SSM - Population Health 26 (2024) 101655

Contents lists available at ScienceDirect

SSM - Population Health

journal homepage: www.elsevier.com/locate/ssmph

Pathways explaining racial/ethnic and socio-economic disparities in brain white matter integrity outcomes in the UK Biobank study

Jordan Weiss [a,1], May A. Beydoun [b,*,1,2], Hind A. Beydoun [b], Michael F. Georgescu [b], Yi-Han Hu [b], Nicole Noren Hooten [b], Sri Banerjee [c], Lenore J. Launer [b], Michele K. Evans [b], Alan B. Zonderman [b]

[a] Stanford Center on Longevity, Stanford University, Stanford, CA, USA
[b] Laboratory of Epidemiology and Population Sciences, National Institute on Aging, NIA/NIH/IRP, USA
[c] Public Health Doctoral Programs, Walden University, Minneapolis, MN, USA

ARTICLE INFO

Key terms:
Racial disparities
Socio-economic status
Aging
Magnetic resonance imaging
White matter integrity

ABSTRACT

Pathways explaining racial/ethnic and socio-economic status (SES) disparities in white matter integrity (WMI) reflecting brain health, remain underexplored, particularly in the UK population. We examined racial/ethnic and SES disparities in diffusion tensor brain magnetic resonance imaging (dMRI) markers, namely global and tract-specific mean fractional anisotropy (FA), and tested total, direct and indirect effects through lifestyle, health-related and cognition factors using a structural equations modeling approach among 36,184 UK Biobank participants aged 40–70 y at baseline assessment (47% men). Multiple linear regression models were conducted, testing independent associations of race/ethnicity, socio-economic and other downstream factors in relation to global mean FA, while stratifying by Alzheimer's Disease polygenic Risk Score (AD PRS) tertiles. Race (Non-White vs. White) and lower SES predicted poorer WMI (i.e. lower global mean FA) at follow-up, with racial/ethnic disparities in FA_{mean} involving multiple pathways and SES playing a central role in those pathways. Mediational patterns differed across tract-specific FA outcomes, with SES-FA_{mean} total effect being partially mediated (41% of total effect = indirect effect). Furthermore, the association of poor cognition with FA_{mean} was markedly stronger in the two uppermost AD PRS tertiles compared to the lower tertile (T_2 and T_3: β±SE: −0.0009 ± 0.0001 vs. T_1: β±SE: −0.0005 ± 0.0001, $P < 0.001$), independently of potentially confounding factors. Race and lower SES were generally important determinants of adverse WMI outcomes, with partial mediation of socio-economic disparities in global mean FA through lifestyle, health-related and cognition factors. The association of poor cognition with lower global mean FA was stronger at higher AD polygenic risk.

1. Introduction

Dementia is characterized in otherwise healthy persons by significant declines in cognitive function that result in a reliance on caregivers for many everyday tasks (M. A. Beydoun et al., 2014). With 4.6–7.7 million new cases added annually, dementia affects an estimated 4.7% of older individuals worldwide, translating to an incidence rate of 3.5–10.6 per 1000 per year (Sosa-Ortiz et al., 2012). It is believed that late onset Alzheimer's Disease (AD) pathology accounts for 60–80% of dementia cases across different subtypes. AD is predicted by environmental risk factors that can be changed as well as hereditary ones (Sosa-Ortiz et al., 2012). AD has a complex etiology and presents as age-related episodic memory decline followed by a deterioration in other cognitive areas (Lindeboom & Weinstein, 2004). Two pathological hallmarks of AD are age-dependent and progressive amyloid β (Aβ) brain deposition (Hardy & Selkoe, 2002) and neurofibrillary tangles (NFT) resulting from hyperphosphorylated tau protein (Turner, 2003). AD accounts for the greatest portion of the health care burden in developed nations and is one of the main causes of old age impairment (Alzheimer's, 2016; Helmer et al., 2006). Age-related cognitive decline is frequently accompanied by brain structural pathologies and vascular

* Corresponding author. NIH Biomedical Research Center, National Institute on Aging, IRP, 251 Bayview Blvd., Suite 100, Room #: 04B118, Baltimore, MD, 21224, USA.
E-mail address: baydounm@mail.nih.gov (M.A. Beydoun).
[1] Co-first authors.
[2] MAB had full access to the data used in this manuscript and completed all the statistical analyses.

https://doi.org/10.1016/j.ssmph.2024.101655
Received 9 December 2023; Received in revised form 14 February 2024; Accepted 11 March 2024
Available online 20 March 2024

Abbreviations

ACR	Anterior corona radiata
AD	Alzheimer's Disease
AD PRS	Alzheimer's Disease polygenic Risk Score
AL	allostatic load
ALCOHOL	Alcohol consumption z-score
ALIC	anterior limb of internal capsule
Aβ	amyloid β
BCC	body of corpus callosum
BMI	body mass index
CCG	cingulum cingulate gyrus
CH	cingulum hippocampus
COGN	Poor cognitive performance z-score
CP	cerebral peduncle
CRP	C-reactive protein
CT	corticospinal tract
DE	direct effect
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
DIET	Diet quality z-score
dMRI	Diffusion weighted magnetic resonance imaging
EC	external capsule
FA	Fractional Anisotropy
FAmean	Global mean of FA
FCST	fornix cres + stria terminalis
FO	fornix
GCC	genu of corpus callosum
FOF	fronto-occipital fasciculus
HDI	Healthy Diet Index
HEALTH	Poor cardio-metabolic and general health z-score
ICP	inferior cerebellar peduncle
IDP	Imaging Derived Phenotype
ICD-10	International Classification of Diseases, Tenth Revision
ICV	Intracranial volume
IE	indirect effect
ML	medial lemniscus
MCP	middle cerebellar peduncle
MESA	Multi-Ethnic Study of Atherosclerosis
MRI	magnetic resonance imaging
NFT	neurofibrillary tangles
NUTR	Nutritional biomarker z-score
PA	Physical Activity z-score
PC	pontine crossing
PCA	Principal Components Analysis
PCR	posterior corona radiata
PLIC	posterior limb of internal capsule
PRS	Polygenic Risk Score
PTR	posterior thalamic radiation
RDW	red cell distribution width
ROIs	regions of interest
RPIC	retrolenticular part of internal capsule
SCC	splenium of corpus callosum
SCP	superior cerebellar peduncle
SCR	superior corona radiata
SD	Standard Deviation
SE	Standard Error
SEM	structural equations models
SES	Socio-economic status
SMOKING	Smoking z-score
SLF	superior longitudinal fasciculus
SS	sagittal stratum
SS	Social Support z-score
T1	First tertile
T2	Second tertile
T3	Third tertile
TE	total effect
TP	tapetum
UK	United Kingdom
UKB	UK Biobank
UNC	uncinate
WM	White Matter
WMI	White Matter Integrity

brain injuries that can be measured with brain magnetic resonance imaging (MRI) (Cavedo et al., 2012; Glymour et al., 2012; Hsu et al., 2018; Louapre et al., 2016; Muller et al., 2020; Walter et al., 2019). Some of these pathologies detected via different MRI modalities are thought to be early markers of AD or to be a component of the AD brain phenome (Andrews et al., 2021).

To date, therapeutic treatments for dementia remain largely ineffective, highlighting the need to identify modifiable risk factors that prevent or delay the onset of dementia, particularly among adults with known genetic risk factors such as the ε4 allele of APOE (Livingston et al., 2020). In terms of modifiable risk factors, and as per the 2020 Lancet commissions, early life education, midlife hearing loss, traumatic brain injury, hypertension, alcohol consumption, obesity, smoking in later life, depression, social isolation, physical inactivity, air pollution, and diabetes account for forty percent of dementia cases across all subtypes (Livingston et al., 2020). The paths between those variables, which are frequently associated, still need to be investigated. Therefore, identifying organized pathways could aid in determining the best means of preventing the onset of AD and the early indicators that make up the AD brain phenome.

In fact, brain MRI measures *in vivo* brain structural pathologies and vascular brain injuries accompanying age-related cognitive decline. Evaluating the presence of racial/ethnic and socio-economic disparities in brain health and their underlying pathways requires simultaneously mapping out relationships between race/ethnicity, socio-economic status (SES), and brain microstructural abnormalities via various imaging modalities. Diffusion-Weighted Imaging (DWI) is one method that targets the diffusion rate of tissue and is known to be useful in the characterization of tumors and cerebral ischemia (Soares et al., 2013). Since the introduction of DWI, a diffusion tensor model was proposed to obtain an indirect measurement of the degree of anisotropy and structural orientation specific to diffusion tensor imaging (DTI) (Soares et al., 2013).

DTI posits that the ways in which water molecules diffuse along tissues is contingent upon tissue type, integrity, architecture, and barriers which in turn produces information regarding the tissue's orientation and quantitative anisotropy (Soares et al., 2013) Fractional anisotropy (FA) is a widely established method for quantifying white matter integrity (WMI) that is sensitive to the degree of myelination, density, and organization of white matter (WM) (Jones, 2008). Specifically, FA determines directionality of water diffusion in the brain, measuring the degree of anisotropy of the diffusion at the voxel level (Jones, 2008). Therefore, FA is sensitive to subtle abnormalities in WM that may otherwise be undetected at the anatomical level. While many studies examine selected regional FA or other DTI measures (e.g. mean diffusivity) in WM that reflect cognitive changes over time (Benitez et al., 2014; Taoka et al., 2009), other studies have tested specific exposures in relation to all available regions of interest (ROIs) in addition to their overall average (M. A. Beydoun et al., 2023b; M. A. Beydoun et al., 2023c; M. A. Beydoun et al., 2020; M. A. Beydoun, Shaked, et al.,

2021; Shaked et al., 2019). We have adopted the latter approach to avoid biased selection of ROIs for WM.

In the US, racial and ethnic disparities in cognitive health and its underlying risk factors are widely documented. Social determinants of health measured at various levels including individual, household and neighborhood levels, including among others racial discrimination, can potentially explain a large portion of these racial and ethnic disparities in brain health and more specifically in WMI (Fani et al., 2021; O. Okeke et al., 2023; Onyebuchi Okeke, Elbasheir, Harnett, et al., 2022). In the UK, racial/ethnic and socio-economic disparities in Alzheimer's disease (AD) and dementia risk and their determinants remain unclear and underexplored, although recent work point to the central role played by SES and lifestyle factors when it comes to racial/ethnic disparities in dementia incidence in the UK (M. A. Beydoun et al., 2023a). Similarly, pathways explaining racial/ethnic and socio-economic disparities in brain markers of the dementia phenome, including reduced WMI, are under-studied.

We assessed patterns of mediation between race/ethnicity, SES and FA through downstream lifestyle, health-related, cognition-relate factors, using structural equation models among a sample of up to 45K middle-aged adults with brain diffusion-weighted MRI measures in the UK Biobank and further tested effect modification hypotheses of race/ethnicity on WMI stratified across AD polygenic risk levels. We hypothesized that racial minority status and poor SES were both associated with poorer WMI, and that a large proportion of the total effect of racial minority status was explained by SES and other downstream factors including lifestyle, health-related and cognition factors. We also hypothesized that AD PRS was an important effect modifier in the relationship between racial minority status and WMI as measured by FA.

2. Methods and materials

2.1. Database

Our analyses were performed using data from the UK Biobank study, a prospective cohort study of more than 500,000 persons aged 37–73 years old at baseline living in the United Kingdom and recruited from 22 centers across the UK between 2006 and 2010 (UK Biobank, 2007). The rationale and design of the study are described elsewhere (URL: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf) (UK Biobank, 2007).

2.2. Study sample

Among the initial 502,399 UK Biobank (UKB) participants aged 37–73 years, 462,400 had missing data on brain MRI and 52,626 had missing data on AD PRS and/or cognitive performance score, as well as household size and other socio-demographics (Fig. 1). We further excluded prevalent dementia cases at baseline assessment, which yielded a final sample size of 36,184 with ages ranging between 40 and 70y, using algorithmically defined dementia outcomes (UK Biobank, 2022). More specifically, UKB fields 42018 and 42020 were utilized and the algorithm used included International Classification of Diseases, Tenth Revision (ICD-10) codes F00 or G30 for incident diagnosis for AD, whereas a number of codes were used for all-cause dementia, including vascular dementia (F01, I67.3), namely A81.0, F00, F01, F02, F03, F05, G30, G31.0, G31.1, G31.8, and I67.3. Date of the earliest occurrence of all-cause dementia was defined using the minimum of several date variables/fields that were available for each of the two outcomes (UK Biobank, 2022). All other mediators, including SES, dietary, smoking, alcohol, social support, physical activity, nutritional biomarkers and cardiometabolic and general health measures were imputed (missingness rate<10%) with 5 imputations and 10 iterations, using chained equations (Lee & Carlin, 2010) as later described in the Statistical analysis section.

2.3. Brain MRI acquisition and processing

The UK Biobank imaging visit performed MRI brain scans in Reading, Newcastle, and Cheadle Manchester. (de Groot et al., 2013; Navale et al., 2022). While data collection is still accruing, the goal was to obtain brain MRI scans on 100,000 UK Biobank participants during the first imaging visit which was initiated in 2014. Data obtained for the present study included up to 45K brain MRI scans given that the data was extracted in December of 2022.Supplementary Method 1 provides more details regarding Imaging Derived, Phenotype (IDP) measures and processing (de Groot et al., 2013). All brain MRI data were acquired on similar 3T Siemens Skyra scanners (protocol: http://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf), documentation: (http://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf, and publication). (Alfaro-Almagro et al., 2018; Cox et al., 2019) Scans from the top of the head to the neck were conducted using a 256-cm superior– inferior field of view (de Groot et al., 2013; Navale et al., 2022). The global tissue volumes, and white matter tract-averaged water molecular diffusion

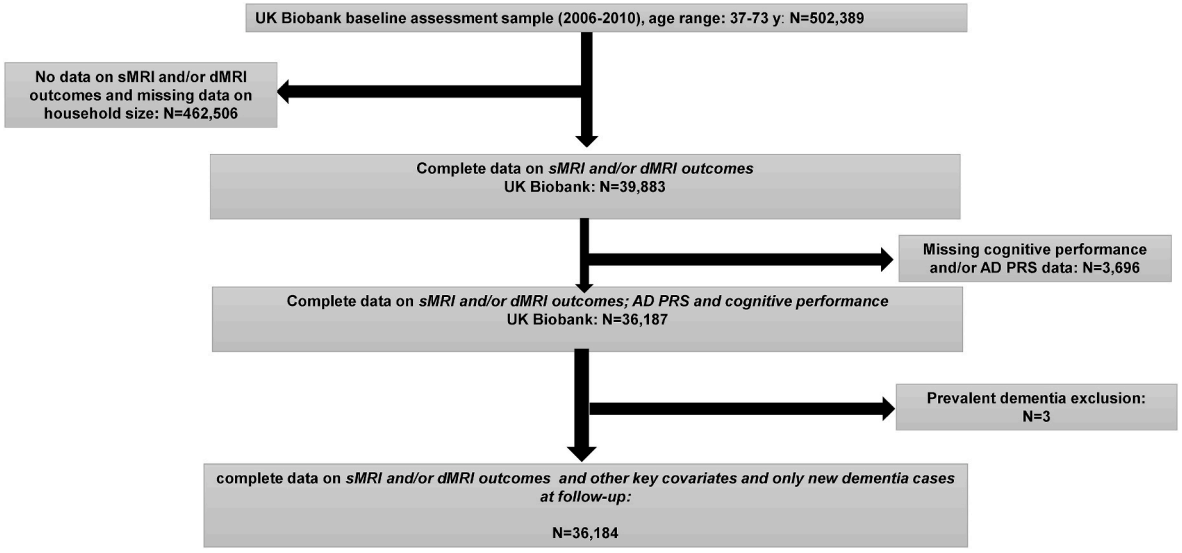

Fig. 1. Consort diagram. *Abbreviations*: AD = Alzheimer's Disease; dMRI = Diffusion-weighted magnetic resonance imaging; PRS=Polygenic Risk Score; sMRI=-Structural magnetic resonance imaging; UK=United Kingdom.

indices were processed by the UK Biobank team and provided to approved researchers as IDPs; details on image processing and quality control pipeline are available elsewhere (Alfaro-Almagro et al., 2018; Cox et al., 2019).

In the present study, the selected imaging phenotypes were *a priori* associated with worse cognitive ability and decline, namely for *dMRI* those were global and tract-specific fractional anisotropies (e.g. (Tank et al., 2021)) (See Supplementary Table 1 for details). The diffusion tensor was used to calculate the diffusion eigenvectors and eigenvalues (λ1, λ2, λ3), which represent the main direction of diffusion and related diffusivity. Then, FA was computed as follows to provide information on the level of diffusion anisotropy in white matter, as follows (Basser & Pierpaoli, 1996):

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{[\lambda_1 - (\lambda)]^2 + [\lambda_2 - (\lambda)]^2 + [\lambda_3 - (\lambda)]^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

whereby

$$(\lambda) = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

FA is unitless and most of the analyses included global mean FA as is, specifically when carrying out linear regression models to enhance comparability with other future studies, as well as most of the structural equations models (SEM) that examined these global mean FA exclusively. However, in part of the analysis, the outcome was standardized z-scored, particularly when examining tract-specific along with global mean of FA within the SEM framework.

2.4. Race/ethnicity

Participant's race and ethnicity were self-reported at baseline which we classified as "Non-White" (racial minority group) vs. "White" (referent category). The "Non-White" category included two larger ethnic groups, namely South Asian and African-Carribbean (Black) and a smaller group labelled as "Others", which included among others Chinese, other East Asian and Middle Eastern ancestries and other less frequent and mixed ethnic groups. A more detailed racial/ethnic categorization (White, Black, South Asian and Other) was used for descriptive purposes and for a sensitivity analysis for part of the regression models.

2.5. Mediators

2.5.1. Socio-economic status

We operationalized SES using educational attainment, income, and the Townsend deprivation index (TDI). Self-reported educational attainment at baseline was coded as low (None, CSEs/Equivalent, NVQ/HND/HNC/Equivalent, and "Other professional qual"); intermediate (O Levels/GCSEs/Equivalent and "A/AS Levels Equivalent"); and higher level ("College/University") (Chadeau-Hyam et al., 2020). On a scale of 1–5, the total household income before taxes was defined as: less than £18,000; between £18,000 and £29,999; between £30,000 and £51,999; between £52,000 and £100,000; and above £100,000. The TDI scores were derived using national census data measuring residential postcode-level car ownership, household overcrowding, owner occupation, and unemployment, and were provided as part of the UK Biobank dataset. Originally coded to reflect higher socioeconomic deprivation with higher TDI scores, (Townsend P & Beattie, 1987) it was multiplied by −1 in the present study to reflect higher SES. The SES summary z-score was the average of z-scores of education, income and TDI (reverse coded), with a higher z-score corresponding to higher SES.

2.5.2. Lifestyle and health-related factors

Six lifestyle factors of relevance were identified: "SMOKING", "ALCOHOL", "PHYSICAL ACTIVITY (PA)", "DIET QUALITY (DIET)", "NUTRITIONAL BIOMARKERS (NUTR)" and "SOCIAL SUPPORT (SS)". Three tobacco exposure variables were generated using a touchscreen questionnaire at the assessment center visit, including smoking status, environmental tobacco smoke, and pack-years of smoking from which an average SMOKING z-score was estimated. Alcohol consumption was assessed through quantity-frequency questions, with the construct ALCOHOL being the standardized z-score for this item. PA was measured using self-reported responses, resulting in MET.min/week for each category of physical activity intensity. Diet quality was measured using dietary recommendations, from which the DIET z-score was estimated, and nutritional biomarkers like Vitamin D and red cell distribution width (RDW) were selected as additional nutritional biomarkers, from which NUTR z-score was generated. Social support was evaluated using three variables: how often do you visit friends or family, how often are you able to confide in someone close to you, and which of the following do you attend once a week or more often? These measures were then transformed into a standardized z-score and averaged into the SS measure.

The general and cardio-metabolic health construct combined body mass index (BMI), allostatic load (AL), a co-morbidity index, and self-rated health. BMI was computed at baseline assessment, while AL total score was computed as an unweighted index of nine cardiovascular, metabolic, and inflammatory risk indicators, with higher scores reflecting high AL total score (Supplemental method 3). Co-morbidity index was constructed using two data fields based on self-reported data on pre-existing cancer and non-cancer co-morbidity. Self-rated health (excellent, good, fair poor) was obtained as part of the touchscreen questionnaire at baseline assessment. Poor cardiometabolic and general health (HEALTH) was created by combining four measured variables: body mass index, allostatic load, a co-morbidity index, and self-rated health in the direction of poorer health.

Cognitive performance and poor cognitive performance score (COGN) were assessed using paired memory tests and reaction time tests measured at the baseline assessment visit, similar to all other potential mediators. The results showed lower test-retest reliability compared to reference cognitive tasks for the test of visual memory. The COGN construct was verified through principal components analysis, with the predicted first principal component used as the COGN z-score. COGN (poor cognitive performance) was determined using three items (reaction time, pairs matching time to completion, and pairs matching number of errors) from two cognitive tests (visual memory, reaction time). Supplementary method 4 has further information on these measurements.

2.6. Effect modifier: Alzheimer's disease polygenic Risk Score (AD PRS)

PRS scores were generated using a Bayesian approach and applied to meta-analyzed summary statistics GWAS data from external or internal UK Biobank data. The Standard PRS Set (also known as the "UKB-Free" set), consisting of 28 diseases and 8 traits, was chosen from the PGS catalog (https://www.pgscatalog.org/). We chose AD PRS score (a standardized z-score reflecting genetic risk for AD), from the UK Biobank-free standard set of PRS which was then used as an effect modifier in part of our analyses, after transforming it into tertiles. Detailed information is found in Supplementary Method 4.

2.7. Exogenous covariates

Exogenous factors in all SEM equations included age at baseline assessment, sex, and household size. Furthermore, the AD PRS and time elapsed from baseline assessment to imaging visit were included in the final outcome equation, as well as the inverse mills ratio, to account for selection bias due to unavailable or missing data on key variables, including neuroimaging outcomes, cognition and several covariates that were not imputed. The inverse mills ratio was included in linear

regression models as a covariate and was also included in SEM models in a similar fashion. Mediator and other covariate detailed descriptions are provided in Supplementary Methods 2–4.

2.8. Statistical methods

Stata 18.0 (StataCorp, College Station, TX) (STATA, 2022) was used for all analyses. The type I error rate was set to 0.05. Variables of interest in this study, particularly potentially mediating variables—with the exception of exogenous measures (e.g. age, sex, race/ethnicity, inverse mills ratio, household size), AD PRS, cognitive performance and dMRI metrics—were imputed by chained equations (5 imputations, 10 iterations), starting from the selected sample after excluding non-available or missing key variables (N = 36,164) (Lee & Carlin, 2010). Specifically, Stata commands *mi impute* was used to impute those potential mediators five times using 10 iterations each time with chained equations; *mi passive* was utilized to generate some of the imputed complex variables which added together or transformed individual imputed variables across these imputations; mi estimate was used to obtain a multiple-imputed estimate of descriptives (means and proportions) and regression coefficients across five imputations using Rubin's rules; *mi xeq* 1 through 5 was used to extract results from each imputation which were then combined using Rubin's rule.

A set of bivariate linear regression and multinomial logit models were used to compare continuous and categorical sample characteristics by race/ethnicity, by adding racial minority status ("Non-White" vs. "White", as the only predictor in the model with outcomes being each of the characteristics.

We further tested for differences in global mean FA by race/ethnicity using multiple linear regression with sequential covariate adjustment and further stratified by AD PRS tertiles. We evaluated heterogeneity of the race effect across these tertiles in a non-stratified model with AD PRS tertile by race/ethnicity interaction.

We further investigated mediation using SEM, with socio-demographic variables included as exogenous variables in all equations, while SES, all LIFESTYLE factors, HEALTH, and COGN were included as endogenous variables, and the outcome was one of numerous dMRI tract-specific and global mean FA outcomes. RACE_ETHN was specifically anticipated to predict SES, which is hypothesized to be related with better LIFESTYLE variables (SMOKING, DIET, PA, SS, and NUTR). These variables were then used to forecast HEALTH (poor cardiometabolic and general health). The association of HEALTH with low cognition (COGN) was then hypothesized. All these lifestyle, health-related and cognition factors were measured simultaneously at the baseline assessment visit, whereas racial minority status was a fixed exogenous variable, SES was assumed to be antecedent to those factors, and dMRI outcomes were measured approximately 10–15 years after the baseline assessment (i.e. 2006-2010 up to 2021). Although cognition is often studied as an outcome for MRI metrics, poor cognitive performance at baseline can be a proxy for low cognitive reserve that ensues from lower SES and poorer lifestyle choices among others. Other paths, including those between endogenous variables and between RACE_ETHN and each endogenous variable, were also allowed (Fig. 2).

The total effect (TE) of race/ethnicity and SES on FA_{mean} and tract-specific FA were divided into direct (DE) and indirect (IE) effects. The IE could result from a combination of several processes and mediational pathways. The TE, IE and DE for each variable connected to the final outcome through a set of mediators were estimated along with their SEs, using the *teffects* command in Stata, applied to each of the five imputations using mi xeq 1 through 5. The average TE, DE and IE were then estimated using Rubin's rule, across the five imputations. Nonetheless, for simplicity, we displayed the tract-specific FA findings by projecting clusters of ROIs out of the available 48 ROIs (see Supplementary Table 1), on a normal MNI brain, illustrating the key mediational patterns of connection in terms of statistical significance of TE, DE, and IE and using various color schemes that illustrate the direction of associations. FSLeyes software was used to visualize the tracts belonging to each of the tract-specific FA SEM mediational patterns classified based on statistical significance of TE, DE and IE (URL: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes). TE, IE, and DE were also plotted using a heat map for those same quantitative findings using R version 4.2.2 (https://www.r-project.org/) to show both statistical significance and directions of associations pertaining to racial minority and SES effect on the FA metrics of interest, based on the SEM model.

Moreover, for global mean FA, several IE were of main interest and were estimated by multiplying and adding effects from race/ethnicity into the final outcome and passing through each serial mediator. This part of the analysis was carried out using *nlcom* commands for non-linear combinations of estimated parameters after SEM for each of five imputations (using *mi xeq* 1 through 5). These non-linear combinations were then averaged using Rubin's rule. Six specific pathways were of interest for each lifestyle factor, and were examined qualitatively for statistical significance at type I error of 0.05: *Pathway A:* RACE_ETHN → SES → FA_{mean}; *Pathway B:* RACE_ETHN → SES →LIFESTYLE → FA_{mean}; *Pathway C:* RACE_ETHN → SES → LIFESTYLE → HEALTH → FA_{mean}; *Pathway D:* RACE_ETHN → SES → LIFESTYLE → HEALTH → POOR COGNITIVE

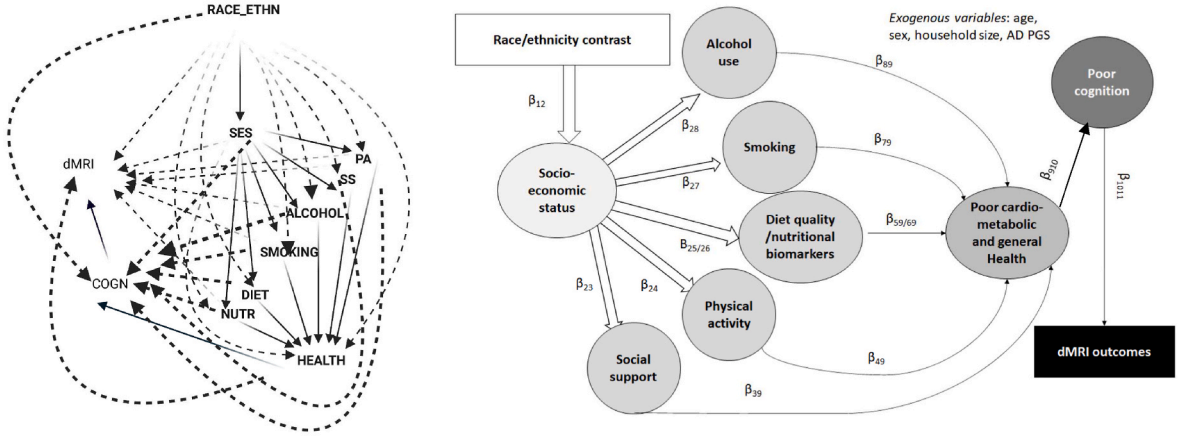

Fig. 2. Conceptual Framework. *Abbreviations*: ALCOHOL = Alcohol consumption z-score; COGN=Poor cognitive performance z-score; DIET = Diet quality z-score; dMRI = Diffusion-weighted magnetic resonance imaging; FA=Fractional Anisotropy; HEALTH=Poor cardio-metabolic and general health z-score; PA=Physical Activity z-score; NUTR=Nutritional biomarker z-score; SEM= Structural Equations Model; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SS=Social Support z-score. Notes: Plain arrows are statistically significant associations ($p < 0.05$) within the hypothesized pathway; Dashed arrows are statistically significant associations ($p < 0.05$) outside the hypothesized pathway.

PERFORMANCE (COGN) → FA_{mean}; *Pathway E:* RACE_ETHN→SES→COGN→ FA_{mean}; *Pathway F:* RACE_ETHN→SES→LIFESTYLE→COGN→ FA_{mean}, with *Pathway D* hypothesized to play a central role in mediating racial/ethnic disparities in FA_{mean}. OLS multiple regression accounted for sample selectivity using a 2-stage Heckman selection approach, by including an inverse mills ratio, a function of the conditional probability of selection given baseline age, sex and race/ethnicity (M. A. Beydoun et al., 2013). Several sensitivity analyses were also conducted. First, the set of OLS multiple linear regression models that tested association of race with FA_{mean} was re-run with a more detailed race/ethnicity definition, comparing self-reported ethnicities of Black (African Caribbean) vs. White, South Asian vs. White and "Other ethnicities" vs. White in incrementally adjusted models. Second, we have examined ore closely the relationship between COGN, its individual cognitive test scores that were included in the PCA and FA_{mean}. A scatter plot and a LOWESS smoothing curve depicted those associations along with Pearson's correlation coefficients which were estimated along with associated P-values.

3. Results

Of the selected 36,184 participants, 1100 were non-White minorities, of whom 48.5% fell in the "Others" category (Chinese, other East Asian and Middle Eastern ancestries and other less frequent and mixed ethnic groups), 32.0% in the South Asian category, and 19.5% in the Black category. Overall, 0.6% of the selected sample was Black, 1.0% was South Asian and 1.5% belonged to the "Others" category. When compared to their White counterparts, non-White individuals were younger, had a lower proportion of females, higher educational attainment and income, but a higher TDI (Table 1). A higher proportion of White individuals were ex-smokers who also drank more regularly. Diet quality was higher in non-White individuals, although White persons had a better profile of nutritional biomarkers. Non-White individuals consistently reported less social support, poorer health, and lower scores on three cognitive test scores when compared to White adults in this study. The preliminary relationship between racial minority status and dMRI outcomes revealed lower global mean of FA among minority groups with variations in the directionality of this association when examining race as a predictor for tract-specific FA. A reduced FA is thought to reflect lower WMI.

Table 2 displays findings from OLS multiple regression with race/ethnicity as the main predictor for global mean FA (unitless measure), and models 1–3 incrementally adjusting for potentially mediating variables, in the overall sample and within AD PRS tertiles. Similar to crude associations displayed in Table 1, minimally adjusted model 1 (M1) suggested lower FA_{mean} among non-White adults vs. White adults, which was only statistically significant in the lowest AD PRS tertile with a statistically significant interaction at a type I error of 0.10 (*t*-test. for interaction term (AD PRS × RACE_ETHN, $\gamma = 0.0014$, $P = 0.053$). Overall, SES was a positive predictor for FA_{mean}, independently of race/ethnicity, other exogenous factors and in M3, independently of potential mediators. Nevertheless, inclusion of potential mediators attenuated the effect from +0.0015 to +0.0009 (M2 vs. M3), keeping in mind that 1 SD of FA_{mean} was ~0.020. Among key potential mediators, those found to be independently associated with FA_{mean} included the most proximal COGN factor suggesting that FA_{mean} was lower with lower baseline cognition test scores. Others that were linked to lower FA_{mean} were poor health, greater alcohol consumption, more tobacco exposure, reduced vitamin D status coupled with increased RDW (or lower NUTR), and unexpectedly greater physical activity. Diet quality and social support were not independent predictors of FA_{mean}, after adjustment for all remaining socio-economic, lifestyle and health-related factors. Most of these mediator-outcome findings did not differ markedly across AD PRS tertiles. Nevertheless, the association of poor cognition with FA_{mean} was markedly stronger in the two uppermost AD PRS tertiles compared to the

Table 1
Study sample characteristics by race/ethnicity: The UK Biobank 2006–2021.

Study sample characteristics	Overall	White	Non-White	P_{race} [a]
	N = 36,184	N = 35,084	N = 1100	
Socio-demographic				
Baseline age, y	55.57 ± 0.04	55.66 ± 0.04	52.49 ± 0.23	<0.001
Sex, % female	53.2	53.3	49.9	0.027
Race/ethnicity				
White	97.0	100.0	0.0	_
Black	0.6	0.0	19.5	
South Asian	1.0	0.0	32.0	
Other	1.5	0.0	48.5	
Household size	2.54 ± 0.01	2.53 ± 0.01	2.97 ± 0.05	<0.001
Socio-economic status				
Education				
Low	16.0	16.0	15.8	0.012
Intermediate	35.2	35.6	24.4	<0.001
High	48.8	48.4	59.8	_
Income, range: 1–5	2.97 ± 0.01	2.97 ± 0.01	2.97 ± 0.04	0.87
Townsend Deprivation Index	−1.89 ± 0.01	−1.93 ± 0.01	−0.384 ± 0.099	<0.001
SES z-score	−0.0066 ± 0.0034	−0.0025 ± 0.0034	−0.137 ± 0.024	<0.001
Lifestyle factors				
Smoking				
Smoking status				
Never	76.6	76.4	80.9	_
Former	17.3	17.5	11.3	<0.001
Current	6.1	6.0	7.8	0.082
Environmental tobacco smoke	0.652 ± 0.022	0.649 ± 0.022	0.738 ± 0.109	0.48
Pack-years of tobacco smoke	0.107 ± 0.001	0.108 ± 0.001	0.085 ± 0.006	0.003
SMOKING z-score	+0.022 ± 0.004	+0.023 ± 0.004	−0.0196 ± 0.021	
Alcohol consumption	3.330 ± 0.007	3.362 ± 0.007	2.296 ± 0.050	<0.001
Alcohol consumption frequency, range: 0–5				
ALCOHOL z-score	−0.0000 ± 0.0053	+0.0234 ± 0.005	−0.7461 ± 0.0358	<0.001
Physical activity, PA				
PA, Met.min.wk^{-1}	1865 ± 13	1868 ± 13	1763 ± 70	0.15
PA z-score	−0.0000 ± 0.0053	+0.0013 ± 0.0053	−0.0427 ± 0.0293	0.15
Diet quality				
HDI	5.235 ± 0.007	5.231 ± 0.008	5.338 ± 0.043	0.016
DIET z-score	0.0000 ± 0.0053	−0.00223 ± 0.0053	+0.0714 ± 0.0300	0.016
Nutritional Biomarkers				
25-hydroxyvitamin D	49.7 ± 0.12	50.2 ± 0.12	34.40 ± 0.56	<0.001
Red cell distribution width	13.404 ± 0.005	13.396 ± 0.005	13.650 ± 0.038	<0.001
NUTR z-score	−0.0007 ± 0.0038	+0.0150 ± 0.0038	−0.5025 ± 0.0249	<0.001
Social Support				
"How often do you visit friends or family or have them visit you?"	5.170 ± 0.006	5.184 ± 0.006	4.747 ± 0.034	<0.001

(*continued on next page*)

Table 1 (*continued*)

Study sample characteristics	Overall	White	Non-White	P_{race}[a]
	N = 36,184	N = 35,084	N = 1100	
"How often are you able to confide in someone close to you?"	1.085 ± 0.005	1.088 ± 0.005	0.975 ± 0.026	<0.001
"Which of the following do you attend once a week or more often?"	3.686 ± 0.010	3.701 ± 0.010	3.226 ± 0.060	<0.001
SS z-score	−0.0003 ± 0.0033	+0.0077 ± 0.0033	−0.2579 ± 0.020	<0.001
Cardio-metabolic and general health-related factors				
Body mass index, $kg.m^{-1}$	26.51 ± 0.02	26.51 ± 0.022	26.42 ± 0.12	0.47
Allostatic load	1.687 ± 0.008	1.686 ± 0.009	1.715 ± 0.041	0.49
Co-morbidity index	1.570 ± 0.009	1.571 ± 0.009	1.538 ± 0.050	0.51
Self-rated health, range: 1–4	1.939 ± 0.003	1.925 ± 0.004	2.060 ± 0.022	<0.001
HEALTH z-score	0.0011 ± 0.0035	−0.0003 ± 0.0036	+0.0453 ± 0.0200	0.025
Cognitive performance				
Reaction Time	6.2724 ± 0.0009	6.271 ± 0.00091	6.306 ± 0.00595	<0.001
Pairs matching, errors	0.5733 ± 0.0036	0.5670 ± 0.0037	0.7748 ± 0.0214	<0.001
Pairs matching, time to complete	5.2367 ± 0.0018	5.2330 ± 0.0018	5.356 ± 0.0123	<0.001
COGN z-score	−0.2986 ± 0.0064	−0.3129 ± 0.0064	0.15773 ± 0.0426	<0.001
dMRI				
Mean FA	0.5611 ± 0.0001	0.5610 ± 0.0001	+0.5636 ± 0.0006	<0.001
AD PRS				
Mean ± SE	0.0406 ± 0.0052	0.043 ± 0.005	−0.045 ± 0.031	0.004
T1	33.3	33.3	36.0	_
T2	33.3	33.3	33.3	0.27
T3	33.3	33.4	30.7	0.030
Follow-up time, days	3289 ± 3	3291 ± 3	3245 ± 19	0.019

Abbreviations: AD = Alzheimer's Disease; ALCOHOL = Alcohol consumption z-score; COGN=Poor cognitive performance z-score; DIET = Diet quality z-score; dMRI = Diffusion weighted magnetic resonance imaging; FA=Fractional Anisotropy; HDI=Healthy Diet Index; HEALTH=Poor cardio-metabolic and general health z-score; ICV=Intracranial volume; PA=Physical Activity z-score; PRS=Polygenic Risk Score; NUTR=Nutritional biomarker z-score; SE=Standard Error; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SS=Social Support z-score; T1 = First tertile; T2 = Second tertile; T3 = Third tertile; UK=United Kingdom.

Note: values are means ± SE or percentages in multiple imputed data. FA_{mean} is unitless and entered as is, without z-score standardization. 1 SD of FA_{mean} is equivalent to 0.020.

[a] P for null hypothesis that β = 0 (T-test.) based on bivariate linear regression models for continuous variables and bivariate multinomial logistic regression models for categorical variables, applied to multiple imputed data (5 imputations, 10 iterations).

lower tertile (T_2 and T_3: β±SE: −0.0009 ± 0.0001 vs. T_1: β±SE: −0.0005 ± 0.0001, $P < 0.001$; , *t*-test.).

Findings from structural equations modeling of the association between race, SES and FA outcomes through serial mediators depicting

Table 2
Racial/ethnic and socio-economic disparities in Mean global fractional anisotropy (FA_{mean}, entered as is), overall and across AD PRS tertiles: The UK Biobank 2006–2021.

Global mean fractional anisotropy (FA_{mean}) vs. Race and SES	β±SE
Overall, N = 36,184	
M1[a]	
Non-White	−0.0011 ± 0.0006
M2[a]	
Non-White	−0.0008 ± 0.0006
SES	0.0015 ± 0.0002***
M3[a]	
Non-White	−0.0002 ± 0.0006
SES	0.0009 ± 0.0002***
SS	−0.0001 ± 0.0002
PA	−0.0003 ± 0.0001**
DIET	−0.0002 ± 0.0001
NUTR	0.0004 ± 0.0001**
SMOKING	−0.0009 ± 0.0001***
ALCOHOL	−0.0003 ± 0.0001**
HEALTH	−0.003 ± 0.0002***
COGN	−0.0008 ± 0.0001***
AD PRS, T1, N = 12,062	
M1	
Non-White vs. White	−0.0026 ± 0.001**
M2	
Non-White vs. White	−0.0023 ± 0.001*
SES	0.0015 ± 0.0003***
M3	
Non-White	−0.0018 ± 0.001
SES	0.0008 ± 0.0003**
SS	−0.0005 ± 0.0003
PA	−0.0001 ± 0.0002
DIET	−0.0001 ± 0.0002
NUTR	0.0003 ± 0.0003
SMOKING	−0.0009 ± 0.0002***
ALCOHOL	0 ± 0.0002
HEALTH	−0.0032 ± 0.0003***
COGN	−0.0005 ± 0.0001***
AD PRS, T2, N = 12,061	
M1	
Non-White vs. White	−0.0002 ± 0.001
M2	
Non-White vs. White	0.0001 ± 0.001
SES	0.0018 ± 0.0003***
M3	
Non-White	0.0006 ± 0.001
SES	0.0012 ± 0.0003***
SS	0.0004 ± 0.0003
PA	−0.0004 ± 0.0002*
DIET	−0.0004 ± 0.0002*
NUTR	0.0004 ± 0.0002
SMOKING	−0.0008 ± 0.0002***
ALCOHOL	−0.0005 ± 0.0002**
HEALTH	−0.0033 ± 0.0003***
COGN	−0.0009 ± 0.0001***
AD PRS, T3, N = 12,061	
M1	
Non-White vs. White	−0.0001 ± 0.001
M2	
Non-White vs. White	0.0002 ± 0.001
SES	0.0013 ± 0.0003***

(*continued on next page*)

Table 2 (*continued*)

Global mean fractional anisotropy (FA_{mean}) vs. Race and SES	β±SE
M3	
Non-White	0.0008 ± 0.001
SES	0.0007 ± 0.0003**
SS	−0.0002 ± 0.0003
PA	−0.0004 ± 0.0002*
DIET	0.0000 ± 0.0002
NUTR	0.0006 ± 0.0003*
SMOKING	−0.0008 ± 0.0002**
ALCOHOL	−0.0003 ± 0.0002
HEALTH	−0.0026 ± 0.0003***
COGN	−0.0009 ± 0.0001***

Abbreviations: AD = Alzheimer's Disease; ALCOHOL = Alcohol consumption z-score; COGN=Poor cognitive performance z-score; DIET = Diet quality z-score; dMRI = Diffusion-weighted magnetic resonance imagingFA = Fractional Anisotropy; FA_{mean} = Global mean of FA; HDI=Healthy Diet Index; HEALTH-=Poor cardio-metabolic and general health z-score; MRI = magnetic resonance imaging; PA=Physical Activity z-score; PCA=Principal Components Analysis; PRS=Polygenic Risk Score; ROIs = regions of interest; NUTR=Nutritional biomarker z-score; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SS=Social Support z-score; TP = tapetum; UK=United Kingdom.

Values are regression coefficients±standard errors (β±SE) from a series of multiple linear regression models with global mean of FA as the outcome and race as the main predictor. M1: Model adjusted for age, sex, AD PRS, household size, follow-up time (days), and inverse mills ratio. ICV adjusted for in the case of subcortical volumes. M2: M1 further adjusted for SES; M3: M2 further adjusted for DIET, SMOKING, ALCOHOL, NUTR, SS, HEALTH and COGN z-scores. FA_{mean} is unitless and entered as is, without z-score standardization. 1 SD of FA_{mean} is equivalent to 0.020.

*P < 0.05; **P < 0.010; ***P < 0.001 for null hypothesis that β = 0, *t*-test based on multiple linear regression models applied to multiple imputed data (5 imputations, 10 iterations).

[a] P < 0.10 for null hypothesis that AD PRS × Race interaction term γ = 0 in an unstratified model, (*t*-test).

lifestyle, health-related and cognitive performance factors are presented in Tables 3 and 4 and Supplementary Table 5, and visualized in Figs. 3 and 4.

Table 3 presents TE, DE and IE of race/ethnicity on global mean FA and tract-specific FA. Those findings are summarized in Fig. 3 on standard brain images for tract-specific FA and heat maps for all volumes (RACE_ETHN→FA), showcasing direction and magnitude of standardized effect sizes for TE, IE and DE, by utilizing z-scores of each FA outcome. Among key findings, "Non-White" vs. White status did not exhibit a significant DE on FA_{mean}, with over 80% of the TE being explained by an indirect effect through a combination of different pathways going through SES, lifestyle, health-related and cognition factors. In addition, TE of racial minority status on FA_{mean} was non-significant. This mediational pattern of association was followed by a select number of tracts (*Pattern 2*, Fig. 3), including the Left anterior limb of the external capsule (ALIC) and the left cingulum (hippocampus). In contrast, numerous tracts followed *Pattern 5,* whereby TE, IE and DE were all statistically significant. Nevertheless, the directionality of the TE differed among tracts, with most of showing a positive TE of racial minority status on FA. Complete mediation (*Pattern 3*), whereby unlike DE, TE and IE for racial minority status were both statistically significant at type I error of 0.05, was observed for several tracts including Left and Right superior longitudinal fasciculus.

Table 4 presents TE, DE and IE of SES on global mean FA and tract-specific FA. Most TEs were statistically significant and could be decomposed into statistically significant DEs and IEs. This was the case for global FA_{mean} and several tracts pertaining to *Pattern 5*, including the Left Cingulum Hippocampus (CH_Left) among many others. Higher SES was linked to greater FA_{mean}. Most notably, 40% of the TE for SES and FA_{mean} consisted of an IE, combining pathways involving lifestyle, health-related and cognitive factors. In contrast to the mediational pattern observed for the Left Cingulum Hippocampus, whereby 17% of TE was explained by the IE, SES's TE on the Right Cingulum Hippocampus FA was for the most part a DE (~99%) and was of one of several tracts within *Pattern 4* (TE and DE with P < 0.05; IE with P > 0.05, *t*-test). These findings and those for Non-White vs. White effects are further visualized in Fig. 3 on standard brain images and the SES-FA heat map. For detailed findings for each imputation and summary findings used for heatmap across 5 imputations, please see datasheets 1 and 2, respectively.

Table 5 and Supplementary Table 5 present the detailed results of the SEM models for FA_{mean}. Those results are qualitatively visualized in Fig. 4. Our findings indicated that *Pathway A* (RACE_ETHN → SES → FA) may play a central role in the total effect of RACE_ETHN on FA_{mean}, whereby Non-White adults had worse outcomes compared to White adults, a total effect partially mediated through SES. There was no significant direct effect of RACE_ETHN on FA_{mean}. Based on Table 5, around 16% of the total effect of RACE_ETHN on FA_{mean} was explained by *Pathway A*. All other selected pathways going through SES, LIFESTYLE, HEALTH and COGN explained only 1–2% of the total effect. Given that 80% of the race TE was an IE, other pathways from race to FA_{mean} are at play in combination explaining 60% of TE.

Moreover, as seen earlier, around 41% of the TE of SES on FA_{mean} was an IE. Some interesting mediational patterns emerged with respect to key mediators that may explain SES-FA_{mean} associations, as visualized qualitatively in Fig. 4 and computed in Supplementary datasheet 3. Most notably, SES had two important indirect associations with FA_{mean}: The first through an inverse relationship with poor cognition (COGN) (*Pathway E*: 7.2% of TE of SES on FA_{mean}) and the second more dominant pathway was through an inverse relationship with poor health (HEALTH) (26.5% of TE of SES on FA_{mean}). In addition, other secondary pathways included SES→LIFESTYLE→HEALTH→FA_{mean}, pathways pertaining to a few lifestyle factors, namely DIET, NUTR, SMOKING and SS (i.e. *Pathway C*), collectively explaining 4% of the total effect. Finally, around 7% of the total effect of SES on FA_{mean} was explained by the SMOKING factor, through the pathway SES(−)→SMOKING (−)→FA_{mean} (See Supplementary datasheet 3 for details). All supplementary datasheets, code and other results-related materials (e.g. heatmap) are provided on github at: baydounm/UKB_paper6_supplementarydata (github.com).

Based on a sensitivity analysis for Table 2 (Supplementary Table 6), which included a more detailed definition of race/ethnicity, model 1 indicated that Black participants had a lower global mean FA compared with White participants, after adjustment for age, sex, AD PRS, time from baseline to neuroimaging visit and household size. However, this difference was markedly attenuated with adjustment for SES and became null after further adjustment for downstream factors. This association in the reduced model was mostly detected in the highest AD PRS tertile without a statistically significant heterogeneity across these tertiles. In another sensitivity analysis, each of the 3 component test scores of COGN PCA z-score along with the composite score COGN were correlated with FA_{mean} and represented as a set of LOWESS smoothed curves and scatter plots. Findings indicated a weak inverse but statistically significant associations of COGN and its component scores reflecting poor cognition with FA_{mean} which reflected better WMI with higher score. Pearson's correlation coefficients were comparable but was the weakest for the time to completion pairs matching score vs. FA_{mean} (r = −0.07, p < 0.001).

4. Discussion

4.1. Summary of findings

We investigated racial/ethnic disparities in diffusion weighted brain MRI measures and potential mediating pathways. Racial minority status (Non-White vs. White), mainly driven by "Black vs. White" ethnic

Table 3
Racial/ethnic disparities (Non-White vs. White) in tract-specific FA dMRI outcomes (standardized z-scores): total, direct and indirect effects through SES, lifestyle, health and cognition factors: The UK Biobank 2006–2021[a,b].

Tract-specific FA, z-scored	Total effect	Direct Effect	Indirect effect	Percent mediated
	β ± SE	β ± SE	β ± SE	
ACR_Left	0.098 ± 0.028***	0.114 ± 0.027***	−0.016 ± 0.006**	−17
ACR_Right	0.060 ± 0.028*	0.080 ± 0.029*	−0.020 ± 0.006**	−34
ALIC_Left	−0.013 ± 0.030	0.018 ± 0.030	−0.032 ± 0.007***	237
ALIC_Right	−0.040 ± 0.030	−0.008 ± 0.030	−0.0319 ± 0.007***	81
BCC	0.111 ± 0.029***	0.130 ± 0.030***	−0.019 ± 0.007*	−18
CP_Left	−0.082 ± 0.029*	−0.055 ± 0.029	−0.028 ± 0.007***	34
CP_Right	−0.156 ± 0.029***	−0.122 ± 0.030***	−0.034 ± 0.007***	22
CCG_Left	−0.091 ± 0.029*	−0.077 ± 0.030*	−0.015 ± 0.006*	16
CCG_Right	−0.031 ± 0.030	−0.026 ± 0.030	−0.005 ± 0.006	17
CH_Left	−0.054 ± 0.030	−0.019 ± 0.031	−0.035 ± 0.006***	64
CH_Right	−0.129 ± 0.030***	−0.104 ± 0.031***	−0.025 ± 0.006***	19
CT_Left	−0.099 ± 0.030**	−0.059 ± 0.030*	−0.041 ± 0.006***	41
CT_Right	−0.186 ± 0.029***	−0.153 ± 0.030***	−0.033 ± 0.006***	18
EC_Left	−0.135 ± 0.029***	−0.083 ± 0.030**	−0.052 ± 0.006***	39
EC_Right	−0.055 ± 0.029	−0.010 ± 0.026	−0.044 ± 0.006***	81
FCST_Left	−0.002 ± 0.027	0.024 ± 0.027	−0.025 ± 0.007***	1522
FCST_Right	−0.069 ± 0.027*	−0.042 ± 0.027	−0.027 ± 0.006***	39
FO	−0.024 ± 0.026	−0.026 ± 0.026	0.002 ± 0.006*	−6
GCC	0.080 ± 0.029*	0.099 ± 0.029***	−0.019 ± 0.007*	−23
ICP_Left	−0.219 ± 0.030***	−0.171 ± 0.030***	−0.048 ± 0.007***	22
ICP_Right	−0.257 ± 0.030***	−0.212 ± 0.030***	−0.045 ± 0.007***	17
ML_Left	−0.222 ± 0.030***	−0.172 ± 0.030***	−0.050 ± 0.007***	23
ML_Right	−0.232 ± 0.030***	−0.177 ± 0.030***	−0.055 ± 0.007***	24
MCP	−0.123 ± 0.029***	−0.096 ± 0.030***	−0.027 ± 0.006***	22
PC	0.084 ± 0.030*	0.098 ± 0.031***	−0.014 ± 0.007*	−17
PCR_Left	−0.008 ± 0.030	0.018 ± 0.031	−0.025 ± 0.006***	324
PCR_Right	0.039 ± 0.030	0.065 ± 0.031*	−0.026 ± 0.006***	−68
PLIC_Left	0.155 ± 0.031***	0.183 ± 0.031***	−0.028 ± 0.007***	−18
PLIC_Right	0.074 ± 0.030*	0.100 ± 0.031***	−0.026 ± 0.006***	−35
PTR_Left	−0.002 ± 0.029	0.027 ± 0.029	−0.030 ± 0.007***	1235
PTR_Right	−0.036 ± 0.029	−0.004 ± 0.029	−0.032 ± 0.007***	88
RPIC_Left	−0.034 ± 0.030	0.008 ± 0.031	−0.041 ± 0.007***	122
RPIC_Right	−0.092 ± 0.030*	−0.059 ± 0.031	−0.033 ± 0.006***	36
SS_Left	−0.203 ± 0.030***	−0.171 ± 0.030***	−0.032 ± 0.006***	16
SS_Right	−0.151 ± 0.030***	−0.121 ± 0.030***	−0.031 ± 0.007***	20
SCC	0.058 ± 0.031	0.090 ± 0.031**	−0.031 ± 0.006***	−53
SCP_Left	−0.383 ± 0.030***	−0.330 ± 0.031***	−0.053 ± 0.007***	14
SCP_Right	−0.363 ± 0.030***	−0.311 ± 0.031***	−0.052 ± 0.007***	14
CR_Left	0.008 ± 0.030	0.033 ± 0.030	−0.025 ± 0.006***	−298
CR_Right	0.106 ± 0.030**	0.124 ± 0.030***	−0.019 ± 0.006**	−18
FOF_Left	0.051 ± 0.029	0.075 ± 0.029**	−0.024 ± 0.007**	−48
FOF_Right	0.030 ± 0.029	0.053 ± 0.029	−0.024 ± 0.007**	−80
SLF_Left	−0.070 ± 0.030*	−0.034 ± 0.031	−0.036 ± 0.007***	51
SLF_Right	−0.052 ± 0.030	−0.014 ± 0.031	−0.039 ± 0.007***	74
TP_Left	0.096 ± 0.030**	0.099 ± 0.031***	−0.003 ± 0.006	−4
TP_Right	0.146 ± 0.029***	0.151 ± 0.030***	−0.005 ± 0.006	−4
UNC_Left	0.163 ± 0.030***	0.179 ± 0.031***	−0.016 ± 0.006*	−10
UNC_Right	0.104 ± 0.030***	0.129 ± 0.031***	−0.025 ± 0.007***	−24
Mean	−0.054 ± 0.028	−0.011 ± 0.029	−0.043 ± 0.007***	80

Abbreviations: ACR = Anterior corona radiata; AD = Alzheimer's Disease; ALCOHOL = Alcohol consumption z-score; ALIC = anterior limb of internal capsule; BCC = body of corpus callosum; CCG = cingulum cingulate gyrus; CH = cingulum hippocampus; COGN=Poor cognitive performance z-score; CP = cerebral peduncle; CT = corticospinal tract; DIET = Diet quality z-score; dMRI = Diffusion-weighted magnetic resonance imaging; EC = external capsule; FA=Fractional Anisotropy; FAmean = Global mean of FA; FCST = fornix cres + stria terminalis; FO = fornix; GCC = genu of corpus callosum; FOF = fronto-occipital fasciculus; HDI=Healthy Diet Index; HEALTH=Poor cardio-metabolic and general health z-score; ICP = inferior cerebellar peduncle; ML = medial lemniscus; MCP = middle cerebellar peduncle; MRI = magnetic resonance imaging; PA=Physical Activity z-score; PC = pontine crossing; PCA=Principal Components Analysis; PCR = posterior corona radiata; PLIC = posterior limb of internal capsule; PRS=Polygenic Risk Score; PTR = posterior thalamic radiation; ROIs = regions of interest; RPIC = retrolenticular part of internal capsule; SCC = splenium of corpus callosum; SCP = superior cerebellar peduncle; SCR = superior corona radiata; NUTR=Nutritional biomarker z-score; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SLF = superior longitudinal fasciculus; SS = sagittal stratum; SS=Social Support z-score; TP = tapetum; UK=United Kingdom; UNC = uncinate.

*P < 0.05; **P < 0.010; ***P < 0.001 for null hypothesis that total, direct or indirect effect is equal to zero (*t*-test). Total, direct and indirect effects are estimated as β±SE. Total effect = Direct + Indirect effect. Percent mediated = indirect effect × 100/Total effect.

[a] Values are total, indirect, and direct effects of race with their associated standard errors and p-values; percent of total effect that is mediated and standard deviation value of each outcome. SEM models used are summarized in Fig. 2. Selected numerical findings of key path coefficients are presented in Supplementary Table 6 and illustrated in Fig. 3. Standardized total, indirect and direct effects are further presented in Fig. 3 (heatmap).

[b] See Methods section for a full list of exogenous variables entered into the SEM model.

Table 4
Socio-economic disparities (per SD in SES) in tract-specific FA dMRI outcomes (standardized z-scores): total, direct and indirect effects through SES, lifestyle, health and cognition factors: The UK Biobank 2006–2021 [a,b].

Tract-specific FA, z-scored	Total effect	Direct Effect	Indirect effect	Percent mediated
	β±SE	β±SE	β±SE	
ACR_Left	0.023 ± 0.007*	0.001 ± 0.008	0.023 ± 0.002***	96
ACR_Right	0.030 ± 0.008***	0.007 ± 0.008	0.023 ± 0.002***	76
ALIC_Left	0.072 ± 0.008***	0.045 ± 0.008***	0.027 ± 0.002***	38
ALIC_Right	0.067 ± 0.008***	0.039 ± 0.008***	0.028 ± 0.002***	42
BCC	0.011 ± 0.008	−0.013 ± 0.008	0.024 ± 0.002***	225
CP_Left	0.073 ± 0.008***	0.051 ± 0.008***	0.021 ± 0.002***	29
CP_Right	0.088 ± 0.008***	0.063 ± 0.008***	0.024 ± 0.002***	26
CCG_Left	0.038 ± 0.008***	0.019 ± 0.008*	0.018 ± 0.002***	49
CCG_Right	0.032 ± 0.008***	0.017 ± 0.008*	0.015 ± 0.002	46
CH_Left	0.058 ± 0.008***	0.048 ± 0.008***	0.010 ± 0.002***	17
CH_Right	0.057 ± 0.008***	0.058 ± 0.008***	−0.001 ± 0.002	−1
CT_Left	0.032 ± 0.008***	0.023 ± 0.008*	0.010 ± 0.002***	30
CT_Right	0.036 ± 0.008***	0.033 ± 0.008***	0.002 ± 0.002	6
EC_Left	0.068 ± 0.008***	0.050 ± 0.008***	0.019 ± 0.002***	28
EC_Right	0.063 ± 0.008***	0.042 ± 0.008***	0.021 ± 0.002***	34
FCST_Left	0.075 ± 0.007***	0.047 ± 0.008***	0.028 ± 0.002***	37
FCST_Right	0.071 ± 0.007***	0.050 ± 0.008***	0.021 ± 0.002***	29
FO	0.008 ± 0.007	−0.005 ± 0.007	0.014 ± 0.002***	172
GCC	0.038 ± 0.008***	0.007 ± 0.008	0.031 ± 0.002***	81
ICP_Left	0.069 ± 0.008***	0.037 ± 0.008***	0.032 ± 0.003***	46
ICP_Right	0.066 ± 0.008***	0.039 ± 0.008***	0.027 ± 0.002***	41
ML_Left	0.080 ± 0.008***	0.058 ± 0.008***	0.022 ± 0.002***	28
ML_Right	0.087 ± 0.008***	0.067 ± 0.008***	0.021 ± 0.002***	24
MCP	0.031 ± 0.008***	0.023 ± 0.008*	0.008 ± 0.002**	26
PC	−0.054 ± 0.008***	−0.038 ± 0.008***	−0.016 ± 0.002***	29
PCR_Left	0.036 ± 0.008***	0.019 ± 0.008*	0.016 ± 0.002***	47
PCR_Right	0.030 ± 0.008***	0.017 ± 0.009*	0.013 ± 0.002***	44
PLIC_Left	0.064 ± 0.008***	0.042 ± 0.009***	0.021 ± 0.002***	34
PLIC_Right	0.051 ± 0.008***	0.038 ± 0.009***	0.013 ± 0.002***	26
PTR_Left	0.052 ± 0.008***	0.026 ± 0.008*	0.027 ± 0.002***	51
PTR_Right	0.052 ± 0.008***	0.026 ± 0.008*	0.026 ± 0.002***	50
RPIC_Left	0.077 ± 0.008***	0.046 ± 0.009***	0.031 ± 0.002***	40
RPIC_Right	0.042 ± 0.008***	0.028 ± 0.009*	0.014 ± 0.002***	34
SS_Left	0.054 ± 0.008***	0.025 ± 0.008*	0.029 ± 0.002***	54
SS_Right	0.046 ± 0.008***	0.023 ± 0.008*	0.023 ± 0.002***	51
SCC	0.017 ± 0.008*	−0.002 ± 0.009	0.019 ± 0.002***	115
SCP_Left	0.132 ± 0.008***	0.098 ± 0.008***	0.034 ± 0.003***	26
SCP_Right	0.135 ± 0.008***	0.097 ± 0.008***	0.038 ± 0.003***	28
CR_Left	0.053 ± 0.008***	0.034 ± 0.008***	0.019 ± 0.002***	35
CR_Right	0.038 ± 0.008***	0.024 ± 0.008*	0.014 ± 0.002***	38
FOF_Left	0.061 ± 0.008***	0.036 ± 0.008***	0.025 ± 0.002***	42
FOF_Right	0.063 ± 0.008***	0.037 ± 0.008***	0.026 ± 0.002***	41
SLF_Left	0.067 ± 0.008***	0.041 ± 0.008***	0.026 ± 0.002***	39
SLF_Right	0.068 ± 0.008***	0.044 ± 0.008***	0.024 ± 0.002***	36
TP_Left	0.005 ± 0.008	−0.003 ± 0.008	0.008 ± 0.002**	177
TP_Right	0.012 ± 0.008	0.004 ± 0.008	0.008 ± 0.002**	67
UNC_Left	0.021 ± 0.008	0.009 ± 0.008	0.012 ± 0.002***	58
UNC_Right	0.027 ± 0.008**	0.009 ± 0.009	0.018 ± 0.002***	66
Mean	0.076 ± 0.008***	0.044 ± 0.008***	0.031 ± 0.002***	41

Abbreviations: ACR = Anterior corona radiata; AD = Alzheimer's Disease; ALCOHOL = Alcohol consumption z-score; ALIC = anterior limb of internal capsule; BCC = body of corpus callosum; CCG = cingulum cingulate gyrus; CH = cingulum hippocampus; COGN=Poor cognitive performance z-score; CP = cerebral peduncle; CT = corticospinal tract; DIET = Diet quality z-score; dMRI = Diffusion-weighted magnetic resonance imaging; EC = external capsule; FA=Fractional Anisotropy; FAmean = Global mean of FA; FCST = fornix cres + stria terminalis; FO = fornix; GCC = genu of corpus callosum; FOF = fronto-occipital fasciculus; HDI=Healthy Diet Index; HEALTH=Poor cardio-metabolic and general health z-score; ICP = inferior cerebellar peduncle; ML = medial lemniscus; MCP = middle cerebellar peduncle; MRI = magnetic resonance imaging; PA=Physical Activity z-score; PC = pontine crossing; PCA=Principal Components Analysis; PCR = posterior corona radiata; PLIC = posterior limb of internal capsule; PRS=Polygenic Risk Score; PTR = posterior thalamic radiation; ROIs = regions of interest; RPIC = retrolenticular part of internal capsule; SCC = splenium of corpus callosum; SCP = superior cerebellar peduncle; SCR = superior corona radiata; NUTR=Nutritional biomarker z-score; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SLF = superior longitudinal fasciculus; SS = sagittal stratum; SS=Social Support z-score; TP = tapetum; UK=United Kingdom; UNC = uncinate.

*P < 0.05; **P < 0.010; ***P < 0.001 for null hypothesis that total, direct or indirect effect is equal to zero (*t*-test.). Total, direct and indirect effects are estimated as β±SE. Total effect = Direct + Indirect effect. Percent mediated = indirect effect × 100/Total effect.

[a] Values are total, indirect, and direct effects of SES with their associated standard errors and p-values; percent of total effect that is mediated and standard deviation value of each outcome. SEM models used are summarized in Fig. 2. Selected numerical findings of key path coefficients are presented in Supplementary Table 6 and illustrated in Fig. 3. Standardized total, indirect and direct effects are further presented in Fig. 3 (heatmap).

[b] See Methods section for a full list of exogenous variables entered into the SEM model.

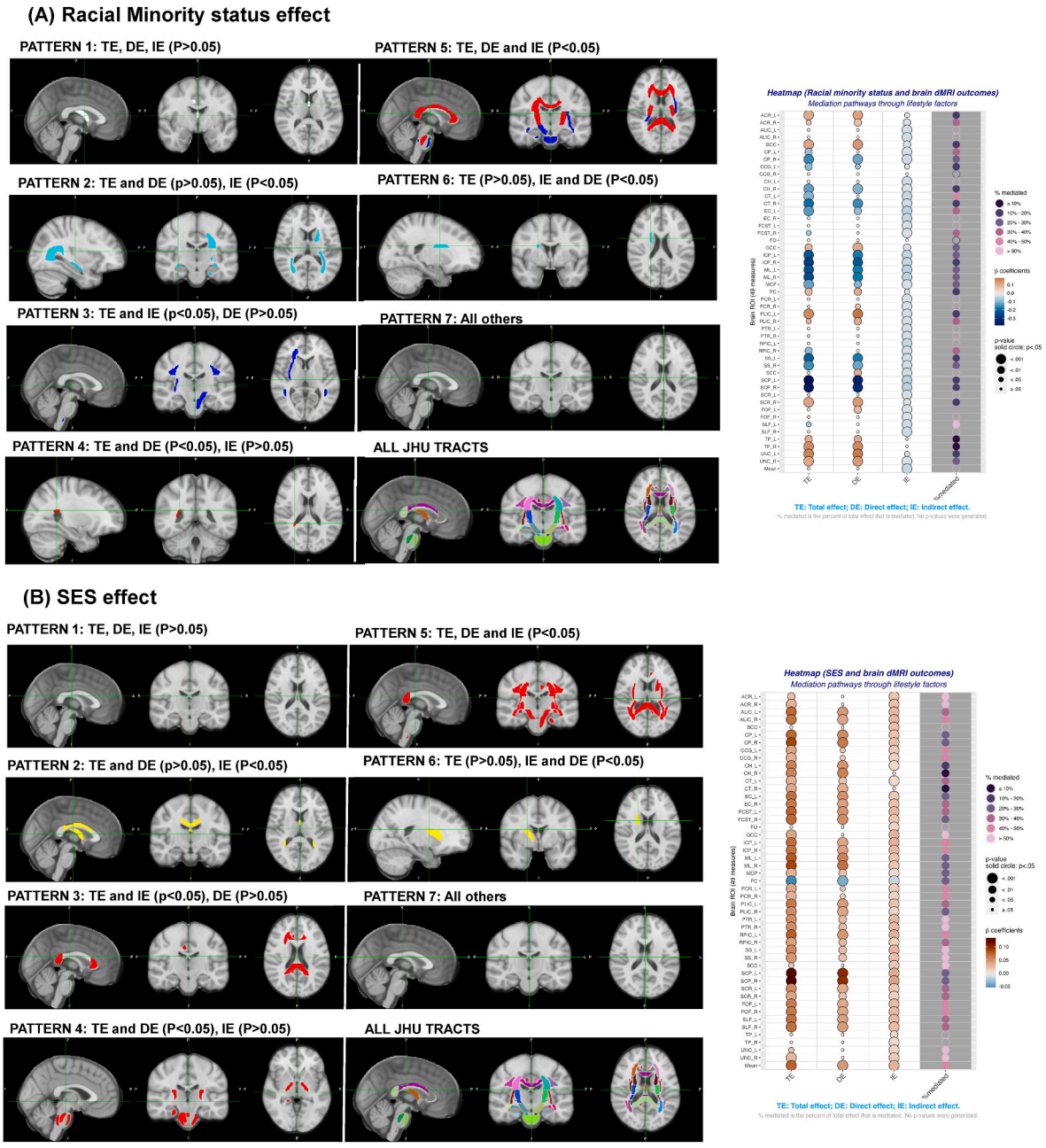

Fig. 3. Main findings from SEM models on standard brain images and heat maps for race/ethnic (Non-White vs. White) and SES total, indirect and direct effects on dMRI outcomes: global mean and tract-specific fractional anisotropy (z-scored)[a,b]. *Abbreviations*: DE = Direct Effect; IE=Indirect Effect; SEM= Structural Equations Model; SES=Socio-Economic Status; TE = Total Effect; [a] Mediational patterns plotted on standard brain images pertain only to subcortical structures, and are based on statistical significance of TE, IE and DE. Dark blue color is for significant TE reflecting an inverse association with the subcortical structure. Light blue color is used when TE is non-significant but IE is significant reflecting an inverse association with the subcortical structure through a series of mediators. Dark red is for a positive association based on a significant, positive TE. Yellow is used for significant positive IE, when TE is not statistically significant at type I error of 0.05. Brain image visualization used a standard MNI 152 brain template and FSLEYES software: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes. [b] Heat map shows the associations of race and SES with all dMRI outcomes, focusing on standardized associations (TE, IE and DE) and percent mediated. For TE, DE and IE, blueish colors are for inverse associations and brownish colors are for positive associations. Size of the circle pertains to p-values associated with TE, IE and DE. Pink/purple colors are for proportion mediated, irrespective of the direction of the IE or TE. However, those were left empty when p-values associated with TE were >0.05. Heatmaps were generated using R Software. FA_{mean} is unitless and entered in this analysis as a standardized z-score. 1 SD of FA_{mean} is equivalent to 0.020. The same applied to tract-specific FA, though with varying SDs. See Tables 3 and 4 for details and abbreviations. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

contrast, and lower SES predicted reduced global WMI, with SES playing a central role in FA_{mean} pathways. FA_{mean} association with poor cognition at baseline was stronger in uppermost AD PRS tertiles. With only a few exceptions, this study is unique in its consideration of various pathways that might link racial minority status to SES and other downstream factors and finally to a widely used measure of WMI, namely FA. The study also goes into details by testing the model across WM tracts in addition to considering effect modification by AD PRS and categorizing patterns of associations with tract-specific FA. This categorization focused on the statistical significance and direction of indirect effects observed from racial minority status into tract-specific FA and SES into tract-specific FA, adjusting for various exogenous variables.

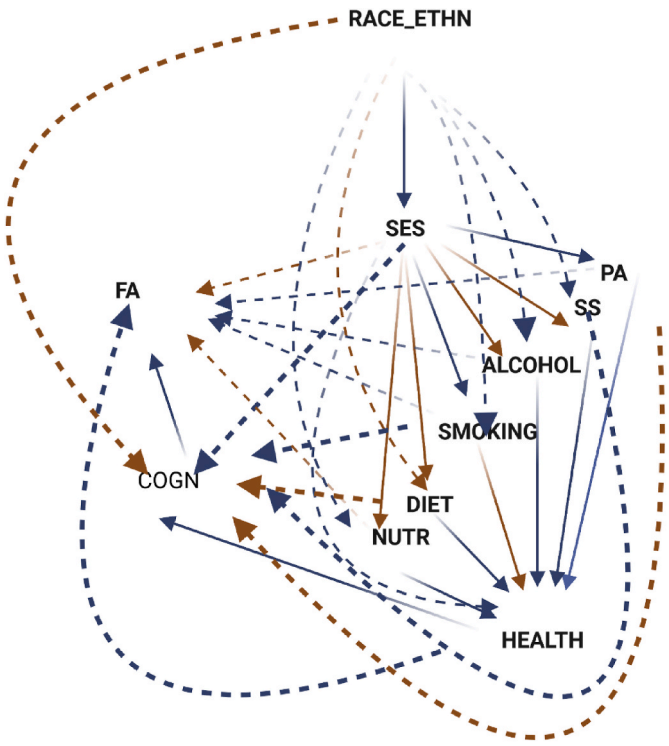

Fig. 4. SEM findings for key dMRI outcomes: Fractional Anisotropy (FA)[a,b]. *Abbreviations*: ALCOHOL = Alcohol consumption z-score; COGN=Poor cognitive performance z-score; DIET = Diet quality z-score; dMRI = Diffusion-weighted magnetic resonance imaging; FA=Fractional Anisotropy; HEALTH-=Poor cardio-metabolic and general health z-score; PA=Physical Activity z-score; NUTR=Nutritional biomarker z-score; SD=Standard Deviation; SEM=Structural Equations Model; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SS=Social Support z-score. [a] Arrows indicate statistically significant direct effects from SEM models. Blue arrows stand for inverse relationships ($\beta < 0$, $p < 0.05$), red arrow stand for positive relationships ($\beta > 0$, $p < 0.05$), solid lines are for direct effects that are part of the hypothesized pathway; dashed lines are direct effects outside the hypothesized pathway. FA_{mean} is unitless and entered in this analysis as a standardized z-score. 1 SD of FA_{mean} is equivalent to 0.020. [b] See Methods section for a full list of exogenous variables entered into the SEM model. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Thus, previous studies are only comparable with respect to regression model results, as very few have employed SEM analyses with outcome being FA.

4.2. Previous studies

Racial and socioeconomic differences in markers of brain health are widely reported yet their underlying drivers remain poorly understood. Potential sources of variation that may contribute to the observed differences in our study may include, for example, structural, environmental, and psychosocial influences that unfold over the life course. Exposure to stressors, for example, may affect brain development and integrity in early life, and numerous studies report such exposures may be patterned by race and SES (Tooley et al., 2021). Access to quality nutrition, pollutants, and healthcare are key inputs into brain health which are also known to vary across race and SES (Alchalabi & Prather, 2021; Olivari et al., 2023, pp. 128–132; Resende et al., 2019). Recent studies also point to the role played by racial discrimination in reducing brain WMI (Fani et al., 2021; O. Okeke et al., 2023; Onyebuchi Okeke, Elbasheir, Harnett, et al., 2022). Among 116 Black American women, racial discrimination was independently related to decrements in white matter microarchitecture throughout the brain, an additive and distinctive effect from other types of adversities (Fani et al., 2021). Another study on 79 African American women concluded that racial discrimination may increase risk for medical disorders through neuroplastic effects on stress-sensitive prefrontal white matter tracts, which may affect health behaviors and vulnerability for medical disorders (Onyebuchi Okeke, Elbasheir, Carter, et al., 2022). Although the present study did not include racial discrimination as a potential mediator, a variable not available in the UK Biobank study at baseline assessment, racial minority status association with FA not explained by SES may be due to those other structural factors and stressors listed above.

Genetic features related to AD may also play a role in the observed findings. It's been reported that black adults are more likely to carry the APOE-e4 allele compared with their white counterparts (May A. Beydoun, Weiss, et al., 2021). Thus, even if APOE-e4 operates identically amongst black and white adults, the higher prevalence of APOE-e4 amongst black adults could help explain the observed differences reported in our study considering our finding that the association between cognition and FA_{mean} was stronger amongst the higher AD PRS tertiles.

The influence of education and other SES-related factors on brain structural changes have been elucidated in several recent studies (T. R. Austin et al., 2022b; Dougherty et al., 2020; Walhovd et al., 2022). Shaked et al. found that lower SES was associated with poorer cognitive performance and white matter integrity, with lower Trails B performance associated with poorer integrity in regions of the ALIC, the external capsule, and the superior longitudinal fasciculus and lower performance on the Stroop Color and Word test was associated with poorer ALIC and EC integrity.

Other studies examined whether SES differences in brain structural metrics were mediated by lifestyle or health-related factors but few evaluated FA or other dMRI outcomes. A recent study examined whether community disadvantage was negatively related to brain morphology via 2 biological factors encompassing cardiometabolic disease risk and neuroendocrine function, using data on 448 middle-aged adults who underwent structural neuroimaging to assess cortical and subcortical brain tissue morphology (P. J. Gianaros et al., 2017). Another recent study suggested that dwelling in the most disadvantaged neighborhoods was associated with significantly lower cerebral volumes, suggesting an association of community socio-economic context, distinct from individual-level socio-economic status, with brain volume during aging (Hunt et al., 2020). Cardiovascular risk mediated this association for total brain tissue volume but not for hippocampal volume, suggesting that neighborhood-level disadvantage may be associated with these outcomes via distinct biological pathways (Hunt et al., 2020). According to a study by Gianaros et al., socio-economic disadvantage confers risk for ill health that may be mediated by systemic inflammatory influences on the integrity of distributed brain networks. Mediation modeling was used to test associations between socio-economic position indicators and measures of WMI. Indirect mediating paths showed that adiposity, cigarette smoking, and CRP partially mediated these effects (Peter J Gianaros et al., 2013). The Multi-Ethnic Study of Atherosclerosis (MESA) study investigated associations of race, ethnicity, and cardiovascular risk factors with brain morphology and WM injury in a diverse population (Thomas R Austin et al., 2022a). Results showed that greater average WM hyperintensity volume was associated with older age and current smoking, while lower FA was associated with higher diastolic blood pressure, use of antihypertensive medication, and diabetes (Thomas R Austin et al., 2022a). Overall, older age, current smoking, hypertension, and diabetes were strongly associated with WM injury (Thomas R Austin et al., 2022a). Importantly, the study did not detect any racial/ethnic differences in those metrics upon adjustment for socio-economic status and health-related downstream factors (Thomas R Austin et al., 2022a).

Lifestyle factors have been more extensively studied in relation to dMRI outcomes without uncovering pathways between them. Using dMRI data on 56 healthy individuals, a study detected changes in hippocampus connected to cardiopulmonary fitness (Chen et al., 2020).

Table 5
Racial disparities in global mean FA: six indirect effects through SES, lifestyle, health and cognition factors: The UK Biobank 2006–2021[a,b].

	Unstandardized			Percent mediated		SD	TE	IE
	β	SE	P	% of TE	% of IE			
Global mean FA						0.020376	−0.0010993	**−0.000876*****
RACE_ETHN→SES→FA_{mean}	**−0.000185**	**0.0000371**	**5.8e-07**	**16.8**	**21.1**			
RACE_ETHN→SES→LIFESTYLE→ FA_{mean}	−0.00001	7.99e-06	0.19	0.91	**1.1**			
RACE_ETHN→SES→LIFESTYLE→HEALTH→FA_{mean}	**−0.000017**	**2.11e-06**	**1.9e-15**	**1.54**	**1.94**			
RACE_ETHN→SES→LIFESTYLE→HEALTH→ COGN→ FA_{mean}	**2.3e-07**	**5.57e-08**	**0.000045**	−0.02	−0.03			
RACE_ETHN→SES→LIFESTYLE → COGN→ FA_{mean}	3.9e-07	3.93e-07	0.32	−0.04	−0.04			
RACE_ETHN→SES→ COGN→ FA_{mean}	**−0.000018**	**3.93e-07**	**<0.001**	**1.63**	**2.05**			

Abbreviations: AD = Alzheimer's Disease; ALCOHOL = Alcohol consumption z-score; COGN=Poor cognitive performance z-score; DIET = Diet quality z-score; dMRI = Diffusion-weighted magnetic resonance imaging; HEALTH=Poor cardio-metabolic and general health z-score; LIFESTYLE = LIFESTYLE factors; PA=Physical Activity z-score; PRS=Polygenic Risk Score; NUTR=Nutritional biomarker z-score; SD=Standard Deviation; SE=Standard Error; SEM=Structural Equations Models; SES=Socio-economic status z-score; SMOKING=Smoking z-score; SS=Social Support z-score; UK=United Kingdom.
*P < 0.05; **P < 0.010; ***P < 0.001 for null hypothesis that indirect effect β = 0 (*t*-test.). Total, direct and indirect effects are estimated as β±SE. Each pathway is also estimated as a partial indirect effect as β±SE using the delta method. Total effect = Direct + Indirect effect. Percent mediated = partial indirect effect × 100/Total effect or partial indirect effect × 100/Indirect effect.
a Values are six partial indirect effects of race with their associated standard errors and p-values; percent of total effect that is mediated; percent of indirect effect that is mediated; standard deviation value of each outcome; total and indirect effects from SEM. SEM models used are summarized in Fig. 2. Selected numerical findings of key path coefficients are presented in Supplementary Table 6 and illustrated in Fig. 4. Standardized total, indirect and direct effects are further presented in Fig. 3 (heatmap for tract-specific FA and FA_{mean}). FA_{mean} is unitless and entered as is. TE and IE were re-adjusted to the unstandardized FA values. FA_{mean} is unitless and entered as is, without z-score standardization. 1 SD of FA_{mean} is equivalent to 0.020.
b See Methods section for a full list of exogenous variables entered into the SEM model.

Using data from the Multidomain Approach for Preventive Trial phase III, researchers found that physical activity levels influence the white matter integrity, (Maltais et al., 2020) findings corroborated by another recent study of healthy subjects (Bashir et al., 2021). Accumulating evidence shows that cigarette smoking and alcohol intake are both connected to white matter disruption. For instance, researchers detected major macroscopic and microscopic differences in white matter integrity with increased alcohol intake (McEvoy et al., 2018). Other researchers found that adiposity and inflammatory biomarkers such as C-reactive protein impacted the structural integrity of networks in the brain (Okudzhava et al., 2022; Wassenaar et al., 2019). Dietary patterns and various nutritional biomarkers, such as vitamin D status and the RDW, play a key role in cognitive aging and have been associated with microstructural brain integrity in several recent studies (M. A. Beydoun et al., 2020; M. A. Beydoun, Shaked, et al., 2021). Social network diversity also has been shown to affect microstructural integrity, independently of socio-economic and demographic factors (Flinkenflugel et al., 2023; van der Velpen et al., 2022). In our present study, smoking appeared to explain a significant portion of the SES disparities in FA_{mean} (7%), while 16% of the TE of RACE→FA_{mean} association was explained by an indirect effect through SES only. Most notably, however, around 26% of the total effect of SES on global mean of FA was explained by the HEALTH factor, reflecting poor cardiometabolic and general health. Thus, future intervention studies should focus their attention on socio-economic changes, smoking cessation and improvement of cardiometabolic and general health to alleviate both racial and socio-economic disparities in WMI.

Hemispherical asymmetry in atrophy patterns is observed with AD, dementia and other neurodegenerative conditions. For example, a meta-analysis comprising 159 studies related to aging and neurodegenerative diseases reported atrophy in the right hippocampus in MCI, but rather left hippocampal atrophy in AD. (Minkova et al., 2017) This is consistent with a general trend that the left hemisphere is more susceptible to neurodegeneration in AD, (Thompson et al., 2003) leading to asymmetrical differences in brain atrophy. Our findings indicated that socio-economic disparities in FA within the left cingulum hippocampus region was partially mediated by downstream lifestyle, health-related and cognitive factors, while those disparities were largely a direct effect in the case of right hippocampal FA. This suggests that lifestyle, health-related and cognition factors could help narrow FA-related socio-economic disparities among individuals at risk for developing AD. Moreover, a recent meta-analysis indicated that atrophy in the left hippocampal volume was associated with decline in the domain of verbal memory whereas that of right hippocampal volume was rather linked to spatial cognitive decline (Burgess et al., 2002).

4.3. Strengths and limitations

To our knowledge, our study is the largest with neuroimaging markers that examined racial and SES differences in brain volumetric outcomes, and the first to do so by uncovering pathways through behavioral and cognitive factors. Potential study limitations include residual confounding, measurement error, and potential selection bias due to incomplete data on cognitive performance and the participants who consented for imaging analysis. Specifically, self-report of many of the key variables, including race/ethnicity, can result in measurement error that may or may not be independent of the outcome of interest, namely FA. In fact, combining racial minorities together could mask important variation that exists within these population subgroups and may underestimate some of the effects of race on FA_{mean}, as shown for the Black vs. White participant contrast in our secondary analyses. Moreover, residual confounding may result from excluding important confounders as exogenous covariates in our SEM models. Potential selection bias was at least partially adjusted for by including an inverse mills ratio in all models including SEM models. Furthermore, there was no systematic adjustment for multiplicity of testing, leading to numerous chance findings at a type I error of 0.05. Thus, we mainly focused on findings with P-values <0.001. In addition, many of the

effect sizes observed were small to very small, except for a few tract-specific FA values which exceeded an effect size of 0.20 difference across race, in absolute value. Nevertheless, most associations with global mean FA had an effect size <0.10 (race or SES effects). It is worth noting also that the percent non-White participants out of the overall sample was <5%, which may result in identification problems in our models and our inability to infer causality due to low variation in the main exposure. Therefore, future studies with more balanced proportions across race/ethnic groups should attempt at replicating our findings. The use of dMRI and specifically FA limits spatial specificity and may not be able to decipher nuanced differences in fiber quantity trajectory or orientation. The findings are further supported by a parallel study among older adults in the US (M. A. Beydoun, Weiss, et al., 2022) which revealed pathways similar to those uncovered in the current study. Other recent work further corroborates other pathways observed in the current study, including mechanisms related to diet and social support across different income groups (M. A. Beydoun, Beydoun, et al., 2022).Given the contemporaneous measurement of cognitive performance and lifestyle factors among others, reverse causality whereby behavior change driven by perceived poor cognition is observed in our mediational pathway models.

5. Conclusions

Race and lower SES were important determinants of WMI outcomes, with partial mediation of socio-economic disparities in global mean FA through lifestyle, health-related and cognition factors. Poor cognition's association with lower global mean FA was stronger at higher AD polygenic risk. These findings have important public health implications suggesting that racial disparities in WMI can be intervened mainly by socio-economic interventions, while socio-economic disparities can be partially alleviated by lifestyle, health-related and cognitive training interventions. Furthermore, the association between WMI and cognition was stronger at higher AD PRS, a possibly bi-directional relationship. This finding suggests that AD polygenic risk is important when it comes to assessing the potential effect of poor WMI on future cognition or the association of poor cognition with poor WMI within an average follow-up time of 10–15 years. Future studies should attempt to replicate our cross-sectional findings and further extend examining those relationships in longitudinal study with at least two repeats on neuroimaging metrics.

Sources of funding

This work was supported in part by the Intramural Research Program of the NIH, National Institute on Aging, National Institutes of Health project number AG000513.

Financial disclosure

All co-authors declare no biomedical or financial conflicts of interest.

Data statement

The data has not been previously presented orally or by poster at scientific meetings.

Ethics statement

The studies involving human participants were reviewed and approved by the UK Biobank has approval from the Institutional Review Boards, namely, the North West Multi-centre Research Ethics Committee for the United Kingdom, from the National Information Governance Board for Health and Social Care for England and Wales, and from the Community Health Index Advisory Group for Scotland. All participants gave informed consent for the study via a touch-screen interface that required agreement for all individual statements on the consent form as well as the participant's signature on an electronic pad. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements. This current work was approved by the Institutional Review Board of the National Institutes of Health.

Disclosures

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or U.S. Government. Reference to any commercial products within this publication does not create or imply any endorsement by Fort Belvoir Community Hospital, the Defense Health Agency, Department of Defense, or U.S. Government.

CRediT authorship contribution statement

Jordan Weiss: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Data curation, Conceptualization. **May A. Beydoun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hind A. Beydoun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Michael F. Georgescu:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Data curation, Conceptualization. **Yi-Han Hu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Nicole Noren Hooten:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Conceptualization. **Sri Banerjee:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Lenore J. Launer:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Conceptualization. **Michele K. Evans:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Alan B. Zonderman:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

The authors do not have permission to share data.

Acknowledgments

The authors would like to thank the UK Biobank investigators, staff and participants, as well as Mr. Matt Hodgson and all the staff and analysts from the UK Biobank access management system. This work uses data provided by patients and collected by the NHS as part of their care and support. This research also used data assets made available by National Safe Haven as part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation (research which commenced between 1st October 2020–31st March 2021 grant ref MC_PC_20029; 1st April 2021–30th September 2022 grant ref MC_PC_20058). Importantly, this research has been conducted using the

UK Biobank Resource under Application Number 77963.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2024.101655.

References

Alchalabi, T., & Prather, C. (2021). Brain health. *Clinics in Geriatric Medicine, 37*, 593–604.

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N. K., Andersson, J. L. R., Griffanti, L., Douaud, G., et al. (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *NeuroImage, 166*, 400–424.

Alzheimer's, A. (2016). 2016 Alzheimer's disease facts and figures. *Alzheimers Dement, 12*, 459–509.

Andrews, S. J., Fulton-Howard, B., O'Reilly, P., Marcora, E., Goate, A. M., & collaborators of the Alzheimer's Disease Genetics, C. (2021). Causal associations between modifiable risk factors and the Alzheimer's phenome. *Annals of Neurology, 89*, 54–65.

Austin, T. R., Nasrallah, I. M., Erus, G., Desiderio, L. M., Chen, L. Y., Greenland, P., et al. (2022a). Association of brain volumes and white matter injury with race, ethnicity, and cardiovascular risk factors: The multi-ethnic study of atherosclerosis. *Journal of the American Heart Association, 11*, Article e023159.

Austin, T. R., Nasrallah, I. M., Erus, G., Desiderio, L. M., Chen, L. Y., Greenland, P., et al. (2022b). Association of brain volumes and white matter injury with race, ethnicity, and cardiovascular risk factors: The multi-ethnic study of atherosclerosis. *Journal of American Heart Association, 11*, Article e023159.

Bashir, S., Al-Sultan, F., Jamea, A. A., Almousa, A., Alnafisah, M., Alzahrani, M., et al. (2021). Physical exercise keeps the brain connected by increasing white matter integrity in healthy controls. *Medicine, 100*.

Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance - Series B, 111*, 209–219.

Benitez, A., Fieremans, E., Jensen, J. H., Falangola, M. F., Tabesh, A., Ferris, S. H., et al. (2014). White matter tract integrity metrics reflect the vulnerability of late-myelinating tracts in Alzheimer's disease. *Neuroimage Clinica, 4*, 64–71.

Beydoun, M. A., Beydoun, H. A., Banerjee, S., Weiss, J., Evans, M. K., & Zonderman, A. B. (2022). Pathways explaining racial/ethnic and socio-economic disparities in incident all-cause dementia among older US adults across income groups. *Translational Psychiatry, 12*, 478.

Beydoun, M. A., Beydoun, H. A., Fanelli-Kuczmarski, M. T., Weiss, J., Georgescu, M. F., Meirelles, O., et al. (2023a). Pathways explaining racial/ethnic and socio-economic disparities in dementia incidence: The UK biobank study. *Aging (Albany NY), 15*, 9310–9340.

Beydoun, M. A., Beydoun, H. A., Gale, S. D., Hedges, D., Weiss, J., Li, Z., et al. (2023b). Cardiovascular health, infection burden and their interactive association with brain volumetric and white matter integrity outcomes in the UK Biobank. *Brain, Behavior, and Immunity, 113*, 91–103.

Beydoun, M. A., Beydoun, H. A., Gamaldo, A. A., Teel, A., Zonderman, A. B., & Wang, Y. (2014). Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis. *BMC Public Health, 14*, 643.

Beydoun, M. A., Beydoun, H. A., Kitner-Triolo, M. H., Kaufman, J. S., Evans, M. K., & Zonderman, A. B. (2013). Thyroid hormones are associated with cognitive function: Moderation by sex, race, and depressive symptoms. *Journal of Clinical Endocrinology & Metabolism, 98*, 3470–3481.

Beydoun, M. A., Noren Hooten, N., Weiss, J., Maldonado, A. I., Beydoun, H. A., Katzel, L. I., et al. (2023c). Plasma neurofilament light as blood marker for poor brain white matter integrity among middle-aged urban adults. *Neurobiology of Aging, 121*, 52–63.

Beydoun, M. A., Shaked, D., Hossain, S., Beydoun, H. A., Katzel, L. I., Davatzikos, C., et al. (2020). Vitamin D, folate, and cobalamin serum concentrations are related to brain volume and white matter integrity in urban adults. *Frontiers in Aging Neuroscience, 12*, 140.

Beydoun, M. A., Shaked, D., Hossain, S., Weiss, J., Beydoun, H. A., Maldonado, A. I., et al. (2021). Red cell distribution width, anemia and their associations with white matter integrity among middle-aged urban adults. *Neurobiology of Aging, 105*, 229–240.

Beydoun, M. A., Weiss, J., Beydoun, H. A., Fanelli-Kuczmarski, M. T., Hossain, S., El-Hajj, Z. W., et al. (2022). Pathways explaining racial/ethnic disparities in incident all-cause and Alzheimer's disease dementia among older US men and women. *Alzheimers Dement (N Y), 8*, Article e12275.

Beydoun, M. A., Weiss, J., Beydoun, H. A., Hossain, S., Maldonado, A. I., Shen, B., et al. (2021). Race, APOE genotypes, and cognitive decline among middle-aged urban adults. *Alzheimer's Research & Therapy, 13*, 120.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron, 35*, 625–641.

Cavedo, E., Galluzzi, S., Pievani, M., Boccardi, M., & Frisoni, G. B. (2012). Norms for imaging markers of brain reserve. *Journal of Alzheimers Diseases, 31*, 623–633.

Chadeau-Hyam, M., Bodinier, B., Vermeulen, R., Karimi, M., Zuber, V., Castagne, R., et al. (2020). Education, biological ageing, all-cause and cause-specific mortality and morbidity: UK biobank cohort study. *EClinicalMedicine, 29–30*, Article 100658.

Chen, F. T., Erickson, K. I., Huang, H., & Chang, Y. K. (2020). The association between physical fitness parameters and white matter microstructure in older adults: A diffusion tensor imaging study. *Psychophysiology, 57*, Article e13539.

Cox, S. R., Lyall, D. M., Ritchie, S. J., Bastin, M. E., Harris, M. A., Buchanan, C. R., et al. (2019). Associations between vascular risk factors and brain MRI indices in UK Biobank. *European Heart Journal, 40*, 2290–2300.

de Groot, M., Vernooij, M. W., Klein, S., Ikram, M. A., Vos, F. M., Smith, S. M., et al. (2013). Improving alignment in tract-based spatial statistics: Evaluation and optimization of image registration. *NeuroImage, 76*, 400–411.

Dougherty, R. J., Moonen, J., Yaffe, K., Sidney, S., Davatzikos, C., Habes, M., et al. (2020). Smoking mediates the relationship between SES and brain volume: The CARDIA study. *PLoS One, 15*, Article e0239548.

Fani, N., Harnett, N., Carter, S., Bradley, B., & Ressler, K. (2021). Effects of racial discrimination on white matter microarchitecture in trauma-exposed Black American women. *Biological Psychiatry, 89*, S330.

Flinkenflugel, K., Meinert, S., Thiel, K., Winter, A., Goltermann, J., Strathausen, L., et al. (2023). Negative stressful life events and social support are associated with white matter integrity in depressed patients and healthy control participants: A diffusion tensor imaging study. *Biological Psychiatry, 94*, 650–660.

Gianaros, P. J., Kuan, D. C., Marsland, A. L., Sheu, L. K., Hackman, D. A., Miller, K. G., et al. (2017). Community socioeconomic disadvantage in midlife relates to cortical morphology via neuroendocrine and cardiometabolic pathways. *Cerebral Cortex, 27*, 460–473.

Gianaros, P. J., Marsland, A. L., Sheu, L. K., Erickson, K. I., & Verstynen, T. D. (2013). Inflammatory pathways link socioeconomic inequalities to white matter architecture. *Cerebral Cortex, 23*, 2058–2071.

Glymour, M. M., Chene, G., Tzourio, C., & Dufouil, C. (2012). Brain MRI markers and dropout in a longitudinal study of cognitive aging: The three-city dijon study. *Neurology, 79*, 1340–1348.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science, 297*, 353–356.

Helmer, C., Pasquier, F., & Dartigues, J. F. (2006). [Epidemiology of Alzheimer disease and related disorders]. *Medical Science, 22*, 288–296.

Hsu, F. C., Sink, K. M., Hugenschmidt, C. E., Williamson, J. D., Hughes, T. M., Palmer, N. D., et al. (2018). Cerebral structure and cognitive performance in african Americans and European Americans with type 2 diabetes. *Journal of Gerontology A Biology Science Medicine Science, 73*, 407–414.

Hunt, J. F. V., Buckingham, W., Kim, A. J., Oh, J., Vogt, N. M., Jonaitis, E. M., et al. (2020). Association of neighborhood-level disadvantage with cerebral and hippocampal volume. *JAMA Neurology, 77*, 451–460.

Jones, D. K. (2008). Studying connections in the living human brain with diffusion MRI. *Cortex, 44*, 936–952.

Lee, K. J., & Carlin, J. B. (2010). Multiple imputation for missing data: Fully conditional specification versus multivariate normal imputation. *American Journal of Epidemiology, 171*, 624–632.

Lindeboom, J., & Weinstein, H. (2004). Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. *European Journal of Pharmacology, 490*, 83–86.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet commission. *Lancet, 396*, 413–446.

Louapre, C., Govindarajan, S. T., Gianni, C., Madigan, N., Nielsen, A. S., Sloane, J. A., et al. (2016). The association between intra- and juxta-cortical pathology and cognitive impairment in multiple sclerosis by quantitative T2* mapping at 7 T MRI. *Neuroimage Clinica, 12*, 879–886.

Maltais, M., Rolland, Y., Boisvert-Vigneault, K., Perus, L., Mangin, J.-F., Grigis, A., et al. (2020). Prospective associations between physical activity levels and white matter integrity in older adults: Results from the MAPT study. *Maturitas, 137*, 24–29.

McEvoy, L. K., Fennema-Notestine, C., Elman, J. A., Eyler, L. T., Franz, C. E., Hagler, D. J., Jr., et al. (2018). Alcohol intake and brain white matter in middle aged men: Microscopic and macroscopic differences. *NeuroImage: Clinical, 18*, 390–398.

Minkova, L., Habich, A., Peter, J., Kaller, C. P., Eickhoff, S. B., & Kloppel, S. (2017). Gray matter asymmetries in aging and neurodegeneration: A review and meta-analysis. *Human Brain Mapping, 38*, 5890–5904.

Muller, T., Payton, N. M., Kalpouzos, G., Jessen, F., Grande, G., Backman, L., et al. (2020). Cognitive, genetic, brain volume, and diffusion tensor imaging markers as early indicators of dementia. *Journal of Alzheimers Diseases, 77*, 1443–1453.

Navale, S. S., Mulugeta, A., Zhou, A., Llewellyn, D. J., & Hypponen, E. (2022). Vitamin D and brain health: An observational and mendelian randomization study. *American Journal of Clinical Nutrition, 116*, 531–540.

Okeke, O., Elbasheir, A., Carter, S. E., Powers, A., Mekawi, Y., Gillespie, C. F., et al. (2022). Indirect effects of racial discrimination on health outcomes through prefrontal cortical white matter integrity. *Biological psychiatry: Cognitive neuroscience and neuroimaging*.

Okeke, O., Elbasheir, A., Carter, S. E., Powers, A., Mekawi, Y., Gillespie, C. F., et al. (2023). Indirect effects of racial discrimination on health outcomes through prefrontal cortical white matter integrity. *Biology Psychiatry Cognition Neuroscience Neuroimaging, 8*, 741–749.

Okeke, O., Elbasheir, A., Harnett, N., Carter, S., Ressler, K., Bradley, B., et al. (2022). Prefrontal cortical white matter integrity mediates associations between racial discrimination and health outcomes. *Biological Psychiatry, 91*, S46.

Okudzhava, L., Heldmann, M., & Münte, T. F. (2022). A systematic review of diffusion tensor imaging studies in obesity. *Obesity Reviews, 23*, Article e13388.

Olivari, B. S., Jeffers, E. M., Tang, K. W., & McGuire, L. C. (2023). *Improving brain health for populations disproportionately affected by Alzheimer's disease and related dementias*. Taylor & Francis.

Resende, E.d. P. F., Guerra, J. J. L., & Miller, B. L. (2019). Health and socioeconomic inequities as contributors to brain health. *JAMA Neurology, 76*, 633–634.
Shaked, D., Leibel, D. K., Katzel, L. I., Davatzikos, C., Gullapalli, R. P., Seliger, S. L., et al. (2019). Disparities in diffuse cortical white matter integrity between socioeconomic groups. *Frontiers in Human Neuroscience, 13*, 198.
Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Neuroscience, 7*, 31.
Sosa-Ortiz, A. L., Acosta-Castillo, I., & Prince, M. J. (2012). Epidemiology of dementias and Alzheimer's disease. *Archives of Medical Research, 43*, 600–608.
STATA. (2022). *Statistics/data analysis: Release, 18.0*. Texas: Stata Corporation.
Tank, R., Ward, J., Celis-Morales, C., Smith, D. J., Flegal, K. E., & Lyall, D. M. (2021). Testing for interactions between APOE and klotho genotypes on cognitive, dementia, and brain imaging metrics in UK biobank. *Journal of Alzheimers Diseases, 83*, 51–55.
Taoka, T., Morikawa, M., Akashi, T., Miyasaka, T., Nakagawa, H., Kiuchi, K., et al. (2009). Fractional anisotropy–threshold dependence in tract-based diffusion tensor analysis: Evaluation of the uncinate fasciculus in alzheimer disease. *AJNR American Journal of Neuroradiology, 30*, 1700–1703.
Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L., Rose, S. E., Semple, J., et al. (2003). Dynamics of gray matter loss in Alzheimer's disease. *Journal of Neuroscience, 23*, 994–1005.
Tooley, U. A., Bassett, D. S., & Mackey, A. P. (2021). Environmental influences on the pace of brain development. *Nature Reviews Neuroscience, 22*, 372–384.
Townsend P, P. P., & Beattie, A. (1987). *Health and deprivation: Inequality and the North*. Andover: Croom Helm.
Turner, R. S. (2003). Biomarkers of Alzheimer's disease and mild cognitive impairment: Are we there yet? *Experimental Neurology, 183*, 7–10.
UK Biobank. (2007). *UK Biobank: Protocol for a large-scale prospective epidemiological resource*.
UK Biobank. (2022). *Algorithmically-defined outcomes (ADOs)*.
van der Velpen, I. F., Melis, R. J., Perry, M., Vernooij-Dassen, M. J., Ikram, M. A., & Vernooij, M. W. (2022). Social health is associated with structural brain changes in older adults: The rotterdam study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 7*, 659–668.
Walhovd, K. B., Fjell, A. M., Wang, Y., Amlien, I. K., Mowinckel, A. M., Lindenberger, U., et al. (2022). Education and income show heterogeneous relationships to lifespan brain and cognitive differences across European and US cohorts. *Cerebral Cortex, 32*, 839–854.
Walter, S., Dufouil, C., Gross, A. L., Jones, R. N., Mungas, D., Filshtein, T. J., et al. (2019). Neuropsychological test performance and MRI markers of dementia risk: Reducing education bias. *Alzheimer Disease and Associated Disorders, 33*, 179–185.
Wassenaar, T. M., Yaffe, K., van der Werf, Y. D., & Sexton, C. E. (2019). Associations between modifiable risk factors and white matter of the aging brain: Insights from diffusion tensor imaging studies. *Neurobiology of Aging, 80*, 56–70.