., 2020. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nat. Commun. 11 (1), 2624.

Lu, H., Xu, F., Rodrigue, K.M., Kennedy, K.M., Cheng, Y., Flicker, B., Hebrank, A.C., Uh, J., Park, D.C., 2011. Alterations in cerebral metabolic rate and blood supply across the adult lifespan. Cerebr. Cortex 21 (6), 1426–1434.

Lyall, D.M., Quinn, T., Lyall, L.M., Ward, J., Anderson, J.J., Smith, D.J., Stewart, W., Strawbridge, R.J., Bailey, M.E., Cullen, B., 2022. Quantifying bias in psychological and physical health in the UK Biobank imaging sub-sample. Brain Communications 4 (3), fcac119.

Mazziotta, J.C., Toga, A.W., Evans, A., Fox, P., Lancaster, J., 1995. A probabilistic atlas of the human brain: theory and rationale for its development. Neuroimage 2 (2), 89–101.

Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., Holmes, C., 2001a. A four-dimensional probabilistic atlas of the human brain. J. Am. Med. Inf. Assoc. 8 (5), 401–430.

Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., Holmes, C., 2001b. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 356 (1412), 1293–1322.

Miller, K.L., Alfaro-Almagro, F., Bangerter, N.K., Thomas, D.L., Yacoub, E., Xu, J., Bartsch, A.J., Jbabdi, S., Sotiropoulos, S.N., Andersson, J.L., Griffanti, L., 2016. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat. Neurosci. 19 (11), 1523–1536.

Momtaz, Y.A., Haron, S.A., Hamid, T.A., Ibrahim, R., Tanjani, P.T., 2018. Body mass index (BMI) and cognitive functions in later life. Curr. Alzheimer Res. 15 (2), 195–200.

Organisation for Economic Co-operation and Development, 2021. United Kingdom: Overview of the Educational System (EAG 2022). Educational Attainment and Labour-Force Status. https://stats.oecd.org/Index.aspx?datasetcode=EAG_NEAC. (Accessed 7 December 2022).

Pai, P.P., Mandal, P.K., Punjabi, K., Shukla, D., Goel, A., Joon, S., Roy, S., Sandal, K., Mishra, R., Lahoti, R., 2020. BRAHMA: population specific t1, t2, and FLAIR weighted brain templates and their impact in structural and functional imaging studies. Magn. Reson. Imag. 70, 5–21.

Pini, L., Pievani, M., Bocchetta, M., Altomare, D., Bosco, P., Cavedo, E., Galluzzi, S., Marizzoni, M., Frisoni, G.B., 2016. Brain atrophy in Alzheimer's disease and aging. Ageing Res. Rev. 30, 25–48.

Rao, N.P., Jeelani, H., Achalia, R., Achalia, G., Jacob, A., dawn Bharath, R., Varambally, S., Venkatasubramanian, G., Yalavarthy, P.K., 2017. Population differences in brain morphology: need for population specific brain template. Psychiatr. Res. Neuroimaging 265, 1–8.

Rigby, R.A., Stasinopoulos, D.M., 2005. Generalized additive models for location, scale and shape. J. Roy. Stat. Soc.: Series C (Applied Statistics) 54 (3), 507–554.

RStudio Team, 2020. RStudio. Integrated Development for R. Studio, PBC, Boston, MA. URL. http://www.rstudio.com/.
Shi, Y., Wardlaw, J.M., 2016. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke.vascular Neurol. 1 (3).
Sierra, C., 2020. Hypertension and the risk of dementia. Front.Cardiovasc. Med. 7, 5.
Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., Iwatsubo, T., Jack Jr., C.R., Kaye, J., Montine, T.J., Park, D.C., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dementia 7 (3), 280–292.
StataCorp, 2021. Stata Statistical Software: Release 17. StataCorp LLC, College Station, Tx.
Strachan, M.W., Reynolds, R.M., Marioni, R.E., Price, J.F., 2011. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat. Rev. Endocrinol. 7 (2), 108–114.
Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., 2015. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 12 (3), e1001779.
Sweeney, M.D., Kisler, K., Montagne, A., Toga, A.W., Zlokovic, B.V., 2018. The role of brain vasculature in neurodegenerative disorders. Nat. Neurosci. 21 (10), 1318–1331.
Thorin-Trescases, N., de Montgolfier, O., Pinçon, A., Raignault, A., Caland, L., Labbé, P., Thorin, E., 2018. Impact of pulse pressure on cerebrovascular events leading to age-related cognitive decline. Am. J. Physiol. Heart Circ. Physiol. 314 (6), H1214–H1224.
Topiwala, A., Ebmeier, K.P., Maullin-Sapey, T., Nichols, T.E., 2021. No Safe Level of Alcohol Consumption for Brain Health: Observational Cohort Study of 25,378 UK Biobank participants.*medRxiv*.
Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., Gee, J.C., 2010. N4ITK: improved N3 bias correction. IEEE Trans. Med. Imag. 29 (6), 1310–1320.
Yang, G., Zhou, S., Bozek, J., Dong, H.M., Han, M., Zuo, X.N., Liu, H., Gao, J.H., 2020. Sample sizes and population differences in brain template construction. Neuroimage 206, 116318.
MATLAB, 2018. Version 9.5 (R2018b), Natick, Massachusetts: The MathWorks Inc.