The Role of Sex and Gender in the Selection of Alzheimer Patients for Clinical Trial Pre-screening

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Abstract

Background: Alzheimer disease (AD) is a progressive neurodegenerative disorder affecting the elderly with a prevalence of 7.1% in women and 3.3% in men aged 55 or older. Sex-related patterns have been reported in prognosis, biomarker status and risk factors. Despite this, the interaction of sex has received limited attention, with AD trials persistently recruiting lower numbers of women than the population distribution and a lack of information on the sex-disaggregated effects of anti-dementia therapies. This is the first study aiming to identify the role of sex in the selection for screening in AD clinical trials.

Methods: This cross-sectional study provides a comprehensive analysis of screening eligibility according to a set of pre-selection criteria currently applied at Fundació ACE memory clinic for a more efficient trial screening process. A cohort of 6,667 women and 2,926 men diagnosed with AD dementia (55%) or mild cognitive impairment (45%) was analyzed. We also assessed the frequencies of men and women effectively screened for trial enrolment over a period of 10 years.

Results: Women showed a significantly lower chance of being eligible for screening than men (OR=1.26; $p<0.01$). This imbalance was confirmed by a lower frequency of women screened for enrolment compared to the study population (63.0% vs 69.5%). Education was revealed as the key criterion contributing to this unbalance, with men showing over twice the chance of being screened compared with women (OR=2.25, $p<0.01$). Education-based differences were greater in earlier born patients, but the gap narrowed and achieved balance with increasing year of birth. Comorbidity was the most limiting criterion with sex differences in frequencies and significant discrimination against the selection of men (OR=0.86, $p<0.01$).

Conclusions: The large number of low-educated elderly women with AD demands for a sex-focused approach in clinical research. New assessment tools insensitive to education level should be developed to enable a proportional representation of women. Although this gender education gap is mostly inexistent in developed countries, economic or cultural factors may lead to different scenarios in other regions. Overlooking the impact of sex may lead to a handicap in AD research with a direct adverse impact on women's health.

Full Text

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Figures

Figure 1

Cohort selection flow diagram. The study cohort was selected among a total population of 23,739 subjects assessed at Fundació ACE clinic according to three selection requisites: (1) assessment performed from 2008 to 2018, (2) confirmed initial diagnosis of AD (either dementia or mild cognitive impairment) and clinical dementia rating (CRD) score of 0.5-2. The resulting study sample comprised a total of 9,593 subjects, 2,926 men and 6,667 women.

Figure 2

Odds ratio values comparing eligibility in men and women according to pre-screening selection criteria (age, comorbidity, medication, MMSE, education and all criteria) in the study population (ALL), in the patients diagnosed with Alzheimer dementia (AD) and with minor cognitive impairment (MCI). Asterisk (*) indicate $p < 0.05$ in test comparing eligibility between males and females by multivariable logistic regression (or univariable logistic regression for all criteria). MMSE: Mini-mental state examination.

Figure 3

Frequencies of eligible candidates for trial screening according to education by year of birth, sex and diagnosis, in the study population (ALL), in the patients diagnosed with Alzheimer dementia (AD) and with minor cognitive impairment (MCI). Asterisk (*) indicates $p < 0.05$ in multivariable logistic regression test comparing eligibility between males and female.

Figure 4

Sex distribution in the sample of patients screened at Fundació ACE memory clinic from 2008 to 2018 (A) compared with the distribution in eligible candidates (B) and in the study population (C) for all the patients (ALL), patients with Alzheimer dementia (AD) and patients with minor cognitive impairment (MCI).