Published Ahead of Print on April 11, 2022 as 10.1212/WNL.0000000000200524

Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000200524

Associations of β-Amyloid and Vascular Burden With Rates of Neurodegeneration in Cognitively Normal Members of the 1946 British Birth Cohort

Author(s):
Sarah E. Keuss[1]; William Coath[1]; Jennifer M. Nicholas, PhD[1,2]; Teresa Poole[1,2]; Josephine Barnes[1]; David M. Cash[1,3]; Christopher A. Lane[1]; Thomas D. Parker[4]; Ashvini Keshavan[1]; Sarah M. Buchanan[1]; Aaron Z. Wagen[1]; Mathew Storey[1]; Matthew Harris[1]; Ian B. Malone[1]; Carole H. Sudre[1,5,6,7]; Kirsty Lu[1]; Sarah-Naomi James[5]; Rebecca Street[1]; David L. Thomas[8,9]; John C. Dickson[10]; Heidi Murray-Smith[1]; Andrew Wong[5]; Tamar Freiberger[1]; Sebastian Crutch[1]; Marcus Richards[5]; Nick C. Fox[1,3]; Jonathan M. Schott[1]

Corresponding Author:
Jonathan M. Schott, j.schott@ucl.ac.uk

Affiliation Information for All Authors: 1. Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK; 2. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; 3. Dementia Research Institute, UCL Queen Square Institute of Neurology, London, UK; 4. Division of Brain Sciences, Department of Medicine, Imperial College London, London, UK; 5. MRC Unit for Lifelong Health and Ageing at UCL, London, UK; 6. Centre for Medical Image Computing, University College London, London, UK; 7. School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK; 8. Leonard Wolfson Experimental Neurology Centre, UCL Queen Square Institute of Neurology, London, UK; 9. Department of Brain Repair and Neurorehabilitation, UCL Queen Square Institute of Neurology, London, UK; 10. Institute of Nuclear Medicine, University College London Hospitals, London, UK

Equal Author Contribution:

Contributions:

Figure Count:
1

Table Count:
5

Search Terms:
[2] All Cerebrovascular disease/Stroke, [26] Alzheimer's disease, [54] Cohort studies, [120] MRI, [122] PET

Acknowledgment:
We are very grateful to those study members who helped in the design of the study through focus groups, and to the participants for their contributions to Insight 46 and their commitment to research over the past seven decades. We are grateful to the radiographers and nuclear medicine physicians at the University College London Institute of Nuclear Medicine; the staff at the Leonard Wolfson Experimental Neurology Centre at University College London; the neuroradiologists Dr Chandrashekar Hoskote and Dr Sachit Shah at the National Hospital for Neurology and Neurosurgery for providing clinical reads for the MRI scans; the Dementia Research Centre trials team for assistance with imaging QC; Dan Marcus and Rick Herrick for assistance with XNAT; and Dr Philip Curran for assistance with data sharing with the MRC Unit for Lifelong Health and Ageing. We are also particularly indebted to the support of the late Chris Clark of Avid Radiopharmaceuticals who championed this study from its outset.

Study Funding:
Insight 46 is funded by grants from Alzheimer's Research UK (ARUK-PG2014-1946, ARUK-PG2017-1946 PIs Schott, Fox, Richards), Alzheimer's Association (SG-666374-UK BIRTH COHORT PI Schott), the Medical Research Council Dementias Platform UK (CSUB19166 PIs Schott, Fox, Richards), The Wolfson Foundation (PR/ylr/18575 PIs Fox, Schott), The Medical Research Council (MC-UU-12019/1 PI Kuh and MC-UU-12019/3 PI Richards), Selfridges Group Foundation (22/3/18 PIs Schott, Keshavan), and Brain Research Trust (UCC14191, PI Schott). This research was funded in whole, or in part, by the Wellcome Trust (Clinical Research Fellowship 200109/Z/15/Z Parker). For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Disclosures:
S.E. Keuss, W. Coath, J.M. Nicholas and T Poole report no disclosures relevant to the manuscript; J. Barnes was funded by an Alzheimer's Research UK Senior Fellowship (ARUK-SRF2016A-2); D. M. Cash was supported by Alzheimer's Research UK (ARUK-PG2017-1946), the UCL/UCLH NIHR Biomedical Research Centre, and the UK Dementia Research Institute which is funded by the UK Medical Research Council, AlzheimerÂ's Society and AlzheimerÂ's Research UK; C. A. Lane is a full time employee of Roche Products Ltd and a shareholder in F. Hoffmann-La Roche Ltd; T. D. Parker has received support from a Wellcome Trust Clinical Research Fellowship and a UK NIHR academic clinical lectureship; A. Keshavan was supported by a Wolfson Clinical Research Fellowship and a Weston Brain Institute and Selfridges Group Foundation award (UB170045); S. M. Buchanan reports no disclosures relevant to the manuscript; A. Z. Wagen is funded by a Wolfson Clinical Research Fellowship; M. Storey, M. Harris and I. B. Malone report no disclosures relevant to the manuscript; C. H. Sudre was supported by the Alzheimer's Society Junior Fellowship (AS-JF-17Â–011); K. Lu, S-N. James and R. Street report no disclosures relevant to this manuscript; D. L. Thomas is funded by the Leonard Wolfson Experimental Neurology Centre and University College London Hospitals Biomedical Research Centre; J. C. Dickson has received payment for consultancy on the running of multi-centre studies from Biogen, Bioclinica and GE Healthcare, and he is supported by the National Institute for Health Research, University College London Hospitals Biomedical Research Centre; H. Murray-Smith reports no disclosures relevant to this manuscript; A. Wong is funded by the Medical Research Council (MC_UU_00019/1, MC_UU_00019/3); T. Freiberger reports no disclosures relevant to the manuscript; S. Crutch is supported by an Alzheimer's Research UK Senior Research Fellowship (ARUK-SRF2013-8); M. Richards is funded by the Medical Research Council (MC_UU_12019/1, MC_UU_12019/3); N. C. Fox has served as a consultant, at advisory boards, or on a data monitoring committee for Roche, Biogen and Ionis, and he acknowledges support from the National Institute for Health Research University College London Hospitals Biomedical Research Centre, Rosetrees Trust, AlzheimerÂ's Research UK, and the UK Dementia Research Institute; J. M. Schott has received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly), has consulted for Roche Pharmaceuticals, Biogen, Merck, and Eli Lilly, given educational lectures sponsored by GE Healthcare, Eli Lilly, and Biogen, serves on a Data Safety Monitoring Committee for Axon Neuroscience SE, and is supported by

University College London Hospitals Biomedical Research Centre, Engineering and Physical Sciences Research Council (EP/J020990/1), British Heart Foundation (PG/17/90/33415), and EUÂ's Horizon 2020 research and innovation programme (666992).

Handling Editor Statement:

Abstract

Objective: To quantify the independent and interactive associations of amyloid-β (Aβ) and white matter hyperintensity volume (WMHV) – a marker of presumed cerebrovascular disease (CVD) – with rates of neurodegeneration, and to examine the contributions of APOE ε4 and vascular risk measured at different stages of adulthood in cognitively normal members of the 1946 British birth cohort.

Methods: Participants underwent brain MRI and florbetapir-Aβ positron emission tomography as part of Insight 46, an observational population-based study. Changes in whole brain, ventricular and hippocampal volume were directly measured from baseline and repeat volumetric T1 MRI using the Boundary Shift Integral. Linear regression was used to test associations with: baseline Aβ deposition; baseline WMHV; APOE ε4; and office-based Framingham heart study-cardiovascular risk scores (FHS-CVS) and systolic blood pressure (BP) at ages 36, 53 and 69 years.

Results: 346 cognitively normal participants (mean [SD] age at baseline scan 70.5 [0.6] years; 48% female) had high-quality T1 MRI data from both time-points (mean [SD] scan interval 2.4 [0.2] years). Being Aβ positive at baseline was associated with 0.87 ml/year faster whole brain atrophy (95% CI 0.03, 1.72), 0.39 ml/year greater ventricular expansion (95% CI 0.16, 0.64) and 0.016 ml/year faster hippocampal atrophy (95% CI 0.004, 0.027), while each 10 ml additional WMHV at baseline was

associated with 1.07 ml/year faster whole brain atrophy (95% CI 0.47, 1.67), 0.31 ml/year greater ventricular expansion (95% CI 0.13, 0.60) and 0.014 ml/year faster hippocampal atrophy (95% CI 0.006, 0.022). These contributions were independent and there was no evidence that Aβ and WMHV interacted in their effects. There were no independent associations of APOE ε4 with rates of neurodegeneration after adjusting for Aβ status and WMHV, and no clear relationships between FHS-CVS or systolic BP and rates of neurodegeneration when assessed across the whole sample, nor any evidence that they acted synergistically with Aβ.

Conclusions: Aβ and presumed CVD have distinct and additive effects on rates of neurodegeneration in cognitively normal elderly. These findings have implications for the use of MRI measures as biomarkers of neurodegeneration and emphasize the importance of risk management and early intervention targeting both pathways.

Introduction

Structural MRI measures are widely used as biomarkers of neurodegeneration in Alzheimer's disease (AD). Reduced brain volumes on MRI are included in the AT(N) framework for classifying individuals on the AD continuum;[1] and rates of atrophy quantified from MRI are often used as outcomes in trials, with the expectation that an effective disease-modifying therapy for AD should attenuate rates of atrophy in treated patients relative to controls. Understanding the factors that influence progression of neurodegeneration is therefore important, particularly in cognitively normal older adults, who are a key target population for strategies aimed at preventing dementia.

Cerebral amyloid-β (Aβ) deposition is an early pathological feature of AD, emerging up to twenty years prior to dementia.[2] It can be quantified using positron emission tomography (PET) and is increasingly used to identify individuals in the preclinical phase of AD who might be eligible for secondary prevention trials.[3] White matter hyperintensity volume (WMHV) – a marker of presumed cerebrovascular disease (CVD) – is increased among individuals at risk of AD and predicts AD dementia, raising the possibility that CVD may be involved in AD pathogenesis.[4] There is therefore considerable interest in understanding the relationship between Aβ and WMHs in cognitively normal elderly, and whether they act separately or together to influence downstream processes such as neurodegeneration.

The MRC National Survey of Health and Development (NSHD; the 1946 British birth cohort) is the world's longest continuously running birth cohort.[5] Members are virtually identical in age and have been extensively studied since birth, resulting in years of prospectively collected data from across the life-course. Now in their 70s and predominantly still dementia-free, a sample have undergone Aβ PET and serial MRI as part of the Insight 46 sub-study.[6] Using this unique dataset, the primary aim of this study was to assess whether baseline Aβ deposition and WMHV were associated with rates of neurodegeneration quantified from MRI and, if so, whether their effects were independent or interactive. A further aim was to investigate the contributions of APOE ε4 and vascular risk measured at different stages of adulthood to progression of neurodegeneration in later life.

Methods

Eligibility criteria have been described elsewhere.[7] In brief, 502 participants were recruited from the NSHD (n=2689 at age 69), prioritising members with relevant life-course data, who took part in a study visit at age 60-64, and previously indicated they would be willing to consider attending a study visit in London. Baseline assessments were performed at University College London between May 2015 and January 2018 and follow-up visits were completed between January 2018 and January 2021.

Standard protocol approvals, registrations, and patient consents

Ethical approval was granted by the National Research Ethics Service Committee (REC reference 14/LO/1173) and all participants provided written informed consent.

Imaging variables

Participants were scanned on a single Biograph mMR 3 Tesla PET/MRI (Siemens Healthcare). They were injected intravenously with 370 MBq of the ^{18}F Aβ PET ligand florbetapir at the start of the imaging session and dynamic data were obtained over 60 minutes. MRI data were acquired simultaneously including volumetric T1, T2 and FLAIR. Further information regarding the imaging protocol is reported elsewhere.[6]

Baseline Aβ PET data was processed using an in-house pipeline including pseudo-computed tomography attenuation correction.[8] Baseline global standardised uptake value ratios (SUVRs) were generated using a composite cortical region of interest, based on a composite that has been evaluated previously,[9] and an eroded subcortical white matter reference region. Baseline Aβ status was determined by applying a Gaussian mixture model to global SUVRs and then taking the 99th percentile of the lower Gaussian as the cut-point for positivity (eFigure 1). SUVRs and Aβ status were also calculated using a whole cerebellum reference region (see sensitivity analysis). Further information on PET methods is provided in eMethods 1.

T1, T2 and FLAIR MRI underwent correction for gradient non-linearity,[10] followed by brain-masked N4-bias correction,[11] and visual inspection of image quality. Baseline white matter hyperintensity volume (WMHV) was measured by applying an

unsupervised automated algorithm, Bayesian Model Selection (BaMoS), to T1 and FLAIR images, generating a global WMHV, which included subcortical grey matter but not infratentorial regions.[12] Baseline total intracranial volume (TIV) was calculated using the tissues utility in Statistical Parametric Mapping (SPM) 12.[13]

Changes in whole brain, ventricular and hippocampal volume were calculated from baseline and repeat MRI using the boundary shift integral (BSI).[14] Specifically, the k-means normalised BSI was used to calculate whole brain atrophy following affine registration of scan pairs and differential bias correction (DBC).[15] Ventricular expansion was determined using affine whole-brain registration, followed by an additional rigid registration using the ventricle regions only, and calculation of BSI without DBC. Hippocampal atrophy was assessed using affine whole-brain registration, followed by an additional rigid registration focusing on the hippocampus and surrounding regions, with DBC and calculation of BSI using a double intensity window approach.[16] Total hippocampal BSI was calculated as the sum of left and right. All registered scan-pairs were reviewed to check for longitudinal continuity.

APOE ε4 and life-course variables

APOE genotyping was performed as described elsewhere,[17] and participants were defined as ε4 carriers or non-carriers. Resting systolic blood pressure and an office-based Framingham Heart Study Cardiovascular Risk Score (FHS-CVS) were determined at ages 36, 53 and 69 years, as previously described.[18,19] The FHS-CVS, which provides a ten-year risk of cardiovascular events, is a weighted sum of age, sex, systolic blood pressure, anti-hypertensive medication (yes/no), diabetic status

(yes/no), current smoking status (yes/no) and body mass index.[20] Socioeconomic position was derived from occupation at age 53 and categorised as manual or nonmanual professions. Smoking status was obtained from a questionnaire at age 68 (or if missing, a questionnaire at age 60-64). Body mass index (BMI) was calculated from measurements at the first Insight 46 visit using the formula: BMI=kg/m^2; where kg is weight in kilograms and m^2 is height in metres squared. Diabetes was determined based on self-reported history prior to age 69, a glycated haemoglobin level greater than or equal to 6.5% (equivalent to greater than or equal to 48 mmol/mol) at age 69 or being on diabetic medication at the first Insight 46 visit.

Statistical analysis

Participants were excluded from analyses if they had dementia, mild cognitive impairment (MCI) or confounding brain disorders at baseline or if they did not have high-quality longitudinal T1 MRI data. Dementia and MCI were defined as described previously.[21] For analyses involving Aβ or WMHV, participants needed baseline Aβ PET or WMH segmentation data that passed quality control; for APOE ε4 analyses, genotype data was also required; and for vascular risk analyses, they needed FHS-CVS or systolic blood pressure (BP) data and covariate data at one or more time-point. A full breakdown of participants is provided as a flowchart (eFigure 2).

Group differences were assessed using t-tests for continuous normally distributed variables, Wilcoxon rank-sum tests for continuous non-normally distributed variables, and χ^2 tests for categorical variables. Spearman's rank correlation was used to test associations involving continuous non-normally distributed variables.

Linear regression was used to test associations between predictors of interest and rates of change in whole brain, ventricular and total hippocampal volume. Each model included the BSI measure of interest in millilitres as the outcome, scan interval in years as the explanatory variable, and interactions between scan interval and (i) each predictor variable of interest and (ii) each covariate, in order to estimate their association with rate of change. Interactions between two variables were tested by including a term for the three-way interaction between each predictor and scan interval. No constant term was included since the model estimates mean change over time. A more detailed explanation of models used is provided in eMethods 2.

Effects of baseline Aβ and WMHV on each volume change measure were examined in separate models and then together as predictors in a single model, with adjustment for sex, age at baseline scan and TIV. Baseline Aβ was considered in separate models as a binary Aβ status (positive/negative) and using the continuous global Aβ SUVR measure. Semi-partial r^2 values were calculated to assess the relative explanatory contribution of Aβ and WMHV, above the explanatory contribution of all other variables in the model (eMethods 2). If relationships were detected with hippocampal atrophy rates, whole brain BSI was added as a covariate to examine whether effects on hippocampi were disproportionate to global changes. Further models examined whether there was an interaction between Aβ and WMHV and whether there was an interaction between sex and each of Aβ and WMHV.

Separate models were fitted to assess the effects of APOE ε4 (carrier/non-carrier) on each volume change measure. Models were initially adjusted for sex, age at baseline

scan and TIV, before further adjusting for baseline Aβ status or WMHV to assess whether effects were attenuated after adjusting for these variables. Similar models were fitted to test the contributions of FHS-CVS and systolic BP at each time-point (ages 36, 53 and 69 years) to each volume change measure. Since FHS-CVS and systolic BP were associated with WMHV but not with Aβ status in previous Insight 46 analyses,[18,19] models were initially adjusted for sex, age at baseline scan, TIV, baseline Aβ status, APOE ε4 status and adult socioeconomic position, before further adjusting for baseline WMHV to assess whether it might explain any effects. Models with systolic BP as a predictor were also adjusted for smoking status, presence of diabetes and body mass index around the time of baseline scan. Interactions between Aβ status and each of FHS-CVS and systolic BP at age 69 were also tested.

Analyses were conducted in Stata 16 (StataCorp, USA). Regression assumptions were checked by examination of residual plots. If assumptions were not fully met, bootstrapping (2,000 replications) was used to produce bias-corrected and accelerated 95% confidence intervals. Non-linear associations were assessed using plots of residuals against each predictor and were formally tested by adding quadratic terms to models. Scatter plots of key relationships are shown in eFigure3.

Sensitivity analyses were also performed to examine the effect of: (i) not adjusting for age at baseline scan (healthier subjects may have been more likely to attend at the start of the study, so age might act as a proxy for recruitment bias); (ii) using the whole cerebellum rather than white matter as a reference region for SUVRs (WMHs

might influence Aβ PET tracer uptake,[22,23] which could confound the results of our analyses).

Data availability

Anonymised data are available on request (https://skylark.ucl.ac.uk/NSHD/doku.php).

Results

346 participants (mean [SD] age at baseline scan 70.5 [0.6] years; 48% female) had MRI data from both time-points (mean [SD] scan interval 2.4 [0.2] years) and were free of dementia, MCI and confounding brain disorders at baseline.

Median baseline Aβ SUVR was 0.54 (IQR: 0.51-0.58) and 16.7% of participants were classified as Aβ positive (SUVR cut-point for positivity 0.61). Median baseline WMHV was 2.7 ml (IQR: 1.5-6.1) and did not differ significantly by Aβ status (Z = -0.667; p=0.50). There was, however, a weak positive correlation between baseline WMHV and Aβ SUVR (r_s = 0.16; p<0.01). Age at baseline scan was not significantly associated with baseline WMHV (r_s = 0.08; p=0.12), Aβ SUVR (r_s = -0.01; p=0.82) or Aβ status (t(339)=0.7032; p=0.48), and there were no significant sex differences in baseline WMHV (Z = -1.533; p=0.13), Aβ SUVR (Z = 0.637; p=0.52) or Aβ status (χ^2 = 0.5617; p=0.45). Further characteristics are summarised in Table 1, together with those of the full Insight 46 sample for comparison.

Mean rates of whole brain and hippocampal atrophy were 5.86 ml/year and 0.039 ml/year (equivalent to 0.5 %/year and 0.6 %/year), and mean rate of ventricular expansion was 1.24 ml/year (Table 2). There were no significant sex differences in rates of neurodegeneration after controlling for TIV, but there were associations with age. Specifically, older age at baseline scan was related to significantly greater rates of ventricular expansion (0.16 ml/year faster per one-year increment in age; 95% CI 0.03, 0.30) and hippocampal atrophy (0.009 ml/year faster per one-year increment in age; 95% CI 0.002, 0.016), and there was a directionally consistent but non-significant association with rates of whole brain atrophy (0.46 ml/year faster per one-year increment in age; 95% CI -0.04, 0.95).

Effects of baseline Aβ deposition

Results of analyses testing associations of Aβ at age 70 years with subsequent rates of neurodegeneration over the next 2.4 years are provided in Figure 1.

Being Aβ positive (compared to negative) was associated with significantly greater rates of neurodegeneration: 0.92 ml/year faster whole brain atrophy, 0.40 ml/year greater ventricular expansion and 0.016 ml/year faster hippocampal atrophy. Similar relationships were seen with higher baseline Aβ SUVR, which had significant associations with greater rates of ventricular expansion (0.20 ml/year faster per 0.1 increment in SUVR) and hippocampal atrophy (0.009 ml/year faster per 0.1 increment in SUVR), and a non-significant association with rates of whole brain atrophy (0.39 ml/year per 0.1 increment in SUVR). There was no evidence of non-linear associations.

There was an interaction between Aβ and sex, whereby Aβ had a greater effect on rate of whole brain atrophy in women than men (eTable 1). Post hoc stratification by sex revealed that being Aβ positive at baseline (compared to negative) was associated with 1.82 ml/year greater atrophy in females (95% CI 0.64 to 3.00) and 0.31 ml/year faster atrophy in males (95% CI -0.93 to 1.56), while a 0.1 increment in baseline Aβ SUVR was associated with 0.85 ml/year greater atrophy in females (95% CI 0.24 to 1.47) and 0.06 ml/year faster atrophy in males (95% CI -0.62, 0.73).

Effects of baseline WMHV

Results of analyses testing associations of WMHV at age 70 years with rates of neurodegeneration over the next 2.4 years are provided in Figure 1.

Higher WMHV was associated with significantly greater rates of neurodegeneration: each 10 ml additional WMHV was related to 1.09 ml/year faster whole brain atrophy, 0.32 ml/year greater ventricular expansion and 0.014 ml/year faster hippocampal atrophy. There was no evidence of non-linear associations.

There were no interactions between WMHV and sex ($p>0.1$, all tests; eTable 1).

Disproportionate hippocampal atrophy

Associations of baseline Aβ and WMHV with rates of hippocampal atrophy were attenuated after adjustment for whole brain atrophy, such that only the effect of Aβ

SUVR remained significant. Specifically, each 0.1 increment in Aβ SUVR was associated with 0.005 ml/year faster hippocampal atrophy (95% CI 0.000 to 0.010), while Aβ positivity was associated with 0.008 ml/year greater hippocampal atrophy (95% CI -0.001 to 0.017), and each 10ml additional WMHV was associated with 0.005 ml/year faster hippocampal atrophy (95% CI -0.001 to 0.012).

Independent and interactive effects of baseline Aβ deposition and WMHV

Effects of Aβ and WMHV on rates of neurodegeneration remained similar when they were assessed together as predictors in the same model (Figure 1).

After accounting for WMHV, in addition to age, sex and TIV, Aβ status explained an additional 1.1% of the variance in whole brain atrophy rate, 2.6% of the variance in ventricular expansion rate and 2.1% of the variance in hippocampal atrophy rate. After accounting for Aβ status, in addition to age, sex and TIV, WMHV explained an additional 3.3% of the variance in whole brain atrophy and ventricular expansion rate and 3.1% of the variance in hippocampal atrophy rate.

There were no interactive effects of Aβ and WMHV ($p>0.1$, all tests; eTable 1).

Effects of APOE ε4 status

Results of analyses testing associations of APOE ε4 with rates of neurodegeneration around age 70 are reported in Table 3.

APOE ε4 carriers had significantly greater rates of hippocampal atrophy (0.011 ml/year faster than non-carriers) and there were directionally consistent but non-significant relationships with rates of whole brain atrophy (0.67 ml/year higher than non-carriers) and ventricular expansion (0.13 ml/year faster than non-carriers). Effects were attenuated after adjusting for Aβ status and, to a lesser extent, WMHV, such that the effect on hippocampal atrophy was no longer significant.

Effects of exposure to vascular risk at ages 36, 53 and 69 years

Results of analyses testing associations of FHS-CVS and systolic BP at different stages of adulthood with rates of neurodegeneration around age 70 years are reported in Table 4 and Table 5 respectively.

Higher FHS-CVS and systolic BP at age 53 were initially found to be associated with faster rates of hippocampal atrophy in later life, but effects were small and no longer significant after exclusion of an influential data-point (eAppendix 1). Otherwise, there were no significant relationships of FHS-CVS or systolic blood pressure with rates of neurodegeneration when assessed across the whole sample, and no evidence of non-linear associations.

Systolic BP at age 69 did not interact with Aβ status, but there were differential effects of FHS-CVS at age 69 by Aβ status (eTable 1). Specifically, higher FHS-CVS at age 69 was related to significantly greater rates of whole brain atrophy (0.20 ml/year faster per 5% increment in FHS-CVS; 95% CI 0.01, 0.40) and hippocampal atrophy (0.004 ml/year faster per 5% increment in FHS-CVS; 95% CI 0.001, 0.006)

in Aβ negative individuals, whereas it had non-significant and directionally opposite effects on rates of whole brain atrophy (0.05 ml/year slower per 5% increment in FHS-CVS; 95% CI -0.32, 0.41) and hippocampal atrophy (0.004 ml/year slower per 5% increment in FHS-CVS; 95% CI -0.001, 0.010) in Aβ positive individuals. There was a substantial difference in sample size between groups, however, with considerably fewer Aβ positive (n=56) than negative (n=274) participants.

Sensitivity analyses

Re-running analyses without adjustment for age at baseline scan did not substantially change our findings (eAppendix 2). After re-running analyses using Aβ SUVRs with a whole cerebellum reference region: slightly fewer participants (15.8% versus 16.7%) were Aβ positive (SUVR cut-point for positivity 1.08); associations between baseline Aβ status and rates of neurodegeneration were similar, while relationships between baseline Aβ SUVR and rates of neurodegeneration were somewhat weaker but directionally the same; there was a reduced correlation between baseline Aβ SUVR and WMHV (r_S = 0.02; p=0.75); and the interactions between Aβ and sex and between Aβ and the FHS-CVS at age 69 were decreased and non-significant (eAppendix 3).

Discussion

In this population-based sample of cognitively normal elderly of almost identical age, we examined predictors of rates of neurodegeneration. Key findings were that Aβ

positivity and higher WMHV were both related to faster rates of whole brain atrophy, ventricular expansion and hippocampal atrophy, and their effects were independent.

WMHs have a heterogenous aetiology and underlying pathology, but in older adults they are largely thought to occur as a result of chronic ischaemia due to small vessel disease (SVD).[24] We found no difference in WMHV between Aβ positive and negative participants, but there was a weak positive correlation between WMHV and Aβ SUVR defined using a white matter reference region. This relationship was no longer observed using SUVRs with a whole cerebellum reference region, raising the possibility that quantification of Aβ using a white matter reference region may be influenced by the presence of WMHs or SVD, as has been described previously.[22,23]

Prior studies investigating the relationship between WMHs and Aβ on PET have reported mixed results, but a recent systematic review concluded that they were mostly independent processes.[25] Some studies have observed increased WMHV in relation to lower Aβ42 in cerebrospinal fluid,[26–28] while others have not, or have only found a relationship in AD dementia rather than in mild cognitive impairment or healthy controls.[29–31] There is also evidence that individuals with cerebral amyloid angiopathy – a form of SVD involving deposition of Aβ in blood vessels – have greater WMHs with a predilection for posterior brain regions.[32,33] This may explain some of the variability in findings between studies.

Irrespective of the reference region used to calculate Aβ SUVR, we observed that Aβ positivity and greater WMHV were both independently associated with faster rates of whole brain atrophy, ventricular expansion, and hippocampal atrophy. The relative

contribution of WMHV was somewhat greater than Aβ, and there was no evidence that Aβ and WMHV interacted in their effects. These findings are supportive of the hypothesis that Aβ and CVD predominantly act via distinct rather than synergistic pathways, and are consistent with a number of other studies that have shown independent effects in relation to rates of atrophy or cognitive decline.[31,34–36]

Notably, Aβ positive (versus negative) individuals had approximately 15% faster whole brain atrophy and 50% greater hippocampal atrophy rates, and higher Aβ SUVR was associated with disproportionate progressive hippocampal atrophy, despite participants being cognitively normal and years before significant numbers are expected to develop dementia. The effect of WMHV on disproportionate hippocampal atrophy was directionally similar but non-significant. Selective vulnerability of the hippocampus is a characteristic feature of early AD, but it has also recently been reported in relation to WMHs, including in healthy controls.[37]

We initially observed an interactive effect of Aβ and sex, whereby higher Aβ deposition at baseline was associated with faster rates of whole brain atrophy in women but not in men, suggesting that females are perhaps more susceptible to the consequences of Aβ. Women are known to be at higher risk of AD, which may be partly related to their longer lifespan, but sex differences in relationships between AD pathologies or risk factors and downstream atrophy or cognition have been reported.[38,39] The interaction we observed between Aβ and sex was reduced and non-significant, however, using SUVRs with a whole cerebellum reference region, which could mean that our original finding was a spurious result or that methods of Aβ measurement may be affected by sex differences in some way.

There were no clear associations between FHS-CVS or systolic blood pressure (at ages 36, 53 and 69 years) and progressive neurodegeneration in later life when assessed across the whole sample. We previously demonstrated that higher FHS-CVS or blood pressure, particularly in early or middle adulthood, was related to smaller brain volumes at age 70.[18,19] This likely reflects that cross-sectional volumes are more indicative of the effects of brain insult(s) prior to the point of brain imaging, and that vascular risk exposure earlier in life is perhaps more detrimental to brain health or associated with greater cumulative risk exposure. We also considered whether differences in findings might be related to a reduction in statistical power, since there were fewer participants with longitudinal data. However, post hoc analyses using the smaller sample of this study showed similar relationships with cross-sectional volumes to those previously reported (data not shown).

There was also no evidence that vascular risk and Aβ acted synergistically to influence rates of neurodegeneration, which contrasts with findings from other studies that examined their effects on tau deposition and cognitive decline.[40,41]

The interpretation of the association between older age at baseline scan (despite the narrow age range of the sample) and faster rates of neurodegeneration is uncertain. Previous studies have demonstrated that rates of ventricular expansion are relatively stable before the age of 70 years at around 1 ml/year, but accelerate thereafter, approaching 4 ml/year towards the age of 80 years.[42,43] This is comparable to the effect we observed (0.16 ml/year faster per one-year increment in age). Alternatively, age effects in Insight 46 might reflect a degree of recruitment bias since healthier

individuals may have been more likely to attend at the start of the study. While there was no evidence of this in a previous analysis looking at self-reported health and disease burden in Insight 46,[7] untested differences may still exist.

The findings of this study have implications for the use of MRI measures as biomarkers of neurodegeneration in AD. The AT(N) framework proposes the use of biomarkers of Aβ [A], tau [T] and neurodegeneration [N] to classify individuals on the AD continuum.[1] However, neurodegeneration is not specific to AD and this study highlights that CVD – as represented by WMHs – has significant independent effects on neurodegeneration, which are potentially greater in magnitude than those of Aβ. As such, the findings of this study are supportive of the view of others,[44] that CVD biomarkers should be added to the AT(N) framework, something that has already been discussed as a possibility in a recent position paper.[1] Our findings also highlight the importance of accounting for CVD in AD trials where MRI measures are included as outcomes, since its presence might confound detection of treatment effects, particularly in the preclinical phase when the relative contribution of CVD may be greater.

The results of this study also have broader relevance to our understanding of the processes leading to dementia. While this was a cognitively normal population, it is reasonable to infer that increased rates of neurodegeneration will have subsequent consequences for cognition, given that the two are known to be correlated.[45] As such, our findings are in keeping with the idea that Aβ and CVD predominantly influence risk of cognitive decline through distinct pathways, and that CVD does not contribute to the development of AD pathology *per se*, but may act by lowering the

threshold for onset of dementia. Early interventions and risk management targeting both potential pathways are therefore likely to be important. The attenuation of the association between APOE ε4 and rates of neurodegeneration after adjusting for Aβ and WMHV suggests that the effects of APOE ε4 were mediated by Aβ and – to a lesser degree – WMHV. This is consistent with APOE ε4 primarily, but not exclusively, influencing risk of dementia via Aβ deposition.[46]

Key strengths of this study include its population-based setting and prospectively collected data. Participants were also almost identical in age and underwent imaging on a single scanner using a standardised protocol. This is reflected in their mean [SD] atrophy rates (whole brain 5.86 [3.19] ml/year; hippocampal 0.039 [0.041] ml/year), which were considerably less variable (SD/mean ratios around half) compared to those reported by the Alzheimer's Disease Neuroimaging Initiative (whole brain 6.27 [6.15] ml/year; hippocampal 0.052 [0.089] ml/year) and Australian Imaging and Biomarker Lifestyle study (whole brain 5.46 [7.0] ml/year; hippocampal 0.031 [0.061] ml/year), despite using the same BSI measurement technique.[47,48]

As documented before, however, Insight 46 has some limitations in terms of generalisability.[21] Participants were all white Caucasian, and so findings may not be translatable to more ethnically and culturally diverse populations. They also had marginally higher educational attainment, socioeconomic position and self-rated health than the larger NSHD sample, which suggests that those with poorer health may have been under-represented.[7] Without tau PET, we were unable to fully characterise participants according to the AT(N) framework, and could not examine whether tau is more strongly related to neurodegeneration than Aβ or whether it

interacts with WMHs, as reported elsewhere.[49,50] Furthermore, since our analyses were limited to global and hippocampal volume measures, we could not exclude the possibility that Aβ interacts with WMHs or vascular risk to influence rates of neurodegeneration in other brain regions. Lastly, future analyses will be important to how longitudinal changes in Aβ and WMHV relate to rates of neurodegeneration, which may provide further support for the independence of these processes.

In conclusion, Aβ and CVD have distinct and additive effects on rates of neurodegeneration in cognitively normal elderly. These findings have implications for the use of MRI measures as biomarkers of neurodegeneration in AD and for understanding the processes that confer increased risk of dementia.

Figure Titles and Legends

Figure 1. Forest plot showing coefficients and 95% confidence intervals for associations of baseline amyloid-β and white matter hyperintensity volume with rates of neurodegeneration quantified from MRI in cognitively normal participants.

Aβ = amyloid-β; SUVR = standard uptake value ratio; WMHV = white matter hyperintensity volume; BSI = boundary shift integral. All models were adjusted for sex, age at baseline scan and total intracranial volume. * p ≤0.05; ** p ≤0.01. ‡ bias-corrected and accelerated bootstrap 95% CIs.

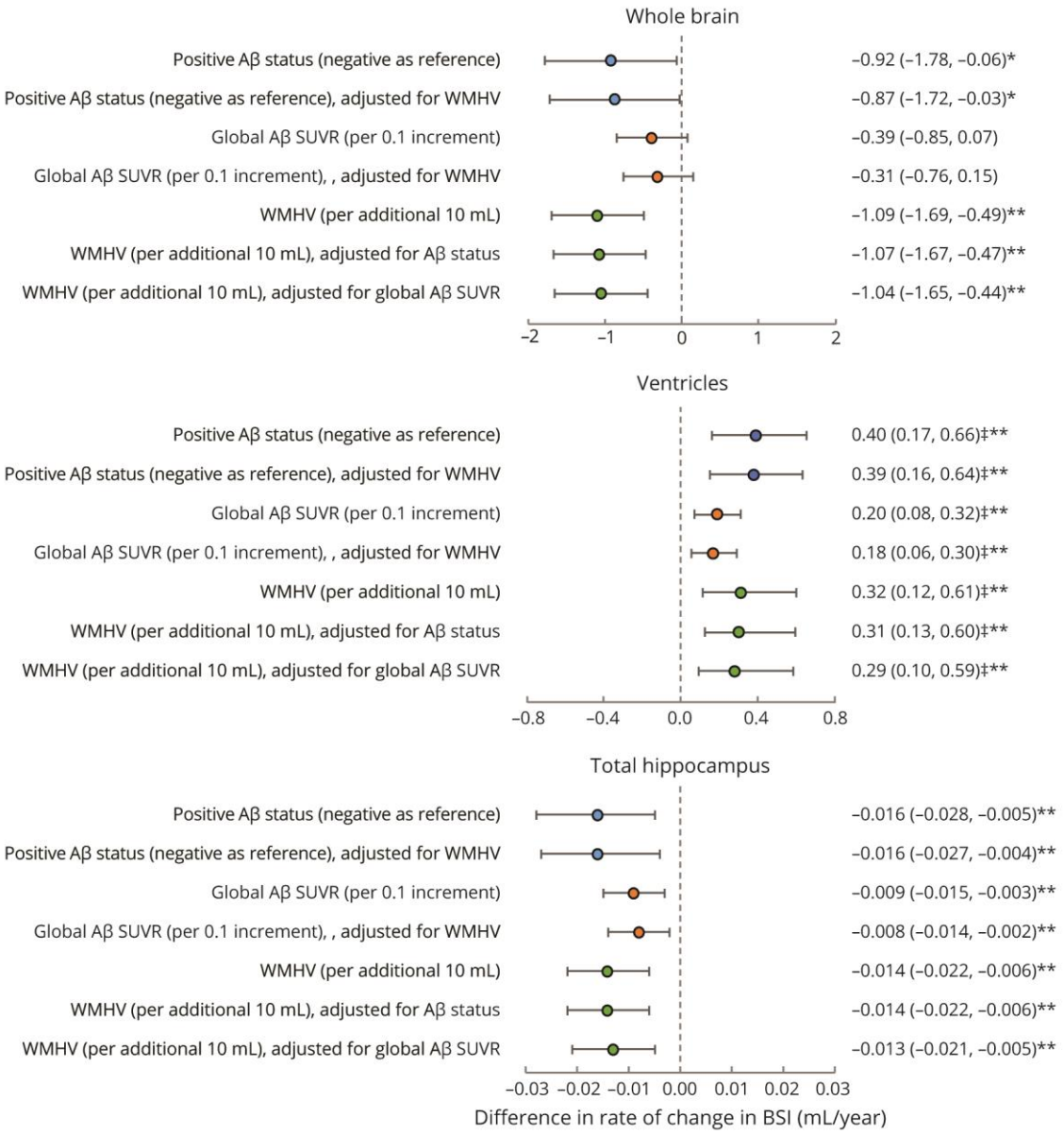

Table 1. Participant characteristics and predictors of interest

Characteristic		Full Insight 46 sample (max. n=502)	Current analysis (max. n=346)
Age at baseline scan, years, mean (SD)		70.7 (0.7) (n=471)[a]	70.5 (0.6)
Sex, % female		49.0	48.3
MMSE at baseline, score out of 30, median (IQR)		30 (29-30)	30 (29-30)
DSST at baseline, score out of 93, mean (SD)		47.6 (10.4) (n=501)[a]	48.6 (10.2)
Socioeconomic position at age 53, % manual		15.1	15.0
APOE ε4 carrier, %	All participants	29.6 (n=500)[a]	29.9 (n=344)[a]
	Amyloid-β positive	58.1 (n=86)[a]	59.7 (n=57)[a]
	Amyloid-β negative	22.7 (n=374)[a]	22.7 (n=282)[a]
Diabetes at baseline, % yes		11.3 (n=497)[a]	10.8 (n=344)[a]
Prior myocardial infarction at baseline, % yes		2.6	2.6
Prior stroke at baseline, % yes		3.6	3.8
Smoking status at baseline, %	Ever smoked	65.9	65.3
	Current smoker	3.6	2.9
Body mass index at baseline, kg/m^2		27.8 (4.6)	27.3 (4.1)
FHS-CVS, %, median (IQR)	Age 36	2.7 (1.5-3.6) (n=455)[a]	2.7 (1.6-3.6) (n=312)[a]
	Age 53	10.9 (6.7-15.6) (n=487)[a]	10.9 (6.5-15.6) (n=337)[a]
	Age 69	24.2 (15.1-34.9) (n=488)[a]	23.5 (14.9-34.7) (n=341)[a]
Systolic blood	Age 36	120.2 (13.7)	120.0 (14.1)

pressure, mmHg, mean (SD)		(n=460)[a]	(n=313)[a]
	Age 53	133.5 (19.0) (n=488)[a]	133.6 (19.0) (n=338)[a]
	Age 69	132.3 (16.0) (n=495)[a]	132.5 (15.9) (n=344)[a]
Global β-amyloid SUVR at baseline, median (IQR)	All participants	0.55 (0.52, 0.58) (n=462)[a]	0.54 (0.51, 0.58) (n=341)[a]
	Amyloid-β positive	0.68 (0.64, 0.73) (n=86)[a]	0.68 (0.64, 0.71) (n=57)[a]
	Amyloid-β negative	0.53 (0.51, 0.56) (n=376)[a]	0.53 (0.51, 0.56) (n=284)[a]
β-amyloid status at baseline, % positive		18.6 (n=462)[a]	16.7 (n=341)[a]
Global WMHV at baseline, ml, median (IQR)		3.1 (1.6, 6.8) (n=455)[a]	2.7 (1.5, 6.1) (n=342)[a]
Total intracranial volume, ml, mean (SD)		1433 (133) (n=468)[a]	1434 (131)
Whole brain volume at baseline, ml, mean (SD)		1100 (99) (n=468)[a]	1104 (97)
Ventricular volume at baseline, ml, mean (SD)		31.1 (16.3) (n=468)[a]	30.0 (14.5)
Total hippocampal volume at baseline, ml, mean (SD)		6.27 (0.67) (n=468)[a]	6.30 (0.64)

MMSE = mini-mental state examination; DSST = digit symbol substitution test; FHS-CVS = Framingham Heart Study Cardiovascular Risk Score; SUVR = standard uptake value ratio; WMHV = white matter hyperintensity volume. [a] number of participants with available data if below maximum possible

Table 2. Rates of neurodegeneration quantified from MRI in cognitively normal participants

	Mean rates of change in volume measured using the boundary shift integral†					
	All participants (n=346)		Amyloid-β positive (n=57)		Amyloid-β negative (n=284)	
Region	ml/yr (SD)	%/yr (SD)	ml/yr (SD)	%/yr (SD)	ml/yr (SD)	%/yr (SD)
Whole brain	-5.86 (3.19)	-0.53 (0.28)	-6.63 (3.07)	-0.59 (0.26)	-5.65 (3.15)	-0.51 (0.28)
Ventricles	1.24 (0.92)	-	1.55 (0.86)	-	1.16 (0.90)	-
Total hippocampus	-0.039 (0.041)	-0.63 (0.66)	-0.051 (0.046)	-0.83 (0.75)	-0.037 (0.040)	-0.59 (0.63)

† negative values represent atrophy and positive values indicate expansion. N.B. 5 participants were missing amyloid-β PET data

Table 3. Associations of APOE ε4 with rates of neurodegeneration quantified from MRI in cognitively normal participants

Model	Difference in rate of change in BSI in ml/year (95% CIs) in APOE ε4 carriers compared to non-carriers		
	Whole brain	Ventricles	Total hippocampus
1	-0.67 (-1.38, 0.04)	0.13 (-0.06, 0.32)‡	-0.011* (-0.021, -0.002)
2	-0.48 (-1.22, 0.27)	0.02 (-0.16, 0.23)‡	-0.008 (-0.018, 0.002)
3	-0.56 (-1.26, 0.14)	0.09 (-0.10, 0.28)‡	-0.010 (-0.020, -0.001)
4	-0.37 (-1.10, 0.37)	-0.01 (-0.22, 0.19)‡	-0.007 (-0.017, 0.003)

BSI = boundary shift integral. Model 1 was adjusted for sex, age at baseline scan and total intracranial volume. Model 2 represents Model 1 plus adjustment for baseline β-amyloid status. Model 3 represents Model 1 plus adjustment for baseline white matter hyperintensity volume. Model 4 represents Model 1 plus adjustment for baseline β-amyloid status and white matter hyperintensity volume. *significant at $p \leq 0.05$; ‡ bias-corrected and accelerated bootstrap 95% CIs.

Table 4. Associations of the Framingham Heart Study Cardiovascular Risk Score at ages 36, 53 and 69 with rates of neurodegeneration quantified from MRI in cognitively normal participants

Model		Difference in rate of change in BSI in ml/year (95% CIs) per 5% increment in the FHS-CVS		
		Whole brain	Ventricles	Total hippocampus
Age 36 (n=301)	1	-0.48 (-1.73, 0.78)	0.12 (-0.25, 0.48)‡	0.004 (-0.013, 0.022)
	2	-0.34 (-1.58, 0.91)	0.08 (-0.28, 0.43)‡	0.006 (-0.011, 0.024)
Age 53 (n=326)	1	-0.10 (-0.39, 0.20)	-0.01 (-0.09, 0.08)‡	-0.002 (-0.006, 0.002)
	2	-0.07 (-0.36, 0.22)	-0.02 (-0.10, 0.06)‡	-0.002 (-0.006, 0.002)
Age 69 (n=330)	1	-0.15 (-0.32, 0.02)	0.05 (-0.00, 0.14)‡	-0.002 (-0.004, 0.001)
	2	-0.11 (-0.28, 0.06)	0.04 (-0.01, 0.12)‡	-0.001 (-0.004, 0.001)

BSI = boundary shift integral; FHS-CVS = Framingham Heart Study Cardiovascular Risk Score. Model 1 was adjusted for sex, age at baseline scan, total intracranial volume, baseline amyloid-β status, APOE ε4 status and adult socioeconomic position. Model 2 was further adjusted for baseline white matter hyperintensity volume. Effects of the FHS-CVS at age 53 refer to results after excluding an outlier (eAppendix1). ‡ bias-corrected and accelerated bootstrap 95% CIs.

Table 5. Associations of the systolic blood pressure at ages 36, 53 and 69 with rates of neurodegeneration quantified from MRI in cognitively normal participants

Model		Difference in rate of change in BSI in ml/year (95% CIs) per 10mmHg increment in systolic blood pressure		
		Whole brain	Ventricles	Total hippocampus
Age 36 (n=302)	1	-0.07 (-0.33, 0.19)	-0.00 (-0.08, 0.06)‡	-0.001 (-0.004, 0.003)
	2	-0.07 (-0.33, 0.19)	-0.01 (-0.08, 0.06)‡	-0.001 (-0.004, 0.003)
Age 53 (n=325)	1	-0.08 (-0.26, 0.10)	0.03 (-0.02, 0.08)‡	-0.002 (-0.005, 0.000)
	2	-0.05 (-0.22, 0.13)	0.01 (-0.04, 0.06)‡	-0.002 (-0.004, 0.000)
Age 69 (n=333)	1	-0.02 (-0.22, 0.19)	0.05 (-0.01, 0.13)‡	-0.001 (-0.004, 0.002)
	2	0.03 (-0.18, 0.23)	0.03 (-0.03, 0.10)‡	-0.000 (-0.003, 0.003)

BSI = boundary shift integral. Model 1 was adjusted for sex, age at baseline scan, total intracranial volume, baseline amyloid-β status, APOE ε4 status, adult socioeconomic position and smoking status, presence of diabetes and body mass index around time of baseline scan. Model 2 was further adjusted for baseline white matter hyperintensity volume. Effects of systolic blood pressure at age 53 refer to results after excluding an outlier (eAppendix1). ‡ bias-corrected and accelerated bootstrap 95% CIs.

References

1. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
2. De Strooper B, Karran E. The Cellular Phase of Alzheimer's Disease. *Cell*. 2016;164(4):603-615. doi:10.1016/j.cell.2015.12.056
3. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: Stopping AD before symptoms begin? *Sci Transl Med*. 2014;6(228). doi:10.1126/scitranslmed.3007941
4. Brickman AM. Contemplating Alzheimer's disease and the contribution of white matter hyperintensities. *Curr Neurol Neurosci Rep*. 2013;13(12). doi:10.1007/s11910-013-0415-7
5. Kuh D, Wong A, Shah I, et al. The MRC National Survey of Health and Development reaches age 70: maintaining participation at older ages in a birth cohort study. *Eur J Epidemiol*. 2016;31(11):1135-1147. doi:10.1007/s10654-016-0217-8
6. Lane CA, Parker TD, Cash DM, et al. Study protocol: Insight 46 - a neuroscience sub-study of the MRC National Survey of Health and Development. *BMC Neurol*. 2017;17(1). doi:10.1186/s12883-017-0846-x
7. James SN, Lane CA, Parker TD, et al. Using a birth cohort to study brain health and preclinical dementia: Recruitment and participation rates in Insight 46. *BMC Res Notes*. 2018;11(1):885. doi:10.1186/s13104-018-3995-0

8. Burgos N, Cardoso MJ, Thielemans K, et al. Attenuation correction synthesis for hybrid PET-MR scanners: Application to brain studies. *IEEE Trans Med Imaging*. 2014;33(12):2332-2341. doi:10.1109/TMI.2014.2340135

9. Landau SM, Breault C, Joshi AD, et al. Amyloid-β imaging with Pittsburgh compound B and florbetapir: Comparing radiotracers and quantification methods. *J Nucl Med*. 2013;54(1):70-77. doi:10.2967/jnumed.112.109009

10. Jovicich J, Czanner S, Greve D, et al. Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. *Neuroimage*. 2006;30(2):436-443. doi:10.1016/j.neuroimage.2005.09.046

11. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: Improved N3 bias correction. *IEEE Trans Med Imaging*. 2010;29(6):1310-1320. doi:10.1109/TMI.2010.2046908

12. Sudre CH, Cardoso MJ, Bouvy WH, Biessels GJ, Barnes J, Ourselin S. Bayesian model selection for pathological neuroimaging data applied to white matter lesion segmentation. *IEEE Trans Med Imaging*. 2015;34(10):2079-2102. doi:10.1109/TMI.2015.2419072

13. Malone IB, Leung KK, Clegg S, et al. Accurate automatic estimation of total intracranial volume: A nuisance variable with less nuisance. *Neuroimage*. 2015;104:366-372. doi:10.1016/j.neuroimage.2014.09.034

14. Freeborough PA, Fox NC. The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE Trans Med Imaging*. 1997;16(5):623-629. doi:10.1109/42.640753

15. Leung KK, Clarkson MJ, Bartlett JW, et al. Robust atrophy rate measurement in Alzheimer's disease using multi-site serial MRI: Tissue-specific intensity

normalization and parameter selection. *Neuroimage*. 2010;50(2):516-523. doi:10.1016/j.neuroimage.2009.12.059

16. Leung KK, Barnes J, Ridgway GR, et al. Automated cross-sectional and longitudinal hippocampal volume measurement in mild cognitive impairment and Alzheimer's disease. *Neuroimage*. 2010;51(4):1345-1359. doi:10.1016/j.neuroimage.2010.03.018
17. Rawle MJ, Davis D, Bendayan R, Wong A, Kuh D, Richards M. Apolipoprotein-E (Apoe) ϵ 4 and cognitive decline over the adult life course. *Transl Psychiatry*. 2018;8(1):18. doi:10.1038/s41398-017-0064-8
18. Lane CA, Barnes J, Nicholas JM, et al. Associations between Vascular Risk Across Adulthood and Brain Pathology in Late Life: Evidence from a British Birth Cohort. *JAMA Neurol*. 2020;77(2):175-183. doi:10.1001/jamaneurol.2019.3774
19. Lane CA, Barnes J, Nicholas JM, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol*. 2019;18(10):942-952. doi:10.1016/S1474-4422(19)30228-5
20. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008;117(6):743-753. doi:10.1161/CIRCULATIONAHA.107.699579
21. Lu K, Nicholas JM, Collins JD, et al. Cognition at age 70: Life course predictors and associations with brain pathologies. *Neurology*. 2019;93(23):E2144-E2156. doi:10.1212/WNL.0000000000008534
22. Goodheart AE, Tamburo E, Minhas D, et al. Reduced binding of Pittsburgh

Compound-B in areas of white matter hyperintensities. *NeuroImage Clin*. 2015;9:479-483. doi:10.1016/j.nicl.2015.09.009

23. Glodzik L, Rusinek H, Li J, et al. Reduced retention of Pittsburgh compound B in white matter lesions. *Eur J Nucl Med Mol Imaging*. 2015;42(1):97-102. doi:10.1007/s00259-014-2897-1

24. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. *Lancet Neurol*. 2013;12(5):483-497. doi:10.1016/S1474-4422(13)70060-7

25. Roseborough A, Ramirez J, Black SE, Edwards JD. Associations between amyloid β and white matter hyperintensities: A systematic review. *Alzheimer's Dement*. 2017;13(10):1154-1167. doi:10.1016/j.jalz.2017.01.026

26. Walsh P, Sudre CH, Fiford CM, et al. CSF amyloid is a consistent predictor of white matter hyperintensities across the disease course from aging to Alzheimer's disease. *Neurobiol Aging*. 2020;91:5-14. doi:10.1016/j.neurobiolaging.2020.03.008

27. Marnane M, Al-Jawadi OO, Mortazavi S, et al. Periventricular hyperintensities are associated with elevated cerebral amyloid. *Neurology*. 2016;86(6):535-543. doi:10.1212/WNL.0000000000002352

28. Pietroboni AM, Scarioni M, Carandini T, et al. CSF β-amyloid and white matter damage: A new perspective on Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2018;89(4):352-357. doi:10.1136/jnnp-2017-316603

29. Kalheim LF, Bjørnerud A, Fladby T, Vegge K, Selnes P. White matter hyperintensity microstructure in amyloid dysmetabolism. *J Cereb Blood Flow Metab*. 2017;37(1):356-365. doi:10.1177/0271678X15627465

30. Van Waalwijk Van Doorn LJC, Ghafoorian M, Van Leijsen EMC, et al. White

Matter Hyperintensities Are No Major Confounder for Alzheimer's Disease Cerebrospinal Fluid Biomarkers. *J Alzheimer's Dis*. 2021;79(1):163-175. doi:10.3233/JAD-200496

31. Soldan A, Pettigrew C, Zhu Y, et al. White matter hyperintensities and CSF Alzheimer disease biomarkers in preclinical Alzheimer disease. *Neurology*. 2020;94(9):e950-e960. doi:10.1212/WNL.0000000000008864
32. Thanprasertsuk S, Martinez-Ramirez S, Pontes-Neto OM, et al. Posterior white matter disease distribution as a predictor of amyloid angiopathy. *Neurology*. 2014;83(9):794-800. doi:10.1212/WNL.0000000000000732
33. Gurol ME, Viswanathan A, Gidicsin C, et al. Cerebral amyloid angiopathy burden associated with leukoaraiosis: A positron emission tomography/magnetic resonance imaging study. *Ann Neurol*. 2013;73(4):529-536. doi:10.1002/ana.23830
34. Barnes J, Carmichael OT, Leung KK, et al. Vascular and Alzheimer's disease markers independently predict brain atrophy rate in Alzheimer's Disease Neuroimaging Initiative controls. *Neurobiol Aging*. 2013;34(8):1996-2002. doi:10.1016/j.neurobiolaging.2013.02.003
35. Gordon BA, Najmi S, Hsu P, Roe CM, Morris JC, Benzinger TLS. The effects of white matter hyperintensities and amyloid deposition on Alzheimer dementia. *NeuroImage Clin*. 2015;8:246-252. doi:10.1016/j.nicl.2015.04.017
36. Provenzano FA, Muraskin J, Tosto G, et al. White matter hyperintensities and cerebral amyloidosis: Necessary and sufficient for clinical expression of Alzheimer disease? *JAMA Neurol*. 2013;70(4):455-461. doi:10.1001/jamaneurol.2013.1321
37. Fiford CM, Manning EN, Bartlett JW, et al. White matter hyperintensities are

associated with disproportionate progressive hippocampal atrophy. *Hippocampus*. 2017;27(3):249-262. doi:10.1002/hipo.22690

38. Koran MEI, Wagener M, Hohman TJ. Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav*. 2017;11(1):205-213. doi:10.1007/s11682-016-9523-8
39. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the *APOE* -related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563-573. doi:10.1002/ana.24135
40. Rabin JS, Yang H-S, Schultz AP, et al. Vascular Risk and β -Amyloid Are Synergistically Associated with Cortical Tau. *Ann Neurol*. 2019;85(2):272-279. doi:10.1002/ana.25399
41. Rabin JS, Schultz AP, Hedden T, et al. Interactive associations of vascular risk and β-amyloid burden with cognitive decline in clinically normal elderly individuals findings from the Harvard Aging Brain Study. *JAMA Neurol*. 2018;75(9):1124-1131. doi:10.1001/jamaneurol.2018.1123
42. Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: A shrinking brain. *J Neurosci*. 2003;23(8):3295-3301. doi:10.1523/jneurosci.23-08-03295.2003
43. Scahill RI, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch Neurol*. 2003;60(7):989-994. doi:10.1001/archneur.60.7.989
44. Schneider JA, Viswanathan A. The time for multiple biomarkers in studies of cognitive aging and dementia is now. *Neurology*. 2019;92(12):551-552. doi:10.1212/WNL.0000000000007120

45. Schott JM, Crutch SJ, Frost C, Warrington EK, Rossor MN, Fox NC. Neuropsychological correlates of whole brain atrophy in Alzheimer's disease. *Neuropsychologia*. 2008;46(6):1732-1737. doi:10.1016/J.NEUROPSYCHOLOGIA.2008.02.015

46. Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurol*. 2011;10(3):241-252. doi:10.1016/S1474-4422(10)70325-2

47. Schott JM, Bartlett JW, Barnes J, et al. Reduced sample sizes for atrophy outcomes in Alzheimer's disease trials: baseline adjustment. *Neurobiol Aging*. 2010;31(8):1452-1462, 1462.e1-2. doi:10.1016/j.neurobiolaging.2010.04.011

48. Andrews KA, Modat M, Macdonald KE, et al. Atrophy Rates in Asymptomatic Amyloidosis: Implications for Alzheimer Prevention Trials. *PLoS One*. 2013;8(3). doi:10.1371/journal.pone.0058816

49. Tarawneh R, Head D, Allison S, et al. Cerebrospinal Fluid Markers of Neurodegeneration and Rates of Brain Atrophy in Early Alzheimer Disease. *JAMA Neurol*. 2015;72(6):656. doi:10.1001/jamaneurol.2015.0202

50. Tosto G, Zimmerman ME, Hamilton JL, Carmichael OT, Brickman AM. The effect of white matter hyperintensities on neurodegeneration in mild cognitive impairment. *Alzheimer's Dement*. 2015;11(12):1510-1519. doi:10.1016/j.jalz.2015.05.014

Associations of β-Amyloid and Vascular Burden With Rates of Neurodegeneration in Cognitively Normal Members of the 1946 British Birth Cohort

Sarah E. Keuss, William Coath, Jennifer M. Nicholas, et al.

Neurology published online April 11, 2022
DOI 10.1212/WNL.0000000000200524