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Cognitive reserve and rate of change in Alzheimer's and cerebrovascular disease biomarkers among cognitively normal individuals

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ABSTRACT

We examined whether cognitive reserve (CR) impacts level of, or rate of change in, biomarkers of Alzheimer's disease (AD) and small-vessel cerebrovascular disease in >250 individuals who were cognitively normal and middle-aged and older at the baseline. The four primary biomarker categories commonly examined in studies of AD were measured longitudinally: cerebrospinal fluid measures of amyloid (A) and tau (T); cerebrospinal fluid and neuroimaging measures of neuronal injury (N); and neuroimaging measures of white matter hyperintensities (WMHs) to assess cerebrovascular pathology (V). CR was indexed by a composite score including years of education, reading, and vocabulary test performance. Higher CR was associated with lower levels of WMHs, particularly among those who subsequently progressed from normal cognition to MCI. CR was not associated with WMH trajectories. In addition, CR was not associated with either levels of, or rate of change in, A/T/N biomarkers. This may suggest that higher CR is associated with lifestyle factors that reduce levels of cerebrovascular disease, allowing individuals with higher CR to better tolerate other types of pathology.

1. Introduction

The concept of cognitive reserve (CR) was originally based on the observation that there can be marked discrepancies between the amount of neuropathology in the brain and the severity of cognitive or clinical impairment. For example, both biomarker and autopsy studies have shown that higher levels of CR (most commonly measured by variables related to lifetime cognitive experience, such as educational attainment, IQ, and literacy) reduce the impact of neuropathology on cognitive performance and clinical symptoms (e.g., Bennett et al., 2003; Brickman et al., 2011; Soldan et al., 2013; Stern et al., 1992).

The term cognitive reserve has been defined in a number of ways, as reflected by several recent publications that have recommended terminology based on varying conceptual frameworks (Arenaza-Urquijo and Vemuri, 2018; Cabeza et al., 2018; Stern et al., 2018). Although there remains debate about the definitions of specific terms, it is widely agreed that CR reflects a property of the brain that mitigates the effects of neuropathology on cognitive performance, and that the neurobiological mechanisms underlying CR are not well understood.

One possibility is that CR affects the rate at which disease-related pathology accumulates in the brain, which has been variously referred to as "brain maintenance" (Stern et al., 2018) or "resistance" (Arenaza-Urquijo and Vemuri, 2018). In the present study, we test this possibility within the context of the recent framework proposed for categorizing individuals on the basis of their Alzheimer's disease (AD) biomarkers, the so-called "A/T/N" framework. This schema classifies AD biomarkers into three categories: amyloid (A), tau (T), and neuronal injury (N) (Jack et al., 2016). Because mixed pathologies are extremely common among older persons (Schneider et al., 2009), Jack et al. also suggested that

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categorization of individuals on the basis of their AD biomarkers might be supplemented with a biomarker of cerebrovascular disease (V). This study therefore examined whether a measure of CR was associated with the level of, or altered rate of change in, A/T/N/V biomarkers in a cohort of individuals who were cognitively normal and middle aged and older at the baseline. It seemed particularly important to examine this issue among individuals who were middle age when first evaluated because there is increasing evidence that the pathological features of AD begin to develop in middle age (Pletnikova et al., 2015, 2018), and that vascular risks present in middle age are associated with late-life cognitive decline (Gottesman et al., 2017).

A number of cross-sectional studies have reported less abnormal levels of biomarkers of AD and small-vessel cerebrovascular pathology among cognitively normal individuals with higher CR, as measured by variables such as education, occupation, and engagement in cognitively stimulating activities (Alemedia et al., 2015; Arenaza-Urquijo et al., 2017a,b; Landau et al., 2012; Liu et al., 2012; Schreiber et al., 2016; Wirth et al., 2014a,b). This is consistent with the notion that CR delays or reduces the accumulation of pathology. However, studies have also reported no difference in AD biomarker levels by level of CR (Alemedia et al., 2015; Gidicsin et al., 2015; Ko et al., 2018; Pettigrew et al., 2017b; Schreiber et al., 2016; Shpanskaya et al., 2014; Vemuri et al., 2012; Wirth et al., 2014a).

The few longitudinal studies that have examined this issue among cognitively normal individuals have provided only weak support for the hypothesis that CR directly impacts biomarker trajectories. For example, some studies with smaller sample sizes have found that measures of CR are associated with a reduced rate of decline in hippocampal volume (Suo et al., 2012) and cerebrospinal fluid (CSF) $A\beta_{42}$ (Lo and Jagust, 2013). However, other studies have found no associations between similar CR proxies and rates of change in hippocampal volume (Lo and Jagust, 2013; Soldan et al., 2015) or other brain regions vulnerable to AD (Soldan et al., 2015; Walters et al., 2018); amyloid levels as measured by positron emission tomography or CSF $A\beta_{1\text{-}42}$ (Soldan et al., 2013; Walters et al., 2018); CSF total tau (t-tau) or phosphorylated tau (p-tau) (Soldan et al., 2013); or white matter hyperintensities (WMHs) (Cook et al., 2004).

Using data from the BIOCARD study, which includes longitudinal biomarker and clinical assessments, the present study expands prior work in a number of ways. First, we examined four categories of biomarkers, A/T/N/V, in the same cohort, using the following measures: (A) CSF $A\beta_{1\text{-}42}$; (T) CSF p-tau; (N) CSF t-tau and magnetic resonance imaging (MRI) measures of medial temporal lobe (MTL) volumes and cortical thickness in "AD vulnerable" regions; and (V) WMH volumes. Second, we examined whether the relationship between CR and change in biomarkers over time differs by other factors that might impact biomarker trajectories, including age and APOE-4 genetic status. Third, the long clinical follow-up available in the BIOCARD study also made it possible to examine whether the relationship between CR and change in biomarkers differed by diagnostic outcomes many years later, by comparing individuals who were initially cognitively normal but subsequently progressed to Mild Cognitive Impairment (MCI) to those who have remained cognitively normal throughout the course of follow-up.

2. Materials and methods

2.1. Study design and participant selection

The data presented here were derived from the BIOCARD study, which is an ongoing longitudinal prospective cohort study designed to identify variables among cognitively normal individuals that predict subsequent development of mild to moderate symptoms of AD. As described previously (Albert et al., 2014; see also Supplementary Materials 1), the BIOCARD study was initiated in 1995 at the National Institutes of Health (NIH). Participants were excluded at the baseline if they were judged to be cognitively impaired, as determined by the cognitive testing or by evidence of clinical symptoms based on reports by collateral sources, or had significant medical problems (such as severe cardiovascular or cerebrovascular disease (CVD), chronic psychiatric disorders, or chronic neurologic disorders). After providing written informed consent, 349 cognitively normal, primarily middle aged (M = 57.3 years, SD = 10.4, range = 20.0–85.8) participants were enrolled over time, beginning in 1995 and ending in 2005. By design, approximately 75% of the cohort had a first degree relative with dementia of the Alzheimer type.

While the study was at the NIH, participants were administered a comprehensive neuropsychological battery and clinical assessment annually, which included a physical and neurological examination, record of medication use, and behavioral and mood assessments. Blood, CSF, and MRI scans were obtained approximately every 2 years. The study was stopped in 2005 for administrative reasons and reinitiated in 2009 when a research team from the Johns Hopkins University (JHU) was funded to re-establish the cohort and continue annual cognitive and clinical assessments, collect blood, and evaluate the previously acquired cognitive and biomarker data. In 2015, biennial collection of CSF and MRI scans was re-established, and the acquisition of positron emission tomography scans, using Pittsburgh Compound B, was begun. Tau positron emission tomography imaging was initiated in 2017. See Fig. 1 for a study timeline. This study was approved by the JHU Institutional Review Board, and data collection is ongoing.

2.2. Clinical assessments

Clinical assessments and consensus diagnosis procedures were completed annually at both the NIH and JHU, and have been described in detail previously (Albert et al., 2014; see Supplementary Materials 1). Briefly, participants received a consensus diagnosis by the staff of the JHU BIOCARD Clinical Core, with all cases handled in a manner comparable with those used in the National Institute on Aging Alzheimer's Disease Centers program. This involves first establishing a syndromic diagnosis using three sources of information: (1) clinical data pertaining to an

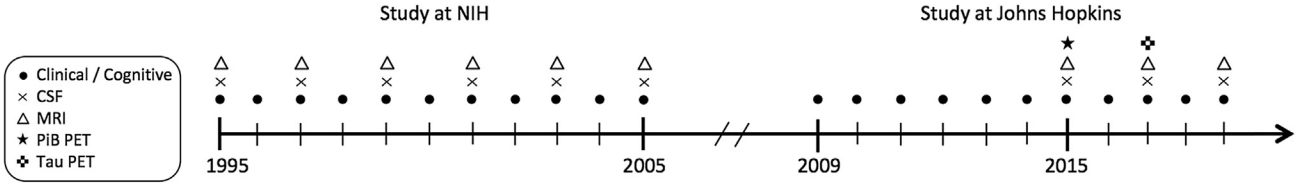

Fig. 1. Timeline showing the design of the BIOCARD study, and types of data collected from 1995 to 2019. Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; NIH, National Institutes of Health; PET, positron emission tomography; PiB, Pittsburgh compound B.

individual's medical, neurological, and psychiatric status; (2) reports of changes in cognition by the individual and by collateral sources (using the Clinical Dementia Rating scale (Morris, 1993); and (3) decline in cognitive performance, based on review of longitudinal testing from multiple domains (and comparison to published norms). We followed the diagnostic recommendations incorporated in the NIA-AA working group reports for the diagnosis of MCI (Albert et al., 2011) and dementia due to AD (McKhann et al., 2011). The diagnosis of Impaired Not MCI typically reflected contrasting information from the Clinical Dementia Rating interview and the cognitive test scores (i.e., the subject or collateral source expressed concerns about cognitive changes in daily life but the cognitive testing did not show changes, or visa versa; see Albert et al., 2014). Individuals with a diagnosis of impaired not MCI were included among the cognitively normal group, as in most prior analyses in this study (e.g., Pettigrew et al., 2017b; Soldan et al., 2017).

All clinical diagnoses were made without knowledge of the biomarker measures. By definition, all participants included in these analyses were judged to be cognitively normal at the baseline. For follow-up diagnoses, each individual's most recent (i.e., last) diagnosis was coded by a dichotomous indicator variable: 0 if participants have remained cognitively normal over time or 1 if they have since progressed from normal cognition to MCI or dementia.

2.3. Biomarker assessments

The analyses presented here are based on CSF and MRI data that were acquired over time while the study was at the NIH (i.e., 1995-2005). These data were later analyzed at a single point in time by JHU investigators, as described below. Biomarker measures acquired at JHU from 2015 onward were not included in the present analyses because harmonization of the biomarker data collected during the NIH and JHU phases is still ongoing. Although 349 participants were enrolled in the cohort, the *N* included in each set of biomarker analyses was smaller, as specified below (see Supplemental Table 1 for reasons participants were excluded from each set of biomarker analyses).

2.3.1. Cerebrospinal fluid assessments

CSF samples were analyzed with the same protocol used in the Alzheimer's Disease Neuroimaging Initiative. This protocol used the xMAP-based AlzBio3 kit (Innogenetics) run on a Bio-Plex 200 system, containing monoclonal antibodies specific for $A\beta_{1\text{-}42}$ (4D7A3), t-tau (AT120), and p-tau_{181p} (AT270), each chemically bonded to unique sets of color-coded beads, and analyte-specific detector antibodies (HT7, 3D6). Each participant had all samples (run in triplicate) analyzed on the same plate. Additional details about the CSF assays and intra-assay coefficients of variation have been published elsewhere (Moghekar et al., 2013). The present study included CSF measures of $A\beta_{1\text{-}42}$, p-tau, and t-tau from 271 participants.

2.3.2. Magnetic resonance imaging assessments

MRI scans were acquired over time on a GE 1.5 T scanner using a standard multimodal protocol, as described in Miller et al. (2013). Relevant to the present study, this protocol included a coronal spoiled gradient echo (SPGR) sequence (TR = 24, TE = 2, FOV = 256 × 256, thickness/gap = 2.0/0.0 mm, flip angle = 20, 124 slices) and an axial FLAIR sequence (TR = 9,002, TE = 157.5, FOV = 256 × 256, thickness/gap = 5.0/0.0 mm, flip angle = 90, 28 slices), which were used to derive our MRI measures of interest.

2.3.3. Volume of medial temporal lobe structures

Volumes of the hippocampus, entorhinal cortex, and amygdala were derived from the coronal SPGR scans using a semiautomated method based on large deformation diffeomorphic metric mapping (LDDMM) techniques (see Miller et al., 2013). Briefly, for each region of interest (ROI), landmarks were manually placed in each scan, as well as a hand-segmented template, to mark the boundaries of the ROI, following previously published protocols. ROI-LDDMM was then used to generate segmented binary images by mapping the template to the individual subject scans. Volumes of the hippocampus, entorhinal cortex, and amygdala were calculated by summing the number of voxels within the volume within each hemisphere. For the present analyses, volumes of the hippocampus, entorhinal cortex, and amygdala were normalized for head size by regressing the average of the left and right hemispheres on intracranial volume, at each time point. The 3 standardized residuals were then averaged to create an MTL composite score for each time point (Pettigrew et al., 2017a). Because the residuals were standardized (i.e., mean of 0, standard deviation of 1), all 3 MTL measures were on the same scale, and therefore given equal weight. The present study included MTL composite scores from 288 participants.

2.3.4. Cortical thickness in “AD vulnerable” regions

Measures of cortical thickness in AD vulnerable regions were derived from the coronal SPGR scans using FreeSurfer, an automated image processing pipeline that is documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). All scans were first processed with FreeSurfer's cross-sectional pipeline (as described in Pettigrew et al., 2016). To extract reliable thickness estimates for longitudinal analysis, the images where then processed with the FreeSurfer longitudinal stream (version 5.3). The longitudinal stream creates an unbiased within-subject template space and image using robust, inverse consistent registration, and initializes several processing steps using common information from the within-subject template, significantly increasing reliability, and statistical power (Reuter et al., 2012). After completion of the FreeSurfer pipeline, all scans were reviewed to assess the quality of skull stripping and ensure that surfaces followed the gray and white matter boundaries. Where needed, manual edits were performed to improve segmentation and parcellation accuracy, which primarily included the correction of pial surface misplacement and errors in white matter segmentation. Regions judged to have unreliable surfaces were excluded from analysis. The dependent variable was a measure of mean cortical thickness in seven FreeSurfer-labeled regions of interest, previously classified as “AD vulnerable”, including temporal pole, inferior temporal gyrus, middle temporal gyrus, inferior parietal cortex, superior parietal cortex, precuneus, and posterior cingulate cortex (Pettigrew et al., 2016). At each time point, the cortical thickness measures were first averaged over the left and right hemispheres; the seven bilateral measures were then averaged to create a measure of mean thickness of AD vulnerable regions. The present study included mean thickness measures from 251 participants.

2.3.5. Volume of white matter hyperintensities

Global WMH volumes were derived from the axial FLAIR scans and quantified using an automated method described previously (Decarli, Maillard and Fletcher, 2013). Briefly, after skull removal, images were nonlinearly registered to a minimal deformation template adapted for age range of 60 years and above. Field inhomogeneity bias was corrected and the bias field was modeled using a spatially smooth thin-plate spline interpolation. An expectation-maximization algorithm was used to segment gray, white, and CSF tissues, and WMH measures were calculated based

on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure based on histogram fitting. Likelihood estimates of the native image were calculated through histogram segmentation and thresholding. All segmentation was initially performed in standard space resulting in probability likelihood values of WMH at each voxel in the white matter. These probabilities were then thresholded at 3.5 SD above the mean to create a binary WMH mask. Further segmentation was based on a modified Bayesian approach that combines image likelihood estimates, spatial priors, and tissue class constraints. The segmented WMH masks were then back-transformed to native space for tissue volume calculation. In the present study, the dependent variable was a log-transformed measure of global WMH volume (to correct for skewness), from each time point. The present study included WMH volumes from 277 participants.

2.4. Cognitive reserve composite score

CR was operationalized by a composite score that included three measures commonly used as proxies of CR, hypothesized to reflect lifetime cognitive experiences. These included (1) baseline scores from the National Adult Reading Test (Nelson, 1982); (2) baseline scores on the vocabulary subtest of the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981); and (3) years of education. To calculate the composite, these measures were z-scored and then averaged. Of note, this composite has previously been shown to be associated with better cognitive and clinical outcomes after adjusting for biomarkers of AD pathology (Pettigrew et al., 2017b; Soldan et al., 2013, 2015, 2017).

2.5. APOE genotype

APOE genotypes were determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (Athena Diagnostics, Worcester, MA). Genotypes were coded dichotomously (APOE-4 carriers = 1, noncarriers = 0). Analyses including APOE-4 excluded APOE $\varepsilon 2/\varepsilon 4$ carriers given these alleles have contrasting effects on dementia risk (Corder et al., 1993, 1994).

2.6. Statistical analyses

Longitudinal linear mixed effects models were used to estimate the association between the baseline CR composite score and level of, and longitudinal change in, the A/T/N/V biomarkers described above. These models included linear effects of time and were specified with random intercepts and slopes (Diggle et al., 1994; Laird and Ware, 1982). Separate models were run for each biomarker, which served as the dependent variable, including baseline measures and all available follow-up. The primary set of models included the following predictors: age at first biomarker measurement, sex, CR composite score, time (years from the baseline), and the interaction (cross-product) of each predictor with time. The main effect of the CR composite score, and the two-way CR composite score x time interaction, were of primary interest, as these terms reflect differences in biomarker levels and biomarker trajectories (respectively) as a function of the CR composite score. Time was modeled in the unit of year. All other continuous variables were standardized before model fitting. Although we previously examined the relationship between CR and longitudinal CSF and MTL biomarker trajectories using simple slope measures to estimate change (Soldan et al., 2013, 2015), the methods used here are more robust because they allow subject-specific trends over time to be estimated on a continuous scale, can account for a different number of observations between subjects, and allow for participants with only one biomarker measure to be included in the same models (McCulloch and Neuhaus, 2005).

The second set of linear mixed regression models tested whether the relationship between the CR composite score and level of, and longitudinal change in, the A/T/N/V biomarkers was modified by age, APOE-4 genetic status, and follow-up diagnosis by including the relevant two-way and three-way interactions (in addition to all lower-order interaction terms). For example, the CR composite score × APOE-4 interaction indicates whether the effect of CR on baseline biomarker levels differed by APOE-4 genetic status, whereas the three-way CR composite score × APOE-4 x time interaction indicates whether the effect of CR on biomarker trajectories differed by APOE-4 genetic status. Where reported below, we used the Benjamini, Hochberg, and Yekutieli (Benjamini and Yekutieli, 2001) method to adjust for multiple comparisons. All analyses were run in R (2017), version 3.5.0.

2.7. Research data

Anonymized BIOCARD study data are available on request from qualified investigators; for more details, visit http://www.biocard-se.org.

3. Results

At their baseline biomarker assessment, the participants were middle-aged and older (approximately 60 years old). Participant characteristics are shown in Table 1, for those included in the MTL analyses. Participant characteristics for the other biomarker categories were comparable (see Supplemental Table 2). Characteristics for the entire BIOCARD cohort are shown in Supplemental Table 3.

Across the 6 biomarkers evaluated, a total of 305 unique participants contributed at least one biomarker measure to these analyses. On average, participants had 5.3/6 (SD = 1.2) biomarkers measured. Of these, 70% (212/305) had at least one data point on all 6 biomarkers, and an additional 14% (42/305) had at least one data point on 5/6 biomarkers. On average, participants had approximately 2.3 biomarker measures over time (range, 1-7; see also Supplemental Table 4), with approximately 2.6 years between an individual's first and last biomarker measurement (range, 0-10). At least 60% of participants had biomarker measures acquired at 2 or more time points. For this subset, participants had an average of approximately 3.1 biomarker measures over time, with approximately 4.0 years between an individual's first and last biomarker measurement.

Results of the linear mixed effects models are shown in Tables 2 and 3. With the exception of t-tau, there were significant main effects of time, indicating increased biomarker abnormality over the follow-up period (see Supplemental Fig. 1 for spaghetti plots of raw biomarker trajectories). For most measures, there were also significant main effects of age, reflecting more abnormal biomarker levels among older adults. For WMH volumes, there was a main effect of the CR composite score, reflecting lower levels of WMHs among participants with higher CR composite scores (Fig. 2; p = 0.078 after correction for multiple comparisons). However, none of the biomarker trajectories were modified by baseline levels of CR (CR composite score × time, all $p \geq 0.56$). The pattern of results was similar for a measure of entorhinal cortex thickness derived from LDDMM, as for the MTL composite score (data not shown). The relationship between CR and WMH remained the same when the WMH models were corrected for intracranial volume (data not shown), and when the CR composite score was replaced with the individual CR measures (Supplemental Table 5).

Table 1
Characteristics of participants included in the MTL analyses

Variable	Participants in MTL analyses
N	288
Age at the baseline biomarker acquisition	59.7 (9.9)
N (%) female sex	169 (59%)
N (%) white race	282 (98%)
N (%) APOE-4 carriers	97 (34%)
N (%) APOE-4 homozygotes	17 (5.9%)
Years of education	17.1 (2.3)
CR composite score	0.05 (0.8)
MMSE score at the baseline biomarker	29.7 (0.7)
N (%) progress to MCI or dementia over follow-up	67 (23%)
Baseline CSF $A\beta_{1-42}$ (pg/mL)	404.0 (98.1)
Baseline CSF t-tau (pg/mL)	69.5 (31.5)
Baseline CSF p-tau (pg/mL)	36.5 (15.0)
Baseline hippocampal volume (mm^3)	2664.4 (298.7)
Baseline amygdala volume (mm^3)	1547.0 (215.0)
Baseline entorhinal cortex volume (mm^3)	438.4 (120.6)
Baseline cortical thickness of AD vulnerable regions (mm)	2.62 (0.13)
Baseline WMH volume (cm^3)	3.49 (6.21)
Number of biomarker measures over time [range]	2.4 (1.3) [1-6]
Years between first and last biomarker measure [range]	2.7 (2.6) [0-8.3]
N (%) with 2+ biomarkers over time	184 (64%)
Number of biomarker measures for participants with 2+ biomarkers over time	3.1 (1.0)
Years between first and last biomarker measure for participants with 2+ biomarkers over time	4.3 (2.1)
Years of clinical follow-up (baseline biomarker to most recent diagnosis) [range]	13.1 (4.5) [0-21.6]
Years between baseline biomarker and age of clinical symptom onset for participants who progress to MCI/dementia	7.5 (3.8)

The number of participants included in each biomarker analysis varies slightly depending on the availability of the data; see Supplemental Table 2 for characteristics of participants included in the analysis of each biomarker domain. Values reflect mean (SD) unless otherwise indicated.
Key: AD, Alzheimer's disease; CR, cognitive reserve; CSF, cerebrospinal fluid; MCI, Mild Cognitive Impairment; MTL, medial temporal lobe; MMSE, Mini-Mental State Examination (Folstein et al., 1975); WMH, white matter hyperintensity.

The second set of models tested whether the relationship between the CR composite score and biomarker levels and trajectories was modified by baseline age, APOE-4 genetic status, and follow-up diagnosis. As shown in Table 1, participants had undergone approximately 13 years of longitudinal clinical follow-up since their first biomarker measure, and approximately 23% of participants later progressed to MCI or dementia.

None of the three-way interactions were significant, providing no evidence that the relationship between the CR composite score and biomarker trajectories differed by baseline age (all $p \geq 0.11$), APOE-4 genetic status (all $p \geq 0.09$), or follow-up diagnosis (all $p \geq 0.34$) (Supplemental Table 6). However, in the models evaluating follow-up diagnosis, there was a significant two-way CR composite score × follow-up diagnosis interaction for WMH volume (estimate = −0.356, 95% CI = (−0.57, −0.14), $p < 0.001$, $p = 0.012$, after correction for multiple comparisons), indicating that the relationship between higher CR composite scores and lower WMH volumes was stronger among individuals who progressed to MCI/dementia over the course of follow-up, relative to those who remained cognitively normal.

4. Discussion

This study examined the association between a CR composite score and level of, and longitudinal change in, A/T/N/V biomarkers of AD pathology and small-vessel CVD among individuals who were cognitively normal and largely middle-aged at the baseline. Higher CR composite scores were associated with lower levels of WMH, but not with rate of change in WMH volumes. This association was particularly evident among individuals who eventually progressed to MCI or dementia (relative to those who remained cognitively normal). However, there was no evidence of a direct relationship between the CR composite score and level of, or rate of change in, the A/T/N biomarkers. Furthermore, the relationship between the CR composite score and biomarker trajectories was not modified by participants' age or APOE-4 genetic status.

Our results suggest that higher CR is associated with lower levels of CVD pathology, as measured by WMH volumes. These findings are consistent with a prior cross-sectional study among individuals with normal cognition (Wirth et al., 2014a). Although some studies among nondemented participants (which includes individuals with MCI) also agree with our findings, others have not found significant relationships between measures of CR and WMHs (Brickman et al., 2011; Raz et al., 2012; Valenzuela et al., 2008), which may reflect variations in pathology levels and participant clinical status across studies. These findings are also consistent with a study of brain tissue in which higher CR, as measured by a composite score reflecting education, occupation, and social engagement, was associated with less CVD in men at autopsy (Valenzuela et al., 2012), although neuropathology studies examining this same question

Table 2
Longitudinal mixed effects model results examining the relationship between the CR composite score and level of, and rate of change in, CSF biomarkers

Model predictors	CSF $A\beta_{1-42}$ (A)		CSF p-tau (T)		CSF t-tau (N)	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Age	−0.162 (−0.27, −0.05)	0.005	0.125 (0.02, 0.23)	0.02	0.312 (0.21, 0.41)	<0.001
Sex (male)	−0.183 (−0.41, 0.05)	0.12	−0.081 (−0.30, 0.14)	0.47	−0.167 (−0.38, 0.04)	0.12
CR composite	0.084 (−0.03, 0.20)	0.15	−0.071 (−0.18, 0.03)	0.19	−0.035 (−0.14, 0.07)	0.50
Time	−0.057 (−0.09, −0.03)	0.001	0.097 (0.06, 0.13)	<0.001	0.000 (−0.03, 0.03)	0.995
Age × time	−0.022 (−0.05, 0.004)	0.10	0.010 (−0.02, 0.04)	0.55	−0.003 (−0.02, 0.02)	0.79
Sex × time	0.021 (−0.03, 0.07)	0.44	−0.047 (−0.11, 0.02)	0.14	−0.001 (−0.04, 0.04)	0.96
CR composite × time	−0.007 (−0.03, 0.02)	0.58	0.009 (−0.02, 0.04)	0.58	−0.005 (−0.03, 0.02)	0.64

Key: (A), amyloid; (N), neurodegeneration/neuronal injury; (T), tau; CR, cognitive reserve; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau.

Table 3
Longitudinal mixed effects model results examining the relationship between the CR composite score and level of, and rate of change in, MRI biomarkers

Model predictors	MTL volume (N)		AD vulnerable region cortical thickness (N)		WMH volume (V)	
	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Age	0.020 (−0.08, 0.12)	0.70	−0.396 (−0.51, −0.28)	<0.001	0.643 (0.55, 0.74)	<0.001
Sex (male)	0.538 (0.32, 0.76)	<0.001	0.061 (−0.18, 0.30)	0.62	−0.087 (−0.28, 0.11)	0.39
CR composite	−0.070 (−0.18, 0.04)	0.22	0.082 (−0.03, 0.20)	0.17	−0.129 (−0.23, −0.03)	0.01
Time	−0.059 (−0.08, −0.04)	<0.001	−0.060 (−0.09, −0.03)	<0.001	0.045 (0.02, 0.07)	0.002
Age × time	−0.005 (−0.03, 0.02)	0.66	0.002 (−0.02, 0.03)	0.85	0.004 (−0.02, 0.03)	0.77
Sex × time	−0.021 (−0.06, 0.02)	0.28	−0.045 (−0.09, 0.00)	0.06	0.026 (−0.02, 0.07)	0.25
CR composite × time	0.003 (−0.02, 0.02)	0.74	0.006 (−0.02, 0.03)	0.56	−0.006 (−0.03, 0.02)	0.63

Key: (N), neurodegeneration/neuronal injury; (V), vascular; AD, Alzheimer's disease; CR, cognitive reserve; MTL, medial temporal lobe; WMH, white matter hyperintensity.

using measures of education as a proxy for CR have produced mixed results (Del Ser et al., 1999; EClipSE Collaborative Members, 2010; Wilson et al., 2019). In addition, a recent study by Aiello Bowles et al (2019) found that both higher education and lower levels of non-AD pathology, including microinfarcts, were independently associated with "cognitive resilience" among individuals with AD pathology at autopsy.

In light of the considerable evidence that cerebrovascular pathology and AD pathology have additive effects on the "threshold" for a dementia diagnosis (Kapasi et al., 2017; Troncoso et al., 2008), the present findings suggest that lower levels of CVD may allow individuals with high CR to tolerate (i.e., be less affected by) higher levels of other types of age- or disease-related brain changes, including AD pathology, with fewer cognitive or clinical consequences. Thus, lower levels of small-vessel CVD may be one mechanism by which CR is associated with reduced symptoms of cognitive decline in the presence of co-existing pathology. Consistent with this, we found a stronger relationship between the CR composite score and lower WMH volumes among the subset of individuals who progressed to MCI/dementia, who have higher levels of AD pathology at the baseline (e.g., Soldan et al., 2017). We have also previously found that individuals with higher levels of baseline CR have an older age of clinical symptom onset of MCI (Soldan et al., 2017). The results of the present study suggest this may be due, at least in part, to lower levels of CVD among individuals with higher CR. Because we and others (Cook et al., 2004; Raz et al., 2012; Valenzuela et al., 2008) have failed to find a relationship between CR and short-term changes in WMH, it may be that CR impacts the severity of WMH, but not the rate of accumulation. However, additional studies are needed to examine WMH change over longer intervals and in participants with greater variability in CVD burden, given that those with severe cardiovascular and cerebrovascular disease were excluded at the baseline in this study.

Importantly, our results also suggest that CR is not related to the development of AD pathology, as measured by the A/T/N biomarkers included here, but instead appears to moderate the impact of AD pathology on cognition. For example, prior studies in this cohort (Pettigrew et al., 2017b; Soldan et al., 2013) and others (Mungas et al., 2018) have found that the protective effect of CR on clinical and cognitive outcomes is reduced at higher levels of biomarkers of (T) and (N) pathology, as measured by CSF p-tau, CSF t-tau, and cortical atrophy. Moreover, several longitudinal studies among cognitively normal individuals indicate that the protective effect of CR is equivalent across observed levels of amyloid, suggesting CR and amyloid have relatively independent effects on cognitive outcomes (for a review, see Soldan et al., 2018).

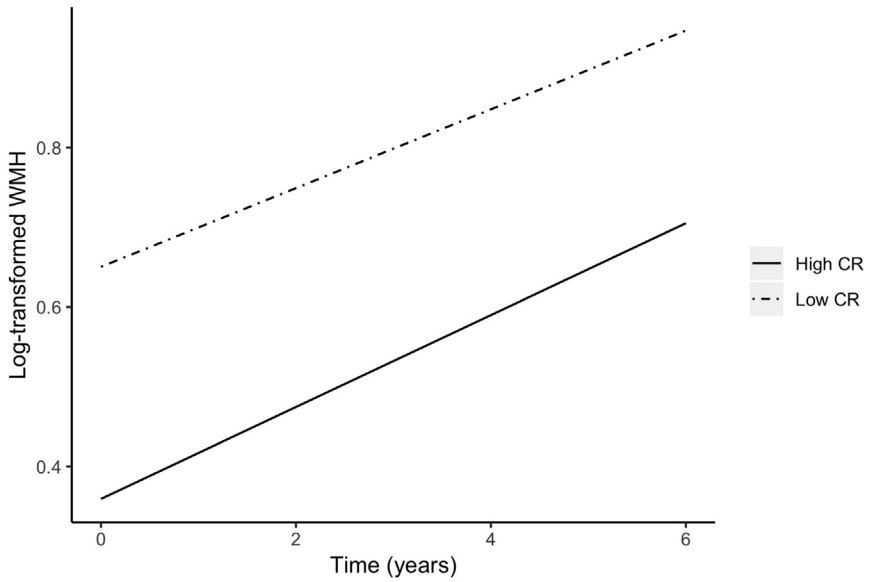

Fig. 2. Adjusted estimates of levels and longitudinal trajectories of log-transformed WMHs for individuals with low and high CR (by median split). There was a main effect of the CR composite score on WMH levels ($p = 0.01$), but no effect of the CR composite score on longitudinal WMH trajectories (as indicated by a nonsignificant CR composite score x time interaction, $p = 0.63$). The depicted linear mixed effects model estimates were adjusted for baseline age, sex, and their interactions with time. In the primary models, CR was modeled as a continuous variable; this variable was dichotomized by median split for illustration purposes only. Abbreviations: CR, cognitive reserve; WMH, white matter hyperintensity.

It is important to note that when measured by variables related to educational attainment, CR is likely conflated with a number of factors that promote healthier lifestyles, including socioeconomic status, management of vascular risks and medical conditions, engagement in cognitive and physical activities, nutrition, etc. (e.g., Hoeymans et al., 1996; Winkleby et al., 1992). The extent to which CR reflects mechanisms that are distinct from these health and lifestyle factors remains to be determined. The fact that the mechanisms underlying CR may be influenced by potentially modifiable factors has important implications for identifying possible biomarkers of CR, so that they might be used in interventions designed to reduce cognitive decline and dementia risk.

It remains to be seen whether CR is associated with other neurobiological features, not measured here, that might also mitigate age- and/or disease-related brain changes. For example, CR may provide resilience by enhancing neural architecture or synaptic integrity (Arnold et al., 2013; Boros et al., 2017; Iacono et al., 2009; Perez-Nievas et al., 2013; Teipel et al., 2009; Valenzuela et al., 2012), which may be mediated by (or preserved through) repeated neurotransmitter expression (Garibotto et al., 2013; Robertson, 2013). These neural characteristics may support more robust functional networks, for maintaining performance or allowing for compensatory recruitment in the presence of pathology (Cabeza et al., 2018; Stern et al., 2018). Thus, there may be several neurobiological characteristics that underlie the mechanisms by which CR is protective. Moreover, as suggested by others, the neural resources underlying reserve are likely complex, highly interactive, and result from a mixture of lifestyle, environmental, and genetic factors, as well as their interactions with each other (Cabeza et al., 2018; Stern et al., 2018). More work is clearly needed to understand these mechanisms.

The results of this study extend prior literature in a number of ways. First, to our knowledge, this is the first study to evaluate the relationship between CR and the 4 categories of A/T/N/V biomarkers together, in the same cohort. Second, prior longitudinal studies on this topic among initially cognitively normal individuals have tended to include individuals who were in their 70s at their baseline biomarker assessment, and have been limited by small sample sizes. Third, few prior studies have examined whether the relationship between proxies for CR and biomarker trajectories is modified by other factors that might affect the accumulation of disease-related pathology, including baseline age, APOE-4 genetic status, and presence of preclinical disease, as indicated by eventual progression to MCI/dementia in a subset of participants (operationalized by last follow-up diagnosis). Notably, because we have previously demonstrated that our CR composite score is related to cognitive and clinical outcomes after adjusting for biomarkers of AD pathology, it is unlikely that the present study's null findings for the A/T/N biomarkers can be attributed to the use of an ineffective CR proxy.

This study must be interpreted within the context of its limitations. Although the mean follow-up of the cohort for the purposes of examining subsequent clinical decline was over 12 years, on average, there were approximately 4 years between an individual's first and last biomarker, which is a relatively brief snapshot of pathological processes that may occur over decades. The effects of CR on A/T/N/V biomarkers may act over longer time frames than were measured here or in prior studies. Because biomarker collection in the BIOCARD study is ongoing, we will be able to address this question in future analyses. In addition, the BIOCARD study is a volunteer sample of well-educated, primarily Caucasian participants, most whom had a family history of AD dementia. Thus, the findings may not generalize to more diverse populations with a wider range of educational attainment and genetic risk, or to other measures of lifetime experiences (e.g., leisure activities, occupational complexity).

5. Conclusions

These results suggest that CR is related to levels of small vessel CVD, but do not provide support for the idea that CR impacts the rate at which AD pathology develops in the brain, as measured by A/T/N biomarkers. Therefore, lower levels of CVD may be one mechanism that enables individuals with high CR to delay the clinical and cognitive consequences of other brain changes, including those related to age and AD pathology. It will be important to determine if other brain mechanisms associated with CR are associated with modifiable lifestyle factors, as these could serve as additional targets for delaying the onset of MCI.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.12.003.

Disclosure statement

Dr. Miller owns a significant equity share in “Anatomy Works”; this arrangement is being managed by the Johns Hopkins University in accordance with its conflict of interest policies. Dr. Charles DeCarli is a consultant to Novartis for trial on heart failure. Dr. Marilyn Albert is an advisor to Eli Lilly. Others have no actual or potential conflicts of interest.

References

Aiello Bowles, E.J., Crane, P.K., Walker, R.L., Chubak, J., LaCroix, A.Z., Anderson, M.L., Rosenberg, D., Keene, C.D., Larson, E.B., 2019. Cognitive resilience to Alzheimer's disease pathology in the human brain. J. Alzheimers Dis. 68, 1071–1083.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 270–279.

Albert, M., Soldan, A., Gottesman, R., McKhann, G., Sacktor, N., Farrington, L., Grega, M., Turner, R., Lu, Y., Li, S., Wang, M.C., Selnes, O., 2014. Cognitive changes preceding clinical symptom onset of mild cognitive impairment and relationship to ApoE genotype. Curr. Alzheimer Res. 11, 773–784.

Almeida, R.P., Schultz, S.A., Austin, B.P., Boots, E.A., Dowling, N.M., Gleason, C.E., Bendlin, B.B., Sager, M.A., Hermann, B.P., Zetterberg, H., Carlsson, C.M., Johnson, S.C., Asthana, S., Okonkwo, O.C., 2015. Effect of cognitive reserve on age-related changes in cerebrospinal fluid biomarkers of Alzheimer disease. JAMA Neurol. 72, 699–706.

Arenaza-Urquijo, E.M., de Flores, R., Gonneaud, J., Wirth, M., Ourry, V., Callewaert, W., Landeau, B., Egret, S., Mézenge, F., Desgranges, B., Chételat, G., 2017b. Distinct effects of late adulthood cognitive and physical activities on gray matter volume. Brain Imaging Behav. 11, 346–356.

Arenaza-Urquijo, E.M., Bejanin, A., Gonneaud, J., Wirth, M., La Joie, R., Mutlu, J., Gaubert, M., Landeau, B., de la Sayette, V., Eustache, F., Chételat, G., 2017a. Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: neuroimaging evidence for protection and compensation. Neurobiol. Aging 59, 72–79.

Arenaza-Urquijo, E.M., Vemuri, P., 2018. Resistance vs resilience to Alzheimer disease: clarifying terminology for preclinical studies. Neurology 90, 695–703.

Arnold, S.E., Louneva, N., Cao, K., Wang, L.S., Han, L.Y., Wolk, D.A., Negash, S., Leurgans, S.E., Schneider, J.A., Buchman, A.S., Wilson, R.S., Bennett, D.A., 2013. Cellular, synaptic, and biochemical features of resilient cognition in Alzheimer's disease. Neurobiol. Aging 34, 157–168.

Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing under dependency. Ann. Stat. 29, 1165–1188.

Bennett, D.A., Wilson, R.S., Schneider, J.A., Evans, D.A., Mendes de Leon, C.F., Arnold, S.E., Barnes, L.L., Bienias, J.L., 2003. Education modifies the relation of AD pathology to level of cognitive function in older persons. Neurology 60, 1909–1915.

Boros, B.D., Greathouse, K.M., Gentry, E.G., Curtis, K.A., Birchall, E.L., Gearing, M., Herskowitz, J.H., 2017. Dendritic spines provide cognitive resilience against Alzheimer's disease. Ann. Neurol. 82, 602–614.

Brickman, A.M., Siedlecki, K.L., Muraskin, J., Manly, J.J., Luchsinger, J.A., Yeung, L.K., Brown, T.R., DeCarli, C., Stern, Y., 2011. White matter hyperintensities and cognition: testing the reserve hypothesis. Neurobiol. Aging 32, 1588–1598.

Cabeza, R., Albert, M., Belleville, S., Craik, F.I.M., Duarte, A., Grady, C.L., Lindenberger, U., Nyberg, L., Park, D.C., Reuter-Lorenz, P.A., Rugg, M.D., Steffener, J., Rajah, M.N., 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat. Rev. Neurosci. 19, 701–710.

Cook, I.A., Leuchter, A.F., Morgan, M.L., Dunkin, J.J., Witte, E., David, S., Mickes, L., O'Hara, R., Simon, S., Lufkin, R., Abrams, M., Rosenberg, S., 2004. Longitudinal progression of subclinical structural brain disease in normal aging. Am. J. Geriatr. Psychiatry 12, 190–200.

Corder, E.H., Saunders, A.M., Risch, N.J., Strittmatter, W.J., Schmechel, D.E., Gaskell Jr., P.C., Rimmler, J.B., Locke, P.A., Conneally, P.M., Schmader, K.E., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1994. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat. Genet. 7, 180–184.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923.

DeCarli, C., Maillard, P., Fletcher, E., 2013. Four Tissue Segmentation in ADNI II. https://www.alz.washington.edu/WEB/adni_proto.pdf. (Accessed 28 May 2019).

Del Ser, T., Hachinski, V., Merskey, H., Munoz, D.G., 1999. An autopsy-verified study of the effect of education on degenerative dementia. Brain 122, 2309–2319.

Diggle, P.J., Liang, K.Y., Zeger, S.L., 1994. Analysis of Longitudinal Data. Oxford University Press, New York.

EClipSE Collaborative Members, Brayne, C., Ince, P.G., Keage, H.A., McKeith, I.G., Matthews, F.E., Polvikoski, T., Sulkava, R., 2010. Education, the brain and dementia: neuroprotection or compensation? Brain 133, 2210–2216.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.

Garibotto, V., Tettamanti, M., Marcone, A., Florea, I., Panzacchi, A., Moresco, R., Virta, J.R., Rinne, J., Cappa, S.F., Perani, D., 2013. Cholinergic activity correlates with reserve proxies in Alzheimer's disease. Neurobiol. Aging 34, 2694.e13–2694.e18.

Gidicsin, C.M., Maye, J.E., Locascio, J.J., Pepin, L.C., Philiossaint, M., Becker, J.A., Younger, A.P., Dekhtyar, M., Schultz, A.P., Amariglio, R.E., Marshall, G.A., Rentz, D.M., Hedden, T., Sperling, R.A., Johnson, K.A., 2015. Cognitive activity relates to cognitive performance but not to Alzheimer disease biomarkers. Neurology 85, 48–55.

Gottesman, R.F., Albert, M.S., Alonso, A., Coker, L.H., Coresh, J., Davis, S.M., Deal, J.A., McKhann, G.M., Mosley, T.H., Sharrett, A.R., Schneider, A.L.C., Windham, B.G., Wruck, L.M., Knopman, D.S., 2017. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA Neurol. 74, 1246–1254.

Hoeymans, N., Smit, H.A., Verkleij, H., Kromhout, D., 1996. Cardiovascular risk factors in relation to educational level in 36000 men and women in The Netherlands. Eur. Heart J. 17, 518–525.

Iacono, D., Markesbery, W.R., Gross, M., Pletnikova, O., Rudow, G., Zandi, P., Troncoso, J.C., 2009. The Nun study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. Neurology 73, 665–673.

Jack Jr., C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Feldman, H.H., Frisoni, G.B., Hampel, H., Jagust, W.J., Johnson, K.A., Knopman, D.S., Petersen, R.C., Scheltens, P., Sperling, R.A., Dubois, B., 2016. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 87, 539–547.

Kapasi, A., DeCarli, C., Schneider, J.A., 2017. Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol. 134, 171–186.

Ko, K., Byun, M.S., Yi, D., Lee, J.H., Kim, C.H., Lee, D.Y., 2018. Early-life cognitive activity is related to reduced neurodegeneration in Alzheimer signature regions in late life. Front. Aging Neurosci. 10, 70.

Laird, N.M., Ware, J.H., 1982. Random effects models for longitudinal data. Biometrics 38, 963–974.

Landau, S.M., Marks, S.M., Mormino, E.C., Rabinovici, G.D., Oh, H., O'Neil, J.P., Wilson, R.S., Jagust, W.J., 2012. Association of lifetime cognitive engagement and low β-amyloid deposition. Arch. Neurol. 69, 623–629.

Liu, Y., Julkunen, V., Paajanen, T., Westman, E., Wahlund, L.O., Aitken, A., Sobow, T., Mecocci, P., Tsolaki, M., Vellas, B., Muehlboeck, S., Spenger, C., Lovestone, S., Simmons, A., Soininen, H., AddNeuroMed Consortium, 2012. Education increases reserve against Alzheimer's disease–evidence from structural MRI analysis. Neuroradiology 54, 929–938.

Lo, R.Y., Jagust, W.J., 2013. Effect of cognitive reserve markers on Alzheimer pathologic progression. Alzheimer Dis. Assoc. Disord. 27, 343–350.

McCulloch, C.E., Neuhaus, J.M., 2005. Generalized linear mixed models. In: Armitage, P., Colton, T. (Eds.), Encyclopedia of Biostatistics. John Wiley & Sons, Chichester, England.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack Jr., C.R., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 263–269.

Miller, M.I., Younes, L., Ratnanather, J.T., Brown, T., Trinh, H., Postell, E., Lee, D.S., Wang, M.C., Mori, S., O'Brien, R., Albert, M., BIOCARD Research Team, 2013. The diffeomorphometry of temporal lobe structures in preclinical Alzheimer's disease. Neuroimage Clin. 3, 352–360.

Moghekar, A., Li, S., Lu, Y., Li, M., Wang, M.C., Albert, M., O'Brien, R., BIOCARD Research Team, 2013. CSF biomarker changes precede symptom onset of mild cognitive impairment. Neurology 81, 1753–1758.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412–2414.

Mungas, D., Gavett, B., Fletcher, E., Farias, S.T., DeCarli, C., Reed, B., 2018. Education amplifies brain atrophy effect on cognitive decline: implications for cognitive reserve. Neurobiol. Aging 68, 142–150.

Nelson, H.E., 1982. The National Adult Reading Test (NART): Test Manual. Nfer-Nelson, Windsor.

Perez-Nievas, B.G., Stein, T.D., Tai, H.C., Dols-Icardo, O., Scotton, T.C., Barroeta-Espar, I., Fernandez-Carballo, L., de Munain, E.L., Perez, J., Marquie, M., Serrano-Pozo, A., Frosch, M.P., Lowe, V., Parisi, J.E., Petersen, R.C., Ikonomovic, M.D., López, O.L., Klunk, W., Hyman, B.T., Gómez-Isla, T., 2013. Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. Brain 136, 2510–2526.

Pettigrew, C., Soldan, A., Sloane, K., Cai, Q., Wang, J., Wang, M.C., Moghekar, A., Miller, M.I., Albert, M., BIOCARD Research Team, 2017a. Progressive medial temporal lobe atrophy during preclinical Alzheimer's disease. Neuroimage Clin. 16, 439–446.

Pettigrew, C., Soldan, A., Zhu, Y., Wang, M.C., Brown, T., Miller, M., Albert, M., BIOCARD Research Team, 2017b. Cognitive reserve and cortical thickness in preclinical Alzheimer's disease. Brain Imaging Behav. 11, 357–367.

Pettigrew, C., Soldan, A., Zhu, Y., Wang, M.C., Moghekar, A., Brown, T., Miller, M., Albert, M., BIOCARD Research Team, 2016. Cortical thickness in relation to clinical symptom onset in preclinical AD. Neuroimage Clin. 12, 116–122.

Pletnikova, O., Kageyama, Y., Rudow, G., LaClair, K.D., Albert, M., Crain, B.J., Tian, J., Fowler, D., Troncoso, J.C., 2018. The spectrum of preclinical Alzheimer's disease pathology and its modulation by ApoE genotype. Neurobiol. Aging 71, 72–80.

Pletnikova, O., Rudow, G.L., Hyde, T.M., Kleinman, J.E., Ali, S.Z., Bharadwaj, R., Gangadeen, S., Crain, B.J., Fowler, D.R., Rubio, A.I., Troncoso, J.C., 2015. Alzheimer lesions in the autopsied brains of people 30 to 50 years of age. Cogn. Behav. Neurol. 28, 144–152.

R: A Language and Environment for Statistical Computing [computer Program]. Version 3.5.0, 2017. R Foundation for Statistical Computing, Vienna, Austria.

Raz, N., Yang, Y.Q., Rodrigue, K.M., Kennedy, K.M., Lindenberger, U., Ghisletta, P., 2012. White matter deterioration in 15 months: latent growth curve models in healthy adults. Neurobiol. Aging 33, 429.e1–429.e5.

Reuter, M., Schmansky, N.J., Rosas, H.D., Fischl, B., 2012. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61, 1402–1418.

Robertson, I.H., 2013. A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. Neurobiol. Aging 34, 298–308.

Schneider, J.A., Arvanitakis, Z., Leurgans, S.E., Bennett, D.A., 2009. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann. Neurol. 66, 200–208.

Schreiber, S., Vogel, J., Schwimmer, H.D., Marks, S.M., Schreiber, F., Jagust, W., 2016. Impact of lifestyle dimensions on brain pathology and cognition. Neurobiol. Aging 40, 164–172.

Shpanskaya, K.S., Choudhury, K.R., Hostage Jr., C., Murphy, K.R., Petrella, J.R., Doraiswamy, P.M., Alzheimer's Disease Neuroimaging Initiative, 2014. Educational attainment and hippocampal atrophy in the Alzheimer's disease neuroimaging initiative cohort. J. Neuroradiol. 41, 350–357.

Soldan, A., Pettigrew, C., Albert, M., 2018. Evaluating cognitive reserve through the prism of preclinical Alzheimer disease. Psychiatr. Clin. North Am. 41, 65–77.

Soldan, A., Pettigrew, C., Cai, Q., Wang, J., Wang, M.C., Moghekar, A., Miller, M.I., Albert, M., BIOCARD Research Team, 2017. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. Neurobiol. Aging 60, 164–172.

Soldan, A., Pettigrew, C., Li, S., Wang, M.C., Moghekar, A., Selnes, O.A., Albert, M., O'Brien, R., BIOCARD Research Team, 2013. Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease. Neurobiol. Aging 34, 2827–2834.

Soldan, A., Pettigrew, C., Lu, Y., Wang, M.C., Selnes, O., Albert, M., Brown, T., Ratnanather, J.T., Younes, L., Miller, M.I., BIOCARD Research Team, 2015. Relationship of medial temporal lobe atrophy, APOE genotype, and cognitive reserve in preclinical Alzheimer's disease. Hum. Brain Mapp. 36, 2826–2841.

Stern, Y., Alexander, G.E., Prohovnik, I., Mayeux, R., 1992. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann. Neurol. 32, 371–375, [Epub ahead of print].

Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup, 2018. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement. https://doi.org/10.1016/j.jalz.2018.07.219.

Suo, C., León, I., Brodaty, H., Trollor, J., Wen, W., Sachdev, P., Valenzuela, M.J., 2012. Supervisory experience at work is linked to low rate of hippocampal atrophy in late life. Neuroimage 63, 1542–1551.

Teipel, S.J., Meindl, T., Wagner, M., Kohl, T., Bürger, K., Reiser, M.F., Herpertz, S., Möller, H.J., Hampel, H., 2009. White matter microstructure in relation to education in aging and Alzheimer's disease. J. Alzheimers Dis. 17, 571–583.

Troncoso, J.C., Zonderman, A.B., Resnick, S.M., Crain, B., Pletnikova, O., O'Brien, R.J., 2008. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann. Neurol. 64, 168–176.

Valenzuela, M.J., Matthews, F.E., Brayne, C., Ince, P., Halliday, G., Kril, J.J., Dalton, M.A., Richardson, K., Forster, G., Sachdev, P.S., Medical Research Council Cognitive Function and Ageing Study, 2012. Multiple biological pathways link cognitive lifestyle to protection from dementia. Biol. Psychiatry 71, 783–791.

Valenzuela, M.J., Sachdev, P., Wen, W., Chen, X., Brodaty, H., 2008. Lifespan mental activity predicts diminished rate of hippocampal atrophy. PLoS One 3, e2598.

Vemuri, P., Lesnick, T.G., Przybelski, S.A., Knopman, D.S., Roberts, R.O., Lowe, V.J., Kantarci, K., Senjem, M.L., Gunter, J.L., Boeve, B.F., Petersen, R.C., Jack Jr., C.R., 2012. Effect of lifestyle activities on Alzheimer disease biomarkers and cognition. Ann. Neurol. 72, 730–738.

Walters, M.J., Sterling, J., Quinn, C., Ganzer, C., Osorio, R.S., Andrews, R.D., Matthews, D.C., Vallabhajosula, S., de Leon, M.J., Isaacson, R.S., Mosconi, L., 2018. Associations of lifestyle and vascular risk factors with Alzheimer's brain biomarker changes during middle age: a 3-year longitudinal study in the broader New York City area. BMJ Open 8, e023664.

Wechsler, D., 1981. Wechsler Adult Intelligence Scale – Revised Manual. The Psychological Corporation, New York, NY.

Wilson, R.S., Yu, L., Lamar, M., Schneider, J.A., Boyle, P.A., Bennett, D.A., 2019. Education and cognitive reserve in old age. Neurology 92, e1041–e1050.

Winkleby, M.A., Jatulis, D.E., Frank, E., Fortmann, S.P., 1992. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. Am. J. Public Health 82, 816–820.

Wirth, M., Haase, C.M., Villeneuve, S., Vogel, J., Jagust, W.J., 2014a. Neuroprotective pathways: lifestyle activity, brain pathology, and cognition in cognitively normal older adults. Neurobiol. Aging 35, 1873–1882.

Wirth, M., Villeneuve, S., La Joie, R., Marks, S.M., Jagust, W.J., 2014b. Gene-environment interactions: lifetime cognitive activity, APOE genotype, and β-amyloid burden. J. Neurosci. 34, 8612–8617.