

A Composite Vascular Burden Score (VCING-Lite Proxy) Modifies *APOE* and Alzheimer’s Neuropathology Associations

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INTRODUCTION

- Evidence indicates that vascular brain pathologies (VBP) may modify the associations between Apolipoprotein E (*APOE*) genotype and Alzheimer’s disease (AD) neuropathologic outcomes.
- However, whether the cumulative VBP burden, recently quantified using VCING-Lite Proxy [2], modifies *APOE*–AD neuropathology associations remain understudied.

OBJECTIVE

- To investigate whether VCING-Lite proxy modifies the association between *APOE* genotypes and AD neuropathologic outcomes.

METHODS

Data Source: The National Alzheimer’s Coordinating Center (NACC). 7153 participants with available *APOE* genotype and vascular pathology lesions.

Variables:

- APOE* Genotype:** ϵ 4-noncarriers (ϵ 33, ϵ 22, ϵ 23 Referent), ϵ 4-heterozygotes (ϵ 24/ ϵ 34) , and ϵ 4-homozygotes (ϵ 44).
- AD neuropathologic outcomes:** AD neuropathologic change (ADNC), Thal phase, neuritic plaques, diffuse plaques, and Braak tangle stage.
- VCING-Lite Proxy:** combines global ratings across three cerebrovascular domains (arteriolosclerosis, cerebral amyloid angiopathy (CAA), and gross infarcts to classify the likelihood of vascular cognitive impairment as **low, moderate, or high**.

Statistical Analysis: Ordinal or simple logistic regression models were used adjusting for age, age-squared, sex, and self-reported ancestry. Statistical significance for the test of interaction was set at False Discovery Rate corrected p-value <0.10 and p-value <0.05 for all other tests.

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RESULTS

Table 1: Participant Characteristics by *APOE* ϵ 4 genotypic model

Characteristic	No. (%)			
	<i>APOE</i> ϵ 4 Allele			
	Overall (N=7153)	ϵ 33, ϵ 22, ϵ 23 (N=3998)	ϵ 24, ϵ 34 (N=2567)	ϵ 44 (N=588)
Age, mean (SD), years	79 (12)	80 (12)	78 (11)	75 (9)
Female	3,405 (48)	1,924 (48)	1,218 (47)	263 (45)
Education, years				
Up to High School	1,629 (23)	913 (23)	592 (23)	124 (21)
Some College	1,298 (18)	738 (19)	442 (17)	118 (20)
Bachelor’s Degree	2,034 (28)	1,113 (28)	756 (30)	165 (28)
Post master’s degree	2,192 (31)	1,234 (31)	777 (30)	181 (31)
Self-reported Ancestry				
White	6,758 (95)	3,800 (95)	2,414 (94)	544 (93)
Black or African American	303 (4)	134 (3)	130 (5)	39 (7)
Other	92 (1)	64 (2)	23 (1)	5 (1)
Alzheimer’s pathology outcomes				
ADNC				
No or low ADNC	1,338 (31)	1,089 (46)	236 (15)	13 (4)
Intermediate or high ADNC	2,921 (69)	1,286 (54)	1,298 (85)	337 (96)
Parenchymal amyloid (A β)				
Thal Phase				
Phase 0	582 (14)	530 (22)	49 (3)	3 (1)
Phase 1 and Phase 2	618 (14)	458 (19)	149 (10)	11 (3)
Phase 3	510 (12)	334 (14)	158 (10)	18 (5)
Phase 4	2,602 (60)	1,094 (45)	1,189 (77)	319 (91)
Neuritic Plaques				
None	1,695 (24)	1,427 (36)	258 (10)	10 (2)
Sparse	917 (13)	558 (14)	319 (12)	40 (7)
Moderate	1,345 (19)	765 (19)	496 (19)	84 (14)
Frequent	3,196 (45)	1,248 (31)	1,494 (58)	454 (77)
Diffuse Plaques				
None	998 (15)	865 (24)	123 (5)	10 (2)
Sparse	854 (13)	592 (16)	233 (10)	29 (5)
Moderate	1,087 (16)	652 (18)	371 (16)	64 (12)
Frequent	3,675 (56)	1,569 (43)	1,667 (70)	439 (81)
Tau pathology				
Braak Stage				
Stage 0	383 (5)	319 (8)	64 (3)	0 (0)
Stage I and Stage II	1,333 (19)	1,042 (27)	272 (11)	19 (3)
Stage III and Stage IV	1,716 (24)	1,114 (29)	536 (21)	66 (11)
Stage V and Stage VI	3,606 (51)	1,431 (37)	1,675 (66)	500 (86)
Vascular brain pathologies				
VCING-Lite Proxy				
Low	2917 (41)	1840 (46)	964 (38)	113 (19)
moderate	2799 (39)	1569 (40)	988 (39)	242 (41)
high	1394 (20)	558 (14)	605 (24)	231 (39)
VCING-Lite Proxy components				
Arteriolosclerosis				
None	1,168 (18)	681 (19)	406 (17)	81 (15)
Mild	2,337 (36)	1,332 (37)	834 (36)	171 (33)
Moderate	2,071 (32)	1,132 (31)	760 (33)	179 (34)
Severe	904 (14)	485 (13)	326 (14)	93 (18)
Cerebral amyloid angiopathy (CAA)				
None	2,730 (39)	2,069 (53)	611 (24)	50 (9)
Mild	2,103 (30)	1,042 (27)	944 (37)	117 (20)
Moderate	1,423 (20)	537 (14)	669 (26)	217 (37)
Severe	786 (11)	282 (7)	306 (12)	198 (34)
Gross infarcts	616 (14)	360 (15)	214 (14)	42 (12)

ADNC: Alzheimer’s Disease Neuropathologic Change; CAA: Cerebral amyloid angiopathy; VCING-Lite Proxy: Vascular Cognitive Impairment Neuropathology Guidelines.

Percentages are calculated using available non-missing data for each variable

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CONCLUSIONS

- Cumulative vascular brain pathology modified the association between *APOE* ϵ 4 genotype and Alzheimer’s disease neuropathologic outcomes. This effect modification was strongest for neuritic plaque (p for interaction < 0.0001), with a similar but weaker pattern observed for Braak tangle stage (p = 0.076).
- APOE* ϵ 4 carriers had higher odds of neuritic plaque and Braak tangle stage than non-carriers across VCING-Lite strata; however, the attenuation of ϵ 4-associated odds with increasing vascular pathology burden was most evident among ϵ 4 homozygotes.
- CAA appeared to be the primary contributor to the observed effect modification, but causal interpretation requires caution. Because *APOE* ϵ 4 and CAA are closely linked biologically, these findings should be interpreted as evidence that vascular co-pathology contextualizes *APOE* ϵ 4–AD neuropathology associations, rather than as proof of an independent causal interaction.

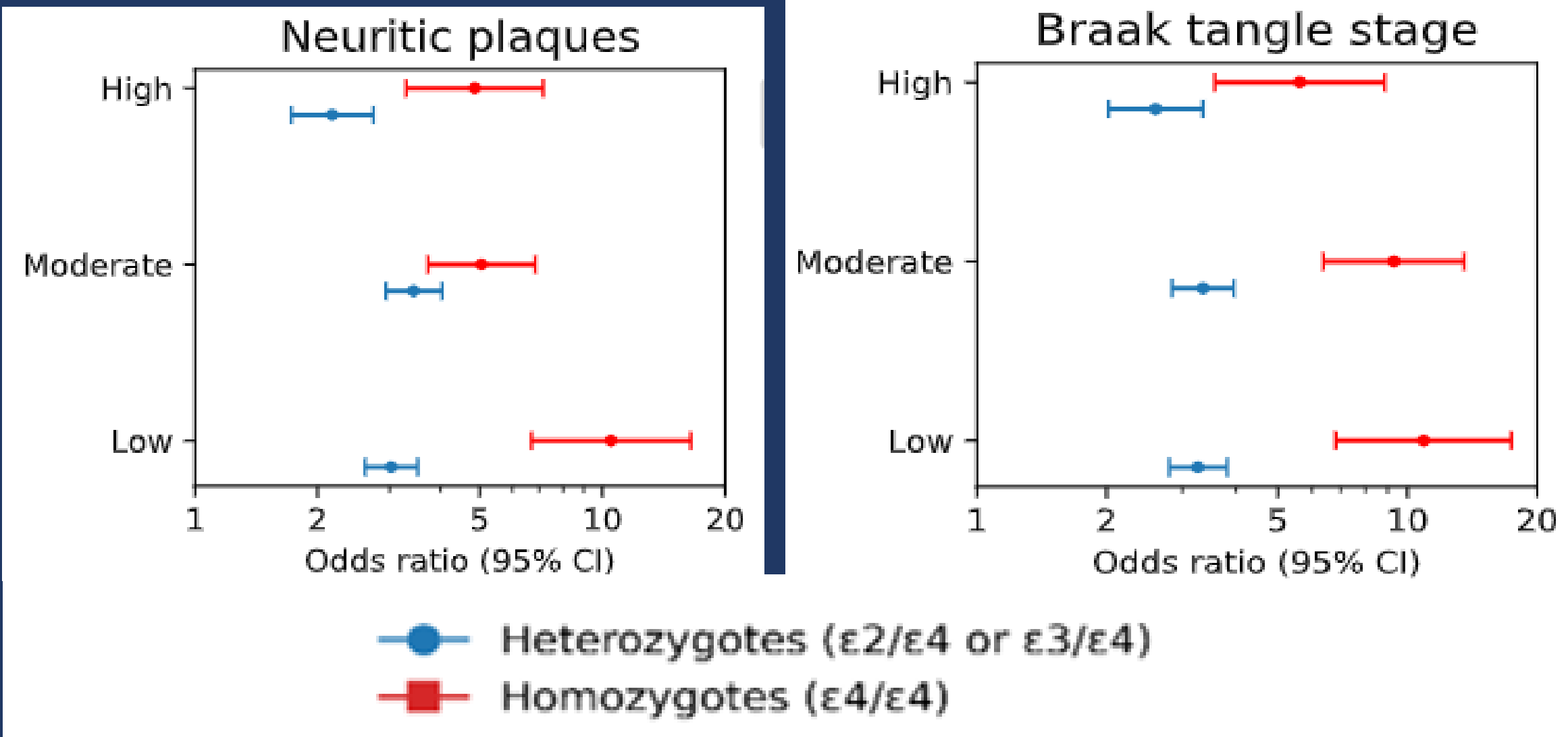


Figure 1. Effect Estimates (OR) of *APOE* Genotypes on Alzheimer’s Pathology by VCING-Lite Proxy

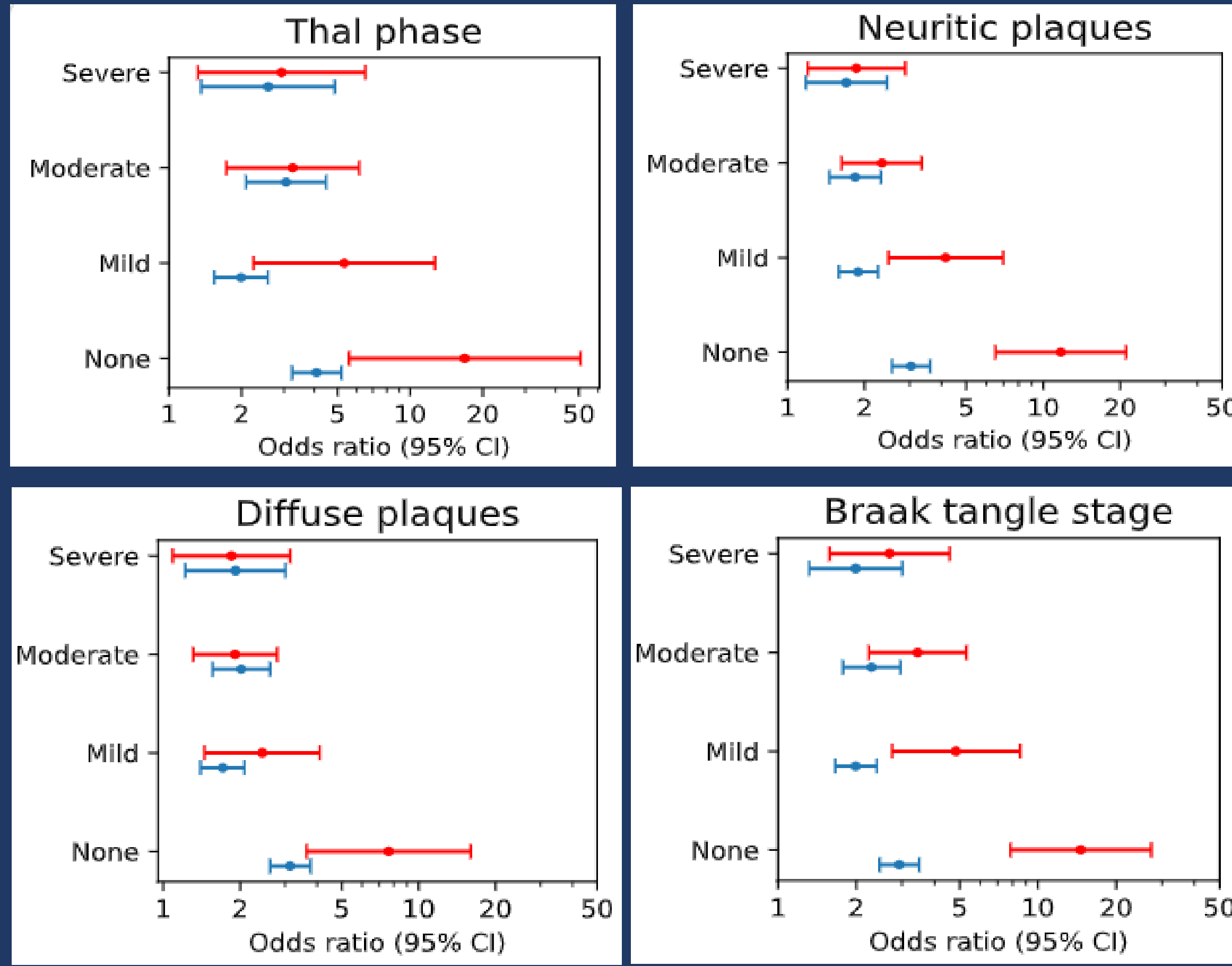


Figure 2. Effect Estimates (OR) of *APOE* Genotypes on Alzheimer’s Pathology by Cerebral amyloid angiopathy , a component of the VCING Lite Proxy

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