Radiomic and proteomic signatures of body mass index on brain ageing and Alzheimer's-like patterns of brain atrophy

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Summary

Background The impact of high body mass index (BMI) states and associated proteomic factors on brain ageing and Alzheimer's disease (AD) remains unclear.

Methods We sought to evaluate machine learning (ML)-based neuroimaging markers of brain age and AD-like brain atrophy in participants with obesity or overweight without diagnosed cognitive impairment (WODCI), in a harmonised study of 46,288 participants in 15 studies (the Imaging-Based Coordinate System for Aging and Neurodegenerative Diseases (iSTAGING) consortium). We also assessed the association between cognition, serum proteins, and brain ageing indices. Data were acquired between 1999 and 2020 and analysed from November 2024 onwards.

Findings The study comprised 46,288 participants, including 24,897 females and 21,391 males, with a mean age of 64.33 years (SD = 8.13) and a mean BMI of 26.81 kg/m^2 (SD = 4.49). The results demonstrate that the impact of obesity on brain ageing, and AD-like brain atrophy is weaker with increasing age and is significantly pronounced in males compared to females. Additionally, in males, obesity was significantly associated with approximately 2 additional years of brain ageing compared to normal weight and 1 additional year compared to the overweight group. Males with overweight also showed higher brain ageing values (8 additional months) than males with normal weight. Regarding AD-like brain atrophy, males with obesity displayed higher AD-like brain atrophy than males with normal weight, but females with normal weight showed higher AD-like brain atrophy than females with overweight. Sex differences within the same BMI categories were observed, with males exhibiting increased brain ageing compared to females, in obesity (1 additional year) and overweight groups (3 additional months). Higher AD-like brain atrophy was observed in males with overweight than in females with overweight. Females with normal weight displayed increased brain ageing (8 additional months) and AD-like brain atrophy relative to males with normal weight. In both retrospective and cross-sectional proteomics studies, five and eight proteins out of 1463 proteins were significantly (positively or negatively) associated with brain ageing and 1-SD BMI change (SD = 4.2 kg/m^2), respectively.

Interpretation The findings demonstrate that higher BMI states are associated with accelerated brain ageing and AD-like atrophy, particularly in males, while females with normal weight demonstrated higher brain ageing and AD-like atrophy than males with normal weight. Moreover, the impact of obesity on brain ageing and AD-like brain atrophy becomes weaker with increasing age. Further research is needed to investigate sex-specific mechanisms by which weight gain influences brain ageing.

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Keywords: Ageing; Alzheimer's; Brain age gap; Proteomics

Research in context

Evidence before this study

We searched PubMed for articles in English published until November 10, 2024, examining the relation between body mass index (BMI) states and brain ageing. Search terms included "dementia", "brain age", "brain ageing", "BMI", "obesity", "brain age prediction", and "proteomics". Obesity, particularly midlife obesity, is known to be a modifiable risk factor for Alzheimer's disease (AD) and related dementias, with long-term obesity associated with cognitive decline and brain atrophy. However, the mechanisms linking obesity to brain ageing and dementia are not fully understood. Studies have demonstrated that high BMI is related to neurocognitive decline and compromised brain integrity, but the specific molecular markers, such as serum proteins, that mediate these effects are still unclear. Additionally, the relationship between obesity and brain ageing, particularly in individuals without cognitive impairments, remains underexplored.

Added value of this study

This study aims to investigate the effects of BMI and related proteomic markers on brain ageing and AD-like brain atrophy in participants without diagnosed cognitive impairment, utilising a comprehensive, diverse, and harmonised dataset along with machine learning methods. Additionally, the study seeks to explore the relationship between BMI, serum proteins, and brain ageing patterns.

Implications of all the available evidence

This study underscores that the impact of obesity and overweight on brain ageing and AD-like brain atrophy is more pronounced in males than females, highlighting potential sex-specific differences and the importance of early preventive measures. These findings contribute to our understanding of the neurocognitive consequences of obesity, paving the way for future studies elucidating mechanisms and pathways of obesity-related and sex-specific effects on the brain. The also highlight the potential role of brain age as an additional biomarker that can inform clinical trials and patient management that aim to control BMI.

Introduction

Obesity is considered a global epidemic of the 21st century.[1–5] Notably, long-term increased body weight or abdominal obesity, as well as weight gain in midlife, is associated with a higher risk for incident dementia.[6,7] Specifically, in the United States, midlife obesity is the most prominent modifiable risk factor for Alzheimer's disease (AD) and related dementias, overtaking physical inactivity.[8] The ageing of the population, along with the rapidly rising prevalence and incidence of overweight/obesity and obesity-related diseases, i.e., cardiovascular-kidney-metabolic diseases, are expected to result in a rise in morbidity, mortality, and healthcare costs in the near future.[9–11] The emerging recognition of neurocognitive decline as part of the cardiovascular-kidney-metabolic continuum, as well as addressing modifiable risk factors and unveiling the early pathophysiological changes before the onset of dementia, would enable personalised, preventive, and therapeutic interventions.[12]

High body mass index (BMI), specifically ≥30 kg/m^2–indicating obesity, is postulated to impact brain integrity, relating to grey and white matter atrophy and dysregulated interregional circuitry, which may explain, in part, their higher risk for dementia.[13,14] Although only midlife obesity is associated with higher dementia incidence, the reason behind this remains unclear[15] and may be attributed to associations of dementia with weight loss in late life.[12] A recent study revealed that individuals with increasing BMI in midlife and subsequently decreasing BMI in late life are at elevated risk for dementia, with BMI declining approximately seven to eight years preceding dementia diagnosis.[14]

In the lack of conclusive evidence, consideration of molecular markers such as proteomics, may provide mechanistic insights into the link between BMI and brain atrophy across the human lifespan.[16,17] Recently, a large community-based prospective cohort study demonstrated that glial fibrillary acidic protein (GFAP), neurofilament light polypeptide (NfL), growth differentiation factor 15 (GDF15), and brevican core protein (BCAN) were associated with a 14-year dementia risk.[18] However, the degree to which proteins modulated by metabolic risk factors, such as obesity, influence the pathophysiological process underlying dementia risk (brain atrophy and advanced ageing) still remains unclear. Therefore, differences in the cognitive state among individuals of the same age are encapsulated in the term brain ageing, which has emerged as a biomarker reflecting the individual's overall brain health. Brain ageing is typically employed to measure the deviation from the normative ageing trajectory, being strongly implicated in neurocognition.[19]

In this multi-cohort study encompassing 46,288 harmonised brain magnetic resonance imaging (MRI)

scans, we investigate brain ageing and AD-like brain atrophy patterns (both quantified via machine learning indices), as well as neurocognitive changes in individuals with obesity or overweight. Second, we examine the links between BMI, proteomic alterations, deviations in brain ageing trajectories, and patterns of AD-like brain atrophy.

Methods

Study populations

MRI scans and clinical data used in this study were consolidated and harmonised by the Imaging-Based Coordinate System for Aging and Neurodegenerative Diseases (iSTAGING) study. The iSTAGING study comprises data acquired via various imaging protocols, scanners, data modalities, and pathologies, including 67,997 participants aged between 22 and 90 years from 17 studies on three continents. Specifically, the current study used MRIs from the following cohorts that met the inclusion criteria (Fig. 1): Alzheimer's Disease Neuroimaging Initiative (ADNI), the Australian Imaging, Biomarkers and Lifestyle (AIBL), the Biomarkers of Cognitive Decline Among Normal Individuals (BIOCARD), the Human Connectome Project (HCP), the Multi-Ethnic Study of Atherosclerosis (MESA), the Open Access Series of imaging Studies (OASIS), the Penn study (PENN), the PResymptomatic EValuation of Experimental or Novel Treatments for AD (PREVENT-AD), the Women's Health Initiative Memory Study (WHIMS), the Wisconsin Registry for Alzheimer's Prevention (WRAP), the UK Biobank, the Baltimore Longitudinal Study of Aging (BLSA), the Coronary Artery Risk Development in Young Adults Study (CARDIA), the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS), and the Study of Health In Pomerania studies (SHIP).

Subsequently, we grouped iSTAGING participants according to BMI categories (proposed by the World Health Organization[20]) as follows: (i) normal weight (BMI 18.5–24.9 kg/m^2), (ii) overweight (BMI 25.0–29.9 kg/m^2), and (iii) obesity (BMI $\geq$ 30 kg/m^2). The study included participants without diagnosed cognitive impairment (WODCI), defined as healthy controls or cognitively normal participants across the studies. Each study has its own criteria for defining cognitively normal or individuals without diagnosed cognitive impairment. The term 'without diagnosed cognitive impairment' encompasses participants labelled as either 'control (CN)', 'CN assumed by study criteria', 'cognitively unimpaired', 'cognitively normal', 'memory complainer (healthy control)', 'non-memory complainer (healthy control)', 'normal', or having 'normal cognition' based on the originating studies, which used study-specific criteria for such designations. The distribution of previous diagnoses across subgroups did not show significant differences. More information about each study separately can be found in our previous publications.[21] Baseline characteristics for each population are presented in Tables 1–4.

Image preprocessing

A fully automated processing pipeline was applied to extract region-of-interest (ROI) volumes from each participant's T1-weighted MRI scan. Preprocessing involved image intensity correction for inhomogeneities,[22] and multi-atlas skull-stripping was applied to remove extracranial material.[23] In this approach, a collection of prelabelled atlases is warped in parallel to a participant's MRI. The warped atlases are combined via a weighted voting procedure, which ensures that the most suitable/similar atlases have the highest weights in this process.[24] 145 anatomic ROIs, predominately in grey matter, were segmented using a multi-atlas, multi-warp label fusion-based method.[24] These multi-atlas segmentation techniques provide robustness to errors in specific deformations by utilising several anatomical reference images (atlases), that are adjusted to align with the target image through deformable registration. Table 5 reports imaging parameters from the parent studies. Additional details about image preprocessing were reported previously.[25,27] Volumes of the 145 ROIs were used in the generation of ML-markers described below and were compared in the proteomic analysis (Table 6).

Spatial Pattern of Abnormality for Recognition of Early Alzheimer's Disease (SPARE-AD) index

We derived machine learning metrics of brain age and AD-signature region brain atrophy, termed Spatial Pattern of Abnormality for Recognition of Early (SPARE) indices. All SPARE scores were obtained from models trained on different datasets, either via 5-fold cross-validation or via out-of-sample application of pretrained models, ensuring no overlapping of the data. More specifically, for the data used in constructing the two SPARE models, 5-fold cross-validation was applied so that all SPARE scores were derived when respective participants were in the test set, i.e., in the 20% not participating in model training. For the datasets that were not part of the training, SPARE scores were obtained by applying already-trained models to these external datasets. One SPARE model predicts brain age (SPARE-BA) using Support Vector Regression.[28] The SPARE-BA model was previously trained on 145 single harmonised multi-atlas parcellation method (MUSE) ROI data from the iSTAGING consortium from four different studies with over 4000 participants and is detailed in Hwang et al.[29] Pooling imaging datasets from multiple studies is prone to study-related effects due to the lack of standardised image acquisition protocols and scanner variability. Systematic differences in sample demographics between studies may also confound analyses. To preserve study-related biological effects while correcting for systematic technical variance, we applied

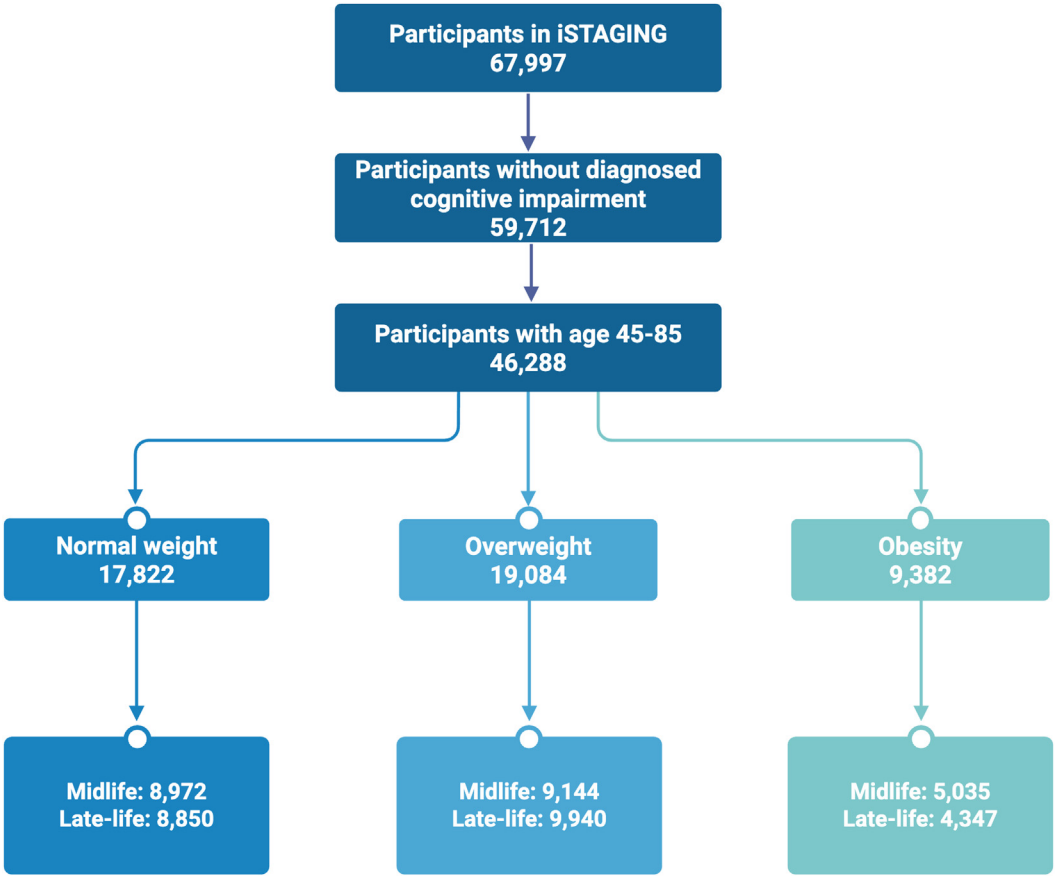

Fig. 1: Pipeline. Abbreviations: WODCI, Without Diagnosed Cognitive Impairment; BMI, Body Mass Index. Created with BioRender.com.

the Neuroharmonize toolbox[29] based on the multivariate ComBat method combined with generalised additive cubic spline models to capture nonlinear age, sex, and deep learning-based intracranial volume measurement (DLICV) effects.[30] This method reduces acquisition-related effects and preserves variability due to biological covariates. Each ROI volume was modelled as a nonlinear function of age, sex, and baseline DLICV. Based on the adjusted data, the remaining systematic differences in shift (location) and variance (scale) were attributed to site-specific acquisition settings and adjusted conservatively with an empirical Bayes regularisation. The harmonisation model was trained on each site's baseline scans of WODCI and then applied to the entire dataset. This method has already been validated in other works.[29] A linear age bias correction was applied to both structural and functional SPARE-BA measures to remove the known systematic bias inherent in brain age calculations.[31] Brain age gap, calculated by subtracting the chronological age from the predicted brain age (SPARE-BA) yielded a Pearson's correlation coefficient r = 0.005 with chronological age. Higher SPARE-BA, relative to chronological age, is due to greater brain atrophy than typical for age, indicating advanced brain ageing. We measured brain atrophy in typical regions (regions from the temporal lobe, the cingulate and the insula) affected by AD using the SPARE Alzheimer's disease (SPARE-AD) model, which was derived using a support vector machine with a linear kernel trained to distinguish controls from participants with AD.[28,32] Detailed information about the SPARE-AD model can be found in previous publications.[28,32] Higher SPARE-AD values indicate a more pronounced presence of the AD-signature of regional brain atrophy, while negative values indicate brain patterns more similar to the control group; SPARE-AD values are unit-less, as they reflect the degree of expression of this imaging signature.

Blood proteomics

The UK Biobank blood sample collection was performed in 22 centres across the UK during the baseline visit in 2007–2010 and then during the imaging visit to the UK Biobank in 2014. Blood samples from each participant were collected in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 2500 g for 10 min at

Study	Sample size	Sex (%)	(%Asian)	(%Black)	(%Other)	(%White)	Age (years, SD)	APOE-e4 (% with one or two alleles)	Intracranial volume (mm^3)
ADNI	908	Males: 44.05 Females: 55.95	0.77	4.3	32.49	62.33	72.01 ± 5.98	28.74	1,408,323 ± 140,698.81
AIBL	634	Males: 42.90 Females: 57.10	0	0	0	100	72.39 ± 5.81	21.81	1,407,718 ± 139,867.99
BIOCARD	209	Males: 38.76 Females: 61.24	1.48	0.99	0.49	97.12	59.13 ± 7.75	34.45	1,402,292 ± 142,628.68
BLSA	881	Males: 43.13 Females: 56.87	4.42	23.95	2.76	69.69	67.41 ± 10.39	24.86	1,388,496 ± 140,222.09
CARDIA	860	Males: 46.63 Females: 53.37	0	40.81	0	59.19	51.63 ± 3.54	22.21	1,213,145 ± 126,950.3
HANDLS	169	Males: 43.79 Females: 56.21	0	36.69	0	63.31	56.97 ± 6.65	0	1,164,199 ± 115,887.2
HCP	923	Males: 45.12 Females: 54.88	NA	NA	NA	NA	63.34 ± 11.42	0	1,409,371 ± 140,042.73
OASIS	718	Males: 42.42 Females: 57.58	0.84	15.18	0.14	83.98	68.99 ± 8.34	32.55	1,394,015 ± 144,311.51
PENN	12	Males: 50 Females: 50	0	25.00	0	75.00	69.13 ± 6.28	41.67	1,395,319 ± 152,054.99
PreventAD	341	Males: 29.33 Females: 70.67	0	0	1.17	98.82	63.64 ± 5.06	38.42	1,368,309 ± 125,066.79
SHIP	1417	Males: 47.92 Females: 52.59	0	0	0	100	59.07 ± 9.21	NA	1,225,329 ± 123,612.5
UK BIOBANK	37,894	Males: 47.41 Females: 52.59	1.34	0.61	0.90	97.12	64.08 ± 7.54	23.06	1,449,157 ± 141,275.97
WHIMS	592	Males: 0 Females: 100	1.35	2.53	2.36	93.75	73.09 ± 3.92	18.92	1,332,944 ± 97,809.41
WRAP	217	Males: 30.41 Females: 65.59	0.46	2.30	2.30	94.93	63.6 ± 6.25	36.87	1,423,501 ± 127,227.91

N = 46.288. Abbreviations: Other races: Hispanic/Latino, Native American, Multiracial, unknown, other; information about races is presented as given in the originating studies.

Table 1: **Demographic summary and volumetric measures of the WODCI sample (baseline scans).**

4 °C to isolate plasma. The resulting supernatant was then portioned into aliquots and frozen at –80 °C until further analysis. Samples were subjected to quantification using the antibody-based Olink Explore Proximity Extension Assay. Proteomic profiling was done on plasma samples from 53,014 UK Biobank participants from the baseline visit in 2007–2010 and 1173 UK Biobank participants from the imaging visit in 2014 (https://biobank.ndph.ox.ac.uk/ukb/field.cgi?id=30900). After quality control, a total of 2922 unique proteins in the baseline visit in 2007–2010, and 1463 unique proteins in the imaging visit in 2014 were measured across four panels focussing on cardiometabolic, inflammation, neurology, and oncology proteins (biobank.ndph.ox.ac.uk/ukb/ukb/docs/PPP_Phase_1_QC_dataset_companion_doc.pdf). The inter- and intraplate coefficients of variation for all Olink panels were lower than 20% and 10%, respectively. Protein levels were represented as Normalised Protein eXpression (NPX) values, calculated by dividing sample and assay counts by extension control counts, followed by log transformation. Variation within and between plates was minimised by considering the median of extension control-normalised counts, batch-specific median NPX value, and the difference of the assay-specific median NPX value of each batch (https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/Olink_1536_B0_to_B7_Normalization.pdf).

Cognitive and CSF biomarkers

We included cognitive tests provided by eight studies (ADNI, BLSA, HANDLS, HCP, OASIS, PENN, UK Biobank, and WRAP), and CSF biomarkers from the ADNI study. More details about the participants of each study can be found in Table 7. Cognitive test measurements include Trail Making Test Parts A (TMT-A) and B (TMT-B), Digit Span Forward (DSF) and Backward (DSB), and Mini-Mental Status Exam (MMSE). CSF biomarkers contain phosphorylated tau (p-tau), total tau (t-tau), and beta-amyloid (Aβ) (Fig. 2), and are measured in CSF aliquots using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) or BioPlex 100 immunoassay platform (Bio Rad, Hercules, CA, USA) with the same Luminex platform, supplied by Innogenetics (kit:INNO-BIA AlzBio3, Ghent, Belgium; for

Age group	Sample size	Sex (%)	Study	Age (years, SD)	Intracranial brain volume
Midlife	8972	Males: 33.58 Females: 66.42	ADNI = 29 AIBL = 24 BIOCARD = 65 BLSA = 123 CARDIA = 243 HANDLS = 30 HCP = 104 MESA = 24 OASIS = 46 PENN = 1 PreventAD = 88 SHIP = 232 UK BIOBANK = 7923 WHIMS = 1 WRAP = 39	57.66 ± 4.80	1,423,498 ± 136,489.85
Late-life	7651	Males: 43.28 Females: 56.72	ADNI = 279 AIBL = 225 BIOCARD = 16 BLSA = 187 CARDIA = 0 HANDLS = 4 HCP = 87 MESA = 235 OASIS = 173 PENN = 3 PreventAD = 38 SHIP = 67 UK BIOBANK = 7368 WHIMS = 151 WRAP = 17	71.14 ± 4.22	1,431,580 ± 139,312.98

Table 2: **Demographic summary of the subgroups in each age group with normal weight.**

Age group	Sample size	Sex (%)	Study	Age (years, SD)	DLICV
Midlife	9144	Males: 52.05 Females: 47.95	ADNI = 30 AIBL = 20 BIOCARD = 64 BLSA = 121 CARDIA = 296 HANDLS = 42 HCP = 106 MESA = 46 OASIS = 67 PENN = 1 PreventAD = 95 SHIP = 423 UK BIOBANK = 7787 WHIMS = 5 WRAP = 41	57.66 ± 4.81	1,453,659 ± 144,234.41
Late-life	9940	Males: 56.23 Females: 43.77	ADNI = 343 AIBL = 249 BIOCARD = 22 BLSA = 234 CARDIA = 0 HANDLS = 13 HCP = 92 MESA = 322 OASIS = 214 PENN = 4 PreventAD = 49 SHIP = 208 UK BIOBANK = 7893 WHIMS = 252 WRAP = 45	71.17 ± 4.12	1,452,121 ± 144,148.25

Table 3: **Demographic summary of the subgroups in each age group with overweight.**

research use only, assay lot #157353, calibrator lot #157379) immunoassay kit-based reagents. The kit reagents contain a mixture of three xMAP colour-coded carboxylated microspheres, each containing a bead set coupled with well-characterised capture mAbs specific for Aβ1–42, t-tau, or p-tau181.[33] For ADNI, all measures were downloaded from the LONI website (adni.loni.ucla.edu).

Statistics

Initially, we employed generalised linear models to analyse each machine learning index (SPARE-BA or SPARE-AD), with BMI groups, age, sex, intracranial volume, and interaction terms for BMI group × age, and BMI group × sex as predictors. We performed post-hoc comparisons between sex groups and BMI categories, adjusting *p* value by Tukey's test using the "emmeans" package in R. Cognitive test measurements were standardised, z-scores were calculated, and associations between BMI groups were derived from linear regression models. CSF biomarkers were log2 transformed and compared between BMI groups using linear regression. For the aforementioned regressions, BMI group, age, sex, and intracranial volume were used as covariates. These covariates are selected based on expertise and the existing literature.

The first proteomic analysis examined 2922 proteins in 5021 participants at the baseline visit and 1460 proteins in 1028 participants at the imaging visit. Then, we used generalised linear models with SPARE-BA as output and each protein, BMI (continuous), age, sex, and intracranial volume as predictors. Similarly, for each protein biomarker we used generalised linear models with SPARE-AD as output and each protein, BMI (continuous), age, sex, and intracranial volume as predictors. For each proteomic feature, adjusted standard deviation (SD) differences and 95% confidence interval (CI) associated with one SD change BMI (SD = 4.2 kg/m^2) were estimated with BMI (continuous), age, and sex as predictors in the linear regression. Results with false discovery rate (FDR) values of <0.05 were considered significant.

We undertook mediation analysis to estimate the proportion of the effect of the BMI on brain ageing mediated by each significant protein from both visits using the mediation package in R. For this analysis, we used BMI measurements from the baseline visit and protein measurements from blood collected at the imaging visit from UKB participants and SPARE-BA from the imaging visit in 2014. In total, 4951 participants had both BMI baseline measurements and SPARE-BA values during the imaging visit. First, we estimated the effect of BMI separately on each protein using a linear regression model. Next, we fitted a second regression model to estimate the effect of BMI on brain ageing. The mediation function was then used to decompose the total effect of BMI on brain ageing into

an average causal mediation effect (ACME) and an average direct effect (ADE), with nonparametric bootstrapping (1000 simulations) to calculate CIs. The proportion of the total effect mediated by each protein was calculated as the ratio of the ACME to the total effect. In all regressions age, sex, and intracranial volume were used as covariates. All analyses were done using R studio (version 2022.12.0+353).

Ethics

The protocols of this study were approved by the University of Pennsylvania Institutional Review Board (reference number: 825722). Participants provided written informed consent to the corresponding studies.

Role of funders

Funders for the current study were not directly involved in the design, data collection, analysis, interpretation or writing of this manuscript.

Results

AD-like brain atrophy indices and BMI categories

This study included MRI scans from 17,822 participants with normal-weight, 19,084 with overweight, and 9382 participants with obesity, with a mean [SD] age of 64.35 [8.11] years, 64.7 [8.09], and 63.54 [8.18], respectively. Fig. 1 depicts a flowchart with inclusion and exclusion criteria. Participant characteristics at baseline scan can be found in Tables 1–4. Overall participants with obesity presented a significant association with brain ageing when compared to participants with normal weight (β = 11.20; SE = 1.13; $p_{adj} < 0.001$, Tukey's test), and to participants with overweight (β = 8.17; SE = 1.11; $p_{adj} < 0.001$, Tukey's test). Participants with overweight displayed higher brain ageing values than participants with normal weight (β = 3.04; SE = 0.927; $p_{adj} = 0.003$, Tukey's test) (Fig. 3). BMI group and age interaction: (Overweight: β = –0.072; SE = 0.113; $p = 0.525$ generalised linear models, Obesity: β = –0.277; SE = 0.137; $p = 0.043$ generalised linear models). Among males, obesity was associated with increased SPARE-BA when compared to normal weight (β = 21.39; SE = 1.71; $p_{adj} < 0.001$, Tukey's test), and overweight (β = 12.63; SE = 1.59; $p_{adj} < 0.001$, Tukey's test) (Fig. 3c). Males with overweight exhibited higher SPARE-BA values than males with normal weight (β = 8.76; SE = 1.37; $p_{adj} < 0.001$, Tukey's test). Females with obesity showed higher SPARE-BA values in comparison to females with overweight (β = 3.70; SE = 1.55; $p_{adj} = 0.044$, Tukey's test). Furthermore, in the normal-weight group, females showed higher SPARE-BA values than males (β = 8.29; SE = 1.51; $p_{adj} < 0.001$, Tukey's test). Males compared to females showed increased SPARE-BA in the group with obesity (β = 12.08; SE = 1.94; $p_{adj} < 0.001$, Tukey's test), and in the overweight group (β = 3.15; SE = 1.44; $p_{adj} = 0.029$, Tukey's test) (Fig. 3d).

Age group	Sample size	Sex (%)	Study	Age (years, SD)	DLICV
Midlife	5035	Males: 44.09 Females: 55.91	ADNI = 26 AIBL = 11 BIOCARD = 35 BLSA = 92 CARDIA = 321 HANDLS = 70 HCP = 77 MESA = 45 OASIS = 70 PENN = 0 PreventAD = 48 SHIP = 329 UK BIOBANK = 3869 WHIMS = 1 WRAP = 41	57.23 ± 4.94	1,431,021 ± 148,293.75
Late-life	4347	Males: 48.03 Females: 51.97	ADNI = 201 AIBL = 105 BIOCARD = 7 BLSA = 124 CARDIA = 0 HANDLS = 10 HCP = 46 MESA = 251 OASIS = 149 PENN = 3 PreventAD = 23 SHIP = 158 UK BIOBANK = 3054 WHIMS = 182 WRAP = 34	70.84 ± 4.08	1,430,786 ± 145,615.76

Table 4: **Demographic summary of the subgroups in each age group with obesity.**

In contrast, females in the normal-weight group exhibited higher SPARE-AD values than females in the overweight group (β = 0.02; SE = 0.005; $p_{adj} = 0.002$, Tukey's test) (Fig. 3e). Males in the obesity group showed higher SPARE-AD than males with normal-weight (β = 0.02; SE = 0.007; $p_{adj} = 0.041$, Tukey's test) (Fig. 3e). Additionally, females displayed higher values of SPARE-AD than males in the normal-weight group (β = 0.02; SE = 0.006; $p_{adj} = 0.009$, Tukey's test), but in the overweight group males showed higher SPARE-AD values (β = –0.01; SE = 0.006; $p_{adj} = 0.045$, Tukey's test) than females (Fig. 3f). BMI group and age interaction: (Overweight: β = –0.006; SE = 0.006; $p = 0.303$, generalised linear models, Obesity: β = –0.019; SE = 0.007; $p = 0.008$, generalised linear models). Age-stratified analysis of brain atrophy indices, and association with neurodegeneration biomarkers and cognitive tests can be found in the Supplementary Analysis s1 and s2, Supplementary Tables s1 and s2, and Supplementary Figures s1–s3.

Proteomic markers and brain ageing

After adjusting for multiple comparisons, significant positive associations between brain ageing and 191 of the 2922 protein biomarkers were identified at the baseline visit (at a 5% FDR; Fig. 4a). Among these, 50 proteins showed a positive significant association with

Study	Scanner	T1 resolution
ADNI-1	1.5T General Electric, Phillips, and Siemens	0.94 × 0.94 × 1.2 mm
ADNI-GO/ADNI-2	3T General Electric, Philips, and Siemens	1 × 1 × 1.2 mm
ADNI-3	3T General Electric, Phillips, and Siemens	1 × 1 × 1/1.2 mm
AIBL	1.5T and 3T Siemens, Avanto, TrioTim, Verio	1 × 1 × 1.2 mm
BIOCARD-1.5T	1.5T General Electric	1 × 1 × 2 mm
BIOCARD-3T	3T Philips, Achieva	1 × 1 × 1.2 mm
BLSA-1.5T	1.5T General Electric Signa	0.94 × 0.94 × 1.5 mm
BLSA-3T	3T Philips	1 × 1 × 1.2 mm
CARDIA	3T Siemens Tim Trio, Philips, Achieva	1 × 1 × 1 mm
HANDLS	3T Siemens Trio	1 × 1 × 1 mm
HCP	3T Siemens Prisma (VE11C)	0.7 × 0.7 × 0.7 mm
MESA	3T Siemens Prisma (VE11C), Siemens Skyra (VD11B)	1 × 1 × 1 mm
OASIS 1.5T	1.5T Siemens	1 × 1 × 1.25 mm
OASIS 3T	3T Siemens	1 × 1 × 1 mm
PENN	3T Siemens Trio	1 × 1 × 1 mm
PreventAD	3T Siemens Trio	1 × 1 × 1 mm
SHIP	1.5T Siemens Magnetom Avanto	1 × 1 × 1 mm
UK BIOBANK	3T Siemens Skyra (VD13)	1 × 1 × 1 mm
WHIMS	1.5T General Electric, Philips, and Siemens	1 × 1 × 1.5 mm
WRAP	3T General Electric, Discovery	1 × 1 × 1 mm

Detailed information about each study protocol can be found in.[25,26]

Table 5: **Imaging parameters of the individual studies included in the iSTAGING consortium.**

both brain ageing and BMI (per one standard deviation increase in BMI as a continuous variable) (Fig. 4b), and 43 proteins demonstrated a negative association with both brain ageing and BMI (Fig. 4b). Growth/differentiation factor 15 (GDF15) was the only protein significantly associated with AD-like brain atrophy (Fig. 4c).

At the imaging visit, 215 of the 1460 protein biomarkers exhibited significant associations with brain ageing (at a 5% FDR; Fig. 4d). Of these, 10 proteins were positively correlated, and 205 proteins were negatively correlated with brain ageing (Fig. 4d). Among the 10 proteins positively associated with brain ageing, eight also showed a significant positive association with BMI. In contrast, from the 205 proteins negatively associated with brain ageing, nine proteins also demonstrated a negative association with BMI (Fig. 4e). At the imaging visit, no protein displayed a significant association with AD-like brain atrophy after adjusting for multiple comparisons (Fig. 4f).

At both visits, five proteins were positively associated with brain ageing, while 15 proteins were negatively associated with brain ageing, all at a 5% FDR correction level (Fig. 5a). All of the five proteins that were associated positively with brain ageing, also demonstrated a significant positive association with BMI (per one SD increase in BMI as a continuous variable): Oxytocin-neurophysin 1 (OXT), chitinase-3-like protein 1 (CHI3L1), GDF15, Polymeric immunoglobulin receptor (PIGR), Lymphocyte antigen 96 (LY96) (at 5% FDR; Fig. 5a, Table 8). On the other hand, eight proteins were associated negatively with both brain ageing and BMI decrease by 1-SD: CD58, Integrin a-11 (ITGA11), CD34, CD200, Seizure protein six homologue (SEZ6L), brevican core protein (BCAN), neurocan core protein (NCAN), Kit ligand (KITLG) (at 5% FDR; Fig. 5a, Table 8). Proteins associated with brain ageing were further investigated regarding their association with BMI categories (Fig. 5b).

We examined the mediating effects of each of the proteins that displayed significant association with brain ageing in both visits (LY96, GDF15, PIGR, CHI3L1, OXT, ITGA11, CD34, CD200, SEZ6L, BCAN, CNTN5, NCAN, and KITLG) on the association between BMI and brain ageing, as measured by the SPARE-BA score (Supplementary Figure s4). The average causal mediation effect (ACME) was statistically significant for all proteins included, indicating that each protein mediates a portion of BMI's impact on brain ageing. In contrast, the average direct effect (ADE) was not significant, suggesting that BMI's influence on brain ageing may occur primarily through other pathways rather than direct pathways. The total effect of BMI on brain ageing was also nonsignificant, while the proportion of the total effect mediated was nonsignificant (Supplementary Tables s3–s15).

Discussion

This multi-cohort study, including 46,288 adults, aims to compare MRI-brain ageing indices in participants with obesity or overweight and elucidate the associations between proteomic features and these MRI-brain ageing indices. Our analysis of this large, diverse MRI dataset revealed that the impact of obesity on brain ageing, and AD-like brain atrophy is more pronounced in males than females, and its effects are weaker with increasing age. Moreover, higher BMI states are linked to accelerated brain ageing and AD-like brain atrophy, especially in males, whereas females with normal-weight exhibited greater brain ageing and AD-like brain atrophy compared to their male counterparts with normal-

Grey and white matter anatomic ROIs				
3rd Ventricle	Lateral orbital gyrus (R)	4th Ventricle	Lateral orbital gyrus (L)	Accumbens area (R)
Middle cingulate gyrus (R)	Accumbens area (L)	Middle cingulate gyrus (L)	Amygdala (R)	Medial frontal cortex (R)
Amygdala (L)	Medial frontal cortex (L)	Brain Stem	Middle frontal gyrus (R)	Caudate (R)
Middle frontal gyrus (L)	Caudate (L)	Middle occipital gyrus (R)	Cerebellum exterior (R)	Middle occipital gyrus (L)
Cerebellum exterior (L)	Medial orbital gyrus (R)	Cerebellum WM (R)	Medial orbital gyrus (L)	Cerebellum WM (L)
Postcentral gyrus medial segment (R)	Hippocampus (R)	Postcentral gyrus medial segment (L)	Hippocampus (L)	Precentral gyrus medial segment (R)
Inferior lateral ventricle (R)	Precentral gyrus medial segment (L)	Inferior lateral ventricle (L)	Superior frontal gyrus medial segment (R)	Lateral ventricle (R)
Superior frontal gyrus medial segment (L)	Lateral ventricle (L)	Middle temporal gyrus (R)	Pallidum (R)	Middle temporal gyrus (L)
Pallidum (L)	Occipital pole (R)	Putamen (R)	Occipital pole (L)	Putamen (L)
Occipital fusiform gyrus (R)	Thalamus (R)	Occipital fusiform gyrus (L)	Thalamus (L)	Opercular part of the inferior frontal gyrus (R)
Ventral DC (R)	Opercular part of the inferior frontal gyrus (L)	Ventral DC (L)	Orbital part of the inferior frontal gyrus (R)	Cerebellar Vermal Lobules I–V
Orbital part of the inferior frontal gyrus (L)	Cerebellar Vermal Lobules VI–VII	Posterior cingulate gyrus (R)	Cerebellar Vermal Lobules VIII–X	Posterior cingulate gyrus (L)
Basal forebrain (L)	Praecuneus (R)	Basal forebrain (R)	Praecuneus (L)	Frontal lobe WM (R)
Parahippocampal gyrus (R)	Frontal lobe WM (L)	Parahippocampal gyrus (L)	Occipital lobe WM (R)	Posterior insula (R)
Occipital lobe WM (L)	Posterior insula (L)	Parietal lobe WM (R)	Parietal operculum (R)	Parietal lobe WM (L)
Parietal operculum (L)	Temporal lobe WM (R)	Postcentral gyrus (R)	Temporal lobe WM (L)	Postcentral gyrus (L)
Fornix (R)	Posterior orbital gyrus (R)	Fornix (L)	Posterior orbital gyrus (L)	Anterior limb of internal capsule (R)
Planum polare (R)	Anterior limb of internal capsule (L)	Planum polare (L)	Posterior limb of internal capsule inc. cerebral peduncle (R)	Precentral gyrus (R)
Posterior limb of internal capsule inc. cerebral peduncle (L)	Precentral gyrus (L)	Corpus callosum	Planum temporale (R)	Anterior cingulate gyrus (R)
Planum temporale (L)	Anterior cingulate gyrus (L)	Subcallosal area (R)	Anterior insula (R)	Subcallosal area (L)
Anterior insula (L)	Superior frontal gyrus (R)	Anterior orbital gyrus (R)	Superior frontal gyrus (L)	Anterior orbital gyrus (L)
Supplementary motor cortex (R)	Angular gyrus (R)	Supplementary motor cortex (L)	Angular gyrus (L)	Supramarginal gyrus (R)
Calcarine cortex (R)	Supramarginal gyrus (L)	Calcarine cortex (L)	Superior occipital gyrus (R)	Central operculum (R)
Superior occipital gyrus (L)	Central operculum (L)	Superior parietal lobule (R)	Cuneus (R)	Superior parietal lobule (L)
Cuneus (L)	Superior temporal gyrus (R)	Entorhinal area (R)	Superior temporal gyrus (L)	Entorhinal area (L)
Temporal pole (R)	Frontal operculum (R)	Temporal pole (L)	Frontal operculum (L)	Triangular part of the inferior frontal gyrus (R)
Frontal pole (R)	Triangular part of the inferior frontal gyrus (L)	Frontal pole (L)	Transverse temporal gyrus (R)	Fusiform gyrus (R)
Transverse temporal gyrus (L)	Fusiform gyrus (L)	Gyrus rectus (R)	Gyrus rectus (L)	Inferior occipital gyrus (R)
Inferior occipital gyrus (L)	Inferior temporal gyrus (R)	Inferior temporal gyrus (L)	Lingual gyrus (R)	Lingual gyrus (L)

Abbreviations: GM, Grey Matter; WM, White Matter; DC, Diencephalon; (L), Left hemisphere; (R), Right hemisphere.

Table 6: **ROIs used in general linear models.**

	Total Tau	p-Tau	Beta amyloid	CVLT	MMSE	DSB	DSF	TMT-B	TMT-A
Total participants	723	725	725	834	980	1023	1025	25,388	25,972
Participants per study	ADNI = 388	ADNI = 390	ADNI = 390	AIBL = 10 BLSA = 823 WHIMS = 1	ADNI = 35 AIBL = 10 BLSA = 755 HANDLS = 150 OASIS = 12 PENN = 11 WRAP = 7	ADNI = 3 AIBL = 6 BLSA = 845 HANDLS = 138 OASIS = 13 PENN = 10 WHIMS = 1 WRAP = 7	ADNI = 3 AIBL = 6 BLSA = 846 HANDLS = 139 OASIS = 13 PENN = 10 WHIMMS = 1 WRAP = 7	ADNI = 10 BLSA = 852 HANDLS = 157 HCP = 509 OASIS = 13 PENN = 10 UK BIOBANK = 23,830 WRAP = 7	ADNI = 10 BLSA = 858 HANDLS = 158 HCP = 508 OASIS = 13 PENN = 10 UK BIOBANK = 24,408 WRAP = 7

If there was a mismatch between scan acquisition dates and those non-imaging feature measurement dates and BMI measurement dates, the search window for matching imaging and non-imaging data was set to 730 days (2 years). Abbreviations: CVLT, California Verbal Learning Test; MMSE, Mini-Mental State Examination; DSB, Digit Span Backward; DSF, Digit Span Forward; TMT-B, Trail Making Test B; TMT-A, Trail Making Test A.

Table 7: **Cognitive and CSF biomarker status data availability for the N = 46.288 WODCI participants within two years of the baseline brain MRI scan.**

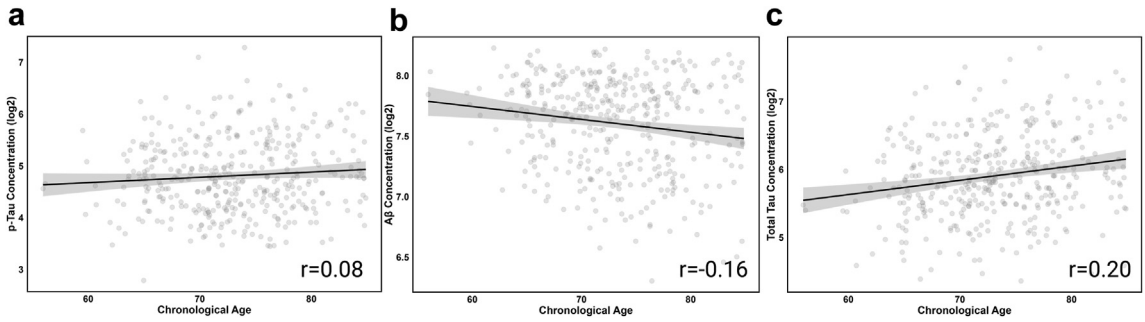

Fig. 2: a) Scatter plot of p-Tau concentration (log2) and chronological age. b) Scatter plot of Aβ concentration (log2) and chronological age. c) Scatter plot of total Tau concentration (log2) and chronological age. The r corresponds to Pearson's r coefficient.

weight. Furthermore, proteomic investigations of two time-points revealed five proteins that are associated positively with both brain ageing and BMI, and eight proteins associated negatively with brain ageing and BMI.

The Lancet Commission estimated that 45% of global dementia cases could be attributed to 14 factors across three life stages: early life, midlife, and late life. Notable were cardiometabolic factors such as high LDL-C, diabetes, hypertension, and obesity primarily affecting midlife adults.[12] Previous research has yielded conflicting results regarding the association between BMI and dementia risk, showing that midlife obesity displays a higher risk for dementia in a 27-year longitudinal population cohort,[34] a result supported by a recent meta-analysis.[35] On the contrary, a large UK cohort study of 2 million participants showed that dementia risk is lower in obesity and falls for every increasing BMI group in a median follow-up of 9.1 years.[36] Shedding light on the existing contradictory evidence about the association of BMI with dementia, a US cohort of 1.3 million suggested that a higher BMI

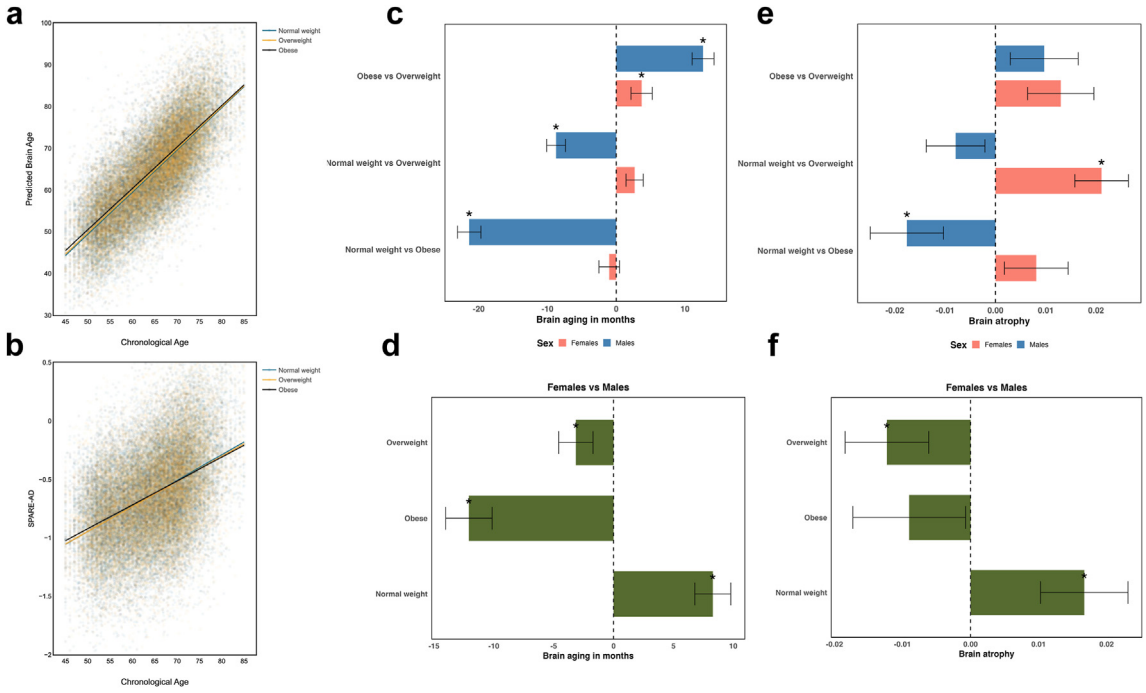

Fig. 3: a) Scatter plot of chronological age and predicted age for each BMI category (normal weight, overweight, obesity). b) Scatter plot of chronological age and SPARE-AD for each BMI category (normal weight, overweight, obesity). c) Bar plot of SPARE-BA between BMI categories in males and in females. d) Bar plot of SPARE-BA of males versus females in each BMI category. e) Bar plot of SPARE-AD between BMI categories in males and in females. f) Bar plot of SPARE-AD of males versus females in each BMI category. Asterisk (*) is put above the bar plot where FDR-adjusted *p*-value is <0.05.

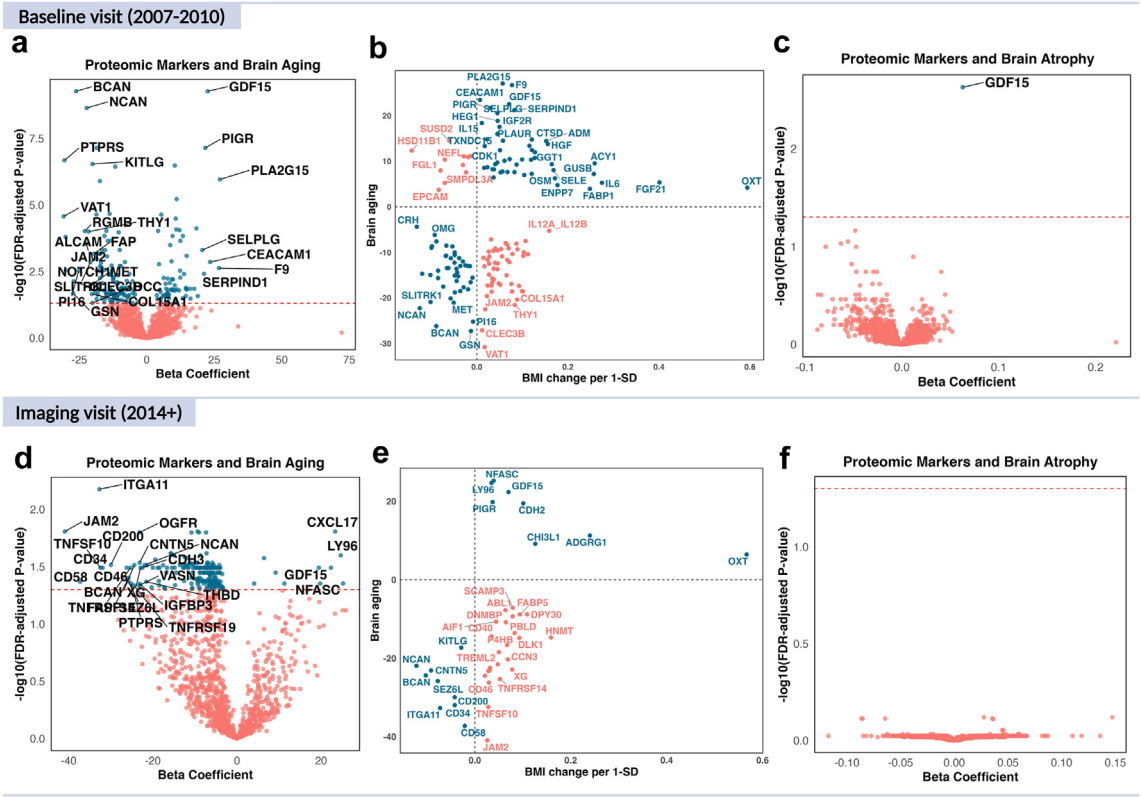

Fig. 4: a) Volcano plot showing the proteins associated with brain ageing (expressed in months) at the baseline visit; the top 25 proteins are labelled. b) Scatter plot of the FDR < 0.05 adjusted proteins associated with both brain ageing and BMI change per 1-SD at the baseline visit. c) Volcano plot showing the proteins associated with brain atrophy at the baseline visit. d) Volcano plot showing the proteins associated with brain ageing (expressed in months) at the imaging visit; the top 25 proteins are labelled. e) Scatter plot of the FDR < 0.05 adjusted proteins associated with both brain ageing and BMI change per 1-SD at the imaging visit. f) Volcano plot showing the proteins associated with brain atrophy at the imaging visit.

measured more than 20 years before dementia diagnosis is associated with higher risk, while a higher BMI measured within 10 years of dementia diagnosis is associated with a lower risk.[37] This suggests that high BMI is directly linked with an increased risk for dementia and that the reduced risk for dementia in obesity may be a result of reverse causation, influenced by the weight loss in the preclinical phase of dementia,[36] which usually precedes 20–30 years before its clinical manifestation.[38] Notably, BMI typically declines several years before a mild cognitive impairment diagnosis,[17] and continues to decrease at a similar rate in both individuals who progress to dementia and those who do not.[17] In alignment with the Lancet's Commission's findings and our own research using imaging and ML-derived brain ageing indices, obesity both in midlife and in late life, appears to contribute to the acceleration of brain ageing in individuals without diagnosed cognitive impairment,[12,25] displaying inferior performance in cognitive tests in comparison with individuals with normal-weight, and we showed that the effects of obesity on brain ageing, and AD-like brain atrophy are weaker with increasing age, with significant sex differences. Furthermore, weight loss in participants with obesity has been shown to decrease the risk for AD.[39] Additionally, a combination of modest caloric restriction and the Mediterranean-Dietary Approaches to Stop Hypertension (DASH) diet intervention for neurodegenerative delay (MIND) diet in individuals with obesity showed improved cognitive outcomes, suggesting a potential reversal of the negative effects of obesity on the brain and cognition.[40,41] Recent studies have also highlighted the potential protective effects of weight loss medications like glucagon-like peptide 1 (GLP-1) analogues in reducing dementia incidence.[42,43]

Sex differences impact dementia risk, but their specific way of influencing it remains elusive. While men have higher rates of alcohol use, more years of education, and a stronger association between APOE4 carriage and dementia risk compared to women,[44] the prevalence of Alzheimer's disease and related dementias (ADRDs) is higher in women. However, the

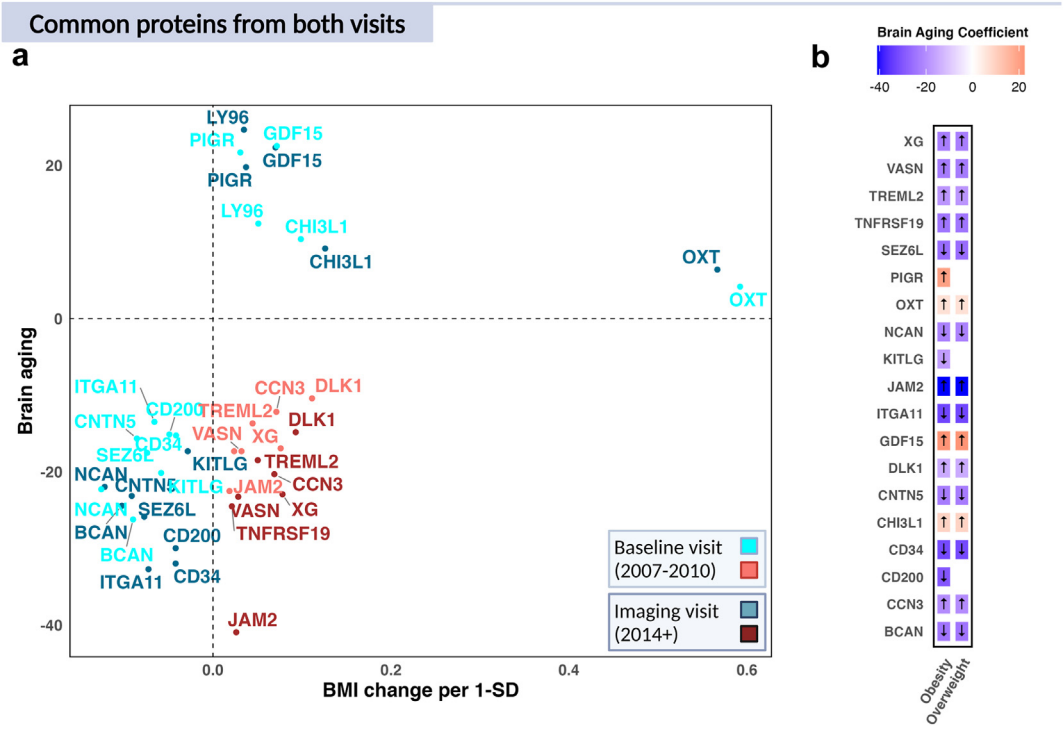

Fig. 5: a) Volcano plot of the proteins associated with brain ageing and BMI change per 1-SD at both baseline and imaging visit. b) Heatmap of the FDR < 0.05 adjusted proteins associated with brain ageing, showing if they are expressed in obesity or in overweight in comparison with controls with normal weight.

population-attributable risk for dementia is higher in men.[45] A US cohort study suggested that men have a higher midlife dementia risk, potentially due to women having fewer cardiovascular risk factors such as coronary artery disease, myocardial infarction, and heart failure which may mitigate their dementia risk.[46] Our findings align with these observations, showing that patterns of brain ageing and AD-like brain atrophy are

Protein	Brain ageing (months)	SE	FDR adjusted p-value	BMI adjusted SD (95% CI)	FDR adjusted p-value	Brain ageing (months)	SE	FDR adjusted p-value	BMI adjusted SD (95% CI)	FDR adjusted p-value
Baseline visit						Imaging visit				
Proteins associated positively with both brain ageing and BMI										
LY96	12.4	3.3	5.41e-03	0.05 (0.04, 0.05)	8.73e-19	24.7	6.7	0.025	0.035 (0.029, 0.041)	6.96e-03
GDF15	22.5	3.1	5.30c-10	0.07 (0.07, 0.07)	3.58e-33	22.3	7.1	0.032	0.070 (0.065, 0.076)	3.22e-09
PIGR	21.7	3.4	7.07e-08	0.03 (0.03, 0.03)	4.38e-08	19.8	7.1	0.044	0.037 (0.032, 0.043)	2.20e-03
CHI3L1	10.4	1.7	3.28e-07	0.099 (0.094, 0.104)	8.91e-19	9.2	3.1	0.036	0.126 (0.113, 0.139)	5.90e-06
OXT	4.2	0.8	9.96e-07	0.59 (0.58, 0.60)	9.46e-153	6.4	1.8	0.027	0.567 (0.545, 0.589)	4.99e-30
Proteins associated negatively with both brain ageing and BMI										
ITGA11	−13.47	3.5	4.19e-03	−0.07 (−0.07, −0.06)	6.53e-34	−32.7	7.1	0.007	−0.072 (−0.078, −0.067)	2.4e-09
CD34	−15.2	4.9	3.22e-02	−0.04 (−0.04, −0.04)	6.87e-27	−32	10.1	0.032	−0.042 (−0.046, −0.038)	9.56e-07
CD200	−15.1	4.5	1.97e-02	−0.05 (−0.05, −0.05)	5.51e-32	−30	8.8	0.031	−0.042 (−0.046, −0.037)	2.04e-05
SEZ6L	−17.5	4.4	2.93e-03	−0.07 (−0.08, −0.07)	2.00e-66	−25.8	9.1	0.042	−0.077 (−0.081, −0.073)	6.67e-16
BCAN	−26.2	3.6	5.3e-10	−0.09 (−0.09, −0.09)	1.81e-63	−24.4	7.2	0.031	−0.102 (−0.108, −0.097)	1.09e-16
CNTN5	−15.6	3.2	1.47e-06	−0.09 (−0.09, −0.08)	1.81e-48	−23	6.5	0.029	−0.091 (−0.097, −0.085)	8.56e-12
NCAN	−22.3	3.2	2.3e-09	−0.13 (−0.13, −0.12)	3.77e-98	−21.9	6.6	0.031	−0.122 (−0.128, −0.116)	8.75e-20
KITLG	−20.1	3.3	2.9e-07	−0.06 (−0.06, −0.06)	2.99e-24	−17	6.4	0.048	−0.028 (−0.034, −0.022)	3.36e-02

Table 8: **Common proteins associated with both positive and negative brain ageing and BMI change per 1-SD in the baseline (2007–2010) and imaging visit (2014+).**

more prevalent in males than in females with obesity or overweight, but females with normal-weight displayed more brain ageing and AD-like brain atrophy compared to males with normal weight. This finding may suggest that weight gain influences brain ageing trajectories differently in males and females, with males exhibiting greater brain ageing and AD-like atrophy at higher BMI levels, while among participants with normal weight, females show greater brain ageing and AD-like atrophy.

So far, it remains unclear whether obesity and age synergistically or additively exacerbate structural brain ageing.[47] While some studies suggest a borderline causal significance of BMI on the white matter-brain age gap,[48] and a 10-year brain age gap both in middle-aged individuals with obesity or overweight,[49] other mechanisms likely contribute more significantly to cognitive decline in obesity. Specifically, metabolic syndrome, characterised by insulin resistance, is increasingly implicated in the development and progression of AD.[50] Specifically, it is postulated that insulin resistance comprises the key link between metabolic syndrome and AD due to the several roles that brain insulin signalling plays, i.e., the regulation of food intake, body weight, reproduction, and learning and memory.[51,52] For instance, brain insulin resistance, referred to also as central insulin resistance, can manifest as impaired central and peripheral regulation of nutrient partitioning, cognitive and mood dysfunction, and brain-specific neuropathology and neurodegeneration,[53] through an increase in neuronal vulnerability, the accumulation of amyloid-β plaques, tau phosphorylation, neurofibrillary lesions, α-synuclein lesions although evidence is yet inconsistent.[53,54] In our study, participants with obesity or overweight did not show any difference in total tau, p-tau, or amyloid-β measurements in their CSF compared to participants with normal-weight, except that amyloid-β appeared to be elevated in individuals with overweight compared to controls with normal-weight. Additionally, another potential pathophysiological explanation for the increased brain ageing in these states derives from the action of proinflammatory adipokines and cytokines that trigger, in addition to insulin resistance, an inflammatory response in microglia, inducing a self-sustaining feedback loop of additional cytokines and inflammation-associated with white matter changes.[50,55–61]

Our proteomic analysis identified GDF15 as significantly associated with AD-like brain atrophy in one of the two visits. GDF15, a cytokine in the transforming growth factor β superfamily, is linked to decreased brain volume in Alzheimer's-affected regions.[62] Elevated in inflammatory states, GDF15 poses a high risk for AD-like brain atrophy patterns[63,64] and influences food intake and energy balance, acting as an anorectic peptide.[65] High serum levels correlate with poor neurocognitive performance and increased dementia risk, and plasma GDF15 levels have also shown a significant linear correlation with BMI ($R^2 = 0.097$; $p = 0.0049$).[66,67] GDF15 is upregulated in neurodegenerative disorders, suggesting its potential as a diagnostic marker[68] and predicting dementia up to 25 years before onset.[18] In the brain, higher ectodysplasin A2 receptor (EDA2R) levels correlate with reduced total brain volume.[69–71]

Additionally, we demonstrated that only five proteins were significantly associated with an increase both in brain ageing and in BMI per 1-SD in both proteomic investigations, i.e., LY96, GDF15, PIGR, CHI3L1, and OXT. LY96, a protein playing a crucial role in the innate immune response against bacterial lipopolysaccharides, age-related immune alterations and increased infiltration of peripheral immune cells like T cells and B cells into the aged brain were previously reported, however, to the best of our knowledge, no study has specifically reported LY96 levels in brain ageing.[72] GDF15 was shown herein to be associated with brain ageing, which aligns with previous research.[73] Evidence of PIGR regarding neurodegeneration and ageing is lacking. Similarly, CHI3L1 is an inflammatory marker increased in obesity and diabetes and related to insulin resistance; it has been frequently investigated in body fluids as a surrogate marker of neuroinflammation in AD and other neurological disorders, with our results demonstrating an association with brain ageing of nine months.[74,75] Additionally, oxytocin, although physiologically reduces food intake and increases energy expenditure, is found to be increased in plasma in obesity.[76] With ageing, substantial changes emerge in the oxytocinergic system and neural circuitry mediating oxytocin's effects; with previous literature suggesting OXT's associations with age-related structural brain changes, herein it is demonstrated for the first time that OXT is associated with six months of brain ageing.[77,78]

In contrast, eight proteins, ITGA11, CD34, CD200, SEZL6, BCAN, CNTN5, NCAN, and KITLG were identified as linked with a decrease in the brain age and BMI per 1-SD. Specifically, ITGA11 has been shown to be significantly associated with decreased odds of incident cognitive impairment.[79] Another study found significantly reduced counts of circulating CD34+ cells in early AD, which significantly correlated with age ($r = -0.66$; $p = 0.001$), cerebrospinal fluid β-amyloid (Aβ) 1–42 ($r = -0.47$; $p = 0.025$), and most pronounced the Aβ42/40 ratio ($r = -0.69$; $p = 0.005$).[80] Additionally, studies have shown that in patients with AD, there is a marked decrease in CD200 and CD200 receptor expression, which may contribute to a pro-inflammatory state in human neurodegenerative diseases.[81] BCAN has been shown to be causally associated with brain age gap, and its dysregulation affects multiple cortical and subcortical structures.[82] Besides, the rs1461684 G variant of the *CNTN5* gene has been associated with an increased risk of sporadic AD and faster disease progression in individuals without cognitive impairments.[83] KITLG was found to be differently expressed between controls and participants with mild cognitive

impairment.[84] SEZL6, NCAN, and FGFBP1 have not been observed to decrease the risk of neurocognitive disorders. The mediation analysis of the effect of the significant proteins on the relationship between BMI and brain ageing suggested that these proteins have a significant effect separately but the influence of BMI on brain ageing may occur primarily through other pathways.

This study has several strengths, including the large, diverse, multisite sample covering a wide age range, and the use of advanced harmonisation methods. However, this study also presents with limitations. First, the associations between the brain atrophy index (SPARE-AD) and BMI groups reflect brain atrophy patterns observed in AD dementia and not necessarily other dementia subtypes. Second, although the UK Biobank provides a comprehensive assessment of circulating proteins, not all the human proteome is captured within this platform, and biases may be present in the priority of measuring secreted proteins. Third, there was no external validation dataset from another country to replicate our findings, which could impact the results' generalisability. Fourth, the lack of long-term follow-up prevents the derivation of robust conclusions regarding the clinical progression. Furthermore, no causal relationship can be inferred from the proteomic associations, warranting additional genomic studies and the elucidation of potential sex-specific mechanisms. Lastly, the mediation analysis of the role of each protein in the relationship between BMI and brain ageing does not address whether other conditions are implicated to this relationship, such as atherosclerotic disease, vascular infarcts, and other cerebrovascular abnormalities related to brain ageing.

In this multi-cohort study, we showed that higher BMI states are associated with faster brain ageing and increased AD-like brain atrophy, particularly in males, while females with normal-weight showed more pronounced brain ageing and AD-like brain atrophy than males with normal-weight males. Second, proteomic analysis revealed 20 proteins postulated to be implicated in the pathophysiological mechanism of brain ageing and AD-like brain atrophy.

Contributors

FA and CD carried out the acquisition, analysis, or interpretation of data. FA and MK wrote the first draft. All authors read and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no authors meeting the criteria have been omitted.

Data sharing statement

Imaging and clinical data used in this study were provided by several individual studies via data-sharing agreements, which do not include permission for us to further share the data. Investigators must apply to the source data providers to access additional data and match their subject IDs to those used in this study under the current protocol (primarily for UKBB). Data from ADNI are available from the ADNI database (adni.loni.usc.edu) upon registration and compliance with the data usage agreement. Data from the UKBB are available upon request from the UKBB website (https://www.ukbiobank.ac.uk/). Data from the BLSA study are available upon request at https://www.blsa.nih.gov/how-apply. Data from the AIBL study are available upon request at https://aibl.org.au/. Data from the OASIS study are available upon request at https://www.oasis-brains.org/. Data requests for BIOCARD, HANDLS, PENN, WRAP, CARDIA, PreventAD, SHIP, and WHIMS datasets should be directed to the corresponding author (CD) who will direct them to appropriate PIs. The R code can be assessed in the following link: https://github.com/FilipposAna/Radiomic_signatures.

Declaration of interests

IMN is an expert reader in Clariti, has received payments from Subtle Medical, Inc. for consulting, has served in the advisory board in Eisai and Premier Inc., and has done educational speaking for Peerview. IMN and DT declare that the University of Pennsylvania receives NIH grants RF1AG054409, U24NS130411. DT receives consulting fees from Roche, Veravas, and Alzheon Imaging, and honoraria from the University of Pennsylvania. KAW serves in the board of directors in the National Academy of Neuropsychology. All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105763.

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