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NEUROIMAGING

Sex Differences in Amyloid PET in a Large, Real-Life Sample from the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) Study

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Abstract

Background: Previous studies on sex differences in amyloid burden have shown inconsistent findings. We examined the effect of sex on amyloid-PET outcomes in a large, real-world, cohort of individuals with cognitive impairment.

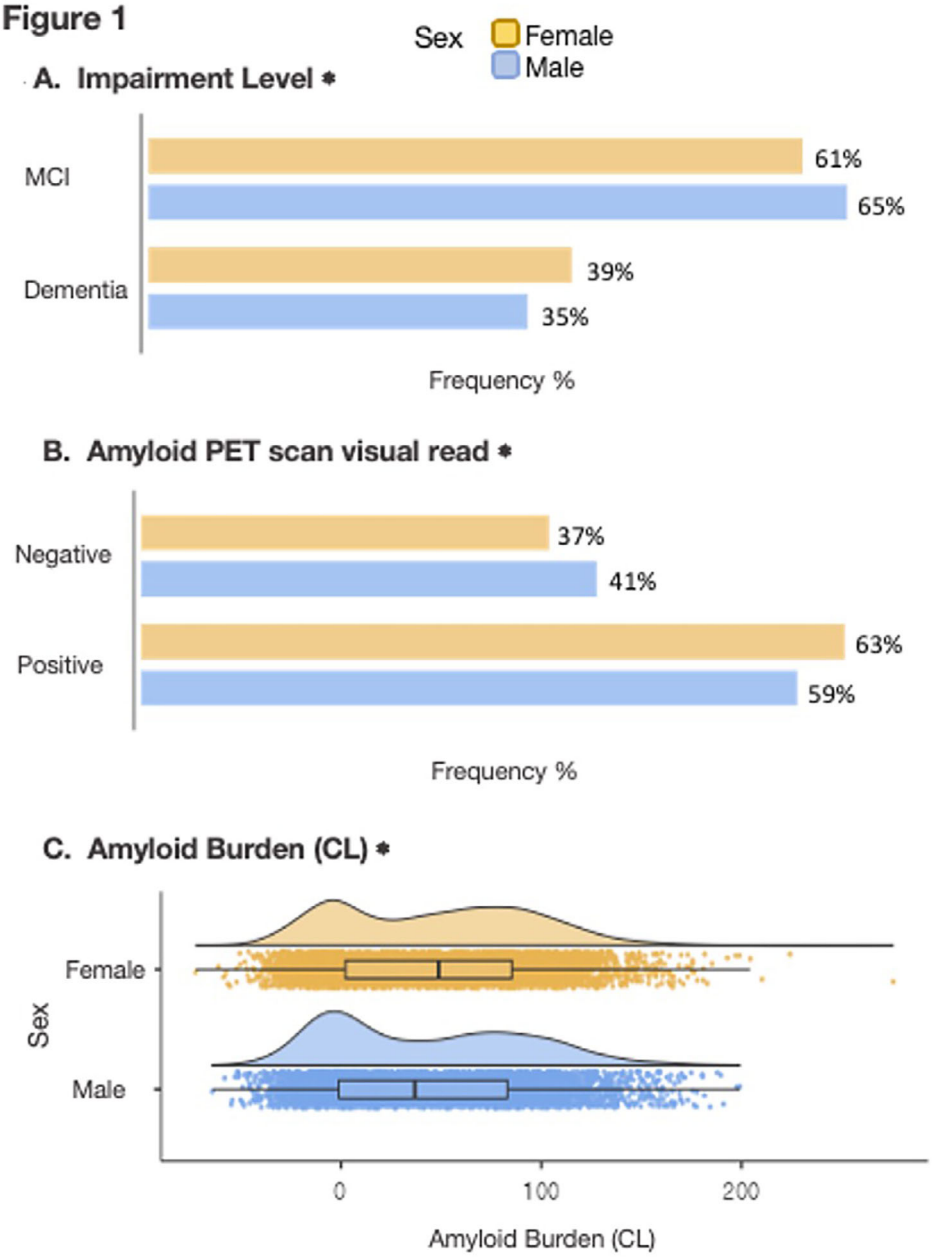
Method: The IDEAS study evaluated the clinical utility of amyloid-PET in 18,295 Medicare beneficiaries age ≥65 years with MCI or dementia. All scans were visually interpreted as positive or negative at each site by a local radiologist or nuclear medicine physician. A subset of 10,361 scans were centrally processed and quantified in

Centiloids. We used multivariate logistic regression to calculate odds ratios of amyloid-PET positivity (based on visual read) for males and females, adjusting for demographic and clinical risk factors. We used linear regression to assess the association between sex and amyloid burden quantified in Centiloids.

Result: Of 10,361 included individuals, 51% were females. Compared to males, females were slightly younger (75 versus 76 median age, p=0.008) and had higher rates of dementia (39.3% versus 35.2%, p<0.001). Rates of vascular risk factors were significantly higher in males than females, whereas females had significantly higher rates of history of depression and family history of AD. Females had higher rates of amyloid-PET positivity than males (63% versus 59%, p<.001) and higher Centiloid values (median=48.7 versus 36.9, p<.01); see Figure 1 and Table 1 model 1. Sex differences remained significant in models adjusted for demographics and clinical risk factors (Table 1, models 2-3). In an analysis that included only individuals with visually positive amyloid-PET, females exhibited higher Centiloid values than males (Table 1 multivariable linear models). In amyloid-positive individuals, we found a significant interaction between sex and age, with greatest sex differences in amyloid burden found in the youngest females (Figure 2A). We also found a significant interaction between sex and race, with greatest differences found in Black females vs. males (Figure 2B).

Conclusion: Females with cognitive impairment exhibited a higher frequency of amyloid-PET positivity and higher amyloid burden. Our findings shed light on sex-specific biological and potential sociocultural differences in Alzheimer's disease pathology.

Figure 1



Note. Figure1 shows percentages (%) of Dementia and MCI **(A)**, Amyloid PET scans visual reads **(B)** and distribution of Amyloid Burden measured by Centiloids (CL) **(C)** stratified by sex. CL presented as median with interquartile ranges IQR calculated as (Q1, Q3). Bivariate comparisons between males and females were made using $\chi 2$ test for categorical variables, medians comparisons using Kruskal-Wallis, Mann-Whitney U/ Wilcoxon.

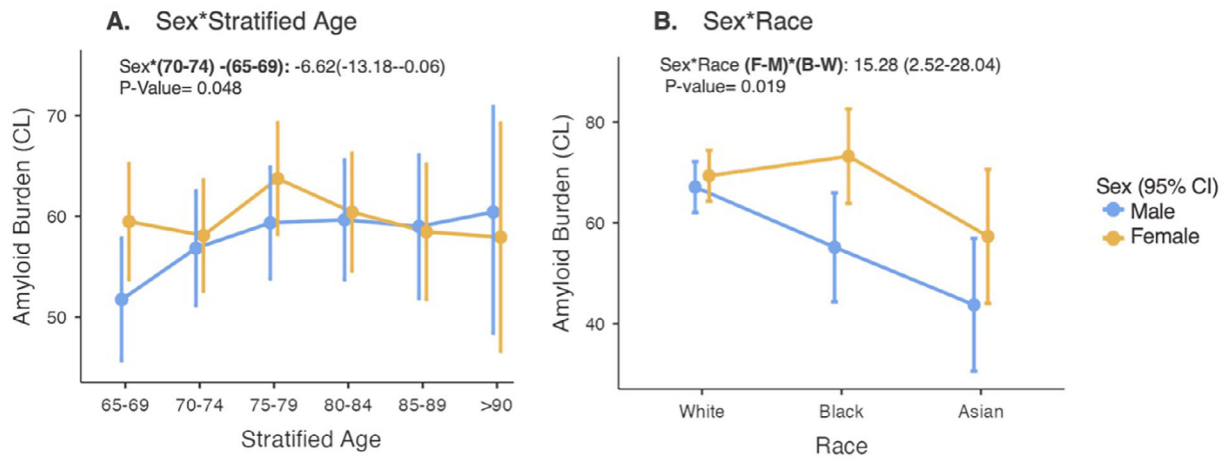
* P-value <0.05 indicates the statistical significance of the difference between the sex groups for each characteristic.

Table 1. Females have higher likelihood of Amyloid PET scan positivity and higher Amyloid burden (CL).

		Predictor: Sex (Female-Male)*					
		Model 1		Model 2		Model 3	
Binomial Regression Model Coefficients							
Outcome	**N**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Amyloid positivity based on visual reads	9266	**1.20** (1.11-1.31)	<0.001	**1.23** (1.13-1.35)	<0.001	**1.19** (1.08-1.30)	<0.001
Multivariable Linear Model Coefficients							
Outcome		**Estimate (95%CI)**	**P-value**	**Estimate (95%CI)**	**P-value**	**Estimate (95%CI)**	**P-value**
Quantitative amyloid burden (CL) **in full sample**	9270	**4.88** (2.89- 6.88)	<0.001	**5.43** (3.44-7.42)	<0.001	**5.06** (3.02-7.10)	<0.001
Quantitative amyloid burden (CL) **in the visually positive scans only**	5721	**2.08** (-0.02-4.18)	0.052	**2.81** (0.66-4.95)	0.010	**3.10** (0.90 -5.31)	0.005

Note: Binomial regression and multivariable linear models were used to identify sex association with amyloid PET scan positivity and amyloid burden, respectively. The findings from these analyses present odds ratios (OR) along with their corresponding 95% confidence intervals (CI) and p-values for the binomial models, as well as adjusted estimates for the multivariable linear models.
Model 1: Outcome~sex
Model 2: Outcome~Sex+age+race+ethnicity+education+MMSE score
Model 3: Outcome~ Sex+age+race+ethnicity+education+MMSE score+ **cardiovascular risk factors+depression+kidney disease+** Traumatic Brain Injury **+ family history of AD**
Abbreviations: CL, Centiloids; MMSE, Mini Mental State Examination
***Male is the reference.**

Figure 2. Sex moderates the effect of age and race on amyloid burden (CL) in individuals with visual positive reads.



Note. Interactions of sex with stratified age (A), and race (B) and their impact on Centiloids in a subgroup of individuals with positive visual reads. We used series of linear models adjusting for demographic variables, impairment level and risk factors and interaction of sex with demographic factors. Shown are the estimates and the 95% CI of estimates for each interaction term included in the model. Abbreviations: (F-M); (Female-Male), male is the reference; W, White; B, Black; A, Asian.