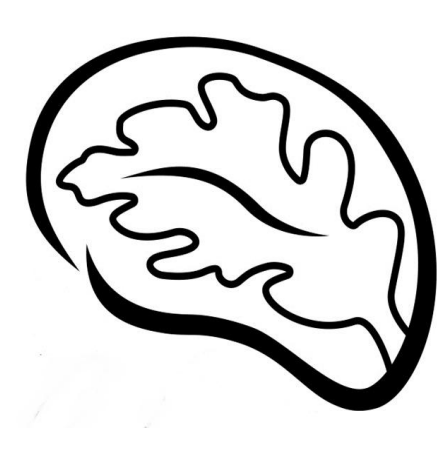


Sex-Specific Association of Apolipoprotein E Alleles with Autopsy Measures of Arteriolosclerosis and Atherosclerosis among Older Adults



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Background

- ❖ Cerebrovascular disease (CVD) is a major cause of mortality in females, and two-thirds of Alzheimer's disease (AD) patients are female.
- ❖ AD and CVD share many genetic risk factors, including the apolipoprotein E (*APOE*) genotype.
- ❖ While sex differences in *APOE* and AD are well-established; it is unclear if associations between *APOE* and CVD are sex-specific.

Methods and Statistical Analyses

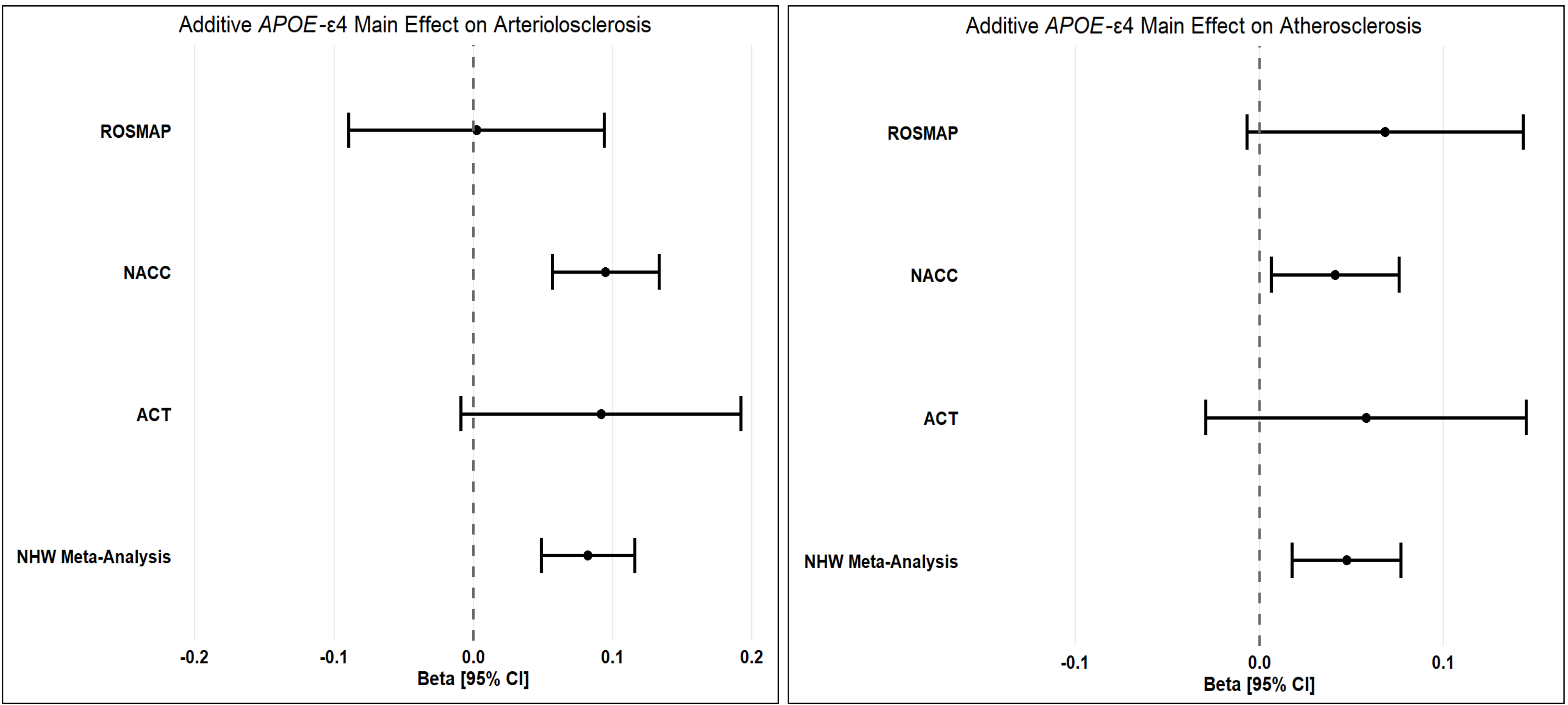
- ❖ Post-mortem brain data were obtained from three AD cohorts: Adult Changes in Thought (ACT), Religious Orders Study/Memory & Aging Project (ROS/MAP), and National Alzheimer's Coordinating Center (NACC).
- ❖ Measures of arteriolosclerosis and atherosclerosis were harmonized by the AD Sequencing Project Phenotype Harmonization Consortium into levels: none [0], mild [1], moderate [2], and severe [3].
- ❖ Non-Hispanic White (NHW) individuals >60 years at death were included (**Table 1**).
- ❖ *APOE*- ϵ 2 and *APOE*- ϵ 4 were coded with dominant and additive models, respectively.
- ❖ Linear regression analyses assessed sex-stratified and *APOE**sex interactions on CVD outcomes covarying for age at death.

Table 1. Participant Characteristics

Atherosclerosis (ATH)			
	Male	Female	Total
Sample Size	4166	4640	8806
Mean age at death, years $\pm$ SD	82 $\pm$ 9	86 $\pm$ 9	82 $\pm$ 9
Mean education at death, years $\pm$ SD	16 $\pm$ 3	15 $\pm$ 3	16.33 $\pm$ 3
Measures of CVD (%)			
None	818 (20)	797 (17)	1615 (18)
Mild	1707 (41)	1841 (40)	3548 (40)
Moderate	1240 (30)	1520 (33)	2760 (31)
Severe	401 (10)	482 (10)	883 (10)
Diagnosis at death (%)			
Normal Cognition	717 (17)	1077 (23)	1794 (20)
Mild Cognitive Impairment	437 (10)	527 (11)	964 (11)
Alzheimer's Disease	2147 (52)	2427 (52)	4574 (52)
<i>APOE</i> - ϵ 4 carriers (%)	1684 (40)	1690 (36)	3374 (38)
<i>APOE</i> - ϵ 2 carriers (%)	467 (11)	594 (13)	1061 (12)

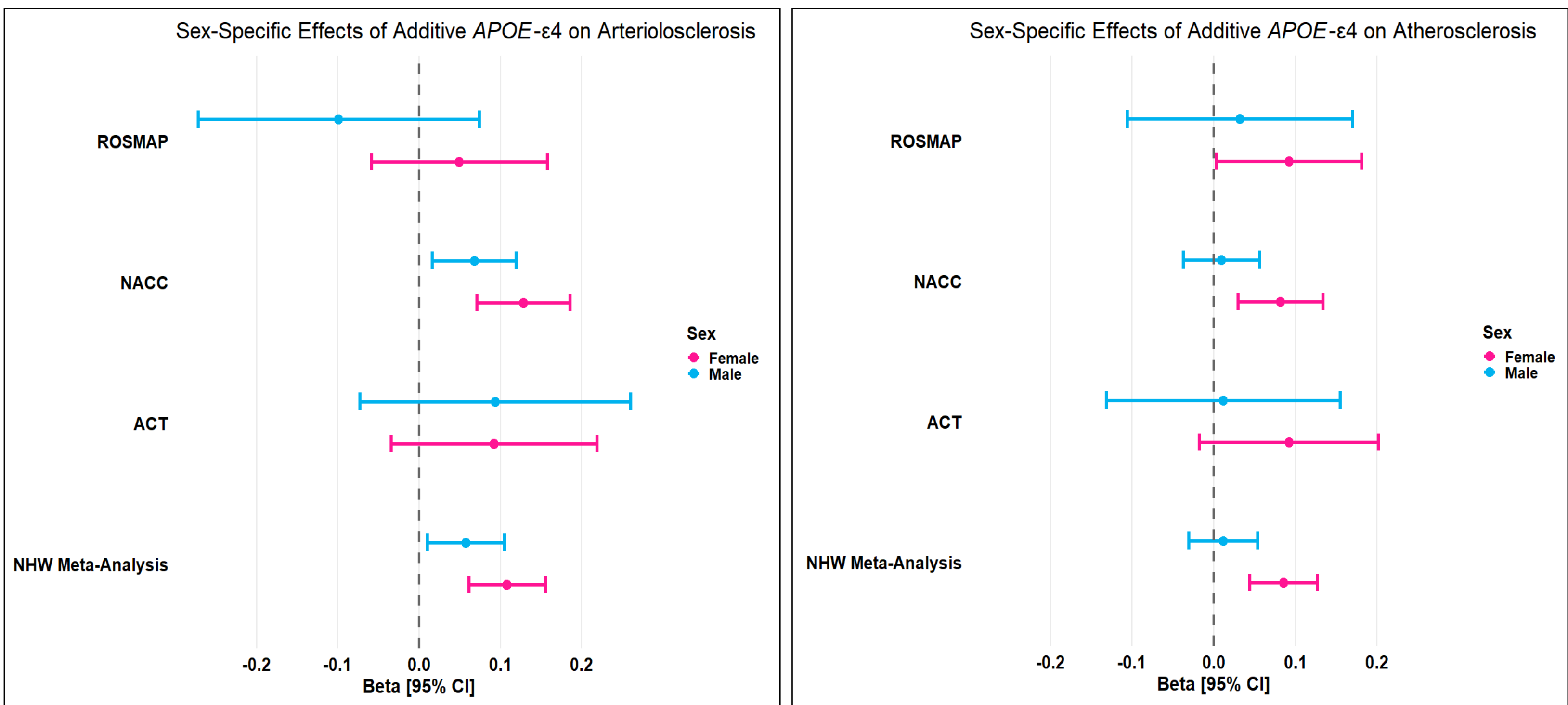
Results

Figure 1. Forest Plots of Significant *APOE*- ϵ 4 Main Effects on Arteriolosclerosis & Atherosclerosis



- ❖ Among males and females, *APOE*- ϵ 4 was related to higher arteriolosclerosis and atherosclerosis.

Figure 2. Forest Plots of Significant *APOE*- ϵ 4 Sex-Specific Effects on Arteriolosclerosis & Atherosclerosis in Females



- ❖ The ϵ 4 allele was more strongly associated with higher arteriolosclerosis and atherosclerosis among females compared to males.

Table 2. *APOE* Results by CVD Outcome

A. Dominant ϵ 2 Model

Dominant ϵ 2 Model				
CVD Outcome	Model	Beta	SE	P.fdr
ART	Main Effect	0.0	0.03	0.988
	Sex Interaction	-0.11	0.06	0.146
	Males Only	0.05	0.05	0.379
	Females Only	-0.04	0.04	0.433
ATH	Main Effect	-0.02	0.03	0.672
	Sex Interaction	0.04	0.06	0.672
	Males Only	-0.04	0.04	0.672
	Females Only	-0.002	0.04	0.955

B. Additive ϵ 4 Model

Additive ϵ 4 Model				
CVD Outcome	Model	Beta	SE	P.fdr
ART	Main Effect	0.08	0.02	1.13e-05
	Sex Interaction	0.06	0.03	0.146
	Males Only	0.06	0.02	0.048
	Females Only	0.11	0.02	2.76e-05
ATH	Main Effect	0.05	0.02	0.007
	Sex Interaction	0.06	0.03	0.133
	Males Only	0.01	0.02	0.677
	Females Only	0.09	0.02	4.71e-04

Boldface indicates an FDR corrected significant p-value of < 0.05.

Conclusion

- ❖ This study provides evidence that the ϵ 4 allele is related to higher levels of arteriolosclerosis and atherosclerosis among females.
- ❖ Larger sample sizes will be needed to better elucidate how *APOE* relates to cerebrovascular injury in the presence and absence of AD neuropathology, and whether such effects differ by sex.

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