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Research Article

Sex differences in risk factors that predict progression from mild cognitive impairment to Alzheimer's dementia

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Abstract

Objectives: To evaluate whether cerebrospinal fluid biomarkers, apolipoprotein e4, neuroimaging abnormalities, and neuropsychological data differentially predict progression from mild cognitive impairment (MCI) to dementia for men and women. **Methods:** Participants who were diagnosed with MCI at baseline ($n = 449$) were classified as either progressing to Alzheimer's dementia at follow-up or as not progressing. Men and women were first compared using bivariate analyses. Sex-stratified Cox proportional hazard regressions were performed examining the relationship between baseline data and the likelihood of progressing to dementia. Sex interactions were subsequently examined. **Results:** Cox proportional hazard regression controlling for age and education indicated that all variables significantly predicted subsequent progression to dementia for men and women. Sex interactions indicated that only Rey Auditory Verbal Learning Test (RAVLT) delayed recall and Functional Activities Questionnaire (FAQ) were significantly stronger risk factors for women. When all variables were entered into a fully adjusted model, significant risk factors for women were Aβ42, hippocampal volume, RAVLT delayed recall, Boston Naming Test, and FAQ. In contrast, for men, Aβ42, p-tau181, p-tau181/Aβ42, hippocampal volume, category fluency and FAQ were significant risk factors. Interactions with sex were only significant for p-tau181/Aβ42 and RAVLT delayed recall for the fully adjusted model. **Conclusions:** Men and women with MCI may to differ for which factors predict subsequent dementia although future analyses with greater power are needed to evaluate sex differences. We hypothesize that brain and cognitive reserve theories may partially explain these findings.

Keywords: Alzheimer's disease; sex stratification; cognitive decline; ATN framework; cognitive reserve; biomarkers

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In November 2017, the Alzheimer's Association's Research Roundtable met to discuss the new National Institute on Aging and the Alzheimer's Association Research Framework (Knopman et al., 2018). The goal of these updated research criteria was not to characterize a clinicopathological disorder (i.e., Alzheimer's *dementia*), but rather to come to a consensus on how to characterize Alzheimer's *disease* (AD). It should be noted that this framework was not developed for clinical purposes. This framework has been named the ATN system with "A," "T," and "N" designating amyloid, tau, and neurodegeneration, respectively (Jack et al., 2018). These biomarkers are most often quantified using markers of cerebrospinal fluid (CSF) protein concentrations and neuroimaging techniques. This framework operates under the assumption that A, T and N are important factors for identifying individuals falling on the AD continuum. Lower levels of CSF Aβ1–42 (Aβ42) is associated with higher neural plaque burden, whereas higher levels of CSF total tau and phosphorylated tau181(p-tau181) is associated with greater axonal damage in the brain (Shaw et al., 2009). A core goal of the ATN framework is to ensure that clinical trials investigating disease-modifying therapies for AD enroll participants who have tested positive for the underlying pathology being targeted.

Prior to the widespread adoption of the ATN framework, it is important that it be validated across demographic groups, such as sex and gender. While some studies have not found a clear sex difference in the degree of A, T, and N accumulation in those who are cognitively normal (Jack et al., 2017) or have subjective cognitive complaints (Wang & Tian, 2018), others have found greater tau accumulation in women. Although the reason for this sex

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difference is unclear, it may be explained by the modulating effects of apolipoprotein e4 (APOE4) (Hohman et al., 2018) and testosterone (Sundermann et al., 2020). Moreover, little is known in terms of how these biomarkers may differentially predict clinical outcomes in men and women (Nebel et al., 2018). That is, there may be sex- and gender-specific vulnerabilities to these biomarkers with respect to clinical expression and disease progression. For example, several studies have found that women appear to be more vulnerable to the effects of APOE4 (Altmann et al., 2014; Farrer et al., 1997; Kim et al., 2015) and AD pathology (Filon et al., 2016; Koran et al., 2017). Unfortunately, many studies control for the effect of sex without performing sex-stratified and sex interaction analyses. The Canadian Institutes for Health Research (CIHR) states that simply controlling for the effects of sex and gender can limit our ability to identify relationships between risk factors and outcome variables. Relationships that differ for men and women may be missed or inappropriately applied to both sexes. CIHR recommends stratifying by sex and gender rather than adjusting for sex as a confounder (CIHR, 2012). In keeping with these recommendations, sex-stratified research of these biomarkers is needed, especially in terms of predicting progression to dementia (Ferretti et al., 2018).

A limited number of published studies have conducted sex-stratified analyses predicting progression from mild cognitive impairment (MCI) to dementia (Artero et al., 2008; Kim et al., 2015) or from normal cognition to MCI (Pankratz et al., 2015). However, these studies did not examine CSF biomarkers. Koran and colleagues (2017) investigated whether AD biomarkers predicted cerebral atrophy and neuropsychological decline with the inclusion of sex interactions. These authors found a stronger association between baseline AD biomarkers (i.e., Aβ42 and total tau) and longitudinal decline in hippocampal volume and executive functioning in women relative to men. Similarly, Sohn and colleagues (Sohn et al., 2018) found that women with MCI and clinical levels of AD biomarkers showed a faster cognitive decline than men. These studies did not include incident dementia as an outcome. Accordingly, we sought to examine whether ATN biomarkers differentially predict progression from MCI to dementia using both sex stratification and sex interaction analyses. Neuropsychological measures were also examined as they are accessible, low-cost, noninvasive measures that also have high predictive value for dementia outcomes (Cloutier et al., 2020), in some cases above and beyond biomarker prediction (Nation et al., 2019). To our knowledge, no study to date has examined how well ATN biomarkers predict subsequent dementia in MCI using sex-stratified methods.

The aims of this study are (1) to examine which baseline biomarkers and neuroimaging measures predict progression to dementia with sex simply included as a covariate, as is common practice, and (2) to examine whether sex differences exist in these risk factors. The second aim was explored using two approaches. Firstly, data were stratified by sex to explore which factors predict progression to dementia for men and women. Secondly, interactions with sex were examined to identify statistically significant sex differences. Analyses were conducted for each variable independently and with all variables entered into the sample model to explore the unique variance explained by each risk factor, above and beyond the other risk factors examined.

Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. Data was downloaded from the ADNI website on July 30, 2018. All ADNI studies are conducted according to the Good Clinical Practice guidelines, the Declaration of Helsinki, and U.S. 21 CFR Part 50 (Protection of Human Subjects), and Part 56 (Institutional Review Boards). Written informed consent was obtained from all participants before protocol-specific procedures were performed. The ADNI protocol was approved by the Institutional Review Boards of all of the participating institutions.

Study participants

Longitudinal data were taken from the ADNI-1, ADNI-GO, ADNI-2, and ADNI-3 phases. Baseline data for the sample analyzed were acquired in person between November 2005 and August 2013 (see www.adni-info.org for the detailed study protocol). Diagnosis of MCI required an Mini-Mental State Examination (MMSE) score between 24 and 30, self or informant subjective memory complaint, objective memory loss on Logical Memory, a clinical dementia rating of 0.5, absence of significant impairment in other cognitive domains or instrumental activities of daily living (IADL) functioning, and absence of dementia. Alzheimer's dementia was based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD (McKhann et al., 2011). Participants were included if they were diagnosed with MCI at baseline, were followed for at least 24-months or progressed to dementia, and possessed baseline data (i.e., visit 1) for all variables analyzed. Sex was self-reported. Each participant was classified as either progressing to dementia or not progressing (i.e., remained as MCI or reverted to cognitively normal). Progression was based on the diagnosis at the latest visit. Therefore, if a participant progressed to dementia and then reverted to MCI, they were classified as not progressing.

CSF and neuroimaging biomarkers

Aβ42, p-tau181, and structural MRI data for bilateral hippocampal and ventricular volumes were taken from the ADNIMERGE table. ATN biomarkers were examined continuously. In addition to examining Aβ42 and p-tau181 levels, the ratio of p-tau181 to Aβ42 (i.e., p-tau181/Aβ42) was also examined. This metric has been shown to better predict clinical decline relative to Aβ42 alone (Fagan et al., 2007) and better discriminates between AD and non-AD related dementias (Santangelo et al., 2019), as this ratio variable is thought to better capture the progression of AD-related pathology. See the supplemental material for a summary of the CSF quantification methods.

Neuropsychological measures

Raw scores for delayed free recall from the Rey Auditory Verbal Learning Test (RAVLT), total score from the Boston Naming Test (BNT) short form, and total scores from a category fluency trial were taken from the ADNIMERGE table. These neuropsychological measures were selected for their sensitivity for predicting

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AD (Belleville et al., 2017). Given that functional impairment is a key distinguishing feature for MCI and dementia, the Functional Activities Questionnaire (FAQ) (Pfeffer et al., 1982) was included as a measure of IADL. The FAQ was dichotomized (<6 coded as 0, no to minimal limitations in IADLs; ≥6 coded as 1, greater dependence in IADLs; Nitrini et al., 2004).

Statistical analysis

All data were analyzed using SPSS version 27 (2020). Independent samples *t*-test, Mann-Whitney U, and chi-square were used to compare men and women on sociodemographic characteristics, biomarkers of interest, and cognitive characteristics. Age at baseline (years) and years of education were included as covariates. Analyses were also stratified by sex (men coded as 1 and women coded as 0). Progression to dementia was coded as 1 and nonprogression was coded as 0. APOE4 status was dichotomized as the presence of one or two e4 alleles (coded as 1) or no alleles (coded as 0).

Cox proportional hazards (PH) regressions were performed examining the relationship between baseline data and the likelihood of progressing to dementia over the follow-up period. In **Analysis 1**, all variables were entered into the same model, with sex entered as a covariate, as is most common practice. Due to high intercorrelations, one model included Aβ42 and p-tau181 (Model 1) and another model included p-tau181/Aβ42 (Model 2).

$$h(t|X_i) = h_0(t)\ \exp\ \beta_{Sex}Sex_i + \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{APOE4}APOE4_i + \beta_{A\beta42}A\beta42_i + \beta_{p-tau181}p-tau181_i + \beta_{VentricularVol}VentricularVol_i + \beta_{HippVol}HippVol_i + \beta_{RAVLT}RAVLT_i + \beta_{BNT}BNT_i + \beta_{CategoryFluency}CategoryFluency_i + \beta_{FAQ}FAQ_i) \quad (1)$$

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Sex}Sex_i + \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{APOE4}APOE4_i + \beta_{p-tau181/A\beta42}p-tau181/A\beta42_i + \beta_{VentricularVol}VentricularVol_i + \beta_{HippVol}HippVol_i + \beta_{RAVLT}RAVLT_i + \beta_{BNT}BNT_i + \beta_{CategoryFluency}CategoryFluency_i + \beta_{FAQ}FAQ_i) \quad (2)$$

Next, we were interested in examining whether these variables differentially predict dementia for men and women, which was examined using several methods. In **Analyses 2a,** data were stratified by sex and individual Cox PH regression analyses were conducted for each variable, adjusting for age and education (Model 3).

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{Predictor}Predictor_i) \quad (3)$$

In **Analyses 2b**, interactions with sex were conducted for variables that were significant in Analysis 2a, adjusting for age and education (Model 4).

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Sex}Sex_i + \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{Predictor}Predictor_i + \beta_{Predictor}Predictor_iSex_i) \quad (4)$$

Analysis 3a examined the incremental value for each variable, above and beyond the effects of the other variables included in the model. Data were stratified by sex and all variables were entered into a fully adjusted model. Due to high intercorrelations, one model included Aβ42 and p-tau181 (Model 5) and another model included p-tau181/Aβ42 (Model 6).

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{APOE4}APOE4_i + \beta_{A\beta42}A\beta42_i + \beta_{p-tau181}p-tau181_i + \beta_{VentricularVol}VentricularVol_i + \beta_{HippVol}HippVol_i + \beta_{RAVLT}RAVLT_i + \beta_{BNT}BNT_i + \beta_{CategoryFluency}CategoryFluency_i + \beta_{FAQ}FAQ_i) \quad (5)$$

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{APOE4}APOE4_i + \beta_{p-tau181/A\beta42}p-tau181/A\beta42_i + \beta_{VentricularVol}VentricularVol_i + \beta_{HippVol}HippVol_i + \beta_{RAVLT}RAVLT_i + \beta_{BNT}BNT_i + \beta_{CategoryFluency}CategoryFluency_i + \beta_{FAQ}FAQ_i) \quad (6)$$

In **Analysis 3b**, interaction effects with sex were then entered into the fully adjusted model for variables that were statistically significant in Analysis 3a. Interaction variables were mean-centered before being entered into this final analysis (Models 7 and 8).

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Sex}Sex_i + \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{APOE4}APOE4_i + \beta_{A\beta42}A\beta42_i + \beta_{p-tau181}p-tau181_i + \beta_{VentricularVol}VentricularVol_i + \beta_{HippVol}HippVol_i + \beta_{RAVLT}RAVLT_i + \beta_{BNT}BNT_i + \beta_{CategoryFluency}CategoryFluency_i + \beta_{FAQ}FAQ_i + \beta_1Sex_iPredictor_{i1} + \ldots + \beta_kSex_iPredictor_{ik}) \quad (7)$$

$$h(t|X_i) = h_0(t)\ \exp\ (\beta_{Sex}Sex_i + \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{APOE4}APOE4_i + \beta_{p-tau181/A\beta42}p-tau181/A\beta42_i + \beta_{VentricularVol}VentricularVol_i + \beta_{HippVol}HippVol_i + \beta_{RAVLT}RAVLT_i + \beta_{BNT}BNT_i + \beta_{CategoryFluency}CategoryFluency_i + \beta_{FAQ}FAQ_i + \beta_1Predictor_{i1}Sex_i + \ldots + \beta_kPredictor_{ik}Sex_i) \quad (8)$$

Individual supplementary analyses were conducted for head-size corrected neuroimaging measures (i.e., [neuroimaging variable/total intracranial volume]*100), and norm-adjusted neuropsychological scores. These analyses were stratified by sex (Model 9) and with sex interactions (Model 10). The RAVLT was adjusted for age (Ivnik et al., 1990), BNT was adjusted for age (Ivnik et al., 1996), and category fluency was adjusted for age and education (Tombaugh et al., 1999).

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Table 1. Baseline characteristics of men and women compared using independent samples *t*-test, Mann-Whitney *U*, or Pearson's chi-square

	Women ($n = 188$)	Men ($n = 261$)	Statistic	*p*-value	Cohen's *d*
Length of follow-up (months)	51.8 (23.2)	52.8 (23.6)	−0.46	.64	0.04
Progression to dementia, n (%)	69 (36.7)	104 (39.8)	0.46	.50	–
Age (years)	70.6 (7.6)	72.8 (7.0)	−3.25	.001	0.30
Education (years)	15.4 (2.7)	16.6 (2.7)	−4.52	<.001	0.44
MMSE (/30)	27.9 (1.8)	27.7 (1.7)	1.22	.22	0.11
APOE4 positive, n (%)	95 (50.5)	126 (48.3)	0.22	.64	–
Elecsys® Aβ-42 (pg/mL)	1013.7 (444.4)	925.7 (436.1)	2.09	.037	0.2
Elecsys® p-tau (pg/mL); MED (IQR)	24.4 (18.6)	23.5 (15.5)	23302.5	.36	–
Elecsys® p-tau/Aβ (%); MED (IQR)	0.03 (0.04)	0.03 (0.04)	23446	.42	–
Hippocampal volume (cc)	6.7 (1.1)	7.0 (1.2)	−2.52	.01	0.26
Ventricular volume (cc); MED (IQR)	26.6 (22.1)	37.6 (27.8)	15315.5	<.001	–
RAVLT 30min delay (/15)	4.9 (4.4)	3.5 (3.4)	3.69	<.001	0.36
Category Fluency	17.5 (5.1)	17.7 (5.0)	−0.41	.68	0.04
BNT (/30); MED (IQR)	27 (4)	28 (3)	21307	.02	–
FAQ (n, % >=6)	26 (13.6)	59 (22.6)	5.48	.02	–

Data are presented as M (SD) and compared using independent samples *t*-tests unless otherwise specified.
Non-normal data are presented as MED (IQR) and compared using Mann-Whitney *U*.
Dichotomous data presented as *n* (%) and compared using Pearson Chi Square.
M = Mean; SD = Standard deviation; MED = median; IQR = Interquartile Range; MMSE = Mini-Mental State Examination; APOE4 = Apolipoprotein E4; Aβ-42 = CSF Amyloid β 1-42; p-tau = phosphorylated tau181; RAVLT = Rey Auditory Verbal Learning Test; BNT = Boston Naming Test; FAQ = Functional Activities Questionnaire.

$$h(t|X_i) = h_0(t)\ \exp\ \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{PredictorCorrected}PredictorCorrected_i \quad (9)$$

$$h(t|X_i) = h_0(t)\ \exp\ \beta_{Sex}Sex_i + \beta_{Age}Age_i + \beta_{Education}Education_i + \beta_{PredictorCorrected}PredictorCorrected_i + \beta_{PredictorCorrected}PredictorCorrected_iSex_i \quad (10)$$

Results

Of the 915 participants who were diagnosed with MCI at baseline, 735 study participants either progressed to dementia or had diagnostic data at 24-months or later. Of these individuals, a total of 286 participants were further excluded for missing Elecsys® CSF data ($n = 195$), hippocampal volumetrics ($n = 111$), ventricular volumetrics ($n = 23$), BNT scores ($n = 1$), and FAQ scores ($n = 4$). The final sample was made up of 449 participants (men $n = 261$; women $n = 188$). Mean follow-up time for the included sample was 52.2 months (SD = 23 months; range = 11.25 to 139.57 months). Compared to excluded participants, the included sample was significantly younger ($p < .001$; $d = .29$), had smaller ventricles ($p < .001$; $d = .25$), larger hippocampi ($p = .02$; $d = .20$), higher BNT scores ($p = .004$; $d = .25$), and higher animal fluency scores ($p = .008$; $d = .18$). Included and excluded samples did not differ in terms of sex ($p = .48$), APOE4 ($p = .54$), education ($p = .11$), CSF biomarkers ($p = .68$ to $.94$), RAVLT delayed recall ($p = .16$), or FAQ ($p = .12$). While effect sizes comparing included and excluded participants were small overall, the findings from this study may not generalize to the excluded ADNI sample who were somewhat older and exhibited worse neuroimaging and neurocognitive functioning.

Baseline descriptive characteristics stratified by sex are summarized in Table 1. Age ranged from 55 to 88 years and education ranged from 6 to 20 years. Continuous data are presented as mean (SD), skewed data are presented as median (IQR), and dichotomous data are presented as *n* (%). At baseline, men were significantly older, had more years of education, lower Aβ42 levels, larger hippocampal volumes, larger ventricular volumes, lower RAVLT scores, higher BNT scores, and worse FAQ scores. Men and women did not differ significantly on duration of follow-up, frequency of progression to dementia, APOE4 status, p-tau181, p-tau181/Aβ42, MMSE scores, or category fluency scores.

Schoenfeld residuals were obtained for each covariate, which were plotted against survival rankings for noncensored participants. Visual inspection of Schoenfeld residuals revealed a random relationship with time for all variables (see Supplemental Figure 1).

Table 2. Fully adjusted Cox PH regression of baseline measures predicting progression to AD, with sex included as a covariate (analysis 1)

	Men and women combined ($n = 449$)		
	HR [95% CI]	Std HR*	*p*-value
Sex	1.15 [0.80–1.65]	–	.45
Age	0.98 [0.95–1.00]	0.86 [0.72–1.03]	.09
Years of education	1.02 [0.96–1.09]	1.06 [0.90–1.25]	.46
APOE4 (dichotomized)	1.33 [0.94–1.90]	–	.11
Elecsys® Aβ42	0.999 [0.999–1.00]	0.66 [0.52–0.83]	<.001
Elecsys® p-tau181	1.02 [1.01–1.03]	1.27 [1.09–1.48]	.003
Ventricular volume	1.01 [0.997–1.01]	1.11 [0.93–1.33]	.24
Hippocampal volume	0.66 [0.55–0.79]	0.61 [0.50–0.76]	<.001
RAVLT Delay Recall	0.93 [0.87–0.99]	0.74 [0.57–0.95]	.02
BNT	0.95 [0.91–1.00]	0.82 [0.68–0.997]	.046
Category Fluency	0.95 [0.91–0.99]	0.77 [0.63–0.93]	.008
FAQ (dichotomized)	3.21 [2.27–4.53]	–	<.001

* Based on variables entered as *z*-scores.
Elecsys® p-tau181/Aβ42 std HR = 1.27, $p < .001$.

Analysis 1: fully adjusted Cox PH regression with sex entered as a covariate

When all variables, including sex, were included in the same model, Aβ42, p-tau181, hippocampal volume, RAVLT delayed recall, BNT scores, category fluency, and FAQ significantly predicted dementia. When this analysis was rerun including p-tau181/Aβ, this ratio variable also significantly predicted time to dementia progression (see Table 2).

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Table 3. Cox PH analyses of baseline measures predicting progression to AD stratified by sex. Regression analyses run separately for each variable, adjusting for age (years) and education (years) (analysis 2a). Data were reaggregated and sex interactions were included within each model (analysis 2b)

	Women ($n = 188$)			Men ($n = 261$)			
	HR [95% CI]	Std HR [95% CI]*	*p*-value	HR [95% CI]	Std HR [95% CI]*	*p*-value	Sex interaction *p*-value
APOE4 (dichotomized)	3.78 [2.15–6.67]	–	<.001	2.12 [1.42–3.15]	–	<.001	.15
Elecsys® Aβ42	1.00 [1.00–1.00]	0.33 [0.23–0.46]	<.001	1.00 [1.00–1.00]	0.45 [0.34–0.59]	<.001	.19
Elecsys® p-tau181	1.04 [1.02–1.05]	1.60 [1.37–1.87]	<.001	1.03 [1.02–1.05]	1.59 [1.33–1.90]	<.001	.93
Elecsys® p-tau181/Aβ42 †		1.55 [1.37–1.75]	<.001		1.76 [1.49–2.08]	<.001	.16
Ventricular volume	1.02 [1.00–1.03]	1.38 [1.06–1.80]	.02	1.01 [1.00–1.02]	1.25 [1.05–1.48]	.01	.69
Hippocampal volume	0.42 [0.34–0.52]	0.36 [0.28–0.46]	<.001	0.54 [0.45–0.65]	0.49 [0.40–0.61]	<.001	.13
RAVLT Delay Recall	0.70 [0.63–0.78]	0.25 [0.17–0.38]	<.001	0.84 [0.78–0.90]	0.50 [0.38–0.67]	<.001	.01
BNT	0.87 [0.82–0.93]	0.58 [0.45–0.74]	<.001	0.88 [0.82–0.94]	0.61 [0.47–0.79]	<.001	.76
Category Fluency	0.84 [0.79–0.90]	0.42 [0.31–0.58]	<.001	0.91 [0.87–0.95]	0.63 [0.50–0.78]	<.001	.19
FAQ (dichotomized)	8.02 [4.76–13.50]	–	<.001	3.94 [2.61–5.95]	–	<.001	.045

*Based on variables entered as *z*-scores.
† HR Women: 2.06×10^6 [3.19×10^4–1.34×10^8]; Men: 1.56×10^8 [6.44×10^5–3.78×10^{10}].

Table 4. Cox PH analyses of baseline measures predicting progression to AD stratified by sex. Regression analyses run entering all variables simultaneously, adjusting for age (years) and education (years) (analysis 3a). Data reaggregated and sex interactions included for significant variables from the sex-stratified analyses (analysis 3b)

	Women ($n = 188$)			Men ($n = 261$)			
	HR [95% CI]	Std HR [95% CI]*	*p*-value	HR [95% CI]	Std HR [95% CI]*	*p*-value	Sex interaction *p*-value †
APOE4 (dichotomized)	1.30 [0.68–2.47]	–	.43	1.44 [0.93–2.25]	–	.11	–
Elecsys® Aβ42	1.00 [1.00–1.00]	0.59 [0.40–0.88]	.01	1.00 [1.00–1.00]	0.71 [0.53–0.97]	.03	.55
Elecsys® p-tau181	1.00 [0.98–1.02]	1.05 [0.80–1.36]	.74	1.03 [1.01–1.04]	1.42 [1.15–1.77]	.001	.07
Ventricular volume	1.00 [0.98–1.02]	0.95 [0.61–1.48]	.82	1.01 [1.00–1.02]	1.15 [0.95–1.41]	.16	–
Hippocampal volume	0.63 [0.45–0.87]	0.58 [0.40–0.85]	.005	0.63 [0.50–0.80]	0.58 [0.45–0.77]	<.001	.90
RAVLT Delay Recall	0.84 [0.74–0.94]	0.50 [0.32–0.78]	.002	0.98 [0.90–1.06]	0.92 [0.67–1.27]	.62	.045
BNT	0.90 [0.84–0.98]	0.67 [0.50–0.91]	.01	0.98 [0.91–1.05]	0.92 [0.70–1.22]	.57	.28
Category Fluency	0.97 [0.90–1.04]	0.85 [0.58–1.24]	.41	0.94 [0.89–0.99]	0.73 [0.57–0.93]	.01	.42
FAQ (dichotomized)	2.70 [1.50–4.87]	–	<.001	3.83 [2.44–6.02]	–	<.001	.19

*Based on variables entered as z-scores.
† Interaction with sex only entered for significant variables.
Note: Analyses rerun replacing Aβ42 and p-tau181 with p-tau181/Aβ42 due to multicollinearity.
Women: Elecsys® p-tau181/Aβ42 (HR = 23.26 [0.02–3.36*104], Std HR = 1.10 [0.88–1.37], p = .40).
Men: Elecsys® p-tau181/Aβ42 (HR = 7.38*105 [613.50–8.87*108], Std HR = 1.50 [1.21–1.86], $p \leq .001$).
Sex interaction: Elecsys® p-tau181/Aβ42 ($p = .01$).

Analysis 2a and 2b: individual sex-stratified Cox PH regression analyses conducted for each variable, adjusting for age and education, with subsequent sex interactions

When stratifying by sex, the main effects were significant for all variables for both men and women (see Table 3). In order of effect size based on standardized hazard ratios, FAQ scores, RAVLT delayed recall, APOE4 status, Aβ42, hippocampal volume, category fluency, BNT scores, p-tau181, p-tau181/Aβ42, and ventricular volume were significant risk factors for dementia over the follow-up period for women. For men, FAQ scores, Aβ42, APOE4 status, hippocampal volume, RAVLT delayed recall, p-tau181/Aβ42, BNT scores, p-tau181, category fluency, and ventricular volume were significant. When reaggregating the data and including interaction effects with sex, only RAVLT delayed recall and FAQ scores revealed a significant interaction effect, with these variables being stronger risk factors for women.

Supplemental analyses were repeated with head-sized corrected neuroimaging variables and norm-adjusted neuropsychological variables. The results were generally unchanged for these variables (see Supplemental Table 1).

Analysis 3a: fully adjusted Cox PH regression stratified by sex

In the fully adjusted Cox PH regression models (see Table 4), significant risk factors for women were Aβ42, hippocampal volume, RAVLT delayed recall, BNT scores, and FAQ scores. Above and beyond the effects of the other variables included in the model, APOE4 status, p-tau181, ventricular volume, and category fluency were no longer independent predictors of dementia progression for women. In contrast, for men, APOE4, Aβ42, p-tau181, p-tau181/Aβ42, hippocampal volume, category fluency, and FAQ scores significantly predicted progression to dementia, whereas APOE4, ventricular volume, RAVLT delayed recall, and BNT scores did not reach the level of significance.

Analysis 3b: fully adjusted Cox PH regression with sex interactions

Interactions with sex (see Table 4) were only significant for p-tau181/Aβ42, with stronger effects for men, and RAVLT delayed recall, with stronger effects for women. Unexpectedly, the sex interaction effect for p-tau181/Aβ42 was highly significant, in contrast to the nonsignificant effect demonstrated when only adjusting for age and education. Follow-up exploratory analyses (results not reported) revealed that this change in effect appears to be primarily explained by the inclusion of FAQ in the model. While p-tau181 demonstrated a somewhat stronger effect for men, the sex interaction effect did not reach statistical significance ($p = .07$).

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Discussion

We sought to examine whether demographic, ATN biomarker, and neuropsychological variables differentially predict progression from MCI to dementia when stratified by sex. The results from our study indicate that the baseline variables that best predict progression from MCI to dementia differ in some respects between men and women. When adjusting for only age and education, individual regression analyses revealed that all baseline cognitive and biomarker variables examined significantly predicted progression to dementia over the follow-up period. Some of these variables (i.e., delayed verbal memory and IADL functioning) were consistently stronger predictors of dementia in women when only adjusting for age and level of education.

Although nearly all variables predicted dementia for men and women in the individual regression analyses, the unique contribution of each variable in the fully adjusted models varied by sex. For women, variables associated with the greatest odds of developing dementia in order of effect were (1) a score of 6 or greater on the FAQ; (2) poorer delayed verbal memory, (3) smaller hippocampi, (4) lower concentrations of Aβ42; and (5) lower scores on a measure of confrontation naming. In men, the strongest predictors were (1) a score of 6 or greater on the FAQ; (2) smaller hippocampi; (3) a higher ratio of p-tau181 to Aβ42; (4) higher concentrations of p-tau181; (5) lower concentrations of Aβ42; and (6) fewer words provided on a test of animal fluency. Although numerous risk factors appeared to differ between men and women according to stratified analyses, only verbal memory was a significantly stronger risk factor for women, and the ratio of p-tau181 to Aβ42 was a significantly stronger risk factor for men, based on sex interactions. Surprisingly, the ratio of p-tau181 to Aβ42 only demonstrated a significant sex interaction in the fully adjusted model. Subsequent exploratory analyses revealed that this may be explained by the inclusion of IADL functioning in the model. In other words, while the ratio of p-tau181 to Aβ42 did not differentially predict dementia for men and women when only adjusting for age and education, this variable did demonstrate a significantly stronger effect for men after controlling for limitations in IADL functioning. Given that men presented with greater IADL difficulties than women in this ADNI sample, these men may be further along the AD continuum at baseline. As a result, the ratio of p-tau181 to Aβ42 may better predict subsequent dementia for men in this sample.

Individuals with MCI and subjective memory complaints, accompanied with IADL difficulties, are considered a high-risk population for developing dementia (Luck et al., 2011, 2012; Roehr et al., 2019). In our analyses, reduced independence in IADLs was the strongest predictor of subsequent dementia for both men and women, with a stronger relationship for women when only adjusting for age and education. A smaller proportion of women than men obtained scores of 6 or greater on the FAQ, which may reflect a resiliency to functional decline for women. This may be explained by greater experience engaging in these IADLs for women in this older cohort. If so, the smaller subset of women with poorer ratings of real-world functioning may demonstrate faster progression to dementia. This is consistent with individuals with higher cognitive reserve who demonstrate faster cognitive decline after reaching an "inflection point" (Stern, 2009). We have proposed a similar "functional reserve" process specific to real-world functioning (Berezuk et al., 2017, 2018).

The detrimental effects of possessing one or two APOE4 alleles did not demonstrate incremental value above and beyond the other variables examined. Hobel and colleagues (2019) found that APOE4 was more detrimental for women; however, their study was cross-sectional in nature and hippocampal atrophy and neurocognitive functioning were examined as outcomes. Lower CSF concentrations of Aβ42 and smaller hippocampal volumes were independent predictors of dementia for both sexes, whereas higher CSF concentrations of p-tau181 and a higher ratio of p-tau181 to Aβ42 were only significant for men. Neuropsychological measures also varied in terms of which variables uniquely predicted subsequent dementia when comparing men and women. Lower delayed verbal memory and naming ability were significant independent risk factors for women, whereas worse category fluency was a significant risk factor for men. Despite these differences between men and women based on stratified analyses, only delayed verbal memory and the ratio of p-tau181 to Aβ42 exhibited a significant sex difference. Nevertheless, these exploratory sex differences identified in the stratified analyses may be avenues for future research with a larger sample.

Our findings, which are uniquely interested in diagnostic progression from MCI to dementia using longitudinal data, are fairly consistent with existing research. Although nearly all biomarker variables were significant risk factors for women, some of these effects were attenuated when neuropsychological measures were included in the model. Greater shared variance between AD biomarkers and cognitive functioning in women may explain why amyloid concentrations or hippocampal volumes did not predict progression to dementia above and beyond the effects of cognition in our study. This is consistent with a study that found cognitive markers to be stronger predictors of progression to dementia relative to biomarkers (Gomar et al., 2011), although that study did not examine the impact of sex. Conversely, greater cognitive resiliency to the effects of AD pathology in men may support why a larger number of biomarker variables remained significant in the multivariate model compared to neuropsychological measures, especially earlier in the disease course. Generally, the literature suggests that women tend to be more vulnerable to the effects of AD pathology. Cognitive reserve (Stern, 2012) and brain reserve (Katzman et al., 1988) hypotheses are possible explanations for greater vulnerability in women (Malpetti et al., 2017; Skup et al., 2011). Barnes and colleagues (2005) found that a 1 unit increase in AD pathology at the time of autopsy was associated with a 3-fold increased odds of clinical AD in men, relative to a 22-fold increased odds in women, with a stronger relationship between AD biomarker burden and cognitive functioning evident for women. Additionally, amyloid, total tau, and phosphorylated tau have been found to correlate with delayed verbal memory in women alone (Haapalinna et al., 2016). However, the relationship between sex and reserve is likely more nuanced. For example, Digma and colleagues (2020) demonstrated that women can endure a higher degree of tau pathology before presenting impaired verbal memory, which may be attributed to a premorbid female advantage in verbal memory.

Importantly, when sex was simply entered into this model as a covariate, as is common practice, most variables were significant risk factors for developing dementia. Since this model controlled for the effects of sex, these results may be interpreted as applying to both men and women. Based on our sex-stratified and sex interaction analyses, this may not be an accurate interpretation for a number of variables. This distinction provides further support for recommendations to stratify by sex and include sex interactions when studying AD risk factors, with further studies needed with greater power.

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There are limitations to this work. Firstly, the ADNI sample is highly educated, contains a higher proportion of men to women, and is predominantly White, which limits the generalizability of our findings. Glymour and colleagues (2018) argue that the ATN framework will work best for White, highly educated, high to middle income countries, and individuals with proximity to major research universities, therefore this work must be replicated in culturally diverse samples. Secondly, sex and gender differences are likely explained by many complex mechanisms (e.g., genetic, hormonal, environmental, psychiatric, vascular, social factors, etc.), which may account for dementia risk. This study did not explore these possible underlying mechanisms. Additionally, prior work examining ADNI revealed sex differences in the aMCI diagnostic error rate, with greater false negative errors for women and greater false positive errors for men. These authors attributed this diagnostic error to the use verbal memory scores that are not adjusted using sex-based normative data (Sundermann et al., 2019). It is possible that sex differences in baseline diagnostic error may account for some of the sex differences identified in this study. Thirdly, reasons for censorship (e.g., death and loss to follow-up) and possible sex differences in these factors was not examined in the current study. Fourthly, while a strength of ADNI is its large sample size, many participants without CSF data were excluded from the current study, limiting generalizability of our findings and statistical power. This is especially true for the fully adjusted models that stratify by sex, which may be especially prone to type 2 error. Given that this sample included fewer women than men, the results derived from the women-only analyses may be particularly vulnerable to statistical artifacts. This a major limitation to many studies examining sex differences and highlights the need for these findings to be replicated in other large longitudinal datasets. Finally, it may be somewhat tautological to use baseline measures of IADL impairment and cognition to predict later dementia, given that these factors are used for the diagnosis of AD. This is further complicated by the fact that the threshold between MCI and dementia is somewhat arbitrary. Therefore, individuals with poorer functioning on these measures at baseline may be later in the disease continuum and more likely to progress to dementia during our study. For example, longitudinal work has found a quadratic decline in complex ADL functioning just prior to dementia diagnosis (Cloutier et al., 2020). Despite these limitations, which we would expect to affect both men and women, sex differences nonetheless were identified.

To summarize, risk factors appear to differ between men and women for predicting progression from MCI to dementia when stratifying by sex, with a greater number of significant brain-based and CSF biomarker for men in the final model and a greater number of neuropsychological measures significant for women. However, only verbal memory and the ratio of CSF p-tau181 to Aβ42 demonstrated a statistically significant sex difference in the final model. As statistical power is a limitation of this work, further sex-based research is needed when validating the ATN framework and other models of Alzheimer's disease.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617722000297

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Conflicts of interest. None.

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