APOE-ε4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia

Saira Saeed Mirza, Saeed U, Knight J, Ramirez J, Stuss DT, Keith J, Nestor SM, Yu D, Swardfager W, Rogaeva E, St. George Hyslop P, Black SE*, Masellis M*, and Alzheimer's Disease Neuroimaging Initiative

****Contributed equally as senior co-authors***

Division of Neurology (Dept. of Medicine), Hurvitz Brain Sciences Research Program and LC Campbell Cognitive Neurology Research Unit, Sunnybrook Health Sciences Centre, Dept. of Psychology (Faculty of Arts and Sciences), Division of Geriatric Psychiatry (Dept. of Medicine), Dept. of Psychiatry, and Dept. of Anatomic Pathology, University of Toronto, Toronto, Canada and Data Science Institute and Medical School, Lancaster University, Lancaster, UK

BACKGROUND

- White matter hyperintensities (WMH) are risk factors for cognitive impairment and Alzheimer's disease (AD), and are prevalent in dementia with Lewy bodies (DLB).
- *APOE*-ε4 is the strongest known genetic risk factor for sporadic AD, and is a risk factor for DLB, cerebral amyloid angiopathy (CAA) and cerebral small vessel disease (SVD).

OBJECTIVE AND HYPOTHESIS

Objective: To determine if *APOE*-ε4 influences the association between WMH and cognitive impairment in AD and DLB.

Hypotheses: (i) higher WMH burden would be more strongly associated with worse cognition in *APOE*-ε4 carriers than non-carriers (allele dosage dependent), (ii) this association would be irrespective of the clinical diagnosis, and (iii) if indeed WMH burden is associated with worse cognition in *APOE*-ε4 carriers, WMH in carriers might be a result of a more toxic vascular pathology, i.e. CAA.

METHODS

- **Setting:** the **Sunnybrook Dementia study (SDS)**
  - **Study population**: 289 stroke-free dementia cases (AD=239; DLB=50)
  - n=34 with autopsy data with CAA staining
- **Replication setting**: **Alzheimer's Disease Neuroimaging Initiative (ADNI-1)**
  - Study population: 198 stroke-free AD cases
- **Predictor variables**
  - Total Intracranial volume (TIV) adjusted WMH
  - Covariates: age, sex, *APOE*-ε4, education, clinical dementia diagnosis (AD and DLB), cardiovascular risk factors
- **Outcome variables:**
  - Factor scores for: Attention/Executive Function, Learning and Memory, and Language
- **Statistical analyses:**
  - Confirmatory Factor Analyses (CFA) to calculate cognitive factors
  - Linear regression models with interaction term (WMH**APOE*-ε4) to test associations of WMH and cognitive scores, followed by analyses stratified on *APOE*-ε4
  - Analyses repeated by *APOE*-ε4 allele dosage
  - All analyses repeated in AD only (SDS)
  - Meta-analysis of SDS and ADNI-1 estimates
  - Prevalence of CAA by *APOE*-ε4 allele dosage

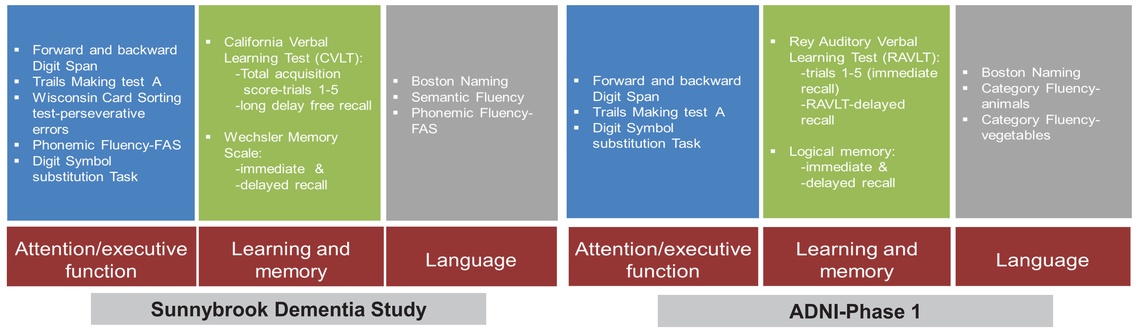
RESULTS

Characteristics of the SDS study population.

Characteristics	Descriptives				
	Total sample N=289 (122+167)	***APOE*-ε4 non-carriers n=122**	***APOE*-ε4 carriers n=167**	Carriers of 1 *APOE*-ε4 allele, n=130	Carriers of 2 *APOE*-ε4 alleles, n=37
Age (years)	71.1 (9.6)	71.7 (10.5)	70.7 (8.9)	71.1 (9.2)	69.4 (7.7)
Women	147 (50.9)	57 (46.7)	90 (53.9)	70 (53.8)	20 (54.0)
MMSE score	23.5 (4.1)	23.5 (4.3)	23.6 (4.0)	23.6 (4.0)	23.5 (3.9)
Smoking (current)	17 (5.9)	4 (3.3)	13 (7.8)	11 (8.5)	2 (5.4)
Hypertension	101 (35.0)	50 (41.0)	51 (30.1)	44 (33.8)	6 (16.2)
Diabetes mellitus type 2	25 (8.6)	12 (9.8)	13 (7.8)	13 (10)	0
AD + varying SVD	239 (82.7)	100 (82.0)	139 (83.2)	110 (84.6)	29 (78.4)
DLB + varying SVD	50 (17.3)	22 (18.0)	28 (16.8)	20 (15.4)	8 (21.6)
Raw WMH, cm^3	7.5 (10.4)	8.1 (10.4)	7.2 (10.4)	7.5 (10.6)	6.1 (9.5)
TIV adjusted WMH	6.2 (8.4)	6.7 (8.8)	5.8 (8.1)	6.0 (7.9)	5.3 (8.8)
TIV adj. WMH, median [IQR]	3.1 [1.1-8.1]	3.3 [1.1-8.5]	3.0 [1.0-7.8]	3.4 [1.1-8.5]	2.2 [0.9-5.6]

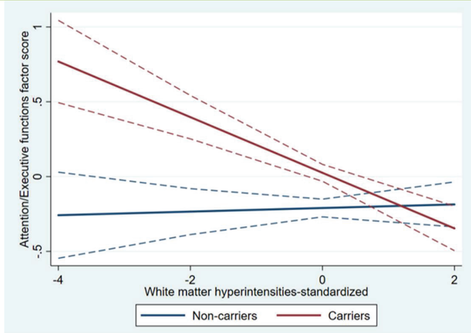
Values are means (standard deviation), counts (percentage), or medians [interquartile range]

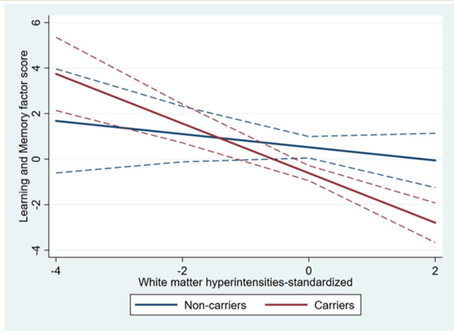
Confirmatory Factor Analyses, SDS and ADNI-1.

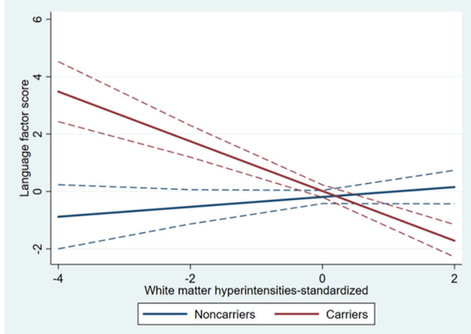


- SDS: Significant interaction between WMH and *APOE*-ε4 for language (p-value=0.02)

Figure: WMH and cognition by *APOE*-ε4 carrier status, SDS





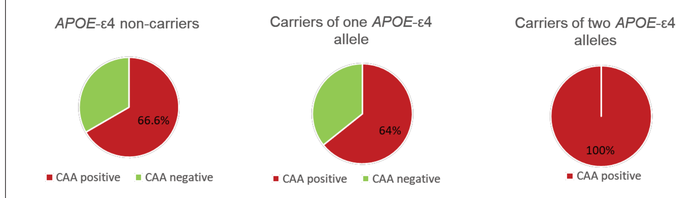


- All associations driven by heterozygotes
- Similar results after excluding DLB cases
- Similar results in ADNI-1 despite a lesser WMH burden
- Results for attention/executive functions and language replicated in ADNI-1

Meta-analyses of SDS and ADNI-1

Factor	Association between WMH and cognition			
	APOE-ε4 non-carriers, n=189		*APOE*-ε4 carriers, n=298	
	Difference per SD (95% CI)	P-value	Difference per SD (95% CI)	P-value
Attention/Executive	-0.092 (-0.215, 0.031)	0.143	-0.191 (-0.271, -0.112)	**2.117x10^{-3}**
Memory	-0.626 (-1.755, 0.503)	0.277	-1.024 (-1.794, -0.254)	**0.009**
Language	-0.032 (-0.550, 0.486)	0.903	-0.749 (-1.191, -0.306)	**0.0009**

Prevalence of CAA by *APOE*-ε4 dosage



- Fisher's exact test, *n*=34
- Non-carriers=8/12; Heterozygotes=9/14; Homozygotes=7/7

CONCLUSION AND REMARKS

- *APOE*-ε4 influences the association of WMH with executive function, memory, and language in dementia patients.
- This association holds irrespective of the clinical dementia diagnosis.
- CAA might be the likely etiology of WMH in *APOE*-ε4 carriers.
- These findings emphasize the importance of WMH (as a marker of SVD) across the AD/DLB spectrum, and open avenues for further research to understand shared etiologies and risk factors across the dementias.
- Information on *APOE*-ε4 status may be useful to understand the relative contributions of different pathologies to an individual's unique dementia syndrome, and to guide therapy as well.

ACKNOWLEDGEMENTS

University of Toronto; Sunnybrook Research Institute; CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada; Alzheimer Society Canada; CIHR STAGE Strategic Training for Advanced Genetic Epidemiology; ADNI Alzheimer's Disease Neuroimaging Initiative

Correspondence: Saira Mirza
saira.mirza@sunnybrook.ca; saira.mirza@mail.utoronto.ca