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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]

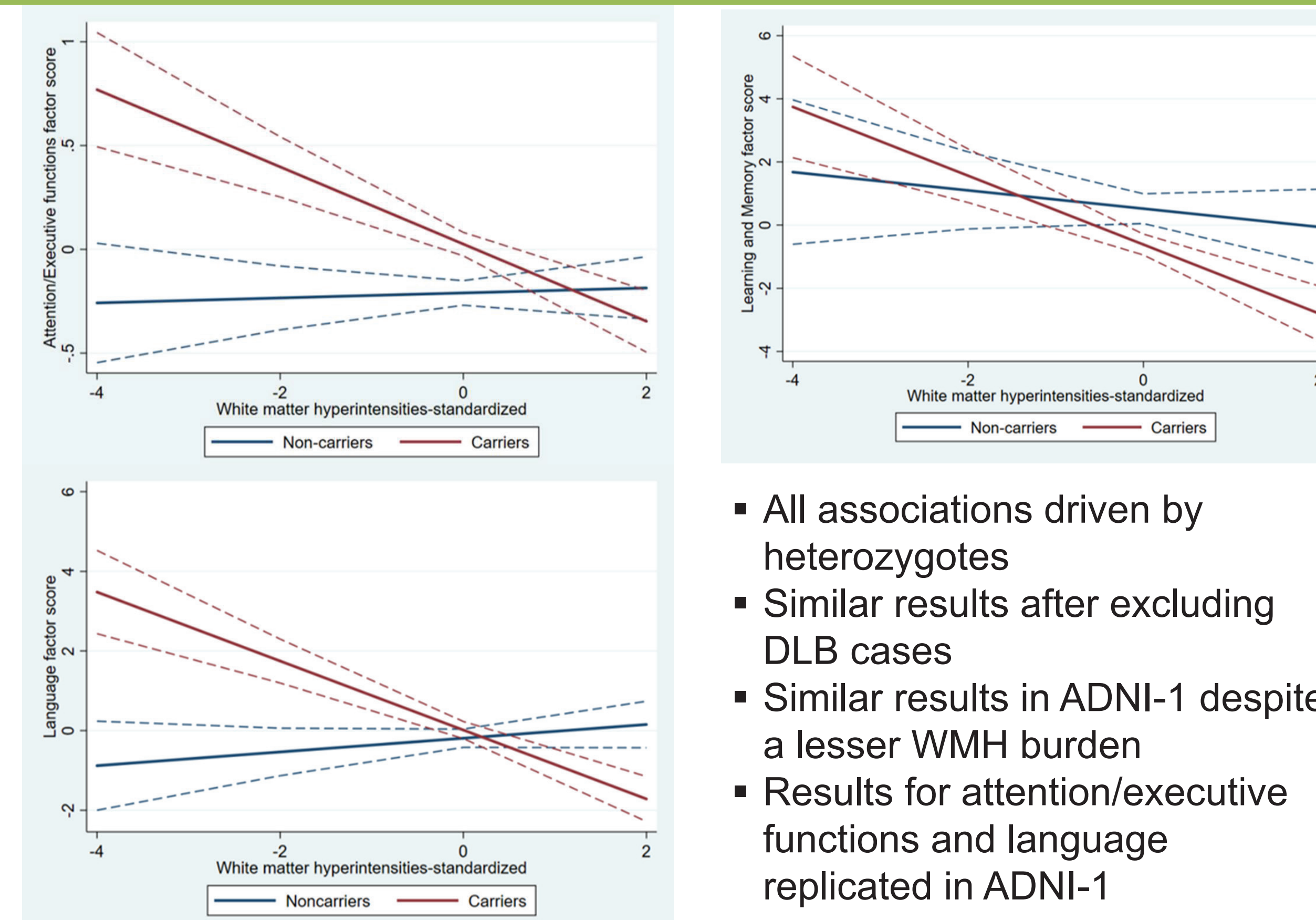
Values are means (standard deviation), counts (percentage), or medians [interquartile range]

Confirmatory Factor Analyses, SDS and ADNI-1.

Attention/executive function	Learning and memory	Language	Attention/executive function	Learning and memory	Language
<ul style="list-style-type: none"> Forward and backward Digit Span Trails Making test A Wisconsin Card Sorting test-perseverative errors Phonemic Fluency-FAS Digit Symbol substitution Task 	<ul style="list-style-type: none"> California Verbal Learning Test (CVLT): <ul style="list-style-type: none"> -Total acquisition score-trials 1-5 -long delay free recall Wechsler Memory Scale: <ul style="list-style-type: none"> -immediate & -delayed recall 	<ul style="list-style-type: none"> Boston Naming Semantic Fluency Phonemic Fluency-FAS 	<ul style="list-style-type: none"> Forward and backward Digit Span Trails Making test A Digit Symbol substitution Task 	<ul style="list-style-type: none"> Ray Auditory Verbal Learning Test (RAVLT): <ul style="list-style-type: none"> -trials 1-5 (immediate recall) -RAVLT-delayed recall Logical memory: <ul style="list-style-type: none"> -immediate & -delayed recall 	<ul style="list-style-type: none"> Boston Naming Category Fluency-animals Category Fluency-vegetables
Sunnybrook Dementia Study			ADNI-Phase 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

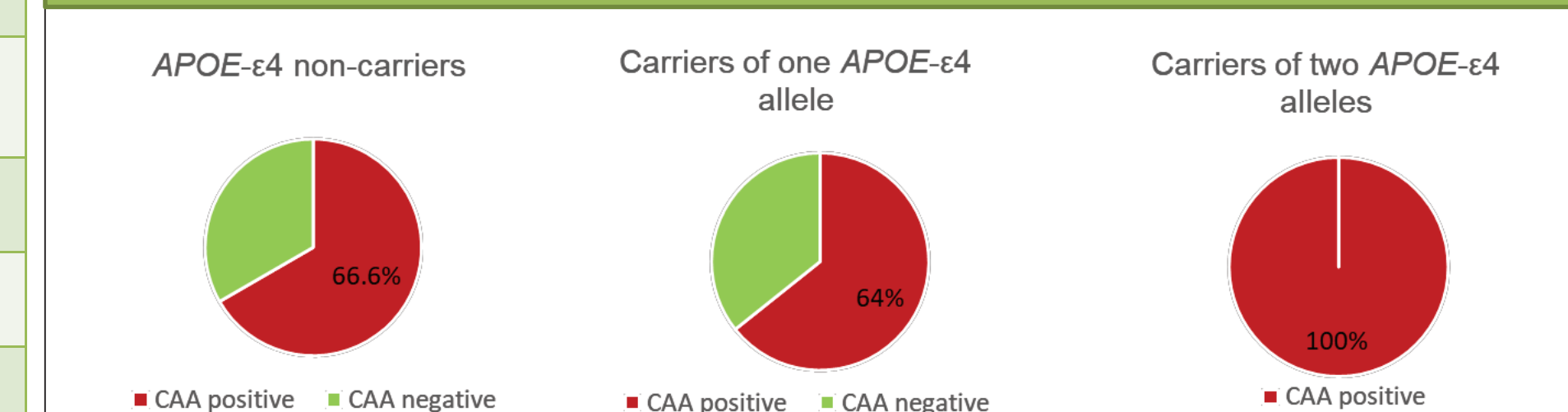


- All associations driven by heterozygotes
- Similar results after excluding DLB cases
- Similar results in ADNI-1 despite a lesser WMH burden
- Results for attention/executive functions and language replicated in ADNI-1

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.

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