Published in final edited form as:

Ann Neurol. 2017 November ; 82(5): 706–718. doi:10.1002/ana.25071.

Age, Vascular Health, and Alzheimer's disease Biomarkers in an Elderly Sample

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Abstract

OBJECTIVE—To investigate the associations between age, vascular health, and Alzheimer's disease (AD) imaging biomarkers in an elderly sample.

METHODS—We identified 430 individuals along the cognitive continuum aged >60 years with amyloid-PET, Tau-PET, and MRI scans from the population-based Mayo Clinic Study of Aging. A subset of 329 individuals had FDG-PET. We ascertained presently existing cardiovascular and metabolic conditions (CMC) from healthcare records and used the summation of presence/absence of hypertension, hyperlipidemia, cardiac-arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke as a surrogate for vascular health. We used global amyloid from PiB-PET, entorhinal cortex tau uptake (ERC-tau) from Tau-PET, and neurodegeneration in AD signature regions from MRI and FDG-PET as surrogates for AD pathophysiology. We dichotomized participants into CMC=0 (CMC−) vs. CMC>0 (CMC+) and tested for age-adjusted group differences in AD biomarkers. Using structural equation models (SEM), we assessed the impact of vascular health on AD biomarker cascade (amyloid leads to tau leads to neurodegeneration) after considering the direct and indirect age, sex, and APOE effects.

RESULTS—CMC+ participants had significantly greater neurodegeneration than CMC− participants but did not differ by amyloid or ERC-tau. The SEM models showed that i) vascular health had a significant direct and indirect impact on neurodegeneration but not on amyloid; and ii) vascular health specifically the presence of hyperlipidemia had a significant direct impact on ERC-tau.

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Author Contributions

Study Concept and Design: PV, TGL, SAP; Data Acquisition, Analysis, and interpretation of the data: PV, TGL, SAP, DSK, VJL, JGR, ROR, MMM, MMM, RCP, CRJ; Drafting of the manuscript and figures: PV, TGL, SAP.

Potential Conflicts of Interest

The authors do not have any pertinent disclosures relevant to this study.

INTERPRETATION—Vascular health had quantifiably greater impact on neurodegeneration in AD regions than on amyloid deposition. Longitudinal studies are warranted to clarify the relationship between tau deposition and vascular health.

Keywords

Alzheimer's disease; Vascular Health; Amyloid; Tau; Neurodegeneration

INTRODUCTION

Age is a significant driver of decline in vascular health¹ and increase in Alzheimer's disease pathophysiology (ADP)². Several studies have shown that decline in vascular health has a significant impact on brain health and also increases the risk of AD dementia^{3–9}. While it is well known that the impact of vascular health on cognitive performance is mediated via vascular brain injury^{6, 8}, the direct impact of vascular health on each individual ADP process, namely amyloid, tau, and AD-associated neurodegeneration, is poorly understood and the interrelationships between ADP and vascular health are highly debated.

We hypothesized that the associations between ADP biomarkers and vascular risk factors can be disentangled by considering the direct and indirect effects of age, sex and APOE on each of these processes. Therefore, in this paper we aimed to investigate the association between age, vascular health, and ADP imaging biomarkers in a population-based elderly sample using two separate methods to understand these complex associations. In the first set of analyses, we evaluated the impact of vascular health on each of the AD biomarkers after accounting for the effects of age (both linear and non-linear). In the second set of analyses, we evaluated these associations by making assumptions about the sequence of AD biomarkers based on the widely accepted amyloid biomarker cascade¹⁰ which posits that amyloid deposition accelerates tau deposition which in turn drives neurodegeneration that underlies cognitive impairment. We undertook this second approach to capture the direct and indirect impact of age and vascular health on each of the ADP biomarkers.

The present study included Mayo Clinic Study of Aging (MCSA) participants who had ADP imaging biomarkers. In this paper, we considered the following main imaging surrogates of ADP – i) Amyloid-PET imaging using ¹¹C-PiB-PET as a surrogate for cerebral amyloidosis¹¹; ii) Tau-PET imaging using ¹⁸F-AV1451-PET (also known as T807 and flortaucipir) as a surrogate for abnormal 3R/4R tau deposition¹²; iii) Neurodegeneration in AD signature regions using MRI and FDG-PET as a surrogate for AD specific neuronal dysfunction¹³. We specifically looked at vascular health in the recent past i.e. in the 5 year time-period prior to the ascertainment of the ADP biomarkers.

METHODS

Selection of Participants

All participants were enrolled in the MCSA, a population based study of Olmsted County, MN residents. The Olmsted County population was enumerated using the Rochester Epidemiology Project (REP) medical records -linkage system^{14, 15} which allowed us to

ascertain vascular health factors from health care records instead of relying on self-report. We included all 430 elderly individuals (ages >60 years) with APOE genotype, vascular health indicators (discussed below), and concurrent imaging (PIB-PET, Tau-PET, and MRI scans). At the time of the scans, 389 were cognitively unimpaired, 33 had mild cognitive impairment, 5 were diagnosed with a neurodegenerative disorder (2 AD and 3 with mixed dementia), and 3 had a missing clinical diagnosis due to incomplete data. A subset of these individuals also had FDG-PET scans (n=329) which was included. The complete details of MCSA design and clinical diagnoses criteria were discussed by Petersen et al.¹⁶ and Roberts et al.¹⁷.

Standard protocol approvals, registrations, and patient consents—These studies were approved by the Mayo Clinic and Olmsted Medical Center institutional review board. Informed consent was obtained from all participants or their surrogates.

Demographics and APOE

Sex and years of education were obtained at the clinical visit. Age at the time of the MRI scan was considered. APOE genotype (presence of an APOE ε4 allele) was determined from blood collected at the clinical visit.

Cognitive Performance

The neuropsychological battery consisted of 9 tests covering 4 cognitive domains, as previously described^{16, 17}. A *global cognitive summary score* was estimated from the z-transformation of the average of the four domain z-scores (executive function, language; memory, and visuospatial performance).

Vascular Health – Cardiovascular and Metabolic Conditions

The REP diagnostic indices were searched in a 5-year capture frame before the MCSA visit^{18, 19} to identify International Classification of Diseases, Ninth Revision (ICD-9) codes and Tenth Revision (ICD-10) codes associated with health care visits. Both ICD-9 (through Sept 2015) and ICD-10 (after Oct 2015) codes were pooled together by the REP under seven cardiovascular and metabolic conditions proposed by the U.S. Department of Health and Human Services in 2010 as indicators of vascular health²⁰: hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke. The specific codes pooled together are tabulated in the supplemental material. In addition to using each individual component of vascular health separately, we also computed a composite score (referred here as CMC) which represents the summation of the presence or absence of each of these conditions. To reduce the false positive rates, we required that individuals received two codes for any given condition separated by more than 30 days within the 5-year capture period as done previously by REP investigators^{19, 20}.

AD Imaging Biomarkers

Amyloid, Tau, and Neurodegeneration Assessment from PET scans—The acquisition and processing details of amyloid PET, Tau-PET, and FDG-PET scans acquired on the study participants were discussed in detail by Jack et al.²¹. For amyloid PET, we

computed the global amyloid load for each subject by calculating median uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest (ROIs) divided by the median uptake in the cerebellar crus gray matter ROI²¹. For Tau-PET, we assessed entorhinal cortex (ERC-tau) in each individual subject by calculating median uptake in the entorhinal cortex divided by the median uptake in the cerebellar crus and used it as a signature for AD related tau pathology²². We used ERC-tau because of two reasons – i) in our recent work we found that it was the most sensitive region to global amyloid deposition²² and ii) entorhinal cortex (and hippocampus) has increased vulnerability to tau deposition² as well as age related atrophy (in the absence of ADP)²³ making it an ideal region for modeling the effects of age, vascular risk, and amyloid effects on tau. Since hippocampus has signal from choroid plexus we did not include hippocampus.

The FDG-PET summary in AD signature regions proposed previously²⁴ were computed for each individual scan by averaging the left and right angular gyri, bilateral posterior cingulate and left middle/inferior temporal gyrus values normalized by the pons and vermis uptake.

AD-pattern Neurodegeneration Assessment from Structural MRI scans—MRI was acquired on two 3T General Electric (GE) scanners. Freesurfer version v 5.3 was used to estimate average cortical thickness in AD signature regions (entorhinal cortex, inferior temporal, middle temporal, fusiform) into a single measure which was used as surrogate for AD related neurodegeneration¹³.

Statistical Methods

Dichotomization by Presence of Risk Factor—Standard summary measures were used to describe characteristics for all participants and for strata determined by CMC=0 (CMC−) vs. CMC>0 (CMC+). The differences in demographic variables between CMC− vs. CMC+ groups were tested using ANOVA for the continuous variables and chi-square for the categorical variables. Since age is a significant driver for ADP, vascular health, and cognition, we adjusted for age via ANCOVA in the group comparisons for cognition and AD imaging biomarkers. We also report Cohen's D based effect-sizes for all variables between the two groups. For AD biomarkers and global cognition summary score, Cohen's D was calculated using age adjusted means and standard deviations. In addition, we performed analyses allowing for nonlinear age adjustments from spline curves with knots at 68, 74, and 82 years. We also tested the group differences between all participants dichotomized by the presence and absence of each of the CMC components i.e. hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke. We also conducted sensitivity analyses in only cognitively unimpaired individuals as well as after dichotomizing individuals based on the CMC<2 and CMC ≥ 2.

Structural Equation Models—We conducted path analyses (structural equation models with only manifest, i.e. observed variables) using Mplus version 8.0 structural equations software and the R Lavaan package. Path analyses are extensions of regression models, and require a weak causal ordering of the variables to be specified before running any models. They allow us to account for complex relationships between the variables, rather than simply

adjusting for confounding variables through ANCOVA. Assuming that the structure is correct (or close; there is reasonable robustness in these analyses), the SEM models should give a cleaner and more detailed picture of the effects. We first fit a saturated model with all possible associations between five levels of variables (plotted from left to right), where Level 1 consisted of sex, age at MRI, and APOE4 genotype, Level 2 consisted of the summary CMC measure (vascular health), Level 3 consisted of amyloid deposition, Level 4 consisted of ERC-tau, and Level 5 consisted of neurodegeneration. For the neurodegeneration variable, we only considered neurodegeneration in AD signature regions from MRI in the SEM models because we did not have FDG-PET scans in the full sample. Sex was added to the model because there are sex differences in the aging process²⁵.

Each level in the SEM analysis is assumed to come later than preceding levels in a causal framework. Thus, any variable can cause changes to variables lying in higher levels. Any variables lying between variables on a lower and higher level are mediators. The possible causal associations are thus direct effects (arrow directly joins variables), indirect effects (arrows pass through one or more mediators), and total effects (sum of direct and indirect). We pruned the path analysis using goodness of fit measures (Bayesian Information criterion (BIC), chi-square test of model fit, root mean square error of approximation (RMSEA), Tucker-Lewis Index (TLI) and Comparative Fit Index (CFI)) and individual p-values until all paths in the final model were significant, and the goodness of fit measures indicated that the model fit the observed data well. We checked the pruning using lasso in the R package RegSEM²⁶ and found that the pruned models were consistent. We report regression coefficients with their associated standard errors and p-values. The coefficients give the predicted change in the outcome (higher level) variable per unit increase in the predictor (lower level) variable. Age was coded to give results per 10-year (decade) increase. CMC units correspond to an increase of one condition. Amyloid deposition and ERC-tau were first log-transformed to better meet the model assumptions, and then standardized so that a unit increase corresponds to one standard deviation. Neurodegeneration was standardized so that a unit increase corresponds to one standard deviation and the sign was flipped such that high values are worse i.e. in the same direction as amyloid and tau. We also conducted a sensitivity SEM analysis using all seven indicators of vascular health as individual predictor variables.

RESULTS

The overall participant characteristics as well as participants dichotomized by CMC are shown in Table 1. The CMC+ group was significantly older but did not differ by sex, APOE genotype, education, or global cognition from the CMC- group. Figure 1 shows the bar plots of mean number of CMC conditions and AD neuroimaging biomarkers by 5 year increments and illustrates the worsening of each of these variables with age. After age adjustment, amyloid and ERC-tau levels were not significantly different between the CMC+ and CMC- group. On the other hand, FDG-PET uptake and MRI cortical thickness were significantly lower between the CMC- and CMC+ groups. The relative differences between the groups were significantly greater for FDG and MRI in comparison to the amyloid and ERC-Tau levels as observed by the magnitude of the effect sizes. Since the association between vascular health and age is fairly linear, the more general analyses that allowed for nonlinear

age adjustment produced very similar results for all biomarkers. In the sensitivity analyses with only cognitively unimpaired individuals (Supplemental Tables 1 and 2) and when all individuals were dichotomized by CMC=2 (Supplemental Table 3), we found similar conclusions.

Supplemental Table 4 summarize the group differences for demographics and cognition between participants dichotomized by the presence and absence of each of the CMC components. Men had a greater frequency of cardiac arrhythmias and coronary artery disease. None of the CMC components were significantly associated with APOE4 carrier status. Education levels were significantly lower in individuals with stroke and congestive heart failure compared to those without these conditions. Cognition was significantly lower or approached significance for cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes mellitus, and stroke but not for hyperlipidemia or hypertension.

Table 2 summarizes the AD biomarker results for all individuals when they were dichotomized by the presence and absence of each CMC component. For each of the CMC components, amyloid load was not significantly different between participants with and without the risk factor. ERC-tau was slightly higher in those with hyperlipidemia versus those without hyperlipidemia ($p=0.070$) as well as those with coronary artery disease and without coronary artery disease ($p=0.075$). Neurodegeneration biomarkers (FDG-PET and/or MRI) were significantly ($p<0.05$) worse for five of the seven vascular health indicators (hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, and diabetes). Supplemental Table 2 summarizes the results for only cognitively unimpaired individuals and shows similar results.

The results of the significant associations in the path analyses are shown in Figure 2. The final model fit the data very well: The chi-square test of model fit (comparing to a saturated model) was not significant ($p=0.24$), the RMSEA (0.026) was less than 0.05, and the TLI (0.990) and CFI (0.996) were both greater than 0.95. Please note that the coefficients across all arrows cannot be compared but coefficients on arrows going to a particular outcome are comparable. These associations are split by paths to outcome variables (vascular health and AD biomarkers) in Figure 3. We have included Table 3 with the complete direct and indirect effects observed in the Figure 2. Here we describe the predictors of each of the outcomes in a stepwise fashion: 1) Age (coefficient=0.616) and being male (coefficient=0.287) were significant direct predictors of vascular health. 2) Age (coefficient=0.446) and APOE4 (coefficient=0.612) were significant direct predictors of amyloid deposition. 3) CMC and Amyloid were significant direct predictors of ERC-tau with the effect of amyloid on ERC-tau (coefficient=0.555) being larger than the effect of CMC on ERC-tau (coefficient=0.067). Age had both an indirect effect through CMC (coefficient=0.041, $p=0.016$) and an indirect effect through amyloid deposition (coefficient=0.247, $p<0.001$) on ERC-tau. 4) Age, sex, CMC, and ERC-tau were significant direct predictors of AD-pattern neurodegeneration. Age again had a large direct effect (coefficient=0.513) and smaller indirect effects through CMC (coefficient=0.057, $p=0.002$), CMC then ERC-tau (coefficient=0.009, $p=0.029$) and amyloid deposition then ERC-tau (coefficient=0.051, $p<0.001$) for a total effect coefficient of 0.630. Sex had a direct impact on AD-pattern neurodegeneration (coefficient=0.186), though the potential indirect paths through CMC and CMC then ERC-tau were not significant. CMC

had both a direct effect (coefficient=0.093) and indirect effect through ERC-tau (coefficient=0.014, $p=0.023$) on AD-pattern neurodegeneration. ERC-tau had a direct effect (coefficient=0.207), and APOE4 had only an indirect effect (coefficient=0.070, $p<0.001$) on AD-pattern neurodegeneration through amyloid then ERC-tau.

The results of the sensitivity SEM analysis results with all seven indicators of vascular health are shown in Figure 4. The final model in this case fit the data fairly well: The RMSEA (0.055) was close to 0.05, and the TLI (0.894) and CFI (0.929) were both close to 0.90, though below 0.95. The chi-square test in this model does not apply in the usual manner. Simple theoretically reasonable additions to the model did not appreciably improve the fit. Of the seven variables, diabetes, cardiac arrhythmias, congestive heart failure, and hyperlipidemia were significant predictors of AD biomarkers. Among these, only hyperlipidemia was a significant predictor of ERC-tau and the rest were significant predictors of neurodegeneration. None of the vascular health indicators were significant predictors of amyloid deposition.

DISCUSSION

The main findings of this paper were that i) poor vascular health does not significantly impact amyloid deposition but has a significant direct and indirect effect on AD neurodegeneration in an elderly sample; and ii) there was a significant impact of vascular health on ERC-tau that was driven by hyperlipidemia but the effect was smaller than the association of amyloid with ERC-tau.

Age is a significant predictor for vascular health as observed in Figure 1 and 2. Aging acts through a number of biological mechanisms at the cellular or tissue level that may lead to multi-system loss of reserve and function as discussed by Fabbri et al²⁷. This multi-system homeostatic dysregulation leads to several chronic diseases including cardiovascular and metabolic conditions^{27, 28}. Age is also a significant predictor for brain changes. Amyloid and tau pathologies² as well as brain shrinkage (even without AD pathologies)²³ increase with age. Therefore, accounting for age in the first set of analyses (Tables 1 and 2) allowed us to understand if vascular health and ADP were associated independently of the impact of age on each of these factors. Additionally, the SEM analyses allowed us to simultaneously look at the direct and indirect effects of age on each of the variables of interest and also take into consideration the step-wise progression of AD processes that is not possible with group comparisons.

Predictors of Vascular Health

In addition to age, being male was a significant predictor of vascular health (Figure 2 and 3A). As seen in supplemental tables, there was a greater frequency of men among those with cardiac arrhythmias and coronary artery disease consistent with the literature²⁹ and this may have driven the path from sex to vascular health. In both the sets of analyses, we did not find an association between APOE4 and vascular health.

Predictors of Amyloid Deposition

As expected, APOE4 along with age were significant predictors of amyloidosis³⁰ in Figure 2 and 3B. In both the analyses, we did not find an association between poor vascular health and amyloid deposition. In the SEM analyses (Figure 2) and Table 1, we specifically tested if vascular health has an impact on amyloid and did not find evidence for an association. In the sensitivity SEM analysis (Figure 4) as well as Table 2, we also tested the impact of each vascular health indicator on amyloid deposition and did not find evidence for an association between vascular health and amyloid deposition. These results are consistent with a systematic review by Chui et. al. that showed that there is insufficient evidence to support that vascular risk increases amyloid pathology⁵. One major issue that may have contributed to the debate in the literature could be the confounding effect of age seen on both vascular health and AD biomarker variables. Amyloid accumulation in the brain is due to the imbalance between amyloid production and clearance. While we found no significant association between vascular health and amyloid accumulation in early stages of the disease, this does not preclude the possibility that in later stages of the disease both processes may interact through mechanisms such as poor clearance of extracellular A β through the glymphatic system^{31, 32} or large extent of hypoperfusion and hypoxia contributing to greater amyloid accumulation³³.

Predictors of Tau Deposition

Amyloid was the strongest predictor of ERC-tau as expected¹⁰. We also found evidence for an amyloid independent direct pathway from CMC to ERC-tau (Figure 2 and 3C). In Table 2, we found weak associations between vascular health and tau deposition as suggested by the group differences seen with hyperlipidemia ($p=0.07$) and coronary artery disease ($p=0.075$). From the sensitivity SEM analyses in Figure 4, we found that the primary predictor of the association between vascular health and ERC-tau seen in Figure 2 was hyperlipidemia. In our recent study³⁴ as well as this paper, we found evidence that lipids play an important role in the pathogenesis of processes upstream to AD neurodegeneration. Using Tau-PET and amyloid PET together here, we were able to further discern that tau deposition is specifically influenced by hyperlipidemia. Cholesterol accumulation and impaired cholesterol metabolism has been found to be toxic to neuronal cells and proposed to be involved in the generation of tau³⁵. Additionally, Statins have been shown to reduce the neurofibrillary tangle burden in animal models^{36, 37} and modulate tau phosphorylation in humans^{38, 39}. Though we found a small effect of poor vascular health, specifically hyperlipidemia on tau deposition, further longitudinal studies are needed to clarify the mechanisms through which these risk factors may increase tau deposition and will be the focus of our future studies.

We did not detect a direct pathway from age to tau consistent with the primary age-related tauopathy (PART) hypothesis⁴⁰. The effect of age on ERC-tau is much smaller compared to the effect of amyloid on ERC-tau since PART (abnormal tau in the absence of amyloidosis) is observed only in advanced ages compared to ages at which abnormal amyloid and tau are observed and in only a smaller proportion of elderly (compared to elderly with both amyloid and tau pathologies). Since our model structure forces amyloid to come before tau, this

could possibly overwrite any direct effect of age especially if the direct effect is small relative to the amyloid effect.

Predictors of Neurodegeneration

Age, being male, ERC-tau, and poor vascular health had a significant direct impact on neurodegeneration. Age (even without amyloid) and being male has been shown to be associated with neurodegeneration²³. Animal models support that there is age-related neural structure alteration specifically reductions in spine density and reductions in neuronal arborization that reflects early neurodegeneration^{41, 42}. Tau deposition and neurodegeneration are well known to be tightly coupled¹⁰. While studies show that poor vascular health is associated with increased risk of Alzheimer's disease^{43, 44} as well as neurodegeneration^{45, 46}, we found evidence for a significant direct and indirect impact of vascular health on AD neurodegeneration that was not mediated by amyloid deposition. This suggests that vascular health lowers the threshold for dementia by independently impacting neurodegeneration and to some extent ERC-tau but has minimal direct impact on amyloidosis^{5, 47}. In Figure 4, we found that among all the variables, the primary predictors of neurodegeneration among the CMC variables were congestive heart failure, diabetes, and cardiac arrhythmias.

Each of the AD biomarkers (tau deposition, amyloid deposition, and neurodegeneration) can be initiated independently but there is sufficient evidence supporting the AD biomarker cascade hypothesis that amyloid deposition accelerates tau deposition, which in turn, is closely associated with neurodegeneration and cognitive decline in AD. An important point to consider is that we included the complete spectrum of population based individuals for the SEM models. If we had included only cognitively unimpaired individuals, we would be excluding individuals in whom there was sufficient pathology (due to amyloid, tau, neurodegeneration, as well as vascular risk factors) to cause cognitive impairment which would create significant bias when modeling the entire disease process. Though we did not test the biomarker cascade hypothesis but assumed a fixed ordering in this paper, we found evidence for the step-wise association of amyloid on ERC-tau and ERC-tau on AD-pattern neurodegeneration. We conducted additional sensitivity analyses and found that i) amyloid and tau at the same level had a poor model fit and ii) tau before amyloid resulted in a model with no direct or indirect effect of amyloid on neurodegeneration, providing support for the ordering we assumed in the paper. The SEM approach we took here was valuable because it allowed us to investigate the independent impact of vascular health on AD biomarkers after accounting for the interrelationships between age and AD biomarkers as well as the between each of the AD biomarkers.

Strengths and Limitations

A major strength of this study is the availability of electronic health records through the REP from which our MCSA study participants are sampled and also allowed us to ascertain vascular health prior to the scans. While the use of health care records might be considered a limitation, the requirement of two clinical visits separated by 30 days limits false positives, as well as previous papers that validated REP based ICD-9 codes support the ascertainment of vascular health from REP based health care records⁴⁸⁻⁵¹. There were also other

limitations to this study. We only focused on an amyloid sensitive tau region seen in the elderly²². The results may be different for Tau-PET uptake in different regions and in atypical AD. We also undertook a global approach here with cross-sectional (vascular health) diagnosis data instead of looking at the mechanistic underpinnings of each vascular health indicator along with blood serum biomarkers^{9, 52} and studying these predictors and outcomes in a longitudinal framework to further understand the casual associations. However, we strongly believe that such a birds-eye view is important and will be helpful in guiding the development of future hypotheses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all the study participants and staff in the Mayo Clinic Study of Aging, Mayo Alzheimer's Disease Research Center, and Aging Dementia Imaging Research laboratory at the Mayo Clinic for making this study possible. We would like to greatly thank AVID Radiopharmaceuticals, Inc., for their support in supplying AV-1451 precursor, chemistry production advice and oversight, and FDA regulatory cross-filing permission and documentation needed for this work. We would also like to thank Jeremiah Aakre, MS with help with the ICD codes.

This work was supported by NIH grants R01 NS097495 (PI: Vemuri), R01 AG56366 (PI: Vemuri), U01 AG06786 (PI: Petersen), P50 AG16574/P1 (PI: Vemuri), P50 AG16574 (PI: Petersen), R01 AG11378 (PI: Jack), R01 AG41851 (PIs: Jack and Knopman); the GHR Foundation grant, the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation, Liston Award, Elsie and Marvin Dekelboum Family Foundation, Schuler Foundation, Opus building NIH grant C06 RR018898, and was made possible by Rochester Epidemiology Project (R01 AG034676). The funding sources were not involved in the manuscript review or approval.

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Figure 1.

Barplots of average vascular risk (CMC variables), amyloid deposition (PIB SUVR), tau deposition (ERC-Tau SUVR), and MRI neurodegeneration (average thickness in AD signature regions in mm) with 95% confidence intervals by 5-year increments.

Figure 2. Final Structural Equation Model along with significant associations shown by solid arrows. The standardized coefficients, standard errors (in brackets), and p-values are shown beside the arrows. The amyloid cascade is shown by the orange boxes. ND denotes neurodegeneration in AD regions on MRI.

Figure 3. Direct and Indirect pathways to (A) vascular health and each of the ADP biomarkers (B) Amyloid; (C) Tau; (D) ND or Neurodegeneration in AD regions on MRI

Figure 4.

Final Structural Equation Model with each individual indicator of vascular health along with significant associations shown by solid arrows. The standardized coefficients, standard errors (in brackets), and p-values are shown beside the arrows. The amyloid cascade is shown by the orange boxes. ND denotes neurodegeneration in AD regions on MRI. CHF denotes congestive heart failure.

Table 1

Study participants dichotomized by the presence/absence of cardiac and metabolic conditions (CMC). The mean (SD) are listed for the continuous variables and count (%) are listed for the categorical variables.

	All n = 430	No CMC n = 66	CMC n = 364	P-value	Cohen's D
Demographics[‡]					
Age, yrs	74.7 (8.4)	70.0 (7.9)	75.5 (8.3)	<0.001	0.676
Range	60.0, 98.0	60.0, 94.0	60.0, 98.0		
Males, no. (%)	240 (56%)	35 (53%)	205 (56%)	0.62	0.066
E4 Carrier, no. (%)	120 (28%)	15 (23%)	105 (29%)	0.31	0.136
Education, yrs	14.7 (2.6)	14.8 (2.4)	14.7 (2.6)	0.62	0.067
Range	7.0, 20.0	7.0, 19.0	7.0, 20.0		
Cognition (zGlobal)[‡]	0.15 (1.08)	0.54 (0.99)	0.07 (1.08)	0.17	0.187
Range	-3.82, 2.43	-2.62, 2.43	-3.82, 2.38		
AD Imaging Biomarkers[‡]					
PIB Ratio, SUVR ^{‡‡}	1.58 (0.43)	1.47 (0.32)	1.60 (0.45)	0.71	0.048
Range	1.13, 3.37	1.14, 2.81	1.13, 3.37		
TAU ERC Ratio, SUVR ^{‡‡}	1.13 (0.17)	1.08 (0.12)	1.14 (0.18)	0.36	0.12
Range	0.86, 2.15	0.91, 1.56	0.86, 2.15		
FDG PET (AD Sig), SUVR	1.52 (0.15)	1.61 (0.18)	1.51 (0.14)	0.002	0.46
Range	1.09, 2.22	1.09, 2.22	1.15, 1.85		
MRI (AD Sig), mm	2.83 (0.19)	2.92 (0.14)	2.81 (0.19)	0.050	0.256
Range	2.07, 3.23	2.51, 3.20	2.07, 3.23		

[‡]P-values for the demographics variables are unadjusted and are from either an ANOVA model or chi-squared test for differences in proportions

^{‡‡}P-values for differences between groups come from an ANCOVA model adjusting for age

^{‡‡‡}These reported p-values are based on the log transformed values.

For the adjusted variables Cohen's D was calculated using age adjusted means and standard deviations
FDG-PET was missing in 101 participants (No CMC: n=16; CMC>0: n=85) and zGlobal was missing in 44 participants (No CMC: n=4; CMC>0: n=40)

Table 2

AD imaging biomarkers in study participants dichotomized by the presence/absence of each of the cardiovascular metabolic components with the mean (SD).

Hyperlipidemia	Absent n= 150	Present n= 280	P-value	Cohen's D
PIB Ratio, SUV _r ^{††}	1.55 (0.42)	1.59 (0.44)	0.82	0.022
TAU ERC Ratio, SUV _r ^{††}	1.10 (0.13)	1.14 (0.19)	0.070	0.182
FDG PET (AD Sig), SUV _r	1.56 (0.17)	1.50 (0.13)	0.013	0.286
MRI (AD Sig), mm	2.87 (0.16)	2.81 (0.20)	0.085	0.172
Hypertension	Absent n= 167	Present n= 263		
PIB Ratio, SUV _r ^{††}	1.54 (0.41)	1.60 (0.44)	0.92	0.01
TAU ERC Ratio, SUV _r ^{††}	1.11 (0.16)	1.14 (0.17)	0.84	0.02
FDG PET (AD Sig), SUV _r	1.55 (0.16)	1.51 (0.14)	0.19	0.145
MRI (AD Sig), mm	2.87 (0.17)	2.80 (0.19)	0.12	0.153
Cardiac Arrhythmias	Absent n= 324	Present n= 106		
PIB Ratio, SUV _r ^{††}	1.57 (0.43)	1.62 (0.44)	0.23	0.127
TAU ERC Ratio, SUV _r ^{††}	1.12 (0.17)	1.15 (0.18)	0.96	0.005
FDG PET (AD Sig), SUV _r	1.54 (0.14)	1.47 (0.15)	0.050	0.244
MRI (AD Sig), mm	2.86 (0.17)	2.74 (0.21)	0.005	0.298
Coronary Artery Disease	Absent n= 351	Present n= 79		
PIB Ratio, SUV _r ^{††}	1.56 (0.42)	1.67 (0.47)	0.92	0.012
TAU ERC Ratio, SUV _r ^{††}	1.11 (0.16)	1.18 (0.20)	0.075	0.213
FDG PET (AD Sig), SUV _r	1.54 (0.14)	1.46 (0.15)	0.032	0.29
MRI (AD Sig), mm	2.85 (0.17)	2.74 (0.23)	0.033	0.255
Stroke	Absent n= 402	Present n= 28		
PIB Ratio, SUV _r ^{††}	1.57 (0.42)	1.73 (0.55)	0.53	0.121
TAU ERC Ratio, SUV _r ^{††}	1.13 (0.17)	1.16 (0.16)	0.94	0.014
FDG PET (AD Sig), SUV _r	1.53 (0.15)	1.49 (0.17)	0.77	0.064
MRI (AD Sig), mm	2.83 (0.18)	2.77 (0.24)	0.94	0.014
Congestive Heart Failure	Absent n= 418	Present n= 12		
PIB Ratio, SUV _r ^{††}	1.57 (0.43)	1.79 (0.46)	0.32	0.288
TAU ERC Ratio, SUV _r ^{††}	1.12 (0.17)	1.21 (0.20)	0.33	0.285
FDG PET (AD Sig), SUV _r	1.52 (0.15)	1.51 (0.15)	0.78	0.109
MRI (AD Sig), mm	2.84 (0.18)	2.64 (0.24)	0.012	0.737
Diabetes	Absent n= 260	Present n= 170		
PIB Ratio, SUV _r ^{††}	1.54 (0.40)	1.64 (0.47)	0.12	0.153
TAU ERC Ratio, SUV _r ^{††}	1.11 (0.15)	1.15 (0.20)	0.13	0.149
FDG PET (AD Sig), SUV _r	1.56 (0.14)	1.46 (0.13)	<0.001	0.653
MRI (AD Sig), mm	2.86 (0.18)	2.79 (0.19)	0.001	0.316

P-values for differences between groups come from an ANCOVA model adjusting for age.

^{††}These reported p-values are based on the log transformed values.

Cohen's D was calculated using age adjusted means and standard deviations

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Table 3

Direct and Indirect effects seen in the final SEM model shown in Figure 2.

Type of effect	Path	Estimate (std. error)	p-value
Total	Age to CMC	0.616 (0.080)	<0.001
Direct	Age to CMC	0.616 (0.080)	<0.001
Total	Male to CMC	0.287 (0.136)	0.034
Direct	Male to CMC	0.287 (0.136)	0.034
Total	Age to Amyloid	0.446 (0.050)	<0.001
Direct	Age to Amyloid	0.446 (0.050)	<0.001
Total	APOE to Amyloid	0.612 (0.095)	<0.001
Direct	APOE to Amyloid	0.612 (0.095)	<0.001
Total	Age to Tau	0.289 (0.036)	<0.001
Total Indirect	Age to Tau	0.289 (0.036)	<0.001
Indirect	Age to Amyloid to Tau	0.247 (0.033)	<0.001
Indirect	Age to CMC to Tau	0.041 (0.017)	0.016
Total	Male to Tau	0.019 (0.012)	0.105
Indirect	Male to CMC to Tau	0.019 (0.012)	0.105
Total	APOE to Tau	0.340 (0.058)	<0.001
Indirect	APOE to Amyloid to Tau	0.340 (0.058)	<0.001
Total	CMC to Tau	0.067 (0.027)	0.012
Direct	CMC to Tau	0.067 (0.027)	0.012
Total	Amyloid to Tau	0.555 (0.040)	<0.001
Direct	Amyloid to Tau	0.555 (0.040)	<0.001
Total	Age to Neurodegeneration	0.630 (0.047)	<0.001
Direct	Age to Neurodegeneration	0.513 (0.050)	<0.001
Total Indirect	Age to Neurodegeneration	0.117 (0.023)	<0.001
Indirect	Age to Amyloid to Tau to Neurodegeneration	0.051 (0.012)	<0.001
Indirect	Age to CMC to Neurodegeneration	0.057 (0.018)	0.002
Indirect	Age to CMC to Tau to Neurodegeneration	0.009 (0.004)	0.029
Total	Male to Neurodegeneration	0.216 (0.078)	0.006
Direct	Male to Neurodegeneration	0.186 (0.077)	0.016
Total Indirect	Male to Neurodegeneration	0.031 (0.017)	0.064
Indirect ^{††}	Male to CMC to Neurodegeneration	0.013 (0.007)	0.072
Indirect ^{††}	Male to CMC to Tau to Neurodegeneration	0.002 (0.001)	0.120
Total	APOE to Neurodegeneration	0.070 (0.018)	<0.001
Indirect	APOE to Amyloid to Tau to Neurodegeneration	0.070 (0.018)	<0.001

Type of effect	Path	Estimate (std. error)	p-value
Total	CMC to Neurodegeneration	0.107 (0.028)	<0.001
Direct	CMC to Neurodegeneration	0.093 (0.027)	0.001
Indirect	CMC to Tau to Neurodegeneration	0.014 (0.006)	0.023
Total	Amyloid to Neurodegeneration	0.115 (0.024)	<0.001
Indirect	Amyloid to Tau to Neurodegeneration	0.115 (0.024)	<0.001
Total	Tau to Neurodegeneration	0.207 (0.040)	<0.001
Direct	Tau to Neurodegeneration	0.207 (0.040)	<0.001

^{††} These indirect effects are not in the final model; coefficients and p-values are from the saturated model.