

Sex differences in Alzheimer risk

Brain imaging of endocrine vs chronologic aging

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ABSTRACT

Objective: This observational multimodality brain imaging study investigates emergence of endophenotypes of late-onset Alzheimer disease (AD) risk during endocrine transition states in a cohort of clinically and cognitively normal women and age-matched men.

Methods: Forty-two 40- to 60-year-old cognitively normal women (15 asymptomatic perimenopausal by age [CNT], 13 perimenopausal [PERI], and 14 postmenopausal [MENO]) and 18 age- and education-matched men were examined. All patients had volumetric MRI, ¹⁸F-fluoro-2-deoxyglucose (FDG)-PET (glucose metabolism), and Pittsburgh compound B-PET scans (β -amyloid [A β] deposition, a hallmark of AD pathology).

Results: As expected, the MENO group was older than the PERI and CNT groups. Otherwise, groups were comparable on clinical and neuropsychological measures and APOE4 distribution. Compared to CNT women and to men, and controlling for age, PERI and MENO groups exhibited increased indicators of AD endophenotype, including hypometabolism, increased A β deposition, and reduced gray and white matter volumes in AD-vulnerable regions ($p < 0.001$). AD biomarker abnormalities were greatest in MENO, intermediate in PERI, and lowest in CNT women ($p < 0.001$). A β deposition was exacerbated in APOE4-positive MENO women relative to the other groups ($p < 0.001$).

Conclusions: Multimodality brain imaging indicates sex differences in development of the AD endophenotype, suggesting that the preclinical AD phase is early in the female aging process and coincides with the endocrine transition of perimenopause. These data indicate that the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process. *Neurology*® 2017;89:1382-1390

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **CMRglic** = glucose metabolism; **CNT** = premenopausal women; **FDG** = ¹⁸F-fluoro-2-deoxyglucose; **FWHM** = full width at half maximum; **GM** = gray matter; **GMV** = gray matter volumes; **HRT** = hormonal replacement therapy; **MENO** = postmenopausal women; **PCC** = posterior cingulate/precuneus; **PERI** = perimenopausal women; **PiB** = Pittsburgh compound B; **QUICKI** = quantitative insulin-sensitivity check index; **RR** = relative risk; **SPM** = statistical parametric mapping; **SUVR** = standardized uptake value ratio; **WM** = white matter; **WMV** = white matter volumes.

After advanced age, female sex is the major risk factor for late-onset Alzheimer disease (AD),¹ even after accounting for women's greater longevity relative to men.² While AD is not unique to women, women constitute the majority of people with the disease, accounting for up to 3.2 million cases in the United States alone.³

Increased risk of late-onset AD in women suggests pathophysiologic changes that may be mediated by endocrine transition states such as menopause, which is both female-specific and age-related.⁴

Perimenopause is a midlife neuroendocrine transition state that occurs on the background of an aging biology and results in reproductive senescence. While typically viewed as a reproductive transition, the symptoms of perimenopause are largely neurologic in nature, including disruption

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in estrogen-regulated systems such as thermo-regulation, sleep, circadian rhythms, and sensory processing, as well as depression and impairment in multiple cognitive domains.⁴

Preclinical evidence indicates that estrogenic regulation of brain glucose metabolism is dismantled during perimenopause, inducing a hypometabolic state, which is accompanied by increased fatty acid catabolism, β -amyloid (A β) (a hallmark of AD pathology) deposition, and declines in synaptic plasticity,^{5–7} which in turn may increase risk of AD later in life.⁴

This multimodality neuroimaging study bridges discovery and clinical science to characterize sex-dependent emergence of well-established AD biomarkers⁸ such as A β deposition (¹¹C–Pittsburgh compound B [PiB]–PET), glucose hypometabolism (¹⁸F-fluoro-2-deoxyglucose [FDG]–PET), and brain atrophy (MRI) in clinically and cognitively normal women at different endocrine transition stages (premenopause vs perimenopause vs menopause) and age-matched men.

METHODS Participants. Among a larger pool of clinically and cognitively normal individuals participating in brain imaging studies at New York University School of Medicine, this study focused on a subset of 60 participants age 40–60 years who completed clinical, MRI, FDG, and PiB-PET examinations between 2010 and 2015. Patients were derived from multiple community sources, including individuals interested in research participation and family members of impaired patients.

The study protocol has been published previously.^{9,10} Briefly, all patients underwent thorough physical examinations with detailed medical histories. Individuals with medical conditions, or history of conditions that may affect brain structure or function (e.g., stroke, unmanaged diabetes, depression, head trauma, any neurodegenerative diseases, hydrocephalus), and those taking psychoactive medications were excluded. Only patients 40–60 years of age, with education ≥ 12 years, Clinical Dementia Rating 0, Global Deterioration Scale ≤ 2 , Mini-Mental State Examination ≥ 27 , Hamilton Depression Scale < 16 , Modified Hachinski Ischemia Scale < 4 , and normal cognitive test performance for age and education were included.^{9,10}

DNA was obtained from venous blood samples to determine *APOE* genotypes using standard quantitative PCR.^{9,10} Individuals with 1 or 2 $\epsilon 4$ alleles were categorized as $\epsilon 4$ carriers (*APOE4+*) and compared to noncarriers (*APOE4-*).

Standard protocol approvals, registrations, and patient consents. Informed consent was obtained from all patients for participation in this institutional review board–approved study.

Determination of menopausal status. Determination of menopausal status was based on clinical judgment, medical records, and detection of cluster symptoms according to the Stages of Reproductive Aging Workshop criteria.¹¹ Detection of cluster symptoms was based on presence of sweatiness/hot flashes, mood swings, insomnia, change in appetite, loss of

libido, cognitive problems/concentration, and short-term memory complaints.¹¹

Detailed medical records of menopausal status were available for 52 women age 40–60 years. Ten of these women were excluded due to medical reasons including hysterectomy (3 cases), thyroid disease (2 cases), cancer (2 cases), and other comorbidities (3 cases).

The remaining 42 women included 15 asymptomatic perimenopausal women by age (e.g., regular cyclers, or premenopausal controls, CNT), 13 symptomatic perimenopausal women (e.g., irregular cyclers, PERI), and 14 postmenopausal women (e.g., no menstrual cycles for ≥ 12 months, MENO). These groups were compared to each other and to 18 age- and education-matched men selected on the basis of a complete imaging dataset.

Data acquisition and preparation. All patients received volumetric MRI, PiB, and FDG-PET scans at Weill Cornell Medical College following standardized procedures.^{9,10,12} For PET, patients were positioned in the scanner 60 minutes postinjection of 15 mCi of ¹¹C-PiB, and scanned for 30 minutes in 3D mode on an LS Discovery (GE Healthcare, Cleveland, OH) or BioGraph (Siemens, Munich, Germany) PET/CT scanner. The FDG scan was performed > 30 minutes after completion of the PiB scan or on a separate day. After an overnight fast, patients were injected with 5 mCi of ¹⁸F-FDG, positioned in the scanner 35 minutes postinjection, and scanned for 20 minutes. All images were corrected for attenuation, scatter, and decay, and smoothed for uniform resolution.¹³

For each patient, summed PET images corresponding to 40–60 minutes of FDG data and 60–90 minutes of PiB data were coregistered to the corresponding MRI and to each other using the normalized mutual information routine of statistical parametric mapping (SPM12).¹⁴ MRIs were segmented into gray matter (GM), white matter (WM), and CSF and normalized to Montreal Neurological Institute space by high-dimensional warping (DARTEL).¹⁴ MRI-coregistered PET scans were spatially normalized using patient-specific transformation matrices obtained from MRI, and smoothed with a 10-mm full width at half maximum (FWHM) filter. Jacobian modulation was applied to restore absolute GM and WM volumes in the segmented MRIs, which were smoothed with an 8-mm FWHM kernel.¹²

Statistical analysis. SPSS (SPSS Inc., Chicago, IL) v22 and SPM12 were used for data analysis. Clinical and demographic measures were examined with univariate general linear models and χ^2 tests at $p < 0.05$.

For SPM analysis, a full factorial model with post hoc *t* contrasts was used to test for regional differences in imaging measures across sex (women vs men) and reproductive aging groups (premenopausal vs perimenopausal vs postmenopausal women vs men), accounting for modality-specific reference values (e.g., total intracranial volume for MRI, pons uptake for FDG, and cerebellar GM uptake for PiB).^{9,10,12}

Age, education, and *APOE* genotype were examined as covariates. *APOE* status was examined for interaction effects with sex and clinical group using adjusted models that included a 2-way interaction term for each comparison.

As we had specific a priori hypotheses on which brain regions would show possible biomarker effects, results were examined at $p < 0.001$, uncorrected (cluster extent ≥ 25 voxels) in the search volume defined by a masking image created from a set of predefined bilateral AD-related regions of interest.^{9,10,12} These included posterior cingulate cortex, precuneus, inferior and superior parietal lobule, lateral and medial temporal cortex, and medial, inferior, and prefrontal cortex. PET analyses were further restricted to a standardized GM mask.¹²

Anatomic location of brain regions showing significant effects was described using Talairach and Tournoux coordinates. Biomarker measures were extracted from clusters of voxels showing significant effects for further analysis.

Linear regressions were used to evaluate the associations among biomarkers, laboratory measures, neuropsychological measures, and clinical group, using the same confounds and interaction terms as above.

To directly compare the degree of biomarker abnormalities, *z* scores were generated for each woman and each biomarker modality against men, and examined with paired *t* tests across

all patients and within groups.^{12,15} Stepwise linear regressions and receiver operating characteristic curves were used to compare biomarkers as predictors of group membership and to calculate associated relative risk and 95% confidence intervals. Results were considered significant at *p* < 0.05.

RESULTS Participants. Participant characteristics are shown in table 1. As expected, postmenopausal women (MENO) were on average 7 ± 3 years older than premenopausal (CNT) and perimenopausal

Table 1 Demographic and clinical characteristics by clinical group

	Women			
	CNT	PERI	MENO	Men
No.	15	13	14	18
Age, y, range	48 (5), 40-55	50 (6), 40-56	57 (2), 52-60	52 (6), 42-60
Education, y	16 (2)	16 (2)	16 (2)	17 (2)
Family history of LOAD, % positive	50	69	79	80
APOE ε4 carriers, n (% positive)^a	8 (57)	6 (46)	5 (36)	11 (52)
Ethnicity, % white	75	71	89	86
Subjective complaints, %	81	76	100	67
Laboratory findings				
Hypertension, % positive	17	21	6	10
BMI	25 (6)	25 (6)	24 (4)	27 (3)
Hip to waist ratio (unitless)	0.9 (0.5)	1.0 (0.4)	1.2 (0.1)	1.0 (0.3)
Systolic blood pressure, mm Hg	113 (18)	124 (19)	113 (8)	119 (13)
Diastolic blood pressure, mm Hg	70 (12)	73 (13)	68 (11)	73 (10)
Fasting glucose, mg/dL	67 (24)	72 (13)	70 (23)	79 (11)
QUICKI score (unitless)	0.17 (0.02)	0.18 (0.02) ^b	0.18 (0.01) ^b	0.15 (0.01)
Cholesterol, mg/dL	190 (63)	203 (32)	210 (66)	185 (36)
HDL:LDL ratio (unitless)	0.63 (0.16)	0.59 (0.16)	0.69 (0.23)	0.39 (0.10) ^c
Triglycerides, mg/dL	71 (44)	80 (21)	68 (37)	118 (40) ^c
Homocysteine, μmol/L	5.5 (6.5)	9.1 (5.8)	5.4 (8.9)	9.1 (6.5)
Plasma vitamin B₁₂, ng/L	407 (255)	630 (294)	717 (546)	630 (302)
Plasma folate, ng/mL	12 (10)	15 (4)	5 (13) ^d	13 (11)
Neuropsychological tests				
Mini-Mental State Examination	29 (2)	29 (1)	29 (1)	29 (1)
Digit symbol substitution	68 (8)	67 (12)	62 (9)	56 (9) ^c
Paired associates delayed recall	11 (3)	9 (3)	8 (5)	10 (3)
Paragraph delayed recall	8 (3)	7 (2)	6 (4)	6 (3)
Designs	8 (2)	8 (2)	6 (4)	7 (2)
Object naming	58 (2)	58 (2)	57 (7)	53 (17)
WAIS vocabulary	69 (7)	66 (15)	63 (15)	65 (20)

Abbreviations: BMI = body mass index; CNT = premenopausal women; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LOAD = late-onset Alzheimer disease; MENO = postmenopausal women; PERI = perimenopausal women; QUICKI = quantitative insulin-sensitivity check index; WAIS = Wechsler Adult Intelligence Scale. Values are mean (SD) unless otherwise specified.

^aAPOE information was not available for 3 patients (1 CNT, 1 MENO, 1 man).

^bDifferent from men.

^cDifferent from women.

^dDifferent from CNT, PERI, and men; *p* < 0.05.

(PERI) groups ($p < 0.05$). Groups were otherwise comparable for clinical measures and *APOE4* distribution, as well as neuropsychological testing, with the exception of lower DSST scores in men relative to CNT and PERI women ($ps \leq 0.01$), and a trend vs MENO ($p = 0.07$). A trend towards higher prevalence of subjective complaints was evident in the MENO group vs other groups ($p = 0.08$; table 1).

While all patients were normoglycemic, the PERI and MENO groups exhibited higher quantitative insulin-sensitivity check index (QUICKI) scores¹⁶ compared to men ($ps < 0.01$; table 1). The MENO group also had reduced plasma folate vs men ($p < 0.05$), while men had higher triglycerides and lower high-density lipoprotein/low-density lipoprotein ratios vs all female groups ($ps < 0.02$).

FDG-PET glucose metabolism. Controlling for age and pons activity, women showed reduced glucose metabolism (CMRglc) in frontal cortex compared to men ($p < 0.001$; table e-1 at Neurology.org). On post hoc analysis, these effects were driven by the MENO and PERI groups ($p < 0.001$), while CNT showed a trend towards reduced CMRglc vs men ($p < 0.01$; figure 1). In addition, both PERI and MENO groups

showed reduced CMRglc in posterior cingulate/pre-cuneus (PCC) and parietal and temporal cortex vs CNT, with a gradient effect of CNT > PERI > MENO ($p < 0.001$; figure 1).

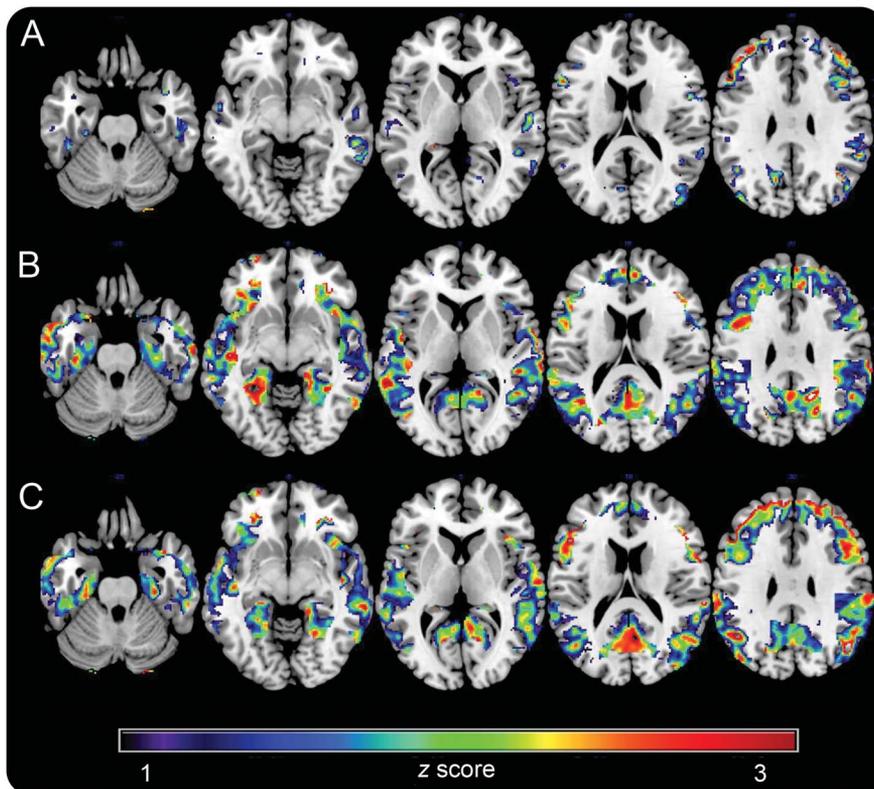
Results remained substantially unchanged including education and *APOE* as covariates. There were no significant *APOE* by group interactions in any of the above regions.

PiB-PET A β deposition. Controlling for age and cerebellar uptake, women exhibited increased PiB uptake in PCC, fusiform, and frontal cortex vs men ($p < 0.001$; table e-2). On post hoc analysis, these effects were more pronounced in MENO and PERI groups, and less so in the CNT group ($ps < 0.001$; figure 2). In addition, both PERI and MENO groups showed increased PiB uptake in frontal and temporal cortex vs CNT (16% and 19%), with a gradient effect of CNT < PERI < MENO ($p < 0.001$; figure 2).

As compared to any of the female groups, no brain regions showed increased PiB uptake in men.

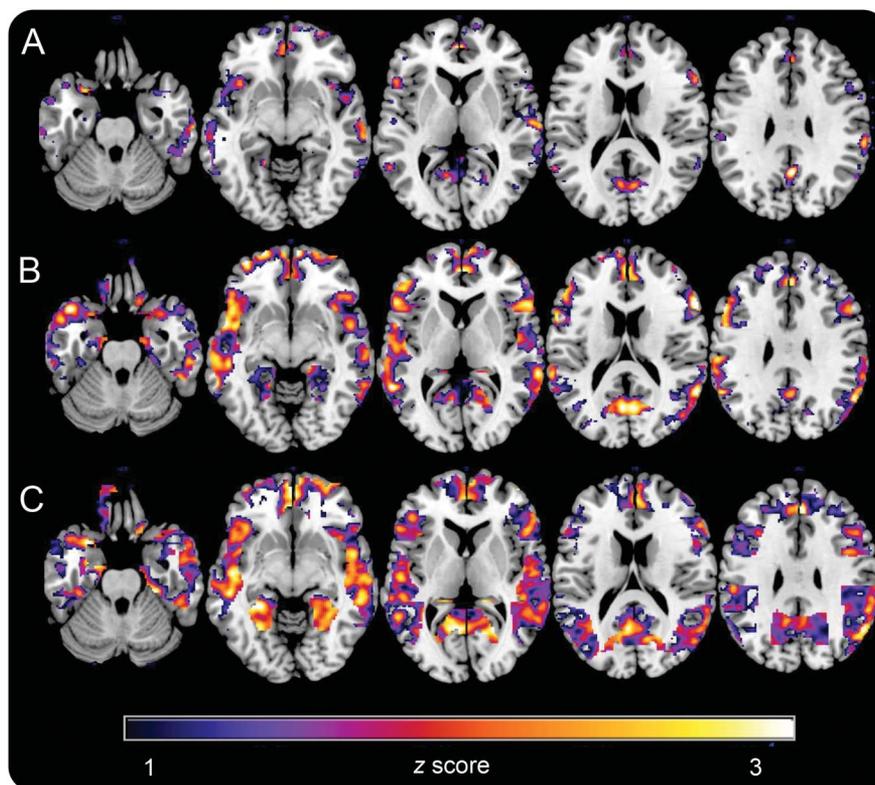
Albeit limited by the small number of patients, *APOE* by group interaction effects were observed in the frontal cortex ($p < 0.001$). In these regions, *APOE4*+ MENO patients showed higher PiB

Figure 1 18F-fluoro-2-deoxyglucose (FDG)-PET brain glucose metabolism as a function of chronologic vs endocrine aging



Statistical parametric maps (SPMs) display FDG uptake reductions in (A) asymptomatic perimenopausal women, (B) perimenopausal women, and (C) menopausal women vs men. SPMs are represented on a color-coded scale (1 < z < 3, where z > 2 corresponds to $p < 0.001$) and displayed on a standardized MRI.

Figure 2 Pittsburgh compound B (PiB)-PET β -amyloid deposition as a function of chronologic vs endocrine aging



Statistical parametric maps (SPMs) display increased ^{14}C -PiB uptake in (A) asymptomatic perimenopausal women, (B) perimenopausal women, and (C) menopausal women vs men. SPMs are represented on a color-coded scale ($1 < z < 3$, where $z > 2$ corresponds to $p < 0.001$) and displayed on a standardized MRI.

binding than all other groups, ranging from 5% as compared to *APOE4+* CNT to 20% compared to *APOE4-* men (figure e-1).

MRI GM and WM volumes. Compared to men and controlling for age and total intracranial volume, women showed reduced GM volumes (GMV) and WM volumes (WMV) in PCC, frontal, temporal, and parietal regions ($p < 0.001$; table e-3). On post hoc analysis, these effects were more pronounced in the MENO and PERI groups than in the CNT group (figure 3). In addition, both PERI and MENO groups showed reduced frontal GMV and WMV vs CNT women, with a gradient indicating CNT > PERI > MENO ($p < 0.001$; figure 3).

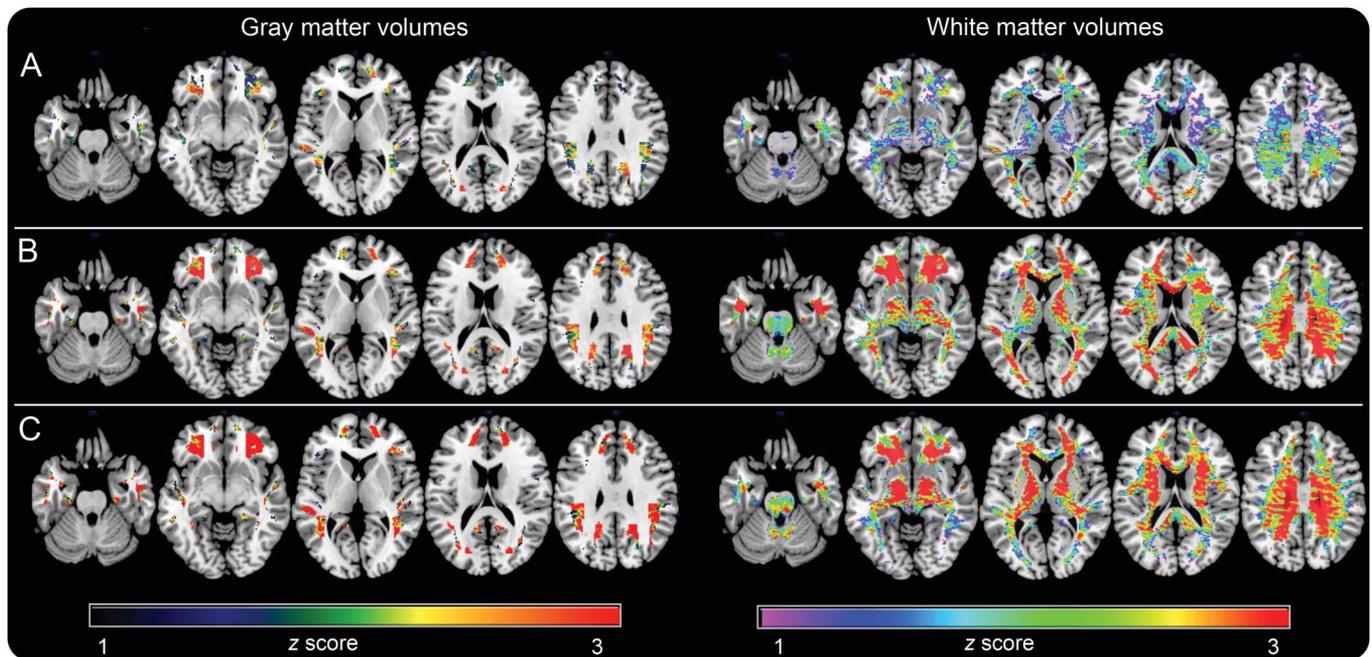
Men exhibited no reduction in GMV or WMV compared to any of the female groups.

Results remained substantially unchanged controlling for education and *APOE* as covariates.

Biomarker comparisons. Within all female groups, the extent of hypometabolism and WMV loss exceeded that of PiB uptake and GMV loss ($p \leq 0.009$; figure 4). Within the MENO group, WMV loss exceeded magnitude of hypometabolism ($p = 0.03$).

Logistic regressions indicated that the combination of CMRglc and WMV was the most accurate predictor of female vs male status with 90% accuracy and 4.5 relative risk (RR) ($p < 0.001$; table e-4). Adding PiB uptake to the model increased the discrimination accuracy of MENO vs men to 100% (36.5 RR; $p < 0.001$). Among female groups, the combination of CMRglc and PiB uptake was the most accurate predictor of MENO vs CNT (96% accuracy, RR 26.5, 1.7–408; $p < 0.001$; table e-4). These biomarkers independently predicted MENO vs PERI (CMRglc: 84% accuracy, 4.0 RR; PiB: 80% accuracy, 4.9 RR; $ps < 0.001$), while PiB uptake was the best predictor of PERI vs CNT (89% accuracy, 11.9 RR; $p < 0.001$; table e-4).

Correlations between biomarkers and clinical and cognitive measures. Across all patients, controlling for age, QUICKI scores were associated with frontal CMRglc (pons-adjusted $\beta = -0.33$, $p = 0.026$) and WMV ($\beta = -0.34$, $p = 0.025$). On post hoc examination, CMRglc effects were driven by the PERI and MENO groups ($\beta = -0.56$ and $\beta = -0.60$, respectively, $ps \leq 0.05$), while no significant associations occurred in CNT women or men. Similarly, WMV effects were evident in the MENO group ($\beta = -0.68$,



Statistical parametric maps (SPMs) display (left) gray matter and (right) white matter volume reductions in (A) asymptomatic perimenopausal women, (B) perimenopausal women, and (C) menopausal women vs men. SPMs are represented on different color-coded scales (1 < z < 3, where z > 2 corresponds to p < 0.001) and displayed on a standardized MRI.

$p = 0.05$), borderline in the PERI group ($\beta = -0.56$, $p = 0.09$), and not significant among CNT women or men.

DISCUSSION The results indicate that as women go through menopause, and relative to age-matched men, multiple imaging endophenotypes indicative of AD risk emerge. These include reduced CMRglc, increased A β accumulation, and GM and WM loss in the same brain regions as patients with clinical AD. AD biomarker abnormalities were most pronounced in postmenopausal women, intermediate in perimenopausal women, and lowest in premenopausal women.

These results indicate progressively increased risk of AD as women undergo menopausal changes, suggesting that endocrine aging accelerates chronologic aging in the female brain several years, if not decades, prior to emergence of possible clinical symptoms of AD.

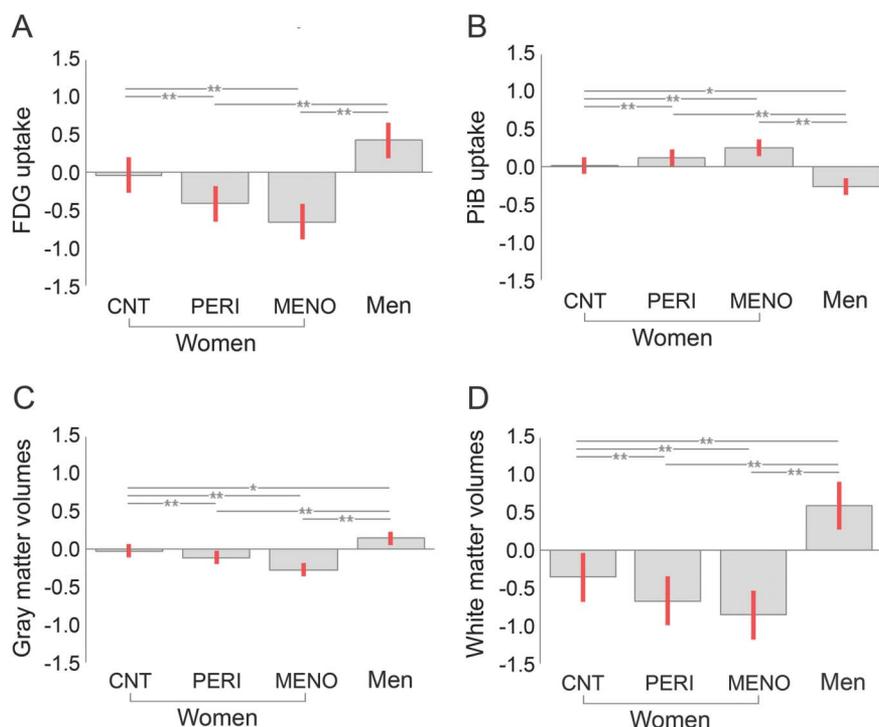
These findings are particularly relevant given current understanding of AD as a progressive disorder characterized by an extended preclinical phase during which the disease is underway but has not led to any recognizable clinical or cognitive symptoms.¹⁷ Given the known relationship between altered AD biomarkers and onset of clinical symptoms,⁸ our data indicate that female-specific endocrine transitions at least in part account for the increased AD risk observed in women.

This is consistent with mechanistic evidence of a bioenergetic crisis in the female brain that emerges specifically during perimenopause.⁴ In animal studies, estrogenic control of glucose metabolism in the brain is disassembled during the perimenopausal transition, leading to an adaptive activation of ketone body metabolism.¹⁸ Ultimately, the reliance of ketone bodies as an alternative metabolic fuel to generate adenosine triphosphate can lead to catabolism of white matter to generate ketones.¹⁹ This in turn promotes neuronal loss and accumulation of AD pathology.²⁰

The human brain imaging findings described herein are consistent with mechanistic preclinical pathway analyses.^{4,18–21} Perimenopausal and postmenopausal women exhibited an energetically compromised brain, as reflected in a 4-fold increased risk of hypometabolism and white matter loss relative to premenopausal women and age-matched men. In addition, although all participants were normoglycemic, brain metabolic markers correlated with indicators of insulin resistance, consistent with prior reports of systemic dysmetabolism during perimenopause and postmenopause.^{4,21}

Our data also suggest that the 3 greatest risk factors for late-onset AD—age, female sex, and *APOE4* genotype²²—interact during the endocrine aging process to cooperatively drive development of AD pathology. PiB uptake in postmenopausal women was exacerbated by *APOE4* genotype, a well-known genetic risk factor that disproportionately affects AD

Figure 4 Comparing Alzheimer disease (AD) biomarker abnormalities across groups



(A) ¹⁸F-fluoro-2-deoxyglucose (FDG) uptake. (B) Pittsburgh compound B (PiB) uptake. (C) Gray matter volumes. (D) White matter volumes. Biomarkers are extracted from frontal cortex clusters showing maximal statistical differences across groups and displayed on the same scale. Values are grand-mean scaled, reference-adjusted mean values, SEM. **p* < 0.05, ***p* < 0.01. CNT = asymptomatic perimenopausal women by age; PERI = symptomatic perimenopausal women; MENO = postmenopausal women.

risk in women.^{1,2,3} Maximum group differences were observed in frontal cortex, a brain region particularly vulnerable to the combined effects of aging and *APOE4* genotype in predisposed individuals.²⁴ Even in the absence of dementia, *APOE4* is known to significantly increase brain atrophy and decrease brain connectivity much more strongly in women than in men.^{25,26} Together with previous reports, our findings of exacerbated Aβ load in postmenopausal women positive for *APOE4* genotype provide a possible pathophysiological as well as endocrine substrate to the clinical data.

While it seems likely that loss of estrogen during perimenopause may be driving the observed AD biomarker shifts, other explanations exist. For example, the drop in estrogen levels may be acting as a surrogate biomarker of other underlying molecular changes, such as age-related declines in bioenergetic function. As mitochondria are needed for estrogen synthesis and mitochondrial deficits have long been implicated in AD,²⁷ studies are needed to investigate whether AD biomarker changes in menopausal women are related to altered mitochondria activity.

The observed sex differences may also be related to lifestyle and vascular risk factors known to affect AD risk.²⁸ While our postmenopausal women showed

lower folate levels compared to the other groups, their homocysteine was not affected, possibly due to their higher plasma vitamin B₁₂ levels. The higher blood lipids in men are also suggestive of increased vascular risk relative to women,²⁸ though this group did not show biomarker abnormalities. Other studies with larger samples are needed to assess whether diet, exercise, and vascular risk factors influence biomarker and cognitive outcomes in aging men and women.

Several issues require further investigation. First, our results are cross-sectional in nature and do not allow for determination of causality or temporal relationships between biomarkers. Second, as with other studies in asymptomatic at-risk individuals,^{12,24,29} imaging biomarkers were not associated with neuropsychological measures, most likely because our patients were all cognitively normal, relatively young, and high school graduates, which could have resulted in a ceiling effect. Other studies with larger samples and longitudinal follow-up are warranted to determine whether biomarker abnormalities observed in perimenopausal and postmenopausal women are predictive of cognitive decline.

Our determination of menopausal state in the absence of hormonal confirmation is vulnerable to error. Characterization of reproductive stage was

based on self-report, clinical judgment, and established diagnostic criteria known to have good agreement with clinical and laboratory findings,¹¹ which reduce potential for misclassification. While we consider it likely that the changes in menstrual cycle frequency reported by our participants reflect their actual menopausal status, because of the synchronous timing of medical assessments and brain imaging examinations, our menopausal group may have included patients still in perimenopause. Likewise, our premenopausal controls may have included patients undergoing perimenopausal changes. This would, however, conservatively reduce power in detecting differences between groups. Our findings of gradual increases in biomarker abnormalities in perimenopausal and postmenopausal patients vs premenopausal controls and vs men are consistent with preclinical and neuropsychological indicators of change in cognitive function^{30–32} and provide support that our group assignment criteria were likely correct. Future studies are warranted to examine hormonal levels,³³ as well as additional metabolic indicators²¹ to further refine reproductive staging.

Two of the 14 postmenopausal women reported being on hormonal replacement therapy (HRT). While these participants' CMRglc values were on the lower end of the spectrum (1.3 and 1.45 standardized uptake value ratio [SUVR], respectively), their A β load was within average (1.1 and 1.25 SUVR). As such, it is difficult to conclude whether these women had benefited from therapy. Clinical trials have shown that HRT is effective at preserving CMRglc in AD regions, especially if initiated prior to menopause,^{34,35} whereas it can be deleterious when initiated after menopause³⁶ or in type 2 diabetic women.^{34,37,38} Our neuroimaging supports further investigation of the potential efficacy of estrogen-based therapies in preventing decline in brain bioenergetic capacity in women of perimenopausal age.

In keeping with previous studies with similar middle-aged cohorts,²⁴ PiB measures were examined as continuous rather than dichotomous variables. Using this method, we observed significant quantitative differences across sex and female groups, which included so-called PiB-negative patients. These findings are consistent with previous evidence that the PiB signal is sensitive to detect early, albeit mild A β accumulation within middle-aged patients at risk for AD, especially *APOE4* carriers.^{10,12,24,39,40}

We caution that the present results were found in small numbers of carefully screened patients under controlled clinical conditions. Replication of these preliminary findings in community-based populations with more diversified socioeconomic and medical status as well as with other AD biomarkers is warranted.

AUTHOR CONTRIBUTIONS

Dr. Mosconi: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Dr. Berti: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Quinn: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. McHugh: acquisition of data, critical revision of the manuscript for important intellectual content. G. Petrongolo: acquisition of data, critical revision of the manuscript for important intellectual content. I. Varsavsky: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Osorio: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Pupi: study concept and design, critical revision of the manuscript for important intellectual content. Dr. Vallabhajosula: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Isaacson: study concept and design, critical revision of the manuscript for important intellectual content. Dr. de Leon: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Brinton: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content.

STUDY FUNDING

Study funded by NIH/NIA (AG035137, AG13616, 2P01AG026572); funding from the Department of Neurology at Weill Cornell Medical College; and philanthropic support of the Alzheimer's Prevention Clinic, Weill Cornell Memory Disorders Program.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 26, 2017. Accepted in final form July 5, 2017.

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