

Sex Differences In Clinical And Biomarker Characteristics Of Early-Onset Dementias : Findings From The LEAF Cohort



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BACKGROUNDS

- Sex-related differences are increasingly recognized across neurodegenerative disorders, influencing clinical presentation, biomarker expression, and prognosis.
- Biological factors such as hormones and APOE genotype, together with sociocultural influences like educational attainment and cognitive reserve, may contribute to these differences.
- Understanding sex-specific patterns is critical for improving diagnostic accuracy, tailoring therapeutic strategies, and designing inclusive clinical trials.
- However, evidence remains particularly limited in early-onset Alzheimer's disease (EOAD) and frontotemporal dementia (FTD).

METHODS

- We analyzed 344 participants from the Longitudinal study of Early-onset dementia : EOAD (men=85, women=173) and FTD (men=33, women=53).
- Between-sex comparisons used chi-square tests and two-sample t-tests for demographics, cognition/neuropsychology, Neuropsychiatric Inventory (NPI), and blood biomarkers (plasma neurofilament light chain [NFL], phosphorylated tau-217 [p-tau217], glial fibrillary acidic protein [GFAP])
- APOE ε4 status was analyzed as carrier (≥1 ε4) vs non-carrier; family history used a modified Goldman classification dichotomized as ≤3.0 (strong) vs ≥3.5 (weak/absent).

RESULTS

- In EOAD**, women had fewer years of education (p=0.006) and lower MMSE scores (p=0.039) than men, although most neuropsychological test performances were comparable.
- Men more frequently reported anxiety on the NPI (p=0.010). Disease severity (global CDR and CDR-SB), APOE ε4 family history strength (p=0.644), and sex distribution of APOE ε4 carriers did not differ.
- In contrast, blood biomarkers showed clear sex differences: **women had higher plasma NFL (p=0.042) and GFAP (p=0.028)**, while no difference was observed for plasma p-tau217.
- In FTD**, women had fewer years of education (p<0.001), whereas men performed worse on Stroop color–reading tasks (p<0.05).
- No sex differences were observed in disease severity (CDR, CDR-SB), NPI scores, blood biomarkers, APOE ε4 frequency, or family history (all p>0.5).

Figure 1. Neuropsychological performance between men and women

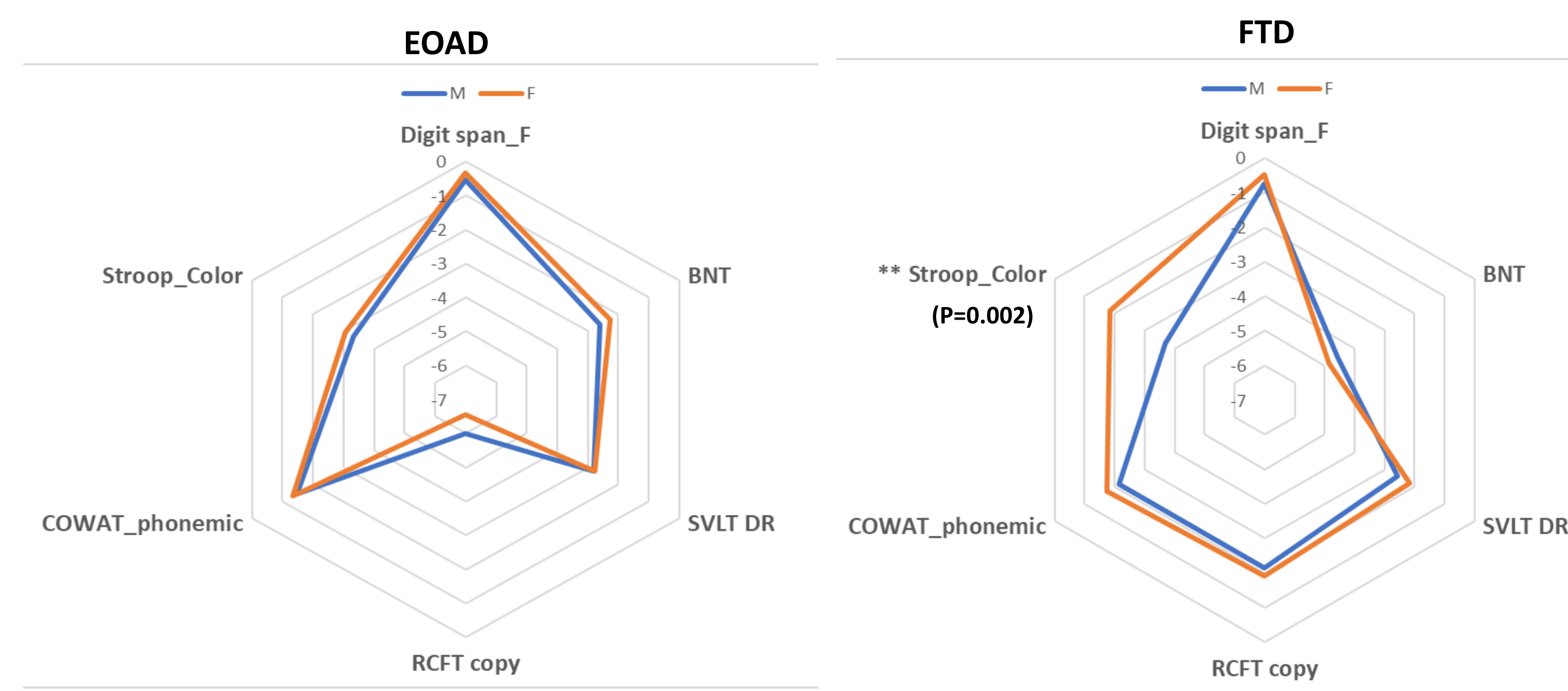
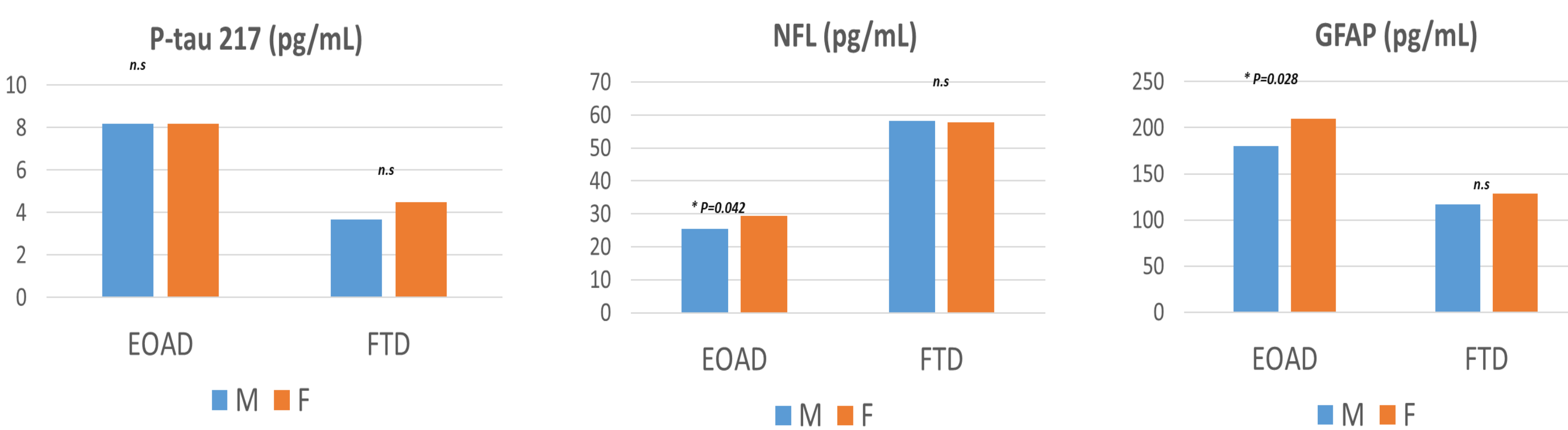


Table 1. Clinical Characteristics

	EOAD			FTD		
	M (n=85)	F (n=173)	p-value	M (n=33)	F (n=53)	p-value
Demographic						
Age	61.2 ± 4.6	60.7 ± 5.9	0.474	63.3 ± 7.4	65.6 ± 7.4	0.167
Education	12.7 ± 3.6	11.4 ± 3.7	0.006*	13.1 ± 3.5	9.3 ± 4.5	<0.001*
K-MMSE	19.9 ± 6.6	17.9 ± 6.7	0.039*	17.9 ± 8.5	17.3 ± 8.7	0.782
CDR	0.9 ± 0.5	1.0 ± 0.6	0.161	0.9 ± 0.5	1.0 ± 0.6	0.478
CDR_SOB	4.8 ± 3.2	5.7 ± 3.4	0.075	5.3 ± 3.2	5.4 ± 4.3	0.897
Co-morbidities (n, %)						
Diabetes mellitus, n(%)	11(12.9%)	11(6.6%)	0.094	9(29.0%)	8(16.0%)	0.162
Hypertension, n (%)	22(25.9%)	55(33.1%)	0.238	16(51.6%)	18(35.3%)	0.146
Hyperlipidemia, n (%)	20 (23.5%)	45(27.3%)	0.523	9(29.0%)	17(34.0%)	0.642
Heart disease, n (%)	5(5.9%)	7(4.2%)	0.558	6(19.4%)	6(11.8%)	0.346
APOE ε4 carrier	35 (41.2%)	99 (57.2%)	0.015*	5(15.6%)	9(17.0%)	0.870
Family History (≤3.0 ,strong)	11 (13.1%)	19 (11.1%)	0.644	2(6.1%)	4(7.7%)	0.775

Figure 2. Plasma biomarkers between men and women



CONCLUSIONS

- Using LEAF cohort data, we found that sex-related patterns in early-onset dementias differed by diagnosis. Women consistently had lower educational attainment.
- In EOAD, women showed higher APOE ε4 frequency and more adverse biomarker profiles (NFL, GFAP) but similar disease severity, suggesting a potential cognitive reserve effect.
- In FTD, sex differences were modest, limited to education and selective executive dysfunction in men.
- These findings underscore the need to consider both biological and sociocultural sex-related factors when evaluating early-onset dementias.