Received: 21 December 2021 | Revised: 6 June 2022 | Accepted: 10 June 2022

DOI: 10.1002/alz.12750

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Vascular burden and cognition: Mediating roles of neurodegeneration and amyloid PET

Julie Ottoy[1] | Miracle Ozzoude[1] | Katherine Zukotynski[1,2,3,4] | Sabrina Adamo[1] | Christopher Scott[1] | Vincent Gaudet[5] | Joel Ramirez[1] | Walter Swardfager[6] | Hugo Cogo-Moreira[1,7] | Benjamin Lam[8] | Aparna Bhan[1] | Parisa Mojiri[1] | Min Su Kang[1,9,10] | Jennifer S. Rabin[11,12,13,14] | Alex Kiss[15] | Stephen Strother[16,17] | Christian Bocti[18] | Michael Borrie[19] | Howard Chertkow[20] | Richard Frayne[21] | Robin Hsiung[22] | Robert Jr. Laforce[23] | Michael D. Noseworthy[24] | Frank S. Prato[19] | Demetrios J. Sahlas[25] | Eric E. Smith[26] | Phillip H. Kuo[27] | Vesna Sossi[22] | Alexander Thiel[20] | Jean-Paul Soucy[9] | Jean-Claude Tardif[28] | Sandra E. Black[1,8,29] | Maged Goubran[1,10,16] | for the Medical Imaging Trial Network of Canada (MITNEC) and Alzheimer's Disease Neuroimaging Initiative (ADNI)*

[1]LC Campbell Cognitive Neurology Unit, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[2]Departments of Medicine and Radiology, McMaster University, Hamilton, Ontario, Canada

[3]Department of Medical Imaging, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada

[4]Department of Radiology, University of British Columbia, Vancouver, British Columbia, Canada

[5]Department of Electrical and Computer Engineering, University of Waterloo, Waterloo, Ontario, Canada

[6]Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada

[7]Department of Education, ICT and Learning, Østfold University College, Halden, Norway

[8]Department of Medicine (Division of Neurology), University of Toronto, Toronto, Ontario, Canada

[9]Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

[10]Physical Sciences Platform, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[11]Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Ontario, Canada

[12]Harquail Centre for Neuromodulation, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

[13]Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[14]Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada

[15]Department of Research Design and Biostatistics, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[16]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

[17]The Rotman Research Institute Baycrest, University of Toronto, Toronto, Ontario, Canada

[18]Département de Médecine, Université de Sherbrooke, Sherbrooke, Quebec, Canada

[19]Lawson Health Research Institute, Western University, London, Ontario, Canada

[20]Jewish General Hospital and Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

[21]Departments of Radiology and Clinical Neuroscience, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

[22]Physics and Astronomy Department and DM Center for Brain Health, University of British Columbia, Vancouver, British Columbia, Canada

[23]Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, Université Laval, Quebec City, Quebec, Canada

[24]Department of Electrical and Computer Engineering, McMaster University, Hamilton, Ontario, Canada

[25]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[26]Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

[27]Department of Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona, Tucson, Arizona, USA

[28]Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada

[29]Dr. Sandra Black Centre for Brain Resilience and Recovery, Hurvitz Brain Sciences Research Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

Correspondence
Maged Goubran, LC Campbell Cognitive Neurology Unit, Hurvitz Brain Sciences Program, Sunnybrook Research Institute, University of Toronto, 2075 Bayview Avenue, M6 West RM 176, Toronto M4N 3M5, Canada.
Email: maged.goubran@utoronto.ca

Sandra E. Black and Maged Goubran are co-senior authors.

*Data used in preparation of this article were obtained, in part, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

It remains unclear to what extent cerebrovascular burden relates to amyloid beta (Aβ) deposition, neurodegeneration, and cognitive dysfunction in mixed disease populations with small vessel disease and Alzheimer's disease (AD) pathology. In 120 subjects, we investigated the association of vascular burden (white matter hyperintensity [WMH] volumes) with cognition. Using mediation analyses, we tested the indirect effects of WMH on cognition via Aβ deposition (^{18}F-AV45 positron emission tomography [PET]) and neurodegeneration (cortical thickness or ^{18}F fluorodeoxyglucose PET) in AD signature regions. We observed that increased total WMH volume was associated with poorer performance in all tested cognitive domains, with the strongest effects observed for semantic fluency. These relationships were mediated mainly via cortical thinning, particularly of the temporal lobe, and to a lesser extent serially mediated via Aβ and cortical thinning of AD signature regions. WMH volumes differentially impacted cognition depending on lobar location and Aβ status. In summary, our study suggests mainly an amyloid-independent pathway in which vascular burden affects cognitive function via localized neurodegeneration.

KEYWORDS
Alzheimer's disease, amyloid, biomarker, cognition, cortical atrophy, glucose metabolism, neurodegeneration, small vessel disease, vascular, white matter disease, white matter hyperintensities

Highlights

- Alzheimer's disease often co-exists with vascular pathology.
- We studied a unique cohort enriched for high white matter hyperintensities (WMH).
- High WMH related to cognitive impairment of semantic fluency and executive function.
- This relationship was mediated via temporo-parietal atrophy rather than metabolism.
- This relationship was, to lesser extent, serially mediated via amyloid beta and atrophy.

1 | NARRATIVE

1.1 | Contextual background

Cerebral small vessel disease (SVD) is a group of diseases that affects small arteries, venules, and capillaries of the brain.[1] Magnetic resonance imaging (MRI)-based markers of SVD include white matter hyperintensities (WMH) and lacunes of presumed vascular origin, cerebral microbleeds, infarcts, and enlarged perivascular spaces (PVS). While brain microbleeds and infarcts are associated with a higher risk of incident stroke and death, both WMH and PVS burden are associated with an increased risk of stroke, death, and dementia.[2] Notably,

these lesions often co-exist with amyloid beta (Aβ) and tau neurofibrillary tangles, the two pathological hallmarks of Alzheimer's disease (AD).[3,4] In fact, >70% of AD dementia cases at autopsy display vascular co-pathology.[3] Yet, the majority of large cohort studies in AD currently excluded subjects with considerable cerebrovascular burden.[5] As such, the AD research field is recognizing the urgent need to investigate mixed cohorts exhibiting both AD- and SVD-related pathologies.

WMH are the most studied neuroimaging biomarker of SVD.[1] WMH are commonly observed in the aging population and are associated with future cognitive decline.[6–8] However, studies assessing the relationship between WMH and cognition in AD remain conflicted.[9,10] This may be related to the heterogeneity in AD cohorts, disease time course, and the multifactorial etiology of WMH. At a microscopic (pathological) level, WMH of presumed vascular origin are thought to largely reflect demyelination, axonal loss, gliosis, and vasogenic edema in the periventricular regions, and are often linked to arteriolar disease or venous collagenosis of the deep medullary veins.[11,12] At a macroscopic (neuroimaging) level, WMH are often linked to neuronal loss/neurodegeneration detected as glucose hypometabolism on ^{18}F fluorodeoxyglucose (FDG) positron emission tomography (PET)[13,14] or reduced cortical volumes on MRI.[15–17] In fact, cortical atrophy in AD-vulnerable regions has been proposed to *mediate* the effect of WMH on cognition,[18–20] suggesting that WMH lead to cognitive impairment via their effect on neurodegeneration. However, prior cohorts were limited in the extent of WMH burden or did not examine AD pathology as a mediator in the model.

A potential explanation for the mediating role of neurodegeneration in the WMH–cognition relationship may be that WMH co-exist and/or interact with Aβ. That is, WMH may impact neurodegeneration directly as well as via promoting Aβ accumulation which, in turn, may drive downstream neurodegeneration and cognitive impairment.[21] Accordingly, some have argued that small vessel ischemic damage and associated impaired oxygen/glucose delivery may be a starting point of a cascade leading to Aβ aggregation, resulting in further neurodegeneration and cognitive decline, both in humans and animals.[22–25] The Dominantly Inherited Alzheimer Network (DIAN) study further supported an early WMH–Aβ relationship, with regional WMH increases >20 years prior to the symptom onset in individuals with definite preclinical AD.[26]

Yet, similar to the association between WMH and cognition, the reported association between WMH and Aβ remains conflicted.[27] Some observed no relationship[28,29] and others proposed that initial rises in Aβ or tau contribute to WM damage rather than the other way around.[30] Indeed, apart from an SVD-related ischemic origin, WMH may also result from Wallerian-type degeneration or compromised perfusion secondary to Aβ/tau[31,32] contributing to different study findings. It is more likely, however, that AD and vascular pathologies act in a vicious circle of which the starting point remains unclear; for example, hypoperfusion/hypoxia triggers increased protein deposition, in turn promoting inflammatory processes and blood–brain barrier breakdown, and leading to exacerbated vascular damage.[27] Another interesting school of thought proposes that the WMH–Aβ relationship is region dependent. For instance, in a subacute ischemic stroke study, increased Aβ was detected only in the unilateral peri-infarct region, suggesting that ischemic injury may relate to focal impaired Aβ clearance.[33] Additionally, locations of WM injury also matter, as Aβ was observed to be more closely linked to parietal/posterior-situated WMH.[34]

In summary, our understanding of the interrelationship among WMH, Aβ, neurodegeneration, and cognitive impairment remains limited. Notably, such research is particularly lacking in subjects with evidence of significant WMH burden in addition to AD pathology. Importantly, to our knowledge, no studies have yet comprehensively studied the potential mediating roles of Aβ, glucose metabolism, and atrophy in the vascular contributions to cognitive impairment, particularly in subjects with more extreme endophenotypes. To address these limitations, our objectives were twofold: To investigate (1) whether vascular burden, quantified as total or lobar periventricular WMH volume, is associated with cognition; and (2) the potential roles of Aβ, glucose metabolism, and/or cortical atrophy as a mediator in the WMH–cognition relationship, in a WMH-enriched cohort. We hypothesized a relationship between WMH volume and cognitive impairment that is (1) primarily mediated by neurodegeneration and (2) to a lesser extent sequentially mediated by Aβ and neurodegeneration. Key to our approach is the inclusion of cognitively normal elderly and a unique cohort of "real-world" patients capturing a wide spectrum of mild to severe WM disease, Aβ pathology, and cognitive impairment, as well as

RESEARCH IN CONTEXT

1. **Systematic Review**: Neuroimaging studies involving white matter hyperintensity (WMH) burden, amyloid beta (Aβ), neurodegeneration, and cognitive assessments in Alzheimer's disease (AD) were reviewed. Despite the frequent co-existence of cerebrovascular injury and AD, studies investigating mixed populations with significant WMH burden and Aβ are scarce.
2. **Interpretation**: We assessed the relationship between WMH burden and cognition in a mixed cohort spanning low to severe WMH and Aβ pathology. We then assessed whether the WMH–cognition relationship was mediated by Aβ (^{18}F-AV45 positron emission tomography [PET]) and neurodegeneration (cortical thickness or ^{18}F fluorodeoxyglucose PET). We found that increased WMH burden negatively affects cognitive performance, which was mainly mediated via cortical thinning, particularly of the temporal lobe, and to a lesser extent serially mediated via Aβ and cortical thinning of AD signature regions.
3. **Future Directions**: Future studies that include longitudinal measurements of cerebrovascular burden, Aβ, neurodegeneration, and cognition are needed to further establish the directionality of the interplay among these biomarkers.

TABLE 1 Demographics

Variables	Low–moderate WMH (*N* = 60)	Moderate–severe WMH[c] (*N* = 60)
Age (years)	74.01 ± 5.47	76.85 ± 8.01*
Sex male, *N* (%)	25 (42%)	34 (57%)
Education (years)	16.13 ± 2.73	14.25 ± 2.66**
Race and ethnicity, *N* (%)		
Non-Hispanic White	49 (82%)	58 (97%)
Hispanic	5 (8%)	0 (0%)
Non-Hispanic Black	3 (5%)	1 (2%)
Non-Hispanic Asian	1 (2%)	1 (2%)
Other	2 (3%)	0 (0%)
Pulse pressure (mmHg)	61.32 ± 14.35 (*N* = 47)	62.32 ± 16.02 (*N* = 59)
Hypertension,[a] *N* (%)	28 (47%)	35 (58%)
Body mass index	27.65 ± 5.89	27.36 ± 5.19
Smoking history, *N* (%)	32 (53%)	26 (43%)
^{18}F-AV45 $SUVR_{whole\ cereb}$[b]		
Non-PVC	0.98 ± 0.18	1.13 ± 0.23**
PVC	0.75 ± 0.35	1.05 ± 0.46**
Aβ positive, *N* (%)	13 (22%)	29 (48%)
^{18}F-FDG $SUVR_{pons}$[b]		
Non-PVC	1.42 ± 0.13	1.41 ± 0.16 (*N* = 57)
PVC	2.30 ± 0.28	2.26 ± 0.36 (*N* = 57)
Cortical thickness (global, mm)	2.33 ± 0.08	2.26 ± 0.10**
Total WMH (cc)	10.61 ± 12.89	34.15 ± 18.80**
Free water (total in WMH)	0.32 ± 0.05 (*N* = 58)	0.51 ± 0.05** (*N* = 59)
Semantic fluency	20.95 ± 5.57	12.8 ± 5.93**
TMT-A (seconds)	36.30 ± 11.11	57.62 ± 32.81**
TMT-B (seconds)	95.78 ± 49.91	186.31 ± 84.79** (*N* = 59)
BNT	27.67 ± 2.14	23.72 ± 5.66** (*N* = 54)
FAQ	0.5 ± 1.23	6.36 ± 8.07** (*N* = 50)
MMSE	28.88 ± 1.44	27.08 ± 2.46**
MoCA	25.62 ± 2.50	22.42 ± 4.39**

Note: All values are indicated as mean ± standard deviation.
Abbreviations: Aβ, amyloid beta; BNT, Boston Naming Test; FAQ Functional Assessment Questionnaire; MITNEC-C6, C6 project of Medical Imaging Trial Network of Canada; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PVC, partial volume correction; SUVR, standardized uptake value ratio; TMT, Trail Making Test; WMH, white matter hyperintensity.
[a]Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.
[b]Composite ^{18}F-FDG and ^{18}F-AV45 SUVR were based on Landau et al.[73] and Jack et al.[74]
[c]MITNEC-C6 subjects were recruited from stroke-prevention (*N* = 17) and dementia clinics (*N* = 43).
*$p = .03$, **$p < .001$ based on a *t*-test.

the use of optimized segmentation tools to determine WMH volumes and cortical atrophy in these populations.

1.2 | Study design and main results

Our study involved a unique WMH-enriched cohort (*N* = 120 participants) that captured the spectrum of low-to-extensive WMH burden and Aβ pathology (Table 1). Participants covered the spectrum of cognitively normal to early AD dementia. Eighty-one out of 120 subjects showed high confluent periventricular WMH volumes (>10 cm^3[35]). Thirty-five percent were Aβ positive based on a meta–region of interest (meta-ROI) covering frontal, temporal, parietal, and cingulate regions associated with Aβ deposition in AD.[36]

First, we investigated the association between total WMH volume and cognition using regression analyses. We observed that greater WMH volume was associated with poorer cognitive performance, particularly of semantic fluency and executive function (Figure 1). Second,

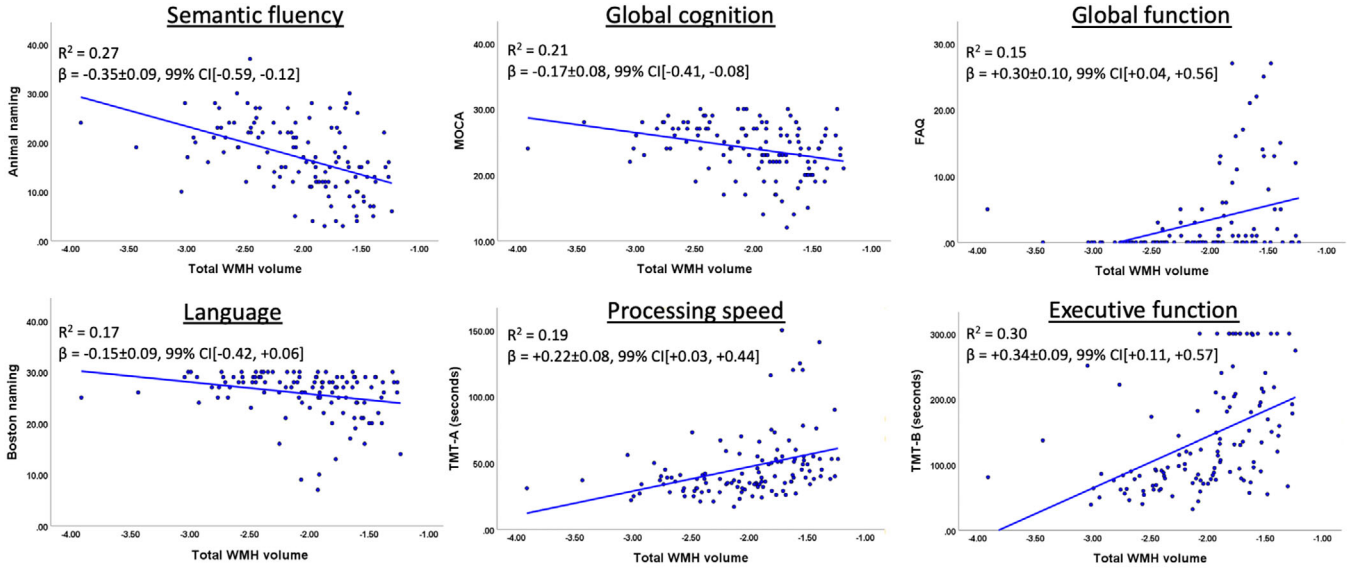

FIGURE 1 Relationship between WMH volumes and cognition. Linear regressions between total WMH volumes and cognitive tests scores across all subjects. Confidence intervals (99% CI) are bootstrapped with 5000 replications and adjusted for age, sex, and education. FAQ, Functional Assessment Questionnaire; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test (part A or B); WMH, white matter hyperintensity

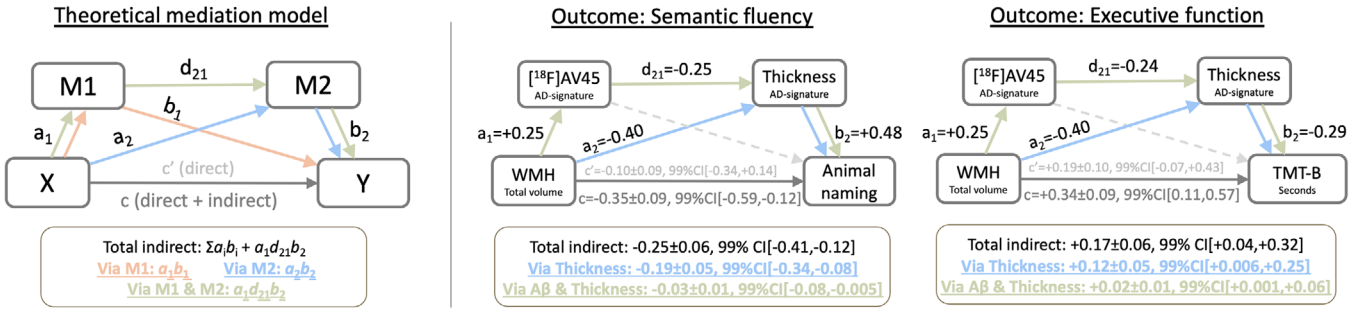

FIGURE 2 Mediation analyses of Aβ and atrophy on the WMH–cognition relationship. Left: Theoretical serial mediation model indicating the independent variable (X), dependent variable (Y), and two mediators (M1, M2). Middle/right: Aβ SUVR and atrophy are mediating the association of total WMH volumes with semantic fluency (middle) and executive function (right). Thick lines are part of a significant pathway, whereas dashed lines represent non-significant pathways. All mediators used an AD signature meta-ROI.[36,37] Values are indicated as mean ± SE and 99% CI are bootstrapped with 5000 replications. Path c represents the total (direct + indirect) effect adjusted only for covariates (age, sex, education), whereas c' represents the direct effect adjusted for covariates and indirect effects. Aβ, amyloid beta; AD, Alzheimer's disease; CI, confidence interval; ROI, region of interest; SE, standard error; SUVR, standardized uptake value ratio; TMT-B, Trail Making Test part-B; WMH, white matter hyperintensity

we investigated whether this association between total WMH volume and cognition was mediated by cortical Aβ and atrophy using mediation analyses. We observed that the WMH–cognition relationship was strongly mediated by atrophy (assessed by cortical thickness in an AD signature meta-ROI consisting of temporo-parietal regions from structural MRI[37]; Figure 2, Figure S1 in supporting information; blue path). In other words, the relationship between WMH and cognition became non-significant when additionally adjusting for cortical atrophy. Besides the mediation through atrophy, we also observed a significant serial mediation through Aβ and atrophy (Figure 2; Figure S1; green path) although this path's effect size was smaller compared to the path through atrophy alone. No interaction effects between WMH and Aβ on atrophy or cognition were detected in our cohort. Taken together, our findings support the idea that the WMH effects on cognitive impairment may be mainly additive to the Aβ pathway, while not being completely independent of it. These results were confirmed by using free water in WMH regions[38,39] as a novel additional (diffusion MRI-based) biomarker of cerebrovascular burden (Figure S2 in supporting information).

While both cortical thinning and ^{18}F-FDG PET are considered metrics of neuronal loss/neurodegeneration (e.g., amyloid/tau/neurodegeneration [A/T/N] framework[40]), we did not find a direct mediating effect of WMH on cognition through glucose metabolism (assessed in an AD-signature meta-ROI consisting of temporo-parietal

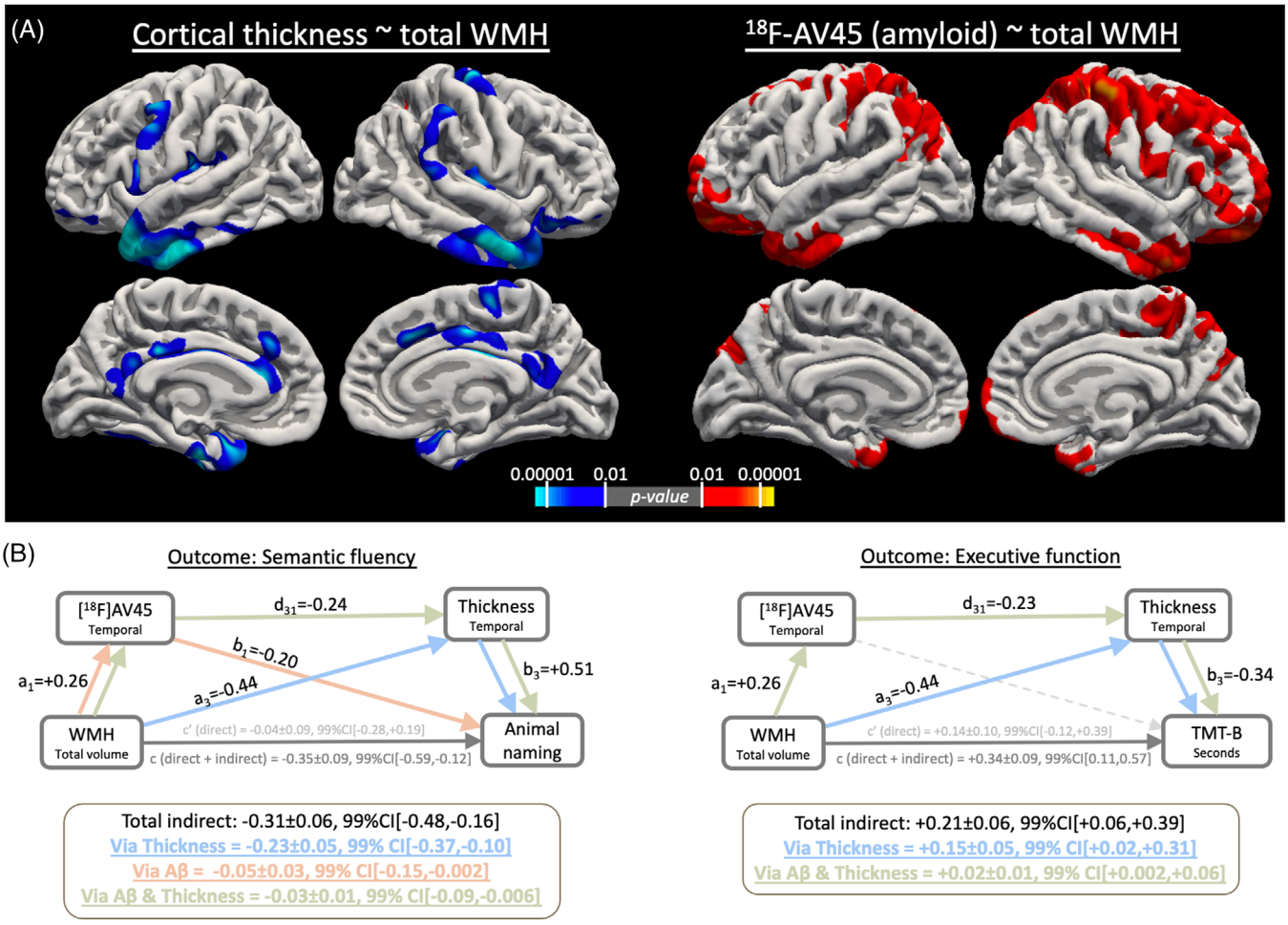

FIGURE 3 Temporal lobe-focused analyses. A, Vertex-wise regression analysis of total WMH volumes with cortical thickness (left) and ^{18}F-AV45 Aβ PET (right) across all subjects. Blue and red represent negative and positive associations respectively. Both modalities showed the strongest association with WMH volumes in the temporal lobe, which was then used as a meta-ROI in subsequent mediation analyses, see (B). Results are displayed at $P < .01$ after Monte Carlo simulations with 5000 iterations and two-tailed cluster-wise correction for multiple comparisons. B, Mediation models showing which paths are significantly mediating the association of WMH volumes with semantic fluency (left) and executive function (right). Thick lines are part of a significant pathway, whereas dashed lines represent non-significant pathways. All mediators used a temporal meta-ROI. Values are indicated as mean ± SE and 99% CI are bootstrapped with 5000 replications. Path c represents the total (direct + indirect) effect adjusted only for covariates, whereas c' represents the direct effect adjusted for covariates and indirect effects. Aβ, amyloid beta; CI, confidence interval; PET, positron emission tomography; ROI, region of interest; SE, standard error; TMT-B, Trail Making Test part-B; WMH, white matter hyperintensity volumes

regions from ^{18}F-FDG PET[36]; Figure S3A in supporting information). This suggests that atrophy rather than hypometabolism in temporo-parietal regions mediates the WMH–cognition relationship.

Last, we conducted a more regional-focused approach. The temporal lobe was selected based on vertex-wise regression analyses showing its relevance in relation to WMH, atrophy, and Aβ in our cohort (Figure 3A), in line with prior work.[19–21] Thus, we performed mediation analysis between WMH and cognition using Aβ and atrophy as mediators evaluated in the temporal lobe. Generally, we observed higher effect sizes of the mediating paths compared to the model based on the AD signature regions (Figure 3B; Figure S4 in supporting information), highlighting a potential important role for the temporal lobe in relation to mixed AD and SVD pathologies.

1.3 | Study conclusions, disease implications, and therapeutic opportunities

1.3.1 | Conclusions and implications

In a unique cohort with a spectrum of low-to-extensive WMH burden and Aβ pathology, we observed that WMH were related to cognitive impairment mainly via pathways that do not involve Aβ accumulation, particularly via atrophy. This suggests that vascular correlates of cognitive impairment are, at least in part, the result of Aβ-independent mechanisms that affect cortical atrophy. This mediating role of atrophy is in line with prior research showing that WMH contributed to atrophy beyond age and AD-related effects, in turn affecting cognition.[15,18–20]

A potential explanation for this mediating role by neurodegeneration in the WMH–cognition relationship may be that WM lesions exert widespread neurodegenerative effects on the gray matter, specifically by damaging WM tracts that subserve cortical regions, subsequently affecting cognition.[41] Our finding was also in line with previously reported lower degrees of AD pathology in the presence of vascular pathology for the same level of cognitive impairment[42] and substantial increases in dementia risk post-stroke.[43] The (anterior) temporal lobe seemed particularly vulnerable to vascular-related atrophy in our WMH-enriched cohort, potentially due to its susceptibility to both AD- and ischemic-related processes[44,45] and WMH crossing its connecting tracts, such as the uncinate fasciculus running between frontal and anterior temporal lobe.[46]

Unlike previous studies, we used PET-based biomarkers of Aβ and glucose metabolism in addition to atrophy as potential mediators in the model. This allowed us to investigate whether the effects of WMH on cognition were indirectly promoted by Aβ, atrophy, and/or glucose metabolism. This resulted in four interesting observations. First, we detected a modest relationship between WMH and cortical Aβ (mostly driven by Aβ-positive subjects in our cohort), highlighting an additional role for Aβ in the WMH–atrophy–cognition relationship. This finding corroborated the idea that Aβ accumulation may partially stem from a vascular etiology where SVD exacerbates AD-related pathology by inducing neuroinflammatory responses and/or reducing the clearance of toxic proteins from the brain.[12,47] This notion may also be supported by our finding that WMH are also related to Aβ deposition within regions not typically associated with the early AD-related Aβ accumulation like the temporal cortex.[48] However, due to the cross-sectional nature of this study, we do not exclude the possibility that WMH are a consequence of Wallerian-type degeneration secondary to AD-related pathology.[31] Nevertheless, our observations on the existing WMH–Aβ relationship, while being supported by some,[6,26,49,50] also differed from others claiming both markers are independent.[28,29] The lack of a clear mechanistic relationship between WMH and Aβ remains puzzling.[23] A second interesting observation of our study was that, while an association between WMH and Aβ may be indicative of an interaction effect on neurodegeneration or cognition, this was not observed in our cohort and is in line with most of the literature.[29,51] Third, our study supported a modest association between Aβ and atrophy; however, the significance of the Aβ–atrophy pathway is less clear. Previous literature remains conflicted on the relationship between Aβ and gray matter volume.[52] Some studies supported a negative association mainly confined to the temporal lobe in predominant symptomatic cohorts[21] while others reported both positive[53] or negative[48,54] associations in cognitively normal or mild impairment. Nevertheless, we also predict that tau pathology could play an important mediating role in this relationship (see section 1.4).[25] A final interesting observation of our study was that, with regard to glucose metabolism in temporo-parietal regions, we did not find a similar mediating effect on the WMH–cognition relationship as with atrophy. Moreover, ^{18}F-FDG PET was only indirectly associated with WMH via global Aβ (and potentially via localized tau, see section 1.4). These findings may suggest that ^{18}F-FDG-based hypometabolism of the temporo-parietal cortex is more closely related to AD than SVD-related processes of neurodegeneration, and supports earlier work that cortical thickness and ^{18}F-FDG PET are not interchangeable measures.[55,56] Future studies applying the A/T/N framework may thus benefit from investigating both atrophy and metabolism as markers of neurodegeneration ("N").[40]

1.3.2 | Therapeutic opportunities

To date, the role of SVD is underrepresented in AD clinical trials. We and others have shown that subjects with elevated WMH burden may represent an at-risk group for increased neurodegeneration. Thus, a key therapeutic or preventative approach may be reducing or slowing down the effects of SVD already from mid-life (for instance through targeting education[57] or vascular risk factors[42]), thus potentially limiting additional neuronal loss and exacerbation of AD pathology later in life.[6] With regard to clinical trials in preclinical or early AD cohorts, our findings advocate for a multi-agent approach as WMH had a significant contribution to neurodegeneration that was independent from Aβ burden. Our results further suggest that WMH may impact cognitive domains independently from Aβ but in a location-dependent manner (Table S1 in supporting information).[58] For example, cognitive correlates of frontal and insular WMH were confined to the Aβ-negative subgroup, while temporo-parietal-cingulate WMH correlated with cognition also in the Aβ-positive subgroup. Differential effects of SVD and AD-related pathologies on cognition may thus be accounted for when evaluating cognitive outcomes as the primary trial endpoint, depending on the population and mechanism being targeted by the therapeutic.

1.4 | Limitations, unanswered questions, and future directions

A limitation of our study is the emphasis on cross-sectional relationships between various imaging signatures and cognition. While our path analysis involved WMH→Aβ, we also tested its opposite direction. Indeed, besides a vascular etiology, AD pathology may arise well before vascular dysfunction (or develop in parallel) and increase WMH burden by accelerating processes that are related to inflammation, oxidative stress, Wallerian degeneration, or cerebral amyloid angiopathy.[32] Nevertheless, both our models resulted in similar conclusions, that is, the indirect effects of Aβ and WMH through each other on atrophy and cognition had lower effect sizes compared to the effect of either Aβ or WMH alone. A valuable future research direction would be to investigate vascular burden at baseline and longitudinally in relation to Aβ accumulation over time in a large preclinical population. This was recently investigated in ADNI data[50] but could be repeated in a community-dwelling cohort (with higher vascular co-pathology) or early-onset AD. Nevertheless, a mechanistic understanding of the causal relationship and thorough understanding of impaired Aβ clearance pathways may likely require animal model studies reflecting different aspects of human SVD such as WMH and peripheral oxidative stress.

A second limitation of our study involves the relatively small sample size ($N = 120$), due in part to the recruitment of a unique cohort of "real-world" patients who demonstrated moderate-to-severe WM disease. Therefore, we set the bootstrapping confidence interval to 99% while also limiting the number of mediation analyses by investigating (1) all subjects combined and (2) using total (rather than lobar) WMH volumes. In addition, our study involved the inclusion of predominantly non-Hispanic White individuals. A recent study by Rizvi et al.[15] observed that WMH were related to AD-typical patterns of neurodegeneration, particularly among non-Hispanic Black individuals. Similarly, a strong association between WMH and Aβ has been observed among Black elderly.[59] Our future work will involve various vascular-related risk factors for AD among diverse ethnic groups.

While we examined a selection of common markers of SVD (WMH volume and free water) and AD (Aβ, glucose metabolism, and cortical thickness in AD-signature regions), additional assays that encompass a broader characterization of SVD/AD will be required to fully understand their potential additive, synergistic, or sequential effects on neurodegeneration and cognitive impairment. One important direction to investigate is the differential effects of various SVD markers (e.g., WMH, enlarged PVS, lacunes, or microbleeds) on cognition in mixed populations, both at the macro- and microstructural (e.g., connectomics) level, which each may reflect different (vascular-related) disease processes/stages.[60] In this regard, high-resolution (7T) MRI may be beneficial to reveal links between AD-related processes and subtle vascular damage on the microscopic level in vivo (e.g., assessed via enlarged PVS or microbleeds). Another useful aspect to study would be the relative contributions of AD and SVD markers on cognition in different diagnostic subgroups (preclinical, prodromal, and AD dementia). Indeed, clear effects of WMH on neurodegeneration in AD dementia groups may seem absent due to inter-subject heterogeneity, lower sample sizes, exclusion of subjects with vascular co-pathology, and/or relative higher contributions of tau pathology.[25] Future work will repeat our mediation analyses in an independent dataset by adding diffusion MRI-based connectivity metrics and tau pathology as mediators.

2 | CONSOLIDATED DESCRIPTION OF METHODS AND RESULTS

The contribution of WMH to cognitive deficits has been thus far poorly understood. Insofar, most large AD/dementia cohort studies excluded patients with a considerable amount of vascular co-pathology as mixed disease. As such, potential contributions of WMH to cognitive impairment are often not well addressed in these "clean" cases of probable AD.[5] In a WMH-enriched cohort (totaling $N = 120$; Table 1), our first step was to investigate WMH volume in relation to different cognitive domains. We observed that greater total WMH volume was associated with poorer performance on the following assessments across all subjects in rank order of effect size: semantic fluency, executive function, global function, processing speed, and global cognition (Figure 1). Further exploratory analyses with regional (lobar) WMH revealed that regional WMH may differentially affect cognition and depend on the Aβ subgroup. Specifically, cognitive correlates of *frontal* and *insular* WMH volumes were significant particularly in Aβ-negative subjects, whereas cognitive correlates of *temporal* and *parietal/cingulate* WMH volumes were more prominent in the Aβ-positive subjects (Table S1).

Based on the significant WMH–cognition relationship, our second step was to investigate the potential mediating roles of Aβ and neurodegeneration within this WMH–cognition relationship. Aβ load was quantified through ^{18}F-AV45 standardized uptake value ratio (SUVR) maps in the global cortical AD signature.[36] Neurodegeneration was quantified through atrophy (cortical thinning) or glucose hypometabolism (reduced ^{18}F-FDG SUVR) in their respective, previously validated AD-signature regions.[36,37] We hypothesized that a serial mediation runs from WMH → Aβ[49,50] → neurodegeneration[21,61] → cognition.[52] Importantly, this model allowed us not only to investigate the indirect effects of WMH volumes on cognition through the hypothesized serial path but also through the predictor and each of the mediators separately while adjusting for the remaining variables in the model. First, using temporo-parietal atrophy as a marker of neurodegeneration, mediation analysis revealed that cortical atrophy alone explained most of the indirect effect between WMH and cognition (i.e., WMH → atrophy → cognition), while the serial mediation through Aβ and atrophy explained a smaller part of the indirect effect (Figure 2). The direct effect of WMH volume on cognition (i.e., after controlling for the mediators and covariates) became non-significant, except for processing speed, for which a significant direct effect remained. Interestingly, while we and others showed that both semantic fluency and executive function are closely linked to WMH,[18] the mediation paths were more profound for semantic fluency. Indeed, semantic fluency is sustained primarily by the (left) temporal lobe, with language processing being a critical component for this task, while executive function is thought to be predominantly frontal-mediated (not being a region-of-focus in the current study based on its limited atrophy in early AD[62]). Exploratory path analyses of WMH with global function and global cognition via Aβ and atrophy are reported in Figure S1. Second, using temporo-parietal glucose hypometabolism as a marker of neurodegeneration, we observed that, in contrast to atrophy, metabolism alone did not mediate the WMH–cognition relationship. Instead, there was a significant single path between WMH and semantic fluency that ran serially via Aβ and hypometabolism (Figure S3). One potential explanation for the lack of a direct WMH–metabolism relationship may be that WMH are more closely related to frontal rather than temporo-parietal hypometabolism[14] (the frontal lobe was not a region of focus in our study).

Mediation analyses were repeated using a temporal meta-ROI, as this region showed the largest effect sizes in the association of WMH with both thickness and Aβ based on vertex-wise regressions (Figure 3A). Generally, we found higher effect sizes of the mediating paths compared to the model based on AD-signature meta-ROIs (Figure 3B; Figure S4), suggesting an important role for the temporal lobe in the vascular–cognition relationship.

To further validate our findings, we performed two sensitivity analyses. First, as Aβ accumulation may start prior to the appearance of WMH, we tested a post hoc mediation model using Aβ as the independent variable and WMH as the mediator (Figure S5 in supporting information). Similar to our main results, the single mediation through atrophy had a higher effect size than the serial mediation through WMH and atrophy, suggesting that Aβ drives atrophy downstream mainly through mechanisms different from WMH (e.g., tau pathology). A second sensitivity analysis was based on the notion that the characterization and measurement of vascular burden are not limited to WMH volume.[60] Therefore, WMH volume was substituted in the model by free water, a novel SVD-related marker of microstructural changes and cognitive impairment derived from advanced tensor modeling of diffusion-weighted MRI data.[38,39] We observed a significant relationship between higher free water in WM lesions and cognitive impairment (Figure S2). Similar to WMH volume, we observed this relationship to be mediated by atrophy and serially mediated by Aβ and atrophy. The main difference was that free water remained significantly associated with all tested cognitive domains even after adjustment for covariates and mediators (except for Montreal Cognitive Assessment [MoCA]); thus, free water within WM lesions may be a more sensitive marker of some cognitive functions compared to WMH volumes.

3 | DETAILED METHODS & RESULTS

3.1 | Methods

3.1.1 | Participants

The study included 120 subjects in total. Sixty subjects were recruited in a multicenter prospective observational study through seven participating sites as part of the C6 project in the Medical Imaging Trial Network of Canada (MITNEC-C6). They were enrolled from stroke-prevention clinics (i.e., transient ischemic attacks or minor subcortical lacunar infarcts) and dementia clinics and presented with moderate-to-severe confluent periventricular WMH burden quantified as Fazekas score > 2 and high volumes (> 10 cm^3, considered to be clinically relevant;[35] median (interquartile range [IQR]): 30.5 (22.1) cm^3). Detailed selection criteria are described in Table S2 in supporting information and in Zukotynski et al.[63] In addition, the study included 60 cognitively normal and mild cognitive impairment (MCI) subjects from the baseline ADNI-2 database with low-to-moderate WMH (median [IQR]: 5.8 [9.3] cm^3). Inclusion criteria for ADNI included age ≥ 60 years, education > 8 years, Mini-Mental State Examination (MMSE) ≥ 20, and WMH volumes > 1000 mm^3. Both cohorts were well matched for vascular risk factors including hypertension, pulse pressure, body mass index, sex, and smoking status. Detailed demographics are reported in Table 1. The institutional review boards at all participating institutions approved this study and all participants provided written informed consent.

3.1.2 | Assessments

A battery of cognitive tests was administered including: processing speed (Trail Making Test part-A [TMT-A], $N = 120$); executive function (assessed as Trail Making Test [i] part-B [TMT-B], [ii] part-B minus part-A [TMT B-A], $N = 119$); semantic fluency (animal naming, $N = 120$); and language (Boston Naming Test [BNT], $N = 120$). Exploratory analyses included global cognition (MoCA, $N = 120$) and global function (Functional Assessment Questionnaire [FAQ], $N = 110$). Individual assessments are described in Table S3 in supporting information.

3.1.3 | Neuroimaging

Each subject underwent a 3T MRI scan, with structural sequences including 3D T1-weighted (T1w) and fluid-attenuated inversion recovery (FLAIR). Subjects also underwent diffusion MRI ($N = 117$) using standardized acquisition protocols across vendor platforms that were compatible with the ADNI-2 diffusion-weighted MRI protocol. Acquisition parameters are described in Table S4 in supporting information and followed a common imaging protocol.[64] Each subject also underwent ^{18}F-AV45 amyloid-PET ($N = 120$) and ^{18}F-FDG PET ($N = 117$). Consistency of PET data between participating sites was maintained by use of the main ADNI-2 PET protocol (see http://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-proceduresmanual.pdf). Last, all imaging data was transferred to a central site for quality check.

ADNI was launched in 2003 as a public–private partnership. The primary goal of ADNI was to test whether MRI, PET, other biological markers, and clinical data can be combined to measure the progression of MCI/AD (see www.adni-info.org).

3.1.4 | MRI processing

Atrophy was quantified as reduced cortical thickness (cortical thinning), extracted based on T1w images using FreeSurfer v6.0. We used a modified FreeSurfer workflow for patients with WMH burden by integrating enhanced skull stripping and lesion masks, to avoid underestimation of the intracranial volume (ICV) and mis-segmentation of the WM.[65] An "AD-signature" thickness meta-ROI was used based on surface-weighted thickness averages of the entorhinal, fusiform, parahippocampal, mid/inferior temporal, and inferior parietal gyri.[37]

To quantify WMH volumes, we used our HyperMapper tool[66] (https://hypermapp3r.readthedocs.io/), a novel Bayesian 3D convolutional neural network (CNN) with a U-Net architecture that automatically segments WMH, provides uncertainty estimates of the segmentation output for quality control, and is robust to changes in acquisition protocols. The CNN was trained using 432 subjects recruited from four multisite imaging studies. Subcortical lacunar infarcts were masked before WMH segmentation.[67] ICV was extracted using our CNN-based "iCVMapper" tool, which was shown to be more robust compared to other state-of-the-art skull-stripping methods.[68] Vascular burden

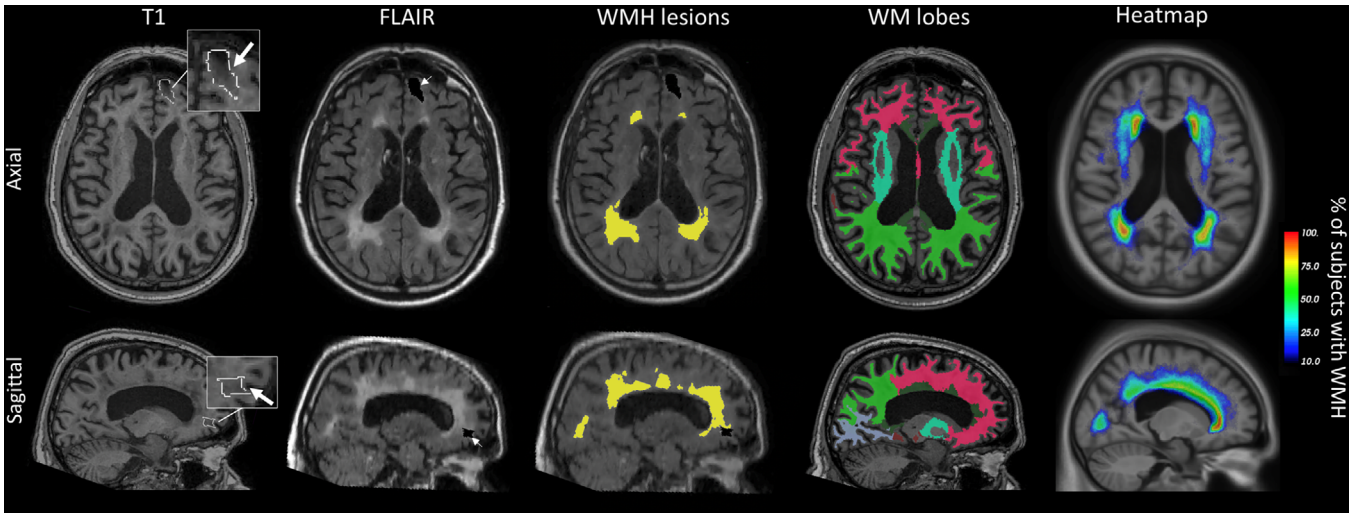

FIGURE 4 Volumetric delineations. Example of brain segmentation for one subject (age range 60 to 70 years, male) and WMH heatmap across subjects (outer right column). Left to right: T1-weighted MRI with delineation of stroke region; FLAIR with the stroke region masked out; FLAIR with WMH delineations in yellow color; WM lobe segmentation (pink: frontal, brown: temporal, light green: parietal, purple: occipital; cyan: insula; dark green: cingulate); WMH volume distribution "heatmap" across the MITNEC-C6 subjects (% of subjects with WMH per voxel) overlayed on the ADNI template. ADNI, Alzheimer's Disease Neuroimaging Initiative; FLAIR, fluid-attenuated inversion recovery; MITNEC-C6, C6 project of Medical Imaging Trial Network of Canada; MRI, magnetic resonance imaging; WMH, white matter hyperintensity

was conceptualized and quantified as WMH normalized by total brain volume (i.e., WMH volume divided by ICV) and log-transformed.

Lobar WMH volumes were determined by intersecting the total WMH mask and each individual lobar WM mask, as delineated in native T1w MRI space based on the Desikan–Killiany–Tourville (DKT) atlas of FreeSurfer. Lobar WM masks included the frontal, parietal, temporal, occipital, insula, and cingulate lobes. Figure 4 shows examples of our structural MRI scans, WMH and lobar delineations, as well as a heatmap of WMH volumes.

Eddy current and motion-corrected diffusion MRI data were fitted to a two-compartment diffusion model in each voxel, separating the free water from the WM tissue compartment.[39] Specifically, a free water map represents the fractional volume (ranging 0 to 1) of freely diffusing extracellular water with a fixed isotropic diffusivity of 3×10^{-3} mm^2/s (the diffusion coefficient of water at body temperature). More details on our free water estimation are reported in Ottoy et al.[69]

3.1.5 | PET image processing

PET images were processed using PetSurfer v6.0.[70] This included motion correction of the individual PET frames to the first frame and averaging to obtain one static frame, co-registration to T1w MRI, smoothing to a common Gaussian kernel of 8 mm across sites,[71] and generating SUVR maps. The ^{18}F-AV45 and ^{18}F-FDG SUVR maps were referenced to the whole cerebellum and the pons, respectively.[36] PVC was applied using the geometric-transfer-matrix method with a point-spread-function of 8 mm. Regional values were extracted based on the DKT atlas in native T1w MRI space. AD-signature meta-ROIs were created for ^{18}F-AV45 and ^{18}F-FDG SUVR based on Jack's mask (volume-weighted average of the lateral/medial frontal, lateral parietal, lateral temporal, and cingulate regions) and the temporo-parietal lobe, respectively.[36] Based on our Aβ-PET pipeline, 22% and 48% of ADNI and MITNEC-C6 subjects, respectively, were considered Aβ positive using a quantitative ^{18}F-AV45 SUVR cut-off of 1.1. This cut-off was derived from Gaussian mixture modelling with two components using non-PVC SUVR in the AD-signature meta-ROI and corresponded to the ADNI cut-off.[36] The PVC-based SUVR values used in our analyses were strongly correlated to non-PVC SUVR (cortical meta-ROI: Pearson $R = 0.96$, $P < .001$) as well as to SUVR based on an alternative reference region, that is, cerebellar gray (cortical meta-ROI: Pearson $R = 0.95$, $P < .001$). The distributions of Aβ SUVR are displayed in Figure S6.

3.1.6 | Statistical analyses

Regional statistics were performed in SPSS v24 (SPSS Inc.) and vertex-wise statistics were performed in FreeSurfer v6.0. All metrics were z-scored to allow for direct comparison between models across predictors and outcome measures. Values were reported as mean ± standard error (SE) unless otherwise stated. A two-tailed *t*-test for continuous variables and chi-square for categorical variables were used to check for significant group differences in the demographics. Linear regressions were used to assess the associations between total/lobar WMH volume (independent variable) and each of the cognitive scores (dependent variable), adjusted for age, sex, and education. Bias-corrected bootstrapping with 5000 replications and a 99% confidence interval (CI) was applied to account for heteroscedasticity and

multiple comparisons. Bias-corrected bootstrapping does not make any assumptions about normality in the sampling distribution and better controls type I errors.

For mediation analyses, the PROCESS macro v3.5 in SPSS was applied. Bias-corrected bootstrapping with 5000 replications and 99% CI was performed for estimation of (in)direct and total effects. We hypothesized that a serial mediation runs from "total WMH → Aβ → atrophy → cognition."[21,49,50,52] Glucose metabolism was tested as an additional mediator within the path analyses.[52,61,72] Imaging mediators were evaluated within AD-signature regions as described above. Age, education, and sex were used as covariates regressed on the mediators and outcome simultaneously. Note that we also tested Aβ SUVR as a potential moderator in each of the paths within "WMH → atrophy → cognition" but it was found to be non-significant.

To test the regional specificity of the mediation analyses, we performed additional path analysis whereby AD-signature meta-ROIs of the imaging markers were substituted by a more focal region. This region was selected through two separate whole-brain vertex-wise linear regressions of total WMH volume with (1) cortical thickness and (2) Aβ SUVR (with PVC), to identify one WMH-signature region in relation to both atrophy and Aβ. These vertex-wise regressions were adjusted for age, sex, education, and regression (1) was additionally adjusted for global Aβ SUVR. Multiple comparisons correction was based on Monte-Carlo simulations with 5000 iterations, which implemented a two-tailed cluster-forming *P*-value of .01.

3.2 | Results

3.2.1 | Associations between WMH and cognition

Greater total WMH volume was associated with poorer performance on the following assessments across all subjects in rank order of effect size: semantic fluency ($\beta = -0.35 \pm 0.09$, $P < .001$), executive function (TMT-B: $\beta = +0.34 \pm 0.09$, $P = .001$; TMT B-A: $\beta = +0.32 \pm 0.10$, $P < .001$), global function ($\beta = +0.30 \pm 0.10$, $P = .005$), processing speed ($\beta = +0.22 \pm 0.08$, $P = .011$), and global cognition ($\beta = -0.17 \pm 0.08$, $P = .040$; Figure 1). The relationship between WMH and processing speed remained significant after outlier removal ($\beta = +0.12 \pm 0.06$, $P = .030$). No significant association was found for language (BNT; $P = .13$).

Cognitive correlates of *frontal* and *insular* WMH volumes were significant only in Aβ-negative subjects, whereas cognitive correlates of *temporal* and *parietal/cingulate* WMH volumes were more prominent in the Aβ-positive subjects (Table S1).

3.2.2 | Aβ and cortical thickness mediate the effects of WMH on cognition

AD-signature meta-ROIs

In the path analysis for semantic fluency, we found significant indirect effects of total WMH volume through (1) "WMH → atrophy → fluency" and (2) "WMH → Aβ → atrophy → fluency" (total of 71% mediation, $\beta = -0.25 \pm 0.06$, 99% CI [−0.41, −0.12]; Figure 2). Path (1) via atrophy explained most of the indirect effects ($\beta = -0.19 \pm 0.05$, 99% CI [−0.34, −0.08]). The direct effect of WMH volume on semantic fluency (i.e., after controlling for the mediators and covariates) became non-significant. When using metabolism instead of atrophy in the model, the indirect path via Aβ (i.e., "WMH → Aβ → hypometabolism → cognition") was significant when semantic fluency was the cognitive outcome, but the overall mediation was not (Figure S3). There was no significant serial path between metabolism and atrophy when entered together in the model (Figure S3B).

A similar path result was found for executive function (i.e., with cortical atrophy explaining most of the indirect effect). The total indirect effects via atrophy and Aβ corresponded to 50% ($\beta = +0.17 \pm 0.06$, 99% CI [+0.04, +0.32]; Figure 2). Exploratory path analyses of global function and global cognition through atrophy and Aβ are reported in Figure S1. The direct effect of WMH volume on these cognitive metrics similarly became non-significant due to mediation. No significant mediating effects were detected for processing speed ($\beta = +0.10 \pm 0.06$, 99% CI [−0.04, +0.27]).

We did not detect a moderating effect of Aβ status in either of the paths within the "WMH → atrophy → cognition" relationship. Conversely, this serial mediation remained significant within the Aβ subgroups. Note that the WMH–atrophy relationship was mainly driven by Aβ-negative subjects in our cohort, while the WMH–Aβ relationship was mainly driven by Aβ-positive subjects (Figure S7 in supporting information). This may suggest that an interplay between WMH and atrophy is already present before significant AD-related neurodegeneration has occurred, while the interplay of WMH and Aβ may be more profound in the presence of Aβ.

Temporal meta-ROI

Vertex-wise regression analyses showed that total WMH volume was positively associated with Aβ load and atrophy, particularly in lateral temporal regions (Figure 3A). As such, we performed further path analysis on cognition using a temporal meta-ROI for all mediators. The temporal meta-ROI consisted of the inferior, superior, and middle temporal lobe, the temporal pole, and the entorhinal cortex. When using a temporal meta-ROI for each of the mediators, we found higher effect sizes of the mediating paths compared to the model based on AD-signature meta-ROIs (Figure 3B). The total indirect effects via atrophy and Aβ corresponded to 89% for semantic fluency ($\beta = -0.31 \pm 0.06$, 99% CI [−0.48, −0.16]), while the total indirect effects via atrophy and Aβ corresponded to 62% for executive function ($\beta = +0.21 \pm 0.06$, 99% CI [+0.06, +0.39]). Exploratory path analyses of global function and global cognition are reported in Figure S4. Similar to the AD-signature regional results, the path "WMH → temporal atrophy → cognition" explained most of the indirect effect.

3.2.3 | Sensitivity analyses

Post hoc mediation model

A post hoc mediation model incorporated Aβ as the predictor and WMH as the mediator: "Aβ → WMH → atrophy → cognition." Rather

than investigating the causal relationships between Aβ and WMH, this model was applied to support our previous findings that the indirect effects of Aβ and WMH through each other on atrophy and cognition have a lower effect size compared to the effect of Aβ or WMH alone. Similar significant paths (Figure S5) were found as described above for each of the cognitive domains (see section 3.2.2). Importantly, the indirect path "Aβ → atrophy → cognition" had a larger effect size than its effect through WMH ("Aβ → WMH → atrophy → cognition"). This paralleled the results described above (see section 3.2.2) where the indirect path "WMH → atrophy → cognition" also had a larger effect size than its effect through Aβ ("WMH → Aβ → atrophy → cognition"). This may suggest that WMH and Aβ exert more additive and fewer sequential effects on atrophy (i.e., potentially driving further atrophy through different underlying mechanisms). Furthermore, the Aβ-independent effect of WMH on atrophy was greater than the WMH-independent effect of Aβ on atrophy in both the initial and post hoc models, which may suggest that the effect of WMH on atrophy exceeds the effect of Aβ on atrophy in a mixed cohort.

Further sensitivity analyses assessing the robustness of our variables yielded similar results using (1) non-PVC data, (2) the cerebellar gray cortex as the reference region for ^{18}F-AV45 SUVR, and (3) TMT B-A instead of TMT-B as the metric for executive function (Figure S8 in supporting information).

Free water as an alternative metric of vascular burden

Free water in the WMH regions was strongly correlated to WMH volume ($R = 0.74$, $P < .001$). Substituting WMH volume with free water in the mediation analyses led to similar results, that is, with cortical atrophy explaining most of the indirect effect (Figure S2). However, indirect effects were generally lower compared to those for WMH volume. Specifically, the total indirect effects via atrophy and Aβ corresponded to 39% for semantic fluency ($\beta = -0.21 \pm 0.06$, 95% CI [−0.33, −0.10]), while the total indirect effects corresponded to 28% for executive function ($\beta = +0.13 \pm 0.06$, 95% CI [+0.02, +0.26]). The direct effect of free water on cognition remained significant (except for MoCA; data not shown).

ACKNOWLEDGMENTS

We would like to express our deepest gratitude toward all the participants and caregivers for their support and participation in this study. We are grateful for the support of the Medical Imaging Trial Network of Canada (MITNEC; https://clinicaltrials.gov/ct2/show/NCT02330510?term=mitnec+sandra+black&rank=1) Grant #NCT02330510, and to Eli Lilly & Company for providing the 18F-florbetapir ligand. In addition, part of the data collection and sharing for this project was funded by ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research provided some funding to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This study was funded by the Canadian Institute for Health Research (CIHR) MOP Grant #13129, CIHR Foundation grant #159910, the L.C Campbell Foundation, and the SEB Centre for Brain Resilience and Recovery. JO is supported by the Alzheimer's Association fellowship (AARF-21-848556). MG is supported by Gerald Heffernan foundation, the Donald Stuss Young Investigator innovation award, and CIHR Grant #PJT178059.

CONFLICTS OF INTEREST

Dr. Black has received in kind support for PET ligands from GE Healthcare and Eli Lilly Avid. She has received personal fees for educational talks from Biogen and for advisory committees from Biogen and Hoffmann La Roche. She is a Principal Investigator or Sub Investigator for clinical trials with funding to the institution only for the following companies: Hoffmann La Roche, Biogen Eisai, Eli Lilly, UCB Biopharma SRL, Novo Nordisk, and Alector Inc. Dr. Tardif reports research grants from Amarin, AstraZeneca, Ceapro, DalCor Pharmaceuticals, Esperion, Ionis, Novartis, Pfizer, RegenXBio, and Sanofi; honoraria from AstraZeneca, DalCor Pharmaceuticals, HLS Pharmaceuticals, and Pendopharm; minor equity interest from DalCor Pharmaceuticals; and authorship of patents on pharmacogenomics-guided CETP inhibition, use of colchicine after myocardial infarction, and use of colchicine for coronavirus infection (Dr. Tardif waived his rights in the colchicine patents). Dr. Bocti reports an investment in IMEKA. Dr. Noseworthy is the CEO/director and cofounder of TBIfinder Inc. Dr. Kuo is an employee of Invicro. He is a consultant and/or speaker for Amgen, Bayer, Chimerix, Eisai, Fusion Pharma, General Electric Healthcare, Invicro, Novartis, and UroToday. He is a recipient of research grants from Blue Earth Diagnostics, and General Electric Healthcare. Dr. Strother is a shareholder and senior scientific consultant for ADMdx, Inc., which receives NIH funding, and this work was partially supported by research grants from Canadian Institutes of Health Research (CIHR), and the Ontario Brain Institute in Canada. Dr. Smith consulted for Eli Lilly and for the Data Safety Monitoring Board for the U.S. NIH. Dr. Borrie is the Medical Director for the Aging Brain and Memory Clinic, an investigator with the Cognitive Clinical Research Group (CCRG), Past President of the Consortium for Canadian Centres for Clinical Cognitive Research (C5R). He is the platform lead

for the Comprehensive Assessment of Neurodegeneration and Aging (COMPASS-ND) observational study of the Canadian Collaboration on Neurodegeneration in Aging (CCNA). Since 1995 the CCRG has been a leading Canadian research site conducting randomized controlled trials of new potential treatments for Subjective Cognitive Decline, Mild Cognitive Impairment and Alzheimer's Disease. Author disclosures are available in the supporting information.

AUTHOR CONTRIBUTIONS

Julie Ottoy, Sandra E. Black and Maged Goubran designed the study and experiments. Julie Ottoy and Maged Goubran wrote the manuscript. Julie Ottoy analyzed and interpreted the data with input from Maged Goubran and Sandra E. Black. Miracle Ozzoude, Katherine Zukotynski, Hugo Cogo-Moreira, Walter Swardfager, and Jennifer S. Rabin revised the manuscript, and participated in experiment design, data analysis, and interpretation. Min Su Kang, Phillip H. Kuo, Sabrina Adamo, Vincent Gaudet, Christopher Scott, Joel Ramirez, Aparna Bhan, Parisa Mojiri, and Benjamin Lam contributed to data generation and manuscript revision. Alex Kiss, Stephen Strother, Christian Bocti, Michael Borrie, Howard Chertkow, Richard Frayne, Robin Hsiung, Robert Jr. Laforce, Michael D. Noseworthy, Frank S. Prato, Demetrios J. Sahlas, Eric E. Smith, Vesna Sossi, Alexander Thiel, Jean-Paul Soucy, and Jean-Claude Tardif participated in study concept and design as site leaders and revised the manuscript. Maged Goubran and Sandra E. Black supervised all aspects of this work.

REFERENCES

1. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822-838. https://doi.org/10.1016/S1474-4422(13)70124-8
2. Debette S, Schilling S, Duperron M-G, Larsson SC, Markus HS. Clinical Significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:81-94. https://doi.org/10.1001/jamaneurol.2018.3122
3. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*. 2013;136:2697-2706. https://doi.org/10.1093/brain/awt188
4. McAleese KE, Firbank M, Dey M, et al. Cortical tau load is associated with white matter hyperintensities. *Acta Neuropathol Commun*. 2015;3:60. https://doi.org/10.1186/s40478-015-0240-0
5. Ramirez J, McNeely AA, Scott CJM, Masellis M, Black SE. White matter hyperintensity burden in elderly cohort studies: the Sunnybrook dementia study, Alzheimer's disease neuroimaging initiative, and three-city study. *Alzheimers Dement*. 2016;12:203-210. https://doi.org/10.1016/j.jalz.2015.06.1886
6. Habes M, Pomponio R, Shou H, et al. The brain chart of aging: machine-learning analytics reveals links between brain aging, white matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans. *Alzheimers Dement*. 2020;17:89-102. https://doi.org/10.1002/alz.12178
7. Bangen KJ, Preis SR, Delano-Wood L, et al. Baseline white matter hyperintensities and hippocampal volume are associated with conversion from normal cognition to mild cognitive impairment in the Framingham offspring study. *Alzheimer Dis Assoc Disord*. 2018;32:50-56. https://doi.org/10.1097/WAD.0000000000000215
8. Brickman AM, Honig LS, Scarmeas N, et al. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Arch Neurol*. 2008;65:1202-1208. https://doi.org/10.1001/archneur.65.9.1202
9. van den Berg E, Geerlings MI, Biessels GJ, Nederkoorn PJ, Kloppenborg RP. White matter hyperintensities and cognition in mild cognitive impairment and Alzheimer's disease: a domain-specific meta-analysis. *J Alzheimers Dis*. 2018;63:515-527. https://doi.org/10.3233/JAD-170573
10. Claus JJ, Coenen M, Staekenborg SS, et al. Cerebral white matter lesions have low impact on cognitive function in a large elderly memory clinic population. *J Alzheimers Dis*. 2018;63:1129-1139. https://doi.org/10.3233/JAD-171111
11. Keith J, Gao F-Q, Noor R, et al. Collagenosis of the deep medullary veins: an underrecognized pathologic correlate of white matter hyperintensities and periventricular infarction? *J Neuropathol Exp Neurol*. 2017;76:299-312. https://doi.org/10.1093/jnen/nlx009
12. Black S, Gao F, Bilbao J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke*. 2009;40:S48-52. https://doi.org/10.1161/STROKEAHA.108.537704
13. Gaubert M, Lange C, Garnier-Crussard A, et al. Topographic patterns of white matter hyperintensities are associated with multimodal neuroimaging biomarkers of Alzheimer's disease. *Alzheimers Res Ther*. 2021;13:29. https://doi.org/10.1186/s13195-020-00759-3
14. Haight TJ, Landau SM, Carmichael O, et al. Dissociable effects of Alzheimer disease and white matter hyperintensities on brain metabolism. *JAMA Neurol*. 2013;70:1039-1045. https://doi.org/10.1001/jamaneurol.2013.1878
15. Rizvi B, Lao PJ, Chesebro AG, et al. Association of regional white matter hyperintensities with longitudinal Alzheimer-like pattern of neurodegeneration in older adults. *JAMA Network Open*. 2021;4:e2125166. https://doi.org/10.1001/jamanetworkopen.2021.25166
16. Schmidt R, Ropele S, Enzinger C, et al. White matter lesion progression, brain atrophy, and cognitive decline: the Austrian stroke prevention study. *Ann Neurol*. 2005;58:610-616. https://doi.org/10.1002/ana.20630
17. Kim SJ, Lee DK, Jang YK, et al. The effects of longitudinal white matter hyperintensity change on cognitive decline and cortical thinning over three years. *J Clin Med*. 2020;9:1-12. https://doi.org/10.3390/jcm9082663
18. Zi W, Duan D, Zheng J. Cognitive impairments associated with periventricular white matter hyperintensities are mediated by cortical atrophy. *Acta Neurol Scand*. 2014;130:178-187. https://doi.org/10.1111/ane.12262
19. Rizvi B, Narkhede A, Last BS, et al. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. *Neurobiol Aging*. 2018;64:25-32. https://doi.org/10.1016/j.neurobiolaging.2017.12.006
20. Swardfager W, Cogo-Moreira H, Masellis M, et al. The effect of white matter hyperintensities on verbal memory: mediation by temporal lobe atrophy. *Neurology*. 2018;90:e673-82. https://doi.org/10.1212/WNL.0000000000004983
21. d'Oleire Uquillas F, Jacobs HIL, Hanseeuw B, et al. Interactive versus additive relationships between regional cortical thinning and amyloid burden in predicting clinical decline in mild AD and MCI individuals. *Neuroimage Clin*. 2018;17:388-396. https://doi.org/10.1016/j.nicl.2017.10.034
22. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun*. 2016;7:11934. https://doi.org/10.1038/ncomms11934
23. Scheffer S, Hermkens DMA, van der Weerd L, de Vries HE, Daemen MJAP. Vascular hypothesis of Alzheimer disease. *Arterioscler Thromb Vasc Biol*. 2021;41:1265-1283. https://doi.org/10.1161/ATVBAHA.120.311911
24. Sweeney MD, Kisler K, Montagne A, Toga AW, Zlokovic BV. The role of brain vasculature in neurodegenerative disorders. *Nat*

Neurosci. 2018;21:1318-1331. https://doi.org/10.1038/s41593-018-0234-x
25. Laing KK, Simoes S, Baena-Caldas GP, et al. Cerebrovascular disease promotes tau pathology in Alzheimer's disease. *Brain Commun*. 2020;2:fcaa132. https://doi.org/10.1093/braincomms/fcaa132
26. Lee S, Viqar F, Zimmerman ME, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network: white matter hyperintensities in familial AD. *Ann Neurol*. 2016;79:929-939. https://doi.org/10.1002/ana.24647
27. Kim HW, Hong J, Jeon JC. Cerebral small vessel disease and Alzheimer's disease: a review. *Front Neurol*. 2020;11:927. https://doi.org/10.3389/fneur.2020.00927
28. Roseborough A, Ramirez J, Black SE, Edwards JD. Associations between amyloid β and white matter hyperintensities: a systematic review. *Alzheimers Dement*. 2017;13:1154-1167. https://doi.org/10.1016/j.jalz.2017.01.026
29. Vemuri P, Lesnick TG, Przybelski SA, et al. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain*. 2015;138:761-771. https://doi.org/10.1093/brain/awu393
30. Dadar M, Camicioli R, Duchesne S, Collins DL. The temporal relationships between white matter hyperintensities, neurodegeneration, amyloid beta, and cognition. *Alzheimers Dement*. 2020;12:e12091. https://doi.org/10.1002/dad2.12091
31. McAleese KE, Walker L, Graham S, et al. Parietal white matter lesions in Alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathol*. 2017;134:459-473. https://doi.org/10.1007/s00401-017-1738-2
32. Gurol ME, Viswanathan A, Gidicsin C, et al. Cerebral amyloid angiopathy burden associated with leukoaraiosis: a positron emission tomography/magnetic resonance imaging study. *Ann Neurol*. 2013;73:529-536. https://doi.org/10.1002/ana.23830
33. Ly JV, Rowe CC, Villemagne VL, et al. Subacute ischemic stroke is associated with focal ^{11}C PiB positron emission tomography retention but not with global neocortical Aβ deposition. *Stroke*. 2012;43:1341-1346. https://doi.org/10.1161/STROKEAHA.111.636266
34. Weaver NA, Doeven T, Barkhof F, et al. Cerebral amyloid burden is associated with white matter hyperintensity location in specific posterior white matter regions. *Neurobiol Aging*. 2019;84:225-234. https://doi.org/10.1016/j.neurobiolaging.2019.08.001
35. DeCarli C, Murphy DGM, Tranh M, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism of glucose in 51 healthy adults. *Neurology*. 1995;45:2077-2084. https://doi.org/10.1212/WNL.45.11.2077
36. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol*. 2012;72:578-586. https://doi.org/10.1002/ana.23650
37. Schwarz CG, Gunter JL, Wiste HJ, et al. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. *Neuroimage Clin*. 2016;11:802-812. https://doi.org/10.1016/j.nicl.2016.05.017
38. Bergamino M, Walsh RR, Stokes AM. Free-water diffusion tensor imaging improves the accuracy and sensitivity of white matter analysis in Alzheimer's disease. *Sci Rep*. 2021;11:6990. https://doi.org/10.1038/s41598-021-86505-7
39. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. *Magn Reson Med*. 2009;62:717-730. https://doi.org/10.1002/mrm.22055
40. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14:535-562. https://doi.org/10.1016/j.jalz.2018.02.018
41. Dey AK, Stamenova V, Turner G, Black SE, Levine B. Pathoconnectomics of cognitive impairment in small vessel disease: a systematic review. *Alzheimers Dement*. 2016;12:831-845. https://doi.org/10.1016/j.jalz.2016.01.007
42. Bangen KJ, Nation DA, Delano-Wood L, et al. Aggregate effects of vascular risk factors on cerebrovascular changes in autopsy-confirmed Alzheimer's disease. *Alzheimers Dement*. 2015;11:394-403. https://doi.org/10.1016/j.jalz.2013.12.025
43. Ivan CS, Seshadri S, Beiser A, et al. Dementia after stroke. *Stroke*. 2004;35:1264-1268. https://doi.org/10.1161/01.STR.0000127810.92616.78
44. Deramecourt V, Slade JY, Oakley AE, et al. Staging and natural history of cerebrovascular pathology in dementia. *Neurology*. 2012;78:1043-1050. https://doi.org/10.1212/WNL.0b013e31824e8e7f
45. Kirschen GW, Kéry R, Ge S. The hippocampal neuro-glio-vascular network: metabolic vulnerability and potential neurogenic regeneration in disease. *Brain Plast*. 2018;3:129-144. https://doi.org/10.3233/BPL-170055
46. Rizvi B, Lao PJ, Colón J, et al. Tract-defined regional white matter hyperintensities and memory. *NeuroImage Clin*. 2020;25:102143. https://doi.org/10.1016/j.nicl.2019.102143
47. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4:147ra111. https://doi.org/10.1126/scitranslmed.3003748
48. Sepulcre J, Schultz AP, Sabuncu M, et al. In vivo tau, amyloid, and gray matter profiles in the aging brain. *J Neurosci*. 2016;36:7364-7374. https://doi.org/10.1523/JNEUROSCI.0639-16.2016
49. Grimmer T, Faust M, Auer F, et al. White matter hyperintensities predict amyloid increase in Alzheimer's disease. *Neurobiol Aging*. 2012;33:2766-2773. https://doi.org/10.1016/j.neurobiolaging.2012.01.016
50. Moscoso A, Rey-Bretal D, Silva-Rodríguez J, et al. White matter hyperintensities are associated with subthreshold amyloid accumulation. *NeuroImage*. 2020;218:116944. https://doi.org/10.1016/j.neuroimage.2020.116944
51. Han JW, Maillard P, Harvey D, et al. Association of vascular brain injury, neurodegeneration, amyloid, and cognitive trajectory. *Neurology*. 2020;95:e2622-34. https://doi.org/10.1212/WNL.0000000000010531
52. Fjell AM, Walhovd KB. Neuroimaging results impose new views on Alzheimer's disease—the role of amyloid revised. *Mol Neurobiol*. 2012;45:153-172. https://doi.org/10.1007/s12035-011-8228-7
53. Parker TD, Cash DM, Lane CA, et al. Amyloid β influences the relationship between cortical thickness and vascular load. *Alzheimers Dement (Amst)*. 2020;12(1):e12022. https://doi.org/10.1002/dad2.12022
54. Villeneuve S, Reed BR, Wirth M, et al. Cortical thickness mediates the effect of amyloid on episodic memory. *Neurology*. 2014;82:761-767. https://doi.org/10.1212/WNL.0000000000000170
55. Strom A, Iaccarino L, Edwards L, et al. Cortical hypometabolism reflects local atrophy and tau pathology in symptomatic Alzheimer's disease. *Brain* 2022;145(2):713-728. https://doi.org/10.1093/brain/awab294
56. Ottoy J, Niemantsverdriet E, Verhaeghe J, et al. Association of short-term cognitive decline and MCI-to-AD dementia conversion with CSF, MRI, amyloid- and 18F-FDG-PET imaging. *Neuroimage Clin*. 2019;22:101771. https://doi.org/10.1016/j.nicl.2019.101771
57. Hamilton OKL, Backhouse EV, Janssen E, et al. Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis. *Alzheimers Dement*. 2021;17:665-685. https://doi.org/10.1002/alz.12221
58. Garnier-Crussard A, Bougacha S, Wirth M, et al. White matter hyperintensities across the adult lifespan: relation to age, Aβ load, and cognition. *Alzheimer's Res Ther*. 2020;12:127. https://doi.org/10.1186/s13195-020-00669-4
59. Walker KA, Silverstein N, Zhou Y, et al. Brain white matter structure and amyloid deposition in black and white older adults: the ARIC-PET

study. *J Am Heart Assoc*. 2021;10:e022087. https://doi.org/10.1161/JAHA.121.022087
60. Vemuri P, Graff-Radford J, Lesnick TG, et al. White matter abnormalities are key components of cerebrovascular disease impacting cognitive decline. *Brain Commun*. 2021;3:fcab076. https://doi.org/10.1093/braincomms/fcab076
61. Förster S, Grimmer T, Miederer I, et al. Regional expansion of hypometabolism in Alzheimer's disease follows amyloid deposition with temporal delay. *Biol Psychiatry*. 2012;71:792-797. https://doi.org/10.1016/j.biopsych.2011.04.023
62. Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. *Proc Natl Acad Sci U S A*. 2002;99:4703-4707. https://doi.org/10.1073/pnas.052587399
63. Zukotynski K, Gaudet V, Kuo PH, et al. The use of random forests to classify amyloid brain PET. *Clin Nucl Med*. 2019;44:784-788. https://doi.org/10.1097/RLU.0000000000002747
64. Duchesne S, Chouinard I, Potvin O, et al. The Canadian dementia imaging protocol: harmonizing national cohorts. *J Magn Reson Imaging*. 2019;49:456-465. https://doi.org/10.1002/jmri.26197
65. Ozzoude M, Ramirez J, Raamana PR, et al. Cortical thickness estimation in individuals with cerebral small vessel disease, focal atrophy, and chronic stroke lesions. *Front Neurosci*. 2020;14. https://doi.org/10.3389/fnins.2020.598868
66. Mojiri Forooshani P, Biparva M, Ntiri EE, et al. Deep Bayesian networks for uncertainty estimation and adversarial resistance of white matter hyperintensity segmentation. *Hum Brain Mapp*. 2022;43:2089-2108. https://doi.org/10.1002/hbm.25784
67. Ramirez J, Gibson E, Quddus A, et al. Lesion explorer: a comprehensive segmentation and parcellation package to obtain regional volumetrics for subcortical hyperintensities and intracranial tissue. *NeuroImage*. 2011;54:963-973. https://doi.org/10.1016/j.neuroimage.2010.09.013
68. Ntiri EE, Holmes MF, Forooshani PM, et al. Improved segmentation of the intracranial and ventricular volumes in populations with cerebrovascular lesions and atrophy using 3D CNNs. *Neuroinform* 2021;19(4):597-618. https://doi.org/10.1007/s12021-021-09510-1
69. Ottoy J, Ozzoude M, Zukotynski K, et al. Lower Aβ-PET signal in white matter lesions relates to higher extracellular free water in mixed small vessel disease and Alzheimer's pathology. Preprint BioRxiv 2021. https://doi.org/10.1101/2021.12.17.473211
70. Greve DN, Svarer C, Fisher PM, et al. Cortical surface-based analysis reduces bias and variance in kinetic modeling of brain PET data. *Neuroimage*. 2014;92:225-236. https://doi.org/10.1016/j.neuroimage.2013.12.021
71. Joshi A, Koeppe RA, Fessler JA. Reducing between scanner differences in multi-center PET studies. *NeuroImage*. 2009;46:154-159. https://doi.org/10.1016/j.neuroimage.2009.01.057
72. Ou Y-N, Xu W, Li J-Q, et al. FDG-PET as an independent biomarker for Alzheimer's biological diagnosis: a longitudinal study. *Alzheimer's Res Ther*. 2019;11:57. https://doi.org/10.1186/s13195-019-0512-1
73. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2011;32:1207-1218. https://doi.org/10.1016/j.neurobiolaging.2009.07.002
74. Jack CR, Lowe VJ, Senjem ML, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain*. 2008;131:665-680. https://doi.org/10.1093/brain/awm336

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ottoy J, Ozzoude M, Zukotynski K, et al. Vascular burden and cognition: Mediating roles of neurodegeneration and amyloid PET. *Alzheimer's Dement*. 2022;1-15. https://doi.org/10.1002/alz.12750