Alzheimer's & Dementia
Diagnosis, Assessment
& Disease Monitoring

RESEARCH ARTICLE

Women's higher brain metabolic rate compensates for early Alzheimer's pathology

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Abstract

Introduction: The female advantage in brain metabolic function may confer cognitive resilience against Alzheimer's disease (AD).

Methods: A total of 1259 participants (44% women; 52% mild cognitive impairment; 18% AD) aged 55 to 90 from the Alzheimer's Disease Neuroimaging Initiative (ANDI) completed tests of global cognition, verbal memory, and executive function, and neuroimaging assessments of regional glucose metabolism, hippocampal volume (HV), and amyloid beta ($A\beta$). We examined sex differences in brain metabolism and cognition by AD biomarker quartiles ($A\beta$, HV). We then examined if metabolism mediates sex differences in cognition.

Results: Metabolism was higher in women versus men when pathology was mild-to-moderate (quartiles 2 to 3). Women outperformed men on all cognitive outcomes at ≥ 1 biomarker quartile, reflecting minimal-to-moderate pathology; however, these differences were eliminated/attenuated after adjusting for metabolism. The female advantage in verbal memory was also observed at minimal pathology quartiles but was unchanged after metabolism adjustment.

Discussion: Women's greater brain metabolism may confer cognitive resilience against early AD.

KEYWORDS
Alzheimer's disease, brain metabolism, brain volume, cognition, sex

1 | SIGNIFICANCE STATEMENT

There are important sex differences in the clinical course of Alzheimer's disease (AD). Women show better memory performance than men in pre-clinical AD—despite men and women having similar AD-related brain changes—followed by more rapid decline in later disease stages. Compared to men, women also show greater glucose metabolism in the brain, a measure of brain energy utilization or function. Findings from this study suggest that the greater brain metabolism in women versus men may provide women with greater resilience against the effects of early AD-related brain changes and serve as a mechanism underlying the better clinical profile in women

HIGHLIGHTS

- The female advantage in brain metabolic function is pronounced in early Alzheimer's disease (AD)
- Women showed better cognition than men when AD pathology was minimal-to-moderate
- The female cognitive advantage was attenuated after adjusting for brain metabolism

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (eg, PubMed) sources and meeting abstracts and presentations. These relevant citations are appropriately cited.
2. Interpretation: Our findings from this study suggest that the greater brain metabolism in women versus men may provide women with greater resilience against the effects of early Alzheimer's disease (AD)–related brain changes and serve as a mechanism underlying the better clinical profile in women in early AD and faster decline thereafter. These sex-based mechanistic differences will have important implications for disease identification and treatment.
3. Future directions: Our findings challenge an assumption that many past studies are based upon—that AD-related brain changes operate in the same manner and temporal pattern in women and men. Upon replication of results in other cohorts, future studies should leverage these sex differences in cognitive and biomarker trajectories in AD to improve diagnostic precision, risk assessment, and intervention in both sexes.

in early AD and faster decline thereafter. These sex-based mechanistic differences will have important implications for disease identification and treatment.

2 | BACKGROUND

The lifetime risk of AD is higher in women than in men, with women comprising two-thirds of AD cases in the United States.[1] In addition, there are perplexing sex differences in the AD clinical profile, whereby women sustain normal (as clinically defined) memory performance for longer in the disease trajectory than men[2–4] but decline more rapidly after diagnosis of mild cognitive impairment (MCI).[2–7] The mechanisms underlying these sex differences in AD remain elusive but likely include a combination of differences related to gender (eg, education) and biological sex. One biological sex difference that may be relevant to sex differences in AD is in brain metabolism. Although normal aging is associated with a reduction in brain metabolic function in both sexes,[8,9] there is evidence of higher levels of brain glucose metabolism in women versus men among healthy older adults and in the early stages of AD.[2,10–14] The higher brain metabolic function in women has been observed across brain regions[10–14] and throughout adulthood.[14] However, how the female metabolic advantage may change with development of AD pathology and the clinical significance of this female metabolic advantage across the course of AD has not yet been elucidated.

We sought to determine whether the female advantage in brain metabolism may represent a brain resilience mechanism that explains our previous findings of a female cognitive advantage in prodromal AD stages.[2–4] Specifically, in the Alzheimer's Disease Neuroimaging Initiative (ADNI), we found that women sustained their verbal memory advantage over men in the early stages of AD despite similar levels of pathology across the two sexes. In more advanced AD stages with high pathological burden, the female advantage was eliminated.[2–4] Consistent with other recent observations,[5–7,15] these findings suggest more accelerated cognitive decline in women versus men in the time proximal to AD dementia diagnosis.

In the present study, we aimed to examine sex differences in brain metabolism across different levels of AD pathology. We hypothesized that the previously observed female advantage in brain metabolism would persist in the presence of mild-to-moderate AD pathology but not when pathology was severe. We next sought to determine the functional significance of this female advantage in metabolic function and whether it confers an advantage to women at early AD stages. Because the sex difference in brain metabolism has been observed across brain regions,[10–14] we predicted that it confers a global cognitive advantage in women. Specifically, we predicted that women would show a global cognitive advantage over men at mild-to-moderate levels of AD pathological burden (ie, cortical Aβ deposition and hippocampal atrophy) and, critically, that adjusting for the greater brain metabolism in women would attenuate their cognitive advantage. Such a pattern would suggest that greater brain energy utilization contributes in women to a better ability to maintain their cognitive function despite the early stages of AD pathology.

3 | METHODS

3.1 | Participants and data source

Cross-sectional data were obtained from the ADNI database (adni.loni.usc.edu). Information about ADNI can be found at www.adni-info.org. ADNI was initiated in 2003 as a public/private partnership with the aim of validating biomarkers for use in AD clinical trials. Recruitment targeted adults 55 to 90 years of age who were either cognitively normal, MCI, or early AD dementia.[16] Since 2004, ADNI has recruited more than 1500 older adults over three phases (ADNI-1, ADNI-GO, ADNI-2) from over 50 sites in the United States

and Canada. Study visits involve neuroimaging, neuropsychological, and clinical assessments. ADNI recruitment procedures and eligibility criteria are described elsewhere.[16] Inclusion criteria for this specific study were the availability for structural magnetic resonance imaging (MRI), [18F]AV45 positron emission tomography (PET), fluorodeoxyglucose-PET (FDG-PET), and covariate data from the baseline visit including age, education, and whether one carried one or more ε4 alleles of the apolipoprotein E gene (APOE). APOE ε4 status was measured via polymerase chain reaction amplification followed by HhaI restriction enzyme digestion and resolution and visualization on a 4% Metaphor Gel by ethidium bromide staining. Detailed methods on APOE ε4 genotyping have been provided.[17] Our sample consisted of 1259 participants including 548 women and 711 men (398 from ADNI1 and 861 from ADNIGO/2). Of the 1259 participants, 377 were cognitively normal, 654 had MCI, and 228 were AD dementia patients. ADNI was approved by the institutional review board at each site and was compliant with the Health Insurance Portability and Accountability Act. All participants provided written consent.

3.2 | Brain glucose metabolism

FDG-PET data were collected as 6 × 5–minute frames 30 minutes after injection of 5 mCi of [18F] FDG. Images were preprocessed at the University of Michigan, following a standard procedure described in http://adni.loni.usc.edu/methods/pet-analysis/pre-processing/. Fully processed images were downloaded from ADNI (http://adni.loni.ucla.edu/). ADNI investigators at the University of California, Berkeley, established FDG-PET regions of interest (ROIs) based on a meta-analysis of studies identifying brain regions most commonly demonstrating metabolic changes in AD and correlated with cognitive performance.[18] Five ROIs were established, labeled "MetaROIs": bilateral posterior cingulate gyrus, bilateral angular gyri, and middle/inferior temporal gyrus. The protocol for image analysis is described in http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/#pet-pre-processing-container. To eliminate between-subject nuisance variability in tracer uptake, standardized uptake value ratios (SUVRs) were calculated by averaging FDG uptake across the MetaROI and dividing by a reference region comprising pons and cerebellum.[18,19]

3.3 | Cognitive outcomes

We examined standard tests of global cognitive status that are used commonly in MCI and AD diagnostic criteria as well as tests measuring cognitive domains that typically show impairment early in the AD trajectory including episodic memory and executive function.[20] Our global cognitive tests included the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating-Sum of Boxes (CDR-SOB). The MMSE is an assessment of global cognitive function, whereby higher scores (score range = 0 to 30) reflect better cognitive function.[21] The CDR-SOB[22] is an assessment of dementia severity

whereby higher scores (score range = 0 to 18) reflect greater dementia severity. The Rey Auditory Verbal Learning Test (RAVLT), a multi-trial list learning and memory test that shows a female advantage,[23] served as our measure of episodic memory. Our RAVLT outcome of interest was the number of words recalled in the Delayed Recall trial (range: 0 to 15). The Trail Making Test (TMT) part B served as our measure of executive function involving mental flexibility and set-shifting. The outcome was the time needed to complete the task (range: 0 to 300 seconds).

3.4 | Neuroimaging markers of AD pathology

Cortical Aβ burden as measured by [18F]AV45 PET and hippocampal volume (HV) as measured by T1 MRI served as our markers of AD pathology.[24–26] [18F]AV45 PET methods are described in http://www.adni-info.org. Mean AV45 uptake was measured within frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortical regions. SUVRs were calculated by averaging tracer uptake across regions and dividing by tracer uptake in a control region typically not affected by Aβ pathology (ie, whole cerebellum). HV was measured via 3T MRI scanners except for a portion of ADNI1 participants who were scanned on a 1.5T scanner. All MRI scans used a standardized protocol that was validated across sites.[27] ADNI MRI procedures have been described in detail[27] and are available at http://adni.loni.usc.edu/methods/. Briefly, high-resolution, T1-weighted volumetric magnetization prepared rapid gradient echo (MPRAGE) sequences were collected in the sagittal plane, and T2-weighted fast-spin echo sequences were collected in the axial plane.[27] Semi-automated extraction of HV was conducted using a previously validated, high-dimensional brain mapping tool (Medtronic Surgical Navigation Technologies, Louisville, CO), that demonstrated similarity to manual hippocampal tracing.[28]

3.5 | Statistical analysis

Study variables were examined for non-normality using the Shapiro-Wilks test and transformed as needed. Sex differences in sample characteristics and variables of interest (eg, FDG-PET SUVR, cognitive test scores) were assessed using one-way analyses of variance (ANOVAs) for continuous variables and chi-square tests for categorical variables. To examine sex differences in FDG-PET SUVR and cognitive function across levels of AD pathology, we divided all participants (across diagnostic groups) into quartiles of AD pathology markers, cortical amyloid beta (Aβ) burden, and HV. Due to sex differences in average brain size, participants were assigned to HV quartiles based on sex-specific distributions. In a series of linear regressions adjusting for age, education, and APOE ε4, we examined how sex relates to FDG-PET SUVR within each quartile of Aβ burden and HV. Next, we used stepwise linear regressions to examine how sex relates to cognitive performance within AD biomarker quartiles and the mediating role of FDG-PET SUVR in these relationships. In step 1, regressions modeled the relationship between sex and cognitive outcomes while adjusting for age, education, and APOE ε4 and, in step 2, the models were additionally

TABLE 1 Sex differences in sample characteristics in the overall sample and within diagnostic group

Parameters	Total sample N = 1259		
	Women N = 548 Mean (SD)	Men N = 711 Mean (SD)	P-value
Age	72.3 (7.1)	74.1 (7.0)	<.001
Education (years)	15.5 (2.8)	16.4 (2.7)	<.001
Caucasian, N (%)	502 (91.6)	670 (94.2)	.09
APOE ε4, N (%)	254 (46.3)	333 (46.8)	.86
Clinical Diagnosis			.02
MCI, N (%)	269 (49.1%)	385 (54.1%)	
AD dementia, N (%)	92 (16.8%)	136 (19.1%)	
MMSE score	27.5 (2.6)	27.2 (2.6)	.002
CDR-SOB score	1.53 (1.84)	1.67 (1.75)	.07
RAVLT-Delayed Recall score	5.5 (0.2)	3.9 (0.2)	<.001
Log_{10} TMT Part B score	2.00 (0.01)	2.01 (0.01)	.58
Hippocampal volume (mm^3)	6677.0 (47.6)	7053.9 (42.1)	<.001
Cortical [18F]AV45 SUVR	1.22 (0.23)	1.20 (0.23)	.13
FDG-PET SUVR[a]	1.25 (0.16)	1.22 (0.15)	.00

Note. Table displays raw means, standard deviations, and percentages. Due to the non-normal distribution of TMT Part B scores, we applied a logarithmic transformation to scores. For all variables besides age and education, *P* values are derived from analyses adjusted for age and education.

AD, Alzheimer's disease; AV45, cortical Aβ burden as assessed by positron emission tomography; CDR-SOB, Clinical Dementia Rating – Sum of Boxes; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; SUVR, standardized uptake value ratio; TMT, Trail Making Test.

[a]FDG-PET SUVR represents the uptake measured in posterior cingulate, angular gyrus, and inferior/middle temporal gyrus over the uptake in the pons and cerebellum.

adjusted for FDG-PET SUVR. Mediation was defined as an attenuation of the beta coefficient in the sex and cognitive function relationship by at least 10%.

4 | RESULTS

4.1 | Sample characteristics

Sample characteristics by sex are provided in Table 1. Women were significantly younger and had fewer years of education compared to men (P's < .001). The distribution of clinical diagnostic categories significantly differed by sex (P = .02), with men having a higher prevalence of MCI than women. As expected, after adjusting for age and years of education, women had significantly lower HV compared to men (P < .001),

TABLE 2 Effect of sex on brain metabolism (FDG-PET SUVR) at levels of AD-associated pathology markers

	B, β	SE	P-value
Cortical Aβ Quartile			
1	−0.02, −0.10	0.02	.12
2	−0.06, −0.27	0.02	<.001
3	−0.06, −0.19	0.02	.003
4	−0.04, −0.11	0.02	.12
HV Quartile[b]			
1	0.002, 0.006	0.02	.92
2	−0.05, −0.17	0.02	.004
3	−0.07, −0.23	0.02	<.001
4	−0.03, −0.12	.0	.053

Note. Statistical results of linear regression modelling the relationship between sex and FDG-PET SUVR within quartiles of AD-associated pathology.

FDG-PET, [18F]Fluorodeoxyglucose positron emission tomography; HV, hippocampal volume; SUVR, standardized uptake value ratio.

[a]FDG-PET SUVR represents the uptake measured in posterior cingulate, angular gyrus, and inferior/middle temporal gyrus over the uptake in the pons and cerebellum.

[b]HV quartiles were calculated in sex-stratified analyses.

whereas MMSE and RAVLT-Delayed Recall scores and FDG-PET SUVR were significantly higher in women than in men (P's < .005).

4.2 | Sex differences in glucose metabolism relative to AD pathology burden

See Table 2 for statistical results of linear regressions modeling the relationship between sex and FDG-PET SUVR by AD biomarker quartiles. As hypothesized, women had significantly higher FDG-PET SUVR than men among those with mild-to-moderate pathology burden (quartiles 2 to 3 of Aβ and HV), whereas this sex difference was absent when pathology burden was more severe (Aβ: quartile 4; HV: quartile 1; Figure 1). Although women showed higher FDG-PET SUVR than men among those with minimal pathology (Aβ: quartile 1; HV: quartile 4), this difference was not significant in quartile 1 of Aβ and approached significance in quartile 4 of HV.

4.3 | Glucose metabolism accounts for sex differences in cognitive function across levels of AD pathology

Overall, our hypotheses were supported in that we found a female cognitive advantage on all tests among biomarker quartiles reflecting mild-to-moderate pathology. With exceptions for the life-long female advantage in verbal memory, this advantage was either attenuated or eliminated at all biomarker quartiles with adjustment for brain metabolism levels. Specific results by cognitive test follow.
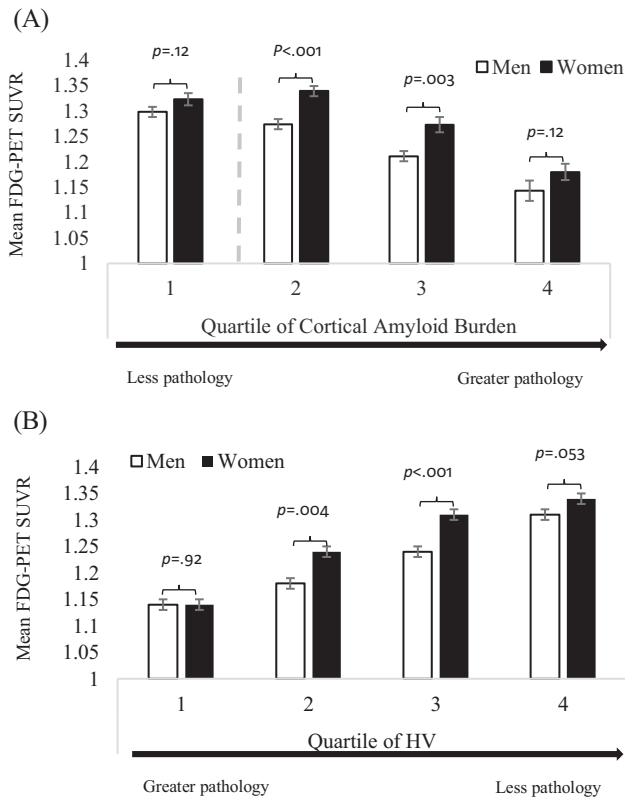
FIGURE 1 Sex differences in brain glucose metabolism (FDG-PET SUVR) across quartiles of (A) cortical Aβ burden (AV45-PET) and (B) hippocampal volume (cm^3; T1 MRI). FDG-PET SUVR represents the uptake measured in posterior cingulate, angular gyrus, and inferior/middle temporal gyrus over uptake in the reference region (pons and cerebellum).

With covariate adjustment (age, education, *APOE ε*4), women demonstrated significantly better MMSE performance than men when Aβ burden was mild to moderate (quartiles 2 to 3) and when HV indicated mild/moderate atrophy (quartiles 2 to 3; Figure 2). When adjusting for FDG-PET SUVR in addition to our standard covariates, the female advantage in MMSE performance in quartiles 2 to 3 of Aβ burden and HV was eliminated (Table 3). Women also demonstrated significantly higher CDR-SOB scores than men when Aβ burden was minimal to moderate (quartiles 1 to 3). When adjusting for FDG-PET SUVR, the female advantage in CDR-SOB performance was attenuated in quartiles 1 to 2 (18% to 34% decrease in beta coefficient) and eliminated in quartile 3 of Aβ burden. Women demonstrated significantly higher CDR-SOB scores than men when HV showed evidence of mild atrophy (quartile 3). Women's higher CDR-SOB scores was a trend in quartile 4 of HV (*P* = .08). When adjusting for FDG-PET SUVR, the female advantage in CDR-SOB performance was eliminated in quartile 3 of HV. The trend for lower CDR-SOB scores in women in quartile 4 of HV was also eliminated (37% decrease in beta coefficient).

In line with the female advantage in verbal memory, RAVLT-Delayed Recall performance was significantly better in women versus men across quartiles of minimal-to-moderate pathology burden (Aβ: quartiles 1 to 3; HV: quartiles 2 to 4). Consistent with our own previous findings,[3,4] the female advantage was absent when pathology burden

was more severe (Aβ: quartile 4; HV: quartile 1). When adjusting for FDG-PET SUVR, the female advantage in RAVLT-Delayed Recall at Aβ quartiles 1 to 3 of was attenuated in quartile 3 only (30% decrease in beta coefficient). When adjusting for FDG-PET SUVR, the female advantage in RAVLT-Delayed Recall performance at HV quartiles 2 to 4 was eliminated in quartile 2, attenuated in quartile 3 (11% decrease in beta coefficient), and unchanged in quartile 4. Women demonstrated significantly better TMT Part B performance than men when HV showed evidence of moderate atrophy (quartile 2); however, there were no sex differences in TMT Part B performance across Aβ quartiles. When adjusting for FDG-PET SUVR, the significant female advantage in TMT Part B performance in quartile 2 of HV was eliminated.

5 | DISCUSSION

There is reliable evidence of higher brain metabolism in women versus men.[2,10–12,14] We took the critical next step of examining how this female metabolic advantage may vary by AD pathology burden and whether it may represent a physiological reserve that confers a cognitive advantage in early AD. Consistent with previous findings in healthy older adults,[10–12,14] we found that women had higher levels of brain metabolism than men among those with evidence of none/minimal pathology (Aβ: quartile 1; HV: quartile 4), although not significantly. However, the higher levels of brain metabolism in women versus men were significant among those with evidence of mild-to-moderate AD pathology (quartiles 2 to 3). Our results reveal that the previously reported female advantage in metabolic function may be more pronounced in the earlier stages of AD. This sex difference in metabolic function was absent among those with evidence of severe pathology (Aβ: quartile 4; HV: quartile 1), suggesting that women may experience a steeper decline in metabolic function than men as AD pathology progresses from moderate to more severe stages. Longitudinal evidence is needed to provide more definitive support for this interpretation.

As a first step in determining whether the female metabolic advantage confers a cognitive advantage, we examined sex differences on clinical tests commonly used in MCI and AD diagnostic criteria across levels of AD pathology burden. As predicted, women demonstrated significantly better global cognitive function (MMSE) and lower dementia severity (CDR-SOB) than men, specifically among those with mild-to-moderate pathology burden. We also observed a female advantage in the TMT Part B; however, this was limited to quartile 2 of HV and was not seen within Aβ quartiles. The specificity of this finding to those with evidence of moderate hippocampal atrophy versus Aβ deposition may be due to the temporal evolution of AD biomarkers, whereby Aβ deposition often occurs prior to neurodegeneration and years before cognitive decline.[29] Thus neurodegeneration is typically more tightly coupled to clinical profile than Aβ burden. Unlike other cognitive outcomes, the female advantage in verbal memory was observed at all quartiles of AD pathology (including none/minimal) except severe (Aβ: quartile 4; HV: quartile 1), likely owing to the well-established, life-long female advantage in verbal memory.[30–32] The persistence of the female advantage in verbal memory across mild-to-moderate, but not severe, pathology levels is consistent with our prior work.[2–4] The present

TABLE 3 Effect of sex on cognitive performance (MMSE, CDR-SOB, RAVLT, and TMT Part B) at levels of AD-associated pathology markers and the mediating role of brain glucose metabolism

	Step 1: Effect of sex on cognitive performance adjusted for age, education, *APOE ε*4			Step 2: Step 1 variables plus additional adjustment for FDG-PET SUVR[a]		
	B, *β*	**SE**	***P*-value**	**B, *β***	**SE**	***P*-value**
MMSE						
Cortical A*β* Quartile						
1	−0.38, −0.10	0.26	.14	−0.26, −0.07	0.24	.29
2	−0.54, −0.15	0.25	.03	−0.33, −0.09	0.26	.20
3	−1.10, −0.21	0.36	.002	−0.59, −0.11	0.32	.07
4	−0.43, −0.07	0.42	.31	−0.03, −0.01	0.34	.93
HV Quartile[b]						
1	−0.16, −0.03	0.35	.65	−0.17, −0.03	0.31	.59
2	−0.76, −0.15	0.30	.01	−0.31, −0.06	0.26	.22
3	−0.56, −0.15	0.22	.01	−0.26, −0.07	0.22	.24
4	−0.39, −0.12	0.20	.06	−0.30, −0.09	0.20	.13
CDR-SOB						
Cortical A*β* Quartile						
1	0.54, 0.20	0.19	.004	0.44, 0.16	0.18	.01
2	0.47, 0.21	0.15	.003	0.31, 0.14	0.16	.05
3	0.52, 0.15	0.23	.02	0.15, 0.04	0.20	.46
4	0.08, 0.02	0.29	.78	−0.18, −0.05	0.24	.44
HV Quartile[b]						
1	0.11, 0.03	0.26	.66	0.13, 0.03	0.23	.66
2	0.04, 0.01	0.19	.82	−0.24, −0.07	0.17	.17
3	0.55, 0.20	0.16	.001	0.26, 0.10	0.15	.07
4	0.19, 0.10	0.11	.08	0.12, 0.06	0.10	.26
RAVLT-Delayed Recall						
Cortical A*β* Quartile						
1	−2.35, −0.27	0.58	<.001	−2.28, −0.26	0.58	<.001
2	−2.37, −0.28	0.57	<.001	−2.22, −0.26	0.59	<.001
3	−2.53, −0.30	0.53	<.001	−1.79, −0.21	0.51	.001
4	−0.75, −0.11	0.48	.12	−0.44, −0.07	0.44	0.32
HV Quartile[b]						
1	−0.19, −0.03	0.35	.58	−0.23, −0.04	0.34	.51
2	−1.15, −1.15	0.44	.009	−0.72, −0.09	0.41	.09
3	−3.35, −0.39	0.48	<.001	−2.99, −0.35	0.48	<.001
4	−2.49, −0.29	0.50	<.001	−2.48, −0.29	0.50	<.001
TMT Part B						
Cortical A*β* Quartile						
1	−0.02, −0.04	0.03	.57	−0.03, −0.06	.03	.32
2	0.01, 0.03	0.02	.68	−0.01, −0.04	0.02	.53
3	0.02, 0.04	0.03	.51	−0.01, −0.03	0.03	.61
4	−0.01, −0.01	0.04	.88	−0.03, −0.06	0.03	.39

(Continues)

TABLE 3 (Continued)

	Step 1: Effect of sex on cognitive performance adjusted for age, education, *APOE ε4*			Step 2: Step 1 variables plus additional adjustment for FDG-PET SUVR[a]		
	B, β	SE	P-value	B, β	SE	P-value
HV Quartile[b]						
1	−0.03, −0.07	0.03	.20	−0.03, −0.07	0.02	.17
2	0.07, 0.14	0.03	.02	0.03, 0.06	0.02	.24
3	0.01, 0.03	0.03	.61	−0.03, −0.06	0.02	.27
4	−0.001, −0.003	0.02	.96	−0.01, −0.03	0.02	.63

Note. Statistical results of stepwise regression analyses examining the effect of sex on MMSE, CDR-SOB, RAVLT-Delayed Recall and TMT, Part B performance at different levels of AD-associated pathology are shown before (step 1) and after (step 2) adjustment for FDG-PET SUVR.

CDR-SOB, Clinical Dementia Rating – Sum of Boxes; FDG-PET, [18F]Fluorodeoxyglucose positron emission tomography; HV, hippocampal volume; MMSE, Mini Mental State Exam; RAVLT, Rey Auditory Verbal Learning; SUVR, standardized uptake value ratio; TMT, Trail Making Test.

[a]FDG-PET SUVR represents the uptake measured in posterior cingulate, angular gyrus, and inferior/middle temporal gyrus over the uptake in the pons and cerebellum.

[b]HV quartiles were calculated in sex-stratified analyses.

study extends that work and suggests that, in the earlier AD stages, women have a more global cognitive advantage than men, even on tests that do not typically show a sex disparity (MMSE, CDR-SOB, and TMT Part B). Notably; however, the female advantage in TMT Part B was specific to one biomarker quartile (HV quartile 2) and, thus, the female advantage on the MMSE and CDR-SOB may be driven more by verbal memory than by executive function. The specificity of women's

cognitive advantage to the mild-to-moderate AD stages suggests that women are better able than men to compensate for underlying brain changes in order to maintain cognitive function.

As a second step in determining whether the female metabolic advantage confers a cognitive advantage, we examined whether the sex differences in cognitive function were mediated by brain metabolism levels. In support of hypotheses, we found that, at all
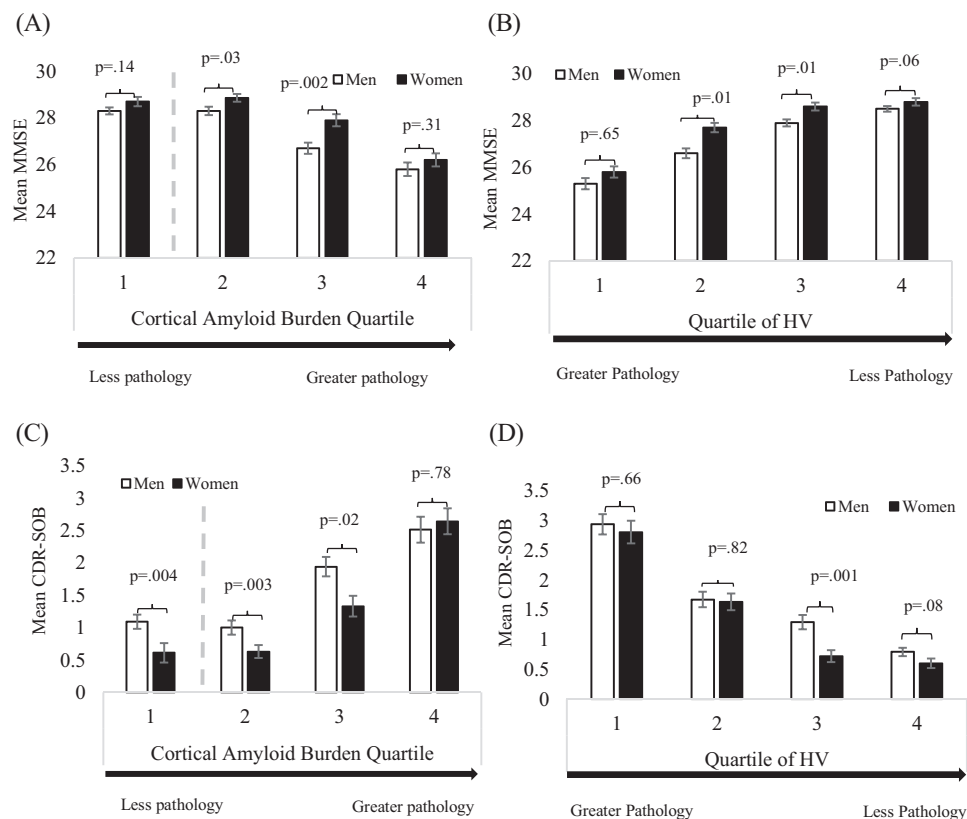

FIGURE 2 Sex differences in the global cognitive measures of MMSE (higher scores = better performance) and CDR-SOB (higher scores = worse performance) by quartiles of (A and C) cortical Aβ burden (AV45-PET) and (B and D) hippocampal volume (cm^3; T1 MRI)
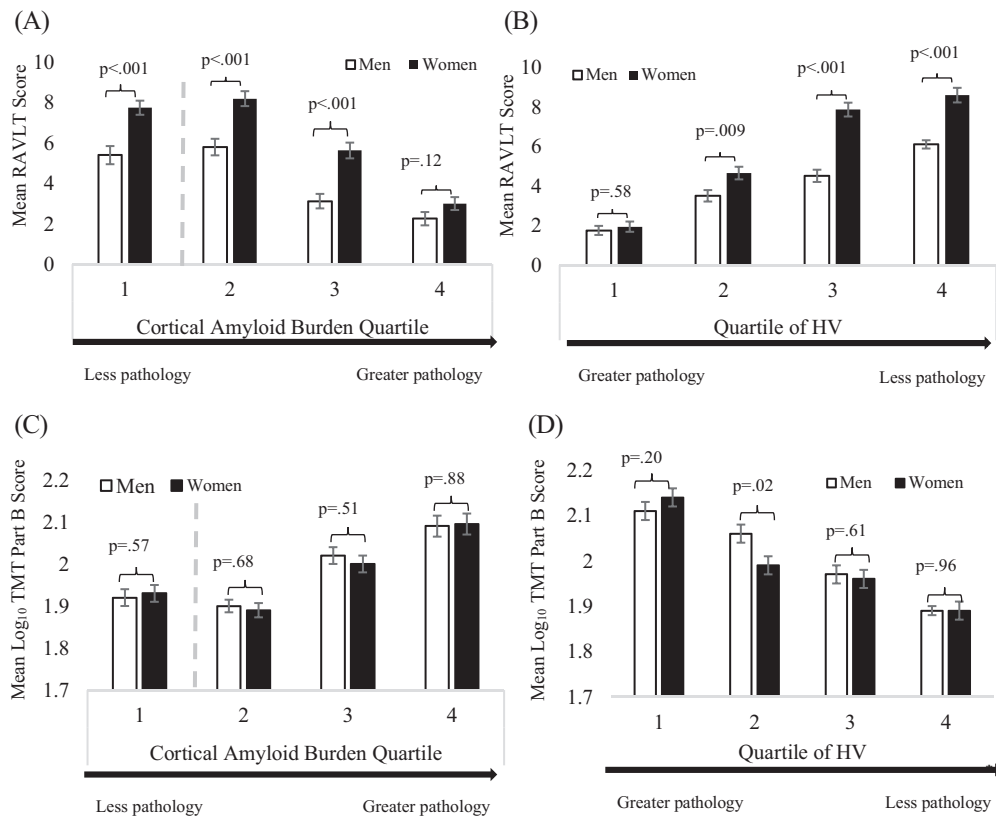
FIGURE 3 Sex differences in RAVLT and log-transformed TMT Part B scores by quartiles of (A and C) cortical $A\beta$ burden (AV45-PET) and (B and D) hippocampal volume (cm^3; T1 MRI)

biomarker quartiles in which a female advantage on the MMSE, CDR-SOB, or TMT Part B was observed, this advantage was either attenuated or eliminated with adjustment for brain metabolism levels. In contrast, the female advantage in verbal memory was observed at all biomarker quartiles except the most severe; however, it was attenuated only with adjustment for brain metabolism when pathology burden was mild-to-moderate ($A\beta$: quartile 3; HV: quartiles 2 to 3). Other than the elimination of the sex difference in verbal memory performance in quartile 2 of HV, this attenuation was relatively modest compared to the other cognitive outcomes and ranged from 11% to 30%. These results suggest that higher global brain metabolism is not a central mechanism underlying the life-long verbal memory advantage, but may help women to sustain this advantage in the face of early AD pathology. It is possible; however, that a measure of brain metabolism specific to the medial temporal lobe would show a different attenuation pattern in the sex difference in verbal memory, and more research using region-specific brain metabolic data is warranted. Overall, results suggest that the female metabolic advantage enables women to better compensate for early AD pathology and maintain cognitive function compared to men.

There is a sex difference in the clinical course of AD, with women showing more rapid decline in cognitive function in later AD stages.[2–7] Similarly, when comparing those with severe versus moderate pathology, we found larger decreases in both brain metabolism and cognitive performance in women compared to men. These findings suggest

that the female advantage in metabolism may contribute not only to their sustained cognitive function in early AD but also to their more rapid cognitive decline in later disease stages. Longitudinal studies are needed to test this possibility.

The biological basis for the female metabolic advantage is unclear. Estrogen is known to enhance brain metabolism and blood flow.[33–35] Primate studies show that estradiol increases glucose transporter and insuline-like growth factor 1 (IGF1) expression in the frontal cortex.[36] In vivo studies demonstrate estradiol modulation of glucose transporter 1 (GLUT-1) protein and messenger RNA (mRNA) expression in blood-brain barrier endothelium.[37] Rodent studies demonstrate that estradiol administration leads to upregulation of the *N*-methyl-D-aspartate (NMDA) receptor,[38] glutamate bindings sites on the receptor,[39] and increases in presynaptic glutamate release.[36,40,41] These are all mechanisms that play a critical role in long-term memory formation and other cognitive processes.[42] Although the participants in our study are postmenopausal with nominal levels of circulating sex hormones, extragonadal estrogen production in the brain does not undergo a similar decline[43] and higher brain levels of estrogen receptors[44] may sustain the female metabolic advantage beyond menopause, in combination with organizational effects of sex hormones on the brain.

Our study has limitations. First, our cross-sectional design does not enable investigation of sex differences in the temporal relationship between changes in FDG-PET SUVR, AD pathology, and cognitive

performance. Longitudinal studies are needed. Second, we would have ideally used a neuroimaging measure of the other AD pathological hallmark, tau; however, only a few participants had PET tau data in conjunction with their baseline FDG-PET scan, since PET tau was more recently added to the ADNI protocol. Third, our measure of FDG-PET SUVR was specific to brain regions in which changes in metabolism are most evident in AD. Thus it is unknown whether our findings generalize to all brain regions. In line with previous reports of higher brain metabolism in women versus men,[2,10–12,14] it is possible that the higher levels of FDG-PET SUVR in women at none/minimal quartiles may have been significant if we used a global FDG-PET measure. Fourth, we reported results without a correction for multiple comparisons because we had specific hypotheses about the type and direction of associations with results supporting hypotheses; however, it is important to consider the possibility of type 1 error in our findings. Finally, the ADNI cohort is a convenience sample comprising volunteers and is, therefore, susceptible to selection bias, thereby limiting the generalizability of the results.

In sum, results suggest that the female brain is better able than the male brain to maintain metabolic function in the face of early AD pathology. Because brain physiology (glucose metabolism) is the link between brain structure and function, the female metabolic advantage may be a contributing mechanism to the better clinical profile of women versus men in early AD stages, perhaps by providing resilience against pathological changes, which some studies indicate are even greater in women than in men.[45–48] The steeper metabolic decline in women may contribute to their more accelerated cognitive decline post MCI diagnosis.[2–7]

We identified a female advantage in cognition on clinical tests commonly used in MCI and AD diagnosis. This finding has important clinical implications for diagnostic accuracy in that the identification of early stage AD in women may be delayed given that they better sustain cognitive function at this stage. A delayed diagnosis on the AD trajectory limits the opportunity to intervene early in the disease when our currently available interventions are most beneficial. These findings along with those of our previous reports[49] raise the potential need for more conservative diagnostic criteria for MCI in women and challenge the assumption that AD-related brain changes operate in the same manner and temporal pattern in women and men. Recognition of sex differences such as these can ultimately help improve understanding of the pathophysiology of AD and improve diagnostic precision, risk assessment, and intervention in both sexes.

CONFLICTS OF INTEREST

All authors report no conflicts of interest related to the current study.

REFERENCES

1. 2017 Alzheimer's disease facts and figures. Alzheimer's Dement 2017. https://doi.org/10.1016/j.jalz.2017.02.001.
2. Sundermann EE, Maki PM, Rubin LH, Lipton RB, Landau S, Biegon A. Female advantage in verbal memory: evidence of sex-specific cognitive reserve. *Neurology*. 2016;87(18):1916-1924.
3. Sundermann EE, Biegon A, Rubin LH, et al. Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy. *Neurology*. 2016;86(15):1368-1376.
4. Sundermann EE, Biegon A, Rubin LH, Lipton RB, Landau S, Maki PM. Does the female advantage in verbal memory contribute to underestimating Alzheimer's disease pathology in women versus men? *J Alzheimers Dis*. 2017;56(3):947-957.
5. Hua X, Hibar DP, Lee S, et al. Sex and age differences in atrophic rates: an ADNI study with n = 1368 MRI scans. *Neurobiol Aging*. 2010;31(8):1463-1480.
6. Holland D, Desikan RS, Dale AM, McEvoy LK. Higher rates of decline for women and apolipoprotein e ε4 carriers. *Am J Neuroradiol*. 2013;34(12):2287-2293.
7. Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM. Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimer's Dement Transl Res Clin Interv*. 2015;1(2):103-110.
8. Goyal MS, Vlassenko AG, Blazey TM, et al. Loss of brain aerobic glycolysis in normal human aging. *Cell Metab*. 2017;26(2):353-360.e3.
9. Martin AJ, Friston KJ, Colebatch JG, Frackowiak RSJ. Decreases in regional cerebral blood flow with normal aging. *J Cereb Blood Flow Metab*. 1991;11(4):684-689.
10. Andreason PJ, Zametkin AJ, Guo AC, Baldwin P, Cohen RM. Gender-related differences in regional cerebral glucose metabolism in normal volunteers. *Psychiatry Res*. 1994;51(2):175-183.
11. Hu Y, Xu Q, Li K, et al. Gender differences of brain glucose metabolic networks revealed by FDG-PET: evidence from a large cohort of 400 young adults. *PLoS One*. 2013;8(12):e83821.

12. Perneczky R, Drzezga A, Diehl-Schmid J, Li Y, Kurz A. Gender differences in brain reserve: an 18F-FDG PET study in Alzheimer's disease. *J Neurol*. 2007;254(10):1395-1400.

13. Araque Caballero MÁ, Brendel M, Delker A, et al. Mapping 3-year changes in gray matter and metabolism in Aβ-positive nondemented subjects. *Neurobiol Aging*. 2015;36(11):2913-2924.

14. Goyal MS, Blazey TM, Su Y, et al. Persistent metabolic youth in the aging female brain. *Proc Natl Acad Sci U S A*. 2019;116(8):3251-3255.

15. Koran MEI, Wagener M, Hohman TJ. Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav*. 2017;11(1):205-213.

16. Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurology*. 2010;74(3):201-209.

17. Saykin AJ, Shen L, Foroud TM, et al. Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: genetics core aims, progress, and plans. *Alzheimers Dement*. 2010;6(3):265-273.

18. Landau SM, Harvey D, Madison CM, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiol Aging*. 2011;32(7):1207-1218.

19. Jagust WJ, Bandy D, Chen K, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement*. 2010;6(3):221-229.

20. Duke Han S, Nguyen CP, Stricker NH, Nation DA. Detectable neuropsychological differences in early preclinical Alzheimer's disease: a meta-analysis. *Neuropsychol Rev*. 2017;27(4):305-325.

21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

22. Morris JC. The clinical dementia rating (cdr): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.

23. Gale SD, Baxter L, Connor DJ, Herring A, Comer J. Sex differences on the Rey Auditory Verbal Learning Test and the Brief Visuospatial Memory Test-Revised in the elderly: normative data in 172 participants. *J Clin Exp Neuropsychol*. 2007;29(5):561-567.

24. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259.

25. Ball M, Braak H, Coleman P, et al. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. *Neurobiol Aging*. 1997;18:S1-S2.

26. Leon MJ ConvitA, AE George, et al. In vivo structural studies of the hippocampus in normal aging and in incipient Alzheimer's diseasea. *Ann N Y Acad Sci*. 1996;777:1-13.

27. Jack CR, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): mRI methods. *J Magn Reson Imaging*. 2008;27(4):685-691.

28. Hsu YY, Schuff N, Du AT, et al. Comparison of automated and manual MRI volumetry of hippocampus in normal aging and dementia. *J Magn Reson Imaging*. 2002;16(3):305-310.

29. Jack CR, Vemuri P, Wiste HJ, et al. Evidence for ordering of Alzheimer disease biomarkers. *Arch Neurol*. 2011;68(12):1526-1535.

30. Bleecker ML, Bolla-Wilson K, Agnew J, Meyers DA. Age-related sex differences in verbal memory. *J Clin Psychol*. 1988;44(3):403-411.

31. Kramer JH, Delis DC, Daniel M. Sex differences in verbal learning. *J Clin Psychol*. 1988. https://doi.org/10.1002/1097-4679(198811)44:6<907::AID-JCLP2270440610>3.0.CO;2-8.

32. De Frias C, Nilsson LG, Herlitz A. Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Aging, Neuropsychol Cogn*. 2006;13:574-587.

33. Nehlig A, Porrino LJ, Crane AM, Sokoloff L. Local cerebral glucose utilization in normal female rats: variations during the estrous cycle and comparison with males. *J Cereb Blood Flow Metab*. 1985;5(3):393-400.

34. Bishop J, Simpkins JW. Estradiol enhances brain glucose uptake in ovariectomized rats. *Brain Res Bull*. 1995;36(3):315-320.

35. Maki PM, Resnick SM. Longitudinal effects of estrogen replacement therapy on PET cerebral blood flow and cognition. *Neurobiol Aging*. 2000;21(2):373-383.

36. Cheng CM, Cohen M, Wang J, Bondy CA. Estrogen augments glucose transporter and IGF1 expression in primate cerebral cortex. *FASEB J*. 2001;15(6):907-915.

37. Shi J, Simpkins JW. 17 β-estradiol modulation of glucose transporter 1 expression in blood- brain barrier. *Am J Physiol*. 1997;272(6 Pt 1):E1016-E1022.

38. Romeo RD, McCarthy JB, Wang A, Milner TA, McEwen BS. Sex differences in hippocampal estradiol-induced N-methyl-D-aspartic acid binding and ultrastructural localization of estrogen receptor-alpha. *Neuroendocrinology*. 2005;81(6):391-399.

39. Weiland NG. Estradiol selectively regulates agonist binding sites on the N-methyl-D-aspartate receptor complex in the ca1 region of the hippocampus. *Endocrinology*. 1992;131(2):662-668.

40. Oberlander JG, Woolley CS. 17β-estradiol acutely potentiates glutamatergic synaptic transmission in the hippocampus through distinct mechanisms in males and females. *J Neurosci*. 2016;36(9):2677-2690.

41. Yokomaku D, Numakawa T, Numakawa Y, et al. Estrogen enhances depolarization-induced glutamate release through activation of phosphatidylinositol 3-kinase and mitogen-activated protein kinase in cultured hippocampal neurons. *Mol Endocrinol*. 2003;17(5):831-844.

42. Harris EW, Ganong AH, Cotman CW. Long-term potentiation in the hippocampus involves activation of N-methyl-D-aspartate receptors. *Brain Res*. 1984;323(1):132-137.

43. Steckelbroeck S, Heidrich DD, Stoffel-Wagner B, et al. Characterization of aromatase cytochrome P450 activity in the human temporal lobe. *J Clin Endocrinol Metab*. 1999;84(8):2795-2801.

44. Gillies GE, McArthur S. Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. *Pharmacol Rev*. 2010;62(2):155-198.

45. Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein e with cerebrospinal fluid levels of tau. *JAMA Neurol*. 2018;75(8):989-998.

46. Buckley RF, Mormino EC, Rabin JS, et al. Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA Neurol*. 2019;76(5):542-551.

47. Damoiseaux JS, Seeley WW, Zhou J, et al. Gender modulates the APOE ε4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. *J Neurosci*. 2012;32(24):8254-8262.

48. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563-573.

49. Sundermann EE, Maki P, Biegon A, et al. Sex-specific norms for verbal memory tests may improve diagnostic accuracy of amnestic MCI. *Neurology*. 2019;93(20):e1881-e1889.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.