

Factors Associated with Cognitive Resilience Among Patients with Moderate-Severe Amyloid-β Burden on Postmortem Autopsy



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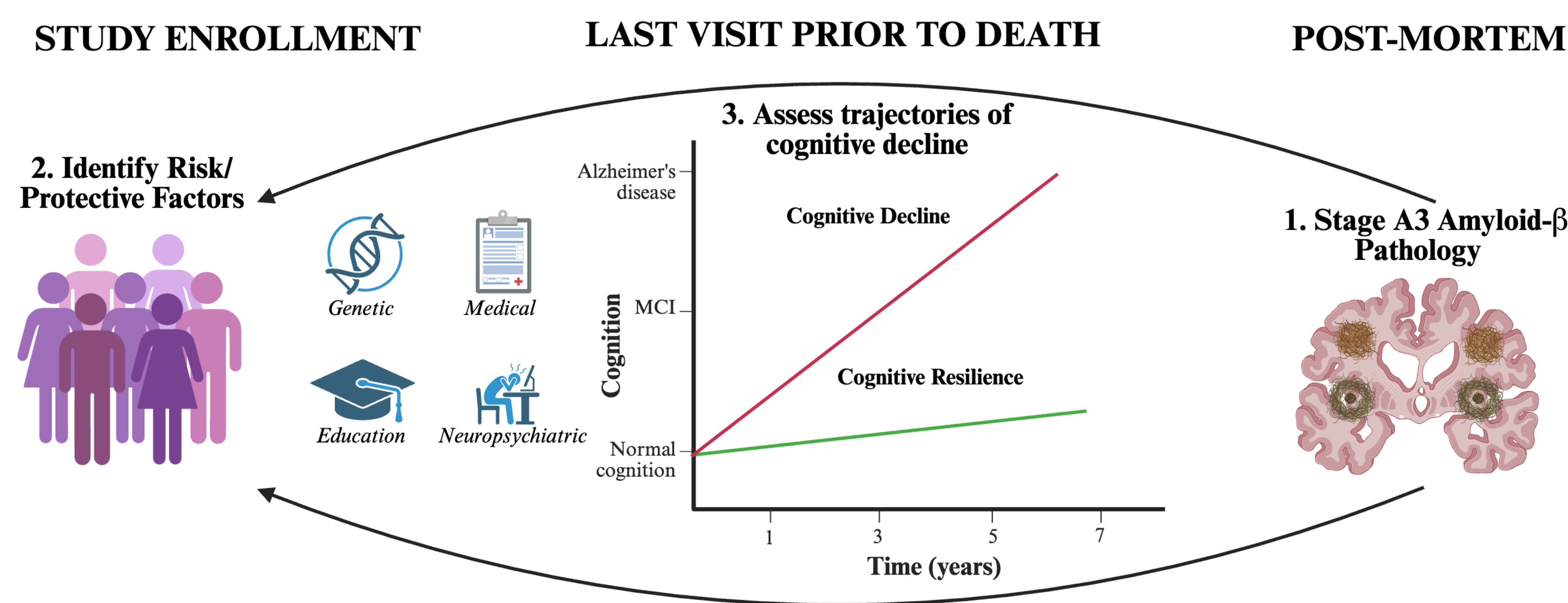
Introduction

- Although a marker of Alzheimer’s disease (AD), amyloid-β (Aβ) plaques are also observed in clinically normal older individuals without cognitive impairment¹
- Variables that may be associated with clinical decline in adults with Aβ pathology during later life include older age, APOE-ε4 genotype, and years of education^{2,3}
- No studies to our knowledge have identified factors associated with cognitive resilience across multiple domains in patients with Aβ plaques on postmortem autopsy, which is the gold standard of diagnosis

Primary aim:

- To examine associations between demographic characteristics, neuropsychiatric symptoms (NPS) and medical comorbidities and odds of cognitive resilience prior to death in autopsy-confirmed Aβ-positive individuals.

Methods



Schematic of study design. Data was leveraged from the National Alzheimer’s Disease Coordinating Center (NACC)⁴. Participants were required to have (1) Braak Stage A3 amyloid-β plaque score⁵ and (2) Clinical Dementia Rating-Global (CDR®) (CDR-G)⁶ <1 at the first NACC visit.

Defining Cognitive Resilience:

- Participants with a CDR-G ≤ 0.5 at the last clinical visit were defined as the “Cognitive Resilience” group, whereas participants with a CDR-G ≥ 1 at the last clinical visit were defined as the “Cognitive Decline” group.

Predictors of Interest:

Demographic:

- Age at initial visit
- Sex
- Baseline cognition
- Years of education

Neuropsychiatric:

- Presence of NPI-Q symptom domains at initial NACC visit

*NPI-Q (Neuropsychiatric Inventory-Questionnaire)

Clinical:

- Hypertension, smoking years, diabetes, traumatic brain injury, thyroid disease, depression

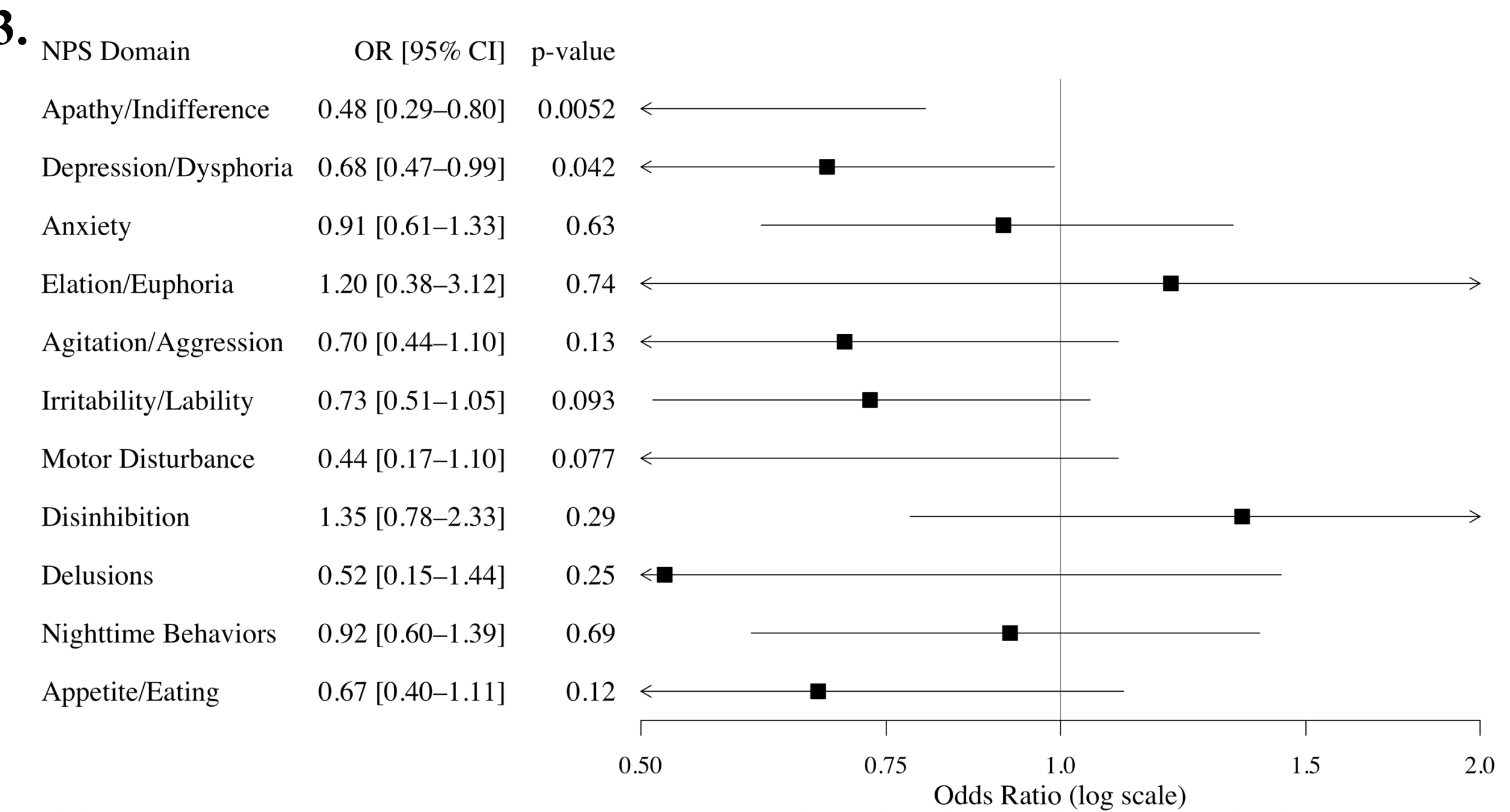
Neuropathological:

- Lewy body disease, frontotemporal, and cerebrovascular disease pathology

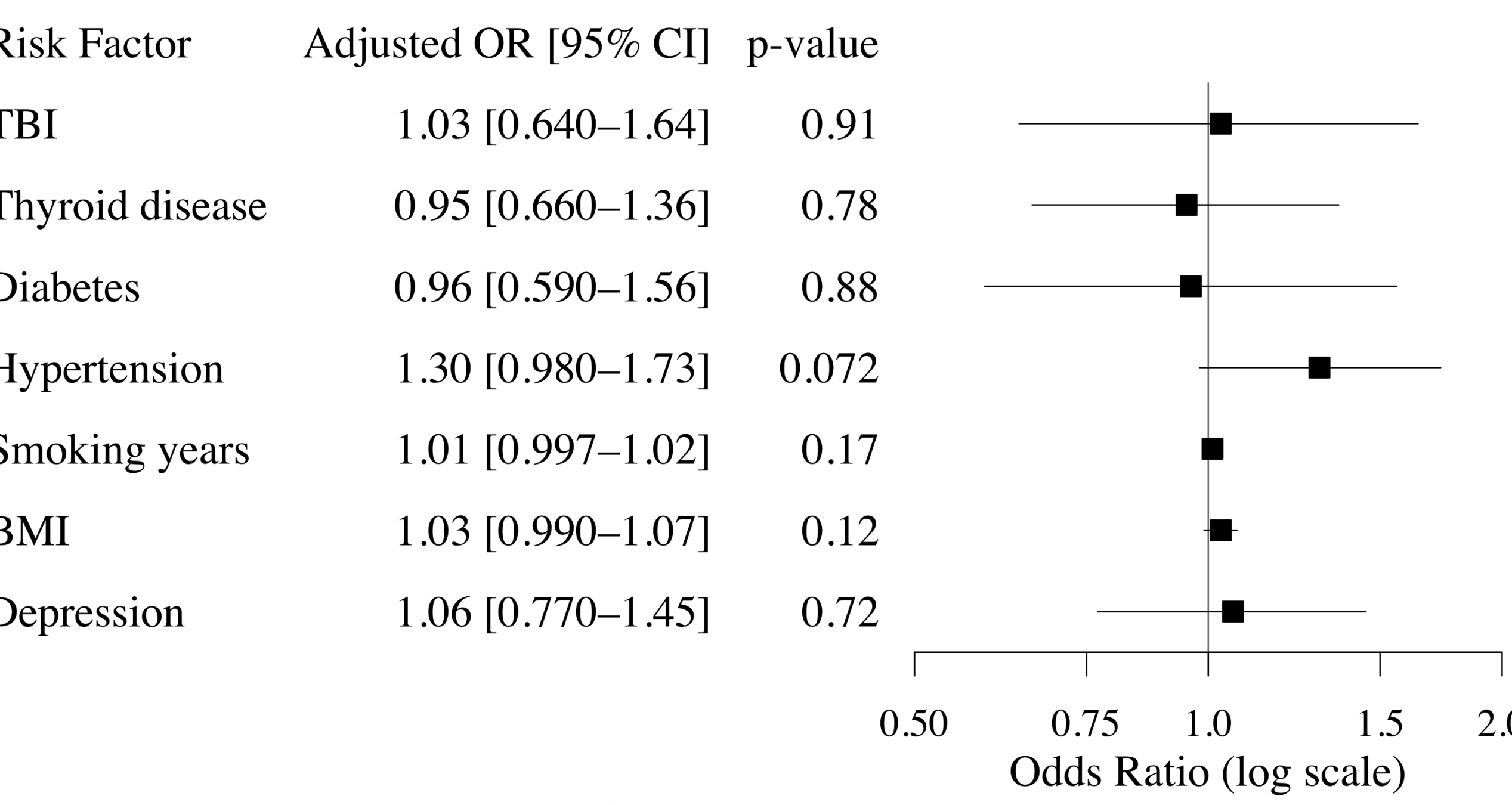
Results

1.	Cognitive Resilience (N=362)	Cognitive Decline (N=877)
Age at first visit, mean ± SD yrs (range)	78.5 ± 8 (44-100)	73.5 ± 9.1 (35-95)**
Age at Death, mean ± SD years (range)	87.8 ± 8.5 (51-109)	82.3 ± 9.8 (44-106)
Education, mean ± SD years (range)	16.2 ± 3 (6-25)	15.9 ± 2.9 (6-30)
Female, N (%)	180 (49.7%)	427 (48.7%)*
White, N (%)	346 (95.6%)	844 (96.2%)
1 APOE-ε4 alleles, N (%)	127 (35.1%)	408 (46.5%)
2 APOE-ε4 alleles, N (%)	20 (5.5%)	115 (13.1%)*

Comparison of (1) demographic and (2) AD and non-AD related neuropathological characteristics between individuals with cognitive resilience and cognitive decline. Bolded rows indicate that variable is significantly associated with odds of cognitive resilience. *<0.05; **<0.01



2.	Cognitive Resilience (N=362)	Cognitive Decline (N=877)
Severe hippocampal atrophy, N (%)	19 (5.5%)	189 (23.1%)**
B score, AD-type neurofibrillary degeneration, N (%)		
Stages V-VI (B3)	174 (48.1%)	734 (83.7%)**
C Score, density of neuritic plaques, N (%)		
Severe (C3)	146 (40.3%)	623 (71.0%)**
Non-AD dementia related pathology, N (%)		
Frontotemporal lobar degeneration	35 (9.7%)	81 (9.3%)
Lewy body disease	95 (26.2%)	379 (43.4%)*
Lacunes/infarcts	50 (13.9%)	152 (17.6%)



Odds of cognitive resilience among individuals with Aβ pathology on autopsy for (3) NPS at initial visit and (4) clinical diagnoses. Lower odds indicate increased risk of cognitive decline.

Discussion

- Demographic variables:** male sex, older age at initial visit, and fewer APOE-ε4 were associated with cognitive resilience, while years of education were not
- NPS:** the presence of depression/dysphoria and apathy were associated with lower odds of cognitive resilience
- Medical history variables:** Medical comorbidities were not associated with odds of cognitive resilience, although statistical power was limited
- Neuropathological variables:** Presence of non-AD related (i.e., Lewy body disease) neuropathology were associated with lower odds of cognitive resilience.
 - Cerebrovascular disease was associated among individuals without high ”B” (staging of neurofibrillary tangles) and ”C” (severity of neuritic plaques) scores

Limitations and Future Directions

- The study design does not allow ascertainment of the temporal relationship between demographic/clinical variables and cognitive resilience
- Future directions should include assessment of neuroimaging and fluid biomarkers to understand their role in predicting cognitive resilience in later life

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