Neuroimaging, clinical and life course correlates of normal-appearing white matter integrity in 70-year-olds

Short title: Normal-appearing white matter correlates

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Abstract

We investigate associations between normal-appearing white matter (NAWM) microstructural integrity in cognitively normal ~70-year-olds and concurrently measured brain health and cognition, demographics, genetics and life course cardiovascular health.

Participants born in the same week in March 1946 (British 1946 Birth cohort) underwent PET-MRI around age 70. Mean standardized NAWM integrity metrics (fractional anisotropy (FA), mean diffusivity (MD), neurite density index (NDI) and orientation dispersion index (ODI)) were derived from diffusion MRI. Linear regression was used to test associations between NAWM metrics and (1) concurrent measures, including whole brain volume, white matter hyperintensity volume (WMHV), PET amyloid and cognition; (2) the influence of demographic and genetic predictors, including sex, childhood cognition, education, socioeconomic position, and genetic risk for Alzheimer's Disease (*APOE-ε4*); (3) systolic and diastolic blood pressure and cardiovascular health (FHS-CVS) across adulthood. Sex interactions were tested. Statistical significance included false discovery rate correction (5%).

362 participants met inclusion criteria (mean age 70 years, 49% female). Higher WMHV was associated with lower FA (b=-0.09 [95%CI:-0.11,-0.06] p<0.01), NDI (b=-0.17 [-0.22,-0.12] p<0.01), and higher MD (b=0.14 [-0.10,-0.17] p<0.01); amyloid (in men) was associated with lower FA (b=-0.04 [-0.08,-0.01] p=0.03) and higher MD (b=0.06 [0.01,0.11] p=0.02). FHS-CVS in later-life (age 69) was associated with NAWM [lower FA (b=-0.06 [-0.09,-0.02] p<0.01), NDI (b=-0.10 [-0.17,-0.03] p<0.01), and higher MD (b=0.09 [0.04,0.14] p<0.01). Significant sex interactions (p<0.05) emerged for midlife cardiovascular health (age 53) and NAWM at 70: marginal effect plots demonstrated, in women only, NAWM was associated with higher midlife FHS-CVS (lower FA and NDI), midlife systolic (lower FA, NDI, and higher MD), and diastolic (lower FA and NDI) blood pressure, and greater blood pressure change between 43 and 53 years (lower FA and NDI), independently of WMHV.

In summary, poorer NAWM microstructural integrity in ~70-year-olds was associated with measures of cerebral small vessel disease, amyloid (in males) and later-life cardiovascular health, demonstrating how NAWM can provide additional information to overt white matter disease. Our findings further show that greater *midlife* cardiovascular risk and higher blood pressure were associated with poorer NAWM microstructural integrity in females only, suggesting that women's brains may be more susceptible to the effects of midlife blood pressure and cardiovascular health.

Keywords: Normal appearing white matter; microstructural integrity; brain health; vascular risk; diffusion.

Introduction

Associations between measures of presumed small vessel disease, e.g., white matter hyperintensities (WMH) on FLAIR or T2-weighted MRI sequences, and ageing, cognitive decline and dementia have been well documented[1–3]. Yet impaired microstructural integrity in seemingly 'normal-appearing white matter' (NAWM) has also been linked with ageing[4], cognitive decline[5,6], conversion from NAWM to WMH[7,8], and exposure to vascular risk factors[9]. Little is currently known about relationships between other disease-related imaging markers, demographic and vascular health across the life course, and NAWM integrity in later life.

NAWM integrity can be assessed using diffusion tensor imaging (DTI). Parameters typically include fractional anisotropy (FA), a measure of fiber tract directionality; and mean diffusivity (MD), a measure of the magnitude of diffusion. Reduced microstructural integrity in WM generally results in a decrease in FA and an increase in MD[10]. Multicompartmental modeling techniques have been developed to address limitations in conventional measures, such as partial volume effects and more complex fiber organization. One technique, neurite orientation dispersion and density imaging (NODDI), can be used to derive the neurite density index (NDI), the fraction of tissue comprised of axons and dendrites; and the orientation dispersion index (ODI), a measure of the variability of neurite orientation[11]. A lower NDI reflects less densely packed neurites (reduced microstructural integrity) and a higher ODI represents increased fanning of tracts.

The National Survey of Health and Development (NSHD, British 1946 Birth cohort) is a UK-population-based sample that has followed participants born in the same week in 1946 throughout their lives and amassed a wealth of prospectively collected longitudinal life course data including demographic, genetic and vascular health metrics[12]. As part of a neuroimaging sub-study, Insight 46, 471 NSHD participants aged ~70 undertook extensive neuroimaging and clinical phenotyping including amyloid PET, structural MRI and diffusion-weighted MRI (DTI and NODDI)[13].

Drawing from this unique sample we aimed to characterize: (1) how measures of NAWM integrity correlate with concurrent brain health measures, including whole brain volume (WBV) and white matter hyperintensity volume (WMHV), PET amyloid burden and cognition; (2) the influence of demographic, life course, and genetic predictors, including sex, age at scan, childhood cognition, educational attainment and parental socioeconomic position, and genetic risk for AD (*APOE-ε4*) on NAWM; and 3) the relationship between vascular health across adulthood (vascular risk and blood pressure (BP)) and NAWM, and to investigate whether these associations are modified by sex and independent of WMHV and *APOE-ε4*. In this population-based sample of 70 years old, we hypothesize that there will be detectable patterns reflecting poorer microstructural integrity in overtly observed NAWM. We further hypothesize that measures of reduced microstructural integrity will be linked with worse concurrent brain health measures including greater WMHV; demographics indexing disadvantaged circumstances; and worse cardiovascular health across adulthood.

Materials and Methods

Study participants were from Insight 46, a sub-study of the NSHD which initially comprised 5362 individuals born throughout mainland Britain in one week in March 1946. Eligibility criteria and an overview of recruitment for Insight 46[14] are outlined in detail elsewhere. Briefly 502 participants aged 69-71 were assessed with detailed and consistent clinical, cognitive, and brain imaging protocols (doi: 10.5522/NSHD/Q103). Ethical approval for Insight 46 was granted by the National Research Ethics Service (NRES) Committee London (14/LO/1173). All participants gave written informed consent.

Imaging acquisition and processing and cognitive data at age 69-71 years

Simultaneous acquisition of dynamic PET and MR data were acquired at age 69-71 years using a single Biograph mMR 3T PET-MRI scanner (Siemens Healthcare, Erlangen), including volumetric (1.1 mm isotropic) T1-weighted, T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) sequences[13]. All T1-, T2-weighted, and FLAIR sequences were reviewed by a consultant neuroradiologist and incidental findings were reported as previously described[13]. Structural images (T1, T2, FLAIR) were corrected for gradient non-linearity and low frequency intensity non-uniformity with N4-bias correction[15]. Multi-shell diffusion MRI (dMRI) was acquired using a twice-refocused spin echo EPI sequence with two non-zero b-values (700 and 2000 s/mm^2), multiple directions (12, 32, and 64 directions for the b = 0, 700, and 2000 s/mm^2 scans respectively) and an isotropic 2.5 × 2.5 × 2.5 mm resolution, with 58 slices to ensure whole brain coverage[16]. B_0 field maps were acquired for distortion correction of the dMRI images. PET data were assessed over 10 minutes, ~50 minutes after injection with MBq florbetapir F18 (Amyvid).

Volumetric T1-, T2-weighted, and FLAIR images underwent visual quality control (QC) before being processed using automated pipelines[13]. Multi-Atlas Propagation and Segmentation[17] was used to generate whole-brain segmentations. Total intracranial volume (TIV) was calculated using Statistical Parametric Mapping (SPM) 12 (https://www.fil.ion.ucl.ac.uk/spm/). White matter hyperintensity (WMH) masks of supratentorial structures were generated from FLAIR and T1-weighted images using Bayesian Model Selection (BaMoS), an unsupervised algorithm validated for cross-sectional segmentation of WMH[18]. Whole-brain and WMH masks were visually checked and edited where necessary.[18]

Global standardized uptake value ratios (SUVRs) were calculated from a cortical composite region of interest, normalized to the cerebellum with partial volume correction applied. Aβ positivity status was determined using Gaussian-mixture modeling with two Gaussians, taking the 99th percentile of the lower distribution as the cut-point (1.031, equivalent to 11.8 centiloids)[19], whereby Aβ+ indicates greater Aβ load. Volume weighted mean SUVR was extracted from a Geodesic Information Flows software (GIF) composite cortical target region closely matched to FreeSurfer regions used in Landau et al. (2013)[20]. The composite consists of lateral and medial frontal, anterior and posterior cingulate, lateral parietal, and lateral temporal regions. For PVC, PET images were resampled to T1-space and the anatomical GIF regions were used to conduct iterative-Yang PVC with a 6.8 mm^3 kernel optimised for the PET/MR scanner that the data were acquired on [21]

Normal appearing white matter (NAWM) metrics.

A NAWM mask (non-WMHV white matter) was generated and used to sample microstructural integrity measures including fractional anisotropy (FA); neurite density index (NDI); mean diffusivity (MD); and orientation dispersion index (ODI).

White matter masks were automatically generated from the T1-weighted scans using GIF)software[22]. Participant-specific masks representing NAWM were generated by subtracting the BaMoS-WMH masks from the GIF-WM masks using NiftySeg (https://github.com/KCL-BMEIS/NiftySeg), before being eroded by 1 voxel (see Fig. 1). Diffusion-weighted images were corrected for inter-volume motion using linear registration and eddy currents using FSL's Eddy tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy), followed by correction for EPI susceptibility distortion using field maps, with volume-preserving modulation based on the Jacobian determinants. Diffusion tensor models were fitted to b700 and b2000 diffusion shells using NiftyFit[23]. The NODDI model was then fitted to the combined shells using the NODDI toolbox (http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDImatlab). All images underwent visual quality control to assess acquisition, pre- and post-processing motion, coverage, blurring, image wrap-around and contrast problems, adequate CSF suppression on FLAIR imaging, segmentation or processing artifacts, sufficient correction of geometric distortion, and slice-wise signal dropout on dMRI (using correlation plots between adjacent slices). Images failing the quality control process for DTI were removed before running the analysis for FA or MD metrics. NODDI models required an extra semi-automated quality control step and images failing this quality control were removed before running analyses including NDI or ODI.

Given that NAWM metrics vary greatly across the brain, averaging absolute values of NAWM metrics over such large regions are not intuitively meaningful. We employ a similar approach used in PET imaging [24] to ease interpretation of abnormality of the NAWM metrics. To do so we derived a model of 'healthy' NAWM metrics (FA, MD, NDI, ODI) from a subset of participants with a very limited amount of WMH (<1mL) and compared each participant's divergence from these models by calculating voxel-wise z-scores per diffusion map. For the diffusion metric of interest, the z-score at each voxel therefore represents how much that voxel deviates from what is assumed to be "healthy" to help ease interpretation of abnormality. This approach also enables us to allow for comparisons across the different metrics. The mean z-score over the individual's NAWM mask was then calculated for each diffusion metric. These mean standardized diffusion metrics were used as the outcome measures in the regression analyses.

Cognitive function at age 69-71

The Preclinical Alzheimer Cognitive Composite (PACC) was used as the main cognitive outcome at age 69-71[25]. This composite consists of the Mini-Mental State Examination (MMSE); logical memory delayed score from the Wechsler Memory Scale-Revised (WMS-R) – a test of verbal episodic recall; digit-symbol substitution test (DSST) from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) – a test of executive function and psychomotor speed; and the 12-item Face-Name test (FNAME-12) – a measure of free memory recall.

Life course predictors

Demographic predictors of sex, educational attainment, parental socioeconomic position (SEP) as well as childhood cognition, APOE- ε4 carrier status

Sex was ascertained at birth. Childhood cognitive ability was measured at age 8 using four tests of verbal and nonverbal ability devised by the National Foundation for Education Research. The sum of scores from these 4 tests was standardized into a z-score representing overall cognitive ability, standardized to the full cohort. The highest educational attainment achieved by 26 years was grouped as: no qualifications; education up to age 16 (O-levels or equivalent); education from age 17 onwards (A-levels or higher). Parental SEP was derived from paternal occupational class and coded according to the UK Registrar General's Standard Occupational Classification as: manual; non-manual. Genotyping of the two single nucleotide polymorphisms, rs439358 and rs7412, was used to determine *APOE*-ε4 genotype and categorized as ε4 carriers and non-carriers.

Cardiovascular predictors across the life course including FHS-CVS and blood pressure.

Framingham Heart Study–cardiovascular risk scores (FHS-CVS) were derived from measurements collected on home visits by research nurses when participants were aged 36 (early adulthood), 53 (midlife), and 69 (early late life), prior to their Insight 46 visit. The FHS-CVS provides a 10-year risk of cardiovascular events from a weighted sum of age, sex, systolic blood pressure (SBP), antihypertensive medication usage (yes/no), history of diabetes (yes/no), current smoking (yes/no), and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared)[26]. Smoking status was defined by questionnaire at ages 36, 53, and 69. Diabetes mellitus status was based on self-reported diagnosis at age 36 years, and at ages 53 and 69 years it was based on self-reported diagnosis or a hemoglobin A_{1C} level of 6.5% or more. BMI was measured at ages 36, 53, and 69 by research nurses.

Seated BP was measured in the upper arm twice after 5 min of rest across adulthood at ages 36, 43, 53, 60–64, and 69 years. In early adulthood (36 and 43 years), a Hawksley Random Zero sphygmomanometer was used, and from midlife onwards (53, 60–64, and 69 years), an Omron HEM-705 automated digital oscillometric sphygmomanometer was used. To ensure compatibility, published conversion equations were applied[27]. The second BP measure was used for analyses (unless only one measure was available). SBP and diastolic blood pressure (DBP) change for the periods between early adulthood (age 36 and 43), midlife (age 43 and 53) (age 53 and 60–64), and early late life (age 60–64 and 69 years of age), conditional on earlier measurements, was calculated as the residual from the regression of each BP measure (from 43 years of age) on the earlier measures for each sex, using individuals with available data at all time-points[28]. Residuals represent changes in BP that differed from changes expected on average given the earlier BP. Residuals were standardized, allowing comparison between periods.

Statistical analysis

We used Stata 17.0 (StataCorp) for all statistical analyses. Only participants with good quality T1-weighted, FLAIR and diffusion MRI scans were included. Ten participants whose BaMoS segmentation failed QC were also excluded. Participants who were cognitively impaired or had a neurological or major psychiatric condition were excluded from analyses. See Fig. 2 for a flowchart of participant exclusions. [29,30]

Multiple testing approach

The Benjamini and Hochberg step-up procedure was applied to control for the false discovery rate (FDR) set at 5%.

Concurrent pathological correlates at age 69-71

Linear regression models were used to analyze the association between WBV (continuous), log-transformed WMHV (continuous) and amyloid load (dichotomous) with each standardized NAWM diffusion metric (FA, MD, NDI, ODI). WMHV and WBV were transformed into z-scores (with a mean of 0 and a standard deviation of 1). The concurrent pathology measures were assessed in the same model to estimate the independence of effects per NAWM metric. All models were adjusted for age at scan and sex. The models investigating the effect of WMHV and WBV on NAWM diffusion metrics were additionally adjusted for TIV. A differential influence of sex on the relationship between pathology and NAWM was tested using an interaction term. The marginal effects are shown (the relationship for each sex) if there was evidence of a sex interaction ($p<0.1$).

Concurrent cognition correlates at age 69-71

Linear regression models were applied to analyze the relationship between the PACC and each standardized NAWM diffusion metric, adjusting for age at scan and sex. Models were fitted with the four cognitive sub-tests in the same model, to estimate the independence of effects, and each NAWM metric, adjusting for age at scan and sex. A differential influence of sex on the relationship between cognition and NAWM was tested using an interaction term and, if significant, marginal effects were reported.

Life course predictors: Demographic predictors, childhood cognition and APOE- ε4 carrier status

Linear regression models were conducted to characterize the relationship between demographic predictors (sex, age at scan, educational attainment, parental SEP), childhood cognition, and genetic risk for AD (APOE-ε4 status) with each NAWM metric at 69-71 years of age. The predictors were assessed in the same model to estimate the independence of effects from these demographic variables.

Life course predictors: cardiovascular risk and blood pressure

Linear regression models were fitted to characterize the relationship between a range of life course cardiovascular health metrics in early, mid and later adulthood (FHS-CVS at ages 36, 53, 69; SBP and DBP at ages 36, 43, 53, 60, 69; and BP change variables between ages 36 and 43; 43 and 53; 53 and 60; 60 and 69 years of age) with each NAWM metric. Measures were transformed into z-scores (with a mean of 0 and a standard deviation of 1). These cardiovascular predictors were tested in separate models, but all adjusted for age at scan and sex. A differential influence of sex on the relationship between cardiovascular health and NAWM was tested using an interaction term and, if significant, marginal effects were reported.

Sensitivity analyses
To investigate whether associations were independent of the amount of presumed cerebral small vessel disease present, we additionally re-ran the significant models adjusting for WMHV and TIV. To investigate whether associations were independent of APOE-e4 status, we additionally re-ran the significant models adjusting for APOE-e4 status.

An overview table of the analytical approach to covariates, interactions and sensitivity analyses is outlined in Supplementary Table 1.

Results

Participant characteristics are shown in Table 1 for participants with available data and excluding those with any neurological disorder.

Concurrent imaging correlates at age 69-71

Higher white matter hyperintensity volume and SUVR were independently and significantly associated with worse NAWM microstructural measures (both were associated with lower FA and higher MD; in addition, WMHV was also associated with lower NDI) (Fig. 3). A significant sex interaction emerged for amyloid SUVR)[*p*<0.01): higher SUVR was associated with worse NAWM microstructural metrics in males (lower FA, and higher MD), but no associations between SUVR and NAWM were significant in females (Fig. 3). The association between whole brain volume and FA did not survive false discover rate correction. There was no evidence of sex interactions with WMHV or BV or attenuation of effects with adjustment for APOE-e4 (Supplementary Table 2).

Concurrent cognitive correlates at age 69-71

Neither cognitive performance as measured using the PACC total score, nor its sub-components, were significantly associated with any NAWM microstructural metrics (Fig. 4). There was an association between digit symbol and higher NDI, but this did not survive FDR correction (Supplementary material). There was no evidence of sex interactions or attenuation of effects with adjustment for WMHV or APOE-e4 (Supplementary Table 3).

Life course predictors

Regression models demonstrated that female sex and older age at scan were independently associated with worse NAWM microstructural measures (female sex with lower FA; older age with lower FA, NDI and higher MD) (Fig. 5). Female sex was also associated with higher ODI. Other demographic variables, including childhood cognition, education, parental SEP and APOE-ε4 status, were not associated with NAWM microstructural measures. There was evidence of an attenuation of all the associations between female sex and older age with NAWM when associations were adjusted for WMHV. There was no attenuation of effects with adjustment for APOE-e4 status (Supplementary Table 4).

Life course predictors: cardiovascular risk score and blood pressure

Higher cardiovascular risk scores – FHS-CVS - in later adulthood (at age 69) were associated with worse NAWM metrics (lower FA, NDI and higher MD) (Fig. 6). Higher SBP and DBP in midlife (at 53) were associated with NAWM metrics (SBP with higher MD and lower NDI; DBP with higher MD and lower FA) (Fig. 6). Greater increases in SBP & DBP in midlife (between ages 43 to 53) were associated with NAWM metrics (SBP with lower NDI; DBP with lower FA) (Fig. 6). Higher DBP at age 60-64 was also associated with lower FA. All p-values were FDR corrected. There was no evidence of attenuation of these effects with adjustment for WMH volume or APOE (Supplementary Table 5).

Models with sex interactions

Statistically significant sex interactions emerged for cardiovascular scores and blood pressure (SBP and DBP) in midlife (at age 53), and blood pressure (SBP and DBP) changes in midlife (between ages 43 to 53: supplementary Table 5). The marginal effects (slope per sex) were subsequently displayed (Fig. 7). In females, NAWM metrics at age 70 were associated with higher midlife (age 53) FHS-CVS scores (lower FA and NDI, and higher MD), higher SBP (lower FA and NDI, and higher MD), higher DBP at age 53 (lower FA and NDI) and greater SBP change (between age 43 to 53: lower FA and higher NDI) (Fig. 7). In males, there were no significant associations between midlife cardiovascular scores or blood pressure with NAWM metrics.

Adjustments

There was no evidence of attenuation of these effects with adjustment for WMH volume or APOE-e4 (Supplementary Fig 1-6). All p-values were FDR corrected.

Discussion

In a population-based sample of dementia-free individuals, all born in the same week and aged ~70 years at the time of imaging, we investigated associations between NAWM integrity and concurrently measured brain pathology and demographic, cognitive, genetic and cardiovascular health measures across the life course. We found that NAWM measures reflecting poorer microstructural integrity were associated with greater white matter hyperintensity volume, supporting the notion that altered NAWM and white matter hyperintensity may be part of a partially overlapping pathological process [7,8]. Our findings also suggest that NAWM is not necessarily “normal” and that white matter hyperintensity volume does not fully capture white matter pathology [4]. A higher amyloid load (SUVR) was associated with reduced microstructural integrity in males, but not females. Being female and being scanned at an older age over the two-year assessment period were independently associated with NAWM microstructural differences but this was explained by differences in cerebral small vessel disease; no evidence emerged for associations between NAWM and childhood cognition, education and the biggest genetic risk factor for “sporadic” AD (*APOE-ε4*). Overall poorer cardiovascular health in later life was associated with impaired microstructural NAWM integrity in later-life in a pooled sample. However, greater *midlife* cardiovascular risk and higher blood pressure were associated with poorer NAWM microstructural integrity in females only, suggesting the increased susceptibility of midlife blood pressure and cardiovascular health for subsequent white matter brain health for women. Together, our findings suggest that assessment of NAWM provides important additional information to overt white matter disease. These findings support the concept that modifiable midlife cardiovascular risk factors are associated with covert late-life brain health, particularly in women.

Concurrent pathological and cognitive correlates at age 69-71

The findings that increased white matter hyperintensity volume was significantly associated with NAWM diffusion metrics adds to a growing body of evidence that poorer white matter microstructural integrity, even in NAWM, is linked with overt white matter disease burden [6–8,31], and this may be an important outcome measure for understanding early white matter pathophysiology throughout adulthood. [6–8,31]Notably, whilst white matter hyperintensity is fairly low in this sample, tract-based DTI in a cross-sectional community study of ~50-year-olds similarly found that lower mean NAWM FA was associated with hyperintensity volumes [31]; these findings suggest that these relationships can be detected even at low levels of focal white matter disease burden. While we report cross-sectional data, our findings support longitudinal studies that have found lower microstructural integrity in NAWM is associated with the subsequent development of white matter hyperintensity[7,8]. These studies suggest that there may be a continuous process pathway of white matter degradation including demyelination and axonal loss due to chronic ischemic vascular processes[7,8] and reduced cerebral blood flow[32]. However, there is evidence that white matter hyperintensity can be reversible[33], and it is plausible that there is a dynamic process between NAWM and white matter hyperintensity, particularly at low levels of disease burden.[34] NAWM DTI metrics may be important for identifying early – and potentially more reversible – vascular damage and for evaluating progression for clinical trials.

We found that a higher amyloid load (SUVR) was associated with lower FA, higher MD, and lower NDI in NAWM in males, but not in females. Associations between white matter microstructural integrity and amyloid load in cognitively normal participants have previously been reported[35–3738]Although beyond the scope of this study, further investigations into the sex differences of this relationship are warranted and could reflect differences in the underlying etiology causing NAWM microstructural alterations, such as amyloid-induced WM alterations[38], or due to sexual dimorphism in white matter organization[39].

There was little evidence that concurrent cognitive performance was related with NAWM metrics at age ~70. As our analysis only included cognitively healthy participants further follow-up in the study, when more study members will be expected to develop cognitive changes and disease, will allow investigation of the link between NAWM metrics and cognitive impairment and decline.

Life course predictors: demographics, childhood cognition and APOE-ε4 carrier status

Being female and having a later age at scan were independently associated with measures indexing differential microstructural integrity, but these findings attenuated with adjustment for white matter hyperintensity, a marker of cerebral small vessel disease. This suggests that the sex- and age-related alterations in NAWM we observed is partly explained by a greater burden of cerebral small vessel disease, which provides evidence that that alterations in NAWM and white matter hyperintensity may be part of an overlapping pathological process [7,8]. Our results are consistent with those from a previous study, in middle-aged to older adults, that found lower FA and higher ODI in females compared to males across multiple tracts[40]. There is growing evidence that older women are more likely to have greater WMHV despite a lower prevalence of vascular risk factors[41–43], suggesting a higher susceptibility to white matter damage[44]. The age range of participants scanned was very narrow, and so rather than an age effect *per se,* it is possible that the observed age effect is due to recruitment bias:

those participants recruited later into the study may be less healthy and more likely to have greater WMHV than those who were keen to enroll at an early stage.

We found no associations between earlier life demographics (childhood cognition, educational attainment, and parental socioeconomic position) and microstructural integrity measures in NAWM. This does not exclude the possibility that there may be regional associations, not detectable when looking at summary measures across the brain, however. A previous study, using data from the population-based Lothian birth cohort, did find that higher childhood cognition was associated with higher FA in the centrum semiovale but not in other regions-of-interest[45].

Life course predictors: cardiovascular health

Worse cardiovascular health only in later life (age 69) was associated with worse NAWM microstructural integrity across both sexes. However, worse cardiovascular health and higher blood pressure in midlife (at age 53 years) and increases in blood pressure in midlife (between ages 43 and 53 years), were associated with measures indexing worse NAWM microstructural integrity at age 70, in women only. These relationships were independent of presumed cerebral small vessel disease present, suggesting that NAWM provides important additional evidence to overt white matter disease of adverse brain health effects, particularly in women. This is in line with findings from a tract-based DTI cross-sectional community study of ~50-year-olds showing that hypertension at this age was associated with lower NAWM FA, independent of adjustment for white matter burden[31]

The sex differences we observed between midlife cardiovascular health and blood pressure with late-life NAWM microstructural integrity are in keeping with previous studies that show a stronger association between blood pressure and FA in middle-aged females than males[46]. [44]. Stronger associations in women between raised blood pressure and higher white matter hyperintensity volume[46,47] as well as between midlife hypertension and later dementia[48] have also been found previously. This generally adds to a pattern of growing evidence suggesting, despite a lower prevalence of midlife cardiovascular risk factors, women with poorer cardiovascular health have a greater susceptibility to white matter damage [44] .

There are known sex differences in the susceptibility of cardiovascular disease (CVD). At younger ages, males have greater risk, but in older age, female risk surpasses males[49]. Survivor bias could explain such patterns, but there is also a growing realization that cardiovascular disease is underrecognized, underdiagnosed and undertreated in females[49]. Declining levels of protective oestrogen during menopause [50], or pregnancy-related issues, including gestational hypertension of preeclampsia[51–54], could increase the susceptibility to midlife cardiovascular health in women. Differences in lifestyle behaviours, such as smoking, alcohol consumption, and physical activity, and differential biological mechanisms linking behavioural factors with cardiovascular health, could differ by sex. Further work is warranted to understand the mechanisms of exacerbated risk of midlife cardiovascular health on later-life white matter brain heath in women, expanding on the body of evidence of sex differences in CVD. For example, studies using MRI and DTI in children and adolescence suggest there is sexual dimorphism in the structural development of white matter and microstructural organization[39] with an implicated role of hormones and puberty[55]. Further investigation into sex differences of the structural organization of white matter in the ageing brain is critical.

Previous analyses in this sample demonstrated that cardiovascular risk and rising blood pressure, particularly in early midlife between age 43 and 53, was linked with greater white matter hyperintensity volume at age 69-71, emphasizing the importance of midlife vascular risk on subsequent white matter disease burden[28]. The current findings expand on this body of work by demonstrating that blood pressure changes in this period of midlife are not only linked to overt white matter disease burden ~20 years later, but are also linked to NAWM microstructural integrity, independently of the presumed cerebral small vessel disease present. Together, these findings support the notion that NAWM is not necessarily “normal” and that white matter hyperintensity volume does not fully capture white matter pathology and damage [4]. Our findings also provide evidence that midlife blood pressure and cardiovascular health is associated with poorer white matter brain health decades later, which may not be fully captured by conventional (MR) imaging. While it is not possible to directly infer the underlying microstructural changes related to diffusion metrics without supporting histology, microstructural changes may be related to axonal loss, demyelination, and gliosis[56]. NAWM may additionally already have low perfusion or microstructural changes[57], but the pathophysiological changes may be more reversible than overt white matter hyperintensities[58]. Detecting differences observed in microstructural integrity in NAWM could therefore be important to characterize early subtle pathological changes linked with vascular health. While longer-term follow-up is required to determine whether these changes have implications for cognitive changes in later life, this supports the importance of emphasizing the role of midlife blood pressure management and cardiovascular health for improving later-life health.

We found no evidence that increased blood pressure in early adulthood (36-43 years), or poorer cardiovascular health in early adulthood (age 36), was associated with worse NAWM microstructural integrity later in life. Interestingly, in our previous study in this cohort, we found no association between blood pressure at age 36 and whole WMHV at age 70 [27]. We did find, however, that higher blood pressure in these earlier ages was associated with smaller brain and hippocampal volume at age 70, independent of WMHV load [27]. Together these findings suggest that blood pressure may be linked with brain volume and WMHV through differential pathways. For example, early adulthood blood pressure may influence brain volume through pathways related to tau pathology[59] hypertension-related infarction[60], or shared common predictors (e.g., genetics), whereas the relationship between midlife blood pressure and white matter damage may be mediated by changes in perfusion and inflammatory processes[58]. Since only cognitively unimpaired participants aged ~70 were included in our study, and few individuals have hypertension in early adulthood, the impact of subtle hypertension influences in early adulthood on late-life NAWM metrics may not be apparent in this cohort.

Strengths and limitations

This study has several strengths. We used a population-based birth cohort with data spanning 70 years, enabling prospectively ascertained demographic and adulthood vascular health. Participants were born in the same week, which reduces the risk of confounding by age. Participants were scanned around ~70 years old, where pathology is expected to accumulate, but clinical manifestations of dementia are still limited. In this context, some of the findings reported here may reflect the relatively early stage of pathophysiological continuum of diseases that we expect some participants to be in, potentially many years before onset of Alzheimer's disease-related neurodegeneration.

This study also has several limitations. First, the British population in Insight 46 is a cohort of selectively healthy, socially advantaged, and exclusively white British participants[14], reducing generalizability to other populations. Second, this analysis uses imaging measures at one time point; Ongoing assessments (including tau-PET) in our sample are planned to gain more detailed information about the pathological and demographic correlates with longitudinal changes in NAWM. Third, white matter hyperintensity volume are not randomly distributed in the brain and specific tracts are more likely to be excluded from the NAWM than others, potentially introducing some bias in the NAWM diffusion metrics. Further investigations are needed to understand if the sex differences observed are due to true microstructural differences rather than potential bias induced by white matter hyperintensity distribution/load differences. Future work will also address whether medications, such as statins and ACE inhibitors, affect these relationships.

In summary, poorer cardiovascular health and higher blood pressure in midlife and increases in blood pressure in early midlife were associated with poorer NAWM microstructural integrity measures decades later in cognitively unimpaired participants in women. Poorer cardiovascular health in late life was also associated with poorer NAWM microstructural integrity measures. These relationships were not fully explained by white matter hyperintensity volume, suggesting that assessment of NAWM provides important additional information to overt white matter disease. These findings support the concept that modifiable midlife cardiovascular risk factors are associated with covert late-life brain health, particularly in women.

Data availability

Anonymized data will be shared by request from qualified investigators (skylark.ucl.ac.uk/NSHD/doku.php).

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Potential competing interests

NCF has consulted for Biogen, Ionis, Eli Lilly and Roche and has served on a Data Safety Monitoring Committee for Biogen. JS has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen, and Eli Lilly, given educational lectures sponsored by GE, Eli Lilly and Biogen, and serves on a Data Safety Monitoring Committee for Axon Neuroscience SE. CAL is now a full-time employee of Roche Products Ltd and a shareholder in Hoffmann La Roche. FB is a steering committee or iDMC member for Biogen, Merck, Roche, EISAI and Prothena. Consultant for Roche, Biogen, Merck, IXICO, Jansen, Combinostics. Research agreements with Merck, Biogen, GE Healthcare, Roche. Co-founder and shareholder of Queen Square Analytics LTD. All other authors have no conflicts of interest to declare. Florbetapir amyloid tracer is kindly provided by AVID Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly) who had no part in the design of the study.

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Figures

Fig. 1: Example of tissue segmentation. T1-weighted (A) and FLAIR (B) images were segmented using automated algorithms to create white matter (WM) (C) and white matter hyperintensity (WMH) (D) masks. The WMH mask was subtracted from the WM mask and eroded by 1 voxel to create the normal appearing white matter (NAWM) mask (E). The NAWM mask was overlayed on the fractional anisotropy (FA) map in the T1 space (F).

Fig. 2: Flowchart of Participant inclusion criteria. QC=quality control; BaMoS= Bayesian Model Selection; NODDI= neurite orientation dispersion and density imaging; NAWM=normal appearing white matter; AD=Alzheimer's disease, TBI = traumatic brain injury, PD=Parkinson's Disease; MCI = mild cognitive impairment.

Fig. 3: Associations between concurrent imaging correlates with standardized global mean normal appearing white matter (NAWM) parameters of fractional anisotropy (FA); neurite density index (NDI); mean diffusivity (MD) and orientation dispersion index (ODI) at age 69-71 years. Regression coefficient plot of the standardized estimates which reflect the differences in mean of the standardized NAWM outcome by one standard deviation change in the predictor variable. Lines indicate the widths of the 95% confidence intervals. All concurrent imaging correlates were assessed in the same model (mutually adjusting for WMHV, brain volume and amyloid) and adjusted for sex and age at scan, per NAWM metric. A sex and amyloid SUVR significant interaction emerged, so amyloid SUVR results show the marginal effects by sex. Associations that survived false discovery rate correction are indicated by an asterisk. *WMHV=White matter hyperintensity volume; SUVR= Standardised uptake value ratio; TIV=Total intracranial volume.*

Fig. *4*: Associations between concurrent cognition correlates (preclinical Alzheimer's cognitive composite (PACC) and its four sub-components) with standardized global mean normal appearing white matter (NAWM) parameters of fractional anisotropy (FA); neurite density index (NDI); mean diffusivity (MD) and orientation dispersion index (ODI) at age 69-71 years. Regression coefficient plot of the standardized estimates which reflect the differences in mean of the standardized NAWM outcome by one standard deviation change in the predictor variable. Lines indicate the widths of the 95% confidence intervals. All models adjust for age at scan and sex; all sub-components of the PACC were assessed in the same model, per NAWM metric*.* Associations that survived false discovery rate correction are indicated by an asterisk. *PACC=Preclinical Alzheimer Cognitive Composite; MMSE=mini mental state examination.*

Fig. *5*: Associations between life course demographics with mean normal appearing white matter (NAWM) parameters of fractional anisotropy (FA); neurite density index (NDI); mean diffusivity (MD); orientation dispersion index (ODI) at age 69-71. Regression coefficients and 95% confidence intervals (CI) of the standardized estimates reflect the differences in mean of the standardized NAWM outcome by one standard deviation change in the predictor variable. Estimates for age reflect the differences in mean associated with a 1-year increase in age and for an increase of 1 standard deviation for childhood cognition. Lines indicate the widths of the 95% confidence intervals. The predictors were assessed in the same model to estimate the independence of effects, per NAWM metric. Associations that survived false discovery rate correction are indicated by an asterisk. *SEP=socioeconomic position.*

Fig. *6*: Life course vascular risk and blood pressure associations with mean normal appearing white matter (NAWM) parameters of fractional anisotropy (FA); neurite density index (NDI); mean diffusivity (MD); orientation dispersion index (ODI) at age 69-71. Regression coefficient plot of the standardized estimates which reflect the change (differences in mean) of the standardized NAWM outcome by one standard deviation change in the predictor variable. Lines indicate the widths of the 95% confidence intervals. All models were run separately and adjusted for age at scan and sex and are false discovery rate corrected*.* Associations that survived false discovery rate correction are indicated by an asterisk. *FHS=Framingham-Heart-Study Cardiovascular Risk Score; SBP=systolic blood pressure; DBP=diastolic blood pressure.*

Fig. 7: Marginal effects demonstrating sex differences in vascular risk and blood pressure associations at age 53 with mean normal appearing white matter (NAWM) parameters of fractional anisotropy (FA); neurite density index (NDI); mean diffusivity (MD); orientation dispersion index (ODI) at age 69-71. Regression coefficient plot of the standardized estimates which reflect the change (differences in mean) of the standardized NAWM outcome by one standard deviation change in the predictor variable. Lines indicate the widths of the 95% confidence intervals. Models for each exposure were run in pooled analysis and adjusted for age at scan and are false discovery rate corrected*.* Associations that survived false discovery rate correction are indicated by an asterisk. *FHS=Framingham-Heart-Study Cardiovascular Risk Score; SBP=systolic blood pressure; DBP=diastolic blood pressure.*

Tables

Table 1: Participant characteristics

	N	Overall	Males	Females
Sample	362		183	179
Age at scanning	362	70.6 (0.7)	70.6 (0.7)	70.7 (0.7)
Educational attainment up to age 26				
No qualifications		57 (16%)	27 (15%)	30 (17%)
Education up to age 16 (O-levels or equivalent)		109 (30%)	39 (21%)	70 (39%)
Education from age 17 onwards (A-levels or higher)	362	196 (54%)	117 (64%)	79 (44%)
Parental socioeconomic position (SEP)				
Non-manual		203 (57%)	113 (62%)	90 (51%)
Manual	357	154 (43%)	69 (38%)	85 (49%)
APOE-ε4 carrier	361	108 (30%)	55 (30%)	53 (30%)
Framingham-Heart-Study Cardiovascular Risk Score (FHS-CVS)%:				
at age 36 years	322	2.6 (1.5, 3.6)	3.5 (2.9, 4.3)	1.5 (1.2,1.9)
at age 53 years	351	10.4 (6.3, 15.4)	14.9 (11.8,18)	6.2 (4.6, 8.5)
at age 69 years	352	23.3 (14.6, 34.5)	33.2 (26.4, 39.7)	14.5 (10.3,18.8)
Systolic blood pressure (SBP):				
at age 36 years	324	119.7 (13.7)	125.6 (12.7)	113.7 (12.1)
at age 43 years	341	124.0 (14.0)	129 (13)	118.9 (13.1)
at age 53 years	352	133.3 (19.4)	137.9 (19.7)	128.6 (17.9)
at age 60-64 years	361	134.8 (17.0)	138.3 (17.5)	131.2 (15.7)
at age 69 years	357	132.2 (16.2)	134.1 (15.2)	130.3 (17.1)
Diastolic blood pressure (DBP):				
at age 36 years	324	78.2 (9.9)	81.2 (9.6)	75 (9.3)
at age 43 years	341	80.3 (8.9)	83.2 (8.4)	77.4 (8.5)
at age 53 years	352	83.1 (11.9)	86.6 (12.3)	79.4 (10.3)
at age 60-64 years	361	76.9 (9.5)	78.7 (9.9)	75.1 (8.7)
at age 69 years	357	73.2 (10.2)	74.1 (10.8)	72.3 (9.5)
Hypercholesterolemia at 69 years of age	362	288 (80%)	137 (75%)	151 (85%)
BMI at age 70 years	362	27.3 (4.2)	27.6 (3.8)	27.1 (4.7)
Diabetes at age 70 years	358	34 (10%)	18 (10%)	16 (9%)
Imaging and cognition at age 70 years				
Amyloid positivity (Aβ+)	359	57 (16%)	25 (14%)	32 (18%)
Standardised uptake value ratio (SUVR)	359	1.0 (0.2)	0.6 (0.1)	0.6 (0.1)
Global white matter hyperintensity volume (WMHV), mL	362	2.9 (1.6, 6.1)	2.7 (1.6, 5.6)	3.4 (1.7,6.8)
Whole brain volume, mL	362	1105.6 (98.6)	1158.5 (84.9)	1051.6 (80.8)
Total intracranial volume, mL	362	1434.0 (134.4)	1522.6 (105.8)	1343.5 (94.4)
Preclinical Alzheimer Cognitive Composite (PACC) score	362	0.1 (0.7)	-0.1 (0.7)	0.2 (0.6)
Digit symbol	362	48.7 (10.2)	47.4 (10.5)	50.1 (9.8)
Logical memory	362	11.6 (3.6)	10.7 (3.6)	12.5 (3.3)
FNAME score	362	66.9 (17.1)	63.3 (17.6)	70.4 (15.9)
Mini Mental State Examination (MMSE) score	362	29.3 (0.9)	29.2 (0.9)	29.4 (0.8)

* Values shown are n (%), mean (SD) or median (q1, q3)

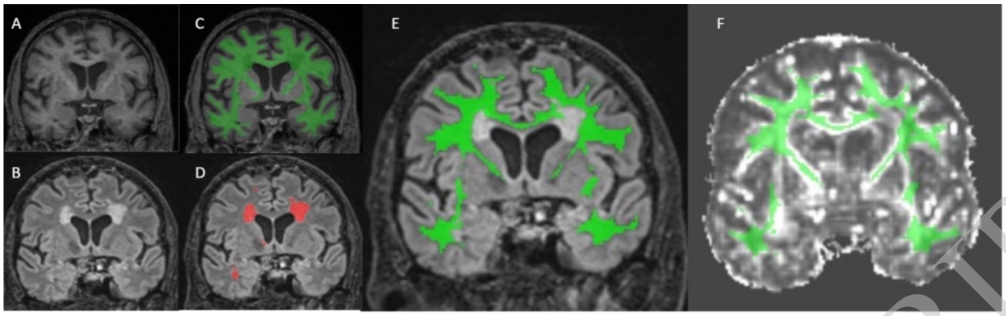


Figure 1

116x36mm (300 x 300 DPI)

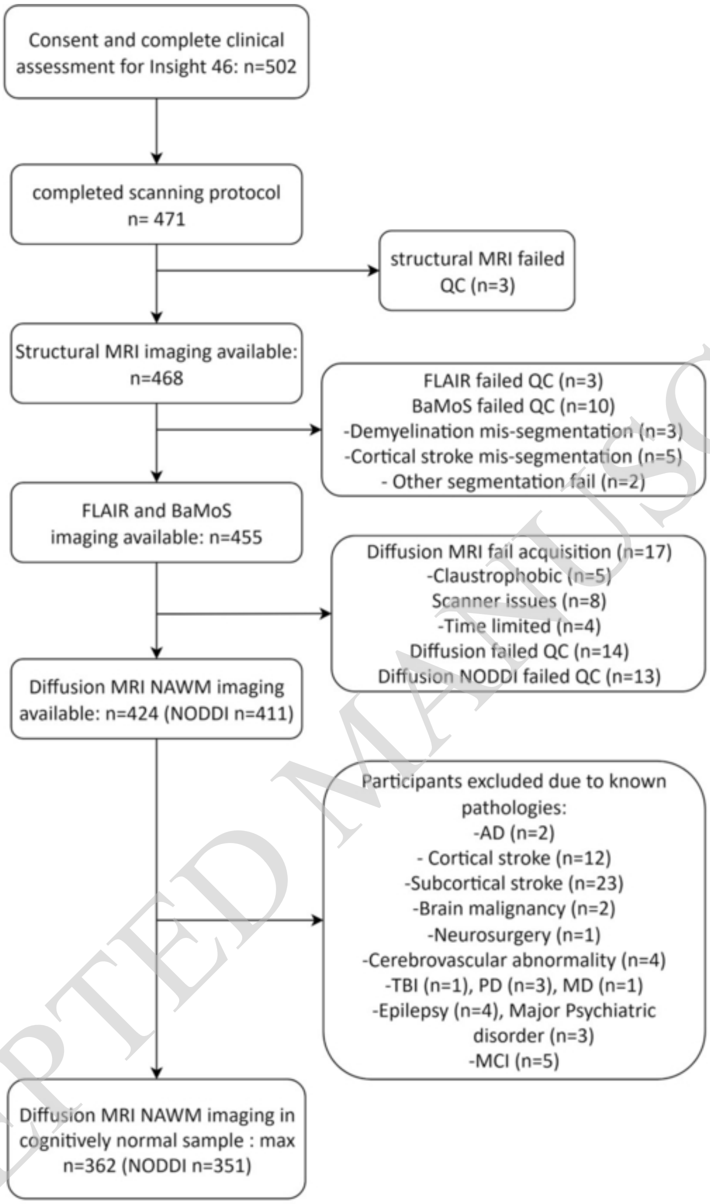
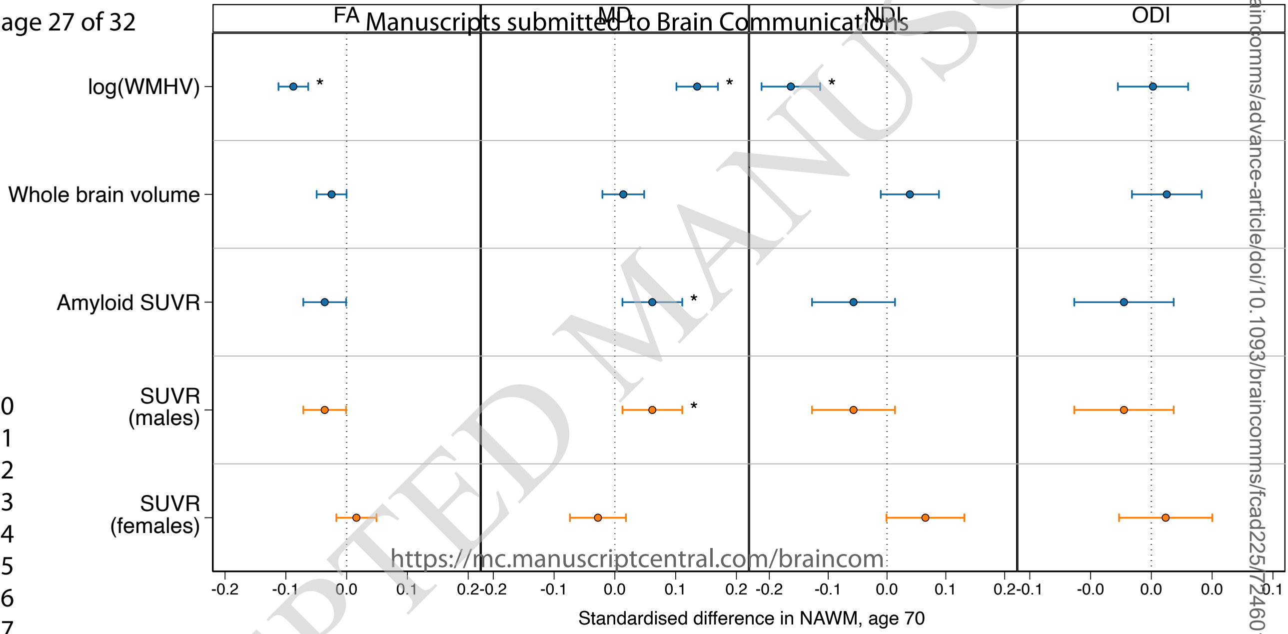
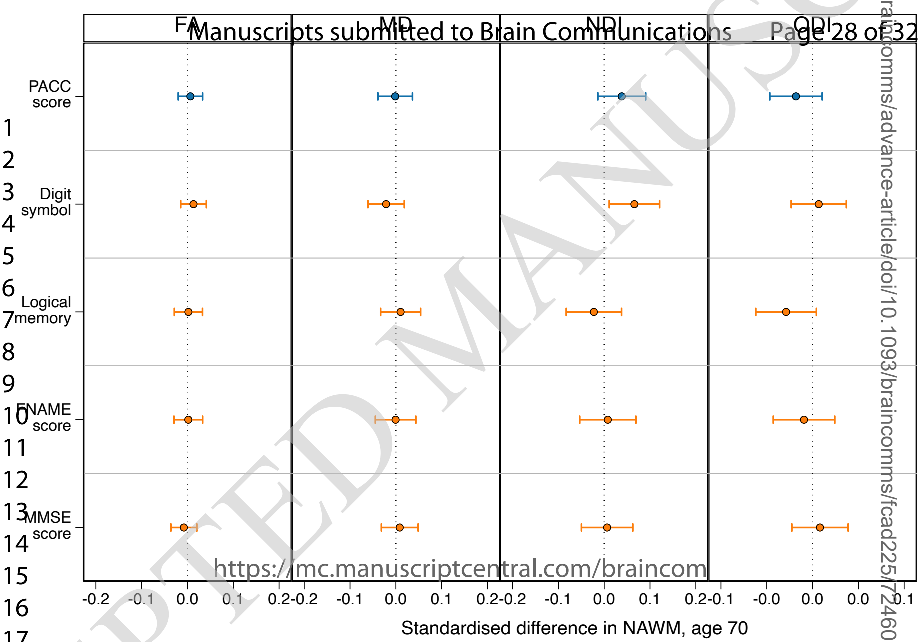
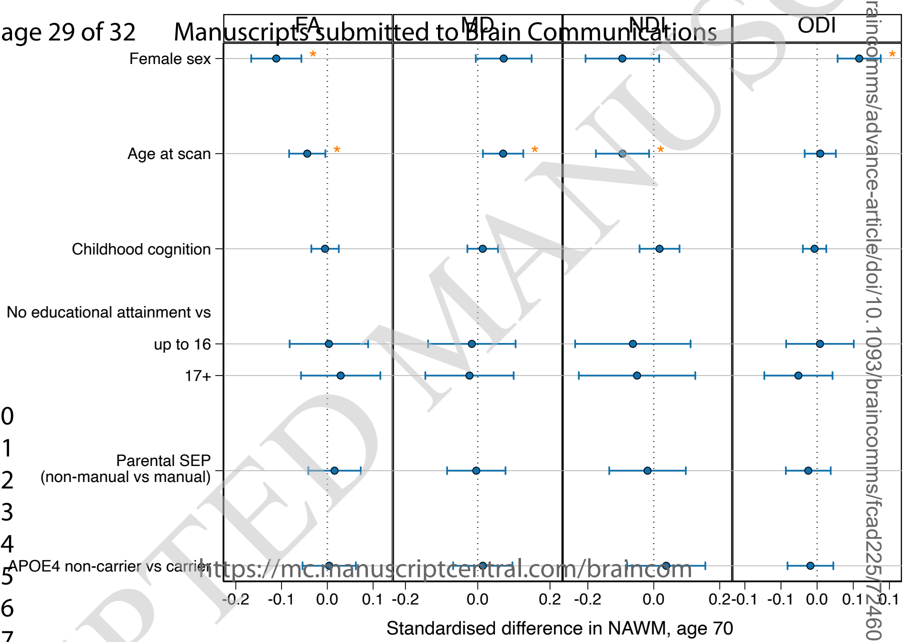


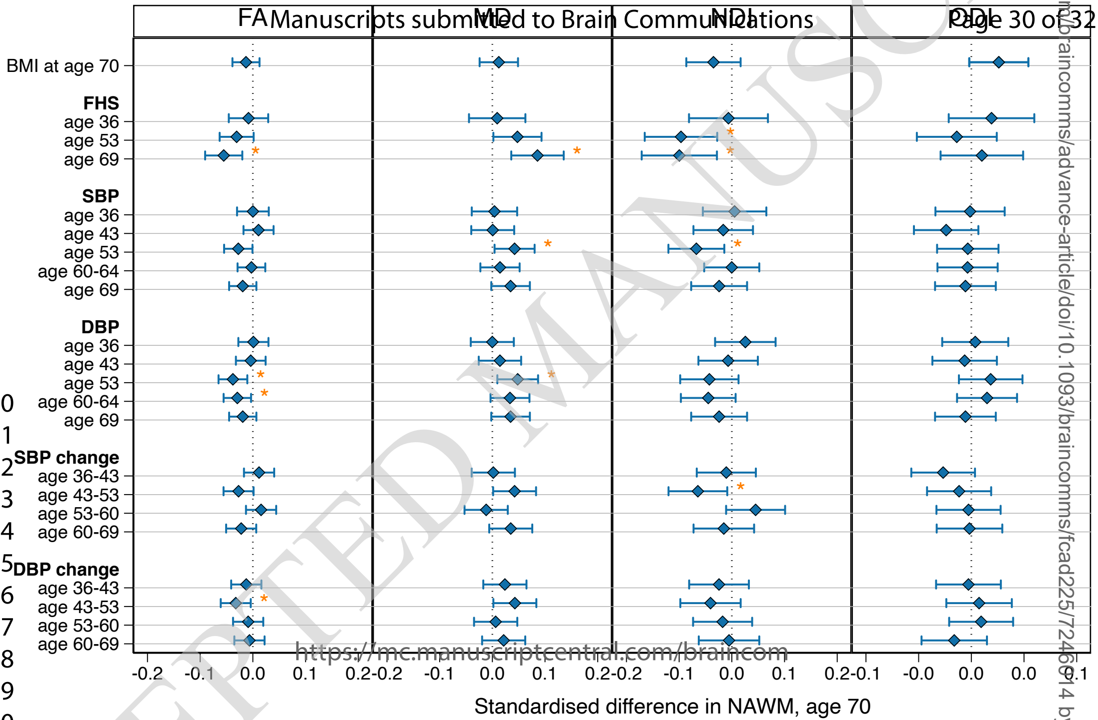
Figure 2

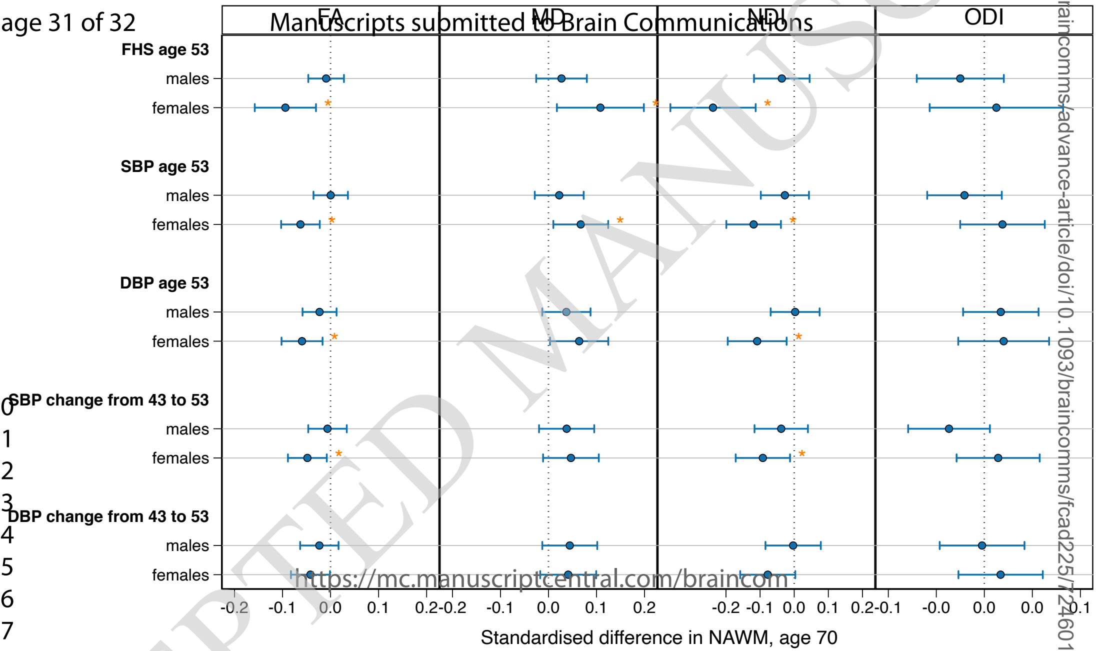
42x72mm (300 x 300 DPI)


FA
MD
NDI
ODI
log(WMHV)
Whole brain volume
Amyloid SUVR
SUVR (males)
SUVR (females)
*
*
*
*
*
-0.2
-0.1
0.0
0.1
0.2
-0.2
-0.1
0.0
0.1
0.2
-0.2
-0.1
0.0
0.1
0.2
-0.1
-0.0
0.0
0.0
0.1
Standardised difference in NAWM, age 70


FA
MD
NDI
ODI
PACC score
Digit symbol
Logical memory
FNAME score
MMSE score
-0.2
-0.1
0.0
0.1
0.2
-0.2
-0.1
0.0
0.1
0.2
-0.2
-0.1
0.0
0.1
0.2
-0.1
-0.0
0.0
0.0
0.1
Standardised difference in NAWM, age 70


FA
MD
NDI
ODI
Female sex
Age at scan
Childhood cognition
No educational attainment vs
up to 16
17+
Parental SEP
(non-manual vs manual)
APOE4 non-carrier vs carrier
*
*
*
*
*
-0.2
-0.1
0.0
0.1
-0.2
0.0
0.2
-0.2
0.0
0.2
-0.1
-0.1
0.0
0.1
0.1
Standardised difference in NAWM, age 70


FA
MD
NDI
ODI
BMI at age 70
FHS
age 36
age 53
age 69
SBP
age 36
age 43
age 53
age 60-64
age 69
DBP
age 36
age 43
age 53
age 60-64
age 69
SBP change
age 36-43
age 43-53
age 53-60
age 60-69
DBP change
age 36-43
age 43-53
age 53-60
age 60-69
*
-0.2
-0.1
0.0
0.1
0.2
-0.2
-0.1
0.0
0.1
0.2
-0.2
-0.1
0.0
0.1
0.2
-0.1
-0.0
0.0
0.0
0.1
Standardised difference in NAWM, age 70

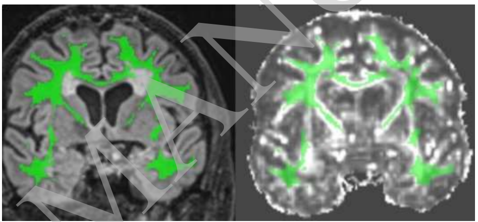

FA
MD
NDI
ODI
FHS age 53
males
females
SBP age 53
males
females
DBP age 53
males
females
SBP change from 43 to 53
males
females
DBP change from 43 to 53
males
females
*
-0.2 -0.1 0.0 0.1 0.2
-0.2 -0.1 0.0 0.1 0.2
-0.2 -0.1 0.0 0.1 0.2
-0.1 -0.0 0.0 0.0 0.1
Standardised difference in NAWM, age 70

What is linked with normal appearing white matter (NAWM) integrity in 70 year olds?

Brain PET-MR scans were acquired

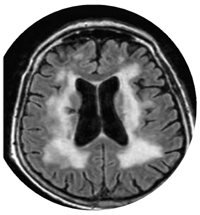
- Participants followed since birth
- n = 362
- Aged 70
- Cognitively-normal

NAWM metrics



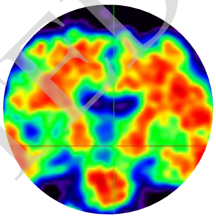
4 NAWM integrity metrics were extracted from diffusion weighted scans

Poorer NAWM was linked with:



Cerebral small vessel disease

In women and men



Amyloid burden

In men only

Midlife blood pressure and poorer cardiovascular health

In women only