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

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† Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Funding information
National Institutes of Health, Grant/Award Numbers: AG049810, AG05131, U01 AG006786, RF1 AG55151, U54 AG44170

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...
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. 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 but decline more rapidly after diagnosis of mild cognitive impairment (MCI). 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, 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. The higher brain metabolic function in women has been observed across brain regions and throughout adulthood. 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. 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. Consistent with other recent observations, 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 and throughout adulthood, 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. 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. 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 Hhal 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. 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. 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 comprisingpons and cerebellum.

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. 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. The CDR-SOB is an assessment of dementia severity whereby higher scores (score range = 0 to 30) reflect greater dementia severity. The Rey Auditory Verbal Learning Test (RAVLT), a multi-trial list learning and memory test that shows a female advantage, 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. [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. ADNI MRI procedures have been described in detail 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. 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.

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)             |
| Age                      | 72.3 (7.1)            |
| Education (years)         | 15.5 (2.8)            |
| Caucasian, N (%)          | 502 (91.6)            |
| APOE ε4, N (%)            | 254 (46.3)            |
| Clinical Diagnosis        |                       |
| MCI, N (%)                | 269 (49.1%)           |
| AD dementia, N (%)        | 92 (16.8%)            |
| MMSE score               | 27.5 (2.6)            |
| CDR-SOB score            | 1.53 (1.84)           |
| RAVLT-Delayed Recall score| 5.5 (0.2)             |
| Log10 TMT Part B score    | 2.00 (0.01)           |
| Hippocampal volume (mm³)  | 6677.0 (47.6)         |
| Cortical [18F]AV45 SUVR   | 1.22 (0.23)           |
| FDG-PET SUVRα            | 1.25 (0.16)           |
| B, β                     | 0.002, 0.006          |
| SE                       | 0.02                  |
| P-value                  | .92                   |

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.

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

| HV Quartileb | B, β         | SE    | P-value |
|--------------|--------------|-------|---------|
| 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     |

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

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), 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%.

4.2  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.
Women demonstrated significantly higher CDR-SOB scores than men, specifically among those with 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 higher global cognitive function (MMSE) and lower dementia severity (CDR-SOB) than men, specifically among those with mild-to-moderate AD pathology (quartiles 2 to 3). Women also demonstrated significantly higher CDR-SOB scores than men when Aβ burden was minimal 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 (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. 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, 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.

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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 ε4 | Step 2: Step 1 variables plus additional adjustment for FDG-PET SUVRβ |
|----------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------|
|                      | B, β                               | SE | P-value | B, β                               | SE | P-value |
| MMSE                 |                                     |    |         |                                     |    |         |
| Cortical Aβ 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 Quartileβ         |                                     |    |         |                                     |    |         |
| 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 Aβ 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 Quartileβ         |                                     |    |         |                                     |    |         |
| 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 Aβ 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 | .32     |
| HV Quartileβ         |                                     |    |         |                                     |    |         |
| 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 Aβ Quartile |                                     |    |         |                                     |    |         |
| 1                    | -0.02, -0.04                       | 0.03 | .57     | -0.03, -0.06                       | 0.03 | .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)
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

![Graph](image-url)
There is a sex difference in the clinical course of AD, with women showing more rapid decline in cognitive function in later AD stages.\textsuperscript{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.\textsuperscript{33–35} Primate studies show that estradiol increases glucose transporter and insulin-like growth factor 1 (IGF1) expression in the frontal cortex.\textsuperscript{36} In vivo studies demonstrate estradiol modulation of glucose transporter 1 (GLUT-1) protein and messenger RNA (mRNA) expression in blood-brain barrier endothelium.\textsuperscript{37} Rodent studies demonstrate that estradiol administration leads to upregulation of the N-methyl-D-aspartate (NMDA) receptor,\textsuperscript{38} glutamate bindings sites on the receptor,\textsuperscript{39} and increases in presynaptic glutamate release.\textsuperscript{36,40,41} These are all mechanisms that play a critical role in long-term memory formation and other cognitive processes.\textsuperscript{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\textsuperscript{43} and higher brain levels of estrogen receptors\textsuperscript{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

**FIGURE 3** Sex differences in RAVLT and log-transformed TMT Part B scores by quartiles of (A and C) cortical Aβ burden (AV45-PET) and (B and D) hippocampal volume (cm\(^3\); T1 MRI)
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 align with those of our previous reports49 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.

ACKNOWLEDGMENT/CONFLICTS/FUNDING SOURCES
E. Sundermann reports no conflicts of interest relevant to the manuscript. P. Maki has consulted for Balchem, Abbvie, and Pfizer. S. Reddy, M. Bondi, and A. Biegon report no conflicts of interest relevant to the manuscript. This work was supported by the National Institutes of Health (NIH) [grant numbers AG049810, AG05131, and U01 AG006786, RF1 AG55151, and U54 AG44170]. Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and Department of Defense (DOD) ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association, Alzheimer’s Drug Discovery Foundation, Araclon Biotech, BioClinica, Inc., Biogen, Bristol-Myers Squibb Company, CereSpir, Inc., Cogstate, Eisai Inc., Elan Pharmaceuticals, Inc., Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc., Fujirebio, GE Healthcare, IXICO Ltd., Janssen Alzheimer Immunotherapy Research & Development, LLC., Johnson & Johnson Pharmaceutical Research & Development LLC., Lumosity, Lundbeck, Merck & Co., Inc., Meso Scale Diagnostics, LLC., NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer Inc., Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

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

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SUPPORTING INFORMATION

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

How to cite this article: Sundermann E, Maki PM, Reddy S, Bondi MW, Biegon A, for the Alzheimer’s Disease Neuroimaging Initiative. Women’s higher brain metabolic rate compensates for early Alzheimer’s pathology. Alzheimer’s Dement. 2020;12:e12121. https://doi.org/10.1002/dad2.12121