Cerebrovascular Disease and Associations with ATN Biomarkers and Cognition in Young Onset Dementia

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Research

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Abstract

Background: Cerebrovascular disease (CVD) and Alzheimer's disease (AD) frequently coexist however the mechanism by which they collectively affect cognition remains unclear, particularly in young onset dementia (YOD). We investigated associations between CVD and AD biomarkers, namely amyloid, tau and neurodegeneration (ATN) in YOD, and explored how CVD and ATN interact to affect cognition.

Methods: 80 YOD individuals with mild dementia, mean age 57.73 (SD = 6.01) years were recruited from a memory clinic. MRI visual ratings were used to operationalize CVD burden (CVD+) as a score >1 on the Staals CVD scale. ATN biomarkers were measured using cerebrospinal fluid (CSF) and cognition was measured using neuropsychological assessments.

Results: CVD+ individuals had lower CSF $A\beta_{1-42}$ compared to CVD- (t[78] = -1.97, p = .05), while demographics, cognition, cardiovascular risk factors, brain volumes and tau were consistent across the groups. CVD+ was associated with lower CSF $A\beta_{1-42}$ (B = -.20, 95%CI: -.32 to -.08) and greater neurodegeneration, indexed as lower grey matter (B = -.15, 95%CI: -.28 to .02) and hippocampal volume (B = -.24, 95%CI: -.40 to -.04). CVD+ was not associated with p-tau or t-tau. Cognitive impairment was associated with CSF $A\beta_{1-42}$ (B = -.35, 95%CI: -.55 to -.18) but not CVD. Rather, CVD was indirectly associated with cognition via reduced CSF $A\beta_{1-42}$, specifically with global cognition (B = -.03, 95%CI: -.09 to -.01) and memory (B = .08, 95%CI: -.09 to -.01). CVD was further indirectly associated with cognition via increased neurodegeneration in total grey matter (Global cognition: B = -.06, 95%CI: -.09 to -.03; Memory: B = .05, 95%CI: .01 to .18) and the hippocampus (Global cognition: B = -.05, 95%CI: -.11 to -.01; Memory: B = .06, 95%CI: .01 to .17). CVD was not found to moderate the strength or direction of the relationship between ATN and cognition.

Conclusion: In YOD, CVD burden is linked to upstream AD mechanisms, such as CSF $A\beta_{1-42}$, as well as downstream neurodegeneration. CVD indirectly contributes to cognitive impairment via these AD mechanisms. Clinical implications support the aggressive management of CVD to delay AD in young adults.

Introduction

Young-onset dementia (YOD) represents individuals with dementia onset before the age of 65 years. YOD is associated with greater economic burden [1], more rapid cognitive deterioration and shorter survival compared to late-onset dementia (LOD) [2]. In addition, patients with YOD are likely to be in paid employment with significant financial commitments and with young children and elders to support. To improve clinical outcomes for this vulnerable group, it is critical to understand disease mechanisms in the young population.

The most common etiology of YOD is Alzheimer's disease (AD), followed by cerebrovascular disease (CVD) [3]. Both AD and CVD frequently co-exist and are strong predictors of cognitive impairment and

dementia [4, 5]. Imaging biomarkers of CVD include white matter hyperintensities (WMH), lacunes, microbleeds and periventricular spaces [6, 7]. Each of these biomarkers increase the risk of cognitive impairment [8–11], with executive dysfunctions being the most vulnerable [12]. Biomarkers of AD pathophysiology involve cerebrospinal fluid (CSF) $A\beta_{1-42}$ plaque deposition, tau accumulation and neurodegeneration [13, 14], which are collectively referred to as ATN. Each ATN biomarker has been associated with cognitive decline, [15] with 60%-80% predictive sensitivity compared to healthy controls [16].

The association between CVD and AD pathology remains controversial. Studies have shown that CVD risk factors, such as pulse pressure, hypertension and diabetes, are associated with abnormal CSF $A\beta_{1-42}$ levels [17, 18] while other studies show that CVD is associated with CSF Tau, independent to $A\beta_{1-42}$ [19]. On the other hand, several studies show that CVD is not associated with CSF $A\beta_{1-42}$ [5, 19–22]. The interaction between $A\beta_{1-42}$ and CVD in the process of cognitive impairment also remains unclear. Some suggest cognitive impairment includes the synergistic effect of both $A\beta_{1-42}$ and CVD [21], while others suggest both pathologies have independent effects on cognition [5, 20, 22]. Most of these studies have focused on sporadic LOD. As such, little is known about the associations of CVD with AD pathology in patients with YOD. Given young age is a strong moderator of vascular injury and AD pathology [21] it is imperative to determine the associations between CVD and AD pathophysiology, and their effect on cognition in patients with YOD.

Here, in a cross-sectional study of YOD patients with mild AD, we tested the associations of CVD and ATN biomarkers. We further investigated how CVD and ATN biomarkers interact to affect cognition using moderation and mediation models. We hypothesized that the prevalence of CVD would be associated with a greater burden of ATN biomarkers. We further hypothesized that CVD would moderate the effect of ATN biomarkers on cognition, that is strengthen the associations between ATN and cognition. We also hypothesized a mediation effect where CVD would indirectly be related to cognitive impairment via increasing burden ATN biomarkers. The direction of CVD affecting ATN biomarkers is in line with pathological studies showing that CVD promotes amyloid aggregation [23], restrict the clearance of amyloid [24] and causes vascular-related amyloid [25].

Methods

Design and setting

Participants

Study participants were selected from the Singapore Young-Onset Dementia Cohort (SYNC), which is a cohort of patients with mild AD experiencing onset of symptoms below the age of 65 years; recruited from a tertiary neurology center (National Neuroscience Institute, Singapore) between 2015–2018. From SYNC, we selected patients with CSF, MRI and neuropsychological assessments (consort diagram in supplementary materials). The diagnosis of mild AD was made based on the NIA-AA Criteria [26] and

supported by a Clinical Dementia Rating Scale (CDR)[27] of .05 to 1. Exclusion criteria for the SYNC study included significant neurological or psychiatric comorbidities, a history of alcohol or drug abuse and presence of other neurodegenerative conditions.

Ethics approvals and patient consents

The SYNC study was approved by the Singhealth Centralized Review Board. Informed written consent was obtained from all participants according to Declaration of Helsinki and local clinical research regulations.

Measures

Demographic characteristics, including the participants' age, gender, race and years of education, were collected using a structured interview with the patient or next of kin.

Cardiovascular risk factors, including blood pressure, diabetes, hyperlipidemia and history of stroke were noted from medical records. Total cerebrovascular burden was indexed using the Framingham office-based cardiovascular disease risk prediction model, which took into account age, gender, BMI, systolic blood pressure, smoking, and diabetes [28].

Cognitive functioning was indexed using global and domain assessments. Global cognition was assessed using the Montreal Cognitive Assessment (MoCA) [29]; memory was assessed using the Wechsler Memory Scale version 4 (WMS-IV) Story Recall delayed and immediate tests [30] and (Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-Cog) delayed and immediate recall tasks [31]; executive functions was assessed using Frontal Assessment Battery [32] and Color Trails 1 and 2 [33]; and visuospatial skills was assessed using and the WAIS-IV Block Design test [34] and the Rey Complex Figure test [35].

CSF

CSF $A\beta_{1-42}$, phosphorylated tau (ptau) and total tau was collected using a lumbar puncture. ELISA immunoassays were used to process the CSF specimens, in accordance to prescribed protocol and requirements (INNOTEST tTau Ag, INNOTEST PHOSPHO-TAU(181) and INNOTEST β-AMYLOID(1–42); Innogenetics Inc., Alpharetta, GA). CSF cut off based on laboratory parameters: CSF Aβ 1-42 <480pg/mL, phospho tau >61 pg/mL, total tau >425pg/m (Fujirebio, Ghent, Belgium).

MRI protocol

Patients underwent a 3T MRI scan (Achieva 3.0; Philips Medical Systems, Best, Netherlands) within six months of clinical and neuropsychological evaluation. Scan specifications include, (a) T1-weighted MPRAGE (axial acquisition, 176 slices, matrix size=256 × 256, voxel size=1.0 × 1.0 × 1.0mm3, echo time (TE)=3.2ms, repetition time (TR)=7ms, inversion time (TI)=850ms, flip angle=8°, field of view (FOV)=256 ×

256mm2), and (b) T2-weighted FLAIR imaging (170 slices, matrix size=256 × 256, voxel size=1.0 × 1.0 × 1.0mm3, TE=340ms, TR=8000ms, TI=2400ms, FOV=240 × 240mm2). Scans were visually-rated for WMH using the 0–3 Fazekas Scale [36] on axial FLAIR sequences for deep and periventricular WMH in the left and right hemispheres; lacunes and microbleeds using STandards for Reporting Vascular changes on nEuroimaging (STRIVE) [37]; and global cortical atrophy using the Pasquier scale [38]. CVD burden was calculated using the Staals score [6] which combines WMH, lacunes, microbleeds and periventricular spaces into a total CVD-related brain damage score, ranging from 0 - 4. Visual-ratings were performed by independent trained raters and any difference in rating scores were addressed and resolved by consensus.

Statistical analysis

Data preparation involved imputing variables with less than 30% missing data, based on recommendations by the American Psychological Association Task Force on Statistical Inference [39]. Multiple imputation using the five chained equations procedure was used to perform logistic regression with original weights to estimate grey matter volumes (19%% missing) using the predictors age, gender, education, MoCa, CSF $A\beta_{1-42}$, Fazekas, lacunes, microbleeds and global cortical atrophy. Patients were grouped as CVD burden (CVD +) based on a Staals score [6] ≥ 1 or the no CVD (CVD -) based on a Staals score of 0. Skewed variables included Staals score, ptau and total tau, and were log transformed. For variables containing 0 (Staals score), a 1 was added prior to transformation.

Main statistical analysis

1. *Group differences* between patients with CVD+ and CVD- were determined for demographics, cardiovascular disease risk factors, cognition, CSF biomarkers, grey and white matter volume and CVD markers visually rated from MRI scans. T-test was used for continuous variables, with Welsh adjustment for unequal variances, and χ^2 test used for categorical variables.
2. *Association between CVD and components of ATN* were assessed using a path analysis linear regression model. All ATN components were included in one regression model in order to control for each other. Neurodegeneration was indexed as total tau, total grey matter volume (as a measure of general neurodegeneration) and hippocampal volume (as a measure of AD-specific neurodegeneration). To control for demographics and cardiovascular risk factors, the Framingham cardiovascular risk score was included as a covariate. A post-hoc exploratory analysis investigated the association between CVD and CSF $A\beta_{1-42}$ on hippocampal atrophy.
3. *The direct association of CVD and ATN with cognition* was assessed using path analysis regression models, where CVD and ATN components were the predictors and cognition was the outcome. Cognitive outcomes included global cognition, memory, executive functions and visuospatial skills, which were each assessed in independent models. All ATN components were included in each model in order to control for each other and an additional covariate included Framingham risk score. Composite scores for each cognitive domain were created by z-scoring each test and averaging the

scores. Population norms were not used to create z-score because the young age range did not fit in with the locally published norms.

4. *Moderation analysis to determine whether CVD affects the strength or direction of the relationship between ATN and cognition.* To test this a-priori hypothesis, first CVD and ATN components were centered. Next CVD was multiplied with each component of ATN to create the interaction variable. This interaction variable was the predictor in the regression analysis and cognition was the outcome, with Framingham cardiovascular risk score as the covariate. An independent analysis was run for each CVD and ATN interaction variable, and for each cognitive outcome (global cognition and cognitive domains). A post-hoc exploratory analysis investigated the interaction between CVD and $A\beta_{1-42}$ with hippocampal volume as the outcome.
5. *Mediation analysis to determine whether CVD indirectly affects cognition via the ATN pathway*. This a-priori hypothesis was tested using regression mediation models where the predictor was CVD burden, the outcome was cognitive impairment (indexed using global cognition or cognitive domains) and the mediators were CSF $A\beta_{1-42}$, CSF tau, CSF total tau and hippocampal volume given it was the only neurodegeneration marker significantly associated with CVD. Each mediator and cognitive outcome was assessed in an independent model with Framingham cardiovascular risk as the covariate.

As a non-parametric estimation of effects, SEs and biases for all moderation and mediation analyses, bias-corrected (BC) bootstrapping was applied with 1000 resamples [40]. Bootstrapping measures the variability of the linear approximation of each path in the model and estimates the bias of this linear approximation to the population [41]. BC bootstrapping has been empirically validated as a tool for multiple comparison correction, deriving robust parameter estimates based on maximized power and limited type 1 error rates [42]. The significance of the BC bootstrap estimate was indicated by confidence intervals that did not contain 0. All moderation and mediation analyses were conducted using path analysis on SPSS AMOS version 20 [43]. Path analysis model fit was assessed using published recommended criteria [44]: (a) χ^2 *p*-value: > 0.05, (b) Bentler comparative fit index (CFI: > 0.95) and (c) root mean error of approximation (RMSEA: < 0.04). Effect sizes for the direct effects were indexed using the standardized coefficient of the slope (B), which is identical to the benchmark set for Pearsons r; a coefficient of .10, .30 and .50 indicated small, moderate and large effects respectively [45]. Effect size for indirect effects were indexed by squaring Cohen's [45] estimations because indirect effects represent a product of two effects [46]; a coefficient of .01, .09 and .25 indicated small, moderate and large effects respectively.

Data availability

Deidentified participant data will be made available upon reasonable request from the corresponding author.

Results

1. **Group differences**

Compared to CVD- patients, CVD+ patients had higher WMH (t[77] = 4.86, p = .00) and perivascular spaces (t[76] = 3.36, p = .00) (table 1). CVD+ patients were trending on having more lacunes (t[45] = 1.89, p = .05), lower CSF Aβ $_{1\text{-}42}$ (t[78] = -1.97, p = .05) and lower hippocampal volume (t[78] = -1.91, p = .05). No differences were observed with demographics, APOE-4, MoCa, cardiovascular risk factors, Framingham cardiovascular risk score, ptau, total tau, total white and grey matter or number of microbleeds.

2. **Associations between CVD and ATN**

The path analysis regression model with CVD as the predictor and ATN as individual outcomes had excellent model fit according to recommended criteria [44].

*CVD and CSF Aβ $_{1\text{-}42}$*were negatively associated, while controlling for cardiovascular risk factors, ptau and total tau (B = -.20, SE = .07, bootstrapped p = .01, BC 95%CI: -.32 to -.08).

CVD and Tau were not associated.

CVD and neurodegeneration indexed as hippocampal volume was negatively associated while controlling for cardiovascular risk factors, CSF Aβ $_{1\text{-}42}$ and ptau (B = -.24, SE = .10, bootstrapped p = .04, BC 95%CI: -.40 to -.04). CVD was not associated with total tau or total grey matter volume.

3. **Direct associations between CVD, ATN and cognition**

The path analysis regression models with CVD and ATN components as the predictors and cognition as the outcome had good model fit according to recommended criteria [44].

Global cognition was related to total grey matter volume (B = .41, SE = .01, bootstrapped p = .00, BC 95%CI: .02 to .06) and hippocampal volume (B = .34, SE = 71, bootstrapped p = .00, BC 95%CI: 1.25 to 3.91), while controlling for cardiovascular risk factors, CSF Aβ $_{1\text{-}42}$, ptau, and CVD. Global cognition was not related to CVD, CSF Aβ $_{1\text{-}42}$, CSF p-tau and CSF t-tau.

Memory was associated with CSF Aβ $_{1\text{-}42}$ (B = -.35, SE = .00, bootstrapped p = .00, BC95%CI: -.55 to -.18), while controlling for cardiovascular risk factors, ptau, total tau and CVD. Memory was associated with total grey matter volume (B = -.25, SE = .00, bootstrapped p = .02, BC95%CI: -.01 to -.00), and hippocampal atrophy (B = -.27, SE = .05, bootstrapped p = .04, BC95%CI: -.21 to -.01) while controlling for cardiovascular risk factors, CSF Aβ $_{1\text{-}42}$, ptau and CVD. A trend was observed between memory and CVD (B = .18, SE = .05, bootstrapped p = .08, BC95%CI: -.00 to .33), while controlling for cardiovascular risk factors, CSF Aβ $_{1\text{-}42}$, ptau and total tau.

Executive functions were not associated with CVD, CSF Aβ $_{1\text{-}42}$, ptau, total tau, total grey matter volume or hippocampal atrophy.

Visuospatial functions were associated with the three markers of neurodegeneration: total tau (B = -.56, SE = .27, bootstrapped p = .04, BC95%CI: -1.07 to -.16), total grey matter volume (B = .48, SE = .00, bootstrapped p = .00, BC95%CI: .00 to .01) and hippocampal volume (B = .42, SE = .10, bootstrapped p = .01, BC95%CI: .15 to .51), while controlling for cardiovascular risk factors, CSF Aβ $_{1\text{-}42}$, ptau, and CVD.

4. **The moderating role of ATN on the effect of CVD and cognition**

The path analysis regression models with CVD interacting with ATN as the predictors and cognition or hippocampal volume as the outcome had excellent model fit according to recommended criteria [44].

CVD did not interact with CSF Aβ $_{1\text{-}42}$, ptau or total tau to affect global cognition or cognitive domains. A post-hoc analysis indicated that CVD did not interact with CSF Aβ $_{1\text{-}42}$ to affect hippocampal volumes.

5. **The mediating role of ATN on the effect of CVD on cognition**

The path analysis regression models with CVD as the predictor, ATN as the mediators and cognition or hippocampal volume as the outcome had excellent model fit according to recommended criteria [44].

Global cognition: An indirect association was observed between CVD and global cognition, as mediated by CSF Aβ $_{1\text{-}42}$, controlling for cardiovascular risk factors, ptau and total tau (table 2). CVD was also indirectly related to global cognition as mediated by total grey matter volume and hippocampal atrophy, while controlling for cardiovascular risk factors, CSF Aβ $_{1\text{-}42}$ and ptau.

Memory: An indirect association was observed between CVD and memory, as mediated by CSF Aβ $_{1\text{-}42}$, while controlling for cardiovascular risk factors, ptau and hippocampal atrophy (table 2). CVD was also mediated by total grey mater volume and hippocampal atrophy in its association with memory.

Executive functions/Visuospatial functions: CVD was not indirectly related to executive functions or visuospatial functions, as mediated by ATN.

Discussion

Main findings

In a young cohort of patients with mild AD, we showed that the prevalence of CVD burden was highly concomitant with the prevalence of low CSF Aβ $_{1-42,}$ even after controlling for age, gender, education, cognition, cardiovascular risk factors and grey and white matter volume. CVD was associated with lower CSF Aβ $_{1-42}$ and greater neurodegeneration in AD specific regions, namely the hippocampus. Meanwhile no associations were observed between CVD and p-tau or total tau. Cognitive impairment was directly associated with low CSF Aβ $_{1-42}$, but not with CVD. Rather, CVD was indirectly associated with global and memory impairment via reduced CSF Aβ $_{1-42}$ levels and increased neurodegeneration in total grey matter and specifically in the hippocampus. CVD was not found to moderate the strength or direction of the

relationship between ATN and cognition. Our findings suggest that CVD is linked to the ATN pathway in patients with YOD and indirectly drives cognitive impairment via this pathway.

Associations between CVD, Amyloid and Neurodegeneration

Amyloid is believed to be first in a line of upstream effects that cause AD-related dementia [13]. Our findings suggest that in YOD patients, CVD is associated with earlier mechanisms of the AD process, namely $A\beta_{1-42}$ deposition. Possible mechanisms of this association may involve the vascular system promoting $A\beta_{1-42}$ aggregation [23], restricting clearance of $A\beta_{1-42}$ [24] and causing vascular-related $A\beta_{1-42}$ [25]. Our findings in YOD are in comparison to past research in patients with LOD, where CVD was found to exhibit a more delayed effect on the ATN sequelae by affecting tau aggregation [19]. Thus it appears that in young age, CVD precipitates the AD process by influencing $A\beta_{1-42}$, while in old age CVD may simply lower the threshold for AD symptomology.

CVD and CSF $A\beta_{1-42}$ were each associated with AD-pattern neurodegeneration, namely hippocampal atrophy. CVD did not interact with $A\beta_{1-42}$ to affect hippocampal atrophy, suggesting each mechanism had an independent effect on neurodegeneration. This is consistent with previous in-vivo studies demonstrating that while hippocampal volume loss is similar between AD and small vessel disease, the cause of neural loss differs; neural loss in AD was caused by amyloid deposition and neural loss in small vessel disease was caused by microvasculature pyramidal cell loss [47]. Therefore, CVD and CSF $A\beta_{1-42}$ may each have additive effects on AD-pattern neurodegeneration, resulting from different pathogenic mechanisms.

Associations between CVD and Amyloid with Cognition

Low CSF $A\beta_{1-42}$ was associated with memory impairment. A moderate effect size suggests that YOD patients with low $A\beta_{1-42}$ may exhibit observable memory deficits. On the contrary, mild CVD was not directly associated with cognitive impairment nor did it interact with $A\beta_{1-42}$ to affect cognition. CVD also did not interact with $A\beta_{1-42}$ to affect neurodegeneration. Thus despite being associated, CVD and $A\beta_{1-42}$ work independently to effect both cognitive impairment and neurodegeneration. Comparatively, studies with LOD cohorts have demonstrated CVD predicts cognitive decline both alone [19] and in some cases synergistically with $A\beta_{1-42}$ [21]. Thus it is likely that young age may protect against the effects of mild CVD on cognition, however may not protect against the effects of AD pathology on cognition.

One mechanism by which CVD was related to cognitive impairment was indirectly via increasing neurodegeneration and lowering CSF $A\beta_{1-42}$. This was observed for both global cognition and memory. The former indirect effect suggests that neural loss may be critical for CVD to manifest clinically in YOD patients. The later indirect effect suggests that while CVD is not related to clinical outcomes in YOD, it is related to other disease mechanisms such as amyloid accumulation. We further note that the size of the mediation effect was small when the outcome was global cognitive impairment, while effect size was

moderate when the outcome was memory; suggesting that the effect of CVD lowering CSF Aβ $_{1-42}$ may be most detrimental for memory functions.

Limitations and future research

We note that the current study recruited patients from the SYNC cohort that underwent lumbar puncture. As a result, patients included in the study had lower cognition and greater depressive symptoms compared to the overall SYNC cohort, resulting in selection bias towards poorer functioning patients (supplementary materials). We note that the mean CSF Aβ $_{1-42}$ level in our cohort was in the normal range, while the Tau levels were in the abnormal range, suggesting AD in our cohort could have been predominantly Tau driven. We note that these findings are relevant to a clinic based cohort and an Asian population. We further note we did not have a comparison group. Future research would benefit from comparing YOD with LOD from a single cohort to ensure consistency in methodology.

Conclusion

In YOD patients with mild AD, CVD and low CSF Aβ $_{1-42}$ may co-exist. Cognitive impairment in this young population was directly associated with low CSF Aβ $_{1-42}$, but not with CVD. Rather, CVD precipitated upstream and downstream phases of the ATN pathway, which consequently led to cognitive impairment. Thus, CVD related mechanisms may accelerate AD pathology in younger patients with negative consequences on cognition at later ages. Clinical implications support the aggressive management of CVD as a potential approach to delay AD in young adults.

Declarations

Ethics approval and consent to participate

The study was approved by the Singhealth Centralized Review Board. Informed written consent was obtained from all participants according to Declaration of Helsinki and local clinical research regulations.

Consent for publication

Not applicable

Availability of data and materials

The dataset analyzed during the current study are not publically available but is available upon reasonable request from the corresponding author.

Competing interests

The authors declare that they have no competing interests

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Author's contributions

CY contributed to the study conception and design, analysis of data and drafting the manuscript. KN contributed to revising the manuscript for intellectual content. AG, BW and TY contributed to acquisition and management of data. NK contributed to the conception and design of the study, and revising the manuscript for intellectual content.

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Tables

Table 1. Participant characteristics

	Total cohort (N = 80)	CVD + (N = 47)	CVD - (N= 33)
Demographics			
Age	57.73 (6.01)	57.60 (6.39)	57.92 (5.50)[a]
Gender (Males)	35 (44%)	21 (45%)	14 (42%) [b]
Education	11.91 (4.48)	11.85 (4.34)	12 (4.74) [a]
APOE-e4[1]	18 (35%)	13 (28%)	5 (15%) [b]
Cardiovascular risk factors			
Diabetes	14 (17%)	7 (15%)	7 (21%) [b]
Hypertension	30 (37%)	21 (45%)	9 (27%) [b]
History of stroke	6 (7%)	3 (6%)	3 (9%) [b]
Hyperlipidemia	36 (45%)	23 (49%)	13 (39%) [b]
Framingham risk score	11.79 (3.64)	12.12 (3.68)	11.75 (3.64) [b]
Cognition			
Moca	19.97 (7.03)	18.47 (7.04)	21.39 (6.75) [a]
FAB	13.71 (4.26)	13.18 (4.33)	14.54 (4.09) [a]
Color trails I	129.52 (176.40)	156.90 (217.45)	88.44 (70.2)[c]
Color trails II	164.89 (133.17)	176.21 (132.53)	148.93(135.66) [a]
ADAS immediate recall	5.00 (2.40)	5.56 (2.45)	4.09 (2.05) [a]
ADAS delayed recall	5.43 (3.68)	6.31 (3.67)	4.00 (3.28) [a] *
Story recall immediate	8.38 (6.02)	7.68 (6.16)	9.52 (5.72) [a] *
Block design	29.56 (15.02)	26.71 (15.10)	34.08 (14.03) [a]
RCFT	26.73 (11.35)	25.35 (12.09)	28.94 (9.90) [a]
CSF biomarkers			
$A\beta_{1-42}$ (pg/ml)	811.09 (391.53)	740.05 (357.69)	912.27 (420.18) [a]
pTau (pg/ml)	68.34 (42.94)	68.91 (44. 88)	67.54 (40.71) [a]
Total Tau (pg/ml)	493.70 (378.50)	511.90 (393.76)	467.77 (360.01) [a]
CVD markers (Mean, SD, median, IQR)			
Staals score	.59 (SD = .49), 1, IQR = 4	1.23 (SD = .69), 1, IQR = 3	0 (SD = 0), 0, IQR = 0 [a] **
Fazekas score[d]	4.65 (SD = 4.09), 4, IQR = 12	6.74 (SD = 3.65), 6, IQR = 12	1.88 (SD= 2.79), 0, IQ = 0 [a] **
Lacunes	.28 (SD= 1.31), 0, IQR = 11	.47, (SD = 1.67), 0, IQR = 11	0, 0, 0 IQR = 0 [a]
Microbleeds	.33 (SD=2.13), 0,	.57, (SD = 2.77), 0,	0, 0, 0, IQR =0 [a]

	IQR = 15	IQR = 15	
Perivascular spaces	2.32 (SD=2.15), 2, IQR = 6	3.15 (SD = 2.09), 3, IQR =6	1.15 (SD = .1.66), 0, IQR = 6 [a]
MRI volumes			
Total grey matter	586.72 (SD = 68.52)	575.03 (SD = 67.54)	603.33 (SD = 67.42) [a]
Total white matter	483.93 (SD = 61.62)	479.47 (SD = 63.01)	490.29 (SD = 59.98) [a]
Hippocampal grey matter	6.12 (SD = 1.03)	5.94 (SD = 1.08)	6.38 SD = (SD =.91) [a]

Abbreviations: CVD +: positive for cerebrovascular burden; CVD-: no cerebrovascular burden; FAB: Frontal assessment battery; ADAS: Alzheimer's Disease Assessment Scale; RCFT: Rey Complex figure test; SD: standard deviation; IQR: interquartile range.

[a] t-test df = 1,78

[b] χ^2 df = 1

[c] Welsh adjusted t-test,

[d] Fazekas rated for deep and periventricular WMH in the left and right hemispheres, with total score of 12

* = p <.05, ** = p < .00

Table 2. Regression weights for the indirect associations between CVD and cognition as mediated by ATN.

X à M à Y	B	SE	BC95% CI	p
Global cognition				
CVD à Aβ 1-42 à Moca	-.03	.02	-.09 to -.01	.01*
CVD à pTau à Moca	.01	.02	-.02 to .04	.99
CVD à Total Tau à Moca	-.01	.03	-.09 to .03	.41
CVD à Total grey matter à Moca	-.06	.04	-.17 to -.03	.03*
CVD à Hippocampus à Moca	-.05	.03	-.11 to -.01	.03*
Memory				
CVD à Aβ 1-42 à Memory	.08	.05	.01 to .21	.03*
CVD à pTau à Memory	.03	.04	-.02 to .09	.28
CVD à Total Tau à Memory	.03	.05	-.01 to .13	.17
CVD à Total grey matter à Memory	.05	.04	.01 to .18	.03*
CVD à Hippocampus à Memory	.06	.04	.01 to .17	.04*

Abbreviations: B: standardized beta; SE: standard error; CI: confidence interval

*bootstrapped p < .05, **bootstrapped p < .01

[1] Total available genetics data N= 31 CVD+ (18 missing) and N= 20 CVD- (13 missing)

Figures

Figure 1

The direct and indirect effect of CVD burden on cognitive impairment, via the ATN pathway.

Supplementary Files

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