

Genetic and Hormonal Contributions to Psychosis Symptoms in Alzheimer’s Disease : A Sex-Stratified Analysis



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Introduction

- **Psychosis** affects 30–50% of individuals with Alzheimer’s disease (AD), presenting as delusions and hallucinations, and occurs more frequently in females.
- **APOE4** is the strongest genetic risk factor for Alzheimer’s disease and influences disease severity.
- Previous papers support a sex-linked association for psychosis, with female APOE4 homozygotes have an increased likelihood of developing Lewy body-related processes.

Gap #1: The mechanistic link between APOE4 genotype and the emergence of psychosis symptoms in AD remains unclear.

- **Estrogen therapy (EHT)** has shown neuroprotective and antipsychotic properties within the context of schizophrenia.

Gap #2: The impact of EHT within the context of attenuating symptoms of psychosis in AD remains understudied.

Objectives: To examine how APOE4 zygosity and sex interact to affect psychosis symptoms in AD, and whether EHT use is associated with a reduced risk of psychosis.

Hypotheses: APOE4 homozygosity will be more strongly linked to hallucinations in females, and EHT will reduce psychosis prevalence.

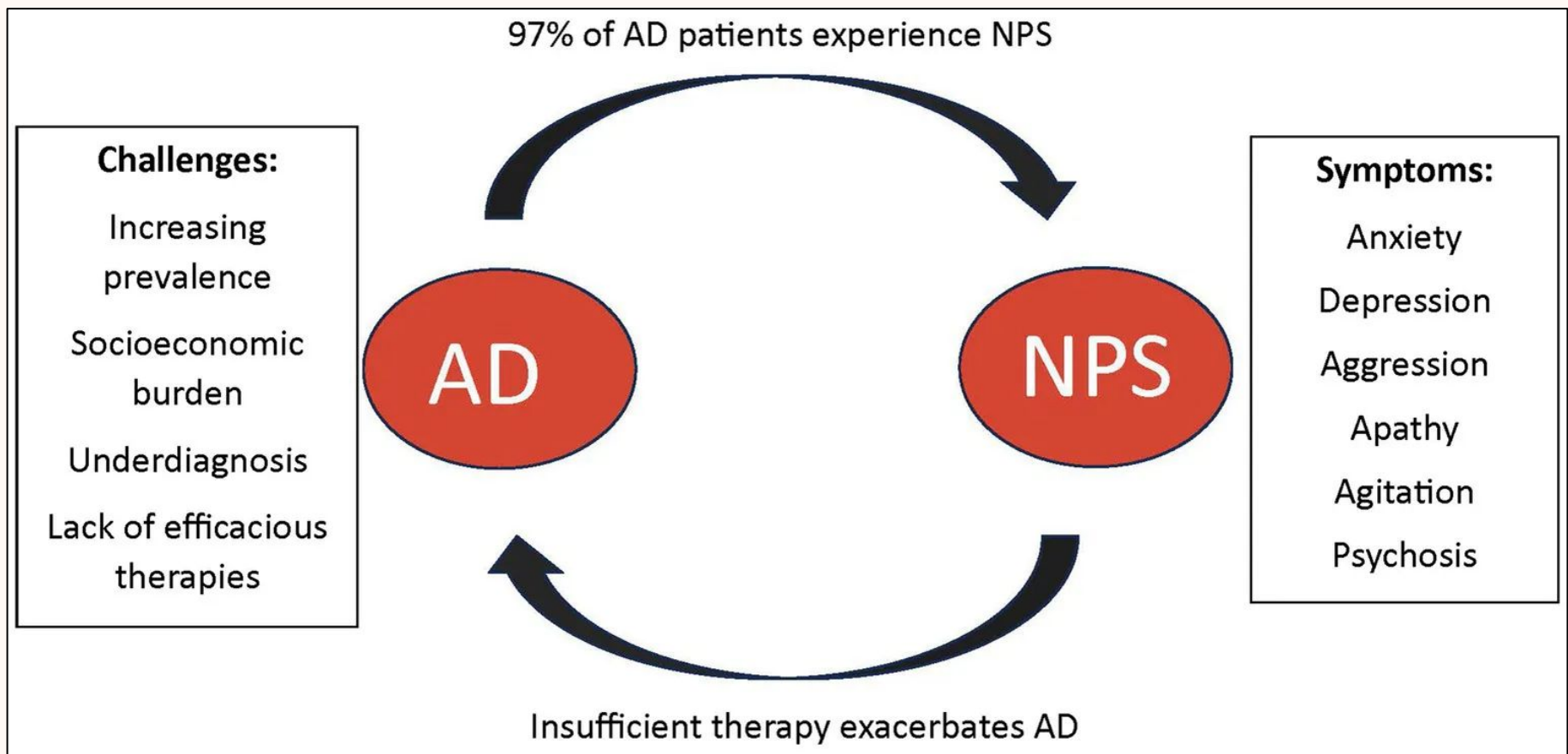


Figure 1. Neuropsychiatric symptoms are highly prevalent in AD and contribute to disease burden.

Methods

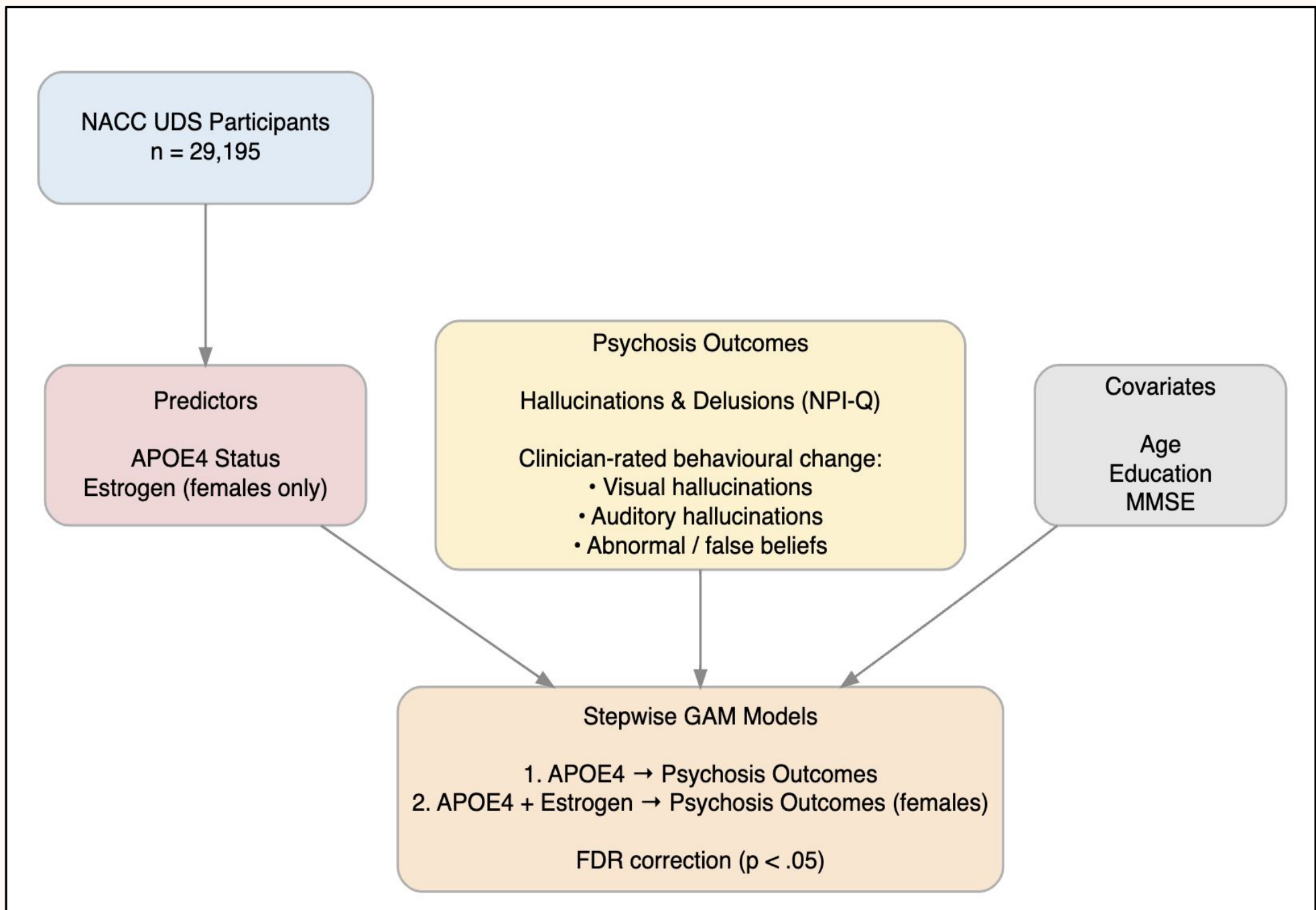


Figure 2. Flowchart illustrating the stepwise Generalized Additive Model analysis of sex-specific associations between APOE4, estrogen therapy and psychosis outcomes in AD.

Results

	Females (n = 15,354)	Males (n = 13,841)	Effect Size	Significance
Clinical Variables				
Age, years (mean ± SD)	77.10 ± 9.89	76.77 ± 9.28	$d = -.035$	$p < .01$
MMSE score (mean ± SD)	23.79 ± 14.61	23.70 ± 12.64	$d = -.0067$	NS
Years of Education (mean ± SD)	14.07 ± 3.48	15.60 ± 3.44	$d = .44$	$p < .001$
APOE4 homozygotes	1735	1683	$\phi = .012$	$p < .05$
Current use of EHT	623/14 731	--	--	--
Presence of Psychosis Symptoms				
Delusions (NPI - Q; %)	16.9	12.1	$\phi = .0552$	$p < .001$
Hallucinations (NPI-Q; %)	7.2	5.3	$\phi = .0350$	$p < .001$
Visual hallucinations (Clinician-rated; %)	5.4	4.3	$\phi = .0224$	$p < .001$
Auditory Hallucinations (Clinician-rated; %)	2.6	1.4	$\phi = .0377$	$p < .001$
Abnormal and false beliefs (Clinician-rated; %)	12.5	8.7	$\phi = .0522$	$p < .001$

Table 1. Participant Demographics and Clinical Characteristics. Females were slightly older and exhibited higher rates of all psychosis-related symptoms, with the largest sex differences observed for delusions and abnormal or false beliefs.

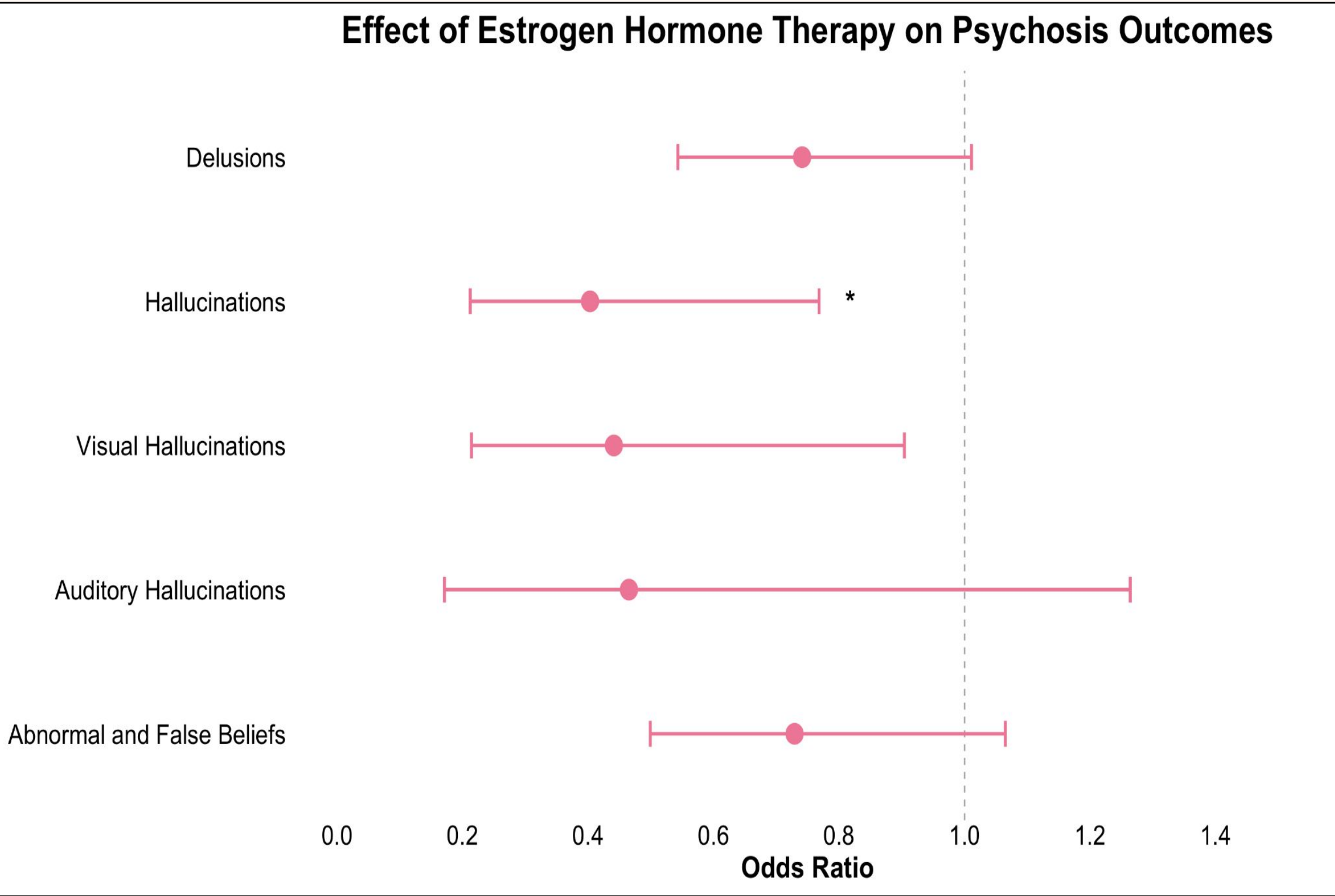


Figure 4. Effect of EHT on Psychosis Outcomes Among Females

Summary. EHT was associated with lower odds of hallucinations (OR = 0.403, $p < .05$).

Discussion

- APOE4 homozygosity was associated with delusions and hallucinations in females, but only with delusions in males, highlighting sex-specific vulnerability to psychosis in AD.
- EHT protected against hallucinations independent of APOE4, supporting its potential as a symptom-specific intervention, possibly via modulation of tau phosphorylation, synaptic function, and neuroinflammation.

Future Directions

- Future research should evaluate APOE4 genotyping to guide risk stratification and early monitoring of psychosis in females with AD.
- Declining estrogen during menopause may reduce neuroprotective effects, increasing vulnerability to psychosis and making this transition a potential window for estrogen-targeted interventions to reduce symptom risk or severity.

Acknowledgements

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National Alzheimer's
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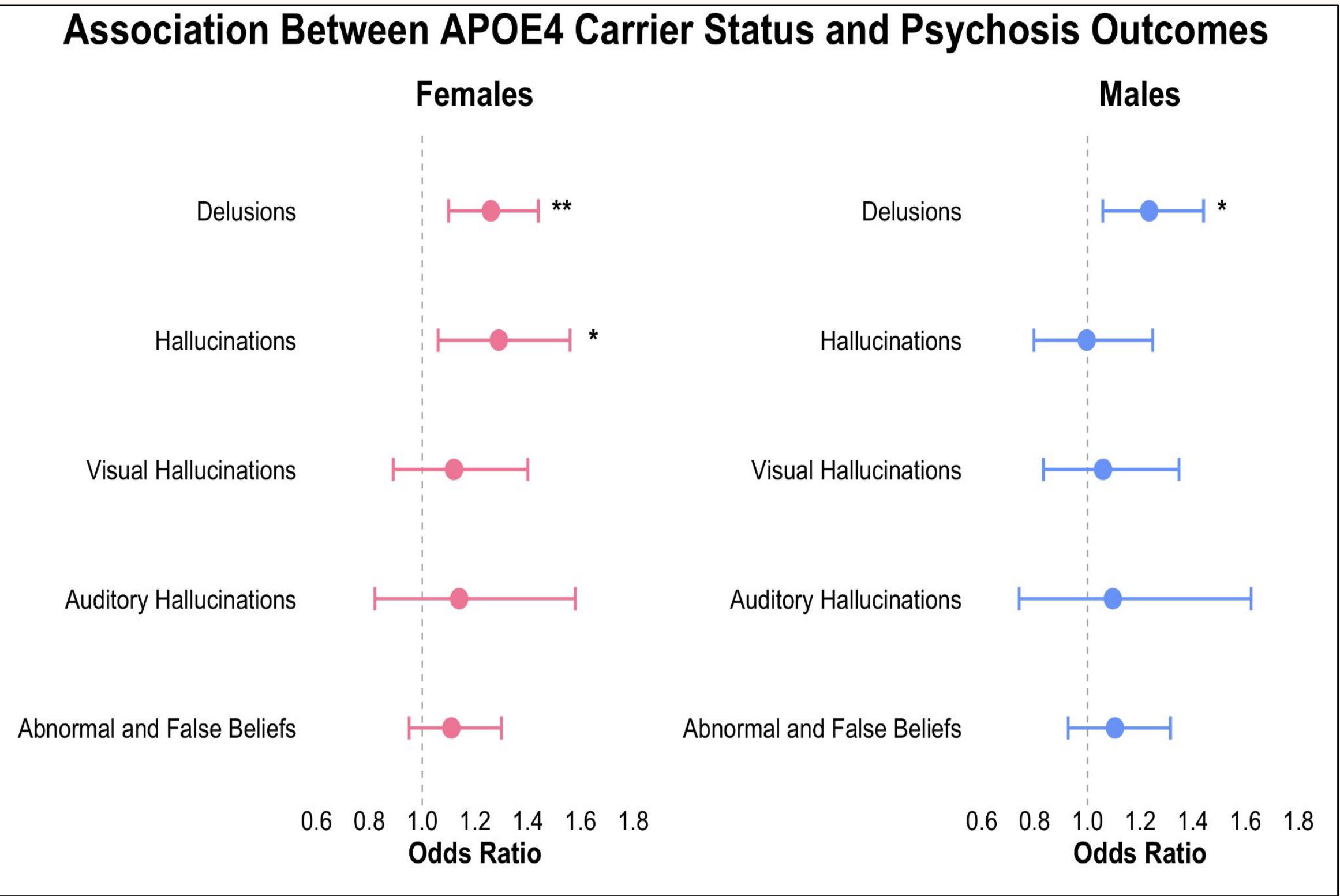


Figure 3. Associations between APOE4 carrier status and Psychosis Outcomes
Summary. In females, APOE4 status was significantly associated with delusions (OR = 1.26, $p < .01$) and general hallucinations (OR = 1.29, $p < .05$), whereas in males, significance was limited to delusions (OR = 1.23, $p < .05$).